JOURNAL OF SCIENTIFIC PERSPECTIVES

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Research Article

A SUPPORT VECTOR-BASED PREDICTIVE MODEL TO REVEAL THE RELATIONSHIPS AMONG ANTIBODY FEATURES AND THEIR EFFECTIVE FUNCTIONS AGAINST HIV

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ABSTRACT

Despite 4 decades' effort, an effective HIV-1 vaccine has not been produced owing to the inevitable antigenic diversity of the virus and millions of people around the world have lost their lives due to HIV. Increasing the knowledge of adaptive immune response to vaccination would ultimately lead to an effective HIV cure. Antibodies, which are responsible for protection and fighting against antigens, are vital parts of immune system response. In order to identify discriminative antibodies, which provide protection against HIV, and to disclose the associations between antibody features and their functional outcomes, computational methods, such as feature selection, regression and classification can be used to construct predictive models. Here we used our unsupervised K-Means Based Feature Selection (KBFS) method which is presented in our previous study, to identify functional antibodies that fight against HIV. The accuracy results for the proposed KBFS framework are compared with those presented in a recent study and are also compared with results from four different state-of-the-art unsupervised feature selection methods, namely MCFS, InFS, LapFS, and SPFS, along with the entire feature set. Then, support vector based systems are utilised to predict the associations between antibody features and their functional activities, namely gp120-specific antibody dependent cellular phagocytosis (ADCP), antibody dependent cellular cytotoxicity (ADCC) and cytokine release activities on RV144 vaccine recipients. Pearson Correlation Coefficient (PCC) metric is used to evaluate the prediction accuracy of the predictive models and to be consistent with the previous study. Our SVR based KBFS framework presented higher accuracy than the original study by improving prediction performance 16% for ADCP assay, 200% for the ADCC assay.

Keywords: *Feature Selection, RV144, HIV*

1. INTRODUCTION

Antibodies are specialised Y-shaped glycoproteins (gp) that are produced by plasma cells to defend against intruders that cause infection. Antibodies are crucial for the immune system since they play a role in protecting against foreign substances or antigens. Antibodies consist of two antigen-binding fragments: fragment antigen-binding (Fab) and fragment crystallisable (Fc). Fab regions are the arms of the antibodies called immunoglobulin G (IgG) which are responsible for the identification of infected cells [1]. On the other hand, Fc regions stimulate the innate immune system to neutralise antigens. Antigens that exist in vaccines stimulate immune system response by instructing B-cells in order to produce antibodies which are responsible for protection. Vaccine-induced immunity effectors, or antibodies, are important defenders against antigens, including HIV viruses. Vaccination provides active protection since it trains the immune system to recognise antigens. Then, the immune system produces specific antibodies to fight against the antigens. The function of antibodies is to recognise and bind to antigens. This detection process begins when antibodies recognise a small region on the surface of an antigen called the epitope [2]. Vaccine-mediated antibodies are important defenders against intruders including Human Immunodeficiency Virus (HIV) [3]. HIV attacks and destroys the immune system; indeed, it causes depletion of CD4-positive lymphocytes. The RNA of HIV has only nine genes that contain the code necessary to produce structural enzymes [5]. HIV poses a number of immunological threats to the human immune system due to its extensive genetic diversity. Furthermore, HIV is capable of developing countermeasures to avoid the effect of antibodies. HIV can prevent itself from being detected by the immune system thanks to its reverse transcription ability. This ability enables HIV to mutate approximately 3x105 per nucleotide base [6].[1] Therefore, producing an effective vaccine which can elicit antibodies to block HIV is vital to neutralise the virus [7]. Novel vaccine strategies are required to overcome the aforementioned challenges posed by HIV. Increasing the knowledge of associations between virus and immune system would ultimately result in producing an effective vaccine; an example is RV144. Functional antibodies are considered to be HIV inhibitors [8]. These inhibitory antibodies are capable of binding to virions, reducing their movement across mucus and mediating a variety of Fc receptor-mediated anti-HIV-1 activities, such as Antibody Dependent Cellular Cytotoxicity (ADCC) [9] [10]. ADCC-mediated antibodies can eradicate HIV infected CD4 cells [11] and block the transmission of HIV within 24 hours after viral entry [12].

Vaccination is a provider of active immunity since it stimulates the immune system to produce antibodies which fight against a virus. Interestingly, specific antibodies provide protection against specific antigens [13]. More- over, the amounts of antibodies that are produced by the immune system are statistically related to the protection given, since antibodies will be needed for the subsequent attacks from antigens [14]. The functional characteristics of antibodies are also crucial for HIV protection; therefore, the identification of specific antibodies that mediate effector functions to neutralise HIV is essential for producing an effective HIV vaccine. Antibodies can also collaborate with other functions to provide prevention against viruses [15] [16]. Therefore, the identification of discriminative antibody features is crucial in producing prevention against HIV.

2. METHODS AND MATERIAL

In this section methods and materials which are used in this study is presented.

2.1. The Dataset

The RV144 data set provided in [1] is utilised in this study to model their antibody feature function relationships and to disclose HIV-specific antibodies. This data set contains

100 plasma samples (20 of them are placebo and 80 of them are vaccine injected) obtained from the individuals who participated in the RV144 vaccine trial at week 26.

Three different cell-mediated assays are used in this thesis: Antibody Dependent Cellular Phagocytosis (ADCP), Antibody Dependent Cellular Cytotoxicity (ADCC), and Natural Killer Cell Cytokine release. ADCC antibodies are capable of identifying infected cells, and these antibodies are involved in the binding of epitopes of HIV-infected cells [18]. Cytotoxicity activities are mediated by Natural Killer (NK) cells which can directly kill virally infected cells by adhering to them. Cytokine release activities includes the NK cell surface expression of CD107a and the quantitative detection of MIP-1-β and IFN-γ levels produced inside the cell. An anti- gen microsphere based liquid array is applied to determine antibodies (gp41, gp140, p24, gp120, and V1V2) and subclasses (IgG1, IgG2, IgG3, IgG4).

HIV-1 vaccine injection has been shown to be less effective due to the intrinsic variability of the virus. The identification of distinctive antibodies which correlate with protection against HIV-1 infection, along with increasing the knowledge of associations between immune mechanisms and HIV, would ultimately result in the development an effective vaccine against HIV.

In this study, three different cell-mediated assays, ADCC, ADCP, and Cytokine release, are used. The purposes of exploiting the RV144 data set are: (i) to differentiate functional antibodies; (ii) to identify the relationships between the human immune system and the HIV virus; and (iii) to test the effectiveness of the DFSFR framework for the given data set. The aim of this study is, therefore, to predict functional relationships between antibody features and their functional activities in RV144 vaccine recipients. Each data sample has twenty antibody features that consist of features related to IgG subclass and antigen specificity.

2.2. Feature Selection Methods

Four different feature selection methods along with the entire feature set are used to identify discriminative antibody features from RV144 dataset.

2.2.1. K-Means Based Feature Selection (KBFS)

KBFS is proposed in our previous study [19] and applied to a high dimensional age dataset. Here we adapted this method to disclose the relationship among antibody features and HIV.

At the first stage of KBFS, the data is transposed in order that samples become features and features become samples. The reason for this is to ensure that instead of samples the features are clustered in k-means algorithm. Next, based on user-specified integer (k), the data will be divided into k- clusters. The K-means clustering algorithm sorts the features based on their distance from the centroids in each cluster, and it usually exploits Euclidean or squared Euclidean distance measure. On the other hand, KBFS identifies three centroids based on their distance to the center of each cluster. The purposes of this is to minimise randomisation error and to deal with outliers.

Euclidean distance which is the most commonly used distance metric is exploited to calculate the distances among centroids and features. Euclidean distance can be calculated from:

$$J = \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_j||^2$$

where $x_i s\ i = 1,2, \dots, n$ are a set of features to be partitioned to K clusters and $C_j s\ j = 1,2, \dots, K$

are the centroid points.

In KBFS, three centroid points are exploited for each cluster and features are ranked based on their absolute distance values to those centroids. A feature with the lowest distance to the any of three centroid points in a cluster is considered as the most important one. In KBFS, distance measure is calculated by:

$$J_{i1} = \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j1}||^2$$

$$J_{i2} = \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j2}||^2$$

$$J_{i3} = \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j3}||^2$$

The weight of a feature is then calculated by:

$$WX_i = \frac{1}{\min\ (J_{i1}, J_{i2}, J_{i3})}$$

The K-means method randomly initialises the centroids and this might profoundly affect the clustering results. Therefore, the process of KBFS is repeated 100 times to minimise the randomisation error. At the end, the mean of the distances between the centroids and the features are calculated in order to rank features. Therefore,

$$\frac{1}{WX_i} = \frac{1}{p} \sum_{t=1}^{p} \min\ (\sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j1}||^2, \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j2}||^2, \sum_{j=1}^{K} \sum_{i=1}^{n} ||x_i - C_{j3}||^2)$$

where $p = 1,2, \dots, 100$, C represents clusters, $x_i s$ are features where $i = 1,2, \dots, n$, K is the number of clusters, WX_I is the weight of *i-th* feature and $C_j s$ are centroids.

2.2.2 Multi-Cluster Feature Selection (MCFS)

MCFS is a clustering based feature selection method that utilises sparse learning technique to select relevant features. MCFS uses spectral analysis to measure the correlation between different features.

2.2.3 Laplacian Score Feature Selection (LapFS)

LapFS is a graph based unsupervised feature selection method that selects features which are important to preserve the data manifold structure. LapFS utilises pairwise similarities between features that are measured by using the heat kernel.

2.2.4 Spectral Feature Selection (SPFS)

SPFS can be defined as an extension of LapFS, however, SPFS works for both supervised and unsupervised scenarios. SPFS selects features which are consistent with the graph structure of the data; however, unlike LapFS, SPFS also independently evaluates features.

2.2.5 Infinite Feature Selection (InFS)

In InFS, each node feature represented with a node in a graph and features are selected according to their centrality score.

2.3. Support Vector Regression

Support Vector Machine (SVM) is a powerful statistical supervised learning model which has been exploited for both regression and classification tasks [24] [25]. In classification scenario, SVM realises a discriminative hyperline which achieves the largest margin between two classes [25]. The hyperline can be formulated as:

$$f(x) = w * x + b$$

where w is normal to hyperline and $\frac{b}{||w||^2}$ is the perpendicular distance from is the perpendicular distance from hyperline to the origin.[SEP]The regression version of SVM is called Support Vector Regression (SVR).

SVR constructs a model function which indicates relationship between features and the target variable. In SVR, ε-intensive loss function is used so that only features out of ε tolerance are penalised given by:

$$C\sum_{i}^{n}\zeta^{p}$$

where p is a positive integer, and ζ is the orthogonal distance away from the ε-region. In this study, SVR is implemented with radial basis kernel using the LIBSVM library [26].

2.4. Performance Evaluation Metrics

In this study, Pearson Correlation Coefficient metric is used to evaluate the effectiveness of predictive models and to compare our results with previous study [1].

PCC is an evaluation metric that is exploited to assess the performance of predictive models. The PCC evaluates the strength of the relationship between two variables. It can be calculated as:

$$PCC = \frac{\{n\Sigma\{x_i y_i\} - \Sigma\{x_i\}\Sigma\{y_i\}\}}{\sqrt{\Sigma x_i^2 - (\Sigma {x_i}^2)}\sqrt{\Sigma y_i^2 - (\Sigma {y_i}^2)}}$$

where x and y are vales the two quantitative variables and PCC indicates the linear association between them. A value of PCC that is equal to 1 indicates a perfect linear correlation.

3. RESULTS AND DISCUSSION

The RV144 data set provided in [1] is used in this study to model the antibody feature-function relationship. This data set contains 100 plasma samples (20 of which are placebo and 80 are vaccine-injected) obtained from the individuals participating in the RV144 vaccine trial at week 26. Three different cell-mediated assays are used: Antibody Dependent Cellular Phagocytosis; Antibody Dependent Cellular Cytotoxicity; and Natural Killer Cell Cytokine Release activities. The accuracy results for the proposed KBFS framework are compared with those presented in a previous study [1], and are also compared with results from four different

state-of-the-art unsupervised feature selection methods, namely MCFS, InFS, LapFS, and SPFS, along with the entire feature set. In this study, the PCC metric is used to be able to perform a consistent comparison with the previous study [1].

The SVR-based predictive models for the regression tasks are constructed using feature selection methods (filtered feature set). Their performance is then evaluated using a five-fold cross validation method. The RV144 data set is divided into two sets of samples. Four out of five samples, with a total of 64 samples, are utilised for training and the rest (16 samples) for testing purposes. This process is repeated 200 times by randomly creating subsets of the samples for the five-fold cross validation in order to avoid a bias towards and to assess the effect of randomisation in the cross validation. At the end, the mean performance and its corresponding standard deviation (std) values are obtained for each of the predictive models.

The prediction performance of unsupervised feature selection methods on three cell-mediated assays are summarised in Tables 1-3. Table 1 shows the PCC results of predictive models for Natural Killer Cell Cytokine release activities. The predictive models aim to estimate the level of cytokine release in order to understand its functionality for protection. The results suggest that KBFS outperforms state-of-the-art methods with 0.52 PCC using 16 features. SPEC yields the second-best result yielding 0.51 PCC, with 16 antibody features. Other methods produce average results.

The prediction results of unsupervised predictive models for ADCC activities are presented in Table 2. KBFS again produces the best result yielding 0.42 PCC using only 10 antibody feature. InFS produces the second-best result with 0.40 PCC utilising 14 antibody features. Other methods produce average results.

Table 1. Comparison of Unsupervised Feature Selection Methods for the Antibody Features and Natural Killer Cell Cytokine Release Activity Relationship

Metrics	PCC
KBFS (16)	0.52 ± 0.17
MCFS (16)	0.49 ± 0.17
Laplacian (16)	0.49 ± 0.18
SPEC (16)	0.51 ± 0.17
InFS (18)	0.49 ± 0.17
Baseline (20)	0.49 ± 0.17

Table 2. Comparison of Unsupervised Feature Selection Methods for the Antibody Features and Cellular Cytotoxic Activity Relationship

Metrics	PCC
KBFS(11)	0.43 ± 0.19
MCFS (18)	0.39 ± 0.18
Laplacian (12)	0.39 ± 0.18
SPEC (18)	0.41 ± 0.18
InFS (14)	0.40 ± 0.17
Baseline(20)	0.38 ± 0.18

Table 3. Comparison of Unsupervised Feature Selection Methods for the Antibody Features and Cellular Phagocytosis Activity Relationship

Metrics	PCC
KBFS(12)	0.65 ± 0.17
MCFS (17)	0.65 ± 0.14
Laplacian (3)	0.65 ± 0.15
SPEC (18)	0.61 ± 0.14
InFS (18)	0.64 ± 0.15
Baseline(20)	0.61 ± 0.15

Table 3 presents the prediction results of USFSMs for ADCP activities. As can be clearly seen in the table, KBFS filtered predictive model outperforms the predictive models implemented with the complete feature set, InFS and SPEC. On the other hand, KBFS, Laplacian Score and MCFS produce the same PCC results with 12, 3 and 17 antibody features respectively.

The prediction results of the proposed method are also compared with those of the previous study [1] where the same data set by using the same cross validation method is utilised (5-fold with 200 replicates) and comparison results are shown in Tables 4-6. The results appear to suggest that KBFS has a better quantitative accuracy than the predictive models constructed using Lars, GP and SVR as presented in the previous study for ADCC and ADCP assays, at 0.43 and 0.65 PCC respectively. In particular, the proposed approach yields as much as 1.16x and 3x better outcomes than the results of SVR for the ADCP and ADCC assays respectively. KBFS has slightly lower quantitative performance as compared to the predictive model for the Cytokine assay constructed using SVR as presented in the previous study. However, it still has better quantitative performance than the Lars and GP predictive models for the Cytokine assay.

Overall, the proposed KBFS method generally achieves the best performance on all cell-mediated assays, which thereby verifies that it is able to select informative antibody features.

Table 4. A Comparison of the Results with the Previous Study for the Antibody Features and Cellular Phagocytosis Activity Relationship

Regression	PCC
Lars [1]	0.61±0.15
GP [1]	0.53±0.16
SVR [1]	0.56±0.19
KBFS	0.65 ±0.17

Table 5. A Comparison of the Results with the Previous Study for the Antibody Features and Cellular Cytotoxic Activity Relationship

Regression	PCC
Lars [1]	0.42±0.18
GP [1]	0.24±0.21
SVR [1]	0.14±0.24
KBFS	0.43±0.19

Table 6. A Comparison of the Results with Previous Study for the Antibody Features and Natural Killer Cell Cytokine Release Activity Relationship

Regression	PCC
Lars [1]	0.51±0.21
GP [1]	0.46±0.24
SVR [1]	0.55± 0.15
KBFS	0.52±0.17

4. CONCLUSION AND FUTURE WORK

In this study, a support vector-based (SV-based) predictive model is used to predict the associations among cell-mediated activities and multivariate antibody features in RV144 data set. Antibody features are filtered out using USFSMs in order to obtain attributes of high efficacy. This data set consists of 20 placebo samples and 80 vaccine injected samples, for a total of 100 data samples. Cross-validated SV-based predictive models presented higher accuracy than in the original study [1].

The RV144 data set is used to test the predictive capability of the pro- posed KBFS model for the given data set and to provide better generalisation and performance compared to a study conducted on the same data set [1].

The goal of the study is to disclose associations among antibody features and their effector functions. The effector functions can be described as actions of the immune system to fight against HIV. Therefore, the identification of specific antibody features involved in fighting against HIV is crucial in neutralising the virus.

Experimental results conducted on RV144 Vaccine data set suggest that the proposed KBFS method, outperforms the state-of-the-art USFSMs as well as the method used in the previous paper on the same data set. KBFS has a better quantitative accuracy performance than the predictive models constructed using Lars, GP and SVR presented in the data set paper for ADCC, and ADCP assays. KBFS has a little less quantitative performance as compared to predictive model for Cytokine assay constructed using SVR presented in the data set paper. However, it still has better quantitative performance than the Lars and GP predictive models for the Cytokine assay. By utilising KBFS framework, the number of features are reduced to 11 for ADCC assay, 12 for ADCP assay and 16 for Cytokine assay. However, in data set paper, the number of selected features are not indicated; instead, filtered set is mentioned without providing the number of selected features.

Experimental results conclude that the proposed unsupervised framework, KBFS, achieves generally the best performance on all assays, which thus verifies that it is able to reveal discriminative antibody features that provide protection against HIV.

