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PROF. DR. MURAT YAKAR

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3rd Advanced Engineering Symposium

I would like to thank all of the contributing authors and reviewers to the 3rd Advanced Engineering Days (AED) Symposium, 08 June 2022. In this international symposium there are 38 presentations, 3 of which are Albania, one of them is from Morocco and the rest are from Türkiye. We would like to see you in the 4th AED which will be held on 21-22 September 2022.

Best regards

Prof. Dr. Murat YAKAR

The proceedings of the
3rd Advanced Engineering Days

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Representing ordinal predictors in real estate valuation with multiple regression

Ümit Işıkdağ[*1]

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Keywords
Real Estate
Valuation
Regression
Ordinal
Predictor

Abstract
There are several different valuation methods used in real estate valuation. Statistical methods such as multiple regression and machine learning techniques such as ANN and Ensemble Methods are among the key ones implemented in recent studies. In all these methods the types of predictor variables for estimation of the price/value range from nominal, ordinal to continuous. Although the representation of nominal and continuous variables are agreed in prediction models, the representation of ordinal variables can change in every model. This paper provides a comparison of the different representations of the same ordinal variable in models. The findings indicate that representation of ordinal variables as continuous can be beneficial when the ordinal variable has many levels.

Introduction

Real estate valuation has been a very active topic of research since many years. Real estate valuation has been done using several methods depending on the purpose of the valuation study. The valuation can be defined as the determination of amount for which the property will transact on a particular date [1]. There are several concepts related with the value, these are price, worth and the value. As explained by [1] price is the observable exchange price in the open market, the value is an estimation of the price that would be achieved if were the property to be sold in the market; and worth is a specific individual's perception of the capital sum that he/she would be prepared to pay for the stream of benefits that she/he expects to be produced by the property. Value models concentrate on predicting the price of the property, the value is considered as the final result. The purpose of the valuation studies is generating reports for sale purposes, accounting purposes in companies, for calculation of loans at banks, for finding a minimum price for auctions, for insurance purposes, for taxation purposes and for compulsory purchase purposes [1]. There are several different valuation methods used in real estate valuation. [2] summarizes these methods into 2 groups as traditional methods and advanced methods. The traditional methods include comparable method, investment/income method, profit method, development residual method, contractor's method/cost method, multiple regression method, stepwise regression method. The advanced methods include, artificial neural networks (ANNs), hedonic pricing method, spatial analysis methods, fuzzy logic and time series methods such as autoregressive integrated moving average (ARIMA). As explained in [3] the real estate valuation efforts are usually focused on two aspects, first one is known as individual valuation and is concentrated on determining the price of a specific (or focused) real estate. The second approach is known as mass valuation, where the value of a group of real estates are predicted. The comparable (sales comparison), contractor's method/cost method, income method, profit methods are suitable for individual valuation. However mass appraisal benefits more from statistical and machine learning approaches including regression-based methods, artificial neural networks, spatial analysis methods. Examples of the use of statistical and machine learning methods from the recent literature include the use of who implemented multiple regression analysis, hedonic models, ANNs, Ensemble Methods, Quantile and Semi-Log Regression [4-7]. Furthermore [7] presents a comprehensive overview of real estate appraisal methods in the era of big data.

Material and Method

As indicated by the literature most modern methods of real estate appraisal involves dealing with statistical and mostly with machine learning techniques. In these techniques the estimation of real estate prices is done following the "regression" family of the estimation and machine learning methods, as the price is a variable having a continuous scale. There are many factors that has an impact on the price including the size, the location, attributes of the unit (if the real estate is a property) such as number of rooms (living rooms, bathrooms ...), existence of different rooms and facilities inside the apartment, scenery, the level of the apartment, the orientation, condition, distance to transport, nearby facilities, schools, markets, health facilities, socio-economic status of the neighborhood and many more. Although the dependent variable, price, has a continuous scale, the independent variables (factors/predictors) that are used to estimate the dependent variable ranges from dichotomous, nominal to ordinal. In statistical and machine learning models, it is agreed that dichotomous variables can be used without any modification, but nominal variables having levels of 2+ need to be converted into (n-1) dummy variables, where n denotes to number of categories in the nominal variable. This process is called the dummy encoding of the nominal variable. In fact, in the case of ordinal variables (variables representing ordered values) there is no such agreement on how to represent them in statistical and machine learning models. One view advocates that these variables "are not continuous in nature" and should be represented, as if they were nominal, and similar to nominal variables, and dummy encoding should be applied to the ordinal variables as well and generated dummy variables should be used as independent variables (IVs) in the model in lieu of the ordinal variable. In fact, once this dummification operation is done, the ordered nature of the data is lost completely. A solution to tackle with that through using dummy variables has been proposed in [8] and this encoding technique is known as staircase encoding. The final view on the use of ordinal variables is treating them as continuous variables in the models. In this study in order to test all these approaches we have collected data on real estate prices in a neighborhood of Istanbul from a well-known real estate web site. The data was collected manually by a human operator. The raw data contained 253 rows, and included 3 fields, 'price', 'sqm' and 'bl'. The price variable represents the price in terms of Turkish Lira, the sqm represents the gross floor area of the apartment, and 'bl' represents the number of bedrooms + living rooms of the apartment. The scale of price and sqm are continuous, while the scale of 'bl' can be considered both as nominal and ordinal, the variable has 14 categories/levels. In this research, we have ordered 'bl' in ascending order by taking b as prior and l as secondary important factor. As a result, we generated a new ordinal variable 'bl_ordinal', and we also kept the raw data in a variable named 'bl_nominal'. On the other hand, we have implemented a natural log transformation to the price variable and generated a new variable named 'lnPrice'. The natural log transformation helped to remove the excess kurtosis and positive skewness of data and ensured the normality of the variable. Later we have implemented both dummy and staircase encoding to the ordinal variable through the program code developed during the study. The staircase and dummy variables generated as a result of this process were 'sc1-sc13' and 'd1-d13' (26 variables in total). The code used in the generation of these variables are provided in [9]. Once the data processing is complete, we have conducted 3 multiple regression analyses. The models proposed and tested is provided below:

$$lnPrice = \beta_0 + \beta_1 sqm + \beta_2 d1 + \ldots\ldots\ldots + \beta_{14} d13$$
$$lnPrice = \beta_0 + \beta_1 sqm + \beta_2 sc1 + \ldots\ldots\ldots + \beta_{14} sc13$$
$$lnPrice = \beta_0 + \beta_1 sqm + \beta_2 bl\_ordinal$$

Results

The results of the multiple regression analysis are provided below. In Model 1(Fig.1), the coefficients of all dummy variables (d1-d13) with exception of 'd8' are statistically insignificant, while the 'β_0' and the coefficient of 'sqm' is statistically significant. On the other hand, in Model 2 (Fig.1), the coefficients of all staircase encoded variables (sc1-13) are statistically insignificant, while the 'β_0' and the coefficient of 'sqm' is statistically significant. In Model 3 (Fig.2), coefficients of all variables were statistically significant. The F value in regression is the result of a test where the null hypothesis is that all of the regression coefficients are equal to zero. The F-test of overall significance shows whether the linear regression model provides a better fit to the data than a model that contains no independent or no significant independent variables. In all 3 models, the null hypotheses of F tests are rejected, showing that all 3 models have a predictive capability.

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	13.84178	0.161728	85.58676	0.0000
D1	0.280101	0.177205	1.580658	0.1153
D2	0.396599	0.410958	0.965060	0.3355
D3	0.174794	0.166891	1.047355	0.2960
D4	0.239222	0.333915	0.716416	0.4744
D5	0.262840	0.179025	1.468172	0.1434
D6	0.490448	0.258933	1.894114	0.0594
D7	0.257455	0.269074	0.956817	0.3396
D8	0.483212	0.204093	2.367600	0.0187
D9	0.356382	0.266651	1.336509	0.1827
D10	0.402968	0.271059	1.486642	0.1384
D11	0.328184	0.293921	1.116570	0.2653
D12	0.057534	0.379933	0.151432	0.8798
D13	0.849007	0.533621	1.591029	0.1129
SQM	0.004273	0.000921	4.641457	0.0000

R-squared	0.439528	Mean dependent var	14.69719
Adjusted R-squared	0.406420	S.D. dependent var	0.490995
S.E. of regression	0.378283	Akaike info criterion	0.951329
Sum squared resid	33.91418	Schwarz criterion	1.161414
Log likelihood	-104.8674	Hannan-Quinn criter.	1.035863
F-statistic	13.27556	Durbin-Watson stat	2.149335
Prob(F-statistic)	0.000000		

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SC1	0.280101	0.177205	1.580658	0.1153
SC2	0.116498	0.390114	0.298625	0.7655
SC3	-0.221805	0.380975	-0.582202	0.5610
SC4	0.064427	0.283586	0.227189	0.8205
SC5	0.023618	0.274019	0.086192	0.9314
SC6	0.227608	0.193131	1.178519	0.2398
SC7	-0.232993	0.250719	-0.929301	0.3537
SC8	0.225757	0.172819	1.306314	0.1927
SC9	-0.126830	0.157424	-0.805654	0.4213
SC10	0.046586	0.230916	0.201746	0.8403
SC11	-0.074784	0.256647	-0.291389	0.7710
SC12	-0.270650	0.309841	-0.873514	0.3833
SC13	0.791473	0.479088	1.652041	0.0999
SQM	0.004273	0.000921	4.641457	0.0000

R-squared	0.439528	Mean dependent var	14.69719
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Prob(F-statistic)	0.000000		

Figure 1. Multiple Regression Analysis Results Models [1,2]

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	13.95263	0.061490	226.9091	0.0000
BL_ORDINAL	0.037358	0.017333	2.155327	0.0321
SQM	0.003820	0.000733	5.207539	0.0000

R-squared	0.412958	Mean dependent var	14.69719
Adjusted R-squared	0.408243	S.D. dependent var	0.490995
S.E. of regression	0.377701	Akaike info criterion	0.902408
Sum squared resid	35.52194	Schwarz criterion	0.944425
Log likelihood	-110.7034	Hannan-Quinn criter.	0.919315
F-statistic	87.58017	Durbin-Watson stat	2.064853
Prob(F-statistic)	0.000000		

Figure 2. Multiple Regression Analysis Results Models [3]

Discussion and Conclusion

The results of the assumptions testing of the Model 3 were as follows. Normality of residuals, Jarque-Bera:3.02 (p>0.05) (Ho: Normality), Breusch-Godfrey Serial Correlation LM Test: Obs*R-squared :1.25(p>0.05) (Ho: No serial correlation), White Test: Obs*R-squared :7.17(p>0.05) (Ho: Homoskedasticity), VIF:3.45 (<5 for both independent variables showing no signs of multicollinearity). In the Model 3, where the ordinal variable was treated as a continuous variable, all coefficients of the model were found significant, in addition all assumptions of the multiple linear regression were met. The results show that treating an ordinal variable as a continuous one provides a statistically significant model, where all assumptions of multiple linear regression are met. On the other hand, models where the ordinal variable is represented with dummy encoding and staircase encoding provided insignificant coefficients for all dummy /staircase variables with an exception for one dummy variable. This insignificance might be result of imbalance between the levels of the ordinal variable (thus in the number of dummy variables generated for each level). In addition, as the variable in focus had 14 levels (13 dummy/staircase variables), some of the dummy/staircase variables might have a very minor contribution in explaining the variance in the dependent variable, especially in the case of linear regression. This in turn might have resulted in the insignificance of the coefficients of dummy/staircase variables. The results have shown that an 'ordinal variable with many levels' can be interpreted/included as a continuous variable in Multiple Regression Analysis based Real Estate valuation. The case provided is a single example only, and more research and testing are required to reach a more comprehensive and general conclusion on the subject.

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Modeling the trend of construction materials industry

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Keywords
Construction
Material
Price
ARIMA
Time Series

Abstract
Construction materials has a key impact on the cost of construction. In construction industry it is important to foresee the trends of material prices to prevent, cost overruns during the construction stage and bankruptcy of the contractors. The material price trends have a time dependent nature, and time series analysis methods can be utilized to model and estimate them. This study focuses on modeling and forecasting the trends in material prices through Box-Jenkins methodology. In this context, an economic indicator named General Trend in Construction Materials Industry is modelled with an ARIMA (1,1,0) model. The forecasts done with the model indicate that the model can successfully predict the future values of the indicator.

Introduction

Construction materials is one of the key factors that has an impact on the cost of construction. Construction industry can be become very fragile in times of economic crisis and especially when material price fluctuations are observed. These fluctuations can be related with raw material costs, production costs, and cost of logistics. The changes in material prices can result in cost overruns which can then lead to unfinished buildings and defaulting contractors. In order to foresee the risks related to the material price fluctuations, it is important to forecast the trends in the construction material industry. The material price trends have a time dependent nature, and time series analysis methods can be utilized to estimate them. In recent years, [1] used Box-Jenkins methods to estimate the maintenance costs of construction equipment, [2] included four quarterly construction industry datasets from C&SD between 1983Q1 and 2014Q4 to accurately predict fluctuations in the construction industry by comparing the accuracy of autoregressive integrated moving average (ARIMA) and Autoregressive Neural Network (ARNET) models. [3] used Artificial Neural Networks (ANN), Linear Regression and Autoregressive Time Series (ARIMA) methods to estimate the Construction Cost Index. [4] proposed the ARIMA-ANN model to estimate construction costs and investigates whether this model can have higher accuracy than the ARIMA or ANN model. This study focuses on modeling and forecasting the trends in material prices through a well-known time series modeling methodology. The methodology is known as Box-Jenkins (ARIMA) Method and can be successfully applied to model time series of a linear nature. The following sections elaborate on the dataset, the modeling process and later presents and discusses the results of forecasts done with the model.

Material and Method

The Association of Turkish Construction Material Producers (IMSAD) is a non-profit organization in Turkey, that represents Construction Materials Industry both locally and internationally. IMSAD is well known with its Construction Material Industry Indices which are published on monthly bases. One of these indices is the Trust Index and is composed of 5 indicators. The value of each indicator is determined on monthly basis, based on responses of members to the indicator questions. The base value for the index (and all indicators) is 100 which is equal to the indicator value of August 2013 (base year/month).

In this study we have chosen to statistically model "General Trend in Construction Materials Industry" indicator which is determined as a response to the question "How has your view of the general trend in the construction materials industry in which you operate this month change compared to your view in the previous month?". The data is obtained through digitization of reports in İMSAD web site, and covers the indicator values between 08.2013-03.2021, in form of a univariate time series. In the start of the modeling process, to efficiently validate the results, the data is divided into training and test sets. The training set covered the period between 08.2013-06.2019 (71 obs.) and the test set covered the period between 07.2019-03.2021 (21.obs). We have named the training variable as 't3' as it is the third indicator of the Trust Index and named our training set as 't3train' and test dataset as 't3test' .
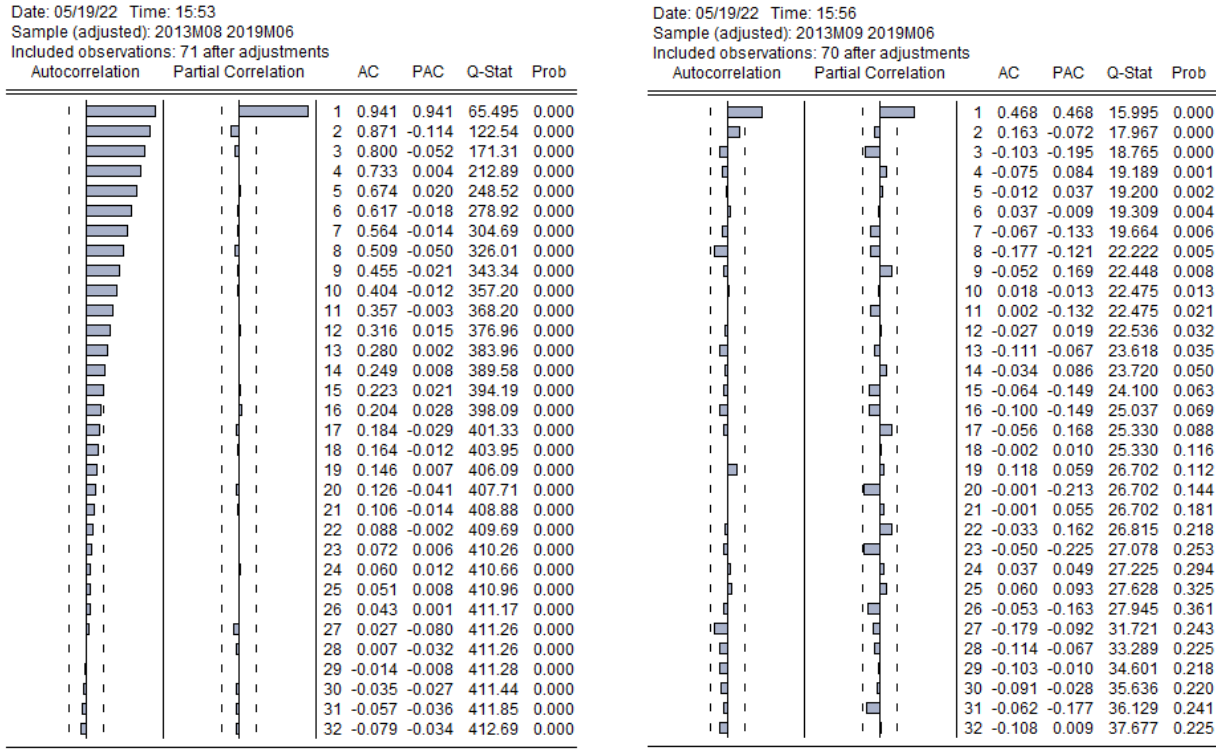
Figure 1. Correlogram of the series at Level (I=0) and at First Difference (I=1)

As illustrated in Fig 1. (left), ACF and PACF plots of the series 't3train', the series is not stationary at level (I≠0), as significant autocorrelations can be observed until Lag14. In contrast, both ACF and PACF plots of first difference of the 't3train' series tend to degrade into the confidence interval quickly i.e., at 1-2 lags. The 't3train' indicator was showing the strong signs of fitting to an ARIMA (Auto-regressive Moving Average) model. In this stage, we have generated 2 new variables by taking first difference of the series, namely dt3train and dt3test, and we further proceeded with the ARMA analysis of these new variables. The dt3train covered the period between 09.2013-06.2019 (70 obs.) and the dt3test covered the period between 08.2019-03.2021 (20.obs).

Results

The correlogram of 'dt3train' (Fig.1. right) indicate that the series have significant Autocorrelation(AC) and Partial Autocorrelation(PAC) at Lag1. According to Box-Jenkins method [5] the number of lags with significant AC and PAC values can be used to determine the nature of the model. As we found out significant AC and PAC values at Lag1 only, we considered modeling the 'dt3train' series with AR(1), MA(1) and ARMA(1,1) models. The coefficients of 3 ARMA models fitted on 'dt3train', and their significance test results are provided in Table 1,Table 2, and Table 3.

Table 1. The estimation results of the AR (1) model for dt3train

Variable	Coefficient	Standard error	t-statistic	Probability(p)
C	-0.942427	0.307625	-3.063555	0.0031
AR(1)	0.468036	0.104281	4.488203	0.0000

Table 2. The estimation results of the MA (1) model for dt3train

Variable	Coefficient	Standard error	t-statistic	Probability(p)
C	-0.855116	0.238541	-3.584769	0.0006
MA(1)	0.416428	0.108026	3.854899	0.0003

Table 3. The estimation results of the ARMA (1,1) model for dt3train

Variable	Coefficient	Standard error	t-statistic	Probability(p)
C	-0.932979	0.297270	-3.138492	0.0025
AR(1)	0.379958	0.207176	1.833991	0.0712
MA(1)	0.121375	0.229949	0.527833	0.5994

As illustrated in Table 3 The MA component of the ARMA(1,1) model was not found significant at 95% Conf. Level(p>0.05). Thus, we have chosen to exclude ARMA(1,1) model from our evaluation. As shown in Table 1 and Table 2, coefficients of both AR(1) and MA(1) models were found significant, and according to F-test results on model significance, the overall AR(1) model was found as significant (F:20.14,p <0.05), and MA(1) model was also found as significant (F:16.88,p<0.05).

The Akaike Information Criterion (AiC) scores for AR(1) model was 3.47 and MA(1) model was 3.55. RMSE values for AR(1) and MA(1) model were found as 1.337 and 1.392. Based on both the AiC and RMSE scores, it is evident that AR(1) performs better than the MA(1) model for this dataset, and thus, the best fit model for the training data has been determined as the AR(1) model. Based on the ARMA modeling exercise, the first difference of the series (I=1) is modelled with an ARMA model, thus level of integration is 1(I=1), and the resulting ARIMA model can be expressed as ARIMA(1,1,0). The equation below (Eq.1) presents the mathematical notation of the model.

$$w_t = 0.4680 w_{t-1} - 0.9424 + \varepsilon_t$$
$$w_t = \Delta^1 y = y_t - y_{t-1}$$

(1)

Discussion & Conclusion

Following the determination of the ARIMA model, two forecasts were made using the ARIMA (1,1,0) model by taking the test data 'dt3test' (20 obs.) as the ground truth. The first forecast was dynamic (out-of-sample) and the model achieved an RMSE of 1.3475, and MAE of 1.192, the second forecast was static (in-of-sample) and an RMSE of 1.073 and a MAE of 0.812 is achieved. The results have demonstrated that the "General Trend in Construction Materials Industry" indicator of the Trust Index of IMSAD can be successfully modeled and estimated with an ARIMA model.

The study aimed to model and forecast the trends in material prices through a well-known time series methodology, namely Box-Jenkins method. In parallel with its aim, "General Trend in Construction Materials Industry" indicator of IMSAD Trust Index is modelled with the proposed method. The results have demonstrated that the future values of the indicator can be estimated with high accuracy especially with in-of-sample forecasting strategy. The results have shown that Box-Jenkins methods (and ARIMA) model can be used to model trends in material prices in construction industry. Successful estimates of trends in material prices would help construction companies to take decision by better foreseeing the trends of material prices and taking precautions in advance regarding the risks related to the material price changes.

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Modeling the trend of construction materials industry with NARNETs

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Keywords
Construction
Material
Time Series
ANN
NARNET

Abstract
The price of materials is dependent on different factors such as raw material costs, production costs, and cost of logistics. The construction industry professionals face difficulties in times when there are fluctuations in material prices. This study aimed to model the expectancy of trends in material prices through a time series analysis, as the expectancy of trend is a time dependent dataset. . In this context, the study is focused on utilization of a special type of ANN (and special type of RNN) architecture known as Nonlinear Autoregressive Neural Network (NARNET). Ten different NARNET configurations were implemented in MATLAB and their performance were tested in the study. The results have shown that NARNETs are able to model the expectancy of trend accurately.

Introduction

The cost of a construction is dependent on several factors, including the direct costs such as the cost of labour, the cost of machinery and equipment, material cost, and other indirect costs such as site mobilization. The price of materials is one of the components of the direct costs and is dependent on different factors such as raw material costs, production costs, and the cost of logistics. The construction industry professionals, especially contractors face difficulties in times when there are fluctuations in material prices. These fluctuations make it difficult to foresee the material prices, which then lead to uncertainties in decision making in the procurement processes. Unexpected price changes can cause cost overruns in the project budgets, which would then cause difficulties both for the owner and the contractor. There are several indicators developed in different countries that provide insights to industry professionals regarding material prices. In Turkey, IMSAD (The Association of Turkish Construction Material Producers) provides an economical indicator that can be defined as (the expectancy of) trends in material prices. This indicator provides insights to professionals in Turkish Construction Industry regarding the trends of the material prices. This study aimed to model (the expectancy of) trends in material prices through a time series analysis, as the expectancy of trend indicator provided by IMSAD is a time dependent dataset.

Time series analysis is used for different purposes in construction industry. Time series estimation methods such as ARIMA, ANN, Hybrid ARIMA-ANN were implemented for different purposes. For example, [1] aimed to estimate the production level of the construction industry in China and investigated whether the forecasting performance can be improved by using neural network (ANN) models for short-term forecasting. [2] aimed to develop a model to estimate the early design construction costs of building projects using an Artificial Neural Network (ANN) model. 169 case studies from the construction industry were collected to develop the ANN model and identify key parameters for building project costs. In order to estimate the Construction Cost Index, [3] used Linear Regression and Autoregressive Time Series (ARIMA), Artificial Neural Networks (ANN) methods. In this study we concentrate on the use of special type of ANNs (i.e., NARNET) for estimation of the (expectancy of) material price trend indicator. The following sections will elaborate on the dataset, the NARNET modelling method used in this study, and later will present the configurations and accuracy metrics of the tested models.

Material and Method

In this study we statistically model "General Trend in Construction Materials Industry" indicator of the Trust Index of IMSAD, which is indicating the expectancy of the trend in material prices. The indicator value is determined as a response to the question "How has your view of the general trend in the construction materials industry in which you operate this month change compared to your view in the previous month?". The base value for the index (and all indicators) is 100, which is equal to the indicator value of August 2013 (base year/month). The dataset is obtained through digitization of reports in İMSAD web site and covers the indicator values between 08.2013-03.2021. The dataset consists of a single variable, and is in form of a univariate time series. In the first stage, we have checked the ACF and PACF plots of the dataset, at level and the plots indicated significant autocorrelations until Lag22. In contrast, both ACF and PACF plots of first difference of the series tend to degrade into the confidence interval quickly in Lag2 (Fig 1.). In order to use a stationary time series, we decided to use the first difference of the series in our estimation.
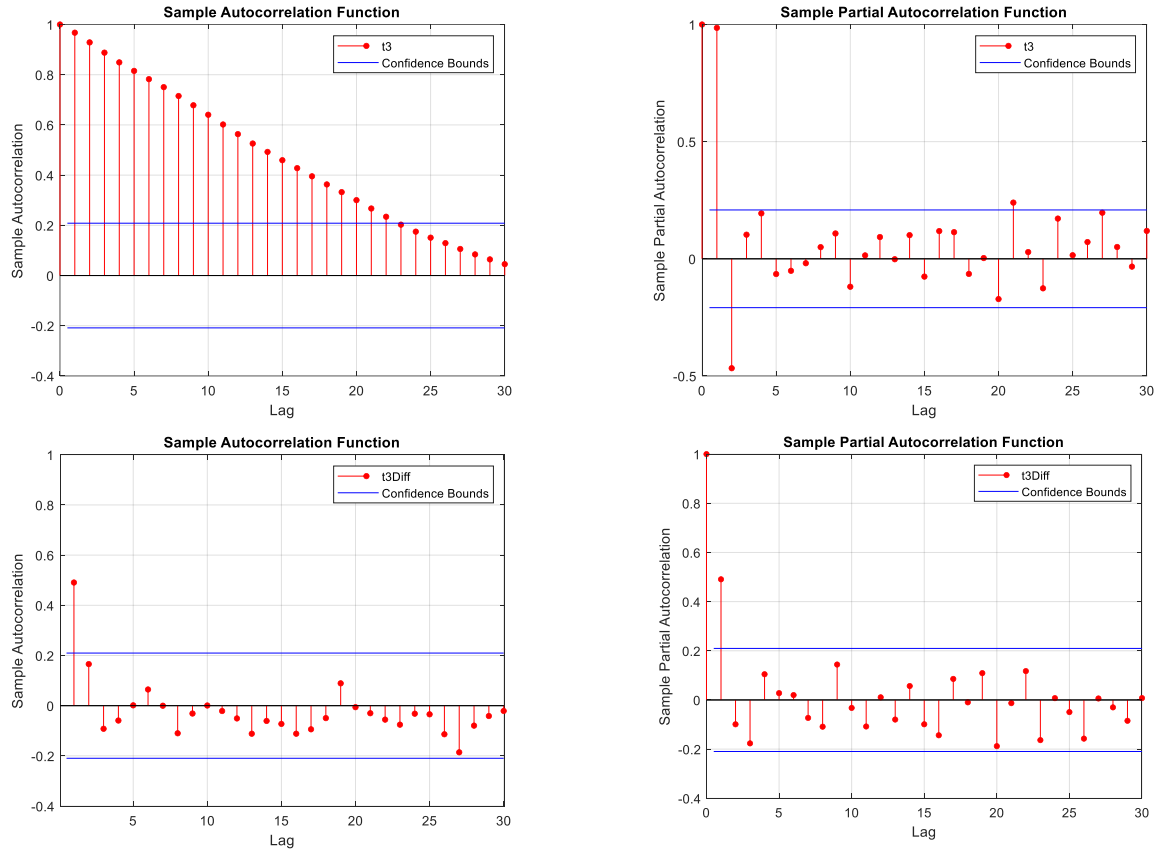
Figure 1. ACF and PACF graphs of the dataset at level(up) and at first difference(down)

As mention earlier, in this study, we have implemented a NARNET architecture to estimate the (expectancy of) Trend in Construction Materials Industry. The Nonlinear Autoregressive Neural Network (NARNET) is a Recurrent Neural Network (RNN) which can be written in the following form:

$$Y_t = h(Y_{t-1}, Y_{t-2}, \ldots \ldots Y_{t-p}) + \varepsilon_t$$

The function h(.) is unknown in advance, and the training of the neural network is aimed at fitting the function by means of the optimization of the weights of the network and bias of neurons. In a NAR network, the network is trained as an open-loop network with feeding in the real values of the target variable as the response variable and after the training the network performs a one-step ahead prediction. In order to perform a multi-step ahead (out-of-sample) predictions a closed-loop network need to be configured [4-5].

In this study we have tested a series of NARNET architectures through modification of a code generated by Neural Network Time Series App of the MATLAB software. 10 different NARNET configurations have been tested by considering 5 different layer sizes [1,2,2,3,5] and 2 different Feedback Delays types [1, 1:12], for one-step-ahead prediction. The train-test split approach is used for validation, where 60/10/30 % of the data is used for training, validation, and testing. The training set covered 55 values, validation set covered 9 values and the test set included 27 values. Each architecture has been trained 500 times and the best (minimum) Root Mean Square Error (RMSE)

scores calculated for the Test Set has been used as the performance metric of the tests. The code and dataset used in the tests is available at [6].

Results

The NARNET configuration tested included an input layer, a single hidden layer, and an output layer. As illustrated in Table 1., the accuracy of the estimation changes slightly depending on the number of neurons used in the hidden layer (referred to as Layer Size). In addition, the number of Feedback Delays has either minor(negative) or insignificant impact on estimation accuracy.

Table 1. Accuracy metrics of different NARNET configurations

Layer Size	Feedback Delays	Mean RMSE Test Set	Feedback Delays	Mean RMSE Test Set
1	1	1.2716	1:12	1.2716
2	1	1.2651	1:12	1.2716
3	1	1.1995	1:12	1.2148
4	1	1.1580	1:12	1.1718
5	1	1.1580	1:12	1.1597

The best among the best RMSE scores of each configuration was achieved with NARNETs having 4/5 neurons in the hidden layer at the configurations with single Feedback Delay as an input (RMSE:1.1580). The worst performance among best RMSE scores of each configuration was identified at configurations having 1 neuron on the hidden layer with single Feedback Delay as an input (RMSE:1.12716), and at configurations having 1/2 neuron(s) on the hidden layer with 1:12 Feedback Delays as input.

Discussion & Conclusion

This study focused on modeling the expectancy of trends in material prices with a time series analysis. The literature in the field indicates the use of several different methods for time series analysis, ranging from ARIMA, Hybrid ARIMA to ANN. In this research, we focused on utilization of a special type of ANN (and special type of RNN) architecture known as Nonlinear Autoregressive Neural Network (NARNET). We have implemented 10 different NARNET configurations in MATLAB and tested their performance in terms of best RMSE scores that can be achieved in 500 train/test rounds. The search approach implemented for discovering the best RMSE scores for each NARNET configuration was a brute-force/uniformed search. The median of the search time was 12 seconds on a desktop computer with i5-9600K CPU. The accuracy metrics of different NARNET configurations indicate that increasing the number of neurons would help in achieving better accuracies, but when optimum number of neurons is reached it is advisable that the principal of parsimony needs to be considered, and the number of neurons should not need to be increased when targeting for better accuracies, especially in small datasets like the one in this study. The ACF and PACF graphs of the first difference of the series (i.e., trained/tested with NARNETs) shows signs of first order Autoregressive Model/Moving Average Model. In this situation, it can be proposed that for a NARNET trained as an open-loop network (where feedback delays = real values of the target variable), the lagged values of the series other than Lag1, would not have a significant contribution to accuracy of the series. This proposal is reinforced with accuracies achieved by the training/testing of the configuration with 1:12 Feedback Delays, where we seek the possible impact of seasonality or any other effect (which would most probably be eliminated through differencing), along with the autoregressive nature of the series. The results of the tests have shown that adding more Feedback Delays would have minor inverse effect on the accuracy. In terms of number of Feedback Delays that would be input into NARNET architectures, the principal of parsimony should also be considered especially when working with differenced series.

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Estimation of freight demand at Bartın Port using time series model

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Keywords
Maritime
Port
Efficiency
Bartın Port
Sustainability

Abstract
Bartın Port is one of the important ports of the Western Black Sea Region. In order to maintain their position in the global market where competition is increasing, ports should develop new strategies by carrying out future capacity estimation and efficiency measurements. It is necessary to strengthen the infrastructure and technologies at the ports according to the region and customer demands. In the study, Türkiye's GDP, total cargo handled in Türkiye, the population of Türkiye, and the population of Bartın were defined as independent variables. The time series model using the data obtained by the documentary scanning method was applied to the total cargo handling forecast at Bartın Port with a 95% confidence interval. According to the forecast time series model based on the collected data, the amount of cargo handled at Bartın port is expected to reach 2.8 million tons in the next ten years.

Introduction

Commercial ports are one of the essential components of maritime transport. Ports, which serve to fulfill many activities in the transportation chain, contact many organizations or individuals such as shippers, exporters, importers, logistics companies and state authorities, banks, insurance companies, and their essential functions [1]. Bartın Port is one of the important ports of the Western Black Sea Region and plays a key role, especially in mineral ore transportation [2], as it is close to the cities of Karabük and Zonguldak. Congestion at Bartın port and loss of efficiency and productivity will adversely affect the transportation network in the region.

Bartın Port, which is 11 km away from the city center of Bartın, is in the Western Black Sea Region of the Black Sea Region, at the mouth of the Bartın River, where it empties into the Black Sea. With the works carried out in 1991-1995, the pier length was increased to 480 meters by adding 260 meters to the existing 220 meters of dock length in the port. In terms of physical capacity, the port has the main administrative building, the additional building used by the Customs Directorate, two warehouses, watchtowers, kiosks, a waste reception facility, bilge tank, and wastewater tank. The depth of the port is 8 meters, and the inner diameter of the port is 300 meters. It has two warehouses of 1500 square meters, a concrete open area of 30 thousand square meters, and a stabilized open space of 2 thousand square meters [3]. In the port area, port service is provided with one pilot boat and one rental tugboat [3].
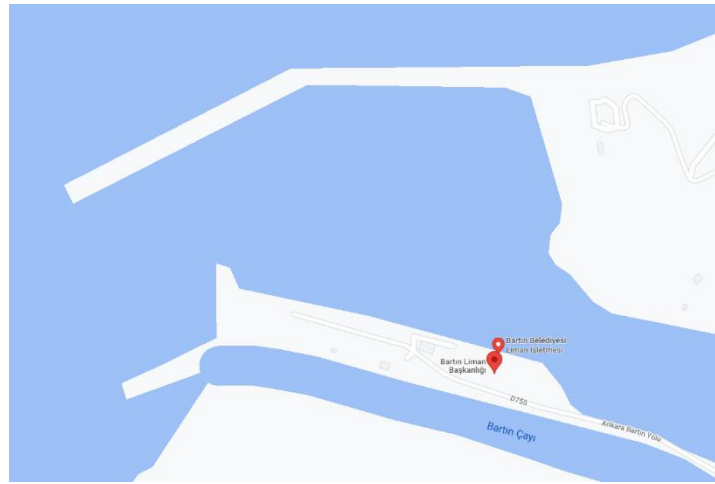
Figure 1. Bartın Port [4]

Private companies and owners carry out loading and unloading services at the port. Firms engaged in loading and unloading at the port organize mobile cranes used for cargo handling. The number of cranes, working days per year, the daily working hours, the average number of movements that the crane can make per hour, the working efficiency coefficient of the crane, the berthing rate, and the unit weight of the part affect the handling capacities of goods, general and dry bulk terminals [5].

Table 1. Data were compiled from UAB, TUIK, and WBG sources [6-8]

Year	Annual development of cargo handled at Bartın port (ton)	Annual development of cargo handled at Turkish ports (ton)	Annual development of Bartın's population	Annual development of Türkiye's population	Türkiye's annual GDP development (USD)
2004	676301	213105438	178122	66845635	408880000000
2005	701070	213025594	179097	67743052	506310000000
2006	1064281	248124426	180117	68626337	557060000000
2007	1105067	291573630	181156	69496513	681340000000
2008	1072963	314604651	182131	70363511	770460000000
2009	1161965	309436705	185368	71241080	649270000000
2010	1110214	348635867	188449	72137546	776990000000
2011	1146328	363346723	187758	74724269	838760000000
2012	1317819	387426232	187291	75627384	880560000000
2013	1778945	384930758	188436	76667864	957780000000
2014	1483978	383120619	189139	77695904	938950000000
2015	1462951	416036695	189405	78741053	864320000000
2016	1123334	430201162	190708	79814871	869690000000
2017	1294824	471173896	192389	80810525	859000000000
2018	1272234	460153560	193577	82003882	778470000000
2019	1358828	484168412	198999	83154997	761000000000
2020	1984035	496642652	198979	83614362	719950000000
2021	1981226	526306784	201711	84680273	795950000000

Studies show that the amount of cargo handled at ports has a significant relationship with GDP and population [9-11]. Bartın Port efficiency decreases in cases such as the contraction of mining operations in the region and increases in the opposite circumstances. In a study conducted by Çelik and Murat [12], the economic structure of Bartın Province was examined, and it was concluded that the most vital aspect of the city was the commercial use of Bartın Port.

Material and Method

The documentary scanning method was used to analyze the current situation in Bartın port. Information on the cargo handling at the port, the number of ships calling at the ports, and the cargo carried in the cabotage were compiled and analyzed. IBM SPSS Statistical Version 26 was used for descriptive analysis and time estimation model with a 95% confidence interval. The study defined Türkiye's GDP, total cargo handled in Türkiye, Turkish population, and Bartın population as independent variables.

Results

According to the estimation time series model based on the collected data, it has been calculated that the amount of cargo handled in Bartın port will be over 2.5 million tons in 2028 and over 2.8 million tons in 2032.
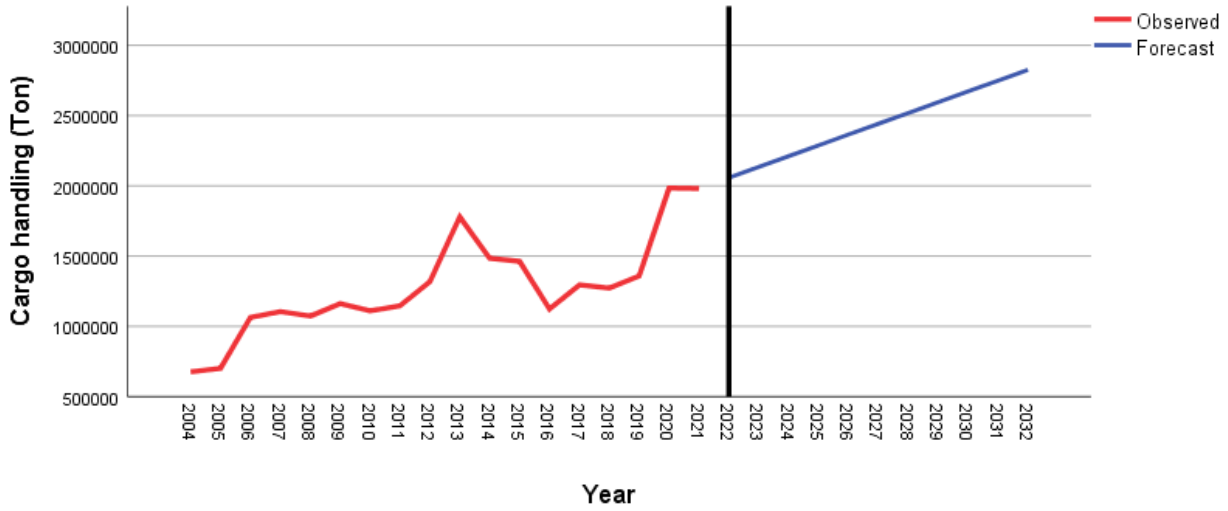
Figure 2. Bartın port cargo handling demand chart

Discussion & Conclusion

It is estimated that the capacity and efficiency of Bartın Port, where mainly plaster, cement, coal, clinker, construction materials, and miscellaneous cargoes are handled, will increase. Considering the efficiency of cranes, berth availability, water depth, and the specific gravity of the transported shipment, the efficiency, and effectiveness of Bartın Port can be increased with structural reforms, if necessary.

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Investigation of the applicability of artificial intelligence and machine learning in the field of health

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Keywords
Composite materials
Hybrid composites
Artificial intelligence
Nano technology
Robots
Human health

Abstract
Today, computers and smartphones, tablets and other electronic gadgets have become indispensable for human life. Human health is paramount. It is very important to know the use of robotic applications in the health sector and to follow the general developments related to this issue closely. The human brain is in a constant state of interaction with this technology. Nano dentistry, which is formed by adapting nanotechnology to dentistry; tissue engineering, dental Nano robots and dental nanomaterials using oral health protection, is very important for people. Artificial intelligence is one of the greatest engineering studies in the history of mankind and the world. Artificial Intelligence technology has become an area that humanity has often heard of with the increase of epidemics. Artificial intelligence is a computer science for short. Artificial intelligence is the ability to exhibit human-like behavior, and it is a branch of science that reveals human abilities programmatically. Artificial intelligence is a tool that makes scientific research, an area where people focus, much more efficient, and has the potential to increase the speed of scientific research by a factor of. In this study, the importance of machine learning in the health sector was investigated with a literature review.

Introduction

Before defining artificial intelligence, we need to know the definition of intelligence. Intelligence can be briefly called all the abilities of a person to think, reason, perceive real events, comprehend, judge and draw conclusions. In addition, Intelligence can also be seen as the ability of the mind to learn, to take advantage of what has been learned, to adapt to new situations, and to find new solutions. In addition, intelligence, in other words, can be called the ability to adapt to technological events that can be developed through education, training, knowledge, accumulation and experience [1]. Artificial intelligence is based on the functions of the human brain, non-organic systems (computer, program, robot, etc.) that think like a human, perceive like a human, interpret like a human, analyze like a human, and make decisions like a human after all these stages). Scientists have defined Artificial intelligence differently. For example, artificial intelligence is the science of computer programs that mimic intelligent behavior, and artificial intelligence is the science of making things that require intelligence into machines when they are made by humans [2-4].

Artificial Intelligence (AI)

A number of processes have been left behind by artificial intelligence scientists. For example, some scientists describe artificial intelligence as "the study of mental abilities using computational models". Others 'artificial intelligence: a modern approach', 4 definitions can be classified under the heading of AI in the book suggest that like-minded people, systems, systems that behave like human beings, rational systems, rational systems [5-6]. Artificial Intelligence and its subsets are given in Figure 1.
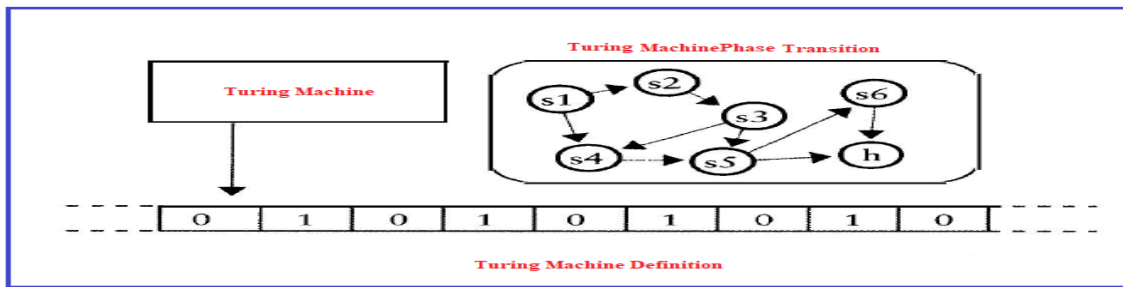
Figure 1. Artificial Intelligence and its subsets [7]

Literature Studies on Artificial Intelligence in the Health Sector

The use of artificial intelligence in the health sector continues rapidly. Artificial intelligence can also be used for dentists and oral health. Only first letter of first word is capital, left aligned, It should be separated from the former paragraph with single line. At a time when human health is paramount; health services are one of the fastest growing sectors in the health sector, generally covering the diagnosis, treatment and prevention of oral diseases. For example, diagnosis is of great importance because dental deficiencies cause malocclusion, loss of function and aesthetic problems in individuals. Intraoral or extra oral radiographs are used to detect dental deficiencies in dentistry. For example, in a study conducted; An artificial atomic algorithm of an individual-specific optimal nutrition schedule was used [9]. In a study conducted, lateral buckling behavior of hybrid composite materials using test data on the effects of different environmental conditions and different fiber combinations was estimated using Artificial Neural Networks (ANN) tool [10]. In a different study, a pilot study of artificial intelligence was conducted to detect dental deficiencies from panoramic radiography using a deep learning method. In a different study, the diagnosis and prediction of periodontically weakened teeth were investigated using an artificial neural network algorithm [11]. Applications of artificial intelligence in the field of health have been investigated [12]. In different studies; they have shared with the literature the software studies they have developed related to the detection of dental caries and dental problems on X-ray images using artificial neural networks, the diagnosis and classification of caries on digital radiographs [13-14].

Machine Learning

Machine Learning (Machine Learning) is a branch of artificial intelligence that uses statistics and computer science and has become very popular recently. Machine learning is all algorithms that mimic human intelligence, but do not need rules that we interpret and enter manually. In the machine learning model, learning is in the form of teaching-teaching (training) and testing (testing). At the learning stage, a learning model is created by learning algorithms and properties to the system using examples in the dataset. In the experimental phase, estimation is made for trial data with the learning model application Engine [8-9].

Deep Learning, Robotics, the Method of Artificial Neural Networks and Genetic Algorithms

Deep learning is a machine learning method consisting of multiple layers that predicts results with a given data set. Deep learning, machine learning and artificial intelligence are terms that have different meanings from each other. Deep learning has been defined as a class of machine learning techniques that uses many nonlinear hidden layers for supervised or unsupervised feature extraction, transformation, pattern analysis and classification [17]. Figure 2 shows the symbolic representation of deep learning and a photograph of Brain tumor, imaging of radiological images with deep learning.
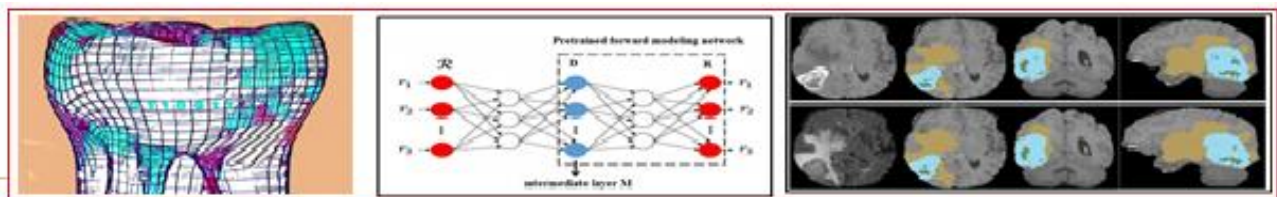
Figure 2. Structure of deep neural networks and Prediction of brain tumor through deep learning [18-19]

It is known that there will be a number of innovations in human life with robotic applications that are the basis of artificial intelligence. With robotic applications, computers and electronic robots are integrated with the principle of compatibility, the result of which is artificial intelligence, especially used in industry and cutting edge

technology, production and design robots are made with the help of computers. Figure 3 shows a symbolic robot produced by coding [20]. Artificial neural networks are a branch developed inspired by the human brain. Each one with its own memory and processing elements are connected through weighted links of parallel and distributed information processing structure. Artificial neural networks find wide application in many fields of science today due to these learning and generalization features and demonstrate the ability to solve complex problems successfully [21-22]. Genetic algorithms, a subDec branch of artificial intelligence, are a search and optimization method that works in a similar way to the evolutionary process observed in nature. It seeks the holistic best solution according to the principle of survival of the Dec in the complex multidimensional search space [21-23]. It has been researched with a literature study that it can be applied in the field of Artificial Intelligence, Food Engineering, Epidemic Artificial Intelligence (Robots) and Law [24-25].

Results

In this study, literature studies on the applicability of Artificial Intelligence and its sub-branch machine learning in the field of health have been investigated. In the study, the definition of artificial intelligence, its sub-branches and its applicability in dentistry and other health fields were investigated. As a result of the study, the following results were obtained: It has been concluded that artificial intelligence techniques can be achieved with a high degree of success in solving various dentistry problems. It is thought that the use of this robot may have a contribution to the health sector and physicians. Current sub branches of artificial intelligence; machine learning, artificial neural networks (ANN), generic algorithms, robotics, deep learning with applications in artificial intelligence technologies in the field of health sector with the popularization of design and are of the opinion that the desired goals can be reached fully. It is thought that online doctor robots, robots that can perform surgical procedures and nurse robots will play an important role in our lives in the future by using records in the hospital database. In the field of health and medicine, health care management with machine learning and artificial intelligence, artificial limb (arm, eye, etc.) applications, analysis of heart sounds, sound analysis for the deaf, classification of respiratory sounds, analysis of side effects of drugs it is thought that studies useful to humans can be produced by doing.

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Psychological problems faced by cancer patients and psycho-oncology

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Keywords
Canser
Psychological problems
Psychological reactions
Psycho-oncology

Abstract
Considering that cancer will continue to exist in the coming years, the fact that patients diagnosed with cancer receive psychological treatments in addition to their physiological treatment will improve the healing process. There are studies on psycho-oncology or psycho-social treatment. Psycho-oncology is a new science that emerged in order to provide the treatment to psychological disorders that occur during the diagnosis period and subsequent periods of cancer. It also helps to provide the patient with a quality of life, social support from family, and an active social environment. These studies are continuing to take place. With the dissemination of this science, we will be able to observe the effects of continued studies better in the coming years.

Introduction

Despite the development of medicine and technology, cancer is a chronic disease that many people suffer from today and will continue to be seen increasingly in the future [1]. It is on the second place after heart diseases in Turkey and threatens human health in a serious way [1]. Cancer is when the nuclei of cells whose chromosomes have undergone structural changes send false messages to the cytoplasm, resulting in loss of control in cell division [2]. In Turkey, 300,000 people are diagnosed with cancer every year [3]. According to the data of the World Health Organization, it is predicted that world population will reach 8.7 billion in 2030, with 27 million new cancer cases and 17 million deaths from cancer annually [3].

Cancer does not only affect the physiological structure of a person, but also causes many irreversible psychological and economical effects, firstly on the patient and then on the family and society [3]. For this reason, purely medical treatment protocols (such as chemotherapy, radiology, surgical intervention) are not sufficient for a patient coping with cancer, no matter how effective they may be [3] The patient gaining and maintaining psychosocial health during and after the treatment is also among the basic treatment measures [3]. Many areas of science should work together in the diagnosis and treatment of cancer, because cancer is a chronic phenomenon that brings many psychological and psychosocial problems with itself, besides being a disease with multifaceted problems [3].

Even the word "cancer" conjures up a lot of negativities in the human mind [3]. It is possible to develop negative emotions and thoughts against patients who are diagnosed with cancer or patients who might have cancer.[3] Cancer is perceived as a catastrophe and causes a crisis in the psychological balance of a person [3]. This crisis is a process that extends from healthy living to getting used to the threat of illness and death [3].

Cancer patients develop various emotional, psychological and behavioral reactions during diagnosis, treatment, relapse and palliative care periods [3]. Following the diagnosis emotions like shock, disbelief, denial, anger, depressed mood, deterioration in sleep, appetite and a break in usual daily activities may develop [3]. In fact, shock, reaction, resistance and adaptation processes are experienced once again in all separate periods [3]. The normal response to a cancer diagnosis ranges from anxiety, tension, grief and sadness due to loss of health, to understanding the importance of the disease, to perceiving this process as a battle, or to accept a fatalistic acceptance [3].

Not only people with cancer, but also their relatives and social circles are affected by this process [1,2,4]. In response to this effect, it is beneficial for the patient to receive psychological support from the social environment in order to provide assistance to the patient during the cancer process [1,2,4].

With the diagnosis of cancer, Bolund has four stages: shock, reaction, resistance and adaptation [3]. Elisabeth Kübler Ross also divided the psychosocial stages in the cancer process into five different categories; denial, anger, bargaining, depression and acceptance [3].

The most common reaction to the diagnosis of cancer, often in the first stage, is shock and disbelief that one has the disease [3,5]. The person becomes alienated from their own body and cannot trust their own body [3,5]. Even for a short time, their inner world is full of confusion [3]. This process can take from a few hours to a few days or weeks [3]. The most common attitude at this stage is denial [2,3,5]. Denial is an effort to keep the reality that is difficult to accept out of one`s consciousness and to protect the integrity of the self [2,3,5].

The second stage is the patient's gradual realization of reality [3,5]. The basic reaction is anxiety [3]. In order to eliminate anxiety, the patient experiences reactions such as rejection, suppression, and oppositional stance. [3]. After the most active period of the treatment is over, the third stage starts and the patient tries to adapt to their new situation.[3] There have been changes in their life that they can no longer restore [3]. After getting so close to death, they may question their perspective on life [3,5]. After that, the question of how to live life becomes one of the most important questions patients ask [3].

The last stage is the adaptation period in which the patient slowly start accepting the truth and they spend their energy and spiritual strength on their new life.[3] The person then begins to adopt their new identity and illness [3]. They begin to reinterpret their life, their past, their future and their entire existence in search of security and balance [3].

Studies have reported that 47% of cancer patients have mental illnesses at a level that can be diagnosed [2,3,4]. This rate is quite high compared to the reported 20-40% rate among other medical patients [3]. The most common mental illnesses are; depression, anxiety disorders, and organic brain syndrome [2-5]. We can classify other psychiatric diseases seen in cancer patients as follows: adjustment disorders, organic brain syndromes (delirium, dementia and other organic psychiatric syndromes, neuropsychiatric side effects of chemotherapeutic agents), personality and attitude changes, psychiatric syndromes accompanying painful syndromes, anorexia and nausea- vomiting (due to chemotherapy) [3].

The incidence of psychiatric disorders among patients reported in studies is 13% severe depression, 68% depressive adjustment disorder, 8% organic mental disorder, 8% personality disorder and 4% anxiety disorder. The frequency of depression in patients receiving radiotherapy reaches as high as 81%. Severe depression is seen in 38% of patients and depressive adjustment disorder in 43% [3].

Social support serves to reduce the damaging effects of life's adverse effects on physical health and well-being [3-5]. It also acts as a morale booster against stress in the face of these adversities [3-5]. It helps strengthen an individual's psychological health, provides material, spiritual and cognitive assistance and it also helps in combating emotional problems [3-5]. This kind of social support can be defined as the support received from family, friends and institutions [3-5].

Psycho-Oncology has emerged as a new branch of science that deals with psychological problems experienced by cancer patients [3,4,7]. Psycho-oncology and modern oncology should now be considered together [3,4]. For this reason, health personnel in the field of oncology are expected to be aware of the psychosocial needs of patients and to have knowledge at a level that can assist treatment [3,4].

The first studies on psycho-oncology in the world started in 1951 in the USA [4,5]. In Europe, EORTC (European Organization for Research and Treatment of Cancer) was established in 1980 to conduct research on the quality of life of cancer patients [4,5]. With these studies, the field of psycho-oncology has developed and has been accepted as a branch of science [4,5]. Training has been provided for healthcare professionals working in the field of oncology in the United States so that they can understand the psychological problems that cancer patients may experience and improve their communication skills [5].

Psycho-oncology or psychosocial treatment should be seen as a complementary branch to physiological treatment. The aim of psycho-oncology is;

- Informing and educating the patient about reducing the rate of psychological morbidity and how to deal with it,

- To increase the patient's adaptation to the disease and quality of life by enabling them to freely express their feelings and thoughts about the treatment with their active participation in the treatment process,

- Helping the patient and their family in developing strategies to support each other,

- Making and implementing arrangements that will make life easier in matters at home, work and child care, and supporting the patients to spare time for themselves,

- To inform about how to reach social support resources and to strengthen the patient's communication with their family and social environment [5].

Discussion

After the grounding of this new science, a study was conducted in which health personnel were trained to make use of psychological treatments as well as physical treatments to help patients diagnosed with cancer [4,5]. With this study, the researchers aimed to teach patients who have been diagnosed with psychological disorders, how they can act against it, how they can strengthen their relationships with family and receive social support from their environment, and also what steps the patients can take to increase their quality of life with medical treatment [3-5].

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The effect of beneficial bacteria on the immunity and cancer treatment

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Keywords
Cancer
Bacteria
Treatment
Immunity

Abstract
Today, many cancer treatment methods are being developed. Most of these methods are aimed at treating the cancerous cells directly. Rather than direct approach, regulating the immunity and metabolism to eliminate the tumor generation and growth can be another way of curing the disease. There are many types of bacteria that are in our lives and live with us to be used in the treatment of people who are at risk of cancer. These bacteria alter the state of the immunity against the tumor cells and their utilization is expected in the near future as an indirect cancer immunotherapy method. Some examples of bacteria that can be used for this purpose can be listed as: *Mycobacterium vaccae*, which is a stress-relieving bacterium, immune-boosting *Bacillus subtilis* and *Bacillus licheni formis.* In some cases, green algae such as Spirulina can also be utilized for this purpose. These methods are also known to eliminate or reduce the detrimental side effects of chemotherapy application to the cancer patients.

Introduction

Cancer cells have a special ability to evade the immune system. Therefore, it is quite difficult to design cancer vaccines [1]. Cancer comes in many different shapes. For example, breast cancer can be different from lung cancer, even two breast cancer patients' progress and disease development can be different from each other. In short, everyone's cancer is unique. Therefore, it is necessary to produce personalized vaccines for each patient [2, 3]. This is a difficult and expensive method. There are studies suggesting the involvement of bacteria to boost the immunity against tumor cells. Beneficial bacteria can be utilized for this purpose. This would enable a treatment method that would be more generalized rather than personalized vaccines to overcome the economical and production burden of the personalized medicine [4].

Results

One of these bacteria is *Mycobacterium vaccae*, has been observed to reduce stress and anxiety. This bacterium was discovered by immunologist John Stanford on the shores of Lake Kyoga in Uganda in the 1970s. Later, University of Colorado Boulder neuroscientist Dr. Chris Lowry showed that this bacterium can reduce stress and anxiety, at least in mice. It does this because it is a bacterium that increases the effectiveness of the tph2 gene, which causes the production of serotonin, an emotion-stabilizing neurotransmitter. With this feature, it can have a positive effect on the immune system by reducing stress and anxiety in people. According to the results of a Phase II trial with oral doses of *M. vaccae*, the patients who are going through TB chemotherapy had improved immunity and the oral administration of this bacteria had immunotherapy effect by shortening the chemotherapy duration and reducing the dosage of the drug [5]. Mycobacteria based immunotherapy has been effective against bladder, prostate, lung and skin cancer patients [6].

The second of these bacteria is *Bacillus subtilis* that can be found in the soil. *B. subtilis* was first described by Ferdinand Cohn in 1872. Animal tests with this bacterium reveal that this bacterium boosts their immune systems, increases antibodies in their bloodstream and increases their ability to fight infections such as Salmonella. This bacterium is already used therapeutically in humans because it produces bacitracin, an antibiotic used as an ointment for skin and eye infections. It is a very resistant microorganism. Its tough endospores have been discovered to survive for six years in space. Studies have shown that co-administration of the vaccine with *B. subtilis* spores had immunomodulatory effect by balancing the Th1 and Th2 response in mice going through papillomavirus type 16 (HPV-16) infection. When these spores are injected IV into mice, they induced the production of IFN-γ cytokines that are effective both against intracellular infections as well as tumor cells. In line with these observations when this bacteria's cellular components are used against colon cancer, hepatocellular cancer, cervical carcinoma, and human leukemia cells; they blocked the cell proliferation *in vitro* [7]. Cyclic lipopeptide (CLP) of *Bacillus subtilis* induced cell death in human leukemia cell line and more studies are required to decipher its effect on the animal models as well as patients [8].

There are signs that the third of these bacteria, *Bacillus licheniformis*, found in the soil, may help us keep our weight in check. This bacterium is also thought to be able to create this effect because some strains of the bacterium produce a substance called polygamma glutamic acid. This biopolymer also has the ability to activate large granular lymphocytes called "natural killer cells" of the immune system, and its use for cancer treatment is still being investigated [9]. Microbial L-asparaginase (ASNase) from this bacterial species blocked the cell proliferation in hepatocyte, breast and colon cancer cell lines [10].

Another species is an algae. Spirulina (Artospira) is a type of seaweed that can grow both in fresh and salt water. It is from the family of single-celled microorganisms (cyanobacteria) called blue-green algae. Studies so far indicate that it is protective against cancer. Studies show that Spirulina is somewhat effective, especially against cancerous lesions that are formed in the mouth called OSMF (Oral Submucous Fibrosis). Animal studies showed that it can inhibit cancer formation and reduce the tumor size. Spirulina is a low-fat and calorie-free, and cholesterol-free protein source containing all essential amino acids. It provides important contributions in the fight against diseases such as diabetes and anemia and in preventing the debilitating effects of the air pollution on the body. Since it contains antioxidant elements, it also has an immunizing effect against oxygen-based radicals, which are thought to be a fundamental factor in health problems such as cancer, arthritis and cataracts as well as aging. Moreover, the gamma-linolenic acid found in Spirulina leads to the dissolution of fatty deposits, helps preventing the heart ailments and lowers the bad cholesterol. The National Cancer Institute of the USA states that the sulfolipids in spirulina also reduce kidney toxicity and reduce the severity of the radiation-induced diseases. One tablespoon (7 grams) of dried spirulina powder has some amount of fat, including Vitamin B1 (thiamine), Vitamin B2 (riboflavin), Vitamin B3 (niacin), copper, iron, carbohydrates, omega-6, omega-3 and omega-9 fatty acids, 4.02 g protein, 8 mg of calcium, 14 mg of magnesium, 8 mg of phosphorus, 95 mg of potassium, 73 mg of sodium, 0.7 mg of vitamin C. It encapsulates almost every nutrient that our body needs, such as small amounts of B6 (pyridoxine), B9 (folic acid), vitamins D, A and E, chromium, selenium, and zinc [11, 12].

Discussion

In summary, there are studies on the positive effects of these four different species on the immunity that eventually leads to the eradication of the tumor cells. Based on these studies, it can be used both for the treatment purposes in cancer cases and to strengthen our immune system and prevent the development of other diseases [1].

Since Spirulina contains many vitamins, minerals and 20 different kinds of amino acids, it can be used in patients undergoing chemotherapy treatment, which can reduce the weakening of the immune system. Chemotherapy applications lead to the immunodeficiency in the patients and Spirulina might overcome this problem due to its nutritious content for the immune system cells.

More studies and clinical trials should be conducted to fully comprehend the effect of microbial or algal species on the immune system through which the treatment of cancer or other immunodeficiencies can be achieved [1, 3].

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The effect of metal oxide nanoparticles in breast cancer treatment

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Keywords
Metal oxide
ZnO
Structural properties
Breast cancer

Abstract
Nano-sized materials have been mostly used in scientific studies recently due to their many functional properties and wide application areas. Among them, metal oxide nanostructures are the most interesting materials. In particular, zinc oxide (ZnO) is a wide band gap semiconductor with properties suitable for cancer therapy studies. When ZnO is doped with various transition metals such as Fe, Mn, its properties such as band gap energy, morphology and crystalline structure can be changed. ZnO nanoparticles can be synthesized by many synthesis methods such as sol-gel, hydrothermal, CVD, co-precipitation. In the present study, the nanoparticles are prepared using sol-gel method for the breast cancer treatment.

Introduction

Nano-sized materials can have new and more advanced structural, magnetic and electronic properties that are not found in micron or larger sized particles composed of the same material systems. Due to these properties, they have the potential to lead to biological and medical applications [1]. In particular, ZnO is a wide band gap semiconductor (3.37 eV) with properties suitable for wide applications such as cancer therapy, bioimaging and drug delivery [2]. When ZnO is doped with various transition metals such as Fe, Mn, it shows different behavior in morphological, crystalline, electrical, magnetic and optical excitation properties [3]. Furthermore, ZnO nanoparticles have good potential in applications with low voltage x-ray or ultraviolet light (UV) radiation due to their luminescence properties. It also has the ability to act as a photosensitizer alone to generate photo-excitation and apoptotic reactive oxygen species (ROS) [4]. ZnO is also widely used in biomedical sciences, micro-electronics, converters, catalysts, textiles and other applications due to its high specific surface and small particle size [5-8]. In the process of obtaining nanoparticles, parameters such as synthesis time and temperature and annealing temperature are important in terms of particle size, morphology, and crystallinity.

Results

Popescu et al. have synthesized zinc oxide powders doped with Mn^{2+} ions (50, 500, and 2000 ppm) using co-precipitation method. These nanoparticles were prepared in PVP and SHMTP, separately. According to XRD pattern, the nanoparticles have hexagonal wurtzite structure. Crystallite sizes of the nanoparticles are about 38

and 49 nm, respectively. In this study, the cytotoxic effect of Mn:ZnO nanoparticles in murine cells was investigated. The Mn:ZnO samples prepared with PVP (polyvinylpyrrolidone) were observed to be more cytotoxic than the ones prepared with SHMTP (sodium hexametaphosphate). Also, for each sample, cell viability was found to be almost zero for concentrations above 16 μg/mL [9].

In the study of Nair et al., ZnO was synthesized in nano and micro sizes (40 nm - 1.2 ⏢m), and its toxic effect on osteoblast cancer cells was investigated by coating it separately with PEG and starch, as well as pure ZnO. Osteoblast cancer cells were exposed to ZnO for 24 hours and it was concluded that ZnO nanoparticles were more toxic on osteoblast cancer cells than micron-sized particles. On the other hand, for PEG and starch coated ZnO, it is also very beneficial that PEG or Starch coating does not reduce cancer cell toxicity because such coatings can more protect normal cells from any cytotoxic effects [10].

In the study of Sekar et al., pure and Fe-doped ZnO (Fe; 4, 8, 12 wt%) nanoparticles were synthesized by electrospinning technique and added in Poly Vinyl Alcohol (PVA) nanofibers solution and investigated to its cytotoxic and antibacterial properties. PVA nanoparticles incorporated with 4, 8 and 12 wt% of Fe-doped ZnO nanoparticles. The nanofibers have diameter ranges from 120 to 250 nm. It was observed that as the amount of Fe-doped ZnO in PVA increased, the crystal structure of PVA deteriorated and a wurtzite ZnO crystal phase was formed. On the other hand, the viability of cell lines was decreased slowly with increasing nanoparticles concentration in PVA. Thus, these nano-structures could be one of the suitable materials for many biomedical applications [11]. The synthesis methods and crystal sizes of these metal oxides are summarized in Table 1.

Table 1. Synthesis methods and crystal sizes of some metal oxides

Samples	Synthesis Method	Crystallite size	Reference
Mn:ZnO in PVP	Co-precipitation	38 nm	[9]
Mn:ZnO in SHMTP		49 nm	
ZnO	wet chemical	40nm-1,2 ⏢m	[10]
Fe: ZnO in PVA	Electrospinning	120-250 nm	[11]

Conclusion

Many study groups have shown that low concentrations and size of nanomaterials can kill human cancer cells, whereas micron-sized materials are relatively non-toxic [8, 12, 13]. Moreover, there are in vitro studies showing that certain metal oxide nanoparticles can only kill cancer cells. These nanoparticles are remarkably less toxic to normal cells [8,14]. Especially ZnO and different metal doped ZnO is a metal oxide that is mostly used in cancer studies due to its distinguished properties. The ZnO nanoparticles in the present study are in hexagonal mikro-rods which are obtained by using sol-gel method.

Acknowledgments

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Determination of the anticancer effects of M (Mn, Ni, B) doped ZnO nanoparticles against ovarian and breast cancer cells

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Abstract
Breast cancer has the second highest worldwide incidence rate and it has the highest prevalence among the women. Breast cancer, with its high prevalence rates, affects the lives, living standards, and economies of many patients and their families as well as the healthcare services in the public health institutions. The treatment options of the breast cancer depend on the stage of the cancer. Currently, endocrine therapy, radiotherapy, chemotherapy as well as surgery are among the treatment options. Although chemotherapy is widely used against breast cancer, it also brings detrimental side effects alongside to the patients. Therefore, it is imperative and urgent to develop novel therapeutic options against breast cancer. In order to overcome the side effects related with the chemotherapy application, nanomedicine-based agents have gathered an immense attention due to their; enhanced targeting properties, better bioavailability, biocompatibility and multiple functions. ZnO nanoparticles have been in use in cosmetics, dye production and surface modifications of the industrial products. It has also been used in biological and biomedical fields in the recent years. In the light of these, we aimed to find out the possible effects of the anti-proliferative effects of pure, Mn, B and Ni doped ZnO nanoparticles in our project proposal. A 2780 ovarian cancer cell line, ER+ breast cancer cell line (MCF7), ER- breast cancer cell line (MDA-MB-231), and human fibroblast cell line (BJ-5TA). In this way, the appropriate concentration of the most effective nanoparticle type to be used in different cancer types was determined for future experiments on breast cancer and ovarian cancer. In addition, with this study, a preliminary study was obtained in order to see in which cancer type the new drug candidates are more effective, and this study is a preliminary study for further studies of possible drug candidates.