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Research Article

THE EFFECT OF NUMBER OF WALLS WITH DIFFERENT THICKNESS ON THE PROPERTIES OF THE POLYCARBONATE PANELS

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ABSTRACT

Polycarbonate is a durable, strong, transparent new polymer material. It is used as building material or element because of its properties such as high strength, light transmittance, recycling, lightweight and vapor transmittance. Unlike most thermoplastics, polycarbonate undergo large plastic deformations cracking or breaking so it can be produced with different dimensions and shapes. Polycarbonate panels consist of different numbers of walls with different thickness. Generally, the properties of the polycarbonate panels are determined with all structures of the panels. However, the effect of the number of walls should be determined on the characteristic properties of the polycarbonate panels. Especially transparency and thermal transmittance should be effected by the number of walls. In this study, characteristic properties of the polycarbonate panels such as light transmittance, water vapor transmission, impact and bending strengths, should be tested with different numbers of walls or thickness. Finally, the characteristic properties of the polycarbonate panels are suitable when the number of walls and thickness are low.

Keywords: *Polycarbonate, impact, light transmittance, bending stiffness.*

1.INTRODUCTION

In the construction of naturally lit structures (e.g., green houses, pool enclosures, conservatories, stadiums, Sunrooms, and so forth), glass has been employed in many applications as transparent structural elements, such as, windows, facings, and roofs. However, polymer sheeting is replacing glass in many applications due to several notable benefits.

One benefit of polymer sheeting is that it exhibits excellent impact resistance compared to glass. This in turn reduces maintenance costs in applications wherein occasional break age caused by vandalism, hail, contraction/expansion, and so forth, is encountered. Another benefit of polymer sheeting is a significant reduction in weight compared to glass. This makes polymer sheeting easier to install than glass and reduces the load-bearing requirements of the structure on which they are installed. In addition to these benefits, one of the most significant advantages of polymer sheeting is that it provides improved isolative properties compared to glass. This characteristic significantly affects the overall market acceptance of polymer sheeting as consumers desire a structural element with improved efficiency to reduce heating and/or cooling costs (Maas *et al.*,2013).

The use of polycarbonate can enhance daylighting in architectural design at lower costs and, at the same time, significant energy savings in commercial and industrial applications could be achieved, thanks also to multiwall polycarbonate panels designed for improving thermal performance. Moreover, in these applications, visual connection to outdoors is not as important as the incoming light, which gives a more comfortable environment, and it should be avoided in some situations like industrial areas (Moretti *et al.*, 2013)

Polycarbonates (PC) are a group of thermoplastic polymers containing carbonate groups in their chemical structures. Polycarbonates used in engineering are strong, tough materials, and some grades are optically transparent. They are easily worked, molded, and thermoformed. Because of these properties, polycarbonates find many applications.

Polycarbonate is a durable material. Although it has high impact-resistance, it has low scratch-resistance. Therefore, a hard coating is applied to polycarbonate eyewear lenses and polycarbonate exterior automotive components. The characteristics of polycarbonate compare to those of polymethyl methacrylate (PMMA, acrylic), but polycarbonate is stronger and will hold up longer to extreme temperature. Polycarbonate is highly transparent to visible light, with better light transmission than many kinds of glass.

Over the past few decades, the demand for polycarbonate as a major engineering plastic has increased because they have attracted a significant attention for a range of applications in several industrial fields. Polycarbonate is an amorphous, clear polymer that exhibits three key characteristic properties: toughness, transparency, self-extinguishing characteristic, and heat resistance (Pham *et al*,1997; Madkour,1999; Pham *et al*.,2000; Schnell,1964)

Unlike most thermoplastics, polycarbonate can undergo large plastic deformations without cracking or breaking. As a result, it can be processed and formed at room temperature using sheet metal techniques, such as bending on a brake. Even for sharp angle bends with a tight radius, heating may not be necessary. This makes it valuable in prototyping applications where transparent or electrically non-conductive parts are needed, which cannot be made from sheet metal. PMMA/Acrylic, which is similar in appearance to polycarbonate, is brittle and cannot be bent at room temperature.

Polycarbonate is a high-performing thermoplastic that is widely used in building and construction products, from windows and skylights to wall panels and roof domes to exterior elements for LED lighting. Polycarbonate has a number of qualities that make it useful in these

applications – it is lightweight and durable, with high optical clarity, high-impact and high-heat resistance, as well as excellent flammability resistance.

Below are some of the many building applications that take advantage of the high performance of polycarbonate (Bonenfant, 2019; Hedges,2018);

- Polycarbonate can be used in place of glass in a variety of window and skylight applications. Polycarbonate panels and sheets allow natural light to enter a building, and they can also be tinted, reducing the sunlight that reflects inside a building and helping to minimize interior cooling costs in the summer. Depending on the gauge, a typical window- and roof-glazing application using solar-control IR multi-wall polycarbonate sheet can help to reduce interior heat, resulting in energy savings in a temperature-controlled environment.
- From opaque cladding panels to canopies, barrel vaults, skylights, translucent walls and signage, roof domes and louvers, polycarbonate sheet products are designed and available in a wide range of thicknesses, structural strengths and configurations that also meet. Polycarbonate can be formed into a variety of complex shapes using thermoforming, a heat-based thermoplastic shaping technique. Polycarbonate sheet also can be cold-line bent similar to metal. A variety of processes to shape polycarbonate facilitate many building features, from stressed curves for arches to simple paneling.
- Light-emitting diode (LED) lighting is a top choice for illuminating homes and businesses, offering energy efficiency, durability and long life. As an exterior element for LED lighting, polycarbonate plastic is sturdy, and its crystal-like clarity holds up over many years. Other benefits of polycarbonate plastic in LED lighting include heat resistance, transparency, impact resistance, low flammability, and increased energy efficiency.
- Polycarbonate is used in security glazing—strengthening prisons, guard booths, bank teller shields, convenience stores, hurricane shutters, hockey rink surrounds and more. Specifically, polycarbonate's impact strength makes it an excellent choice for security applications, including blast and bullet-resistant glazing. Clear as glass, it also presents an advantage over alternatives such as wire glass and metal screens. When used in a multi-wall format, polycarbonate provides significant insulation, with resulting energy efficiency benefits. When treated with solar control technology, polycarbonate also provides protection from IR radiation and can also increase energy efficiency.
- Polycarbonate is used extensively in sports stadium roofs to protect fans from bad weather – and let the game go on – while allowing in natural light and saving energy at the same time.

Hollow polycarbonate is also often named as a structural polycarbonate, cellular polycarbonate, channel polycarbonate or multiwall polycarbonate. The definition «cellular» is used due to its special internal structure. Air, which is present in the space (cells) between the dividing walls inside of the polycarbonate sheet (called chambers), provides thermal insulation properties, and the existing stiffeners (dividers), ensure a great structural rigidness and flexibility of polycarbonate sheet at the same time.

The unique feature of these glazing products include:

1. They have air spaces within the chamber which provide excellent thermal insulation. This is the reason why they are used in glazing applications where heat conservation is of essence.
2. The dividing walls act as supportive structure which provide a strong structural rigidness and flexibility of the polycarbonate sheet (Lu, 2015).

Cellular polycarbonate hollow sheets offer the higher level of glazing performance where transparency along with high impact strength is of vital importance. They have excellent physical, mechanical, electric as well as hot property which explains their high reputation in buildings and decoration industry. They are sold all over the world, making great contributions to consumer's beautiful life. Their versatility makes them the ideal choice for glazing in hospitals, schools, sporting areas and public infrastructure projects. They are available in transparent & textured finishes.

Cellular polycarbonate panels are used at sunshades for stadiums and bus shelters, lighting for corridors, passages and subway entries, sound and heat insulation for constructions such as houses, canopies for agricultures greenhouses, zoos, PC sheets mainly used for building and decorating materials, greenhouse materials , and the block of insulation materials, wall and roof of greenhouse, department stores , exhibition centers , telephone booth , insulation shield in express ways & highways, office buildings, hotels, villas, stadiums, schools, bus stop, terminals, hospitals, subway entry and exit doors.

In this study, characteristic properties of the polycarbonate panels such as light transmittance, water vapor transmission, impact and bending strengths, should be tested with different numbers of walls or thickness. Therefore, the relationship between the properties of polycarbonate panels and the number of walls should be determined and evaluated.

2.EXPERIMENTAL ANALYSIS

6 different polycarbonate panels are tested. The panels have 9 walls and 40 mm thickness, 5 walls and 10 mm thickness, 5 walls and 20 mm thickness, 6 walls and 40 mm thickness, 6 walls and 30 mm thickness, 5 walls and 16 mm thickness. The experimental tests are linear thermal expansion, light transmittance, energy transmittance, water vapor transmittance, bending and shear stiffness, buckling, sound transmission.

2.1. Determination of Coefficient of Linear Thermal Expansion and Glass Transition Temperature

According to TS 1065-2 1SO 11359-2, 3 rectangular prism samples are prepared with 5 mm width and 5 mm length. The change in the length with the temperature in the sample are measured by settling the samples in the Thermo-Mechanical Analysis instrument which measures the change in the temperature by loading $4 \pm 0{,}1$ kPa. The change in the length of the sample is recorded for every temperature. The Coefficient of Linear Thermal Expansion (α) at T temperature, is calculated as K^{-1} and the coefficients are demonstrated in Table 1.

$$\alpha = (dL/dT) \times 1/L_0$$

Lo: The length of the sample at room temperature (μm)

L: The length of the sample at T temperature (μm)

T: Temperature (K)

Table 1. The Coefficients of Linear Thermal Expansion of Polycarbonate Samples

The Number of Walls-Thickness	The Coefficient of Linear Thermal Expansion
9 walls- 40 mm thick	0,0308
5 walls – 10 mm thick	0,0311
5 walls – 20 mm thick	0,0309
6 walls – 40 mm thick	0,0311
6 walls – 30 mm thick	0,0311
5 walls – 16 mm thick	0,0310

2.2 The Calculation of Thermal Transmittance

According to TS EN 674, 400 mm x 400 mm 2 samples are prepared in order to measure the thermal transmittance with the plate method. The upper and lower surfaces of the sample are connected with the deferential thermo-probes and they are settled between the heating plate and the cooling plate. While one surface of the sample is heated with the electricity power, (ϕ_T, Watt), the other surface of the sample is cooled with water. Therefore, the difference in the surface temperature is measured. The thickness (d) of the sample and the area of plate is recorded. At 5 points of the sample, the difference in the temperature is measured. The thermal transmittance of the polycarbonate sample is calculated according to above formula in the regard of TS EN 673, and the results are shown in Table 2.

$$\lambda = (\Phi_T . d) / (2. A. \Delta T)$$

Table. 2 The Thermal Transmittance of Polycarbonate Samples

The Number of Walls-Thickness	The Thermal Transmittance (W/m^2K)
9 walls- 40 mm thick	7,1
5 walls – 10 mm thick	1,9
5 walls – 20 mm thick	5,6
6 walls – 40 mm thick	7,1
6 walls – 30 mm thick	6,5
5 walls – 16 mm thick	4,1

2.3 The Light Transmittance

According to TS EN 14500, at first, the thickness of the samples is measured and then the samples are settled in the spectrophotometer. The absorption amount of the opal samples is recorded by transmitting 500-550 nm wave-length light through every sample. According to these absorption amounts, the percentage of the light transmittances are determined. Therefore, the samples are aged artificiality by holding under 400 W UV lamp for the specific time according to TS EN ISO 4892-2. After the artificial ageing, the absorption amount and the light transmittance of the samples are measured again and the results are demonstrated in Table 3.

Table 3. The Light Transmittance of Polycarbonate Samples

The Number of Walls-Thickness	The Light Transmittance (%)	The Light Transmittance After Artificial Ageing (%)	The Difference in Light Transmittance the artificial ageing Transmittance After Artificial Ageing (%)
9 walls- 40 mm thick	90	85	5
5 walls – 10 mm thick	77	74	3
5 walls – 20 mm thick	77	72	5
6 walls – 40 mm thick	82	81	1
6 walls – 30 mm thick	81	80	1
5 walls – 16 mm thick	77	73	4

2.4 Total Solar Energy Transmittance

According to TS EN 410, the total solar energy transmittance is measured with spectrophotometer. T, the amount of the reflection, is measured by the spectrophotometer to determine the total solar energy transmittance. At first, the amount of reflection of the samples are recorded under 20 W light and then the amount of reflection is recorded after the samples are held under 400 W UV lamp in the regard of TS EN ISO 4892-2. The total solar energy transmittance is calculated with the difference between two reflections and the amount of the reflections and the coefficients of shading are shown in Table 4. The coefficient of shading is calculated as the ratio of the total solar energy transmittances of the polycarbonate samples and 3 mm thick glass.

Table 4. Total solar energy transmittance and the coefficient of shading of polycarbonate samples

The Number of Walls-Thickness	Total Solar Energy Transmittance (%)	Solar Direct Transmittance-T_e (%)	Coefficient of Shading
9 walls- 40 mm thick	87	83-91	1,01
5 walls – 10 mm thick	72	68-76	0,84
5 walls – 20 mm thick	73	71-75	0.85
6 walls – 40 mm thick	87	84-90	1,01
6 walls – 30 mm thick	87	84-89	1,00
5 walls – 16 mm thick	72	71-74	0,85

2.5 Water Vapor Transmission

According to TS EN ISO 12572, 3 polycarbonate circular samples for every type are cut with 80 mm diameter. The thickness of the samples is chosen according to the production of the firm. $CaCl_2$, the humidifier, is put in the bowls which has the same diameter as the samples and then the samples are settled in the mouth of the bowls without spaces. The dimension between the sample and $CaCl_2$ should be 15 ± 5 mm. The circumstance of the samples is covered with the paraffin. After the bowls with the sample are weighed in the analytical scale, the bowls are put in the closet with $23\pm0,5$°C and 93 ± 3 relative humidity. The samples are weighed every day at the same time. When the measurement of weights becomes constant, the test is finished. The resistance factors of the water vapor transmission of the samples are calculated according to the difference in the weights in the time and demonstrated in Table 5.

Table 5. The resistance factors of the water vapor transmission of the polycarbonate samples

The Number of Walls-Thickness	The resistance factors of the water vapor transmission (gr/mm^2.h.Pa)
9 walls- 40 mm thick	62
5 walls – 10 mm thick	19
5 walls – 20 mm thick	48
6 walls – 40 mm thick	32
6 walls – 30 mm thick	33
5 walls – 16 mm thick	35

2.6 The Mechanical Resistance and the Deformation Behavior

According to TS EN 16153, at least 3 samples are prepared according to the cutting directions in the standard. For the x-axis loading, the samples are cut parallel to the levels whereas for y- axis loading, the samples are cut perpendicular to the levels. The samples are tested with 3- points bending test and loaded according to the cutting direction. The distance between the supports is chosen as 200 mm. The samples are loaded in the attitude to x and y axis. The maximum force and the deformation are recorded and the deformation behavior for x and axis is calculated according to below formula. Also, the shear stiffness through y-axis is calculated.

$$B_x = \frac{F_x \cdot {L_x}^3}{48 \cdot s_x \cdot b}$$

B_x : The bending stiffness in x-axis

F_x : The maximum force in the attitude to x-axis.

L_x: The distance between the supports

s_x : The deformation at 0,6 min.

b: The width of the sample

$$B_y = \frac{F_y \cdot ({L_{y1}}^3 - L_{y1} \cdot {L_{y2}}^2)}{48b \cdot (s_{y1} - s_{y2} \frac{L_{y1}}{L_{y2}})}$$

B_y : The bending stiffness in y-axis

F_y: The maximum force in the attitude to y-axis

L_{y1} : The distance between the supports at first measurement in y-axis

L_{y2} : The distance between the supports at second measurement in y-axis

s_{y1} : The deformation at 6 min at L_{y1}

s_{y2} : The deformation at 6 min at L_{y2}

b: The width of the sample

$$S_y = \frac{F_y \cdot (L_{y1} - \frac{{L_{y1}}^3}{{L_{y2}}^2})}{4b \cdot (s_{y1} - s_{y2} \frac{{L_{y1}}^3}{{L_{y2}}^3})}$$

S_y : The shear stiffness in y-axis

F_y : The maximum force in the attitude to y-axis

L_{y1} : The distance between the supports at first measurement in y-axis

L_{y2} : The distance between the supports at second measurement in y-axis

S_{y1} : The deformation at 6 min at L_{y1}

S_{y2} : The deformation at 6 min at L_{y2}

b : The width of the sample

In Table 6, the bending stiffness in x and y-axis (B_X, B_Y) and the shear stiffness in y-axis (s_Y) is demonstrated.

Table 6. The bending stiffness (B_X, B_Y) and the shear stiffness (s_Y) of polycarbonate sample

The Number of Walls-Thickness	B_X (Nm^2/m)	B_Y (Nm^2/m)	s_Y (Nm^2/m)
9 walls- 40 mm thick	1093	1115	1,13
5 walls – 10 mm thick	599	230,8	1,47
5 walls – 20 mm thick	1166	137	0,81
6 walls – 40 mm thick	788	423	0,47
6 walls – 30 mm thick	780	390	0,48
5 walls – 16 mm thick	880	168	0,84

Also, the bending and shear stiffness of the polycarbonate samples are measured after the artificial ageing. The results are shown in Table 7.

Table 7. The bending stiffnesses (Bx, By) and the shear stiffness (sy) of polycarbonate sample after artificial ageing

The Number of Walls-Thickness	B_X (Nm^2/m)	B_Y (Nm^2/m)	s_Y (Nm^2/m)
9 walls- 40 mm thick	874	746	0,86
5 walls – 10 mm thick	607	514	2,22
5 walls – 20 mm thick	1332	410	1,65
6 walls – 40 mm thick	1229	946	1,22
6 walls – 30 mm thick	1208	931	1,17
5 walls – 16 mm thick	976	463	1,93

$$M_b = \frac{F_b(L - L_c)}{4b}$$

F_b: The maximum buckling force

L: The distance between the supports

L_c : The distance between the loads

b: The width of the sample

The buckling moment is calculated before and after the artificial ageing (Table 8).

Table 8. The mechanical resistance of polycarbonate samples

The Number of Walls-Thickness	Buckling Moment (Nm/m)	Buckling Moment After Artificial Ageing (Nm/m)
9 walls- 40 mm thick	22	36
5 walls – 10 mm thick	35	50
5 walls – 20 mm thick	31	55
6 walls – 40 mm thick	26	29
6 walls – 30 mm thick	27	30
5 walls – 16 mm thick	32	52

2.7 Impact Test

According to TS EN 16153, the effect of the impact is tested by the small hard body and large soft body. All the samples are placed on the supports as 40 cm distance with 90°.

In the regard of TS EN 6603-1, in the small hard body test, 250 gr steel ball is fell down on the sample from I meter. The steel ball is fell down on 3 points of the sample. In the standard, these 3 points are outer surface of the sample, the middle and the corner. According to TS EN 1873, in the large soft body, 50 kg bag is fell down on the sample from the specific height. The heights are determined as 0,6-1-1,2-1,6 meter in the standard. The results of both impact test are shown in Table 9.

Table 9. The impact resistance of polycarbonate samples

Impact Test	9 walls- 40 mm thick	5 walls – 10 mm thick	5 walls – 20 mm thick	6 walls – 40 mm thick	6 walls – 30 mm thick	5 walls – 16 mm thick
Small hard body	Damage (no crack or break)	Pass	Pass	Pass	Pass	Pass
Large soft body	Pass	Pass	Pass	Pass	Pass	Pass

According to TS EN ISO 6603-1, the specific weight is fell down on the samples from the specific heights. The impact body should be fell down on the middle of the sample. The impact energy is determined by changing the heights. The heights are between 0,6-1,6 m. The mostly used statistical method is stair method. I kg spherical iron ball is used for the impact testing. The samples are cut as 140 x 140 mm sguare section. The thickness is chosen as the production. The iron ball is fell down ftom the specific heights. The damage is observed visually. In the regards of the different heights, 50 W impact energy is calculated as Joule with below formula.

$$E_{50} = m \times g \times H_{50}$$

E_{50}: 50 % impact energy (J)

m: The constant weight of impact body (kg)

g 'The gravity velocity (9,81 m/s^2)

H_{50}: The height of 50 % impact energy (m)

H_{50} is calculated by below formula;

$$H_{50} = H_a + \Delta H\left(\frac{A}{N} \pm 0.5\right)$$

H_a: The smallest height (m)

ΔH: The change in the height (m)

A: The damaged and non-damaged samples according to the heights

N: The total number of damaged and non-damaged samples

The standard deviation 1s calculated according to change in the heights by below formula;

$$s = 1{,}62\Delta E\left(\frac{NB - A^2}{N^2} + 0{,}029\right)$$

s: The standard deviation

ΔE: The difference in energy

A: The damaged and non-damaged samples according to the heights

N: The total number of damaged and non-damaged samples

B: The damaged and non-damaged samples according to the sguare of heights

In Table 10. 50 % impact energy and the standard deviation is demonstrated.

Table 10. The impact energy and standard deviation of polycarbonate samples in instrumented impact testing

The Number of Walls-Thickness	E_{50} (J)	s(J)	Damage
9 walls- 40 mm thick	5,89	4,07	Small (No crack or break)
5 walls – 10 mm thick	9,81	4,07	Pass
5 walls – 20 mm thick	5,23	5,04	Pass
6 walls – 40 mm thick	9,16	5,04	Pass
6 walls – 30 mm thick	9,11	5,04	Pass
5 walls – 16 mm thick	8,3	4,07	Pass

2.8. Laboratory Measurement of Sound Insulation of Building Elements

According to TS EN ISO 10140-1: Annex D, I m x 40 cm samples are used. 5 constant loudspeakers at different situations are used to measure the sound insulation. The value of the sound from the loudspeaker is measured by the receivers behind the sample. The distance between the receivers, samples and the loudspeakers should be 1,2 meter. The frequency band

should be 6 seconds at the 100 Hz and 400 Hz. According to TS EN 717-1, the average of 5 measurements is the value of the sound insulation in Table 11.

Table 11. The values of sound insulation of polycarbonate samples

The Number of Walls-Thickness	Sound Insulation (dB)
9 walls- 40 mm thick	18
5 walls – 10 mm thick	18
5 walls – 20 mm thick	16
6 walls – 40 mm thick	22
6 walls – 30 mm thick	21
5 walls – 16 mm thick	16

3. RESULTS AND DISCUSSION

3.1 Thermal Properties

The coefficients of linear thermal expansion of polycarbonate samples are smaller than the coefficient of linear thermal expansion of pure polycarbonate of which is 0,065. All the coefficients are closer each other so the number of walls do not affect the coefficient.

When the thickness of the sample increases, the thermal transmittance increases. In Polygal technical specification, the results support the relationship between the thickness and thermal transmittance.

The resistance factors of the water vapor transmission of 9 walls- 40 mm thick and 5 walls – 20 mm thick samples are between 50-250 gr/mm^2. h. Pa When the thickness increases, the water vapor permeability decreases.

These polycarbonate panels are suitable to use with the other materials. The polycarbonate materials cannot supply the humidity transfer when the thickness of the panels increases.

3.2 Optical Properties

Before ageing, the percentages of the light transmittance are more than 74 % which is the minimum value of European Union CE standard and the percentages are suitable. After artificial ageing, the difference in light transmittances should be lower than and equal to 5 % for *ΔA* Class according to TS EN 16153. As a result of the measurements, all the samples are *ΔA* Class.

In the regard of the percentages of the total solar energy transmittance, all the polycarbonate samples are “Clear” class. The coefficients of shading support high light transparency.

Polycarbonate panels are counted as the clear material and supply light transmission but under the atmospheric conditions due to the surface deformations the value of light transmission decreases.

3.3 Mechanical Resistance and Deformation Behavior

5 walls with 20 mm thick has the highest of the bending stiffness in x-axis while 9 walls with 40 mm thick has the highest bending stiffness in y-axis. 5 walls with 10 mm thick has the highest shear stiffness.

Except 9 walls with 40 mm thick, the bending stiffness and the shear stiffness of other polycarbonate samples increase after the artificial ageing. Like the deformation behavior, the

buckling momentum increases after the artificial ageing. The panels are not affected by the ageing effect.

When the thickness increases of the polycarbonate panels, the small impact deformations occur but generally the polycarbonate panels have the optimum impact strength.

The 5 walls polycarbonate panels have the sufficient tensile strength and buckling moment. The bending stiffness of the polycarbonate panels is high so that the panels should be used mostly in the roof construction.

3.4 Sound Insulation

All the samples are smaller than 27 dB according to DIN 52210-75 and they are counted as the sound insulation materials.

CONCLUSION

As a result of the measurements of the characteristic properties of the polycarbonate samples, this material is the light transparent, clear under the sun-light and protect its color. The coefficient of the thermal transmission is like the polymer based materials. The coefficient of linear thermal expansion is lower. İt is suitable to use with the other polymers and the metals. This polycarbonate is hard and has higher impact strength. The water vapor transmission decreases when the thickness increases. The mechanical resistance and the deformation behavior are high. Except the sample with 9 walls, the bending and shear stiffness of all the samples increase after the artificial ageing. Also, the magnification and reduction factors are used for this result. The polycarbonate samples have the sound insulation. Finally, this characteristic properties of the polycarbonate sample are suitable when the number of walls and the thickness are low.

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ON SOME BULLEN-TYPE INEQUALITIES VIA CONFORMABLE FRACTIONAL INTEGRALS

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Abstract

In this study, the Author has established a new lemma for $\alpha-$differentiable function and some inequalities of Bullen-type inequalities for conformable fractional integrals. Some applications are also given. Examples are given to show the results.

MSC: 26B25, 26D10

Keywords: Bullen type inequality; Conformable fractional integrals; Hölder's inequality; Power-mean inequality.

1 Introductions

To establish analytic inequalities, one of the most efficient way is the property of convexity of a dedicated function. Notedly, in the theory of higher transcendental functions, there are many significant applications. We can use the integral inequalities in order to study qualitative and quantitative properties of integrals (see [6, 7, 9]). Thing continuing to bewilder us by indicating new inferences, new difficulties and also new open questions are a major mathematical outcome.

The Hermite-Hadamard inequality: Let $\varphi : I \subseteq \mathbb{R} \to \mathbb{R}$ be a convex function and $\imath_1, \imath_2 \in I$ with $\imath_1 < \imath_2$.

$$\varphi\left(\frac{\imath_1+\imath_2}{2}\right) \leq \frac{1}{\imath_2-\imath_1}\int_{\imath_1}^{\imath_2}\varphi(\varkappa)\,d\varkappa \leq \frac{\varphi(\imath_1)+\varphi(\imath_2)}{2}H \tag{1}$$

If φ is concave, this double inequality hold in the inverse way. See [1, 2, 5, 7] for details.

The Bullen inequality:

$$\frac{1}{\imath_2-\imath_1}\int_{\imath_1}^{\imath_2}\varphi(\varkappa)\,d\varkappa \leq \frac{1}{2}\left[\frac{\varphi(\imath_1)+\varphi(\imath_2)}{2}+\varphi\left(\frac{\imath_1+\imath_2}{2}\right)\right],B \tag{2}$$

provided that $\varphi : [\imath_1, \imath_2] \to \mathbb{R}$ is a convex function on $[\imath_1, \imath_2]$ (see for example [3, 4, 8, 10]) for details.

Lemma 1 *[11]Let $\varphi : I \to \mathbb{R}$, $I \subset \mathbb{R}$ be a differentiable mapping on I°, and $\imath_1, \imath_2 \in I, \imath_1 < \imath_2$. If $\varphi\prime \in L([\imath_1.\imath_2])$, $t \in [0,1]$ then*

$$\begin{aligned} & \int_0^1 (1-2t)\left[\left(\varphi'\left(t\imath_1+(1-t)\left(\frac{\imath_1+\imath_2}{2}\right)\right)+\varphi'\left(t\left(\frac{\imath_1+\imath_2}{2}\right)+(1-t)\imath_2\right)\right)\right]dt \\ = & \frac{4}{\imath_2-\imath_1}\left(\frac{\varphi(\imath_1)+\varphi(\imath_2)}{2}+\varphi\left(\frac{\imath_1+\imath_2}{2}\right)-\frac{2}{\imath_2-\imath_1}\int_{\imath_1}^{\imath_2}\varphi(x)\,dx\right). \end{aligned}$$

Here I° denotes the interior of I.

2 "Definition and Properties of Conformable Fractional Derivative and Integral

The following definitions and theorems with respect to conformable fractional derivative and integral were referred in [12]-[17].

Definition 2 *(Conformable fractional derivative) Given a function $\varphi : [0,\infty) \to \mathbb{R}$. Then the "conformable fractional derivative" of φ of order α is defined by*

$$D_{\alpha}(\varphi)(t) = \lim_{\varepsilon \to 0} \frac{\varphi\left(t+\varepsilon t^{1-\alpha}\right)-\varphi(t)}{\varepsilon}$$

for all $t>0$, $\alpha \in (0,1]$. If φ is $\alpha-$differentiable in some $(0,\imath_1)$, $\alpha>0$, $\lim_{t\to 0^+}\varphi^{(\alpha)}(t)$ exist, then define

$$\varphi^{(\alpha)}(0) = \lim_{t\to 0^+}\varphi^{(\alpha)}(t).$$

We can write $\varphi^{(\alpha)}(t)$ for $D_{\alpha}(\varphi)(t)$ to denote the conformable fractional derivatives of φ of order α.In addition, if the conformable fractional derivative of φ of order α exists, then we simply say φ is $\alpha-$differentiable.

Theorem 3 *Let $\alpha \in (0,1]$ and φ, Λ be $\alpha-$differentiable at a point $t>0$. Then,*

1) $D_{\alpha}(a\varphi+b\Lambda) = aD_{\alpha}(\varphi)+bD_{\alpha}(\Lambda)$, for all $\imath_1, \imath_2 \in \mathbb{R}$,
2) $D_{\alpha}(\lambda) = 0$, for all constant functions $\varphi(t) = \lambda$,
3) $D_{\alpha}(\varphi\Lambda) = \varphi D_{\alpha}(\Lambda)+\Lambda D_{\alpha}(\varphi)$,
4) $D_{\alpha}\left(\frac{\varphi}{\Lambda}\right) = \frac{D_{\alpha}(\varphi)\Lambda+D_{\alpha}(\Lambda)\varphi}{\Lambda^2}$,
5) If φ is differentiable, then

$$D_{\alpha}(\varphi)(t) = t^{1-\alpha}\frac{df}{dt}(t).$$

Also,

a) $D_{\alpha}(1) = 0$
b) $D_{\alpha}(e^{at}) = at^{1-\alpha}e^{at}$, $\imath_1 \in \mathbb{R}$
c) $D_{\alpha}(\sin(at)) = at^{1-\alpha}\cos(at)$, $\imath_1 \in \mathbb{R}$
d) $D_{\alpha}(\cos(at)) = -at^{1-\alpha}\sin(at)$, $\imath_1 \in \mathbb{R}$

e) $D_\alpha\left(\frac{1}{\alpha}t^\alpha\right)=1$
f) $D_\alpha\left(\sin\left(\frac{t^\alpha}{\alpha}\right)\right)=\cos\left(\frac{t^\alpha}{\alpha}\right)$
g) $D_\alpha\left(\cos\left(\frac{t^\alpha}{\alpha}\right)\right)=-\sin\left(\frac{t^\alpha}{\alpha}\right)$
h) $D_\alpha\left(e^{\frac{t^\alpha}{\alpha}}\right)=e^{\frac{t^\alpha}{\alpha}}$.

Theorem 4 *(Mean value theorem for conformable fractional differentiable functions). Let $\alpha\in(0,1]$ and $\varphi:[0,\infty)\to\mathbb{R}$ be a continuous on $[\imath_1,\imath_2]$ and an $\alpha-$fractional differentiable mapping on $(\imath_1,\imath_2)$ with $0\leq\imath_1<\imath_2$. Then, there exist $c\in(\imath_1,\imath_2)$, such that*

$$D_\alpha(\varphi)(c)=\frac{\varphi(\imath_2)-\varphi(\imath_1)}{\frac{\imath_2}{\alpha}-\frac{\imath_1}{\alpha}}.$$

Definition 5 *(Conformable fractional integral). Let $\alpha\in(0,1]$ and $0\leq\imath_1<\imath_2$. A fucntion $\varphi:[0,\infty)\to\mathbb{R}$ is $\alpha-$fractional integrable on $[\imath_1,\imath_2]$ if the integral*

$$\int_{\imath_1}^{\imath_2}\varphi(x)\,d_\alpha x:=\int_{\imath_1}^{\imath_2}\varphi(x)\,x^{\alpha-1}dx,$$

exists and is finite. All $\alpha-$fractional integrable on $[\imath_1,\imath_2]$ is indicated by $L_\alpha^1([\imath_1,\imath_2])$.

Remark 6

$$I_\alpha^{\imath_1}(\varphi)(t)=I_1^{\imath_1}\left(t^{\alpha-1}\varphi\right)=\int_{\imath_1}^{t}\frac{\varphi(x)}{x^{1-\alpha}}dx,$$

where the integral is the usual Riemann improper integral and $\alpha\in(0,1]$.

Theorem 7 *Let $\varphi:(\imath_1,\imath_2)\to\mathbb{R}$ be differentiable and $\alpha\in(0,1]$. Then, for all $t>\imath_1$ we have*

$$I_\alpha^{\imath_1}D_\alpha^{\imath_1}(\varphi)(t)=\varphi(t)-\varphi(\imath_1).$$

Theorem 8 *(Integration by parts). Let $\varphi,\Lambda:[\imath_1,\imath_2]\to\mathbb{R}$ be two functions such that φg is differentiable. Then,*

$$\begin{aligned}&\int_{\imath_1}^{\imath_2}\varphi(x)\,D_\alpha^{\imath_1}(\Lambda)(x)\,d_\alpha x\\ =\;&\varphi g|_{\imath_1}^{\imath_2}-\int_{\imath_1}^{\imath_2}\Lambda(x)\,D_\alpha^{\imath_1}(\varphi)(x)\,d_\alpha x.\end{aligned}$$

Theorem 9 *Assume that $\varphi:[\imath_1,\infty)\to\mathbb{R}$ such that $\varphi^{(n)}(t)$ is continuous and $\alpha\in(n,n+1]$. Then, for all $t>\imath_1$ we have*

$$D_\alpha^{\imath_1}(\varphi)(t)\,I_\alpha^{\imath_1}=\varphi(t).$$

Theorem 10 *Let $\alpha\in(0,1]$ and $\varphi:[\imath_1,\imath_2]\to\mathbb{R}$ be a continuous on $[\imath_1,\imath_2]$ with $0\leq\imath_1<\imath_2$. Then,*

$$|I_\alpha^{\imath_1}(\varphi)(x)|\leq I_\alpha^{\imath_1}|\varphi|(x).$$

Many studies in the literature on integral inequalities related to conformable fractional integration have been performed by many researchers. For more details and properties concerning the conformable integral operators, we refer, for example,to the works [18]-[21]. In this paper, we establish the Bullen type inequalities for conformable fractional integral and we will investigate some integral inequalities connected with Bullen-type inequalities for conformable fractional integral. The results presented here would provide generalizations of those given. In this study, some new Identity and Bullen type integral inequalities for differentiable functions are established, and are applied to produce some inequalities of special means."

3 Bullen Type Inequalities for Conformable Fractional Integral.

By using the following lemma, we will give some integral inequalities connected with Bullen-type inequalities for conformable fractional integral.