Introduction

Breast cancer poses a serious threat to public health with its highest prevalence rate among women. 25% of cancers seen in women are diagnosed as breast cancer. In terms of being fatal, breast cancer ranks 5th when compared to other cancer types in women. Ovarian cancer comes right after breast cancer. A definite solution has not been produced yet against these two cancer types, which are numerically high in terms of both mortality rate

and incidence [1]. With the side effects of radiotherapy and chemotherapy, they significantly reduce the living standards of the patients. There is a serious need for new generation drug candidates, especially in the field of chemotherapy [2]. Nanoscience and nanotechnology, nanomaterials, have attracted great attention in the last decade due to their unique and superior physical/chemical characteristics and have been utilized in a wide range of applications [3]. Zinc oxide (ZnO) has a relatively wider bandgap (3.37 eV) as a semi-conductor [4] with properties suitable for wide applications such as cancer medicine, bioimaging, and drug delivery. (60 meV). When doped with various transition metals such as ZnO, Fe, Mn, it exhibits different behavior in electrical, magnetic and optical excitation properties [5]. ZnO nanoparticles are not biologically inert and cause cytotoxicity, apoptosis, cell cycle alteration, and DNA damage [4]. Nanobiotechnology has been shown to have the potential to offer a more targeted approach to treating cancer patients. At the nanoscale, materials can have new and more advanced physico chemical properties that are not found in micron or larger sized particles composed of the same material systems. With these characteristics, they have the potential to lead to unique biological and medical applications [6].

Material and Method

Cell Viability Test

Cancer cells cultured by MTT method can be detected colorimetrically and quantitatively. This method is based on the principle that the MTT dye of intact mitochondria can cleave the tetrazolium ring. MTT is a water-insoluble formazan reduced substance and appears in color by a mitochondria-dependent reaction. The MTT reduction property of cells is calculated according to the correlation of the dye density obtained as a measure of cell viability with the number of viable cells. Cell viability will be evaluated using the Vybrant® MTT Cell Proliferation Assay (Invitrogen Corporation, CA, USA). In the study, treated with ZNO at different concentrations (1 µg/ml, 50 µg/ml, 100µg/ml). Effects on proliferation of A 2780-CP, ER + breast cancer cell, ER - breast cancer cell, human fibroblast cell lines by MTT cell proliferation method researched. After the cells were plated, they were incubated at 37 °C for 24 hours and 1 night in a 5% carbon dioxide incubator. Compounds were then added to each well and after 72 hours MTT was added to each well to incubate the samples for 4 hours. Absorbance measurements were then made at 570 nm with a spectrophotometer. IC50 values were calculated using the SPSS program (SPSS. Inc, Chicago).

Results

The data have been doped with different metals after exposure to ZnO and after the cell proliferation index value, after 72 hours of treatment (all comparisons p>0.05) were decreased in a time dependent manner in comparison with the control group and after IC50. The value of ZNO derivatives was calculated. It was found that there was a time-dependent decline in the proliferation of cancer cells 72 hours after administration of ZNO and its derivatives in ER- and ER+ breast cancer cells compared to the control group (all comparisons p<0.05). A time-dependent decrease in cell proliferation was observed in ovarian cancer cells 72 hours after administration (all comparisons were p<0.05), but the IC 50 value was higher in the A2780-CIS cancer cell line than in SKOV cells.

Discussion

Breast and ovarian cancer are the most common cancer types among women globally and in our country. Although it is aimed to be treated with chemotherapy, radiotherapy and surgical interventions, the frequency of relapse in patients and especially the side effects that occur after chemotherapy or radiotherapy emphasize the necessity of developing new generation drug candidates in this area. Preliminary study data of nanoparticles used in this project are important in terms of presenting an alternative to the deficiencies in this regard In previous studies, ZnO, one of many nanoparticles; It has been shown that it increases oxidative stress in cancer cells by causing an increase in reactive oxygen radicals (ROS), and ultimately causes cytotoxicity, apoptosis, cell cycle changes and DNA damage in cancer cells [4,6,7].
Previous studies have shown that ZnO nanoparticles increase oxidative stress and intracellular Ca+2 levels and decrease mitochondrial membrane potential (MPT) in different cancer cell lines. It has been reported that ZnO nanoparticles stimulate interleukin (IL-8) expression and reduce mitochondrial membrane potential (MPT) in BEAS-2B bronchial epithelial cells and A549 alveolar adenocarcinoma cells [8]. It has also been shown that these nanoparticles activate the p53 pathway in RAW264.7 cells [9,10]. It has also been reported that metal nanoparticles stimulate the expression of Bcl-2, a pro-apoptotic protein, in human breast cancer, PC12, and fibroblast cells, activate the PARP and caspase cascades, and induce apoptosis by causing mitochondria and DNA damage [11-13]. Ghaemi et al. conducted a study on preventing organelle damage and stopping the cell cycle progression of the melanoma cells by altering the intracellular ROS level of Ag: ZnO nanoparticles. According to

this study, in the process of photodynamic therapy, it was concluded that the production of ROS by Ag: ZNO nanoparticles under UV light can disturb the homeostasis of melanoma, while it did not affect the fibroblasts [14]. In studies conducted in ovarian cancer, it has been shown that ZnO nanoparticles do not damage fibroblast cells when triggering apoptosis in cancer cells (38). In this study, we aimed to determine the in-vitro efficacy levels of ZnO nanoparticles doped with different metals that have not been studied before against breast and over cancer. In this study, we have shown that ZNOs doped with different metals cause a decrease in the proliferation of breast and ovarian cancer cells depending on concentration and time, and these findings support previous studies. However, further studies are needed to compare these ZNOs doped with different metals with drugs used in routine cancer treatment, and through which pathways these ZNOs affect cancer cells.

Acknowledgment

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Photodynamic cancer therapy and its future potentials

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Keywords
Cancer
Photodynamic therapy
Photosensitizer

Abstract
About 6 million people die of cancer every year in the world. Today, surgical operations, chemotherapy and radiotherapy are commonly used methods in cancer treatment. Chemotherapy and radiotherapy methods cause serious side effects because they damage healthy cells as well as cancerous cells. Photodynamic therapy (PDT) is a new therapeutic model that may provide an advantage to patients who are not suitable for surgical operations and traditional treatment methods. PDT is a minimally invasive treatment modality that provides selective cytotoxic activity against malignant cells. The basis of cancer treatment with PDT is the application of a photosensitizer, followed by light at the wavelength corresponding to the absorbance band of the photosentizer. PDT increases curing in early tumor stages and prolongs survival in patients who cannot be operated on. Since it has minimal healthy tissue toxicity, it is a therapy option with fewer side effects than other treatment methods.

Introduction

Every year, 10 million people are diagnosed with cancer in the world, and more than half of them die from this disease. Surgery, chemotherapy and radiotherapy are commonly preferred methods in the treatment of the disease. Radiotherapy and chemotherapy methods, which are preferably applied after surgical treatment, have serious side effects as they damage healthy cells as well as cancerous cells. These side effects include nausea, diarrhea, vomiting, alopecia, loss of appetite and fatigue. A new therapeutic model that may provide an advantage to patients who are not suitable for surgical operations and traditional treatment methods is photodynamic therapy (PDT) [1,2].

Results

Photodynamic therapy uses a photosensitive chemical substance, which is used together with light and molecular oxygen, to effect cell death [3]. In PDT, certain wavelengths of light and photosensitizers are activated over time in the tumor and vascular system and show an apoptotic effect. Due to the special structure of the tumor tissue, the photosynthesizing substance remains in the tumor tissue for a longer time compared to normal tissues. Then, cell death is promoted by applying certain doses of light to the tumor area [4]. As a result of the reaction of the cell with PDT, reactive oxygen molecules and superoxide anion radicals are produced and death mechanisms in the cell are activated. The effectiveness of PDT in cancer treatment differs according to the photosensitizing agent applied and the light source. While porphyrin and its derivatives are generally preferred as photosensitizing agents, laser and incoherent light sources are used as light sources [5].

Porphyrin is a macromolecule formed by the fusion of four pyrrole rings. It is a conjugated system consisting of 20 carbons and 4 nitrogens. It is an aromatic structure with an 18-II electron system [6]. Porphyrins are N-heterocycle class molecules found in the form of vitamin B12 for cell metabolism, cytochrome for different

oxidative reactions, catalase for the decomposition of hydrogen peroxide, chlorophyll in green plants for photosynthesis, and hemoglobin in the blood for oxygen transport [7]. Porphyrins have been reported to exhibit a variety of biological activities. This is because natural or synthetic porphyrins have low toxicity in vitro and in vivo, have antitumor and antioxidant effects, and have the potential to form ion complexes [8]. Approaches to the application of porphyrin-derived molecules for the development of new non-toxic materials capable of destroying a wide variety of bacteria and fungi have been a sought-after target [9]. Porphyrin compounds have important functions such as photosynthesis, oxygen and electron transport. Synthetically produced porphyrins, which are widely used for photodiagnosis and cancer therapy in PDT, are generally produced from the meso position [10]. Singlet oxygen quantum yields of porphyrin-derived molecules are high. Considered as a long wavelength absorbent sensitizer for PDT owing to its talent to generate singlet oxygen [11].

For the use of PDT in cancer treatment, a photosensitizing substance is first injected into the blood stream. While this photosynthesizing substance is absorbed by all cells in the body, cancer cells are more involved than healthy cells. 24-72 hours after the injection, this agent leaves the normal cells, while leaving the cancerous cells later due to the tumorigenicity of the cancer cells. At this time, the tumor cells are exposed to light. The photosensor in the tumor absorbs the light and produces reactive oxygen, which also destroys the surrounding cancerous cells. PDT also activates the immune system against cancerous cells. In addition, the photosensitizer substance also damages the angiogenesis of the tumor and stops the metastasis of the cancer.

Laser and incoherent light sources are used for the light used in PDT. It can be delivered to the parts of the body by endoscopic methods with thin fiber optic cables transmitting laser light. Other light sources such as light-emitting diodes (LEDs) are used to treat surface tumors such as melanoma cancer.

Discussion

PDT is considered to be a promising antitumor strategy that has not yet become widespread in cancer treatment. Compared with other cancer treatment methods, the long-term reduction of morbidity and less side effects are the advantages of PDT. While many of the traditional antitumor treatments have immunosuppressant effects, PDT also activates the immune system against cancerous cells. In addition, the photosensitizer substance also damages the angiogenesis of the tumor and stops the metastasis of the cancer.

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Pathogenesis and treatment approaches of Alzheimer's disease

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Keywords
Neurodegeneration
Alzheimer's disease
Treatment
Senile-amyloid plaques
Neurofibrillary tangles

Abstract
One of the most common neurodegenerative diseases can be listed as Alzheimer's disease. The physiopathology of the disease includes senile-amyloid plaques and neurofibrillary tangles that accumulate in certain regions of the brain. Therapeutic treatments developed for the disease are limited and aim to reduce specific clinical symptoms and slow the course of the disease.

Introduction

Alzheimer's disease is a fatal neurodegenerative disease that becomes more common with age, resulting in loss of cognitive functions, which is considered the most common cause of dementia. The disease progresses slowly and starts with the death of neurons in the brain and spreads to all neurons, causing brain damage. These damages are seen in the hippocampus entorhinal cortex and cerebral cortex of the brain. Damages in this area result in the loss of glial cells, which help neurons and neurons, and play a major role in their functioning. These cell losses are also associated with disruption of cognitive functions [1-4].

Although there are short-term memory loss and difficulty in remembering recent events at the beginning of the symptoms seen in the first stage of the disease, towards the last stages it results in cognitive forgetfulness where even daily personal care needs are not remembered in the individual. There are 7 stages of Alzheimer's disease that are clinically recorded and followed. The first stage is also defined as the early stage. At this stage, the disease is the stage in which mutated genes in the central nervous system begin to show their effects. The patient has very mild cognitive symptoms at the initial level. In the second stage, the symptoms of the disease are very similar to the first stage, and the patient begins to experience cognitive loss even if it is very mild. The effects of cognitive loss in the patient's communication with his environment are not yet seen. In the third stage, the patient's mild cognitive loss is noticed and it affects his daily life, albeit slightly. In this stage, patients have difficulty in remembering situations such as planning, organization, the location of their belongings and names. The fourth stage can also be described as the stage of moderate cognitive weakness. At this stage, patients experience losses in short-term memory and in remembering information such as personal background information, which can affect their lives and distance themselves from social life. The fifth stage is the stage in which moderate-to-severe cognitive weakness is seen and is described as early dementia. At this stage, symptomatic conditions called agnosia and apraxia occur in patients. Agnosia is the experience of recognizing sounds, smells, names, objects, shapes and entities that are known/recognized before, without any loss of sense, due to Alzheimer's disease. Apraxia, on the other hand, includes defects in acquired/learned motor movements and speech without any muscle loss. Patients with apraxia and agnosia disrupt their daily routine and need the help of a second person for these tasks, including personal care. In the sixth stage, severe cognitive losses and moderate dementia are seen. In addition to agnosia and apaxia, patients also have aphasia. Aphrasia is characterized as the inability to remember in the speech order of the person without any loss of sense in speaking skills, and as a result, the disruption in speaking ability. In this

stage, which is accepted as the seventh and clinical final stage of the disease, severe cognitive deficits and late dementia are seen in patients. This stage includes all the symptoms seen in the previous stages, but indicates the most severe and last degree of the symptoms of these stages. At this stage, patients experience losses in basic needs such as speaking, swallowing, and going to the toilet, and they need surveillance all day [5].

Discussion

The pathogenesis of Alzheimer's disease can be elucidated by the evaluation of autopsy results. In addition to genetic approaches*, in vitro* or *in vivo* studies also play a role in determining the pathogenesis of the disease. In the light of these studies, senile beta-amyloid plaques that accumulate excessively outside the cell and neurofibrillary tangles that accumulate inside the cell are counted among the molecular differences in the formation of Alzheimer's disease [6,7].

Neurofibrillary tangles consist of double-strand breaks as a result of the accumulation of neurons in the cell body and dendrite regions by hyperphosphorylation as a result of differences in kinase and phosphatase levels responsible for the phosphorylation of tau proteins within the cell. In addition to kinases and phosphatases, which are responsible for the hyperphosphorylation of tau proteins, some proteins also play a role. CDK5 serine threonine kinase protein is involved in the phosphorylation of tau protein. In addition, proteins such as GSK-3β protein, protein phosphatase 2A, and proyl isomerase pin1 cause hyperphosphorylation of tau proteins, resulting in the formation of neurofibrillary tangles. Neurofibrillary tangles accumulating in the cell induce apoptosis, disrupt the functional structure of microtubules that make up the cytoskeleton, create toxic effects within the cell, and impair transmission between neurons. The formation and course of neurofibrillary tangles progress in direct proportion to the clinical course of the disease [6].

In addition, cellular events such as oxidative stress, Down syndrome, insulin resistance, neuronal glucose metabolism and neuroinflammation are effective in the pathophysiology of the disease [6,7].

The most obvious and most important symptom of the disease is the formation and accumulation of senile-amyloid plaques in certain regions of the brain. It forms/accumulates in the amygdala, hippocampus and neocortex regions of the brain. Amyloid β consists of 40-45 amino acids and consists of APP protein. Amyloid plaques are based on the intracellular proteolytic formation of the amyloid precursor protein, APP. Amyloid beta consists of the part of the transmembrane APP protein in the extracellular membrane [7-9].

There are some genes responsible for Alzheimer's disease. These genes are; There are 4 amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (ApoE). It is known that Alzheimer's disease occurs as a result of mutations in these genes. As a result of the mutation in the APP gene, an increase in the level of amyloid beta plaques has been observed. It is known that Alzheimer's disease occurs when any mutation in the PS1 gene causes changes in tau proteins, forming neurofibrillary tangles associated with these proteins and accumulating in the cell. While the e4 allele of the ApoE gene has an enhancing effect on the emergence of Alzheimer's disease, the e2 allele has a reducing or protective effect [7,8,10].

Conclusion

The drugs used for the treatment of Alzheimer's disease aim to eliminate the specific clinical manifestations of the disease. Tacrine was the first drug used and approved for Alzheimer's disease. This drug significantly reduces the symptoms of people with Alzheimer's disease. In addition, it greatly increases the expression level of liver enzymes. However, the hepatotoxic effect of this drug limits its use in the disease. It is thought that developing and suggesting drugs that reduce the effects of Alzheimer's disease in its holistic and basic form, instead of nonspecific drug treatment approaches, may reduce the disease [10,11].

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Promoting tissue regeneration with supramolecules

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Keywords
Supramolecules
Tissue regeneration
Regenerative medicine
Hydrogel supramolecules

Abstract
Supramolecules are the polymeric molecules which are generated by macromolecular non-covalent bonding. Since they can mimic the natural cell microenvironment which plays an important role in tissue regeneration with a plethora of aspects, supramolecules are highly popular in regenerative medicine area. They are non-toxic, biodegradable, biocompatible and they can be modified for the purpose of disease treatment and control. They can be used for encapsulation of the important growth factors, particular stem cell types and drugs; they are able to release those molecules by stimulation or changes in their surface or bond structures. They are injectable for localized applications and in some cases, they degrade to become nutrients for the surrounding cells after they complete their mission.

Introduction

Repairing or replacing lost limbs and serious tissue damages are one of the hot topics in the medicine for a long time. Particular tissues and organs cannot regenerate properly. Some events such as birth defections, traumatic injuries, aging, illnesses or cancers cause tissue damages and limb losses, which eventually alter human functions and life quality. In order to create solutions in the field, regenerative medicine has been extensively dedicating effort and resources on this topic for a long time.

Biomaterials are the most popular elements of the regenerative medicine. Their biocompatible, biodegradable, nontoxic and functionalization by modifications in their chemical structures are the main foundations of their popularity [1].

Supramolecules are one of the most popular biomaterials in the regenerative medicine. They hold advantages over other biopolymer types; they can be modified, functionalized, they are self-healing, non-toxic, stimuli responsive and non-immunogenic [1,2]. Supramolacules are the polymers which consist of macromolecules with noncovalent bonds such as hydrophobic interactions, hydrogen bonds and metal-organic interactions [1,2,4]. Their functions depend on their structures similar to those of the proteins and they can also be changed by modifications during manufacturing or by nature. The changes in their structures play an important role in their stimuli responsive properties [4].

Supramolecules mimic fibril structure of the extracellular matrix (ECM) which consists of proteins like elastin, laminin, proteoglycans and collagens [3]. ECM is the natural microenvironment of cells; they support and act as scaffolds for cell and tissue [5]; they also promote strong interactions between important bioactive proteins, protein subunits and polysaccharides which plays important role in cell signaling [3]. These signals provide cell migrations, adhesions, proliferations and differentiations which promotes tissue regeneration [2,5].

Results

Treating brain injuries and defects are really hard and almost impossible in some cases because of the characteristic of brain structure and neuronal cell features. Presence of blood-brain barrier; and neuronal cells inability to proliferate limit the treatment methods and tools. Recent study about the treatment of the brain injury is promising by using special shaped self-assembling peptide hydrogels which mimic ECM and allow release of growth factors. In this study, scientists designed a jigsaw-shaped protein hydrogels which contains specials motifs for generating different surface structures which provides multiple functions for this supramolecule. This supramolecule is injectable when it is encapsulated, in that way it is useful for a localized treatment method. This fiber forming peptide has hydrophobic surface which allows strong binding, self-assembling and efficient release of the growth factors. The interactions between guest and host molecules are processed thermodynamically. The strong affinity between host and guest molecules increases slowly as controlled release of the guest molecules is achieved. On the other hand, host-guest molecule pairs can arrest guest molecules for inhibiting their release. As a result, this study showed that the injection of this supramolecule promoted growth factor release which leads to the angiogenesis and neuro-protection which is a must for neuronal recovery [5].

In another study, scientists enhanced motion of supramolecules for the treatment of the spinal cord injury. They synthesized ''dancing'' supramolecules with two peptide sequence as scaffolds for enhancing growth factor release. This supramolecules released two distinct signals: one of them activated FGF-2 receptor, the other one activated β1-integrin receptor; both of them allowed neuronal cell survival. As a result, in paralyzed mice, overly-motive supramolecules promoted blood vessel formation, nerve regeneration, myelination, motor neuron survival, axon regrowth and glial scarring reduction when injected in the injured part of the spinal cord. After the supramolecule completed its mission, it degraded and released nutrient molecules for the surrounding cells [6].

Bone-cartilage tissue recovery is also critical for the mobility and life quality. The mostly used strategy is delivering bioactive factors and stem cells locally. These elements play important role in bone-cartilage repair. In this study, scientist prepared supramolecular hydrogel and they delivered this material with SDF-1 chemokine which promotes proliferation of bone marrow stem cells and BMP-2 which stimulates differentiation of bone marrow stem cells for promoting periodontal bone regeneration. Also, this supramolecular hydrogel mimicked ECM that enabled a convenient macroenvironment for the stem cell adhesion and function [7].

Wound healing includes multiple factors like epidermal growth factors (AGF) and FGF-2 and it is a complex process. These factors are activated and released for stimulating the wound healing. In wound healing, growth factors are critical but they are prone to proteolytic degradation because of the inflammation process in the wounded area. Scientists designed photo-sensitive supramolecules for UV controlled EGF release. In mouse models, supramolecular hydrogel encapsulated EGF application showed the fast wound recovery and 10% in the wound size reduction. Also, these materials showed antimicrobial activity when they were enriched with chitosan and silver ion on the wound area [7].

Conclusion

As damaged tissues are hard to recover, biopolymers like supramolecules are the main focus of the regenerative medicine. They have versatile properties such as non-immunogenic, non-toxic, stimuli-responsive and degrading into the nutrients therefore they hold advantages over other biopolymer types. Supramolecules can gain functions by modifications in their chemical structures, as a result of that, in theory, their potential in regenerative medicine has no boundary. There are a wide variety of studies in the literature about supramolecules and their modified versions for skin treatment to central nervous system regeneration. Besides, some of those studies report successful outcomes in the animal models; still, there is a very long way ahead. Working with supramolecules for the regenerative medicine requires multidisciplinary understanding and ability. With the help of disciplines such as Medicine, Biology, Biotechnology, Bioengineering, Chemical engineering, Material sciences and Physics engineering, the road can be shortened.

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Transgenic plants and their impact on the agricultural yield

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Keywords
Transgenic plant
Herbicide recombinant
DNA technology

Abstract
Despite the positive and negative opinions about transgenic plants, the cultivation of transgenic plants is increasing day by day. A significant portion is for plant health. One of the goals of working with transgenic plants is to reduce herbicides and achieve higher yields with transgenic plants. Thanks to the genes transferred to the plants by applying recombinant DNA technology, product loss has decreased and it has been observed that herbicide resistance has decreased. Despite the criticism against the genetically modified organisms (GMOs) and their utilization, biotechnological approaches for transgenic plants are promising solutions to increase the agricultural yield and enable food security.

Introduction

Weeds have a structure that makes them stronger than cultivated plants. In this way, they can suppress plants, grow and spread. The use of chemical pesticides in the fight against weeds is an effective, reliable and simple need [1]. When using these drugs, it should be used appropriately to increase the efficiency and quality. Pesticide in these products is an integral component of the modern agriculture [2]. One of the most commonly used methods in agricultural control is herbicides, which fall into the pesticide group [3]. In addition to the importance of the pesticides, herbicides are also widely used in sustainable agriculture. More than 200 herbicides are used today, and the most of them have been evaluated for their toxicity potential and approved daily by JMPR (Joint Meeting on Pesticide Residues) [4]. But pesticide residues can contaminate the air, soil, water and food. Thus, it can pose a danger to animals, plants and humans [3]. According to the previous studies, it has been determined that the toxic effect of newly developed herbicides on mammals is low. In another study, development and reproduction were affected in one or a few species of animals exposed to the herbicide effect [4]. Some weed species can show resistance to the conditions such as herbicides, UV, ozone, and drought [5]. More herbicides are used against this resistance, but as a result of using too much herbicide, it causes accumulation and pollution in the soil. These deposits can also build up in the product and cause deadly diseases such as cancer [6]. Such problems are on the increase with the increasing population. With the increase in population, agricultural fields shrink down. In order to solve the problem with the food insecurity, we need to increase the yield from agricultural areas [7].

Today, thanks to the biotechnological studies, important solutions are tried to be found for this purpose. There are 2 purposes in the aim of those studies; the first is to increase product quality and quantity, the second is to increase the resilience to the adversity. In addition to the classical methods, modern methods have been developed. The biggest advantage of these methods is that there is no kinship obligation between the species to be transferred. Thus, it was possible to transfer the gene to be taken from a plant, animal or microorganism to a completely different organism and act as if it were a part of the genome [7]. A plant whose genome has been transferred from another organism by biotechnological methods is called a "transgenic" plant. The origin of this

transferred gene may be another plant species that cannot be crossed with the plant to which the gene is transferred, or it may be an organism from other realms other than the plant universe [8]. The studies carried out to obtain these plants The use of technology with the gene transfer of the bacteria *Agribacterium tumafaciens* has revolutionized the field. In the continuation of the technology, many GMO plants including tomatoes have been started to be developed. Thanks to recombinant DNA technology, crop losses have decreased all over the world, and herbicide resistance has decreased significantly compared to traditional agriculture. Apart from these, plants that are endangered due to biotic and/or abiotic stress can now be produced and reproduced by cloning, thanks to recombinant DNA technology. Thanks to the genetically modified plants, soils that are polluted and cannot be cleaned or that will take a long time to clean can also be cleaned with bioremediation methods such as phytoremediation method and recycled to the nature [6].

Results

The use of transgenic plants is increasing day by day, and its effect on human health, environment and living things causes controversy. New methods should be found to prevent these concerns and risks, and new varieties should be revealed thanks to the biotechnological methods. In order to increase the yield of the plants under cultivation, high yielding new varieties can be obtained by means of traditional breeding methods and/or recombinant DNA technologies of foreign genotypes, and plant product loss can be prevented by intervening harmful ones at the gene level [2,6].

Discussion

Before obtaining transgenic plants, it is extremely important to take the necessary legal, ethical and legal measures to protect biological diversity and natural resources. This should be done in a timely manner, based on the conservation of biodiversity. It is important to protect Turkey's geographical structure and plant gene resources, including special conditions, and to implement the obligations arising from international conventions, taking into account the rules of the European Union on this subject. Comprehensive measures should be taken to minimize the negative effects of genetically modified plants by realizing the richness of our country, especially in terms of the number of endemic species [6]. GMO plants can also be utilized without spoiling the nature with novel genes as well as chemicals that have been used as herbicides or pesticides. Legal and ethical actions should be taken together with the training of the farmers and the society for the safe usage of GMOs and their potential to increase the yield. GMOs might be an important tool to overcome food shortages and insecurities all around the World.

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Immunostimulatory and immunomodulatory functions of a novel phenothiazine derivative

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Keywords

Immunomodulatory
Immunostimulatory
Phenothiazine
Immune cells

Abstract

Immune cells are involved in every part of the human body and are affected by many factors such as nutrition, exercise and sleep. In reactions called immune response, the body is basically protected from the microorganisms and their harmful soluble products. The decrease in the functions of cells in the immune system increases the susceptibility to infectious diseases. The immune system, which is the body's security force; also acts as a means of interaction between the central nervous system, the cardiovascular system and the digestive system. Phenothiazine derivatives have high affinity for many receptors, enzymes and proteins and play an important role in medicinal chemistry field. Many studies have been carried out on phenothiozine derivatives and positive outcomes have been obtained as a result of those studies for their drug potential. The immune system, on the other hand, is a defense system that creates the reactions of living things. During autoimmune or inflammatory disorders, it is imperative to have drug molecules that can modulate the immune reaction to prevent harmful excessive inflammation. Our studies aim to generate novel drug candidates that can be utilized against inflammatory and autoimmune diseases.

Introduction

Our body has an immune system made up of cells and molecules to protect itself against infections and foreign substances. The task of the immune system is preventing organisms that try to enter the body or harmful substances formed in the body, or not allowing them to spread throughout the body [1].

Immune system cells secrete a large number of protein messengers. These protein messengers regulate host cell division and are involved both in the innate and adaptive immune responses. These messengers are called cytokines, and each has its own name. The general purpose of the cytokines is to provide communication between the cells. Cytokines are among the glycoprotein products of immune cells such as lymphocytes and macrophages. Cytokines mediate defense functions through effectors. They generally do not show cytotoxic properties against the cells themselves. Among the cytokines; Interleukins, interferons (IFN), colony -stimulating factors and TNF are involved in the immune responses. They have a very important role in the immune reactions, inflammatory and infection conditions. Cytokines are related to the growth, development, differentiation, activation and orientation of the immune system cells [2,3]. Phenothiazine derivatives are involved in various biological processes. They are used as popular medicine to treat various diseases as they are characterized by low toxicity. In previous studies, it was investigated that phenothiazine and its derivatives have anti- psychotic, antibacterial, anti- fungal, and anti – oxidant properties [4-6]. Phenothiazine and its derivatives have been used in the treatment of various diseases. In this study, the immunomodulatory and immunostimulatory effects of phenothiazine on the immune system cells will be examined.

Results

We know that immune system cells play an important role against different kinds of danger signals or sources in our body. The immune system is examined under two main umbrellas as the innate immune system (the inherited immune system) or adaptive immune system. The components of the innate immune system are the specialized cells called natural killer cell (NK), the epithelial barriers of the skin, respiratory and digestive systems that prevent the entry of microbes, phagocytic leukocytes called neutrophils and macrophages. Macrophages, one of the innate immune system cells, can recognize danger and produce different types of inflammatory signals. It also has the ability to present the antigen to the other immune system cells to produce an appropriate immune response. Researchers are focusing on regulating the immune system cells to eliminate chronic inflammation due to infections or autoimmune reactions, to create longer lasting cure compared to the current treatment methods [6].

Phenothiazine consists of a tricyclic nucleus of two benzene rings. A central ring joins these two benzene rings and this central ring contains a sulfur and nitrogen atom. We know that the chemical structure of phenothiazine, which can interact with a range of biological processes, is very important [7]. Phenothiazines and its derivativeshave very different etiology and symptomatology. In addition to being useful as therapy agents for versatile diseases, these molecules are currently used clinically mostly because they show stark antipsychotic effects and are also useful as antihistamine drugs. In other words, they show antiallergic, antiemetic, sedative and antipruritic activities. Some derivatives have exerted anti- inflammatory, antioxidants, antispasmodics, antitussive, and radioprotective effects.

When we examine the work done; in the study of [6] phenothiazine-based cyanoacrylamide was synthesized from phenothiazine by a multi-step synthetic strategy. Antioxidant and anticancer properties of the synthesized compounds were investigated by *in vitro* methods. As a result of that study, it had high antioxidant properties and *in vitro*anti-cancer effects on pancreatic tumor cells [8].

Alzheimer's, which is among the neurodegenerative diseases, occurs with the accumulation of beta- amyloid plaques in the brain, which has also been used as disease diagnosis marker. Phenothiazine derivatives seem to inhibit the beta - amyloid aggregation and fluorescence. In the study of Dao et al., beta- amyloid, which provides NIRF imaging of amyloid plaques. The phenothiazine derivative that they utilized prevented the formation of those plaques and also resolution of the fibrils. With this system, they showed that a phenothiazine derivative could bind beta- amyloid in the brain of the mice with the Alzheimer's disease model [9].

In the study of Kışla et al.; for the synthesis of phenothiazine derivative compounds, phenothiazine core structures were generated either in non-substituted form or as 2-chlorophenothiazine with acetyl chloride/ propionyl chloride and as phenothiazine 10-yl acyl chlorides. They reacted with amines in the presence of K_2CO_3 and NaI and obtained phenothiazine 10-carboxamides. As a result of the studies, they found twelve phenothiozine derivatives and stated in their studies that the obtained compounds showed anticancer properties [10].

Discussion

In summary; above studies strongly suggest that phenothiazine derivatives have anticancer properties and may be effective against Alzheimer's disease. Based on some other studies, phenothiazine derivatives may exert immunomodulatory and immunostimulatory effects on the immune system. In addition, these results also imply that phenothiazine derivatives will play an important role in the development of new drug candidates and more research should be done in the field to fully decipher their drug potentials.

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Treatment approaches against rheumatoid arthritis (RA)

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Keywords
Rheumatoid arthritis
Treatment
Inflammatory
Drug

Abstract
Rheumatoid arthritis (RA) disease has inflammatory properties and causes some problems in the joints and decreases the quality of life of the individuals. It is thought that some factors such as environmental, genetic, hormonal, psychological and age have an effect on the development of rheumatoid arthritis, which affects the musculoskeletal system and can cause damage to some organs. Glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) are preferred within the scope of the treatment.

Introduction

Rheumatoid arthritis (RA), whose etiology is not clearly determined, is an autoimmune disease with inflammatory features and chronic progression. Rheumatoid arthritis is a common joint disease among inflammatory diseases [1,2]. RA joint disease causes disability as well as a decrease in the quality and duration of life [3,4].

Rheumatoid arthritis joint disease is generally more common in the advanced age of the population (40 to 50 years old) and in women (may vary according to geographical conditions) compared to men [2].

In the course of RA disease, which is characterized by damage to the joints; stiffness in the hand, shoulder, elbow, ankle and knee joints, pain in the joints, swelling in the joints, musculoskeletal pain, joint fractures, weakness, fatigue, muscle weakness, weight loss, fever, sleep disorders, joint deformity are among the most common symptoms [1-5].

Although RA affects the musculoskeletal system, it can also cause damage to the nervous and immune system, heart, skin, eyes, lungs, kidneys and vessels [1,5].

Although the exact cause of RA cannot be determined, some factors are thought to be effective in the development of the disease. In general terms, these risk factors include; environmental factors, genetic factors, hormonal factors, psychological factors, age factor [3,5,6]. It is known that genetic factors have a 40%-60% effect on the formation of the disease. Some genetic polymorphisms and epigenetic modifications are considered among genetic factors that may affect the development of the disease. The "Human Leukocyte Antigen (HLA)" locus is very important in the development of RA [7].

Discussion

Although cytokines are thought to have an important role in the pathogenesis of RA, IL-1, IL-6 and TNF-α cytokines are detected at high rates in the synovial fluids of the joints of individuals with rheumatoid arthritis [8-10].

Th17 cells, which have an effect on joint damage, are involved in the pathogenesis of rheumatoid arthritis. Th17 cells; It is responsible for the production of IL-17A, IL-17F, IL-22 and IL-26 cytokines. IL-17 proinflammatory cytokine causes joint damage. TGF-β and IL-6 cytokines (with IL-23) or IL-23 and IL-1β cytokines provide the differentiation of naive T cells into Th17 cells. IL-17A is produced by both Th17 cells and some cells such as neutrophils, eosinophils, and macrophages [7,11-13].

Regulatory T cells, which accumulate in the joints of individuals with rheumatoid arthritis, exist as a subset of naive CD4+ T cells and are involved in autoimmune diseases as suppressive type of cells. These cells are crucial to eliminate the inflammation. Increasing their activity in the joints is one of the immunotherapy approaches against RA [13].

Although there is no definitive treatment method for rheumatoid arthritis, which initially affects the joints and then the internal organs, the symptoms of the disease are handled in an individual way [5]. Early diagnosis of rheumatoid arthritis and initiation of appropriate treatment as a result of this condition allows to increase the quality of life of the individual. In addition, the occurrence and progression of joint damage in 90% of patients is slowed down by early diagnosis of the disease and the application of the necessary treatment method [14].

One of the treatment strategies applied to rheumatoid arthritis patients is drug treatments. In this context, glucocorticoids, non-steroidal anti-rheumatic drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs) are used [14,15].

Conclusion

Reducing joint pain and swelling seen in rheumatoid arthritis, preserving the functions of the joints, reducing the sensitivity and damage in the joints, slowing down or stopping the joint destruction, preventing the progression of the disease to an advanced level are possible with the disease-modifying anti-rheumatic drug (DMARD) group [6,14,15].

One of the treatment options applied to reduce pain and inflammation in the treatment of RA disease is the non-steroidal anti-inflammatory drug (NSAID) group. Some drugs included in this drug group (for example, drugs such as ibuprofen, aspirin) have anti-inflammatory and analgesic effects and are therefore preferred as an adjunctive treatment in rheumatoid arthritis [5,15].

Glucocorticoids, which have a strong anti-inflammatory effect, can reduce the progression of damage to cartilage and bone. Diabetes, osteoporosis, gastrointestinal bleeding, hypertension and weight gain are among the side effects of glucocorticoids in sick individuals [6,14].

In addition to the positive effects of drug treatments on the disease, it can also cause some side effects in sick individuals. Among these side effects; some infections, anemia, kidney and liver damage, loss of appetite, nausea and vomiting, allergies [2].

Different antibody-based therapy approaches are being developed, including immunotherapy, in order to eliminate the side effects of traditional drug treatments for the disease [16-18].

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The effect of biochar on the plant under stress conditions

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Keywords
Plant
Stress
Biochar

Abstract
Stress conditions such as drought and salt negatively affect plant growth and yield. Many methods are used to alleviate these negative effects. Biochar application is also a method used to eliminate the negative effects on the plants stimulated by the stress conditions. According to many studies, biochar application to the soil increases the yield of the plants under different stress conditions. Moreover, biochar increases photosynthesis rate, water usage efficiency and relative water content in the plants struggling with the drought stress.

Introduction

Plants, like other living things, do not have the ability to move under stress conditions or escape from the environment that have stress factors. Therefore, they have different mechanisms to survive under stress conditions. These mechanisms aim to keep plants alive and maintain their vitality. For example, when plants faced with a lack of water, they close their stomata as the first physical response. However, this causes the plants to perform less photosynthesis, and thus reducing its yield [1,2].

The protection mechanisms of plants under stress conditions also have negative aspects in terms of yield, and the decrease in yield is perhaps the most important of these negative aspects. In order to prevent the decrease in plant yield under stress conditions, many methods are tried to make the stress conditions less effective or to alleviate the response to stress [3,4].

One of these methods is application of biochar to the plant that are struggling with stress conditions. In these studies, researchers observed that the application of biochar mitigates the effects of stress conditions. However, there are researches who has shown that biochar has an important role in the plant growth and yield that are grown in the absence or presence of the stress conditions [5-7].

Results

In the literature, there are many studies showings that biochar has a positive effect on the response of plants to the stress conditions.

Akhtar et al. [8] observed that the biomass of the wheat plant in the region with the semi-arid Mediterranean climate increased with the application of biochar. In addition, they added to the literature that biochar significantly increased chlorophyll content, stomatal conductivity, photosynthesis rate, water use efficiency and relative water content in plants struggling with the drought stress.

Batool et al. [9] observed an increase in plant height and leaf area compared to the control groups when they applied biochar to okra plants under the drought stress. However, Haider et al. [10] reported in the literature that similar results are also valid for maize plants.

Kanwal et al. [11] investigated salinity stress on the wheat. They applied different concentrations of biochar. They observed that biochar alleviated the negative effects of the salinity stress such as water deficiency in the wheat. In addition, root and shoot lengths increased in the groups with the biochar application.

Discussion

In summary, it has been observed many studies suggest that application of biochar in the soil of the plants that are grown under stress conditions overcame the detrimental effect of the stress on the plant growth and immunity [5-7]. In line with these observations, biochar application in the absence of the stress conditions further stimulated the plant growth and yield.

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The use of new generation sequencing technologies for aquaculture genetics studies

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Keywords
Aquaculture
NGS
Biotechnology
Sustainability

Abstract
The new generation sequencing is a novel biotechnological method that has been used in versatile fields. In this study, we are sharing the latest literature in aquaculture field and how the new generation sequencing can be utilized to increase the efficiency in production. Aquaculture technologies are older than terrestrial animal production technologies. It is almost a necessity today to use high-tech biotechnological methods for a more sustainable and efficient operation of this sector, which occupies a very important place in the world's food needs. For this reason, we should start to manage the aquaculture production sector in a more controlled way by using new generation sequencing methods to decipher the genomes of the organisms and easily generate safe genetically modified or more resistant individuals.

Introduction

New generation sequencing technologies started in 1977. In the last 40 years, DNA sequencing methods have developed through many different stages and has progressed by expanding its sequencing capacity. If we look at the place of new generation sequencing techniques in aquaculture production; the use of gene sequencing has made it possible for the characterization and mapping of genes, population genetics, ecological speciation, genomic evaluation, sex control and determination, quantitative research to understand the diseases, and the use of biomarkers. In addition, with the advent of NGS technologies, the discovery of multiple types of high- throughput variants have become possible. NGS is considered a highly efficient, reliable and inexpensive method to achieve the abundant genetic diversity of organisms [1,2]. Through NGS, we can pinpoint the reason behind the disease susceptibility and decrease in the production efficiency at the genetic level. This method enables more knowledge on the genes that play essential roles in these processes and how to overcome these hurdles to increase the production efficiency either by targeting certain gene products specifically or by altering the genes to get genetically modified organisms with higher production efficiencies during aquaculture applications [1, 2].

Results

Aquaculture is the fastest growing fresh food sector. For this reason, aquaculture must be sustainable. Direct genotyping with the help of NGS is known as GBS. Genotyping can be done with in the genome in aquaculture with GBS [1]. It is a method preferred by companies for small research types without GBS model. The discovery of GBS has revolutionized genome-wide studies by speeding up certain steps [2]. This revolution has affected aquaculture in terms of genetic mapping of species and improving the production efficiencies by genetic selection methods. In particular, it is used with the DNA sequencing method (RAD-seq), which works with the restriction region logic. RAD-seq contains DNA sequencing of the reduced versions of the examined genome and are restriction-based

libraries [3]. If we look at where RAD-seq techniques are used; it can be used in the creation of genomic maps, editing and debugging of the genomes, sex determination in aquaculture, creating disease resistance and growth in the individuals. At the same time, it is important to understand the development of health biomarkers to prevent viral bacteriological diseases that cause huge losses to fish farming industries globally. Reliable marker technologies capable of genome wide screening are essential for the development of isogenic fish lines, and NGS provides this potential. With NGS, more reliable markers with a lower error rate are prepared with a much faster pace. With these developments, tens of thousands of markers for aquatic species can be prepared quickly. This also prepared the ground for proving previously untested hypotheses. If we look at where these technologies can be used in aquaculture production and what benefits they can provide; we can say the creation of genomic maps that can be reference, the creation of population genetics, its use in verification and validation studies, the possibility of sustainable and environmentally friendly production, the genotyping of fish for breeding purposes, the determination of sex maps to increase the efficiency of production. If we examine what some of the researches made with the aquatic species whose reference genome maps were created; genetic markers associated with the disease resistance of *Flavobacterium psychrophilum* and infectious hematopoietic necrosis virus (IHNV) disease have been identified on rainbow trout and they used these markers (marker assisted selection) to establish improving populations resistant to the diseases mentioned above. Thus, viral and bacteriological diseases are prevented and major damages that may occur in the production are prevented. In another study, markers close to the Atlantic halibut sex determination regions were determined. Functional males were determined with these markers, and then all female populations needed by the industry were created. In this study, sex determination and yield increasing properties of NGS on aquaculture were used. In some studies, it is used in improving programs used in high throughput genotyping studies with the help of chips named according to the number of markers to determine the level of polymorphisms for different populations. Among the species used in studies using these chips; we can give examples of channel catfish, rainbow trout, Atlantic salmon. If we look at the research and studies on the environment for aquaculture and genetics, the fish were monitored with the TNP markers made with the RAD-seq on sturgeon fish and studies were carried out to protect them with these inferences. In general, when we look at these studies, we can see the benefits of using NPP in academic research, economic studies and minimizing the damage to the environment. If we want to create more productive aquatic cultures, we must base our cultures on selective breeding programs. As in the case of the terrestrial animal production, aquaculture has an important place in the world's food needs [1]. Direct genotyping with the help of NGS is known as GBS. Genotyping within the genome can be done in aquaculture with GBS [2]. It is a method that can be preferred by companies for small scale research set up that do not have the GBS model. The discovery of GBS has revolutionized genome-wide studies by accelerating certain steps during the process [3]. This revolution has affected the aquaculture in terms of the genetic mapping of the species and improving the yield studies. In particular, it is used with the DNA sequencing method (RAD-seq), which works with restriction region logic. If we look at where RAD-seq techniques are used; it can be used in the creation of genomic maps, editing, and debugging of genome studies, sex determination in aquaculture, establishing disease resistance and improved growth.

Discussion

Overall, it has been concluded that NGS provides better and sustainable production of the aquaculture products through the knowledge-based advantages it provides with the high throughput genetic sequencing. There are many studies in this area to increase the information about the genes involved in the aquaculture product quality and quantity. In particular, using the RAD-seq sequencing method, one of the GBS techniques, has helped to produce modern fishery products by means of increased growth, sex determination and prevention of diseases. From this point of view, biotechnological methods have great potential in aquaculture [1-4]. More studies should be conducted in the field to further improve the sequencing quality and pace to further expand our knowledge for improved yield and product quality in aquaculture practices.

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Phage therapy review "as alternative treatment of bacterial infection"

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Keywords
Bacteriophage
Bacterial Infection
Phage Therapy

Abstract
The rapid increase of multidrug-resistant bacteria around the world provides an opportunity to explore phage therapy as a replacement to antibiotic usage or a complementary treatment for some bacterial diseases. A number of clinical literatures have recently documented for the results of administering bacteriophages and phage cocktails to treat various infections. Although the phage therapy has given positive results, phage therapy has not been approved or used in the clinics. The variety of phage formulations, as well as the different routes of phage administration and treatment times, make it difficult to develop such systems. In particular, the different localizations of bacterial infections make it necessary to determine the best routes of administration and treatment regimens for phages. If bacteria grow resistant to phages, phages will naturally evolve to infect the resistant bacteria, reducing the possibilities of bacterial escape, which is still another advantage of the phage over antibiotics. Because of the diminished microcirculation and the production of microbial biofilms, which are typically diverse and antibiotic resistant, antibiotic treatment of infected ulcers is sometimes hampered by low antibacterial drug bioavailability. As a result, new treatments, either as an alternative to or in addition to antibiotic therapy, are necessary. The use of lytic bacteriophages as a therapy strategy is one of the options. A simple approach of bacteriophage treatment of diabetic foot ulcers is described here.

Introduction

Since their discovery, bacteriophages have been regarded possible antibacterial treatments for the therapy of many contagious diseases' "infection" in human. At the beginning, bacteriophages were used in clinical trials to treat acute intestinal disorders and skin infections [1]. Later, bacteriophages were utilized in surgical procedure to treat purulent wounds and post-operative contaminations, and these methods were popular in the Soviet Union in 1930s and 1940s [2]. Phage therapy was phased out in most nations after the introduction of antibiotics, and surgical methods in the USSR (Union of Soviet Socialist Republic) were drastically reduced. However, in eastern part of Europe and the union of Soviet, in the clinical management of infectious wounds by using bacteriophage wasn't discontinued, since presence of antibiotic resistance bacteria create challenges to the antibiotic therapy for such infections sometimes. In Poland, Republic of Georgia and Russian Federation, phage related preparations for clinical use have been approved, and a numerous studies of bacteriophage therapy have been published in that region [3-4].

The key benefit of phages is their specificity for the target bacterium, which decreases the amount of damage to the host's regular flora. A cocktail of phages should be employed if the bacteria to be targeted cannot be identified. Bacteriophages are self-limiting, which means they need their hosts to keep growing all the time; if the bacterial pathogens they're looking for aren't there, they won't last long [5-6]. Another advantage of phages is that phage can multiply (replicate) in the infectious wound. Beside that phage are risk-free and have few or no negative effects [7-8].

Results

Phage therapy was applied in 550 cases "between" 1981-1986; it was reported that 92.4% of the patient's showed improvement, 6.9% regressed in the symptoms, and 0.7% of the patients did not experience any effect. In phage therapy applied against *Staphylococcus* and Gram-negative bacteria (*Escherichia, Pseudomonas, Proteus, Klebsiella*), which are causative agents in chronic skin infections caused by postoperative or other causes, 77% of the patients recovered, and the remaining 23% due to the development of side effects or no sign of improvement, treatment was stopped [9]. A successful phage study in the field of ophthalmology has been carried out. (Dautova et al) treated 30 patients with traumatic bacterial keratitis, 16 of whom had prulent corneal ulcers, with "Pio" bacteriophage. Patients treated with phage were discharged earlier than those treated with gentamicin, while an equal number of controls were treated with gentamicin eye drops [10]. In cancer; Phage therapy was administered to 20 cancer patients who had bacterial infection due to *S. aureus, P. aeruginosa*, *Klebsiella pneumoniae, Klebsiella oxytocave E. coli* and did not respond to antibiotic treatment. All patients given phage orally three times a day fully recovered between 2 and 9 weeks (mean 32 days) following treatment. 94 antibiotic-resistant septicemia cases were treated with phage, in 71 of the cases, antibiotic treatment and phage treatment were applied together, and the remaining 23 were treated with phage alone. With this treatment, 85.1% of 94 cases improved, while 14.9% had no effect [11]. The average success of phage therapy is around 80-85%, and its efficacy has been proven for combating against bacterial pathogens when the antibiotic therapy is not effective [12].

Discussion

The therapeutic use of phages is promising given the potential offered by the combined therapy of phage preparations and antibiotics, compared to monotherapy. Undoubtedly, the main challenge for the safe use of phages will be large-scale clinical trials, in accordance with the most rigorous regulatory entities. This will require the implementation of new regulations to evaluate the therapeutic efficiency of phages, which must be different from the standards established for antibiotics. Fortunately, phage therapy is now overcoming suspicions about it. Stimulated by the expected threat of a return to the pre-antibiotic dark ages, there is a major shift in the view of phage therapy and a more open attitude from government and scientific establishments. Reviews and articles on phage therapy appear more and more frequently and all this also generates a better grasp of its utilization regarding the experimental therapy, which in its current stage allows treatment for patients who have failed all the clinical options available.

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Gas plasma hydrogen peroxide (H$_2$O$_2$) sterilization

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Keywords
Sterilization
Hydrogen Peroxide- Sterilization
Low temperature
Sterilization methods

Abstract
Sterilization is a critical process and its effectiveness is vital. For this reason, the most important feature to be considered when determining the correct and effective sterilization method is determining the appropriate sterilization management for the appropriate material and ensuring the continuity. The inadequacy of High Temperature Sterilization methods has created an urge for the development of alternative methods. With the Gas Plasma Hydrogen Peroxide (H$_2$O$_2$) sterilization method, effective and reliable sterilization performance is provided for materials with lumen, and sterilization efficiency can be evaluated with lumen tests. The lumen materials used in these tests and sterilized medical devices (endoscope, bronshoscpe, etc.) are simulated. Inner diameter of Sterrad 100NX and Sterrad 100S sterilization devices min. Single channel stainless steel lumens with 0.7 mm and maximum length of 500 mm were tested using different numbers of loads. It is difficult for the sterilization agent to reach the hollow part of the device and compared to other methods, Gas Plasma Hydrogen Peroxide (H$_2$O$_2$) Sterilization is preferred because of its effectiveness. In addition to these advantages, Gas Plasma Hydrogen Peroxide (H$_2$O$_2$) Sterilization is not suitable for the sterilization of the materials containing cellulose.

Introduction

Sterilization is the process of purifying surfaces from microorganisms, and its effectiveness is very important [1]. For this reason, it is necessary to determine the appropriate sterilization management and test the effectiveness of the determined method. The inadequacy of the High Temperature Sterilization methods, which were used in the 1950s, supported the development of alternative methods. We can divide the hospital-type sterilization methods into two main groups as low temperature sterilization and high temperature sterilization. High Heat Sterilization methods were started to be used in the 1950s. These methods are; Dry Temperature Sterilization Method is Pressurized Steam Sterilization Method. However, High Temperature Sterilization methods are not suitable for sterilization due to the long sterilization period, very high heat requirement, unsuitable for fabric and rubber materials, the development of laparoscopic surgical instruments and the increase in the use of lumen materials in these surgeries. The need for new sterilization methods arose due to reasons such as Low Temperature Sterilization methods have gained diversity in order to meet these needs. The most common Low Temperature Sterilization Methods can be grouped as follows a) Ethylene Oxide (EO) Sterilization, b) Formaldehyde Sterilization, c) Gamma (Irradiation) Sterilization, d) Gas Plasma Hydrogen Peroxide (H$_2$O$_2$) Sterilization, Ozone Sterilization [2]. Among these methods, Gas PlasmaHydrogen Peroxide(H$_2$O$_2$) Sterilization comes to the fore in the sterilization of heat and humidity sensitive materials. With the H$_2$O$_2$ sterilization method, effective and reliable sterilization performance is provided for lumen materials, and it is easy to install, easy to use, short sterilization time, environmentally friendly due to no toxic residue, has no corrosive effect, and provides

safe use for users [3].Hydrogen Peroxide (H_2O_2), which is used as a sterilization agent, is injected into the environment by the sterilization device after it is placed in the area in the sterilization unit by the user, and the Hydrogen Peroxide (H_2O_2) is evaporated and dispersed in the vacuum environment. Hydrogen Peroxide (H2O2), which is a biocide, enters the diffusion stage and has a lethal effect on microorganisms. With the applied radio frequency (RF) energy, a plasma is created that will react with microorganisms and stop their vital functions. With the effect of plasma unit in sterilization systems, the amount of residue is below 1PPM TLV. It is also defined as an environmentally friendly method [4-5]. The steps of the H_2O_2 Sterilization cycle (45 min at 45 °C on average) in five successive phases; Vacuum Phase, H_2O_2 Injection Phase, Diffusion Phase, Gas Plasma Phase, Verification Phase are taking place [4].

Results

With the Gas Plasma (H_2O_2) Sterilization method, all devices sensitive to heat and humidity can be sterilized and serious economic gains are achieved. It is one of the most preferred methods, especially in the sterilization of lumen materials. With Table-1, Steam Sterilization is evaluated in terms of Ethylene Oxide (EO) Sterilization and Gas Plasma Hydrogen Peroxide (H_2O_2) Sterilization advantages and its advantages are included [6-7].

Table 1. Steam Sterilization, Ethylene Oxide (EO) Sterilization and Gas Plasma (H_2O_2) Sterilization Comparison Chart

TYPE	Steam Sterilization	Ethylene Oxide (EO) Sterilization	Gas Plasma (H2O2)Sterilization
Sterilization Method	High temperature, pressure, steam	Injection of EO(ethylene oxide) gas	Injection of Hydrogen Peroxide (H2O2) gas
Sterilization Time	Sterilization time: 10 min.-1 hour Ventilation time: Use after cooling	Duration: 2-3 hours Ventilation time: 7-10 hours Can only be used once a day	Duration: 30-60 min. Ventilation time: 0
Sterilization Agent	Steam created from high-temperature water	EO gas + CFC (Freanon) or CO2	Hydrogen Peroxide (H2O2)
Security	Special precautions must be taken to create high pressures and high temperatures.	Harmful to User/Patient Not environmentally friendly	No harm to the user/patient environmentally friendly
Setup	Electricity/ Water Supply/ Gas Pipe/ High pressure resistant boiler	Electricity/ Water Supply/ Gas Pipe/ Gas tank	Plug & Play
Effect on MIS Device	Serious damages and abrasions caused by 120-135°C high temperature and high pressure	55-60°C damage and wear from low heat and high pressure	Very limited wear effect in 50-55°C low temperature and vacuum environment

Lumen tests of the Gas Plasma Hydrogen Peroxide (H_2O_2) Sterilization method for Serrad NX and Sterrad 100S devices are summarized in Table-2, lumen material sterilization with Sterrad NX [7] and Table -3, lumen material sterilization with Sterrad 100S [7]. It has been determined that effective sterilization is performed in the loading made according to Table-2 and Table-3, which includes the length, diameter and load amount of the lumen material.

Table 2. Lumen sterilization with Sterrad NX [7]

Load Characteristic	Duration	Lumen Diameter	Length	Suggestion
Metal lumen materials	28min.	≥ 1mm	≤ 150 mm	It can be sterilized, provided that it does not exceed 10 in a normal load.
	28min.	≥ 2mm	≤ 400 mm	
	38min.	≥ 1 mm	≤ 500 mm	
In non-metal lumens (polyethylene and teflon)	28 min.	≥ 1 mm	≤350mm	Without any other load, 10 can be sterilized at a time.
	38min.	≥ 1 mm	≤1000mm	
Flexible Endoscope	38 min.	≥1 mm	≤850 mm	1 single-channel flexible endoscope can be sterilized. There should be no other burdens.

Table 3. Lumen sterilization with Sterrad 100S [7]

Load Characteristic	Lumen Diameter	Length	Suggestion
Metal Lumen Materials	≥1 mm	≤125 mm	It recommends sterilization in short or long cycles without the use of boosters/adapters.
	≥2 mm	≤250 mm	
	≥3 mm	≤400 mm	
Metal Lumen Materials	≥1 mm	>125/≤500mm	It recommends sterilization by adding booster/adaptor in short or long cycle.
	≥2 mm	>250mm/≤500mm	
	≥3 mm	>400 mm/≤500mm	
In copper and similar alloy lumens	≥3 mm	≤500mm	It recommends sterilization by adding booster/adaptor in short or long cycle.
In non-metal lumens (polyethylene or Teflon)	≥1 mm	≤1000mm	It recommends sterilization in short or long cycles without the use of boosters/adapters.
	≥1 mm	≤1000mm/≤2000mm	
Flexible Endoscope	≥1 mm	≤500mm	It recommends sterilization by adding booster/adaptor in short or long cycle.
	≥1 mm	≥500mm/2000mm	
Multi-lumen Flexible Endoscope	≥1 mm	≥500mm/2000mm	In the long cycle, it recommends sterilization by adding a booster/adaptor to each lumen.

Discussion

Medical devices (e.g., endoscopes) used in Minimally Invasive Surgical Operations (MIS), which are preferred instead of traditional open surgical operations, can be safely sterilized by Gas Plasma (H_2O_2) Sterilization method, which is one of the low-temperature sterilization methods, due to its much more expensive, complex and sensitive structure. Steam and ethylene oxide sterilization methods, which are widely used in this study, are not replaced by hydrogen peroxide sterilization devices due to high installation and operating costs, and the chemicals used pose serious risks to human health and the environment. The Gas Plasma (H_2O_2) Sterilizer, which has low operating costs and high sterilization efficiency, is user-friendly and environmentally friendly, and is preferred because of its performance in lumen material tests. However, this method should not be used for the sterilization of the materials containing cellulose.

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Novel methods to improve the plant immunity

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Keywords
Wood vinegar
Plant health
Pesticide
Biopesticide

Abstract
The aim of the agricultural activities is obtaining high quality products with higher yields without adversely affecting the ecological balance, but today the presence of the pesticide residues in agricultural products and their accumulation on the soil surface adversely affect human and environmental health. The problems arising from the excessive use of synthetic pesticides have made it important to do research on the alternative methods and on utilization of natural pesticides in plant protection studies. Wood vinegar, a product that can be used in this context, is a by-product produced by the pyrolysis of side products such as agricultural wastes, fruit peels or wood wastes at 200-600 °C in the absence of oxygen. Wood vinegar contains more than 200 chemicals, including acetic acid, methanol, phenol, ester, acetal, ketone, formic acid and many other organics. In many studies, it has been proven that wood vinegar has antimicrobial, antioxidant, antifungal effects and can be used as a biopesticide due to these effects. It has also been reported in studies that wood vinegar, which is effective in the growth of some bacterial species, also increases the fertilizer retention in the soil, and is good for plant rooting and plant health.

Introduction

Although the benefits of pesticides, which have been used for the plant protection in agricultural activities for centuries, cannot be denied, their negative effects on soil ecology and human health cannot be ignored as well. Pesticides, which remain on the soil surface for a long time, inhibit the activities of the beneficial microorganisms, reduce their numbers or make them ineffective [1]. Despite important chemicals such as glyphosate, glufosinate, diquat and paraquat used in the weed control in traditional agriculture, unfortunately many weed populations have developed resistance to these chemicals [2]. Considering all these situations, alternative new methods and biopesticides have begun to be investigated in order to minimize the damage to the soil ecology and environmental health [1].

Wood vinegar emerges as a by-product of the carbonization process, and its first use was found to date back to Neanderthal times [3]. Scientific studies on the use of wood vinegar in agriculture first started in Japan in the early 1950s. In the continuation of these studies, Japan took the efficiency and use of wood vinegar into the research agenda, and today, wood vinegar is widely used in Japan, Taiwan and Korea, and it is known that the annual production is around 14,000 tons [4].

Results

Wood vinegar is an aqueous solution of a yellowish or dark brown color with an acidic nature. Wood vinegar is derived from pyrolysed lignocellulose, the essential element of biomass (4h). Wood vinegar contains more than 200 chemicals, of which 80-90% is water, 10-20% is acetic acid, methanol, phenol, ester, acetal, ketone, formic acid and many other organics [4].

Wood vinegar, which is produced by the pyrolysis of wood waste, acts as herbicide against many broad leaf and weeds. Wood pyrolysis is a process that decomposes the biomass with a thermal system at a temperature of 200-600 ℃ without oxygen, resulting in a variety of product output such as solid coal (biochar). The main product of the pyrolysis process is biochar and the by-product is wood vinegar. Although the content of wood vinegar may vary according to the raw material used in the pyrolysis process, it has been reported that the content of wood vinegar in general terms has acetic acid content of 4.34% by weight, together with many organic acids including acetyloxyacetic acid, butanoic acid and propanoic acid [5].

Wood vinegar with antimicrobial and antioxidant properties can be used mostly as an animal feed additive, anti-odor or anti-inflammatory agent, while low doses can be used as soil or foliar fertilizer. It has also been suggested that wood vinegar, which is used in low doses, prevents harmful algae formation [2]. It has been observed that wood vinegar eliminates the fungus in the PDA medium, which is caused by the strong phenolic compounds it contains [3]. Due to the high acidity, ethanol and phenol it contains, it has bactericidal properties at high concentrations [4]. Some studies have also reported that wood vinegar restricts or completely destroys the growth ability of microorganisms such as *E.coli*, *Salmonella*, *B. Subtilis*, *S.aureus*, *Listeria monocytogenes*, *Colletothricumcapsici* and *Phytophthora palmivora* [6]. At the same time, as a result of the leaf application with the wood vinegar, it was observed that the leaves got a brighter and more lively appearance by increasing the chlorophyll thanks to the wood vinegar ester that promotes photosynthesis. As a result of the application of wood vinegar made from leaves, some bacteria die directly and the microbiological ecosystem prevents the spread of the pathogenic bacteria [4].

Discussion

In summary, wood vinegar can be used as a new alternative method, considering the harm caused by pesticides used in traditional agriculture to the environment and human health, and the resistance gained by the pests [6]. It has been stated that wood vinegar has no harmful effects on the humans and animals, if it is used in agricultural activities. It also acts by improving plant and soil quality, combating plant diseases and harmful insects, and reduces the fertilizer need by the plant during the plant growth [7]. Correct dosage and use also increases the uptake of the fertilizer components from the soil and reduces the damage of most of the diseases, regulates the conditions of nutrients in the soil, increases rooting and balances the microbiological population. The change in the microbiological population not only reduces soil-related diseases, but also increases the resilience of the roots, thus providing better uptake of the nutrients [4]. A highly diluted tree vinegar shows antioxidant and anti-bacterial activities as well [5]. More studies in the field will definitely encourage the utilization of similar products for the agricultural activities.

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Transgenic plants resistant to harmful insects

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Keywords
Resistant transgenic plant
Bacillus thuringiensis (Bt)
Cry protein
Insect

Abstract
Insects are the most common living group in the world. Fighting insects is one of the important issues today because of their negative effects on humans and plants. One of the most useful and common biological control methods is the use of preparations of *Bacillus thuringiensis* (Bt) bacteria. Bt is a gram-positive, facultatively aerobic, spore-forming soil bacterium that produces versatile proteins that have stark toxicity against the insects within parasporal crystals during the dormant phase of its growth cycle. These proteins, called Cry proteins, are divided into many groups according to their sequence similarity (Cry1-Cry67). It is aimed to obtain higher yields in agricultural production with transgenic plants resistant to weed pesticides (herbicides), insects and viral diseases, and to reduce the use of pesticides, especially insect-resistant plants, all over the world. Soy, corn, canola, potato, pumpkin and papaya are transgenic plant species cultivated in the world today.

Introduction

Increasing the yield per unit area in order to eliminate the nutritional problem that arises due to the continuous increase in the world population; agricultural production has gained more importance than increasing arable land and studies have been focused on this direction [1]. The period after the Green Revolution in crop production is called the "Biotechnology Revolution". Herbal modern biotechnological methods; it consists of the stages of finding, characterizing, isolating and transferring the desired genes to the target cell. Techniques used; it is based on the principle of placing a piece of DNA carrying the desired gene into the chromosomes in the tissue cell, and then obtaining genetically modified (transgenic, GM) plants from these cells by applying tissue culture techniques. Many methods have been applied to obtain insect-resistant GM plants using biotechnological methods. The most common of these methods today is the transfer of a gene of *B. thuringiensis* bacteria, which produces toxic proteins against the insects, to protect the cultivated plants. It is hoped that product loss can be minimized by applying this method to the maize plant [2]. Genetically Modified products protect plants against insect damage depending on the transmitted trait and contain selected genes found in the common soil bacterium, *Bacillus thuringiensis* (Bt). The Bt genome uses genetic information from the plant to produce a protein that is not harmful to human health but is toxic to the larvae of some pests. Since the insects that damage the plant cannot damage the plants with Bt, the productivity of the plants increases and there is no need for pesticide use [3]. B. thuringiensis is a member of the genus *Bacillus*, which includes more than 20 bacterial species that are gram-positive, aerobic, spore-forming and similar in basic biological characteristics. The bacterium was first seen in silkworm larvae in 1901, where fainting disease was encountered, and was isolated from there. The insecticidal activity of *B. thuringiensis* is due to protein inclusions produced during spore formation. These inclusions consist of ICP (insecticidal crystal protein) and ICPs (Cry protein or δ-endotoxin) are effective against many insect species. These proteins are toxic to insects of Lepidoptera, Diptera and Coleoptera. They are also active against Hymenoptera, Homoptera, Orthoptera, Mollophaga, Nematodes, Mites and Protozoa [2,4,5,6]. The active part of B. thuringiensis δ-endotoxin

consists of 3 separate sites. Zone 1 causes attachment to the insect gut and the formation of holes. The second region has the feature of binding to the receptors of the epithelial cells of the insect gut. The function of the 3rd region is not known exactly, but it is assumed that this region prevents the digestion of Cry toxins by intestinal proteases, provides the formation of ion channels, binds to the receptor and is responsible for insect specificity. Bt Cry proteins act as midgut toxin in insects. Proteins must be digested by the target insect in order to become active [4]. After digesting insect parasporal crystals, insecticidal proteins are activated by proteases in an alkaline (pH 8 – 10.5) medium in the midgut. ICP then crosses the midgut barriers to interact with the epithelium, forming pores, causing the loss of transmembrane potential; resulting in cell lysis, leakage of midgut contents, paralysis of the insect or death [2,7].

If the use and diversity of products with *Bacillus thuringiensis* continues to increase in this way, it is possible for many insect species and populations to acquire resistance to transgenic plants. Despite all its limitations, the "shelter strategy" is currently recognized by many experts as the most effective method of delaying the emergence of resilience. This strategy is based on finding host plants that do not contain Bt toxin, which will allow sensitive pest species to survive, near crops with Bt [1,2,5]. Not all pests are susceptible to plants with *Bacillus thuringiensis*. For this reason, secondary pests may gain advantage due to reduced competition with the main pest and cause economic losses as they did not do before. Another concern due to the use of transgenic plants is the damage these plants can cause to biodiversity and natural balance. It is thought that the transferred genes may jump to natural plant species, leading to the loss of genetic diversity in the natural species of their environment and a deviation in the natural structure of wild species. The rapid disappearance of natural species that cannot compete with genetically modified plant species threatens biological diversity as well as genetic diversity. This decrease; some insecticides are no longer used, the frequency of application is reduced or the area applied is reduced [1,2,5].

Results

There has been some public concern due to the negative effects of these new transgenic varieties, whose use is increasing day by day, on human health, environment and biodiversity. It is thought that these new features brought to plants will cause the deterioration of the environment and flora of the plant, the loss of genetic diversity of some natural species, the loss of species distribution and balance in the ecosystem and the extinction of some wild species. In order to prevent these concerns and biodiversity risks, new varieties should be developed using new methods and biotechnological methods as an alternative to genetically modified plants. For example, in order to increase the yield of already cultivated crops, traditional breeding methods of wild genotypes and/or recombinant DNA technologies can be used to obtain new varieties with high nutritional content, or crop loss can be prevented by intervening pests by modulating the plant immunity at the gene level. Although transgenic plants have some potential risks, considering the many advantages they provide, more comprehensive studies should be conducted on the subject matter [1,5].

Discussion

With this perspective, there should be more studies on generation of transgenic resistant plant species with higher yields without spoiling the nature for the future while obtaining these transgenic plants and products. Since Turkey is very rich in terms of biodiversity, genetically modified products should be handled comprehensively, especially in agricultural production. In fact, research, development, processing, placing on the market, monitoring, use, import and export of transgenic products are prohibited in our country in accordance with the "biosafety law" that entered into force in 2010. However, there are transgenic products that are allowed to enter our country, especially for some animal feeds, by obtaining the necessary permits. Another issue that should be emphasized is that it is an increasing possibility that each agricultural product we import from abroad is genetically modified. Therefore, a holistic approach should be adopted without delaying any necessary legal regulations and based on the protection of biodiversity while utilizing from these products by stringent control conditions to increase the agricultural yield in our country [1,2,5].

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Gold nanoparticles in sunscreen formulations

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Keywords
Gold nanoparticle
Sunlight
Treatment
Skin

Abstract
These days, many sunscreens are being produced. According to each skin type, sunscreen, which contains different ingredients, has not only beneficial aspects but also harmful aspects. The treatment of these sunscreens is superficial and protects from UV-B rays but not from UV-A rays. These harmful rays that can reach us from the sun, invisible to the naked eye, may cause DNA damage, cancer formation, skin aging, genetic mutations such as photo allergy and phototoxicity. AuNPS that are ultra-small, stable, absorption as properties with biocompatiple particles are known to have qualifications such as stronger irradiance and benefits to the skin. Thanks to these features, they can assist us on this topic. Furthermore, as the zinc oxide in the content of sunscreen is not absorbed through the skin, it does not harm the skin. However, recently, zinc oxides with nanoparticles have been produced. It is aimed to eliminate the white effect of zinc oxide on the skin directly. Namely, since the nanomaterial is absorbed through the skin, it is likely to cause harm, and it has been shown in some studies that ZnO causes breast cancer. Therefore, it is thought that the use of AuNP instead of ZnO may be beneficial.

Introduction

The sun's rays emit UV rays that provide the most harmful wavelengths to the skin. UV light can provoke DNA damage and genetic mutations that lead to cancer [1]. UV radiation is divided into 3 wavelengths with regard to the biological effects of these wavelengths; UVA 400-320 nm, UVB 320-290 nm, and UVC 290-200 nm wavelengths.