Lemma 11 *Let $\alpha \in (0,1]$ and $\varphi : I \subset \mathbb{R}^+ \to \mathbb{R}$ be an $\alpha-$fractional differentiable function on $(\imath_1, \imath_2)$ with $0 \leq \imath_1 < \imath_2$. If $D_\alpha(\varphi)$ be an $\alpha-$fractional integrable function on $[\imath_1, \imath_2]$, then the following identity for conformable fractional integral holds:*

$$\begin{aligned} & \frac{1}{4}\int_0^1 (1-2t^\alpha)\left[D_\alpha(\varphi)\left(t^\alpha \imath_1^\alpha + (1-t^\alpha)\frac{\imath_1^\alpha + \imath_2^\alpha}{2}\right)\right. \\ & \left. + D_\alpha(\varphi)\left(t^\alpha \frac{\imath_1^\alpha + \imath_2^\alpha}{2} + (1-t^\alpha)\imath_2^\alpha\right)\right] d_\alpha t \\ = \; & \frac{\alpha}{\imath_2^\alpha - \imath_1^\alpha}\int_{\imath_1}^{\imath_2} \varphi(x^\alpha)\, d_\alpha x - \frac{1}{2}\left[\frac{\varphi(\imath_1^\alpha) + \varphi(\imath_2^\alpha)}{2} + \varphi\left(\frac{\imath_1^\alpha + \imath_2^\alpha}{2}\right)\right] \end{aligned} \tag{3}$$

Proof. Integrating by parts

$$\begin{aligned} & \int_0^1 (1-2t^\alpha) D_\alpha(\varphi)\left(t^\alpha \imath_1^\alpha + (1-t^\alpha)\frac{\imath_1^\alpha + \imath_2^\alpha}{2}\right) d_\alpha t \\ & + \int_0^1 (1-2t^\alpha) D_\alpha(\varphi)\left(t^\alpha \frac{\imath_1^\alpha + \imath_2^\alpha}{2} + (1-t^\alpha)\imath_2^\alpha\right) d_\alpha t \\ = \; & (1-2t^\alpha)\varphi\left(t^\alpha \imath_1^\alpha + (1-t^\alpha)\frac{\imath_1^\alpha + \imath_2^\alpha}{2}\right)\Big|_0^1 \\ & + 2\alpha \int_0^1 \varphi\left(t^\alpha \imath_1^\alpha + (1-t^\alpha)\frac{\imath_1^\alpha + \imath_2^\alpha}{2}\right) d_\alpha t \\ & + (1-2t^\alpha)\varphi\left(t^\alpha \frac{\imath_1^\alpha + \imath_2^\alpha}{2} + (1-t^\alpha)\imath_2^\alpha\right)\Big|_0^1 \\ & + 2\alpha \int_0^1 \varphi\left(t^\alpha \frac{\imath_1^\alpha + \imath_2^\alpha}{2}\imath_1^\alpha + (1-t^\alpha)\imath_2^\alpha\right) d_\alpha t \end{aligned}$$

$$
\begin{aligned}
&= -\varphi\left(\imath_1^\alpha\right)-\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)+\frac{4\alpha}{\imath_1^\alpha-\imath_2^\alpha}\int_{\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\frac{1}{\alpha}}}^{\imath_1}\varphi\left(x^\alpha\right)d_\alpha x\\
&\quad -\varphi\left(\imath_2^\alpha\right)-\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)+\frac{4\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\frac{1}{\alpha}}}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x\\
&= -\left[\varphi\left(\imath_1^\alpha\right)+\varphi\left(\imath_2^\alpha\right)+2f\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right]+\frac{4\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\imath_1}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x.
\end{aligned}
$$

■

Remark 12 *If we choose $\alpha=1$ in the Lemma 11, then we obtain the Lemma 1.*

Theorem 13 *Let $\alpha\in(0,1]$ and $\varphi:I\subset R^+\to R$ be an $\alpha-$fractional differentiable function on I° and $D_\alpha(\varphi)$ be an $\alpha-$fractional integrable function on I with $0\le\imath_1<\imath_2$. If $|\varphi'|$ be a convex function on I, then the following inequality for conformable fractional integral holds:*

$$
\begin{aligned}
&\left|\frac{\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\imath_1}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x-\frac{1}{2}\left[\frac{\varphi\left(\imath_1^\alpha\right)+\varphi\left(\imath_2^\alpha\right)}{2}+\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right]\right|\\
\le\ &\frac{\left(\imath_2^\alpha-\imath_1^\alpha\right)}{32}\left[\left(\imath_1^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_1^\alpha\right)\right|\right.\\
&\left.+2\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right|+\left(\imath_2^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right|\right].
\end{aligned}
$$

Proof. Since $|\varphi'|$ is a convex function on I, by the using the properties $D_\alpha\left(\varphi\circ\Lambda\right)(t)=\varphi'\left(\Lambda\left(t\right)\right)D_\alpha\left(\Lambda\left(t\right)\right)$ and $D_\alpha\left(\varphi\left(t\right)\right)=t^{1-\alpha}\varphi'\left(t\right)$ and by Lemma 11 and using the well known absolute value inequality, and we have

$$
\begin{aligned}
&\left|\frac{\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\imath_1}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x-\frac{1}{2}\left[\frac{\varphi\left(\imath_1^\alpha\right)+\varphi\left(\imath_2\right)}{2}+\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right]\right|\\
\le\ &\frac{1}{4}\int_0^1\left|1-2t^\alpha\right|\left|D_\alpha\left(\varphi\right)\left(t^\alpha\imath_1^\alpha+\left(1-t^\alpha\right)\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right|d_\alpha t\\
&+\frac{1}{4}\int_0^1\left|1-2t^\alpha\right|\left|D_\alpha\left(\varphi\right)\left(t^\alpha\frac{\imath_1^\alpha+\imath_2^\alpha}{2}+\left(1-t^\alpha\right)\imath_2^\alpha\right)\right|d_\alpha t\\
\le\ &\frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\left(\imath_1^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_1\right)\right|\int_0^1\left|1-2t^\alpha\right|t^\alpha d_\alpha t\right)\\
&+\frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right|\int_0^1\left|1-2t^\alpha\right|\left(1-t^\alpha\right)d_\alpha t\right)\\
&+\frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right|\int_0^1\left|1-2t^\alpha\right|t^\alpha d_\alpha t\right)
\end{aligned}
$$

$$
\begin{aligned}
&+\frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\left(\imath_2^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right|\int_0^1\left|1-2t^\alpha\right|\left(1-t^\alpha\right)d_\alpha t\right)\\
=\;&\frac{\left(\imath_2^\alpha-\imath_1^\alpha\right)}{32}\left[\left(\imath_1^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_1^\alpha\right)\right|\right.\\
&\left.+2\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right|+\left(\imath_2^\alpha\right)^{\alpha-1}\left|D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right|\right].
\end{aligned}
$$

where

$$
\begin{aligned}
&\int_0^1\left|1-2t^\alpha\right|t^\alpha d_\alpha t\\
=\;&\int_0^1\left|1-2t^\alpha\right|t^\alpha t^{\alpha-1}dt\\
=\;&\int_0^{\frac{1}{2^{1/\alpha}}}\left(1-2t^\alpha\right)t^\alpha t^{\alpha-1}dt+\int_{\frac{1}{2^{1/\alpha}}}^1\left(2t^\alpha-1\right)t^\alpha t^{\alpha-1}dt\\
=\;&\frac{1}{4\alpha}
\end{aligned}
$$

and

$$
\begin{aligned}
&\int_0^1\left|1-2t^\alpha\right|\left(1-t^\alpha\right)d_\alpha t\\
=\;&\int_0^1\left|1-2t^\alpha\right|\left(1-t^\alpha\right)t^{\alpha-1}dt\\
=\;&\int_0^{\frac{1}{2^{1/\alpha}}}\left(1-2t^\alpha\right)\left(1-t^\alpha\right)t^{\alpha-1}dt+\int_{\frac{1}{2^{1/\alpha}}}^1\left(2t^\alpha-1\right)\left(1-t^\alpha\right)t^{\alpha-1}dt\\
=\;&\frac{1}{4\alpha}.
\end{aligned}
$$

■

Remark 14 *If we choose $\alpha=1$ in Theorem (13), then we obtain the following inequality:*

$$
\begin{aligned}
&\left|\frac{1}{\imath_2-\imath_1}\int_{\imath_1}^{\imath_2}\varphi\left(x\right)dx-\frac{1}{2}\left[\frac{\varphi\left(\imath_1\right)+\varphi\left(\imath_2\right)}{2}+\varphi\left(\frac{\imath_1+\imath_2}{2}\right)\right]\right|\\
\leq\;&\frac{\imath_2-\imath_1}{32}\left[\left|\varphi'\left(\imath_1\right)\right|+2\left|\varphi'\left(\frac{\imath_1+\imath_2}{2}\right)\right|+\left|\varphi'\left(\imath_2\right)\right|\right].
\end{aligned}
$$

Theorem 15 *Let $\alpha\in(0,1]$ and $\varphi:I\subset R^+\to R$ be an $\alpha-$fractional differentiable function on I° and $D_\alpha(\varphi)$ be an $\alpha-$fractional integrable function on I with $0\leq\imath_1<\imath_2$ and $p,q>1$, $1/p+1/q=1$. If $|\varphi'|^q$ be a convex function on I, then the following inequality for conformable fractional integral holds:*

$$
\left|\frac{\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\imath_1}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x-\frac{1}{2}\left[\frac{\varphi\left(\imath_1^\alpha\right)+\varphi\left(\imath_2^\alpha\right)}{2}+\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right]\right|
$$

$$\leq \frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\frac{1}{\alpha\left(1+p\right)}\right)^{\frac{1}{p}}\left(\frac{1}{2\alpha}\right)^{\frac{1}{q}}\times$$
$$\left[\left(\left(\imath_1^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_1^\alpha\right)\right)^q+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\right)^{\frac{1}{q}}\right.$$
$$\left.+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q+\left(\imath_2^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right)^q\right)^{\frac{1}{q}}\Bigg].$$

Proof. Since $|\varphi'|^q$ is a convex function on I, by the using the properties $D_\alpha\left(\varphi\circ\Lambda\right)(t)=\varphi'\left(\Lambda\left(t\right)\right)D_\alpha\left(\Lambda\left(t\right)\right)$ and $D_\alpha\left(\varphi\left(t\right)\right)=t^{1-\alpha}\varphi'\left(t\right)$ and by Lemma 11 and using the well known Hölder inequality, we have

$$\left|\frac{\alpha}{\imath_2-\imath_1}\int_{\imath_1}^{\imath_2}\varphi\left(x^\alpha\right)d_\alpha x-\frac{1}{2}\left[\frac{\varphi\left(\imath_1\right)+\varphi\left(\imath_2\right)}{2}+\varphi\left(\frac{\imath_1+\imath_2}{2}\right)\right]\right|$$
$$\leq \frac{1}{4}\left(\int_0^1\left(1-2t^\alpha\right)^p d_\alpha t\right)^{\frac{1}{p}}\left(\int_0^1\left(D_\alpha\left(\varphi\right)\left(t^\alpha\imath_1^\alpha+\left(1-t^\alpha\right)\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q d_\alpha t\right)^{\frac{1}{q}}$$
$$+\frac{1}{4}\left(\int_0^1\left(1-2t^\alpha\right)^p d_\alpha t\right)^{\frac{1}{p}}\left(\int_0^1\left(D_\alpha\left(\varphi\right)\left(t^\alpha\frac{\imath_1^\alpha+\imath_2^\alpha}{2}+\left(1-t^\alpha\right)\imath_2^\alpha\right)\right)^q d_\alpha t\right)^{\frac{1}{q}}$$
$$\leq \frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\frac{1}{\alpha\left(1+p\right)}\right)^{\frac{1}{p}}\left(\left(\imath_1^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_1^\alpha\right)\right)^q\int_0^1 t^\alpha d_\alpha t\right.$$
$$\left.+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\int_0^1\left(1-t^\alpha\right)d_\alpha t\right)^{\frac{1}{q}}$$
$$+\frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\frac{1}{\alpha\left(1+p\right)}\right)^{\frac{1}{p}}\left(\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\int_0^1 t^\alpha d_\alpha t\right.\right.$$
$$\left.\left.+\left(\imath_2^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right)^q\int_0^1\left(1-t^\alpha\right)d_\alpha t\right)^{\frac{1}{q}}$$
$$= \frac{\alpha\left(\imath_2^\alpha-\imath_1^\alpha\right)}{8}\left(\frac{1}{\alpha\left(1+p\right)}\right)^{\frac{1}{p}}\left(\frac{1}{2\alpha}\right)^{\frac{1}{q}}\times$$
$$\left[\left(\left(\imath_1^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_1^\alpha\right)\right)^q+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\right)^{\frac{1}{q}}\right.$$
$$\left.+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha\left(\varphi\right)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q+\left(\imath_2^{q\alpha}\right)^{\alpha-1}\left(D_\alpha\left(\varphi\right)\left(\imath_2^\alpha\right)\right)^q\right)^{\frac{1}{q}}\Bigg].$$

where

$$\int_0^1\left(1-2t^\alpha\right)^p d_\alpha t = \int_0^1\left(1-2t^\alpha\right)^p t^{\alpha-1}dt$$

$$\begin{aligned} &= \int_0^{\frac{1}{2^{1/\alpha}}} (1-2t^\alpha)^p\, t^{\alpha-1} dt + \int_{\frac{1}{2^{1/\alpha}}}^1 (2t^\alpha - 1)^p\, t^{\alpha-1} dt \\ &= \frac{1}{\alpha\,(1+p)} \end{aligned}$$

and

$$\begin{aligned} \int_0^1 t^\alpha d_\alpha t &= \int_0^1 t^\alpha t^{\alpha-1} dt = \frac{1}{2\alpha} \\ \int_0^1 1 - t^\alpha d_\alpha t &= \int_0^1 (1-t^\alpha)\, t^{\alpha-1} dt = \frac{1}{2\alpha} \end{aligned}$$

■

Corollary 16 *If we choose $\alpha = 1$ in Theorem 15, then we obtain the following inequality.*

$$\begin{aligned} &\left| \frac{1}{\imath_2 - \imath_1} \int_{\imath_1}^{\imath_2} \varphi(x)\, dx - \frac{1}{2}\left[\frac{\varphi(\imath_1) + \varphi(\imath_2)}{2} + \varphi\left(\frac{\imath_1 + \imath_2}{2} \right) \right] \right| \\ \leq\ & \frac{\imath_2 - \imath_1}{8} \left(\frac{1}{1+p} \right)^{\frac{1}{p}} \left(\frac{1}{2} \right)^{\frac{1}{q}} \times \\ & \left[\left((\varphi'(\imath_1))^q + \left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^q \right)^{\frac{1}{q}} + \left(\left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^q + (\varphi'(\imath_2))^q \right)^{\frac{1}{q}} \right]. \end{aligned}$$

Remark 17 *If we choose $p = q = 2$ in Corollary 16, then we obtain the following inequality.*

$$\begin{aligned} &\left| \frac{1}{\imath_2 - \imath_1} \int_{\imath_1}^{\imath_2} \varphi(x)\, dx - \frac{1}{2}\left[\frac{\varphi(\imath_1) + \varphi(\imath_2)}{2} + \varphi\left(\frac{\imath_1 + \imath_2}{2} \right) \right] \right| \\ \leq\ & \frac{\imath_2 - \imath_1}{8} \frac{1}{6^{1/2}} \times \left[\left((\varphi'(\imath_1))^2 + \left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^2 \right)^{\frac{1}{2}} \right. \\ & \left. + \left(\left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^2 + (\varphi'(\imath_2))^2 \right)^{\frac{1}{2}} \right]. \end{aligned}$$

Theorem 18 *Let $\alpha \in (0,1]$ and $\varphi : I \subset R^+ \to R$ be an $\alpha-$fractional differentiable function on I° and $D_\alpha(\varphi)$ be an $\alpha-$fractional integrable function on I with $0 \leq \imath_1 < \imath_2$ and $q \geq 1$. If $|\varphi'|^q$ be a convex function on I, then the following inequality for conformable fractional integral holds:*

$$\begin{aligned} &\left| \frac{\alpha}{\imath_2^\alpha - \imath_1^\alpha} \int_{\imath_1}^{\imath_2} \varphi(x^\alpha)\, d_\alpha x - \frac{1}{2}\left[\frac{\varphi(\imath_1^\alpha) + \varphi(\imath_2^\alpha)}{2} + \varphi\left(\frac{\imath_1^\alpha + \imath_2^\alpha}{2} \right) \right] \right| \\ \leq\ & \frac{\alpha\,(\imath_2^\alpha - \imath_1^\alpha)}{8} \left(\frac{1}{2\alpha} \right)^{1-\frac{1}{q}} \left(\frac{1}{4\alpha} \right)^{\frac{1}{q}} \times \end{aligned}$$

$$\left((\imath_1^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_1^\alpha)\right)^q+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\right)^{\frac{1}{q}}$$
$$+\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q+(\imath_2^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_2^\alpha)\right)^q\right)^{\frac{1}{q}}.$$

Proof. Since $|\varphi'|^q$ is a convex function on I, by the using the properties $D_\alpha(\varphi\circ\Lambda)(t)=\varphi'(\Lambda(t))D_\alpha(\Lambda(t))$ and $D_\alpha(\varphi(t))=t^{1-\alpha}\varphi'(t)$ and assume that $q\geq 1$, by Lemma 11 and using the well known power-mean inequality, we have

$$\begin{aligned}
&\left|\frac{\alpha}{\imath_2^\alpha-\imath_1^\alpha}\int_{\imath_1}^{\imath_2}\varphi(x^\alpha)\,d_\alpha x-\frac{1}{2}\left[\frac{\varphi(\imath_1^\alpha)+\varphi(\imath_2^\alpha)}{2}+\varphi\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right]\right| \\
\leq\ & \frac{\alpha(\imath_2^\alpha-\imath_1^\alpha)}{8}\left(\int_0^1(1-2t^\alpha)\,d_\alpha t\right)^{1-\frac{1}{q}}\times \\
&\left((\imath_1^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_1^\alpha)\right)^q\int_0^1(1-2t^\alpha)\,t^\alpha d_\alpha t\right. \\
&\left.+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\int_0^1(1-2t^\alpha)(1-t^\alpha)\,d_\alpha t\right)^{\frac{1}{q}} \\
&+\frac{\alpha(\imath_2^\alpha-\imath_1^\alpha)}{8}\left(\int_0^1(1-2t^\alpha)\,d_\alpha t\right)^{1-\frac{1}{q}}\times \\
&\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\int_0^1(1-2t^\alpha)\,t^\alpha d_\alpha t\right. \\
&\left.+(\imath_2^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_2)\right)^q\int_0^1(1-2t^\alpha)(1-t^\alpha)\,d_\alpha t\right)^{\frac{1}{q}} \\
=\ & \frac{\alpha(\imath_2^\alpha-\imath_1^\alpha)}{8}\left(\frac{1}{2\alpha}\right)^{1-\frac{1}{q}}\left(\frac{1}{4\alpha}\right)^{\frac{1}{q}}\times \\
&\left((\imath_1^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_1^\alpha)\right)^q+\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q\right)^{\frac{1}{q}} \\
&+\left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{q(\alpha-1)}\left(D_\alpha(\varphi)\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)\right)^q+(\imath_2^{q\alpha})^{\alpha-1}\left(D_\alpha(\varphi)(\imath_2^\alpha\imath_2)\right)^q\right)^{\frac{1}{q}}.
\end{aligned}$$

where

$$\int_0^1(1-2t^\alpha)\,d_\alpha t=\int_0^{\frac{1}{2^{1/\alpha}}}(1-2t^\alpha)\,t^{\alpha-1}dt+\int_{\frac{1}{2^{1/\alpha}}}^1(2t^\alpha-1)\,t^{\alpha-1}dt=\frac{1}{2\alpha}$$

and

$$\int_0^1(1-2t^\alpha)\,t^\alpha d_\alpha t$$

$$
\begin{aligned}
&= \int_0^{\frac{1}{2^{1/\alpha}}} (1-2t^\alpha)\, t^\alpha t^{\alpha-1} dt + \int_{\frac{1}{2^{1/\alpha}}}^1 (2t^\alpha - 1)\, t^\alpha t^{\alpha-1} dt = \frac{1}{4\alpha}, \\
&\int_0^1 (1-2t^\alpha)\,(1-t^\alpha)\, d_\alpha t \\
&= \int_0^{\frac{1}{2^{1/\alpha}}} (1-2t^\alpha)\,(1-t^\alpha)\, t^{\alpha-1} dt + \int_{\frac{1}{2^{1/\alpha}}}^1 (2t^\alpha - 1)\,(1-t^\alpha)\, t^{\alpha-1} dt = \frac{1}{4\alpha}.
\end{aligned}
$$

■

Corollary 19 *If we choose $\alpha = 1$ in Theorem 18, then we obtain the following inequality.*

$$
\begin{aligned}
&\left| \frac{1}{\imath_2 - \imath_1} \int_{\imath_1}^{\imath_2} \varphi(x)\, dx - \frac{1}{2}\left[\frac{\varphi(\imath_1) + \varphi(\imath_2)}{2} + \varphi\left(\frac{\imath_1 + \imath_2}{2} \right) \right] \right| \\
\leq\ & \frac{\imath_2 - \imath_1}{8} \left(\frac{1}{2} \right)^{1+\frac{1}{q}} \times \left[\left((\varphi'(\imath_1))^q + \left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^q \right)^{\frac{1}{q}} \right. \\
&\left. + \left(\left(\varphi'\left(\frac{\imath_1 + \imath_2}{2} \right) \right)^q + (\varphi'(\imath_2))^q \right)^{\frac{1}{q}} \right].
\end{aligned}
$$

Remark 20 *If we choose $q = 1$ in Corollary 19, then we obtain Remark 14.*

4 Applications

Let

$$
\begin{aligned}
A(\imath_1, \imath_2) &= \frac{\imath_1 + \imath_2}{2}, \\
L_p(\imath_1, \imath_2) &= \left(\frac{\imath_2^{p+1} - \imath_1^{p+1}}{(p+1)(\imath_2 - \imath_1)} \right)^{1/p}, \imath_1 \neq \imath_2, p \in \mathbb{R}, p \neq -1, 0
\end{aligned}
$$

be the arithmetic mean, generalized logarithmic mean for $\imath_1, \imath_2 > 0$ respectively.