Sunscreens help to reduce the radiation reaching the epidermis and dermis by covering the stratum corneum surface of the skin. They have been observed as organic or inorganic substances in the form of creams, lotions, gels, or sprays that prevent the penetration of UV rays reaching the skin by causing absorption, reflection, or scattering. While the first sunscreens produced in the 1930s were only effective against UVB, new products targeting the UVA spectrum have started to be produced in recent years, with the understanding that UVA can cause cancer formation, skin aging, photoallergy, and phototoxicity. Hence, preparations with UVA+UVB combined effect have come to the fore [2]. Nevertheless, these sunscreens do not show their full protective function. So, it shows a superficial protection function. Therefore, by using AuNP, we can provide both deep protection and benefit from the natural benefits of gold to the skin. In this way, we do not have to use separate products for both sunscreens and chemical-containing products for imperfect skin. This saves us in terms of the economy.

Results

In ancient times, gold was used in the treatment of diseases such as smallpox, skin wounds, syphilis, and measles in ancient Egypt, India, and China.

Melanin production in the skin may increase and stains may occur due to aging of the skin and excessive exposure to sunlight.

Gold balances the production of this pigment and corrects the unevenness in skin tone. Gold, which activates basal cells, increases the regeneration rate of the skin and supports the removal of details that impair the skin texture, such as fine wrinkles, lines and scars.

This ingredient, which stimulates the cells, nerves, and vessels in the skin, accelerates blood circulation and provides a healthier, quality, and brighter skin structure. Gold is also a powerful antioxidant. It strengthens the skin barrier and protects the skin against free radicals that damage the skin due to environmental factors such as UV rays and pollution.

After a certain age, sagging and wrinkles appear more easily as the rate of collagen and elastin production in the skin decreases. Gold delays the formation of signs of aging by reducing the breakdown of these building blocks in the skin. This gold, which triggers cell activity, accelerates blood circulation and allows more oxygen to go to the cells, thus ensures the removal of inflammation from the skin [3].

At the same time, this element, which has antibacterial properties, improves skin texture, eliminates acne and creates a healthier skin structure in general. Gold is a noble metal and shows non-toxic properties. Gold is insoluble in water but soluble in hydrochloric acid and other acids [4].

In this study, we will examine the gold nanostructure. In nanosystems, it is very important that the nanomaterial can be targeted to the diseased area and exhibit low toxicity in addition to its high biocirculation and pharmacokinetic properties. According to conventional methods, gold nanoparticles show chemical, mechanical, optical, and electronic properties in the early diagnosis, diagnosis, and treatment of diseases.

Although nanotechnology has been utilized extensively in drug targeting and controlled release, gold nanoparticles occupy a very special place [5].

Targeted nanoparticles release the drug loads they carry to the target tissues and cells with intracellular interaction (pH, glutathione) or external stimuli (radiation).

Researchers have given special attention to gold nanorods due to their ease of synthesis and larger surface area per unit volume that can interact with light compared to other AuNP types [6].

These structures, unlike other shapes, have superior absorption and stronger light scattering properties. Seed-mediated synthesis, which is a synthesis technique, is one of the best-known methods for preparing gold nanorods and can provide higher size ratios compared to particles synthesized by other methods.

Drug release from AuNPs is mediated by internal or external stimuli. In external stimulation (external stimulation), an active substance is released with the stimulation of external stimuli such as light and temperature.

Sreejivungsa et al. investigated AuNPs containing photosensitive ligands and non-covalently bound active substances as a potential drug delivery system that can be triggered by UV light [7]. It was found that the substance was released at a higher rate.

The optical properties of AuNPs are based on their SPR properties. SPR is the resonance process that allows gold electrons to both absorb and scatter light in response to incoming radiation. As a result, an electromagnetic field appears on the AuNP surface and optical properties develop on the nanoparticle surface.

Discussion

In summary, the use of AuNP in cosmetic products is very common. We can take advantage of these features to include them in the content of sunscreens. In terms of these studies, we can enrich the content of sunscreens.

Concurrently, we can prevent the formation of skin cancer, DNA damage, skin spot problems, and the increase in aging problems. Clinical studies should be managed to prevent surface protection by using AuNP instead of ZnO (Zinc Oxide) [8].

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Gene therapy applications as treatment approach

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Keywords
Hereditary disease
Faulty gene
Gene transfer
Transformation

Abstract
What is gene therapy? It is one of the treatment methods developed to be used in the treatment of hereditary diseases. It is based on a plan to rearrange faulty gene functions with gene therapy, which is still very new research, or to replace faulty genes with healthy ones through gene transfer. The gene therapy method was first introduced by Martine Cline in 1970. Martine Cline also suggested that viruses can be vectors that can be used to perform gene transfer. In 1980, he showed that genes can be transferred by ex vivo and in vivo methods. Then, in 1990, two children were fully cured as a result of gene therapy with a retrovirus vector carrying the ADA gene by Michael Blaese and William French Anderson in severe combined immunodeficiency (SCID) disease, and thus the first successful gene therapy procedure took place.

Introduction

On being treated, some treatment modalities require expression of the corrective gene, but others may be expressed in a shorter time. Most gene delivery methods use viruses as vectors to deliver genes into cells, both in vivo and ex vivo [1]. The viral vector uses the viral genome to deliver the therapeutic gene to human body cells, thereby delivering the gene to the body. Scientists use a variety of viruses as potential vectors for gene transfer, such as adenovirus, which causes the common cold, influenza virus, called adeno-associated virus (AAV), which causes flu, herpes viruses, which cause herpes and some sexually transmitted diseases [2]. Scientists need to make sure that these viruses that will be used as viral vectors are genetically modified and inactivated so that they do not cause both a disease and spread throughout the body and infect other tissues. Most viruses infect human body cells by binding to and entering the cell, then releasing their genetic material into the stoplasm or nucleus in the human cell [3]. This genetic material is usually DNA, but some viruses contain an RNA genome. The infected human cell then acts as the host for the replication of the viral genome and the production of viral RNA and proteins. Viral proteins eventually combine to form more viral particles, and the host cell breaks down, the viruses are released and transmitted to other cells, and in this way the life cycle repeats. Viruses can be used very well as a therapeutic tool or vector in gene transfer [2-4]. For example, adenovirus can infect a wide variety of body cells quite effectively. Retroviruses such as lentivirus, even HIV, can be used as vectors because they enter the cell and copy their RNA genome into DNA and stay there permanently [5]. This process is called integration. The main reason for the use of retroviruses in gene transfer is that they can integrate therapeutic genes into the DNA of the human host cell. It ensures that gene therapy is permanent by permanently placing the genes in the chromosomes of the cells in the patient [6].

Germ cell gene therapy

In the human zygote, genetic modification of the germ cells is theoretically possible. Technologies applied in animals can in principle be applied to humans [7]. However, the aim here is germline gene therapy rather than human transgenesis.

Steps Followed in Germ Cell Gene Therapy;

- Totipotent embryonic cell isolation,
- Determination of the genetic structure of the embryo,
- culturing embryonic stem cells,
- Transfer of genetic material to embryonic cells,
- Selection of cells that receive the transfected gene,
- Selection of cells with the target gene integrated into the genome
- Marker removal
- Confirming genomic integrity
- Nucleus transfer,
- Reimplantation to the mother

The aim of germ cell gene therapy is to transfer the therapeutic gene to both body and germ cells. As a result, both the disease of the person will be eliminated and gametes with corrected genotype will be formed and healthy generations will be obtained [7]. In the germ cell gene therapy method, these changes can be transferred to future generations, since the genetic period made in the early embryo, gamete and zygote, which can form all the cells of the body, is applied with the genetic changes made in the embryo, gamete and zygote [7].

Somatic gene therapy

In somatic gene therapy, the therapeutic gene is transferred to somatic cells. Gene transfer to the patient's bone marrow, blood and skin cells is included in the category of body cell gene therapy [8]. As a result, the changes made at the level of genes and the changes made at different levels of gene therapy and the different effects of gene therapy remain only at the level of body cells and are not transferred to the germ cells and then to the next generations.

Gene Transfer Purposes Used in Gene Therapy

Transfer of genes to the recipient cell can be carried out in the laboratory (ex vivo) or in the patient's body (in vivo).

Ex vivo Gene Therapy; The cells are taken from the patient and the cloned gene is transferred by multiplying in the cell culture medium. The cells where the gene transfer takes place are selected and reproduced in vitro in cell culture and given to the patient [9]. The patient's own cells (autologous cells) are preferred as much as possible so that these cells are not rejected by the patient's immune system.

In Vivo Gene Therapy; It is the only option when in vitro culture of recipient cells is insufficient (e.g., brain cells) or when the cultured cells cannot be effectively re-implanted to the patient. The transferred gene can be delivered directly to the target tissue or the general circulation, but the vector used for delivery must be designed to be taken up only by the targeted cells or to express the gene only in the targeted cells. In this method, the success of in vivo gene therapy depends on the efficiency of gene transfer and expression (expression), since it is not possible to reproduce and select cells that have received or expressed the gene [9].

Results

How are gene therapy studies progressing?

From a chronological point of view, it is noticeable that from 1990 to 1999 there was a rapid increase in the number of clinical gene therapy trials Although there was a stable period for a short time in 2002-2003, there was a renewed increase in annual approved clinical gene therapy trials thanks to the path taken and the achievements of clinical trials in recent years [9].

In which countries is it made?

We can say that a clinical gene therapy trial has been conducted in 29 countries. The United States leads with 975 gene therapy clinical trials (63.4%). The United Kingdom ranks second with 184 studies (12%). These countries are followed by Germany (4.9%) with 76 studies, Switzerland (3%) with 46 studies, and France (2.7%) with 41 studies [10]. The numbers recorded in the clinical gene therapy database may be much lower than the actual numbers. For example, although it is reported that there is only one officially approved study in Russia, in reality it is known that a much larger number of clinical gene therapy trials are being conducted. In addition,

despite the fact that there are more than 50 studies in Canada, only 20 of them have been registered in the database of gene therapy clinical trials [10].

Targeted diseases

Gene therapy was initially developed as a method of treating hereditary single-gene diseases. However, today, the majority of gene therapy clinical trials (% 64.6), is one of the most common and deadly diseases; and multigenetic has a mechanism to treat cancer are used.

After all, at the moment, approaches to treating hereditary single-gene diseases give the most successful results in gene therapy clinical trials conducted so far, but it ranks third in the ranking, accounting for only 8.1% of total clinical trials [10].

Genes transferred to humans

In gene therapy clinical trials, more than 200 genes are transferred to humans using the methods mentioned above (viral and non-viral methods). It is necessary to say that the genes transmitted to humans in this way are mostly aimed at treating cancer, which is one of the most common and deadly diseases. In this context, the immune system genes that encode tumor antigens trigger (19.9%) was cytokine genes (% 18.7), tumor suppressor genes (% 10.8), pushed the genes that cancer cells to commit suicide (% 7.1), receptor genes (5.4 percent) of the genes in this study preferred one [10].

7.9% of the genes used in gene therapy clinical trials are genes encoding reproductive factors, and almost all of these genes are used to treat cardiovascular diseases. Genes used for gene transfer to treat hereditary single-gene diseases (deficiency genes) also make up 7.4% of the genes used in all trials [10].

As a result, although the gene therapy method is a new method, it is believed that if the research gives a positive result, it will greatly contribute to the treatment of many hereditary diseases [10].

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Novel anti-cancer drug candidates with immunotherapeutic potentials

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Keywords
Phenothiozine
Derivatives
Anti-cancer activity
Immune system
Colon Cancer
Macrophages

Abstract
Cancer is a group of diseases that occurs when cells grow rapidly and uncontrollably, divide and metastasize to the other tissues and organs. In addition, it was stated that the total number of cases worldwide in 2018 was 18.1 million, while the death rate was 9 million. In cancer therapy, treatment is done by using radiotherapy, chemotherapy, surgical intervention and various other anti-cancer drugs. These methods damage normal cells as well as cancerous cells, and their side effects are versatile and severe. It is important to do research and develop the potential specific drug candidates with fewer side effects. In addition, the immune system is of great importance because of its effects in the emergence and development of cancer and in preventing its spread to the other tissues. It is known that cancer cells have an interplay with the immune system cells which eventually leads to the suppression of the anti-tumor activity. Therefore, various immunomodulation methods as part of cancer immunotherapy have been developed and utilized in the field. Phenothiazine derivatives, which have a wide range of uses, are very important because of our ability to generate novel varieties with different functions as anti-cancer drug candidates. In our study we are aiming to generate and characterize novel phenothiazine derivatives and decipher their anti-cancer as well as immunomodulatory activities.

Introduction

Colon cancer ranks third among the cancer types in terms of the mortality [1]. Colon cancer is diagnosed with more than 1 million new patients annually in the world and its incidence is third among other cancer types [2]. It has been reported that an average of 600,000 people die annually due to the colon cancer. Colon cancer occurs more frequently in men than in women [3]. Various treatment methods are used, but they cannot be cured completely. Various drug candidates are being investigated in these treatment methods. Phenothiazine derivatives form the basis of drugs in different fields, some of which are used in drugs for diseases such as Schizophrenia, Parkinson's, Alzheimer's, and migraine. In addition, it is used as anti-helminthic (insecticidal), insecticides [4], as a sedative, antispasmodic, anti-bacterial and anti-fungal, etc. It has also been used in alleviating the side effects of chemotherapy and its anti-tumor activity against different cancer cell lines have been studied.

Results

Cancer is one of the diseases that causes the most deaths in the world, and since the side effects of the methods used for treatment are very high, new agents with minimal side effects should be investigated. Chemotherapy, one of the techniques used in the treatment of cancer, is also known as drug therapy. It aims to cause damage by preventing cancer cells from growing and multiplying. The purpose of the chemotherapy drugs is directly destroying the cancer cells without harming normal cells in the body. But one of the biggest problems in this

treatment method is that it seriously damages normal cells and chemotherapy agents cause very severe side effects. For these reasons, researchers are still working on the production and design of new agents. In the synthesis of widely used phenothiazines, a change in the skeletal structure causes a wide variety of changes in their biological activities. These derivatives are used both in the industrial and medical fields. Therefore, it attracts attention in many areas and is used in drugs for the treatment of different diseases. It has been previously investigated in many studies that phenothiazine derivatives have anti-oxidant, anti-cancer, anti-tumor, antifungal, and anti-bacterial activities [5,6].

Macrophages, one of the most important cells of the immune system, form the first immune response of the innate immune system against the infections. Macrophages are one of the most important cell types in terms of being cells of both the hereditary immune system and the adaptive immune system, by functioning as antigen-presenting cells and producing pro-inflammatory cytokines [7,8]. Macrophages have many tasks, they can perform phagocytosis, provide wound repair, produce enzymes, cytokines and reactive oxygen species. As a result of excessive stimulation of these cells, inflammation occurs, pro-inflammatory cytokines are produced and lead to chronic inflammatory diseases and autoimmune diseases. Macrophage cells provide defense by synthesizing inflammatory mediators, namely cytokines and reactive oxygen species, and activating the immune system against tumor cells. Cytokines are non-structural protein or peptide molecules that establish communication between cells. These molecules take different names according to the tissues that they are produced and their functions change accordingly. Some of them can be listed as interleukins, interferons, tumor necrosis factors, chemokines. It is known that macrophages partially support cancer after a certain stage due to the suppressive messages they get from the tumor cells.

Pro-inflammatory cytokine production is provided by activating macrophage cells stimulated by LPS. Due to the relationship between macrophage cells and cancer, colon cancer treatment is provided in the presence of phenothiazine derivatives, while its effect on the immune system cells is also important to determine its immunomodulatory hence cancer immunotherapy potentials.

Discussion

According to literature reviews, the methods used in the cancer treatment led to damage to the other healthy cells in the body, and it is very important to develop novel and better methods. Since the drugs used in chemotherapy, which is one of these methods, cause too many side effects, it is necessary to develop a more effective drug candidate [9]. The activities of phenothiazine derivatives, known for their anti-tumor effects on the cancer cells and many other drug activities, on colon cancer cells and the immune system cells should be examined more extensively to determine their drug potentials [5,6]. The ability to develop drug candidates for cancer therapy and other diseases is critical, therefore new and more effective agents must be designed and tested more rigorously.

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Converting small-scale aquaculture systems from characterization one to an indicator system for assessing sustainability and its contribution to food safety

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Keywords
small-scale aquaculture,
sustainability,
 indicators,
conservation,
food safety

Abstract
In the last decades the contribution of small-scale aquaculture to particular areas of Albania has played important role for income generation and helped towards goals for sustainable rural development. Given to the fact that these systems: (i) are lacking health standards for securing requirements of food safety; (ii) are not integrate din the local territorial development of regions and (iii) there is a poor integration of development practices into conservation approaches, this study aims at establishment of set indicators that measure the role of aquaculture into sustainable economy and food safety. So, it describes the scientific needs of converting approach from simple characterization of small-scale aquaculture towards the indicator system. Following FAO examples, best practices, and different references the indicator system includes a roster of economic, health state, incidence of disease, value chain, contribution to local economy, gender access to resources, employment generation, etc. In our approach from the potential indicators, a matrix was developed showing the rationale for the indicator, the means of measurement and the methods of data collection in the Albanian circumstances of small-scale farming system. From the list of initial ca. 40 indicators, we narrowed the list to 13 indicators that will assess the contribution of small-scale aquaculture to sustainability, integration to conservation approaches and food safety.

Introduction

The contribution of small-scale aquaculture to global aquaculture production as well as rural livelihood development is generally well recognized [1,2]. These include providing livelihoods and income generating opportunities for rural communities, enhancing food security, improving social equity and enhancing the quality of life of rural poor communities [3]. The aim of this paper is to introduce the FAO approaches and best practices with regard to aquaculture indicators and assessment of its sustainability and contribution towards food safety. Following different references [1] the indicator system that includes a roster of economic, health state, incidence of disease, value chain, contribution to local economy, gender access to resources, employment generation, etc. In our approach from the potential indicators, a matrix was developed showing the rationale for the indicator, the means of measurement and the methods of data collection in the Albanian circumstances of small-scale farming system. From the list of initial ca. 40 indicators, we narrowed the list to 13 indicators that will assess the contribution of small-scale aquaculture to sustainability, integration to conservation approaches and food safety. In line to UN developments and in order to support SDG action, Albania has prepared an SDG baseline report to explore the specific components of the National Strategy for Development and Integration (NSDI) components [4]. Albania's baseline report underscores that the national strategic policy framework is most harmonized with the SDG targets in SDG 14 (life bellow water); SDG 14 life bellow water) is directly connected with aquaculture production and its role in prosperity of the local economies and directly contributing at the biodiversity conservation.

The standard definition of sustainable development has been expanded by the 2002 World Summit on Sustainable Development to include three major pillars: economic, social and environmental. The review of three pillars of sustainable development [5] has underlined that while the three pillars are acceptable to most nations, no agreement was made on details. The major variants are in terms of the social pillar. These variants include social development or social progress (a generic one); human development, human well-being or people; and lastly, one that focuses on issues of justice and equity, i.e., "social justice", "equity" and "poverty alleviation" [2].

(a)
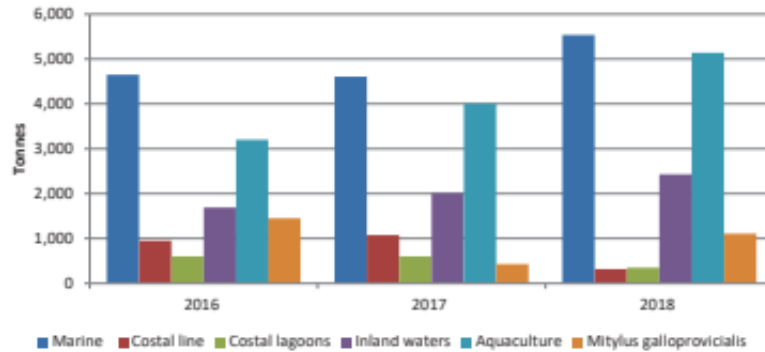
Categories	In tonnes		
	2016	2017	2018
Total fishing	**12,534**	**12,719**	**14,875**
Marine	4,646	4,609	5,537
Costal line	952	1,074	315
Costal lagoons	598	599	350
Inland waters	1,688	2,007	2,427
Aquaculture	3,200	4,000	5,138
Mitylus galloprovicialis	1,450	430	1,108

(b)

Figure 1. (a) Contribution of fishery and aquaculture in total production in Albania; (b). Production in tones of main categories (INSTAT, 2019)

Following [6] the fish catch during 2018 has increased by 20.0 % compared to 2017. The Aquaculture sector has risen rapidly as a new sector with perspective. During the year 2018, were cultivated in different reserves and specialized fish tanks about 5,138 tonnes of fish or 28. 5 % more than 2017. This amount represents approximately 35.0 % of the total fish production, following the marine fishery production by 37.0 %.

Material and Methods

Fish catch data (fish and aquaculture production) are collected by water categories and mostly are based on official sources (INSTAT, 2018). The aquatic fisheries categories are: marine fishing, brackish waters, lagoons, inland waters, aquaculture and molluscs.

Development of indicators is based on two major sources of physical macroeconomic indicators are the National Accounting Matrix including Environmental Accounts (NAMEA) and the Material Flow Accounts (MFA), which are closely related to environmental accounts [2, 7]. The NAMEA provides indicators for major environmental policy themes: climate change, acidification of the atmosphere, eutrophication of water bodies and solid wastes.

Results and Discussions

In line to national policy for biodiversity conservation [8] and from an environmental perspective, the goal for sustainable aquaculture is to ensure that society benefits not only from the production of food and materials but also from the maintenance, restoration or enhancement of ecosystems services such as the protection of mangroves and other wetlands, corals, watershed, water resources, soil, and the biodiversity that depends on them [7].

One of the biggest problems with developing indicators of sustainability is that frequently the best indicators are those for which there is no data [7], while the indicators for which there is data are the least able to measure sustainability, which usually leads to the choice of traditional data sources and measures for indicators. This is a typical case for the developing countries including Albania.

Table 1. Indicators, their measures and possible data sources (Derived and adapted from [8])

Sustainability Indicators	Measures	Data Source
Investment into farm improvements	Quantitative on farm information	Farmers
Loan repayment/loan default	Quantitative – No. of farmers; percentage repayment	Bank, financial institution, lenders
Farm workers' wages compared to other sectors	Quantitative – community information	Government labor office, job brokers, farmers
Diversity of farm products	Quantitative on farm information	Farmer, local market
Ready availability of farm workers/non-seasonality of labor	Qualitative expressed in a scale: Low-Medium-High	Key informants, farmers
Lack of conflicts	Quantitative (frequency) or scale (Low-Medium-High); Number, nature of and intensity	Local government, key informants in community
Membership in an active farmer association or group (FMO-Albania)	Quantitative: presence of association and membership; also, qualitative such as status of association and even motivations for membership.	Farmer association officers; key informants
Rapidity and prevalence (among farmers) of adoption of new practices	Qualitative: adoption rate and speed of adoption; quantitative: adoptors and non-adoptors	Extension workers, farmers, key informants
Preference for the products of the farm	Qualitative: Scale or Yes/No	Traders, buyers, local market
Percent of recycled farm waste	Quantitative on farm information	Farmer
Lack of conflicts	Quantitative (historical frequency) or Scale: Low-Moderate-High	Key informants, farmers
Non-use of antibiotics and chemicals	Yes/No; If yes, in which operations are they used?	Farmer, extension worker, traders
On farm soil and water conservation structures and practices	Yes/No or Low-Medium-High	Farmer, extension worker

Conclusion

In context of this study the practical use of sustainability indicators is that they provide guides to an integrated approach to sustainable development. Such approach enables to problem solving at both the farm and local community levels. It would also be a useful basis for integration to local and regional planning practices, development planning that considers also the small-scale farmers.

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Phytochemical and antimicrobial activities of *Cistus incanus* L., samples from Central Albania

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Abstract
From immemorial time plants have been the basis for medical treatments for different human disorders and diseases. At the current circumstances, researchers are increasingly interested in medicinal plants as alternative medicine, due to their good pharmacological properties, fewer side effects, and low cost. The genus *Cistus* L. (Cistaceae) comprises many interesting medicinal plants, distributed primarily in the Mediterranean region. The purpose of this study is to present the Phytochemical and Antimicrobial Activities of Cistus incanus L. samples From Central Albania. The phenolic contents in aqueous and hydromethanolic extracts of CS were found to be from 390 - 425 mgGAE/g edw. Moreover, mineral and phenolic contents of CS and CM were analyzed. The extracts of samples exhibited potent antioxidant activity in all used systems and possess strong inhibitory effect towards α-glucosidase (IC50: 0.97 ± 0.14 to 14.62 ± 1.21 μg/mL). Furthermore, the result showed high levels of phenolic content and unexpectedly some higher levels of mineral content in CS. The results suggest that the phenolic rich extracts of CS and CM may have a therapeutic potential against diseases associated with oxidative stress and may be useful in the management of hyperglycemia in diabetic patients.

Introduction

In the Albanian economy Medicinal & Aromatic Plants (MAPs) hold a very special place within national economy. Following [1] during the communist era, exports of MAPs earned close to $50 million. The domestic consumption of MAPs has always been very limited. Currently the MAPs continue to be a large export earner for the country at a size of $28million, or about 18% of total agricultural exports [2]. Also at the micro-economy level, MAPs contribute to a large portion of income of a household. In northern Albania, income from MAPs contributes to ~35% of total income.

Following different references [2], in Albania there are about 200 species of MAPs that are traded in the international market. Of these, the largest is sage, contributing to about 33% of the total export volume as against about 50% five years ago.

The genus *Cistus* L. (Cistaceae) comprises many interesting medicinal plants, distributed primarily in the Mediterranean region. Among them, twelve species are members of Albanian flora. *Cistus* species are frequently used in traditional medicines for the treatment of hyperglycemia and diabetes [3,4], peptic ulcers, and diarrhea and also as general remedies for several skin diseases and as anti-inflammatory and antispasmodic agents [4]. Furthermore, phytochemical studies on different *Cistus* species have revealed the presence of several phenolic compoundsmainly flavonoids and tannins [3]. Following different sources those compounds are generally involved in many biological activities, essentially in oxidative stress prevention.

According to [4,5] the diabetes mellitus is a serious chronic metabolic disorder that causes serious health complications and is a major cause of mortality [5]. Excessive postprandial glucose excursions are a known risk factor for developing diabetes. One interesting approach for limiting the excursion is to inhibit the activity of digestive enzymes of glucose production such as α-amylase and α-glucosidase.

The Cistus species are rich in polyphenolic compounds (the main components are polyphenolic compounds, commonly known as catechins). This characteristic makes these plants able to withstand extreme conditions. The metabolism of polyphenols protects the plants against different stresses, whether biotic or abiotic [6, 7].
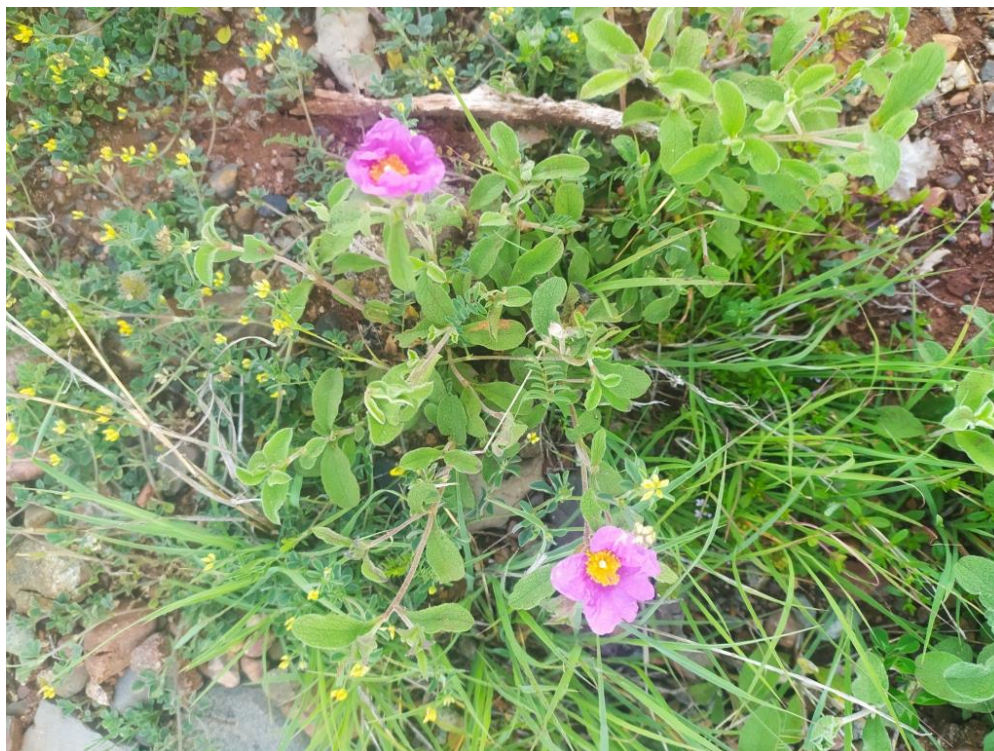
Figure 1. *Cistus incanus*, National Park Shebenik Jabllanica

Material and Methods

Plant Material: Cistus incanus L. were collected in May 2021 from the area of National Park Shebenik-Jablanica (east Albania). The aerial parts were cleaned and dried in the shade at room temperature until reaching a constant weight and were then powdered and used for further investigation.

Preparation of Plant Extracts: For hydromethanolic extract preparation (hydromethanolic extract of Cistus incanus (CSM) and hydromethanolic extract of Cistus incanus (CMM)), 50 g of dried sample was extracted with 500mL of 80% aqueous methanol at room temperature and under mechanical stirring for 24 hours. The GC-MS analyses were carried out using a Hewlett-Packard 6890.

Results and Discussions

Total phenolic, flavonoid, and proanthocyanidin contents are presented in Table 1. Following the analyses of *Cistus incanus* samples the phenolic contents in aqueous and hydromethanolic extracts of CS were found to be 399 mgGAE/g edw and 340mg GAE/g edw, respectively. Results of flavonoid and proanthocyanidin contents show that hydromethanolic extraction resulted in significantly higher values of those compounds in analysed samples. Based on detailed analyses the amounts of flavonoid and proanthocyanidin in hydromethanolic extracts of CS and CM, respectively, were 185mg RE/g edw, 159mg CE/edw, 155 mg RE/g edw, and 186.2mg CE/g edw, while in aqueous extracts they were 133 mg RE/g edw, 151 mg CE/g edw, 81mg RE/g edw, and 153 mg CE/g edw, for CSA and CMA, respectively. It is worth to mention that similar results are revealed by [3] where the phenolic contents of other *Cistus* species plants indicate an important health promoting activity. Those compounds are secondary plant metabolites involved in the normal growth and development and act as defense mechanisms of plants against pathogenic and parasite infection and free radicals' generation. Further on [3] emphasizes that the phenolic compounds have been reported to have multiple biological effects and are considered as a major group of chemicals that contribute to the antioxidant potential of plant extracts.

Table 1. Total phenolic, flavonoid, and proanthocyanidin contents

	Phenolic content	Flavonoid content	Proanthocyanidin content
CSA	399	185	159
CSP	340	153	161
CMA	378	133	151
CMM	369	146	81

The results are expressed as (1) mg of gallic acid equivalent, (2) mg of rutin equivalent, (3) mg of catechin equivalent

CSA: aqueous extract of *Cistus incanus*; CSM: methanolic extract of *Cistus incanus*; CMA: aqueous extract of *Cistus incanus*; CMM: methanolic extract of *Cistus incanus*.

Conclusion

The aqueous and hydromethanolic extracts of the aerial parts of *Cistus incanus* L. samples from National Park Shebenik-Jabllanica (East Albania) presented considerable contents of phytochemical and antimicrobial activities compared with values of other species of genus Cistus. The results suggest that the CS and CM extracts may have therapeutic potential against diseases associated with oxidative stress. This study recommends the importance of further studies to this and other species of spontaneous flora.

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Antioxidant activity of Vitex Agnus Castus subcritical CO₂ extracts from two different regions of Albania

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Keywords
Medical plant
Vitex agnus castus
Extracts
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GC-FID

Abstract
Medicinal plants include various types of botanicals used in herbalism, known and employed for their variety of medical usefulness. Recently, there has been a great interest in obtaining natural antioxidants from plant materials, as studies show that most of them possess significant antioxidant activity, and some of their phytotherapeutic potential properties include antimicrobial activity, antineoplastic, antidiabetic, anti-atherosclerotic, immunomodulatory, and in some cases, renoprotective or hepatoprotective effects are observed. The aim of this study is to differentiate the biological activity of the same plant (Vitex agnus castus) as a result of geographical variety. The plants used for this study are harvested in two separate Albanian regions, (Milot and Qeparo) extracted with subcritical CO2 extraction method. The extracts were analyzed for antioxidant activities using the DDPH assays and the composition of the botanical extract was analyzed with 436-GC FID detector (Scion Instrument). The major compound detected in black and green fruits of Vitex agnus castus, collected in Milot, was (E)-trans- β- respectively 22.01% and 20.47% and in CO2 extracts of Qeparo fruits (E) - Farnesene 20.1%. The plants collected in northern Albania resulted with a higher antioxidant activity compared to the plants collected in southern Albania. A significant difference was also noticed between the two maturation stages of the Vitex agnus castus fruit, the black fruit resulted to be more active than the green.

Introduction

For years, medicinal plants have been a valuable source of therapeutic agents, and still many of today's drugs are plant-derived natural products or their derivatives [1]. Natural products, especially those of vegetable origin, have always been an important source of therapeutic agents. About 25%–30% of drugs available for the treatment of diseases are derived from them [2]. Medicinal plants are the richest natural resource of drugs for traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs [3]. Vitex agnus castus is one of 250 species of Vitex genus native to the Mediterranean region and Asia. Vitex agnus castus L. was formerly classified within the family of Verbenaceae, but now the phylogenetic classification located it in Lamiaceae. It is cultivated in warm temperate regions of the world, and obtained primarily from Mediterranean countries, especially Albania and Morocco [4].

The fruits have been applied for more than 2500 years in ancient Egypt, Greece, Iran, and Rome for a variety of gynecologic problems. It has been used for its claimed activity for reduction of libido [5]. The fruit of Vitex agnus castus has been recommended as carminative, energizer, sedative, antiepileptic [6], anaphrodisiac, emmenagogue agent and antispasmodic [7]. Fruits of Vitex agnus castus have been also used in the treatment of many female conditions, including menstrual disorders (amenorrhea, dysmenorrhea), premenstrual dysphoric disorder (PMDD), corpus luteum insufficiency, hyperprolactinemia, infertility, acne, menopause, disrupted lactation, cyclic breast pain, cyclical mastalgia and inflammatory conditions, diarrhea and flatulence. Other effects of this plant include tumoricidal, antioxidant, immunomodulatory, antimicrobial, antifungal, fracture healing, digestive complaints, infertility, acne and also for lactation support [8,9].

Material and Method

The plants used for this study are harvested in two separate Albanian regions, (Milot and Qeparo) extracted with subcritical CO_2 extraction method. In Milot, there were collected two types of plant fruit in two different maturation stages, the black and the green fruit. These samples were then placed in a shady room to be naturally dried. After they were completely dried, the fruits were separated from the flowers. The fully dried samples were cut into small pieces before extraction procedure began.

Antioxidant activity assay.

The DPPH radical scavenging antioxidant assay was employed to estimate antioxidant potential of Vitex agnus castus fruit extracts, obtained by subcritical extraction method. The interaction between the latter and the DPPH in an ethanol solution is monitored through the measuring of absorbance at 517 nm using spectroscopy.

Chromatographic analysis

The botanical extract was obtained by subcritical CO_2 extraction method and further analyzed for volatile compounds by chromatograph model 436-GC, flame ionization detector (FID) by Scion Instrument, using nonpolar-low polar column (60m x 0.32 mm, 0.1um df) with following parameters: injection temperature 180°C, oven temperature 70°C, detection temperature 280°C, carrier gas flow 1ml/min, volume of injected extract 2 ul [10].

Results

Table 1. IC_{50} and R sq valeus of each extraction

Sample	IC_{50}	Rsq
CO_2 extract of black fruit colected in Milot	0.01104	0.9904
CO_2 extract of green fruit colected in Milot	0.01969	0.9714
CO_2 extract of fruit colected in Qeparo	0.04758	0.9852
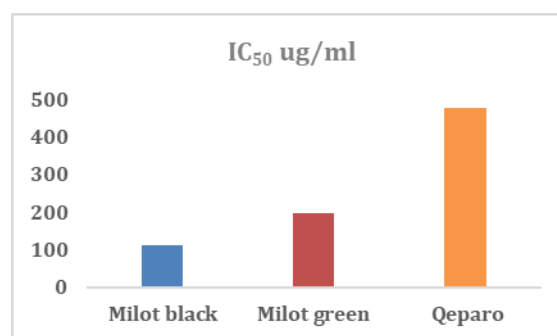
Figure 1. Comparison of the IC50 of different regions plant harvesting. Analyzed with [Inhibitor] vs. Response (three parameters). Valeus represent means±SD.[*]p<0.033; [**]<0.002; [***]<0.001

Table 2. GC-FID results of subcritical CO2 extracts of black and green fruit of Vitex agnus castus collected in Milot.

No.	Black Milot [%]	Green Milot [%]	Compound	No.	Black Milot [%]	Green Milot [%]	Compound	No.	Black Milot [%]	Green Milot [%]	Compound
1	5.91	4.87	(E)-Caryophyllene	11	4.53	4.52	α-Terpinyl acetate	21	1.43	1.3	Globulol
2	22.1	20.47	(E)-trans - β- Farnesene	12	0.87	0.99	α -trans-Bergamotene	22	1.57	1.51	Ledol
3	1.1	1.63	(Z)--Farnesene	13	0.61	0.63	β -Acorenol	23	0.31	0.61	Limonene
4	8.79	6.41	1,8-Cineole	14	7.55	13.53	Bicyclogermacrene	24	3.5	2	Manool
5	2.05	2.73	7- α -Hydroxy-manool	15	0.79	0.87	Bicyclo-vetivenol	25	2.33	1.44	Myrcene
6	1.12	1.02	α- Terpinene	16	3.69	3.58	β-Phellandrene	26	0.81	0.94	Pimaradiene
7	2.82	2.72	α-Gurjunene	17	0.63	1.62	β -Pinene	27	2.06	2.17	Sabinene
8	1.4	1.39	α -Phellandrene	18	1.47	1.18	cis-Sabinene hidrate	28	3.11	2.07	Spathulenol
9	3.96	2.84	α-Pinene	19	1.02	1.04	Citronellyl-acetate	29	0.31	0.69	Terpin-4-ol
10	10.3	11.28	α-Terpineol	20	0.29	0.75	epi- α -Cadinol7	30	0.98	0.75	Trans-γ-Cadinene
								31	2.59	2.45	Viridiflorol

Table 3. GC-FID results of subcritical CO_2 extracts of fruit of Vitex agnus castus collected in Qeparo

No.	%	Compound	No.	%	Compound	No.	%	Compound
1	1.04	cis-Sabinene hidrate	11	12.37	α-Terpineol	21	0.94	Citronellyl-acetate
2	0.44	Limonene	12	1.11	Ledol	22	3.65	β-Phellandrene
3	2.33	7-α-Hydroxy-manool	13	1.10	α-Phellandrene	23	1.00	Globulol
4	4.28	Sabinene	14	1.07	(Z)-Farnesene	24	2.75	epi-α-Cadinol7
5	10.30	Bicyclogermacrene	15	1.76	Viridiflorol	25	4.71	α-Pinene
6	0.59	Trans-γ-Cadinene	16	0.54	β-Acorenol	26	1.25	β-Pinene
7	3.00	Spathulenol	17	7.22	1,8-Cineole	27	0.64	Pimaradiene
8	0.65	α-trans-Bergamotene	18	5.37	Manool	28	1.21	Myrcene
9	0.48	α-Terpinol	19	5.37	α-Terpinyl acetate	29	1.32	α-Gurjunene
10	0.58	Terpin-4-ol	20	2.32	(E)-Caryophyllene	30	0.60	Bicyclo-vetivenol
						31	20.01	(E)-Farnesene

Discussion

The GC-FID analysis was carried out using standards of the main compounds. The results were interpreted based on the studies done on Vitex agnus castus in Albania and nearby regions.

The major compounds detected in CO_2 extracts of black and green fruits of Vitex agnus castus collected in Milot, was (E)-trans- β- Farnesene respectively 22.01% and 20.47% a sesquiterpene, a group typically extracted with CO_2; α –Terpineol 10.3-11.28%; Bicyclogermacrene 7.55-13.53%. Regarding Qeparo fruits, extract major compounds found were (E)- Farnesene20.01%; α –Terpineol 12.37%; Bicyclogermacrene 10.3 %. There are no significant differences between black fruit and green fruit content of compounds. However, the green fruit extracts had a slightly higher percentage of compounds. CO_2 extraction has an advantage compared to other organic solvent extraction methods when it comes to the isolation of compounds with high volatility. The antioxidant activities were measured using the DPPH assays. In general, all the extract samples showed a high antioxidant activity. In the DPPH assay, the elevated antioxidant responses are probably due to the phenolic components of the studied extracts. The extract of the black fruit of Vitex agnus castus collected in Milot showed higher DPPH radical scavenging activity than the green one and Qeparo fruits.

Conclusion

Our survey data obtained shows that there is indeed a correlation between the region where the plant was harvested and the maturation of the plant, with the extract biological activity. The extract of the black fruit of Vitex agnus castus collected in Milot showed higher DPPH radical scavenging activity compared to the green one and fruits collected in Qeparo. No significant differences were found on the concentration of major component regarding volatile compounds identified by GC-FID.

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Towards 3D CNN for precise crop yield estimation using multimodal remote sensing data: Case study of wheat in Morocco

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Keywords
Precision agriculture
Yield estimation
Deep learning
Remote sensing
3D CNN

Abstract
Crop yield is a primary measure in Moroccan agriculture, with various connections to human needs. Its estimation represents a troublesome task in light of its fundamental relation to crop market planning. Conventional techniques are simple, but require human effort and time. Advancement has been made in remote sensing by using deep learning architectures. This paper discusses different estimation techniques and presents a methodology to estimate wheat yield based on multimodal remote sensing data and exploiting 3D CNN (3-Dimensional Convolutional Neural Network) architecture which can be used to extract dynamic features over consecutive time. Unlike the 2D convolution kernel, which only moves in the two dimensions of height and width and passes through images horizontally and vertically, the 3D kernel establishes convolution while adding an additional dimension generally represented by time and therefore moves through these three dimensions. Our paper suggests this architecture as a methodological solution to develop a precise yield determination.

Introduction

Agriculture provides food, fuel, and natural substances, which are all fundamental for human life [1]. To meet this demand, farmers and policymakers are working hard to improve crop yield. Despite the possibility of cropland extension [2], the accentuation ought to increase production within actual agricultural lands to avoid harmful effects on the environment.

For a long time, yield samples have been among conventional techniques to estimate agricultural yield. The principle of this method is the exploitation of a piece of iron with a square shape placed at random in a plot to count all the plants in it [3]. To lay these squares, we determine the area of the plot and identify the diagonals. For a plot of a minimum of 1 ha, each diagonal must have five samples while avoiding edges, whereas for plots having an area of less than 1 ha, it is necessary to place two to three squares per diagonal, without having less than four squares in total. To calculate yield using the square, we divide the total amount of harvest weighted by the area of the considered yield square. Crop simulation models can simulate the growth of agricultural crops [4]. They can work at different scales and help replicate key plant development processes in detail. Statistical models have been mainly used to develop an empirical relationship combining many current season yield characteristics with historical yield data [5]. More than a linear regression approach for predicting crop yield has been developed and used by studies dealing with crop yield estimation.

Recent advances in sensor technology have infiltrated agriculture, so different remote sensing systems are now available and allow generating data and providing relevant results to optimize various agricultural products. These systems offer temporally relevant spatial data on land surfaces at different scales [6].

Deep learning, a subfield of machine learning, has a significant advantage in agriculture, especially in estimating yield. Mu et al. [7] reported that deep learning, specifically convolutional neural network, can extract specific characteristics of crop growth and use it with multitemporal MODIS (MODerate resolution Imaging Spectroradiometer) data to predict winter wheat yield. Their results showed that winter wheat yield based on remote sensing time series images correlates strongly with yield. They had Pearson R and RMSE (Root Mean Square Error) values of 0.82, 724.72 kg.m-2 and concluded that CNN represents an essential technical reference for the large-scale crop yield prediction. At the same time, Wang et al. [8] estimated the winter wheat yield using LSTM (Long Short-Term Memory) networks for meteorological data with AVHRR (Advanced Very High-Resolution Radiometer) inputs and convolutional neural networks for static soil characteristics inputs; their model performed well, with an overall R^2 and an RMSE of 0.77 and 721 kg/ha, respectively. Garcia et al. [9] determined corn yield using UAV (Unmanned Aerial Vehicle) images with different multispectral vegetation indices, RGB, canopy cover, and plant density in a multilayered perceptron model; their results demonstrated that neural networks had a high correlation coefficient and the spectral data collected by remote sensors mounted on UAV and processed into vegetation indices, canopy cover and plant density data is extremely useful and have more sense in characterizing and estimating agricultural crops.

Material and Method

Our study focused on estimating wheat yield in Morocco by exploiting multimodal remote sensing data. Our study area concerns the region of Rabat-Sale-Kenitra, which is considered among the best ranked in cereals production in Morocco. We started our methodology by acquiring UAV imagery using different sensors and the extraction of multimodal informations, ground field yield, and other auxiliary data collection, which can improve the DL (Deep Learning) model results. The use of deep learning is especially proposed to capture the non-linearity that exists between yield data and predictors; in particular, the 3D CNN (Fig. 1) is proposed to allow the processing of temporal data and, at the same time, the ability to explore the spatial information and its variety when it comes to crop yield. A detailed methodological diagram is presented below (Fig. 2).
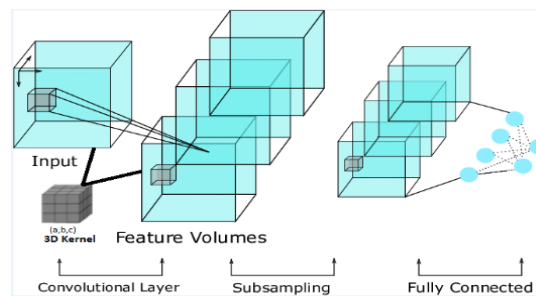
Figure 1. Architecture of 3D CNN (modified [10])
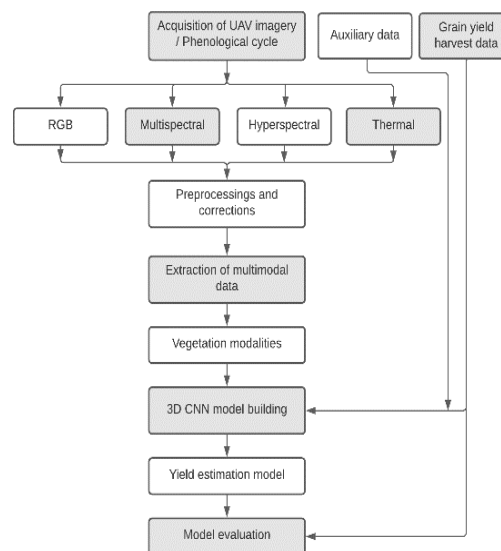
Figure 2. Methodological workflow of our study

Results and perspectives

Our research project particularly aims to demonstrate the advantage and the accurate estimation provided by deep learning algorithms, in particular three-dimensional convolutional neural networks. The latter will undoubtedly make it possible to determine the agricultural yield, whether it is that of wheat or another crop, given its particularity in capturing different dimensions of aerospace imagery. Our research project is still in progress and aims to demonstrate all these hypotheses.

Discussion

We have focused on estimating crop yield through our methodology, more specifically wheat as a crop. The reason behind the choice of combining remote sensing multimodal data is, in particular, to group together all the characteristics that describe a crop as long as the majority of studies have focused on vegetation indices which consider them alone to be able to reflect the relationship between plants and their yields, this is the case for example of the work carried out by Astaoui et al. [11]. Also, the choice of features which corresponds perfectly to the type of crop considered and not to vegetation and its cover, in general, have been little explored. To collect all these multimodal data, it is indeed remarkable that they are spread over the entire period of growth, and this is why we have opted for the 3D CNN architecture, which can process both spatial and temporal aspects when it comes to crop yield.

Conclusion

This study explored the precise estimation of agricultural yield by exploiting remote sensing imagery, particularly multimodal data. Our methodology is mainly based on acquiring images from various UAVs sensors, ground field data, and other information that may improve our determination. We chose to obtain our data in the region of Rabat, which is well known for its annual wheat yield production. Our project focused on the 3D CNN architecture as an algorithm to process spatial and temporal variations. In our future work, we will apply similar architectures for estimating the yields of other crops.

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Hydrophobic and superhydrophobic material surfaces and properties

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Keywords
Hydrophobic
Superhydrophobic
Contact Angle
Surface Energy
Morphology

Abstract
Hydrophobic and superhydrophobic properties are found in the structure of many living plant or animal species in nature. With the discovery of this mysterious world of nature, researchers have fabricated different surfaces or surface coatings to be used in different application areas. Hydrophobic and superhydrophobic materials have a wide range of utilizations because of their hygienic surface properties for example antibacterial, antiviral, antimicrobial, easy cleaning, and self-cleaning which they provide to products used in different areas. The fact that hydrophobic surfaces are easy to clean and the self-cleaning feature of superhydrophobic surfaces have led to the emergence of new products in many different fields such as the health sector, textile sector, ceramic and glass sector, and construction sector. Superhydrophobic surfaces are an area needed especially in today's applications, and they are preferred because they add increased value to the products they are used in, such as being hygienic, saving energy and labor, and increasing the service life of the products. In this study, the basic principles and concepts in the production of these surfaces, examples inspired by nature, industrial application areas, properties, production techniques and analysis methods used in the examination of these surfaces are systematically explained and discussed.

Introduction

Hydrophobic materials are sometimes described as water-repellent, but hydrophobic materials actually attract water, but this attraction between water and surface molecules is weaker than between water molecules [1]. The contact angle is the result of a method used to measure the hydrophobicity of a surface and is a measure of the wetting characteristics of the surface. According to the contact angle value, surfaces are classified as wet (CA<90°), non-wetting (CA>90°) and (CA>150°). If the test liquid used is water, these surfaces are called hydrophilic, hydrophobic and superhydrophobic according to the contact angle [2-6]. The contact angle of hydrophobic and superhydrophobic surfaces with water is the main factor in the easy cleaning of material surfaces and the self-cleaning properties.

When a drop of liquid is dropped on a hydrophobic surface, the shape of the liquid drop formed on the surface is determined by the equilibrium contact angle between the surface and the liquid and the liquid volume. If the volume of the droplet is a multiple of μl or fewer, the gravitational effects are less effective and the shape of the droplet is very similar to that of a sphere. The equilibrium contact angle changes depending on the condition of the surface. If the surface is in ideal condition, the equilibrium contact angle is equal to Young's angle. Young's equation is determined by the force balance between the interface tensions in the liquid, solid and vapor three-phase contact line. This force balance is expressed by the well-known Young's equation [2-6]. According to Young's equation, the lower the surface tension, the larger the contact angle. The lowest free energy among all surfaces was obtained with hexagonal tightly packed CF3 groups. The water contact angle for such a surface was measured as 119°. This is the highest contact angle for all materials known so far [7]. On real surfaces, the equilibrium contact angle does not exactly match the Young's value. However, it changes in a range close to that value. The angle at the liquid edge in the direction of rotation of the water is called the 'advancing contact angle', the angle at the edge where the liquid leaves the surface is called the 'receding contact angle'. The difference between them creates the contact angle hysteresis [3]. Rough and microstructured surfaces naturally increase the hydrophobicity of hydrophobic surfaces through two very different mechanisms. Wenzel assumes that the liquid fills the voids of the

rough surface. The wetted surface area is greater on a rough surface compared to a flat surface. Therefore, the net energy decreases in wetting, and the water-repellent surface property is more for a rough surface than for a flat surface. Therefore, the water repellency of the rough surface increases. In the Cassie-Baxter approach, the liquid drop creates a composite surface on the rough surface on the substrate. The liquid does not fill the voids of the rough surface, and the liquid-surface interface is actually a two-phase interface. That is, it is the liquid-solid and solid-gas (air) interface [3, 4, 6, 8, 9].

Many living things in nature show superhydrophobic properties. Lotus leaf, rose petal, rice leave, butterfly wing, water strider's foot are examples of these creatures (Figure 1) [C10-14]. These surfaces appear as materials needed in many sectors due to their superhydrophobic properties in self-cleaning, anti-corrosion, antibacterial properties, anti-fogging properties, oil-water separation applications, and similar areas [15-20].
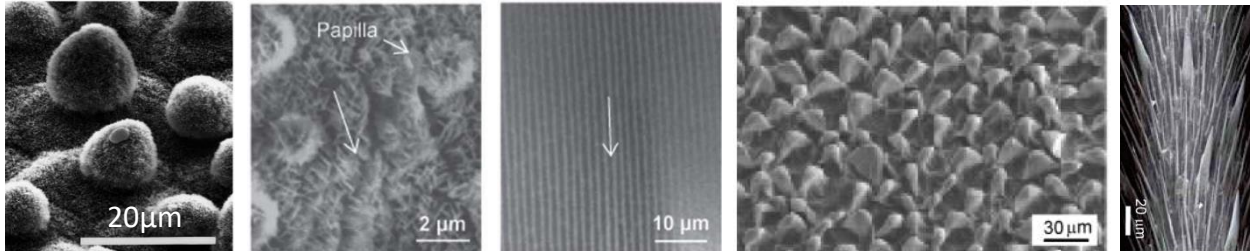
Figure 1. SEM microstructure images of lotus leaf, rice leaf, butterfly wing, rose petal, water strider leg, respectively.

Therefore, it is important to produce superhydrophobic surfaces and determine their surface properties. In this study, the production methods of superhydrobic surfaces and the contact angles of the produced surfaces were examined.

Material and Method

The production methods used to obtain superhydrophobic surfaces are given in Table 1. In order to obtain a superhydrophobic surface, appropriate surface morphology and surface chemistry must be provided together and appropriate contact angle hysteresis must be obtained within these two criteria. The superhydrophobic surface production process by lithography technique is shown in Figure 2.

Table 1. Production method and contact angle SHP

Artificial Superhydrophobic (SHP) Surfaces Production Method	Contact Angle	References
Litography	150.3, 167	21, 22
Sol-gel	165, 157	23, 24
electrospinning	150-166.7	25
etching	153	26
electrochemical deposition	≤174.6	27, 30
chemical vapor deposition	>160	28
Spreying	>160, 155	29, 20
Template	157	31
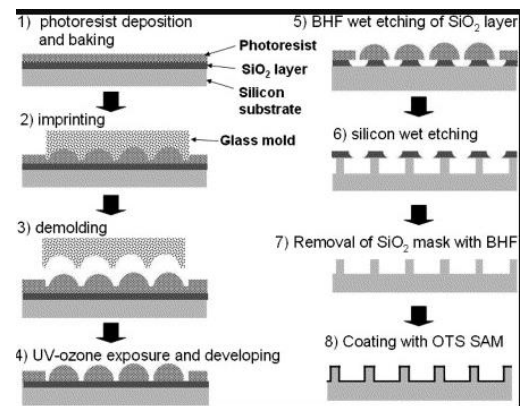
Figure 2. Schematic of fabrication process(lithography), [22]

Superhydrophobicity is achieved by using organic materials, inorganic materials, and both in combination on product surfaces.

Conclusion

The contact angles of the surfaces obtained by the techniques used to obtain a superhydrophobic surface are shown in Table 1 and schematic representation is given in Figure 3.
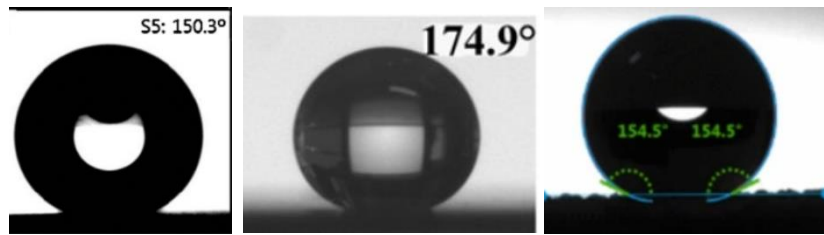
Figure 3. Contact angle images and results [20,21,30]

Considering the contact angles in the studies examined, the criterion of >150 contact angle, which is one of the basic criteria for superhydrophobicity, is met. Successful results were obtained when the surfaces were tilted at 3 degrees, and the difference between the angles of advancing and leaving the droplet remained below 5 degrees. Another important case is how long these surfaces can maintain these properties under usage conditions. Scientists continue to work on material surfaces to be used in different areas according to the conditions of use.

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Controlled drug delivery systems

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Controlled release systems
Bio erosive systems
Drug targeting
Nanocarriers

Abstract
Conventional systems, which are widely used and known as sustained release, have the disadvantages such as harming the human body and short duration of action due to the fact that the drug goes out of the therapeutic zone. These systems can cause toxic effects by causing drug accumulation in the body. With the developing technology, controlled drug release systems have started to take the place of conventional systems. The aim of controlled drug release systems is to provide the treatment of diseases by sending the right drug in the right amount and time to the target area. Controlled drug release systems do not require excessive doses and do not cause drug accumulation in the body due to their long-term therapeutic properties. In this study, the benefits, applications and types of controlled drug release systems were investigated and presented.

Introduction

In recent years, the development of nanotechnology has inspired studies in the field of nanomedicine and studies in this field have gained acceleration. Controlled drug release systems are one of the important developments in the field of nano medicine. Intelligent drug delivery systems have important advantages in that they can only release the drug to specific areas in the body and treat the disease without causing any damage to healthy tissues [1]. In controlled drug release systems, the release rate and the amount of drug in the blood can be adjusted. In this way, the drug release can be kept stable by preventing fluctuation [2]. Controlled drug release is a treatment method that is more effective than similar drug treatments. For example, degradation or elimination of the drug over time will weaken its effectiveness. However, keeping the ideal drug concentration constant for certain periods of time will increase the effectiveness of the drug and shorten the treatment period. In addition, continuous drug use and sudden drug loading, such as in injection, have some side effects on the patient. Another problem is that the active substance cannot reach the target area by crossing the barriers in the body. Controlled drug release also has advantages such as reducing these side effects, preventing the degradation of drugs with a short half-life, and preventing undesirable side effects in local applications [3].

Controlled drug release is widely used in medicine, pharmacy, chemistry, environment, agriculture and veterinary fields. Many pesticides used in agriculture and applications related to environmental protection can be used in controlled release systems, and effective results can be obtained by using a small amount without harming the nature. In chemical processes, continuity in production can be ensured by the controlled release of expensive and waste-causing materials such as enzymes added to the fermentation medium [4].

Methods of controlled drug release systems

Controlled drug release systems have two different classifications: according to the application site and the release mechanism. In systems with a release mechanism, the main focus is on the release method, while in application site-based systems, the main target is the absorption center where the application will be performed.

Systems according to the release mechanism are examined under different headings as chemical, swelling, diffusion and dissolution-controlled systems. Diffusion-controlled systems are divided into two as membrane or matrix-controlled systems. In membrane-controlled systems, the drug is loaded onto the capsule-type membrane and the drug is released with a difference in concentration after it is taken into the body. In matrix-controlled systems, on the other hand, the drug dispersed into the polymer matrix dissolves over time and is released. In swelling-controlled systems, drug release is realized by using polymers with a hydrophilic structure. The polymer, which swells and disperses depending on time with the water it receives, distributes the drug concentration it contains to the environment. In bioerosive systems, the surface of the system erodes over time, allowing the drug to be released [2].

Controlled drug release systems according to the application site are divided into ocular, nasal, buccal, transdermal, implant, vaginal, cervical and intrauterine systems. The most widely used among these systems are transdermal and implant systems. Transdermal systems consist of a pad attached to the skin surface and a polymer matrix containing a drug, as shown in Fig. 1. The permeable layer at the bottom ensures that the drug is sent to the epidermis layer in a controlled manner, and from there, the hair follicles, intracellular or intercellular drug enters the blood circulation via capillaries. This system is preferred in nicotine addiction or in cases where long-term drug use is required, such as the treatment of persistent pain [5].
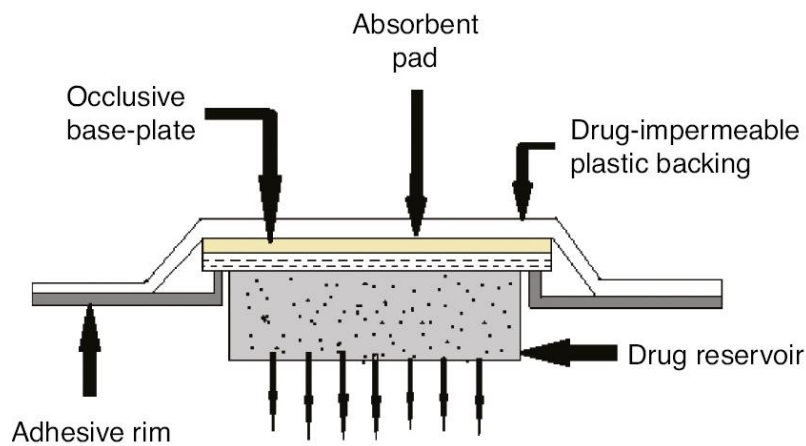

Figure 1. Matrix dispersion system [5]

Fig. 2 compares the drug plasma concentrations of conventional drug release methods and controlled drug release methods. The graph above shows the blood drug plasma concentration curves of the delayed release, immediate release, and extended release systems. According to this graph, delayed release and immediate release systems show higher toxicity and lower efficacy than extended release systems. In the graph below, the concentration curves of conventional systems and controlled drug release systems are given. According to this graph, while there was a high dose requirement in conventional systems, toxicity was also observed at high rates. Controlled drug release systems, on the other hand, have managed to keep the drug concentration in the blood stable for a long time [6].

Conclusions

In this study, the advantages of controlled drug release systems compared to other systems, as well as the types that have been put into practice, were examined. Controlled drug release systems were found to be by far the most successful system in terms of efficiency compared to traditional methods. The application of controlled drug release systems with different methods is also of great importance in terms of the wide area of use. However, since it contains advanced technology, its high cost prevents its rapid development. If this obstacle is overcome, it will completely replace traditional methods.
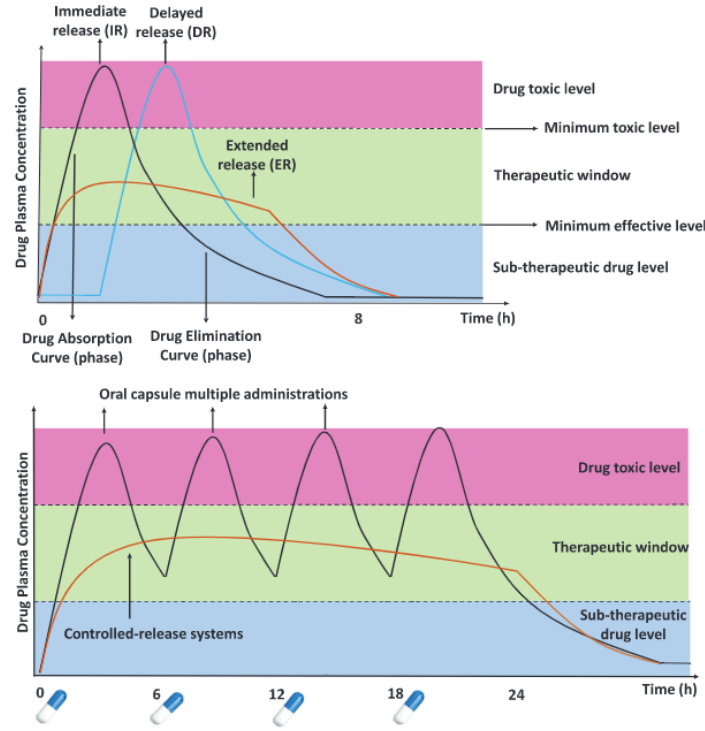
Fig. 2. Comparison of controlled drug release systems with other methods [6]

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Remineralization agents used in dental fillings

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Keywords
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Abstract
Tooth decay is an infectious microbiological disease that causes damage and loss of dental hard tissues. Rotten is a dynamic process that occurs when demineralization becomes dominant among the demineralization-remineralization reactions that occur as a result of ion exchange between dental hard tissues and saliva in the mouth. Prevention of tooth decays is based on shifting the demineralization-remineralization balance towards the remineralization direction. The most effective remineralizing agent proven by many studies is fluoride. Although fluorine is the gold standard in remineralization, new remineralization agents and methods have been sought that can increase the efficiency of fluoride or be an alternative to fluoride in order to reduce fluoride concentrations due to its possible side effects. With the developing dental technologies, new materials and methods are being discovered that increase remineralization and prevent demineralization. In the study, remineralization agents used as alternatives to fluoride, applications for remineralization and remineralization characterization methods were investigated and presented.

Introduction

In restorative dental treatment, biocompatible dental filling materials lead to modern biomaterials research as they replace biological tissue both in appearance and function. Polymer matrix composites have continued to be developed for about 60 years in restoring the loss or malformations of tooth enamel or dentin tissue as a result of caries, trauma or congenital anomalies and providing the aesthetic appearance of anterior teeth [1].

Tooth decay is explained by the process of demineralization. The demineralization process is explained by the transition of H^+ ions from the plaque structure to the tooth surface and the diffusion of dissolved mineral ions (Ca^{2+}, $(PO_4)^{-3}$) from the tooth surface to the outer surface. This reaction takes place due to increasing H^+ ion concentration. The rapid increase in the concentration of H^+ ions in the environment (100-1000 times) causes the rapid push and diffusion of H^+ ions towards the liquid in the pores surrounding the hydroxyapatite crystals in the surface and sub-surface regions of the enamel. As a result of this reaction, Ca^{2+} and $(PO_4)^{-3}$ ions present in the superficial enamel also move into the mouth. This event is expressed as the beginning of the demineralization process on the enamel surface [2].

The most important preventive application in the prevention of dental caries, which is seen at a very high rate in the society, is remineralization treatments. Reversing the decay process and stopping the decay by placing tooth minerals on demineralized (rotten) lesions is called remineralization. Diffusion of $CaHPO_4$ and associated calcium and phosphate ions through demineralized enamel pores filled with protein and water occurs during mineralization (Figure 1) [3,4].
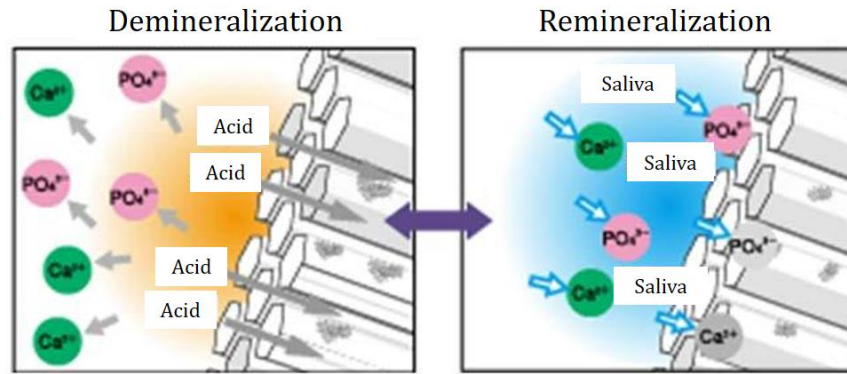
Fig. 1. Demineralization and Remineralization diagram [4]

Thanks to the numerous researches on the tooth remineralization process, technologies or new agents that can promote remineralization and/or reduce demineralization have been started to be used. Although fluoride is frequently used in tooth remineralization, fluoride and similar current remineralization agents do not have the potential to support the formation of hydroxyapatite crystals. For this reason, with the effect of developments in tissue engineering, biomimetic methods that can provide enamel regeneration with bio mineralization have begun to be investigated [3-8].

Materials used in studies on the remineralization of demineralized dentin include nano Hydroxyapatite (nHAP), Calcium Phosphate, Calcium Silicate, Bioactive Glass and Functional Biomimetic Analogs. Hydroxyapatite is a synthetic biomaterial that is similar to the structure of tooth enamel in terms of morphology, structure and crystallinity, and it has been proven to have remineralization efficiency in restorative dentistry. It has been reported that nanoparticles with increased efficiency are deposited on demineralized enamel, thanks to nano hydroxyapatite crystals, the mechanism of which is still unknown. β-Tricalcium phosphate (β-TCP) is an important calcium-phosphate system and is a bioactive component with its mineralizing components. Bio glasses are another remineralizing agent, they influence cell signals to initiate tissue regeneration and restructuring of functions, and act as a biomimetic mineralizing agent that mimics natural mineralization mechanisms that occur in vivo [3-8].

In addition to agents, laser and ozone applications, which are alternative methods, are also used as auxiliary methods in the prevention of dental caries. It has been reported that the use of laser accelerates mineralization and can also control hydroxyapatite crystal growth [9-11]. It has been reported that ozone gas can support the remineralization cycle without removing the tissue affected by the caries lesion, thanks to its strong antibacterial properties as well as its strong oxidizing properties [3, 12-14].

The addition of a new agents to the remineralization products developed to be used in the non-invasive treatment of initial caries lesions by remineralization has brought along studies comparing the efficacy of these products. In such studies, iodine permeability test, micro hardness test, especially transversal microradiography and polarized light microscopy, are used in the measurement of mineral changes due to de-/re mineralization in initial caries lesions. Laser fluorescence, confocal laser scanning microscopy and computerized micro tomography are also used for determining remineralization efficacy [15,16].

Conclusion

In the study, remineralization agents used as alternatives to fluoride, applications for remineralization and remineralization characterization methods were investigated and presented. The most important preventive application in the prevention of dental caries is remineralization treatments. As a result of scientific researches made in recent years, many promising new materials have been developed as an alternative to florid, which is a good remineralization agent, and although it has been proven that these agents have remineralization potential, studies on this subject are still ongoing.

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Dental composites: An overview

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properties

Abstract
Composite materials are emerging as materials whose use is increasing day by day in all areas of our lives. The superior properties of composite materials compared to monolithic materials have played an important role in the preference of these materials in many important sectors such as defense, construction, space, aviation, automotive and health. There are different types of composite materials according to the matrix type, and the most widely used of them is polymer matrix composites. Polymer matrix composites have a great importance especially in the field of health due to the superior properties they offer. Polymer matrix composites used in dental fillings have an important place in this field due to their outstanding properties. In this study, polymer materials used in dental fillings, filling types and commercial polymer matrix composite products and their properties are presented.