Proposition 21 *Let $s \in (0,1]$, $\imath_1, \imath_2 > 0$, then*

$$
\begin{aligned}
&\left| L_n^n(\imath_1^\alpha, \imath_2^\alpha) - \frac{1}{2}\left[A(\imath_1^{n\alpha}, \imath_2^{n\alpha}) + A^n(\imath_1^\alpha, \imath_2^\alpha) \right] \right| \\
\leq\ & \frac{n(\imath_2^\alpha - \imath_1^\alpha)}{16} \left[A\left((\imath_1^\alpha)^{n-1}, (\imath_2^\alpha)^{n-1} \right) + A^{n-1}(\imath_1^\alpha, \imath_2^\alpha) \right].
\end{aligned}
$$

Proof. The claim follows from Theorem 13 applied to convex function $\varphi(\varkappa) = \varkappa^n$ where $n \in \mathbb{N}$. ■

Example 22 *If we take $\alpha = 1, n = 2$ in Proposition 21, then we can obtain inequality following*

$$\begin{aligned} & \left|L_2^2(\imath_1,\imath_2) - A\left[A(\imath_1,\imath_2), A^2(\imath_1,\imath_2)\right]\right| \\ \leq & \frac{(\imath_2-\imath_1)}{4} A(\imath_1,\imath_2). \end{aligned}$$

Proposition 23 *Let $\alpha \in (0,1]$, $\imath_1, \imath_2 > 0$, $p, q > 1$, then*

$$\begin{aligned} & \left|L_n^n(\imath_1^\alpha,\imath_2^\alpha) - \frac{1}{2}\left[A(\imath_1^{n\alpha},\imath_2^{n\alpha}) + A^n(\imath_1^\alpha,\imath_2^\alpha)\right]\right| \\ \leq & \frac{n\alpha(\imath_2^\alpha-\imath_1^\alpha)}{8}\left(\frac{1}{\alpha(1+p)}\right)^{\frac{1}{p}}\left(\frac{1}{2\alpha}\right)^{\frac{1}{q}} \times \\ & \left[\left(\left((\imath_1^\alpha)^{n-1}\right)^q + \left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{n-1}\right)^q\right)^{\frac{1}{q}}\right. \\ & \left. + \left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{n-1}\right)^q + \left((\imath_2^\alpha)^{n-1}\right)^q\right)^{\frac{1}{q}}\Bigg]. \end{aligned}$$

Proof. The claim follows from Theorem 15 applied to convex $\varphi(\varkappa) = \varkappa^n$ where $n \in \mathbb{N}$. ■

Example 24 *If we take $\alpha = 1$, $p = q = n = 2$ in Proposition 23, then we can obtain the following inequality*

$$\begin{aligned} & \left|L_2^2(\imath_1,\imath_2) - \frac{1}{2}\left[A(\imath_1^2,\imath_2^2) + A^2(\imath_1,\imath_2)\right]\right| \\ \leq & \frac{\imath_2-\imath_1}{4} \times \left[\left(\imath_1^2 + \left(\frac{\imath_1+\imath_2}{2}\right)^2\right)^{\frac{1}{2}} + \left(\left(\frac{\imath_1+\imath_2}{2}\right)^2 + \imath_2^2\right)\right]^{\frac{1}{2}}. \end{aligned}$$

Proposition 25 *Let $\alpha \in (0,1]$, $\imath_1, \imath_2 > 0$, $q \geq 1$, then*

$$\begin{aligned} & \left|L_n^n(\imath_1^\alpha,\imath_2^\alpha) - \frac{1}{2}\left[A(\imath_1^{n\alpha},\imath_2^{n\alpha}) + A^n(\imath_1^\alpha,\imath_2^\alpha)\right]\right| \\ \leq & \frac{\alpha(\imath_2^\alpha-\imath_1^\alpha)}{8}\left(\frac{1}{2\alpha}\right)^{1-\frac{1}{q}}\left(\frac{1}{4\alpha}\right)^{\frac{1}{q}} \times \\ & \left[\left(\left((\imath_1^\alpha)^{n-1}\right)^q + \left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{n-1}\right)^q\right)^{\frac{1}{q}}\right. \\ & \left. + \left(\left(\frac{\imath_1^\alpha+\imath_2^\alpha}{2}\right)^{n-1}\right)^q + \left((\imath_2^\alpha)^{n-1}\right)^q\right)^{\frac{1}{q}}\Bigg]. \end{aligned}$$

Proof. The claim follows from Theorem 18 applied to convex $\varphi(\varkappa) = \varkappa^n$ where $n \in \mathbb{N}$. ■

Example 26 *If we take* $\alpha = 1, q = 2,\ n = 2$ *in Proposition 25, then we can obtain inequality following*

$$\begin{aligned} & \left| L_2^2(\imath_1, \imath_2) - \frac{1}{2}\left[A\left(\imath_1^2, \imath_2^2\right) + A^2(\imath_1, \imath_2)\right]\right| \\ \leq\ & \frac{(\imath_2 - \imath_1)}{8}\left(\frac{1}{8}\right)^{\frac{1}{2}} \times \\ & \left(\imath_1^2 + \left(\frac{\imath_1 + \imath_2}{2}\right)^2\right)^{\frac{1}{2}} + \left(\left(\frac{\imath_1 + \imath_2}{2}\right)^2 + \imath_2^2\right)^{\frac{1}{2}}. \end{aligned}$$

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Research Article

VOLTAMMETRIC AND CHROMATOGRAPHIC DETERMINATION OF NAPROXEN IN DRUG FORMULATION

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ABSTRACT

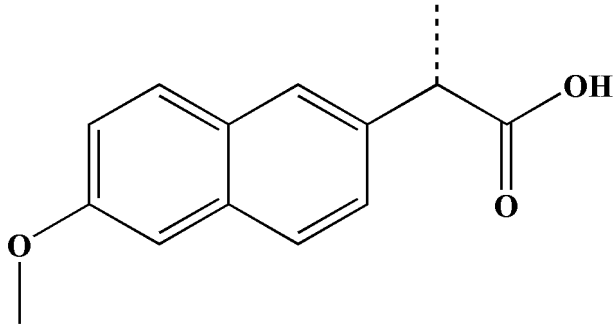
In this work, the electrochemical oxidation of naproxen (NAP) was studied at an ultra-trace graphite electrode (UTGE). The cyclic voltammetry (CV) technique was used to determine the optimum conditions and the effect of pH on the electrochemical oxidation of NAP. Acetate buffer (pH 4.50) was selected as the support electrolyte due to obtaining the highest electronic signal increase during oxidation of NAP at UTGE. The differential pulse voltammetry (DPV) technique was performed for electrochemical determination of NAP. In the optimum conditions, the limits of detection (LOD) and quantification (LOQ) were determined to be 8.66□10-8 M and 2.88□10-7 M. In addition, the amount of NAP was determined in drug tablets. The recovery studies of NAP from the drug tablet were completed in order to check the accuracy and precision of the applied voltammetric method. Furthermore, the determination of NAP was performed with the high-performance liquid chromatography (HPLC) method. These two methods were compared in terms of accuracy, precision and recovery studies.

Keywords: *naproxen; voltammetric method; differential pulse voltammetry; cyclic voltammetry; high performance liquid chromatography; ultra-trace graphite electrode; commercial drug tablets.*

1. INTRODUCTION

Naproxen, 2-(6-methoxynaphthalen-2-yl) (NAP), is a non-steroidal anti-inflammatory drug frequently used in the treatment of moderate or severe pain (**Figure 1**). It is also widely used for the reduction of stiffness caused by kidney stones, rheumatoid arthritis and other inflammatory diseases [1]. NAP, which needs a larger amount of tablet than non-steroidal anti-inflammatory drugs, strongly binds to albumin. Therefore, it has a longer half-life in blood than other drugs. Non-steroidal anti-inflammatory drugs have been associated with many cardiovascular events. However, according to recent studies, it was stated that naproxen is the least harmful non-steroidal anti-inflammatory for cardiovascular conditions [2].

Figure 1. Chemical formula of naproxen



Up to now, NAP was determined with different methods such as liquid chromatography [3], spectrophotometry [4], high-performance liquid chromatography [5,6], potentiometry [7], spectrofluorimetry [8] and electrochemical methods [9,10]. Sensitive, simple, rapid and economical methods are still needed. Therefore, electrochemical methods could be preferred to determine of NAP. The working electrodes such as a carbon paste electrode modified with activated carbon nanoparticles [11], a platinum electrode [12], a boron doped-diamond (BDD) electrode [13], ZnO nanoparticles and multi walled carbon nanotubes (MWCNTs) modified carbon paste electrode [14], a novel carbon paste electrode modified with NiO/CNTs nanocomposite and an ionic liquid (n-hexyl-3-methylimidazolium hexafluoro phosphate) [15], and graphite electrode [16] were used to determine NAP with electrochemical methods.

In this work, UTGE was used for voltammetric determination of NAP. A new electrochemical method for the determination of NAP using the DPV technique in 0.2 M acetate buffer (pH 4.50) media at UTGE was performed and used to determine the amount of NAP in drug tablets. In addition, the amount of NAP in pharmaceutical form was determined with the HPLC method. The results obtained from both methods were compared.

2. MATERIAL AND METHOD

2.1. Apparatus

A Model Metrohm 757 VA Trace Analyzer (Herisau, Switzerland) was used for the voltammetric measurements, with a three-electrode system consisting of UTGE as working electrode (UTGE; φ = 3 mm, Metrohm), a platinum wire as auxiliary electrode and Ag/AgCl (KCl 3 mol/L, Metrohm) as reference electrode. The UTGE electrode was polished with alumina (prepared from φ = 0.01 μm aluminum oxide) on an alumina polish pad before each experiment and then rinsed with ultra-pure deionized water and ethanol. Then, the deoxygenating process of the supporting electrolyte solution was carried out with argon gas for 5 min before all experiments. The argon gas was also passed through the solutions for 60 s after the addition of each sample solution during the experiments. All pH measurements were made with Model Metrohm 744 pH meter (Herisau, Switzerland) at ambient temperature of the laboratory (15 to 20 °C).

For the analytical applications, the following parameters were employed for differential pulse voltammetry (DPV); pulse amplitude 50 mV, pulse time 0.04 s and voltage step 0.009 V. Potential step 10 mV and scan rate in the range 100-750 mVs^{-1} for cyclic voltammetry (CV).

2.2. Reagents and materials

In this study, CH_3COOH (Riedel-de Haen, 99 %), CH_3OH (Merck, 99.5 %), NaOH (Merck, 99.8 %), acetonitrile (Merck 99 %), ethanol, and 0.05 μm sized Alumina powder (CH Instruments and metkom) were used. In addition, the drug active substance naproxen and drug dosage form Naprosyn was obtained from the Abdi Ibrahim Company. The stock solution of 1×10^{-2} M NAP was prepared by dissolving 4.3×10^{-3} mg NAP in 100 mL of ethanol. The working solutions for the voltammetric investigations were prepared by dilution of the stock solution. All solutions were protected from light and were used within 24 hours to avoid decomposition. 0.067 M phosphate buffer (pH 4.50-7.50), 0.2 M acetate buffer (pH 3.50- 5.50) and 0.04 M Britton-Robinson (B-R) buffer (pH 2.00-10.00) were selected as the support electrolyte solutions. The CV and DPV voltammograms of NAP were recorded to determine the support electrolyte type and optimum conditions. Ultra-pure water (UPW) obtained from Sartorius Arium model Ultra-Pure Water Systems was used to prepare the supporting electrolyte solutions. All chemicals used were analytical-reagent grade.

2.3. Calibration graph for quantitative determination

The diluted NAP solutions were obtained by diluting with water from the stock solution. In acetate buffer (pH 4.50) medium, a linear calibration curve for DPV analysis was constructed in the concentration range of NAP from 4×10^{-7} M to 1×10^{-5} M. The repeatability, accuracy and precision were checked.

2.4. Working voltammetric procedure for spiked tablet dosage forms

Five Naprosyn tablets were weighed and powdered to determine the amount of naproxen in Naprosyn tablets. Then, 5×10^{-6} M naproxen sample solution with an adequate amount of this powder was prepared and the DPV voltammogram of the sample was recorded.

The calibration curve was obtained from DPV voltammograms of NAP in the concentration range from 4×10^{-7} M to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) at UTGE. The equation of the curve was $y = 8.87\times10^{4}\,x + 0.0045$. According to this equation, the amount of NAP in one tablet was determined to be 247 mg.

3. RESULTS AND DISCUSSION

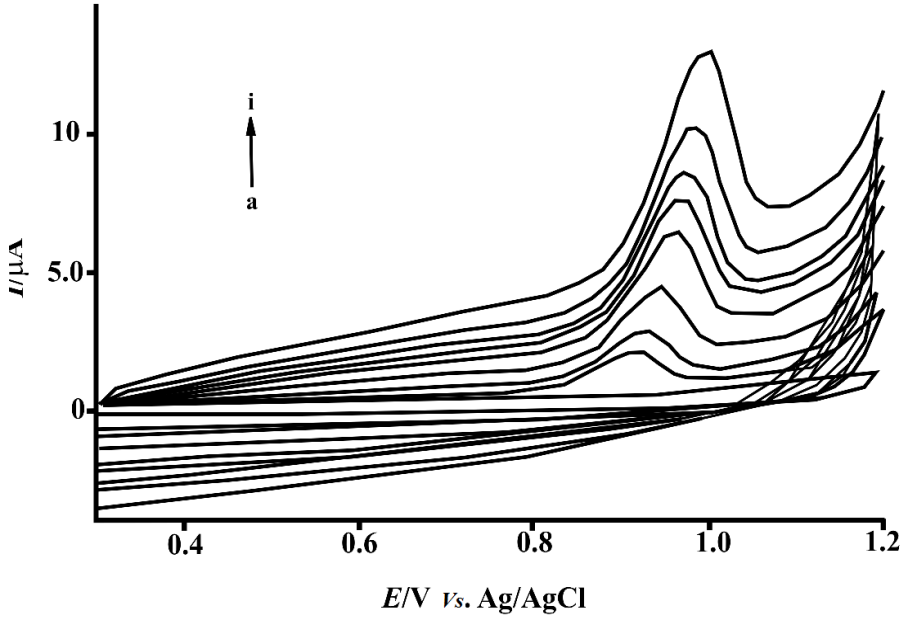
3.1. Electrochemical oxidation of naproxen

In order to determine the optimum conditions for the oxidation of NAP, 0.067 M phosphate buffer (pH 4.50 to pH 7.50), 0.2 M acetate buffer (pH 3.50 to 5.50) and 0.04 M B-R buffer (pH 2.00 to 12.00) were used as support electrolytes. DPV voltammograms of the NAP solutions of $5x10^{-5}$ M prepared in different electrolytes were recorded. Maximum peak current was obtained in the acetate buffer (pH 4.50) medium. Therefore, acetate buffer (pH 4.50) was chosen for further work.

3.2. The nature of the oxidation peak of naproxen

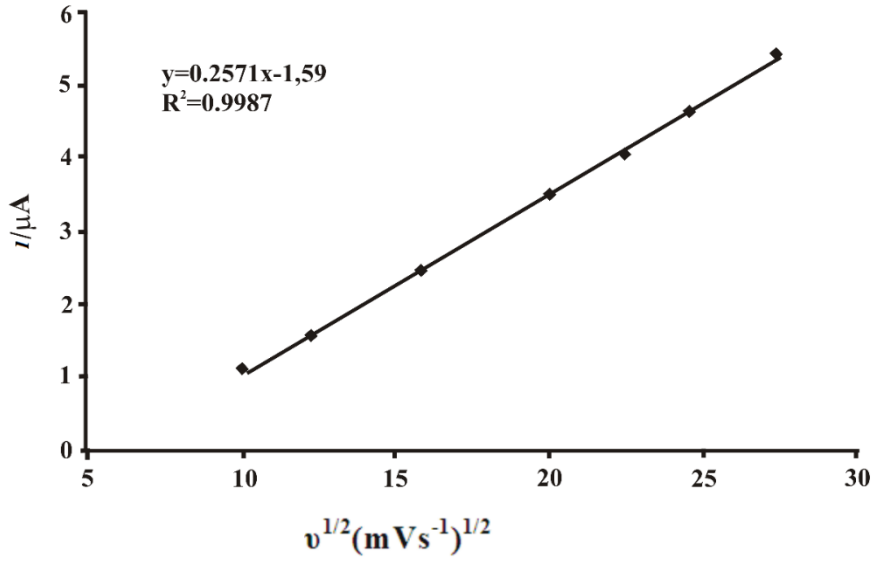
The cyclic voltammograms of $5x10^{-5}$ M NAP in 0.2 M acetate buffer (pH 4.50) at scan rates of 10-750 mVs^{-1} at UTGE were recorded (**Figure 2**).

Figure -2. CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) the support electrolyte (0.2 M acetate buffer, pH=4.50), b) 100, c) 150, d) 250, e) 300 f) 400), g) 500, h) 600, j) 750 mVs^{-1}.



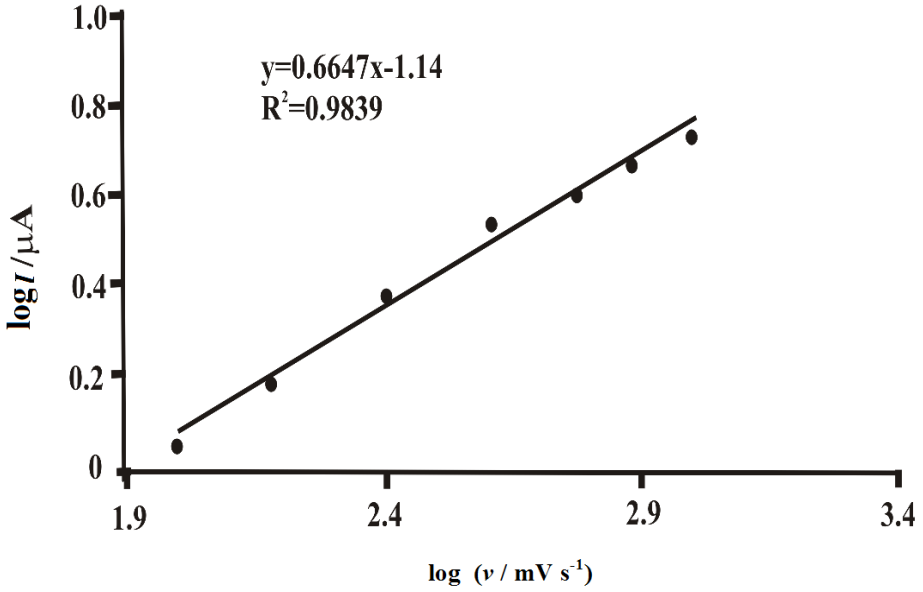
The peak current values increase with the increase in the scan rate. In addition, the peak potential values shift to more positive values when the scan rate increases. The peak current values plotted against $v^{1/2}$ are shown in **Figure 3.**

Figure - 3. The peak current values plotted against $v^{1/2}$ obtained from the CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) 100, b) 150, c) 250, d) 400), e) 500, f) 600, g) 750 mVs^{-1}).



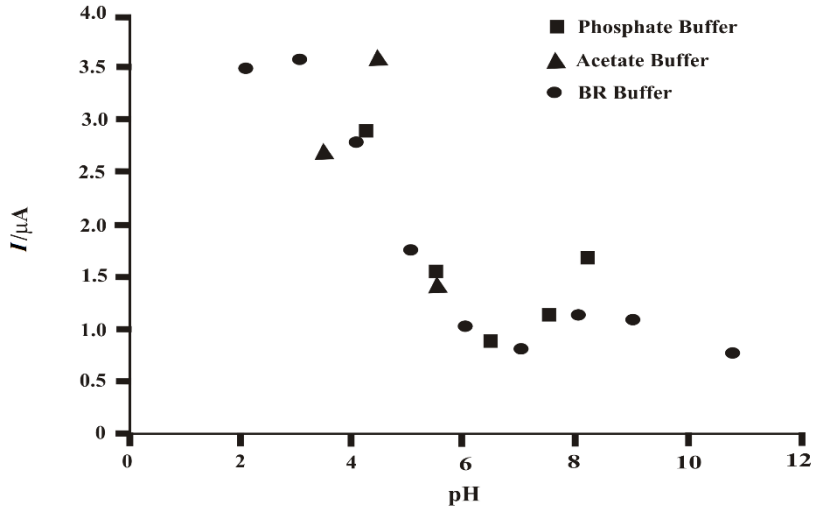
The peak current values plotted against $v^{1/2}$ was obtained with good linearity in the scan rate range of 100-750 mVs^{-1}. The linear regression equation was $Ip(\mu A) = 0.2571\upsilon^{1/2}-1.59$ with correlation coefficient (r=0.996). The correlation coefficient is very close to 1.0. Consequently, it is understood that the electrochemical-oxidation is diffusion controlled [12,17,18]. The logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) is shown in **Figure 4.**

Figure - 4. The logarithm of peak current (log *I*) against the logarithm of scan rate (log *v*) obtained from the CV voltammograms of 5×10^{-5} M NAP in 0.2 M acetate buffer (pH 4.50) at UTGE (Scan rates: a) 100, b) 150, c) 250, d) 400), e) 500, f) 600, g)750 mVs^{-1}).



The plot of logarithm of peak current (log *I*) versus logarithm of scan rate (log *v*) has a slope of 0.6647 (theoretical value of 0.50-0.75) indicate that the peak is diffusion controlled [12,17,18]. The peak current values of the oxidation peak obtained from the DPV voltammograms of the solutions of 5×10^{-5} M NAP prepared with different support electrolytes in the range from pH 2.0 to 10.0 are showed in **Figure 5**.

Figure - 5. Oxidation peak current values obtained from DPV voltammograms of 5×10^{-5} M NAP in the range from pH 2.0 to 10.0 in 0.2 M acetate, 0.067 M phosphate and 0.04 M B-R buffers at UTGE

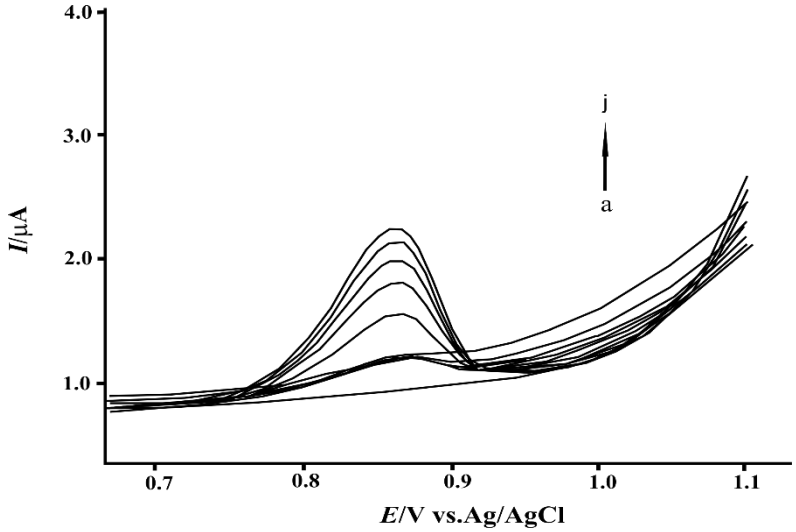


As seen in Figure 5, the oxidation peak current of NAP in 0.2 M acetate buffer reached the maximum value at pH 4.50. In addition, the anodic peak potential shifts towards lower positive values.

3.3. Determination of the analytical concentration range of NAP using the DPV technique

The assay of NAP at UTGE was performed using the DPV technique in 0.2 M acetate buffer (pH 4.50). The DPV voltammograms recorded in the potential range from + 0.6 V to +1.1 V for the different concentration of NAP are shown in **Figure 6.**

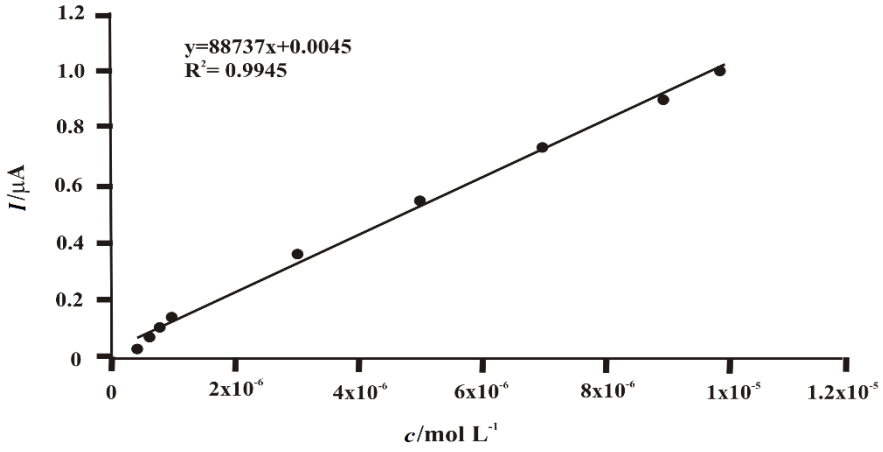
Figure - 6. DPV voltammograms recorded at UTGE for increasing concentrations of NAP in 0.2 M acetate buffer (pH 4.50). a) the support electrolyte (0.2 M acetate buffer, pH=4.50); b) 4.0×10^{-7}; c) 6.0×10^{-7}; d) 8.0×10^{-7}; e) 1.0×10^{-6}; f) 3.0×10^{-6}; g) 5.0×10^{-6}; h) 7.0×10^{-6}; i) 9.0×10^{-6} ; j) $1.0\text{x}10^{-5}$ M naproxen.



A linear calibration curve was constructed for NAP in the range 4×10^{-7} to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) supporting electrolyte (**Figure 6**).

The plot of concentration versus current obtained from DPV voltammograms of NAP is given in **Figure 7.**

Figure - 7. Plot of concentration versus current obtained from DPV voltammograms of NAP in the concentration range from 4×10^{-7} to 1×10^{-5} M in 0.2 M acetate buffer (pH 4.50) at UTGE.



As shown in Figure 7, the plot was linear in the concentration range of 4×10^{-7} to 1×10^{-5} M NAP. For the regression plot of the peak current versus NAP concentration, the slope was 8.87×10^{4} μA/M, the intercept was 0.0045μA and the correlation coefficient was R^2=0.9945.

Limit of detection (LOD) and limit of quantification (LOQ) values were calculated using the following equations [12,17,18].

LOD = 3 s/m and LOQ = 10 s/m

Where, s is the standard deviation of the peak currents (for five runs) and m is the slope of the calibration curve. To determine LOD and LOQ values, the standard deviation of peak currents for five measurements recorded at 6×10^{-7} M, which is the concentration above the lowest concentration in the calibration graph, was determined to be 4.46×10^{-3}. The LOD and LOQ obtained were 8.66×10^{-8} M and 2.88×10^{-7} M at UTGE, respectively.

The different detection limits, pH, linear range and potential values for determination of NAP with several electrochemical methods were recorded in the literature. The results obtained in this study and the other references for the determination of TNX are given in Table I with different parameters.

Table - 1. The reported electrodes and analytical parameters for determination of NAP by voltammetric technique.

WE	Technique	Linear range	LOD	Ref.
MCPE	DPV	0.1-120 μM	0.0234 μM	11
PE	DPV	1.0-25 μg mL^{-1}	0.24 μg mL^{-1}	12
BDDE	DPV	0.5-50 μM	30 nM	13
MCPE	SWV	1.0×10^{-6}- 2.0×10^{-4} M	2.3×10^{-7} M	14
MCPE	SWV	7.5×10^{-7}- 8.0×10^{-4} M	1.2×10^{-7}	15
GBE	DPV	1.96-28.18 μg mL^{-1}	0.68 μg mL^{-1}	16
UTGE	DPV	4.0×10^{-7}- 1.0×10^{-5} M	8.66×10^{-8} M	This work

WE: Working electrode; MCPE: Modified carbon paste electrode; PE: platinum electrode; BDDE; GBE: graphite bar electrode; UTGE: Ultra trace graphite electrode; DPV: Differential pulse voltammetry; SWV: Square wave voltammetry

As can be seen in Table I, the quantitative determination of NAP by using several working electrodes was performed with different voltammetric techniques.

3.4. Determination and recovery of the amount of NAP in the drug form at UTGE

Five tablets of Naprosyn were weighed and powdered to determine the amount of NAP in Naprosyn tablets using the DPV technique in 0.2 M acetate buffer at UTGE. Then, $5x10^{-6}$ M naproxen solution was prepared. The DPV voltammogram of this solution was recorded. The amount of NAP in the sample was calculated by using the equation y= 88737x+0.0045 obtained from the calibration curve and the amount of NAP in one tablet was found to be 247.40 mg. This value was compared with the value indicated on the tablet (Table 2).

Table2. The assay of NAP in Naprosyn tablets with the DPV technique and recovery of NAP

Parameters	**Results**
Labeled NAP, mg	250
Amount found, mg	247
Relative Standard deviation (*RSD* / %)	0.81
Bias, %	1.04
Added NAP, mg	40.00
Found NAP, mg	39.64
Average recovery, %	99.10
Relative standard deviation of recovery (*RSD* / %),	2.17
Bias, %	0.90

3.5. Interference Studies NAP was formulated either in pure form or with some additives in drug tablets.

In present study, Naprosyn tablets contained only 250 mg NAP. Therefore, we observed only one peak without interferences. So, in order to investigate the effect of co-formulated substances such as glucose, starch, citric acid and magnesium stearate acid on the voltammetric response of NAP was carried out. Differential-pulse voltammetric experiments were carried out $1x10^{-6}$ M NAP in the presence of $1x10^{-4}$ M of each of the interferents (concentration ratios,1:100) are given Table 3.

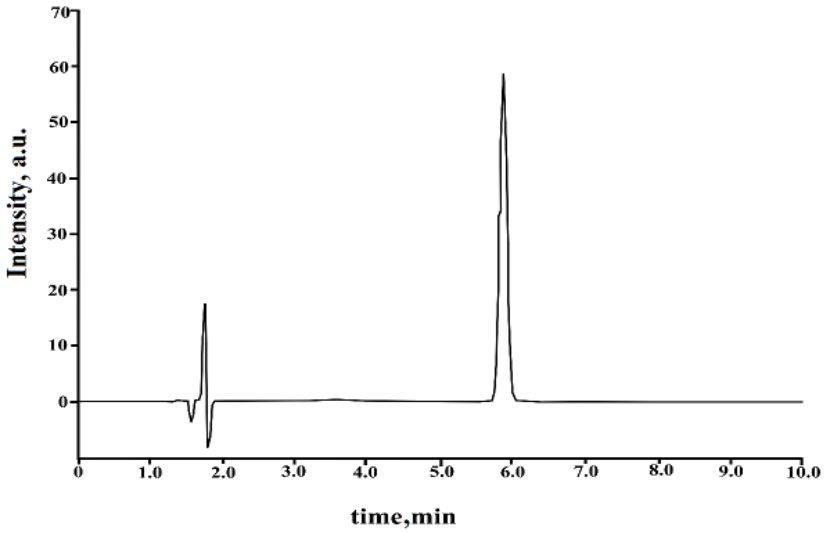
Table - 3. Influence of potential interferents on the voltammetric responses of $1x10^{-6}$ M NAP

Interferent	Concentration (M)	Current signal change, %
Glucose	1×10^{-4}	-1.12
Starch	1×10^{-4}	-1.40
Citric acid	1×10^{-4}	+ 1.25
Magnesium stearate	1×10^{-4}	+ 1.35

3.6. Determination of the amount of NAP in pharmaceutical form with the HPLC method

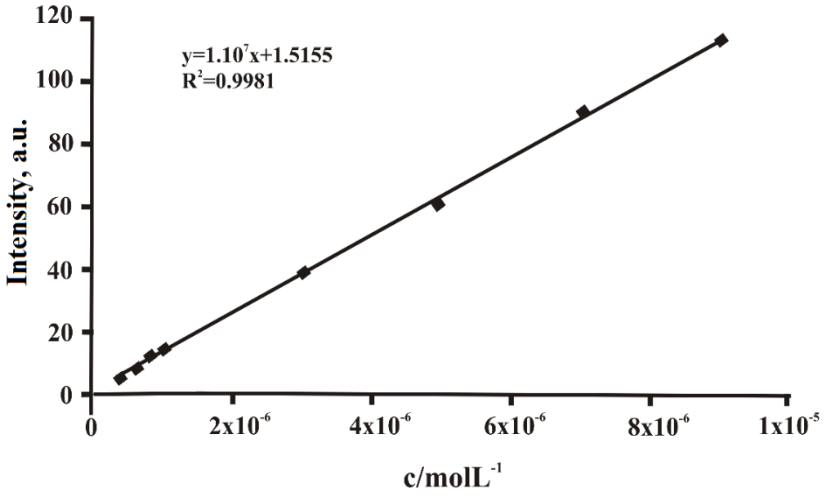
With 1% acetic acid as mobile phase, methanol and acetonitrile (40:20:40 v/v) as a detector, the retention time (t_R) for naproxen was 6.35 minutes, using the Diode-Array Detector (DAD) and the C18 Thermo Acclaim (3) M; 4.6 mm x 150 mm) column. The chromatogram of $5x10^{-6}$ M naproxen is given in **Figure 8**.

Figure - 8. The HPLC chromatogram of 5×10^{-6} M NAP



Different concentrations of naproxen were used to determine the analytical concentration range. A calibration graph was created from the peak-peak values of these chromatograms (**Figure 9**).

Figure - 9. Calibration line of naproxen standard obtained by HPLC with DAD detector



3.7. Statistical comparison of the results obtained with voltammetry and HPLC techniques

In order to verify the validity of the applied voltammetric method, the same analysis was performed with HPLC and the results were compared with each other (Table 4).

Table - 4. Comparison of parameters for Analysis applied voltammetry and HPLC techniques

Parameters	**Voltammetry**	**HPLC**
Linearity range of concentration, M	$4x10^{-7}$–$1x10^{-5}$	$4x10^{-7}$ – $1x10^{-4}$
LOD (M)	$8.66x10^{-8}$	$1.55x10^{-7}$
LOQ (M)	$2.88x10^{-7}$	$5.16x10^{-7}$
Amount of Naproxen indicated on tablet, mg	250.00	250.00
Amount of Naproxen found (mg)	247.00	253.00
Added Naproxen (mg)	40.00	40.00
Found in Naproxen (mg)	39.64	40.61
Recovery, %	99.10	101.52

LOD and LOQ values obtained by the voltammetry method are lower than those obtained by the HPLC technique. Therefore, the voltammetric technique is more advantageous.

Voltammetry and HPLC techniques were compared statistically. Accordingly, the t-test was applied in order to determine whether there were any differences between the means of analysis of the two techniques and to show the validity of the voltammetric technique. N = 6 degrees of freedom and 95% confidence interval based on the calculated value is greater than the calculated value ($t_{calculated}<t_{critical}$, 0.0085 <2.45). There were no differences found between the results of the two methods.[19, 20]

The F test was used to compare the accuracy of the measurement results of the two methods. With 6 degrees of freedom, $F_{critical}> F_{calculated}$ was 4.28> 0.057. Thus, it was concluded that there was no significant difference between the accuracy of these two methods [19, 20].

4. CONCLUSIONS

Ultra-trace graphite electrode was used for determination of NAP. A simple, sensitive and selective determination was performed with the DPV technique based on the electrochemical oxidation of NAP. It is understood that the electrode reaction process is irreversible and pH dependent from the CV and DPV measurements. NAP in pharmaceutical preparations was successfully determined using the DPV technique in 0.2 M acetate buffer (pH 4.50). In addition, the amount of NAP in pharmaceutical form was determined with the HPLC method. When the results obtained from both methods are compared, it is understood that the results obtained from the voltammetric method are more sensitive.