Introduction

Polymer matrix composite dental filling materials are important repair materials used in the restoration of broken or decayed teeth in the anterior and posterior parts of the mouth. These composite materials are classified according to the rheological properties, the polymerization method in the application and the properties of the inert or reactive filling material in the matrix. While dental fillings that were polymerized by chemical methods were used in the past, dual systems that are polymerized with visible light and self-curing by both light and chemical methods are used today. While filling materials with large inorganic particles were initially used in composite dental filling materials, new generation inorganic filling materials have been developed due to the low mechanical properties and insufficient physical properties provided by these coarse particles. Hybrid composite filling materials have been developed by using finer particle size fillers, different particle size distributions and different inorganic material components in new generation composite fillers. The dimensional and structural development of the fillings used in dental composites is given in Fig.1. [1, 2].
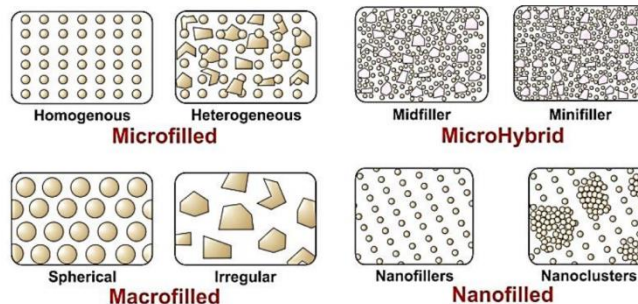

Fig. 1. The dimensional and structural development of the fillings used in dental composites [1]

In this way, many material properties such as color, gloss, abrasion, compression strength, impact resistance, hardness, excessive shrinkage and reduced stickiness in application, which are required and important in polymer matrix composite dental fillings, have been brought to the desired levels and new commercial products have been introduced to the market. Important studies on the development of new products in this field are still continuing and this field is still a very untouched field for our country. The composition and classification of resin-based dental composites have improved significantly since the materials were introduced to dentistry. (Fig. 2a,b) [2,3].

(a)   (b)
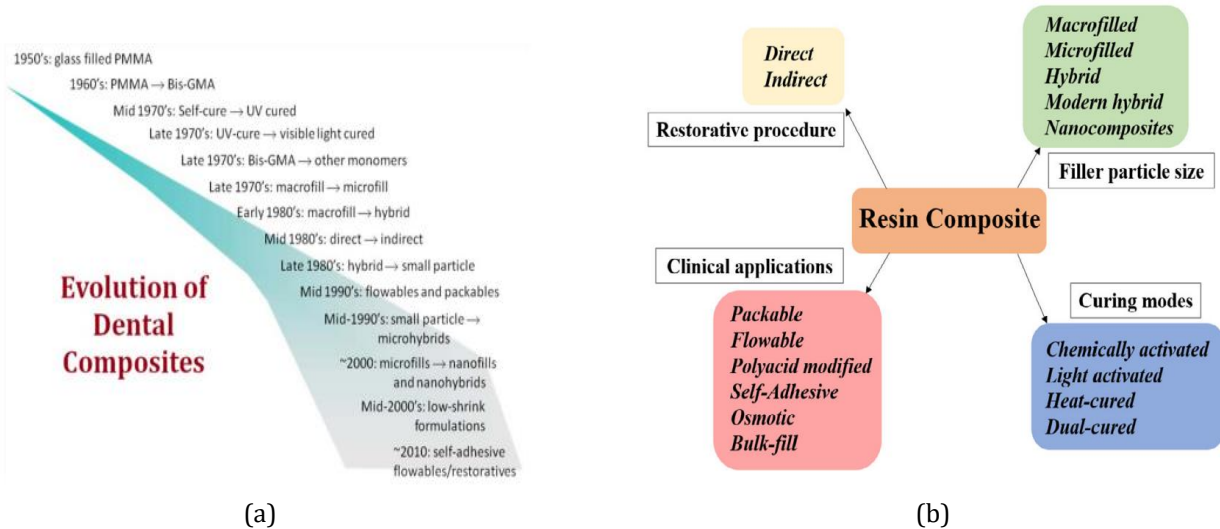
Fig. 2 (a) Evoluation of Dental Composites,**(b)** The classification of dental resin composites [2, 3]

In this study, information about the development of composite dental filling materials and the materials used in this field will be given, and scientific studies in the literature on the physico-mechanical properties of commercial dental composites are presented.

Materials and Method

Composite dental filling material components can be examined under three headings: matrix materials used, inorganic filling phases and other auxiliary materials (Table 1).

Simply, the production process of dental composites is produced by using matrix materials, filling materials and auxiliary materials, by subjecting these materials to mixing and homogenization processes using ultrasonic systems and/or mechanical systems. The hardening of the obtained composite products is generally carried out by using LED or visible light systems of different power and duration. The physico-mechanical and biological properties of the composite product vary depending on the type and amount of matrix and filler phase used the size of the filler and the properties of auxiliary materials.

Table 1. Composite dental filling material components [4-7]

Matrix (Resin)	Fillers	Auxiliary materials
Bisphenol A-glycidyl methacrylate, Bis-GMA	Amorphous Silica	Coupling agent, 3-metakrilloxipropiltrimetoksisilan
Urethane di-methacrylate, UDMA	Hydroxyapatite	Photoinitiators, ethyl-4-(N,N - dimethylamino) benzoate (4EDMAB)
Tri-ethylene glycol di-methacrylate, TEGDMA	Zirconia	Photoinitiators, Camphorquinone (CQ)
Hydroxyethyl methacrylate (HEMA)	Aluminum silicate,	
Silorane	Barium (Ba), strontium (Sr), zirconium (Zr), and zinc glasses	
Addition-fragmentation monomer (AFM)	Borosilicate glass	
Aromatic urethane dimethacrylate (AUDMA)	ytterbium fluoride	
	lithium aluminum silicate	

Conclusion

The physico-mechanical properties (fracture toughness, flexural strength and modulus, compressive strength, volume shrinkage) of some dental composites currently available in the market are given in Fig. 3 (a-e). It has been observed that flexural strength values of dental composites vary between 95-170 MPa, flexural modulus values between 7.8-15 GPa, compressive strength values between 260-355 MPa, fracture toughness values between 1.4-2.3 MPam$^{1/2}$ and volumetric shrinkage values between 1.5-2.4%.
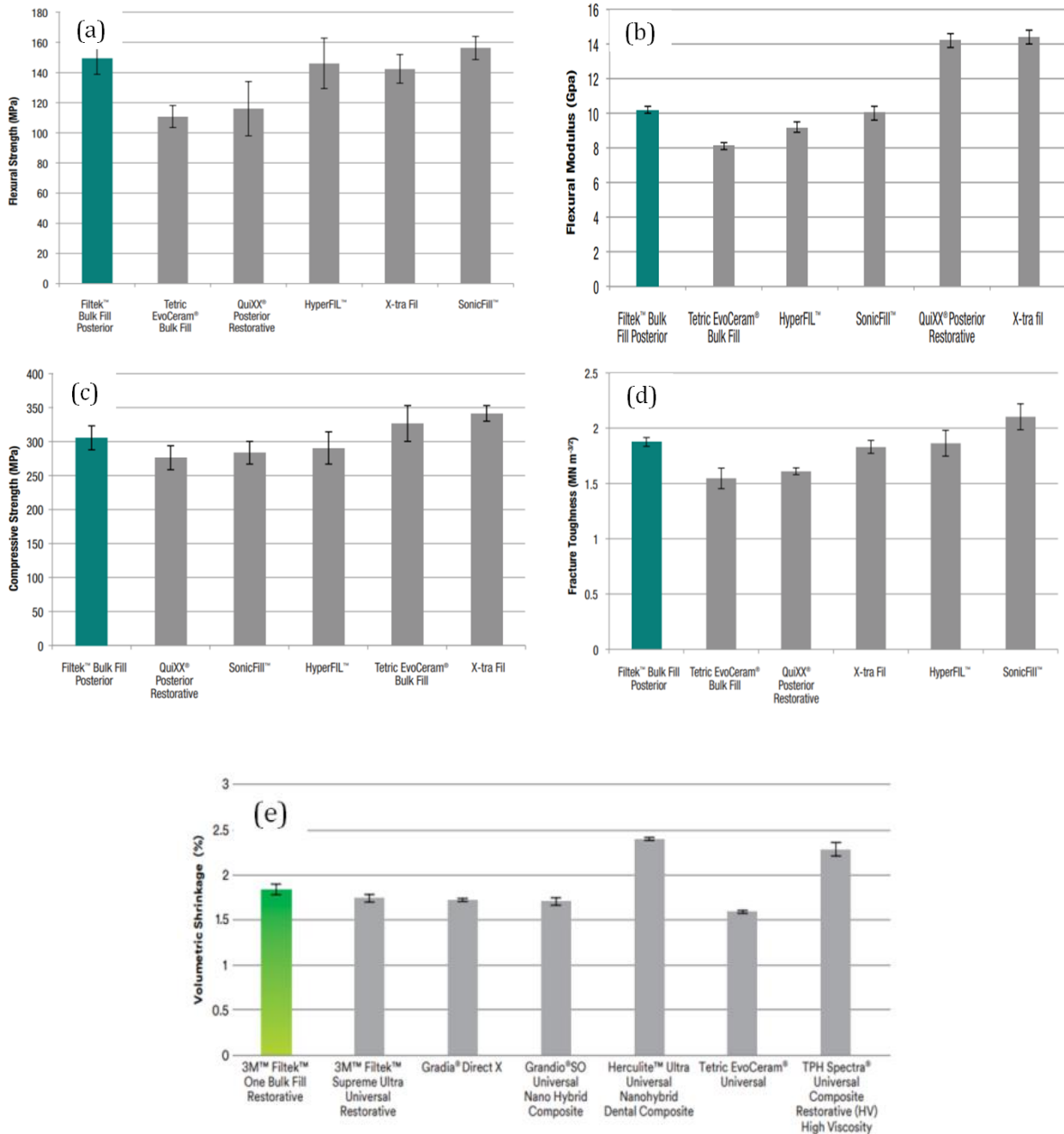
Fig. 3. The physico-mechanical properties of some commercial dental composites [7,8]

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Wave energy convertor applications

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Keywords
Wave Energy Convertor
Renewable Energy
Wave Power

Abstract
The demand for renewable energy sources is increasing rapidly due to the fact that the fossil fuels tend to run out and the oil crisis in the 1970s, which is likely to be experienced in the following years, has affected the world economically due to the dependence on fossil fuels. Wave energy is a type of energy that stands out among renewable resources with its advantages such as having the potential to work 24 hours a day, not needing panel cleaning like solar energy, and not occupying space on fertile agricultural lands like solar energy. Studies on wave energy converters continues rapidly today. Wave energy converters reach a much more widespread usage rate in the world with the decrease in the initial investment cost, the decrease in the amortization period and the increase in the amount of power obtained from the unit. Today, the development of Computational Fluid Dynamics (CFD), Computer Aided Manufacturing (CAM) and computer aided kinematic analysis applications of mechanisms enables the design of prototypes on the waves by completing these studies in a computer environment, thus reducing research and development costs. In this study, studies on wave energy converters are stated.

Introduction

Countries need to use their own resources to reduce foreign dependency in energy. Not every country has a source of coal, oil or natural gas, and since fossil fuels are an exhaustible resource, the trend towards renewable energy alternatives is quite common. Here, the geographical location of the countries is of great importance.

Wave energy, one of the renewable energy sources, is a type of energy originating from the wind energy on the oceans and seas; contains potential and kinetic energy [1]. Ocean wave energy is developing technology and renewable energy source that still is almost unexploited [2].

The approximate wave power density in a sea can be estimated by multiplying the 0.49 constant of the apparent wave height squared, H_s^2, and its period, T_e which stated at formula (1) [3];

$$P(kW/m) = 0.49\ H_s^2\ T_e \tag{1}$$

As seen in Fig. 1., a maximum of 127.7 kW/m sea wave power can be obtained in the world.

As can be seen in Fig. 2, the rate of use of hydro energy and renewable energy resources in many countries such as Germany, Japan, Portugal, USA, UK is increasing every year. The studies carried out by researchers in many countries in this field are important to meet the increasing demand for energy and to prevent the energy crisis.
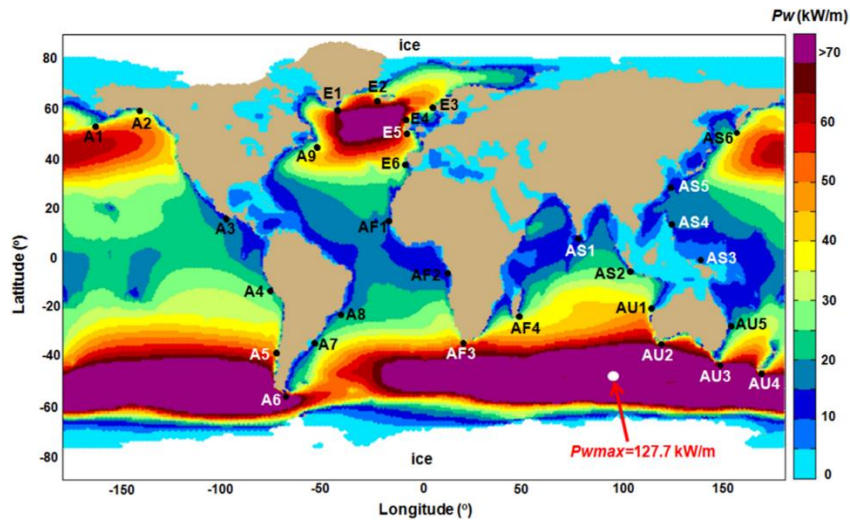
Figure 1. Map of the mean wave power density (in kW/m) corresponding to the 15-year interval from January 2000 to December 2014; the positions of 30 reference points, distributed along the coastal environments of: America (A1–A9), Europe (E1–E6), Africa (AF1–AF4), Asia (AS1–AS6) and Australia (AU1–AU5), are also indicated [4]
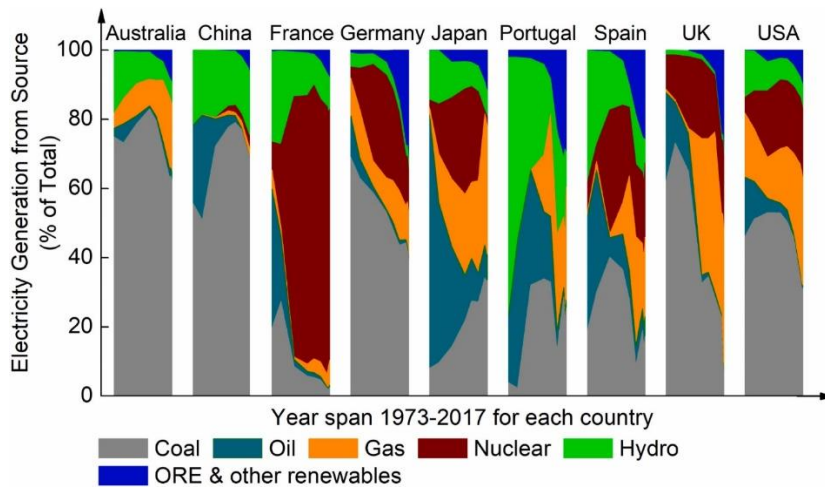
Figure 2. Evolution of the worldwide <u>electricity generation</u> by source between 1973 and 2017. The results are summarized from the data presented in the report of World Energy Balances 2018 by the International Energy Agency [5]

Material and Method

Experimental Studies
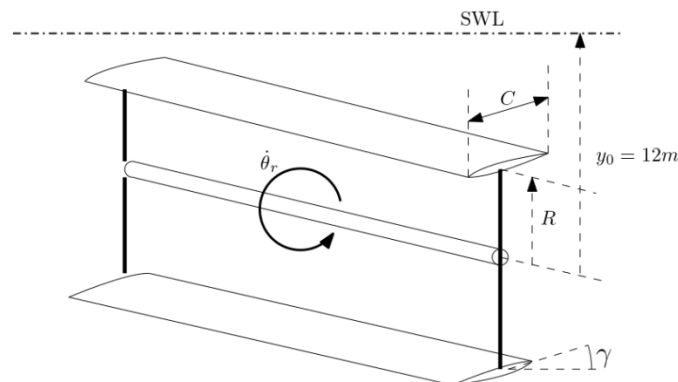
**Figure 3.** Cyclorotor-based wave energy device (SWL: Still water level) [6]

Ermakov et. al. [6] designed cyclorotor-based wave energy devices shown in Fig. 3. Their operational principle is based on the generation of lift forces on the rotating hydrofoils due to their interaction with wave-induced

circulation of water particles. It is a design that can be said to be promising because it has a design produced at a low cost for generating energy.
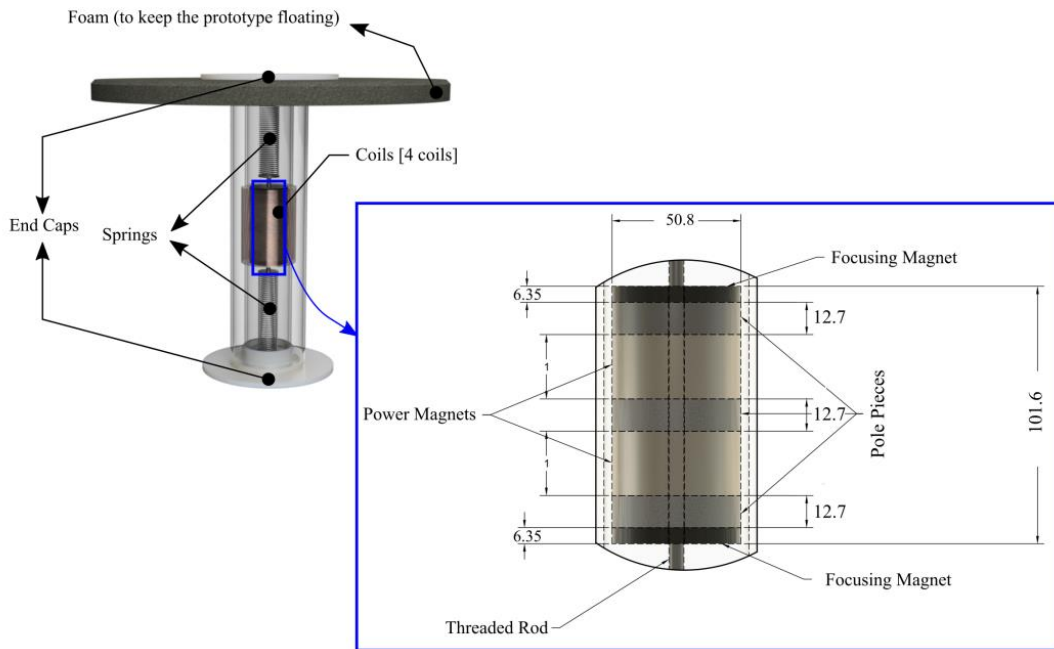
Figure 4. A Modular Wave Energy Converter for Observational and Navigational Buoys [7]

More than 80% of the ocean is not fully mapped or even observed. Observational and navigational buoys used in many countries and those buoys needs power to operate. Some buoys use solar panels, but solar panels not always ideal for every conditions. Vella et. al [7] designed WEC which shown in Fig. 4. for powering observational and navigational buoys. Experimental testing showed that device can get 81 milliwatts for waves with a wave period of 1 s, a wave height of 10 cm, and a water depth of 91 cm.
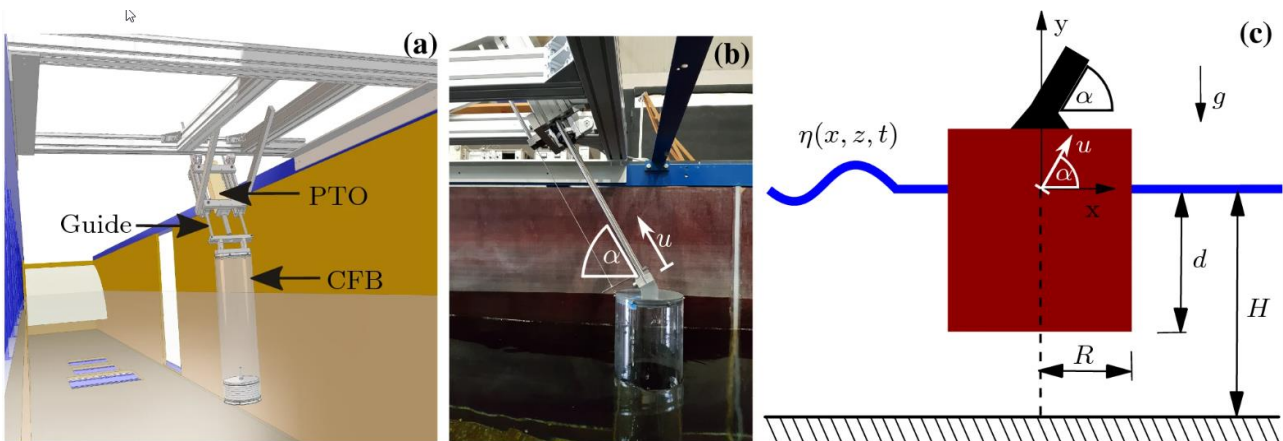
Figure 5. Experimental rig in the wave flume of the Institute of Mechanics and Ocean Engineering from two different perspectives (a, b) and a sketch of the resulting wave energy converter (c) [8]

Hollm et. al. [8] designed guided point absorber for harvesting wave energy shown in Fig. 5. Experimental and simulational tests shown that the inclination angle has a significant influence on the energy harvesting output.

Carandell et. al. [9] studied electromagnetic rolling mass energy harvester that uses kinetic energy of waves for the use of ocean monitoring systems sensor platforms. This Kinetic energy harvester system is based on a rolling mass resonator with permanent magnets that oscillate with respect to a frame which includes a coil system. Electromagnetic rolling mass energy harvester is shown in Fig. 6.
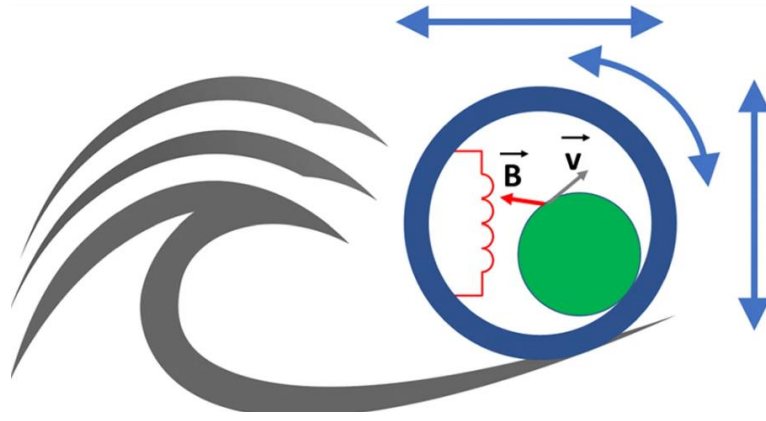
Figure 6. Electromagnetic rolling mass energy harvester [9]

Conclusion

It is estimated that almost 150 WEC projects (either conceptual or operational) have been reported at a global scale [4]. Most of projects are funding by governments. Wave energy converter designs and approaches differ. Factors such as wave frequency and height values of the country's coasts, the location of the wave energy converter device to the shore, and initial and maintenance costs are the main reasons for these differences. The location of the wave energy converter devices to the shore is more important with the inclusion of the cable installation costs stated in the table (Table 1).

Table 1. Cable installation costs [10]

Cable laying/ km trenched	€282000
Cable laying/ km untrenched	€282000
Cable coverage (rock coverage/ km	€282000

WEC devices is used for generating energy that alternative to fossil fuels. Additionally, WEC devices designing to use for powering observation devices of seas. There are too many promising theoretical and experimental studies in the world and wave energy convertor devices becoming widespread again nowadays.

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Development in nanomaterials for prevention and treatment of COVID-19 and other viruses

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Keywords

Nanomaterials
COVID-19
Silver
Gold
Graphene oxide
Antiviral

Abstract

Nanotechnology is an exciting field that is studied by many different disciplines from industry to medicine. The improvement in nanotechnology is increasing day by day. The Coronavirus known as COVID-19 became most difficult health cries that affected the whole world. The World Health Organization reported the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic in 2020. Public health strategies such as isolation and quarantine have been formed to control the rapidly spreading pandemic. Metal nanoparticles (silver, coper, gold, boron, etc.) and carbon-based nanoparticle (graphene oxide) include antiviral and antibacterial activity by causing damage to the cell membranes of microorganisms. Recently, studies show that particularly, the nanomaterials are mostly preferred not only for antiviral effect but also for virus detection, drug delivery and vaccination. In this study, nanomaterials and their application in detection, prevention and treatment for COVID-19 are compared and discussed in detail.

Introduction

The materials, which have less than 100 nm in size at least in one dimension, are called nanomaterials. The surface area per unit cell increases once the size of the material decreases. Most atoms in a lattice are located on the surface or near the surface as a result of an increase in surface area. This case cause that the bonds between surface atoms become weak and high reactivity property ready for physical and chemical interaction [1]. Nanotechnology is used for improving the physical and biological properties of biomaterials, mainly in the field of drug delivery system, tissue engineering, bioimaging, stem cell research, diagnosis, and treatment of cancer.

The studies demonstrate antiviral activity of silver nanoparticles (Ag NPs). Ag NPs can inhibit a pathogenic virus in two different ways: either Ag nanoparticle binds to the virus surface protein and prevents it from binding to cell receptors or binds to the DNA or RNA of the virus so that it blocks the replication and reproduction of the virus in the host cells [2]. Lara et al. evaluated that antiviral effect of Ag NPs (30-50 nm) against HIV-1 (Human Immunodeficiency Virus) at non-cytotoxic concentrations using two different methods in vitro assays. The results show that the Ag NPs inhibit viral replication of HIV-1. Compared with the control (0.0 mg/mL), the interaction between glycoprotein (gp120) of HIV virus and cell receptor (CD4) decrease over 60% at the 5mg/mL Ag NPs. In addition, the Ag NPs retained their antiviral activity even 12 h after the HIV inoculation [3]. Chen et al. investigated that the antiviral activity of 0.6-9 nm graphene oxide (GO) nanosheets and GO nanosheets with 5-25 nm Ag NPs against enveloped (feline coronavirus) and non-enveloped (infectious bursal disease virus) viruses. Both GO nanosheets with Ag NPs and pure GO nanosheets exhibited antiviral activity against feline coronavirus (FCoV) [4]. Mori et al. searched the antiviral effect of chitosan (Ch) and Ag NPs composites of different sizes (3.5, 6.5 and 12.9 nm) against the H1N1 /Influenza A virus. As a result of the study, stronger antiviral activity has been observed in composites containing Ag NPs [5]. Jeremiah et al. evaluated the antiviral effect of Ag NPs of different concentrations. It was observed that the one with 10 nm size covered with PVP (polyvinylpyrrolidone) reduce the cytotoxicity effect and still inhibit extracellular SARS-CoV-2 [6]. Ghaffari et al. examined the antiviral activity of

zinc oxide nanoparticles (ZnO NPs) and PEG- ZnO NPs for H1N1 influenza virus. As shown in the TCID50 assay results, PEG- ZnO NPs exhibited antiviral effect on H1N1. However, there was not any decrease in H1N1 influenza virus at pre-exposure of cells to ZnO nanoparticles [7]. In another study, about the effect of metal nanoparticles on the HIV/AIDS virus, demonstrate that gold nanoparticles (Au NPs), which are stabilized with polyethylene glycol have antiviral effect on HIV virus by preventing CD4 dependent virion binding [8]. Nanoparticles are preferred to design smart drug delivery systems for controlled release behavior. In a study, Ag NPs was used as nanocarrier and the effect of Ag NPs against glycoproteins of COVID-19 virus. The SEM images showed that the damage of spike (S) glycoprotein and the protein membrane of COVID-19 virus after treatment with the Ag NPs/hydroxychloroquine (HQ, a known antiviral drug). In addition, TCID50 assay drug, which prepared 400 mg/ml of Ag NPs/HQ decrease the viability of COVID-19 virus to ~22% [9]. Uncontrolled spread of COVID-19 has caused the global health threat that has affected millions of people. Vaccination is the most effective health strategy in order to control and prevent the widespread of infectious diseases. The Moderna and Pfizer/BioNtech vaccines were designed using lipid nanoparticles for delivery mRNA, which codes the S glycoprotein of the COVID-19 virus surrounding by phospholipid membrane. When lipid-based vaccine is injected to host, the phospholipid membrane of the nanoparticle decomposes into host membrane and release the mRNA into the cytoplasm of the target cell. Then, host immune system is activated, and T-helper cells produce antibodies during recurrent attack of S glycoprotein on SARS-CoV-2 [10].

Material and Method

The particle size and shape of nanomaterials strongly depend on the synthesis techniques and preparation parameters (pH, temperature, duration times, etc.). Nanoparticles are produced by using physical (high energy ball milling, laser ablation, ion implantation, etc.), chemical (sol-gel, colloid), and biological (using biomolecule or plants) techniques [11]. Ag NPs were prepared by the green method. The phoenix dactylifera extract and Ag^+ solution was mixed by vigorous stirring at 60°C for 15 min. [9]. Then, the resultant solution that was in clear red color was saved under 10°C. Thereafter, Ag NPs were conjugated with the HQ. The prepared solution of Ag NPs and HQ was well mixed with stirring for 3h under ambient pressure and 40°C and then resulted Ag NPs/HQ solution was stored under 10°C [9].

GO nanosheets were prepared by using Hummers' method. Potassium manganate was added to graphite solution, including sodium nitrate and sulfuric acid. The obtained GO powders were dispersed in the silver-containing solution. According to pulse microwave-assisted (MA) synthesis, the GO-Ag solution was placed in the microwave according to supply the growth of silver seeds deposited on the GO surface. Finally, drying of the GO-Ag solution was completed inside a vacuum oven and the temperature was 60 °C [4].

Gold (III) chloride trihydrate ($HAuCl_4.3H_2O$), which dissolved in distilled water was blended with a magnetic stirrer until the gold solution was brought to boil. Sodium citrate dehydrate ($C_6H_5Na_3O_7.2H_2O$) which act reducing agent was dissolved in deionized water and then added to the gold solution. The mixture which was cooled overnight, filtered through a 0.2 μm membrane filter. The mixed solution of 17 nm Au NPs and PEG solution was centrifuged for 20 min. [8].

Chitosan solution was mixed with Ag NPs solution along with NaOH at room temperature, followed by stirring to precipitate the Ag NPs/Ch composite, and then the obtained Ag NPs/Ch composite was centrifuged for 10 min. [5].

Results

The Ag NPs and Au NPs efficiently blocked the fusion of HIV-1 viruses to the cell by interfering with gp120-CD4 interaction depending on the dose [3, 8]. Additionally, it was observed that the Ag NPs effectively inhibit extracellular SARS-CoV-2 to protect the target cells from infection [6]. After a time-of-addition experiment was performed, it was determined that Ag NPs retained their antiviral activity even 12 h after the HIV-1 inoculation [3]. The result shows that the Ag NPs intervene with the viral life cycle besides fusion or entry. The Au NPs were observed to be more effective than the Indinavir, which is a drug used as a component of highly active antiretroviral therapy [8]. The size and antiviral activity relation of Ag NPs was examined by using immunofluorescence analysis. Immunofluorescence imaging show that 100 nm Ag NPs had not antiviral an activity on SARS-CoV-2 virus. While 10 nm Ag NPs effected to SARS-CoV-2 virus [6].

By means of luminescent cell viability assay, the 50% cytotoxic concentration (CC_{50}) of the Ag NPs was determined as 3.9 ± 1.6 mg/mL, 1.11 ± 0.32 mg/mL, and 1.3 ± 0.58 mg/mL against HeLa-CD4-LTR-b-gal cells, human PBMC, and MT-2 cells, respectively [3]. The cell viability of The Hela-CD4-LTR-B-gal cell line defined after added Au NPs. The IC50 of Au NPs was found to be 1.12 ± 0.05 mg/ml [8]. Besides, the concentration of Ag NPs becomes cytotoxic to the cell lines Calu-3 (human lung epithelial cell) at 20 ppm and above [6].

The CC_{50} of GO and GO-Ag NPs in fcwf-4 cells was 17.4 mg/mL and 19.7 mg/mL, respectively [4]. The cytotoxicity of PEGylated ZnO NPs and ZnO NPs was measured as 75 μg/mL and 200 μg/mL, respectively. In contrast, it was observed that the antiviral activity of PEGylated ZnO NPs is greater than ZnO NPs [7].

Discussion

It was analyzed that the antiviral activity of nanocomposites enhanced by doping with Ag NPs. It was concluded that the Ag/Ch composite exhibited antiviral properties in all Ag NPs sizes while pure Ch did not have any antiviral effects. The GO nanosheets with Ag NPs exhibited antiviral activity for non-enveloped viruses even though viruses without envelopes are quite resistant to environmental stresses. However, the pure GO nanosheets could only inhibit the infection of the enveloped virus. Another point, there is a correlation between size of Ag NPs and antiviral activity.

Increasing the amount of nanometals in biomaterials leads to enhancing the antiviral effect. The cytotoxic effect on living cells may occurred by nanoparticle aggregation or using high dose of nanometals for strong antiviral activity. Nanometals are covered by polymers or doped with other biocompatibility materials to provide the immobilization of nanoparticles; thus, the cytotoxicity is decreased by preventing the release of unchecked ions (such as Ag^+, Zn^+). Regarding the studies aforementioned, we concluded that the Ag NPs/GO composites have less cytotoxic effect compared to polymer conjugated. One reason for that may be the strong immobilization of Ag NPs within the composites used.

The antiviral effect of Ag NPs on viruses is comprised of two ways: (1) The interaction of the virus before viral attachment to the host cell and (2) damaging viral surface protein in viral replication after infection of the host cell. The Au NPs have an antiviral mechanism similar to Ag NPs. The Au NPs prevent the attachment of glycoprotein found in virus to host cell receptors. The ZnO NPs inhibit viral life cycle, which occur after viral taken up by cells. However, the ZnO NPs are not able to prevent the host cell from the entry of viruses, unlike the Ag NPs and the Au NPs.

Conclusion

Nanotechnology is of interest to interdisciplinary researches due to the physical and chemical properties of nanomaterials. Some nanometal particles exhibit antimicrobial, anticancer, and anti-inflammatory activity. Therefore, biocompatible nanomaterials are used in the diagnosis and treatment of diseases. It was evaluated that the antiviral activity of nanomaterials (Ag, Au, ZnO, GO) even at non-cytotoxic dose. Nanomaterials can play a key role in the combat the COVID-19 pandemic or future global pandemics and/or diseases. For this reason, researches should focus on the enhancing the physical, chemical and/or biological properties of nanomaterials.