The differential pulse voltammetry technique can be used for the determination of NAP in pharmaceutical preparations in optimum conditions with UTGE as the working electrode and 0.2 M acetate buffer (pH=4.50) as the supporting electrolyte.

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Research Article

FEASIBILITY OF NEARLY-ZERO ENERGY BUILDING RETROFITS BY USING RENEWABLE ENERGY SOURCES IN AN EDUCATIONAL BUILDING[1]

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ABSTRACT

Dissemination of education is vital especially in developing countries like Turkey. Besides, proper use of energy resources is required while dissemination of education is ensured. Considering the regions where energy is limited, renewable energy sources should be used to achieve the goal of a zero-energy building. Moreover, an increase of smart technologies has potantial in order to decrease energy consumption in educational buildings. This paper aims to investigate renewable energy sources to decrease energy consumption to achieve nearly-zero energy building goal by implementing different energy efficient retrofitting scenarios. The retroffitting scenarios are based on renewable energy sources and are presented for an educational building located in Ankara-Turkey, through a Building Energy Simulation Tool, Design Builder Software. In order to develop an accurate model, educational building is monitored and the model is calibrated. Then, various energy efficient retrofitting scenarios are defined such as implementing PV panels, solar collectors and adding wind turbines for electricity generation.

Keywords: *Nearly-zero energy buildings, Educational buildings, Renewable energy*

[1]*This study 2-3 May 2019 Canakkale date / place the turkey in "IV. International Rating Academy Congress: Village Institutes and New Searches in Education".*

1. INTRODUCTION

Energy intensity of Turkey is higher compared with Western European countries. However, energy consumption of the country is expected to grow significantly together with increasing young urban population and industrial development potential. At the same time, elementary education of population in rural region is vital with the development of industry (Tonguc Vakfi, 2019). Besides dissemination of education, proper use of energy resources become a significant issue in developing countries such as Turkey where energy is limited. On the other hand, the building sector holds significant opportunity as 40% of the current energy consumption (Eshraghi *et al.,* 2014). Therefore, the implementing zero-energy building applications becomes crucial to meet energy saving goals, specially for educational buildings. For example, Ascione *et al.* (2015) provided renewable energy resources for an educational building in Italy. The authors investigated potential energy savings such as changing glazing with efficient ones and insulating roofs and calculated pay-back period as 10 years. Similarly, Sait (2013) suggested to increase the efficency of air-conditioner systems of educational buildings. 31% of energy was saved with a pay-back period of 2.3 years.

Nearly-zero energy building (NZEB) is not new concept for educational buildings in Europe. Zeiler and Boxem (2013) compared NZEBs with traditional educational buildings in Netherlands. The authors indicated that NZEBs produces their own energy from renewable energy resources such as solar panels and wind turbine parks. However, initial costs of investments were found high. Considering there are approximately sixty thousand schools in Turkey, educational buildings have great energy saving potential by applying energy efficient retrofit scenarios (Basarir *et al.,* 2012). Moreover, energy efficient educational buildings can improve thermal comfort of students and teachers while decreasing energy consumption of buildings. Many papers have been published to revive educational buildings in rural regions (Tonguc Vakfi, 2019; Vexliard and Aytaç, 1964; Eshraghi *et al.,* 2014; Korur, 2002; Karaomerlioglu, 1998). According to the authors' knowledge, there is no study on predicting energy consumption of educational buildings in rural zones and implementing energy efficient retrofits in Turkey.

The aim of this study is to apply nearly zero-energy applications to an educational building in a rural region. Hasanoğlan Atatürk Science High School which is located in Ankara/Turkey is selected as case building. A detailed building energy simulation tool is used to determine the influence of energy efficient retrofit scenarios. The model of Hasanoğlan Atatürk Science High School is calibrated by comparing the measured and simulated indoor air temperatures and total electricity consumptions. The applicability of the scenarios are evaluated with pay-back period criteria.

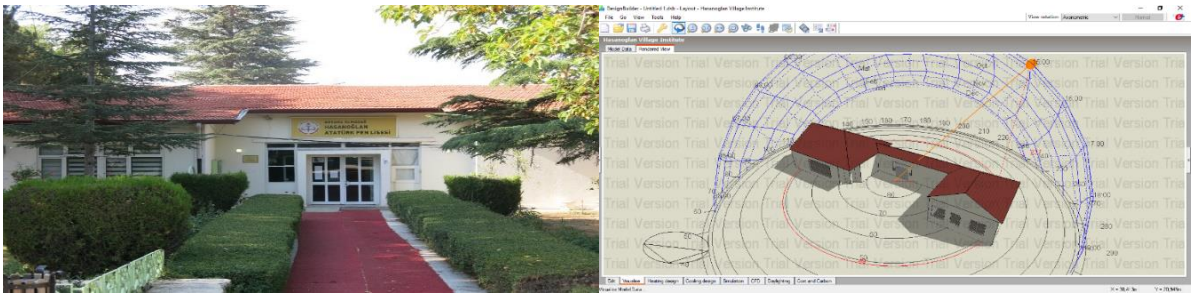
2. CASE STUDY

Ankara is situated in Central Anatolia Region of Turkey (at 32.52 E 39.56 N) which is Dsb type climate zone under the Koppen-Geiger climate classification (World Map of Koppen-Geiger Climate Classification, 2006). The average temperature is 22.3^{o}C and 1.4^{o}C during summer (May-October) and winter (December-March), respectively (Turkish State Meteorological Service, 2019). The case building is the Hasanoğlan Atatürk Science High School which is located in Ankara and lays on Northeast- Southwest direction (Figure 1).

Figure 1. The location of the Hasanoglan Atatürk Science High School

Hasanoglan Atatürk Science High School was built in 1941 by village institute students who founded other village institutes and the teachers to solve the failure in constituting the teaching staff problem for Turkey (Figure 2). The selected building is one-storey with 18 seperate zones. The total floor area of the case flat is 150.85 m^2 including administrator offices, editorial offices and long corridors. The people density is assumed as 0.11 ppl/m^2 while density of computers is 1 W/m^2. Since there are many editorial offices in the building, the density of office equipments is selected as 11 W/m^2.

Figure 2. The out-view and model of the case building

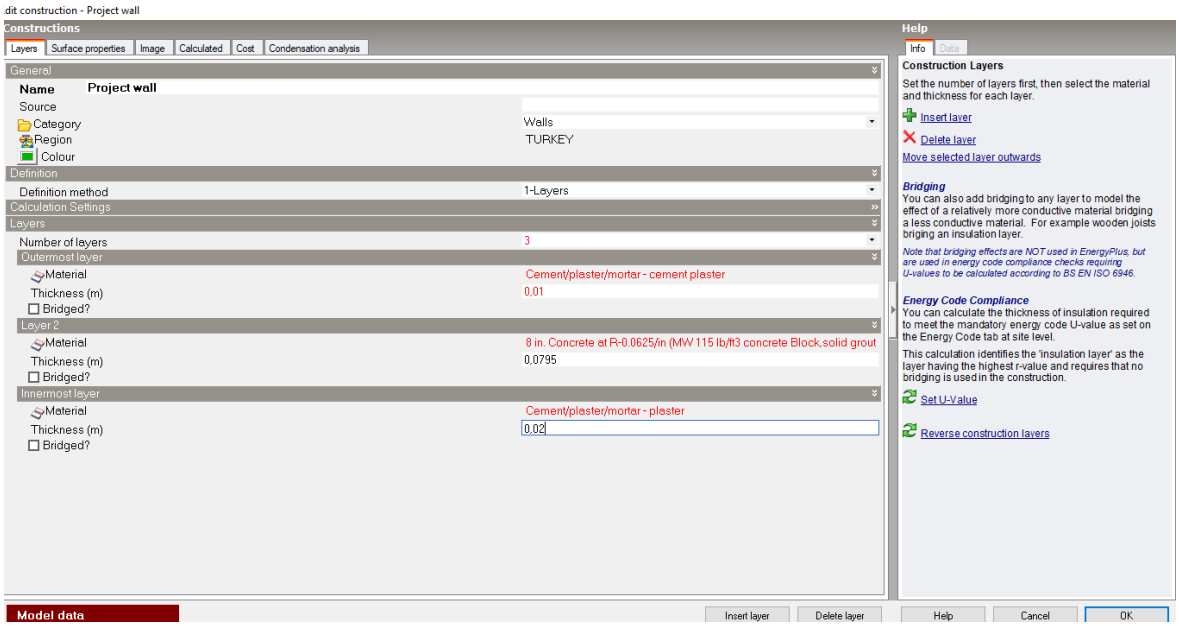


The heating and cooling system of the flat is fan-coil unit (COP=1.8) with no fresh air. The heating period is 6 months (October-April) with a set point temperature of 23°C and the cooling period is approximately 3 months from June to September with the same temperature. The operation period of heating and cooling system is from 08.00 to 19:00 on weekdays. The exterior walls consist of inner gypsum plastering (0.02 m) , brickwork inner leaf (0.19 m), XPS extruded polystyrene (0.05 m) and outer gypsum plastering (0.03 m), respectively. The walls are well-insulated with 5 cm XPS. The doors and the windows are double glazed with a PVC frames. Air tightness of the elements is 0.7 (1/h).

The Hasanoglan Atatürk Science High School is modelled and simulated in a Building Energy Simulation (BES) tool, DesignBuilder (2019). DesignBuilder is a 3D BES tool which uses EnergyPlus simulation engine. The software is capable of modelling buildings according to their heating/cooling systems, construction metarials, building geometries, weather data and occupant schedules. The outputs of the software are heating/cooling loads and energy consumption of the building. The main advantage of using DesignBuilder is to analyse energy consumption of case building by adding renewable energy technologies such as solar panel, wind turbines etc.

The case building is modelled according to the geometry of the building, energy relevant properties of the materials, monthly climate parameters of Ankara, office equipments such as computers and photocopiers and occupant behaviours (Figure 3). Before the simulation, the model is calibrated with temperature and electricity consumption data of the case building.

Figure 3. Model construction for Hasanoglan Atatürk Science High School



Eq. (1) and (2) were used to obtain heating and cooling energy requirements of case building according to the European Standards (EN 892, 1999).

$$Q_h = Q_{hL} - \eta_{hg} Q_{gh} \quad \textbf{Eq. (1)}$$

$$Q_c = Q_{cL} - \eta_{cg} Q_{gc} \quad \textbf{Eq. (2)}$$

where Q_h and Q_c heating and cooling energy requirements, respectively. Q_{hL} is total heat transfer for heating mode, η_{hg} and η_{cg} are dimensionless gain utilisation factors while Q_{gh} and Q_{gc} depict total heat sources for heating and cooling modes.

The energy retrofit scenarios are implemented in order to reduce energy consumption of Hasanoglan Atatürk Science High School after the current energy performance is analysed via DesignBuilder simulation tool. Six different energy retrofit scenarios are taken as given below.

A: Decreasing or increasing the set-temperature by 1 ^{o}C according to the season (from 23 ^{o}C to 22 ^{o}C for winter, from 23 ^{o}C to 24 ^{o}C for summer).

B: Decreasing the air tightness in order to reduce energy consumption (from 0.7 1/h to 0.51/h).

C: Changing windows with quadruble low-e windows.

D: Ten PV panels (1.6 X 1 m, with standard 60 cells) with a total area of 16 m^2 were applied to produce electricity for the building.

E: Solar collector with a total area of 2.06 m^2 were implemented to decrease energy consumption and supply domestic hot water.

F: Adding one three-bladed wind turbine to generate electricity (with 31 m height and 55kW rated power output) (Figure 4)

Figure 4. Adding wind turbine in BES tool for Hasanoglan Atatürk Science High School

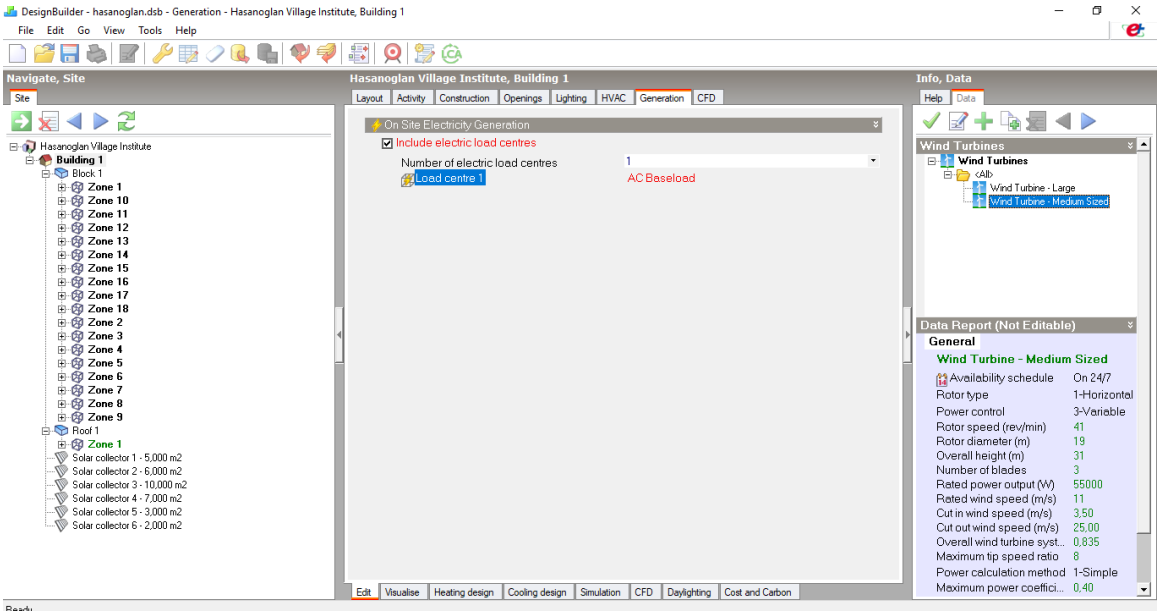


Table 1 depicts the description of six retrofitting scenarios in detail. Based on the reduction of energy consumption, pay-back periods are calculated according the formula in Eq.3 (Turhan *et al.*, 2016).

Pay-back Period: Investment Cost/ Annual Cash Savings **(Eq.3)**

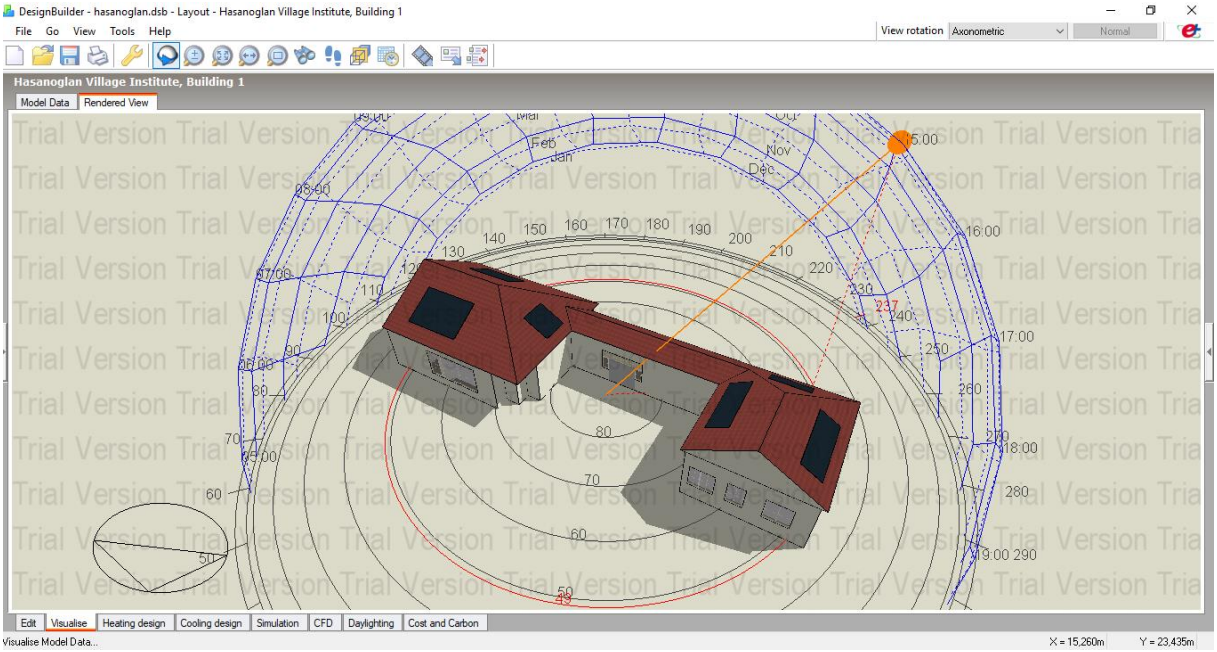
Table 1. Retrofitting Scenarios

Scenarios	***Retrofits***	***Existing***	***Improved***
Case 1	*A*	*23 °C*	*22 °C for winter, 24 °C for summer*
Case 2	*A+B*	*0.7 1/h*	*0.5 1/h*
Case 3	*A+B+C*	*1.98 (W/m²K)*	*0.77 (W/m²K)*
Case 4	*A+B+C+D*	-	*2 kWp*
Case 5	*A+B+C+D+E*	-	*2 kWh*
Case 6	*A+B+C+D+E+F*	-	*55 kW*

3. RESULTS AND DISCUSSION

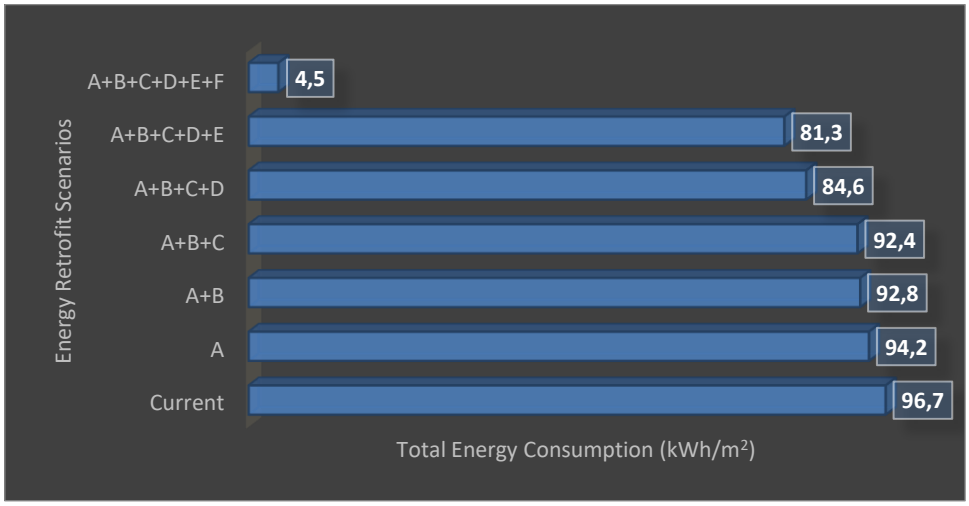
The BES model is calibrated according to the ASHRAE Guideline 14 (ASHRAE, 2002). Six different energy retrefitting scenarios are implemented after constructing and calibrating model accurately. Figure 5 shows the final model of the Hasanoglan Atatürk Science High School after implementing six energy retrofitting scenarios including renewable energy technologies.