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Achievements in nanomaterials for solid oxide fuel cells for clean and sustainable energy

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Abstract

The energy need in the world is increasing each year, but the fossil fuel reserves that meet this need are decreasing much faster. Between 2030 and 2050, it is predicted that fossil fuel reserves will be depleted to a large extent or will not be able to meet the need. In addition, the accumulation of greenhouse gases in the atmosphere increases due to the continuous emission of gases namely CO_2, CO, CH_4, nitrogen oxides, and sulfur dioxide with the burning of fossil fuels. Due to all these economic and environmental factors, countries have turned to renewable energy sources in recent years. Hydrogen energy, which is one of the renewable energy sources, is preferred because it is more efficient than fossil fuels and is not harmful to the environment. Fuel cells convert a variety of fuels directly into electricity, including hydrogen, hydrocarbons and methanol. Solid oxide fuel cells (SOFC) have attracted much attention of researchers due to their fuel flexibility, high efficiency and good reaction kinetics. SOFCs, consisting of anode, cathode and electrolyte layers, show different performances depending on the type of each layer and the production conditions. The cathode electrode is the layer where oxygen is reduced. The cathode electrode must have high conductivity as well as high catalytic activity. The purpose of this study is to specify achievements in nanomaterials for cathode electrode.

Introduction

Fuel cells are new generation devices that allow electricity to be produced by an electrochemical reaction. It can basically continuously convert the chemical energy of a fuel and an oxidizer directly into electricity and heat [1]. Basically, the system has three main components: two electrodes (anode and cathode) with a porous structure and an electrolyte layer between these electrodes. A fuel cell is usually supplied with hydrogen gas as fuel from the anode section. On the other hand, from the cathode part, oxygen is supplied to the cell in the air. An electrical voltage is generated between within the electrodes, resulting from the chemical potential differences of hydrogen and oxygen. This voltage creates the electron transition from anode to cathode once the circuit is closed [2]. In general, fuel cells are assorted with respect to electrolyte type for instance, alkaline fuel cells (AFC), proton exchange membrane fuel cells (PEMFC), phosphoric acid fuel cells (PAFC), molten carbonate fuel cells (MCFC) and solid oxide fuel cells (SOFC) [3].

In SOFCs, dense electrolyte is placed between two porous anode and cathode electrolytes, forming a sandwich structure. When oxygen gas is supplied to the cathode the oxygen reduction reaction takes place in the cathode layer. When fuel gas is supplied to the anode, an electromotive force is created in the two layers. This force is used for producing power by connecting the electrodes with an external circuit [4]. Cathodes must have many properties such as high electronic and ionic conductivity, high catalytic activity for oxygen reduction, and compatibility with other cell components. Besides, the material used as cathode and the electrolyte material should not react at cell production and high operating temperatures.

SOFCs generally operate at 800-1000°C. These high operating temperatures cause chemical and microstructural deterioration in SOFC components in long-term use and thus decrease the performance over time [5]. As an approach to prevent these performance losses, the development of new materials that will not cause a significant performance loss at temperatures lower than 700°C, which is the medium temperature (IT) value, is considered. However, lowering the operating temperature will also slow down the ionic conductivity in the electrolyte and the kinetics of the reactions at the electrodes. As can be seen in Figure 1, especially the cathode polarization resistances will increase rapidly as the temperature decreases [6-7]. Therefore, achieving high SOFC performance at low temperatures depends on the development of cathodes that can show low polarization resistance at these temperatures. For this reason, this study focused on SOFC cathodes that can operate at low temperatures.
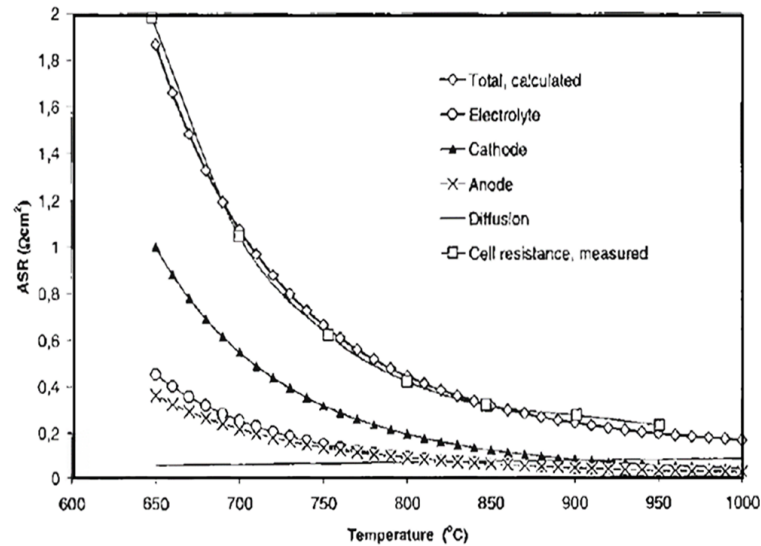

Figure 1. Polarization resistance variation graph in SOFC components [7]

Material and Method

Lanthanum strontium manganese oxide (LSM) perovskites are the most widely used cathode for SOFC application. It remains that the practical choice for operation is higher than 700°C. It is only possible to obtain high electrical conductivity, high electrochemical activity for the O_2 reduction reaction, high thermal stability and compatibility with electrolyte at high temperature for these cathode materials [8]. In many studies in the literature, different transition metals (Cr, Mn, Co, Fe, Ni) or their combinations have been substituted for B in the $La_xSr_{1-x}BO_3$ perovskite structure to obtain minimum ion transfer resistance and maximum electrical conduction. In Table 1, the electrical conductivity of the cathode materials is given which are developed for IT-SOFCs at different temperatures [9].

Table 1. Electrical conductivity of the cathode materials

Composition	σ_e/Scm^{-1}		
	900 °C	**800 °C**	**600 °C**
$LaCoO_{3-\delta}$	1259	1122	1000
$La_{0.8}Sr_{0.2}CoO_{3-\delta}$	1125	1221	1375
$La_{0.8}Sr_{0.2}FeO_{3-\delta}$	84	87	90
$LaCo_{0.2}Fe_{0.8}O_{3-\delta}$	9	4.2	
$La_{0.8}Sr_{0.2}Co_{0.8}Fe_{0.2}O_{3-\delta}$	945	1000	1050
$La_{0.8}Sr_{0.2}Co_{0.2}Fe_{0.8}O_{3-\delta}$	210	280	332

Since LSC cathode material show high electronic conductivity, it is promising to be used instead of LSM. However, the widespread use of this cathode is restricted because LSC reacts with the commonly used YSZ electrolyte, its thermal expansion coefficient is not compatible with YSZ, and it is toxic and expensive [10-11]. As seen in Table 1, LSCF has a high electrical conductivity (1050 Scm⁻¹ at 600 °C). This is much higher than the aforementioned LSM materials (~420 Scm⁻¹ at 600 °C).

Various synthesis methods can be used to produce nanostructure perovskite oxides. The synthesis parameters; chemical stoichiometry, temperature and etc. are important to improve the properties of cathode materials. Combustion, sol-gel, co-precipitation, solid-state reaction and mechanical alloying are some of the methods generally used. In the solid state reaction, the determined substance amounts are weighed after the necessary molar calculations are made. The weighed starting raw materials are regularly ground for a certain period of time in an agate mortar at room temperature to obtain a homogeneous mixture. The grinded mixture is placed in a platinum crucible and placed in the ash furnace. Annealing is carried out at the appropriate temperature and time. Solid state synthesis method has an advantage to increase the yield with reduced costs. Besides, it also decreases the amount of chemical wastes [12].

Discussion

This study focuses on the new generation nanostructured cathode materials and their production methods for IT-SOFCs. The cathode layer used in SOFCs is generally ABO_3 perovskite structure containing trivalent transition metal ions in the B region and a trivalent rare earth in the A region. LSM is used in commercial applications. However, corrosion and deterioration problems are seen due to its use at high temperatures. In the literature, there are intensive studies on the cathode material that can operate with higher performance at temperatures below 700 °C. Some of these studies are on synthesizing new cathode materials with alternative combinations in regions A and B as A *(La, Sr, Ca)* and B *(Cr, Mn, Co, Fe, Ni)*O_3. Some studies are on synthesizing nano-structured cathode material by making changes in production methods or parameters. It is concluded that nanostructured LSCF cathode material shows promise in IT-SOFC applications.

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Time series modelling for goat and cow milk price index forecasting by trend analysis and Holt's method

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Abstract
Goat and cow milk is a fundamental agricultural product. Multiple factors can affect the price of milk over time such as production conditions, consumption demand, financial crisis and inflation. Dynamics of the milk price data should be considered to determine trend, cycle, or seasonality in the milk market so each pattern may affect the forecasting method should be used and the estimation results. Hence, the aim of this study is finding the pattern of the milk price time series data and estimation for the next 3 monthly periods. Historical data of Goat Milk and Cow Milk was used from the Agricultural Products Producer Price Index data between January 2016 to March 2022 published by Turkish Statistical Institute. Considering the trend pattern, trend analysis and Holt's method (double exponential smoothing) were used. The results demonstrated that the trend pattern may continue in near future, indicating that the procedures used were reasonable.

Introduction

Forecasting is required for many fields including business, industry, government, economics, environmental sciences, medicine, social science, politics, and finance and so on. Forecasting is critical since it gives input to the majority of decision-making and planning concerns. Forecasting problems could be classified as short, medium and long term. Short- and medium-term forecasting is typically based on identifying, modeling, and extrapolating the patterns found in historical data. Time series data is observed in many forecasting situations based on historical data. Collection. A time series is a chronological or time-oriented collection of observations on a dependent variable [1]. Many variables are assessed sequentially across time in most quantitative academic topics, as well as in business and commerce [2]. Time series data analysis for forecasting is one of the most important aspects of the practical usage. In the present study, the patterns are analyzed for goat milk and cow milk and then, regarding to the results, trend analysis and holt's methods are decided as appropriate methodologies to estimate price for 3 monthly period.

Material and Method

In time series plots, data could represent one or more possible patterns, trend, cycle, seasonality and randomness. Moving Average or Single Exponential Smoothing could be used if dataset does not have a trend component or a seasonality. To apply a general trend model to time series data and produce forecasts, trend analysis can be used. The linear, quadratic, exponential growth or decay, and S-curve trend models are all options. When the time series data has a steady trend and no seasonality, trend analysis could be used to fit a trend. Holt's method is a type of double exponential smoothing technique designed to track time series with linear trend. If there is an exact linear trend, Holt's Method is appropriate for forecasting. When the data has a trend and a seasonality component, and these two components are additive or multiplicative, Winters' Method could be applied. This method generates dynamic estimates for three variables: level, trend, and seasonality [3].
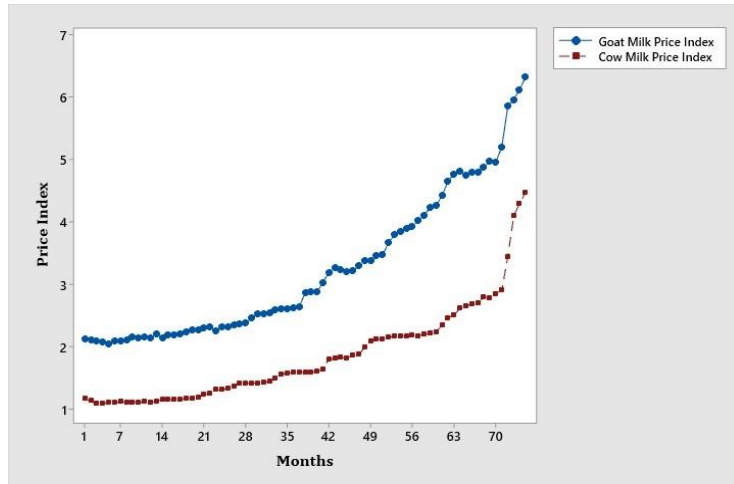
Figure 1. Time Series Plot of of Goat Milk (a) and Cow Milk (b) Price Index between Jan. 2016 to March 2022

In this study, the historical data of goat and cow milk price index was gathered from The Turkish Statistical Institute's Agricultural Products Producer Price Index between January 2016 to March 2022 (75 months). At first step, time series plots were examined to gain a clear understand of patterns (Fig 1.). Trend pattern was observed in the time series graph of goat milk data and cow milk data. Trend analysis [4] and Holt's method [5] is selected as appropriate methods. When a trend analysis demonstrated a linear trend, the linear trend model is:

$$Y_t = \beta_0 + \beta_1 t + e_t \tag{1}$$

β_0 is the constant, β_1 is the average change from one period to the next, t is the value of the time unit and e_t is the error term.

Holt's method uses two weights, also called smoothing parameters to update the components at each period. The equations are as follows:

$$L_t = \alpha Y_t + (1 - \alpha) [L_{t-1} + T_{t-1}] \tag{2}$$
$$T_t = \gamma [L_t - L_{t-1}] + (1 - \gamma) T_{t-1} \tag{3}$$
$$\hat{Y}_t = L_{t-1} + T_{t-1} \tag{4}$$

L_t is level at time t. α is weight for the level. T_t is trend at time t. γ is weight for the trend. Y_t is data value at time t. $\hat{Y}_t$ is fitted value, or one-step-ahead forecast, at time t. The forecast for m periods ahead from a point at time t is as follows:

$$\hat{Y}_t = L_t + mT_t \tag{5}$$

Results and Discussion

As a result of trend pattern that is observed in the time series graph of goat and cow milk data, it can be concluded there is a linear increasing tendency at price index data between January 2016 and March 2022 (Fig.2). A significant indicator of the existence for linear trendline pattern is R-squared (R^2) values for goat and cow milk of 0.81 and 0.88, respectively. These values could be provided by the Regression analysis [6].
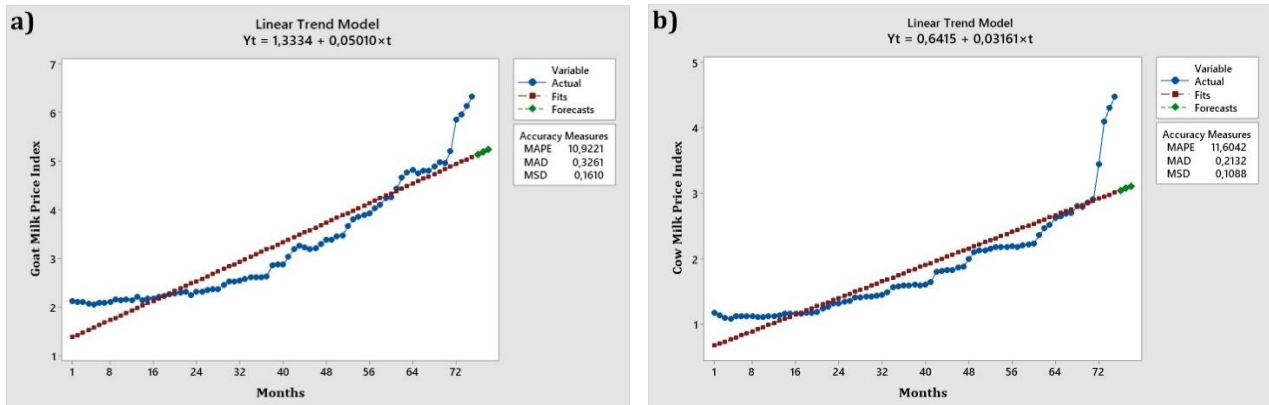
Figure 2. Trend Analysis of Goat Milk (a) and Cow Milk (b) Price Index and Forecasting Results

Based on trend analysis, 76nd, 77nd, and 78rd month price predictions for goat milk is gathered by the equation given below;

$$Y_t = 0{,}0501t + 1{,}3334 \tag{6}$$

Estimation of 76nd, 77nd, and 78rd month price for goat milk is gathered as 5.140, 5.191, 5.242, respectively (Table 1).

The equation below calculates the 76th, 77th, and 78th month price estimations for cow milk based on trend analysis;

$$Y_t = 0{,}0316t + 0{,}6415 \tag{7}$$

The forecasted prices for cow milk in the 76th, 77th, and 78th months are 3.043, 3.075, and 3.107, respectively (Table 1).
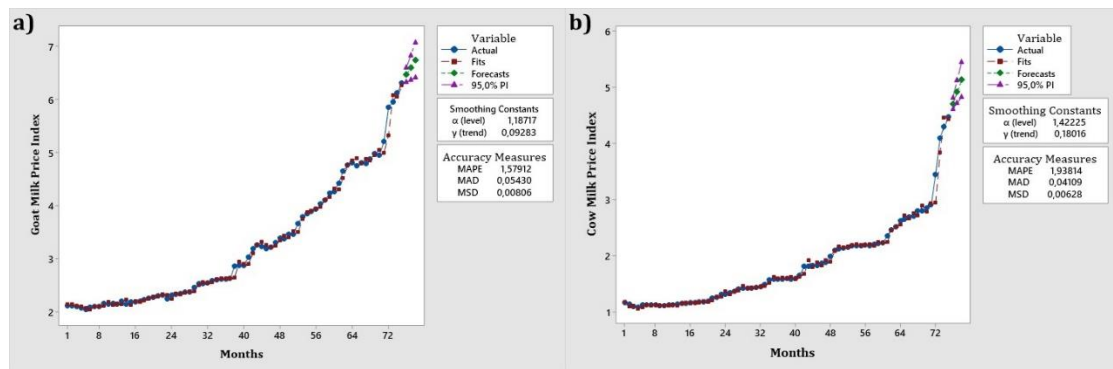
Figure 3. Holt's Method for Goat Milk Price Index (a) and Cow Milk (b) Price and Forecasting Results

Minitab was used for the application of Holt's method. As can be seen from the Minitab output shown in Fig. 3, using optimal level and trend values will minimize the sum of the squared residuals so accuracy measures represent the possible lowest values. As a result of this analysis, the 76. Month, 77. Month and 78. Month price index prediction for goat milk are 6.470, 6.608, 6. 746, respectively. The price index predictions for cow milk for the 76th, 77th, and 78th months are 4.710, 4.928, and 5.142, respectively (Table 1).

Table 1. Overall Results of Trend Analysis and Holt's Method

	Trend Analysis		Holt's Method	
	Cow Milk	Goat Milk	Cow Milk	Goat Milk
Period	Forecast	Forecast	Forecast	Forecast
76	3.04355	5.14089	4.71467	6.47046
77	3.07515	5.19099	4.92852	6.60832
78	3.10676	5.24109	5.14237	6.74618

Conclusion

The goal of this research is to determine the pattern of milk price time series data and provide predictions for the following three months. The Turkish Statistical Institute's Agricultural Products Producer Price Index data from January 2016 to March 2022 was utilized to compile historical Goat Milk and Cow Milk statistics. Trend analysis and Holt's approach were used to examine the trend pattern. The findings showed that the current trend pattern is likely to continue in near future. Results of each analysis represented different prediction values. To express which is the most appropriate method, MAD, MSE or MAPE values should be calculated. Considering MAD values for trend analysis has greater value than Holt's method for goat milk price index. Also, for cow milk price index, MAD value is greater than Holt's method. As a conclusion, Holt's method showed better performance for forecasting of goat and cow milk price index. For future study, nonlinear trend models as well as ARIMA analysis could be applied.

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Response surface methodology optimization of hydraulic conductivity change by microbially induced CaCO₃ precipitation

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Keywords
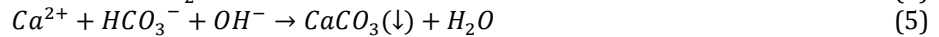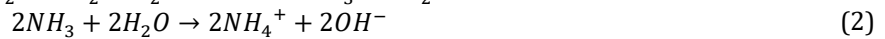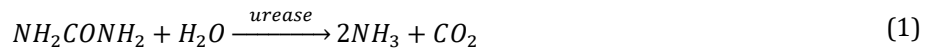Hydraulic conductivity
Microbially induced
calcium carbonate
precipitation
Number of cells
Design of experiment
Response surface
methodology

Abstract
In columns packed with glass beads in the range of 0.25 mm to 3 mm in diameter, the effect of the number of cells deposited in hydraulic conductivity of porous media using CaCO₃ precipitation produced by *Sporosarcina pasteurii* (ATCC 11859) was investigated in the present study. Following the introduction of resting *Sporosarcina pasteurii* cells into the columns, a precipitation solution containing 500 mM CaCl₂ and 500 mM urea was injected into the columns under continuous flow conditions. To investigate the relation between deposited cell number and hydraulic conductivity, Response surface methodology was applied. The results indicated that each response has been affected by factors in a different scale. By creating models, experimental design dimension can be declined.

Introduction

Many researchers have studied microbially induced calcium carbonate (MICP) to develop biotechnology methods such as improving construction materials [1], reducing hydraulic conductivity of porous media [2,3], changing soil behaviors [4,5], sealing cracks [6] using ureolytic bacteria. The precipitates can fill the pores within the soil matrix and bridge the loose sand particles, enhancing the soil's strength and stiffness while decreasing its permeability. The formation of calcium carbonate crystals from urea hydrolysis catalyzed by urease can be characterized as follows [2]:

$$NH_2CONH_2 + H_2O \xrightarrow{urease} 2NH_3 + CO_2 \tag{1}$$
$$2NH_3 + 2H_2O \rightarrow 2NH_4{}^+ + 2OH^- \tag{2}$$
$$CO_2 + OH^- \rightarrow HCO_3{}^- \tag{3}$$
$$CaCl_2 \rightarrow Ca^{2+} + 2Cl^- \tag{4}$$
$$Ca^{2+} + HCO_3{}^- + OH^- \rightarrow CaCO_3(\downarrow) + H_2O \tag{5}$$

Urea is hydrolyzed to ammonia and carbon dioxide by ureolytic bacteria, and the generation of ammonia causes a rise in pH in the environment, which causes calcite precipitation when the environment contains calcium ions [2]. The effectiveness of the MICP process is affected by physiochemical and biological parameters such as pH, temperature, the presence of nutrients, their concentration, the concentration of precipitation reagents, and oxygen availability [7,8]. The density of cells, which is linked to the urease enzyme, is one of these factors.

In the present study, the experiments were conducted using columns packed with glass beads to investigate the effect of cell density on reduction in hydraulic conductivity. The relation between decrease in hydraulic conductivity and cell density was also investigated used design of experiment approach. Response surface methodology was selected as an appropriate method for this study.

Material and Method

Sporosarcina pasteurii [American Type Culture Collection (ATCC) 11859] was used in the experiments to obtain calcium carbonate precipitation. Resting cells of *Sporosarcina pasteurii* were provided by inoculating cells in Tris-YE medium which consisted of Tris buffer (130 mM, pH 9.0), ammonium sulphate (10 g/L) and yeast extract (20 g/L), overnight at 30°C with 120 rpm agitation. The optical densities (OD) of 0.15, 0.75, and 2.25 (abbreviated as OD_{600} 0.15, 0.75, and 2.25) at 600 nm was obtained using distilled water after harvesting the cells to investigate to the relationship between cell concentration and hydraulic conductivity.

In the experiments, 50 mL plastic syringes were utilized as columns, with an inner diameter of 3 cm and a height of 10 cm. For each experiment, the glass beads with an average diameter of 0.25 mm, 0.50 mm, 1.0 mm, 2.0 mm, and 3.0 mm were employed and saturated conditions were provided. The precipitation solution which contained 500 mM $CaCl_2$ and 500 mM urea was prepared aseptically.

First, cell suspension was introduced to the column. Then, the samples were collected from the effluent to calculate the number of cells deposited in the columns. Finally, the precipitation solution was introduced into the column until the hydraulic conductivity became stable. Manometer was employed to measure the hydraulic conductivity of the columns during the experiments.

Table 1 presents the factors and their design combinations showing the levels.

Table 1. Factors and levels of experiment

Factor Name	Units	L1	L2	L3	L4	L5
OD_{600}	-	0.15	0.75	2.25	*	*
Glass Bead Size	mm	0.25	0.5	1	2	3

Design of experiment

The goal of Design of Experiment (DoE) is to prepare and run experiments in order to collect data from appropriately specified experiments. It is feasible to gather a big quantity of information from smaller trials while using a predefined chart for a group of experiments and reviewing the results utilizing various methods. Because more than one factor can be investigated at once, the experiment becomes less expensive [9].

Response surface methodology

RSM is a modeling technique that employs mathematical and statistical methods [10]. The link between some input variables and one or more output variables, which is a response, is investigated. This process entails optimizing data gathered through preset experiments using polynomials fitted to the data. The variables that should be greater than one is represented by x_i in this approach, and the response is expressed as a value that needs to be optimized by y_i. x_i and y_i have a relationship. ε represents the error or noise in the response y_i, and x_i represents the independent variable – factor [11].

$$y_i = f(x_1, x_2, x_3, ..., x_i, ..., x_n) + \varepsilon \qquad (6)$$

Results and Discussion

In the present study, in a random order, 15 experimental trials were completed in keeping with the optimal (custom) design. Design-Expert 11.0.5 was used to get the results. The operating factors were optical density OD_{600} (A), and glass bead size (B). The responses were hydraulic conductivity (K) value (Y_1), deposited cell no (Y_2) and average amount of $CaCO_3$ (Y_3) were considered as the dependent factors. The performance of the design was evaluated by analyzing the minimization of the K value. The results of the experiment are given in Table 2.

The ANOVA results for the current investigation at a 95% confidence interval are summarized in Fig. 1. If the p-value is less than 0.05, this indicates that the model terms are significant. In the present study, for both response of hydraulic conductivity and deposited cell no; A, B and AB are significant model terms and for response of average amount of $CaCO_3$; A, B, AB, A^2 and B^2 are significant model terms.
The actual mathematical model for Y_1 is as follows:

K(cm/s) = 0.0351-0.0170 * OD_{600} + 0.2546 * Glass Bead Size – 0.0578 * OD_{600} * Glass Bead Size

The actual mathematical model for Y_2 is as follows:

Depozite Cell No = 3.0789E+08 + 1.6391E+09 * OD_{600}-1.27754E+08 * Glass Bead Size -5,8293E+08 * OD_{600} * Glass Bead Size

The actual mathematical model for Y_3 is as follows:

Average Amount of $CaCO_3$ (g)=-0.000393+ 0.000799 * OD_{600} + 0.014305 * Glass Bead Size – 7.99002E 06 * OD_{600} * Glass Bead Size -0,000288 * OD_{600}^2

For each model of Y_1, Y_2 and Y_3, R^2 and R^2 adjusted (abbreviated as R^2 adj) values was calculated. Response Y_1 has 0.9423 of R^2 value and 0.9423 of R^2 adj value. Response Y_2 has 0,9126 of R^2 value and 0.8888 of R^2 adj value. Response Y_3 has 0.6752 of R^2 value and 0.4947 of R^2 adj value. As seen in Fig. 2, there are nonlinear relationship between OD_{600} and Glass Beads Size for all response types. A three-dimensional response surface plot is represented.

Table 2. Results of experiment with actual value

	Factor 1	Factor 2	Response 1	Response 2	Response 3
Run	A: OD_{600}	B: Glass Bead Size	K (cm/s)	Deposited cell No	Average Amount of CaCO3 (g)
3	2,25	1	0,191396	3,23874E+09	0,006
8	2,25	3	0,369667	9,37517E+07	0,00152753
12	2,25	2	0,222667	1,81727E+08	0,0123517
13	2,25	0,25	0,0108472	3,49731E+09	0,0020502
14	2,25	0,5	0,0271667	3,4482E+09	0,00950438
1	0,75	2	0,428667	7,37517E+07	0,0128517
4	0,75	3	0,632667	5,37517E+07	0,00158753
5	0,75	1	0,366396	7,81727E+08	0,0062
10	0,75	0,5	0,0871667	9,81727E+08	0,00910438
11	0,75	0,25	0,0348472	1,29731E+09	0,0022502
2	0,15	0,25	0,0424847	8,81727E+08	0,0026402
6	0,15	3	0,722667	2,37517E+07	0,00146875
7	0,15	1	0,366396	2,85727E+08	0,00624
9	0,15	2	0,568667	3,22517E+07	0,0118517
15	0,15	0,5	0,113485	5,81727E+08	0,00820438

ANOVA for 2FI model

Response 1: K (cm/s)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0,7328	3	0,2443	59,87	< 0.0001	significant
A-OD 600	0,1230	1	0,1230	30,15	0,0002	
B-Glass Bead Size	0,6023	1	0,6023	147,63	< 0.0001	
AB	0,0406	1	0,0406	9,95	0,0092	
Residual	0,0449	11	0,0041			
Cor Total	0,7776	14				

ANOVA for 2FI model

Response 2: Deposited Cell No

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2,117E+19	3	7,057E+18	38,29	< 0.0001	significant
A-OD 600	6,698E+18	1	6,698E+18	36,34	< 0.0001	
B-Glass Bead Size	7,854E+18	1	7,854E+18	42,61	< 0.0001	
AB	4,135E+18	1	4,135E+18	22,43	0,0006	
Residual	2,027E+18	11	1,843E+17			
Cor Total	2,320E+19	14				

ANOVA for Quadratic model

Response 3: Average Amount of CaCO3 (g)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0,0002	5	0,0000	3,74	0,0414	significant
A-OD 600	2,342E-07	1	2,342E-07	0,0261	0,8752	
B-Glass Bead Size	7,401E-06	1	7,401E-06	0,8256	0,3872	
AB	7,768E-10	1	7,768E-10	0,0001	0,9928	
A^2	2,107E-07	1	2,107E-07	0,0235	0,8815	
B^2	0,0002	1	0,0002	18,48	0,0020	
Residual	0,0001	9	8,964E-06			
Cor Total	0,0002	14				

Figure 1. ANOVA for each response's model by using Type III – partial sum of squares
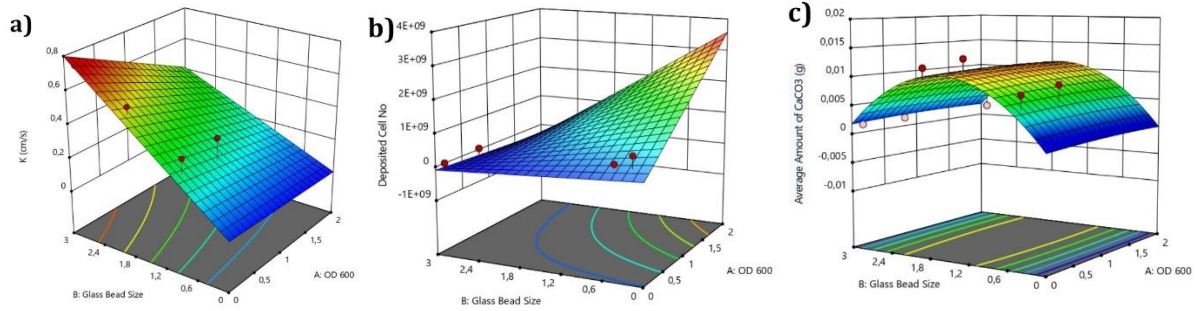
Figure 2. Surface plot of (a) response Y_1, (b) response Y_2, (c) response Y_3

Conclusion

The effect of the number of cells deposited on the decrease in hydraulic conductivity of porous media utilizing $CaCO_3$ precipitation produced by *Sporosarcina pasteurii* (ATCC 11859) was examined in columns packed with glass beads in the range of 0.25 mm to 3 mm in diameter. A precipitation solution containing 500 mM $CaCl_2$ and 500 mM urea was fed into the columns under continuous flow conditions after the resting *Sporosarcina pasteurii* cells were introduced into the columns. Response Surface Methodology was used to study the relationship between deposited cell number and hydraulic conductivity. The findings revealed that factors on a different scale influenced each response. The experimental design dimension can be reduced by creating models. Based on the results of the experiments with various factors and levels, it can be stated that a determined prediction model produced with RSM is effective for analyzing the optimum points and values of preset factors while remaining flexible.

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Investigation of landslide mapping types

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Abstract
Natural disasters are seen in almost every part of the earth's surface and cause the reshaping of the earth's surface. In recent years, people's awareness of disasters has increased and the number of solution-oriented studies has increased. The first step is to create maps of disaster areas in order to minimize the damage that disasters can cause to people and the environment. Creating maps of landslide areas provides great convenience to earth scientists in combating landslides. The development of remote sensing techniques in recent years has enabled the creation of a sensitive and detailed mapping of the land. In this study, different landslide mapping types (inventory, hazard, risk and susceptibility) were discussed.

Introduction

The morphology of the earth's surface is changing and reshaping due to mass movements. A small change on forces acting on rocks and soils may cause slope failure. This is an unavoidable situation. However, with the help of some measures that can be taken, it is possible for people and the environment to get rid of this situation with the least damage. Monitoring and mapping failure prone areas using high spatial resolution images are the basis for disaster management [1].

Field study have been performed by well-trained geologists until recent years. However, it is time consuming and labor intensive. Fine-scale terrain structures may be omitted with the traditional mapping. The developments in remote sensing technology enable us to obtain high resolution and actual data from field. Unmanned aerial vehicles and laser scanners have been frequently used since last decade [2-3].

Landslide is the most common natural disaster and can be seen almost everywhere on the earth's surface. Landslides develop with geological, geomorphological, meteorological factors and human influence. Landslides cause loss of life and property. Landslide areas, which is a major environmental threat, can be modelled by using a UAV. Now, there is a great interest in utilizing UAV in natural hazard applications. Non-invasive techniques are preferred in recent years.

The rapid increase in population requires the creating of new settlements. Rough lands are prone to landslides. It damages buildings and farmland. It has fatal or injury consequences. It closes the highways, thus preventing transportation. Landslides prevents economic development.

During the land use planning stage, landslide inventory, hazard, risk and susceptibility maps are essential to reduce the damages [4].

Landslide inventory map

Landslide inventory maps are maps that show the areal distributions, characteristics, geological features and historical records of existing landslide areas in the field. They are used as a base for many analyzes. With these maps, hazards can be identified and reliable and up-to-date data can be presented to decision makers. Inventory maps also help in choosing the right place. The landslides that have happened in the past give information about the landslides that may happen in the future.

The methods used to create a landslide inventory map are Satellite images, Literature studies, Field observations and Aerial photographs. Moreover, it is necessary to talk to the local people.

Landslide risk map

Landslide risk maps are studies that evaluate the economic and environmental damages together with the estimation of the damage to occur, as well as the loss of life and property that may occur as a result of the landslide.

Landslide hazard map

The landslide hazard is the probability of a landslide occurring in a certain area and within a certain time. It is necessary to identify the potentially risky places before the disaster, in order to minimize the damage. This map shows type, speed and intensity of landslide.

Landslide susceptibility map

The landslide susceptibility map shows the tendency of a region to landslide and potential areas where landslides can occur will be identified. The factors affecting the sensitivity vary from region to region. It is necessary to determine the importance levels of the parameters. The more detailed information is available, the more precise the study will be done.

In the production of landslide susceptibility maps, generally, aspect, distance to drainage network, distance to fault, distance to ridges, distance to road, drainage density, height, fault density, geology, land cover, plan and profile curvature, road density, slope, slope length, river flow strength, surface area ratio and topographic humidity index are used.

The methods generally used in the production of landslide susceptibility maps are probability method (frequency ratio), Analytical hierarchy method, bivariate, multivariate, logistic regression, Fuzzy logic, artificial neural networks and frequency ratio method.

Discussion

Geographic Information Systems (GIS) have been efficiently used to create and analyze landslide maps. Parameters that have different weights can be used in the map production phase. Mapping the landslide site with high-precision and accuracy is vital to lessen the damage. GIS technology enable us to see the details in geomorphology of the environment.

Conclusion

Mapping the potentially dangerous areas is the first step to prevent a possible disaster. In this study, utility of different landslide mapping types was discussed. These maps will be used to represent the slope movements in computer environment. In order to take precautions to landslides these maps need to be prepared accurately.

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