Figure 5. Decreasing energy consumption of Hasanoglan Atatürk Science High School towards a nearly-zero energy building



The reduction in energy consumption for the case building is shown in Figure 6. Changing the set-temperature of heating and cooling system saves 2.6% of energy without any pay-back period. Since the window number in the building is low, changing the window type to high performance low-e windows seems not logical (pay-back period is 7.8 years). Results show that retrofit Case 4 reduces the total annual energy consumption by 12%. With adding solar collector to the system, 15% of energy can be saved with a pay-back period of 8.4 years.

Figure 6. The total energy consumption of retrofits



However, the most important retrofit is implementing wind power system to the Hasanoglan Atatürk Science High School building. The initial costs of constructing a 31 m wind turbine is around 50000 pounds. This number can be seemed as high with a pay-back period of 14 years. However, implementing wind power system to the Hasanoglan Atatürk Science High School saves 95.3% of energy. Furthermore, by increasing the number or power of wind turbines, the Hasanoglan Atatürk Science High School can sell electricity to the city

electricity grids which can make the building "positive-energy building". Table 2 summarizes the energy retrofit scenarios and energy savings with pay-back periods.

Table 2. Energy consumption of the Hasanoglan Atatürk Science High School with respect to energy retrofits

	Total energy consumption (kWh/year)	Total energy consumption per area (kWh/m^2 year)	Energy Saving (%)	Cost (TL)	Pay-back period (Year)
Case educational building	*14586*	*96.69*	-	-	-
Case 1	*14203.7*	*94.15*	*2.62*	-	-
Case 2	*14001.04*	*92.81*	*4.01*	*150*	*0.48*
Case 3	*13949*	*92.40*	*4.36*	*4750*	*7,81*
Case 4	*12763.14*	*84.60*	*12.49*	*20990*	*8.41*
Case 5	*12261.73*	*81.28*	*15.93*	*26240*	*8.49*
Case 6	*678.24*	*4.49*	*95,35*	*405095*	*14,11*
Note: Labour charges are added to the prices, 1 $= 5.8 TL, 1£ = 7.57 TL, 1 € =6.55 TL					

4. CONCLUSIONS

An administrive building in Hasanoglan Atatürk Science High School Campus was selected as a case study in order to apply zero-energy building concept. The energy performance of the case building was simulated via of Design Builder building energy performanse simulation program. The tool was calibrated with real data according to the standards. The improvements in decreasing the energy consumption applying various retrofitting scenarios were shown. The results show that using renewable energy sources such as solar and wind power, 95% of energy consumption can be saved. Another outcome of the study is that the energy consumption of educational buildings such as Hasanoglan Atatürk Science High School should be lower with a development of technology and using renewable energy sources. Note finally that this study is an elementary work which does not include whole buildings in campus. By applying energy retrofits to the whole buildings, more energy savings would be obtained. Furthermore, energy efficiency of the Hasanoglan Atatürk Science High School can be improved by using more efficient appliances, lighting system and raising awareness on energy efficiency of the administrator and students.

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Research Article

BIOCHEMICAL EVALUATIONS OF QUINALPHOS EXPOSED ZEBRAFISH LIVER ORGANOTYPIC TISSUE CULTURE

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ABSTRACT

As being a broad-spectrum, organophosphorus insecticide and acaricide, quinalphos is widely used against a range of pests and has a great threat to aquatic systems. Although the methods for detecting and predicting the harmful effects of chemicals on non-target organisms are traditionally perfected by in vivo experiments, cell culture methods that were used widely in recent decades are also an important tool for these kinds of research. In order to evaluate the effects of quinalphos on liver organotypic culture system of zebrafish, tissue cubes (1-2 mm3) were prepared by dissection and slicing of the liver tissues, embedded in agarose and cultured. The cubes were exposed to three different concentrations of quinalphos (2, 4 and 8 mg/L) for 24 and 96 hours. By performing the comet assay as an emerging tool for cytotoxicity, it was detected that quinalphos causes DNA damage. Increased levels of catalase, superoxide dismutase and glutathione-s-transferase were also measured. All of these parameters were noted as concentration- and time-dependent. Our data suggest that organotypic liver tissue culture of zebrafish is a practical alternative to the whole fish..

Keywords: *Zebrafish liver organotypic culture, quinalphos, oxidative stress*

1. INTRODUCTION

Pesticides are widely used in agriculture to enhance food production by eradicating unwanted insects and controlling disease vectors (1). These chemicals have made great contributions to plant protection but at the same time, their unbounded and indiscriminate applications have resulted in serious health and environmental problems (2). It has been estimated that only 0.1 % of the applied pesticides reach the target pests and the remaining 99.9% find their way to different components of the environment (3). Pesticides are one of the major contaminants of our environment and many of them persist for longer durations (4), and pose great threats to the health of humans and non-target organisms (5).

Organophosphorus insecticides (OPIs) are the most usually applied pesticides, accounting for 50% of global insecticidal use due to their extensive insecticidal property, low mammalian toxicity, a lesser amount of persistence and rapid biodegradability in the environment (6,7). Unfortunately OPIs lack target specificity and cause severe, long-lasting population effects on terrestrial and aquatic nontarget species, particularly fish (8, 9).

Quinalphos (QP: O,O diethyl O-2 quinoxalinoxalinyl phospharothionate) is an OPI that extensively used in agriculture for pest eradication (10). It is effective against a wide range of pests of cotton, groundnuts, rice, tea, coffee, soybeans and so forth. QP has been classified as a moderately hazardous pesticide by WHO but has become a matter of concern because of its potentiality and hazardous effect on nontarget organisms. the primary target of QP action is the inhibition of AChE activity, the enzyme that degrades the neurotransmitter acetylcholine in cholinergic synapses. Experimental evidence showed that QP, besides its inhibitory effect on AChE, also induced oxidative stress.

Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses (11). It occurs when the critical balance between oxidants and antioxidants is disrupted owing to the depletion of antioxidants or excessive accumulation of the reactive oxygen species (ROS), or both, leading to damage

Pesticides are known to modulate antioxidant defense systems and to cause oxidative stress in aquatic organisms via ROS production. Pesticides are known to regulate antioxidant defense mechanisms and to cause oxidative stress in aquatic organisms via ROS Production (12, 13, 14). ROS such as hydrogen peroxide (H_2O_2) and the free radicals superoxide (O2 •) and hydroxyl radical (HO•) can react with biological macromolecules and produce enzyme inactivation, lipid peroxidation (LPO), DNA damage, and protein oxidation, resulting in oxidative stress (13, 15, 16). To reduce the adverse effects of ROS, fish possess an antioxidant defiance system similar to other vertebrates that use enzymatic and nonenzymatic mechanisms. The most important antioxidant enzymes are superoxide dismutase (SOD; EC 1.15.1.1), catalase, (CAT; EC 1.11.1.16), and glutathione-S-transferase (GST; EC.2.5.1.18, GST) (17; 18). One of the most important targets of ROS is the membrane lipids which undergo peroxidation (LPO). Thus, the estimation of LPO has also been successfully employed to signify oxidative stress and most frequently used as a biomarker in the evaluations of toxicological assays.

Fish are mainly used to evaluate the situation of aquatic systems and physiological changes in fishes serve as biomarkers of environmental pollution, and thus can ben used for the quality assessment of the aquatic system (19, 20, 21, 22). Zebrafish is one of the commonly used ecotoxicological models for understanding interactions of xenobiotics with living organisms. Especially in ecotoxicological studies, zebrafish is widely used for this purpose. From an ethical perspective, researchers need to minimize animal use in experiments. So that in vitro methods replace in vivo methods day by day. In vitro, toxicological methods are widely used for the assesment of chemicals effects. In this perspective, 2D and 3D culture methods

are used. Understanding the biochemical and metabolic characteristics of 3D models are important criteria for promoting their application in this field of ecotoxicology. A major promise in vitro systems is to obtain mechanism derived information that is considered pivotal for adequate risk assessment. Although two-dimensional (2D) cell culture enabled biologists to observe and manipulate cells and laid the foundation for cell and molecular biology, they do not completely recapitulate the three dimensional (3D) organization of cells and extracellular matrix (ECM) within tissues and organs. In the present study, we tried to explore genotoxic, biochemical effects of quinalphos with using in vitro organotypic liver 3D culture.

2. MATERIALS AND METHODS 22

2.1. Test Compound and Zebrafısh Maıntenance

Test compound, quinalphos was commercially obtained from local suppliers (Ekalux). Wild type zebrafish specimens were reared in glass aquaria (60 x 30 x 30 cm) of 40 L water capacity and carried out to standard husbandry procedures (23).

2.2. Liver Organotypıc Culture

Male healthy zebrafishes were selected randomly and anaesthetized by MS222 (0,5 mg/L, Sigma), liver samples were dissected and transferred into phosphate-buffered saline solution (PBS, Sigma). Tissue samples that were randomly pieced small cubes and embedded into %1 agarose dissolved in PBS; transferred into six-well plates. Leibovitz's 15 (L15) cell culture medium supplemented with %10 FBS were added to plates for incubation in 28 °C overnight.

2.3. Quınalphos Exposure

Quinalphos stock solution (10 mg/L) was prepared. Three different concentrations (2, 4, 8 mg/L) of test solution were diluted from stock with complete culture media. Organotypic culture of liver samples was exposed to different concentration of quinalphos with two different exposure duration. (24-96 hours).

2.4. Comet Assay

The alkaline comet procedure was performed. Briefly fully frosted slides were layered with normal melting point agarose (NMPA) and dried; then 100 µL of low melting point agarose (LMPA) were mixed with each disaggregated tissue sample and applied as a second layer onto the pre-coated slides. Finally the third layer of LMPA was added on top. The slides were placed in freshly prepared lysing solution (NaCl 2,5 M, EDTA 100 mM, Trizma base 10 mM (pH: 10), 1% Triton X-100 and 10% DMSO) for 24 h at 4 °C to leave the DNA uncovered; and were immersed in alkaline buffer (NaOH 300 mM and Edta 1 mM, pH > 13 for 30 min to allow the unwinding of DNA. Electrophoresis was conducted for 20 min at 25 V (0,66 V/cm) and 30 mA at the same pH. The slides were then placed in neutralizing buffer (pH: 7,5) three times each for 5 min. and dried at room temperature. They were stained with 50 µL of ethidium bromide for 1 min. The stained nucleoids were examined at 40x in an epifluorescent microscope (Leica LM200) with a digital camera (Leica) and images were evaluated with Image J. Tail lengths were also measured and statistical analyses were performed by SPSS v14.0 statistical program (IBM).

2.5. BIOCHEMICAL ANALYSES

2.5.1. Sample Preparatıon

The post mitochondrial fractions from the cultured tissues were used for biochemical assays. Cultured tissues were washed in ice-cold 1,15 % KCl solution, blotted and weighed. The tissues were homogenized with a homogenizing solution (50 mM phosphate buffer pH 7,4

containing 1 mM EDTA, 1 mM dithiothreitol (DTT), 0,15 M KCl and 0,01 % (w/v) PMSF). Homogenization was performed at 4 C by using homogenizer (sartorius), and centrifuged at 10,000 rpm for 20 min at 4 °C with a refrigerated centrifuge (Eppendorf 5810 R). The supernatants were stored at -20 °C until performing biochemical analysis.

2.5.2. Assay Of Lıpıd Peroxıdatıon

Lipid peroxidation was determined by thiobarbituric acid (TBA) reaction (24). The absorbances were read at 532 nm after the removal of any flocculated material by centrifugation. The amounts of thiobarbituric acid reactive substances (TBARS) were then calculated by using an extinction coefficient of 1.56 x105 M^{-1} cm^{-1} and expressed as nmol TBARS formed/mg protein.

2.5.3. Assay Of Antıoxıdant Enzymes

Superoxide dismutase (SOD) activities were measured based on the inhibition of oxidation of NADH by SOD (25). One unit of enzyme activity was defined as 50% inhibition of oxidation of NADH in the reaction. The reaction rate was recorded at 340 nm and expresses as units/mg protein. Catalase (CAT) activities were determined based on the decomposition rate of H_2O_2 by the enzyme. Absorbance was measured at 240 nm and enzyme activity was expressed as units/mg protein. One unit of catalase activities were defined as decomposition of 1.0 nm of H_2O_2 to oxygen and water per minute at pH: 7.4 and 25 C. Glutathione –S-Transferase (GST) activities were measured by using 1-chloro-2, 4-dinitrobenzene as a substrate (26). The reaction rate was recorded at 340 nm and the activities were expressed as nmol CDNB conjugate formed/min/mg protein using a molar extinction coefficient of 9.6 Mm-1CM-1.

3. RESULTS AND DISCUSSION

Comet assay or single nuclear electrophoresis are commonly used methods to observe DNA damage and genotoxicity can be identified by measuring tail lengths. As expected, highly genotoxic effects of quinalphos are seemed to be depended on concentration and exposure duration (Figure 1). In rats genotoxicity of quinalphos was reported with similar findings obtained by micronucleus and comet assay (27).

Figure 1. Tail lengths of DNA damaged cells were depended on concentration and exposition time.

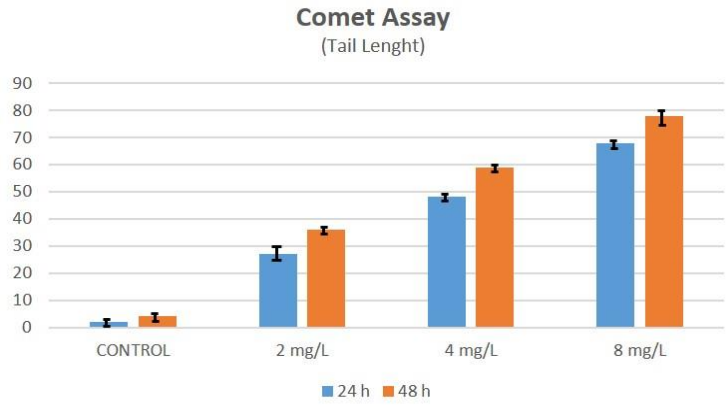
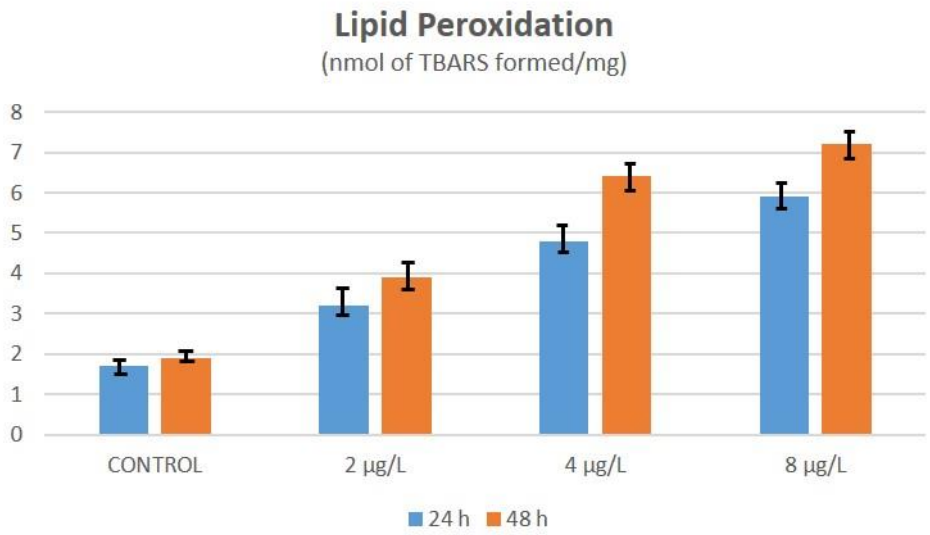


Figure 2. shows the results of MDA analysis in the organotypic liver culture of zebrafish after 24 h and 96 h of exposure. There was a significant increase in MDA levels that showed the level of lipid peroxidation in liver tissue in all test concentrations when compared with control groups. Lipid peroxidation (LPO) has been widely used for a biomarker of oxidative damage in fish exposed to xenobiotics (28). LPO is the process of oxidative degeneration of

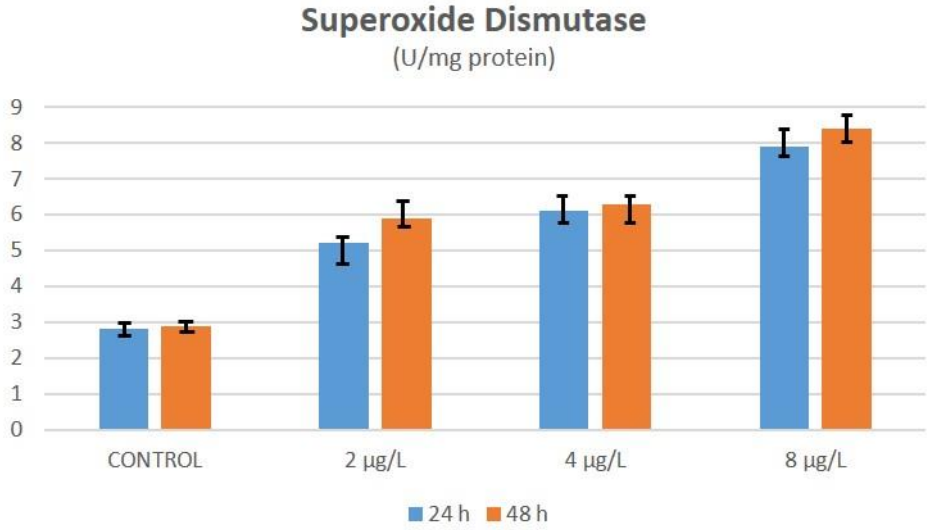
polyunsaturated fatty acids (PUFAs) that is essential for membrane function, structural integrity and inactivation of several membranes bound enzymes (29). MDA is a major oxidation product and the measurement of MDA provides a convenient index of LPO (30). A similar increase in MDA level in the fish liver was reported chronic exposure to lindane, an organochlorine pesticide in an in vivo study (31). Also another study showed that MDA levels in the liver of O. Mykiss were increased by exposure to methyl parathion and diazinon (32). However, there is no data in the literature to combine about in vitro organotypic liver culture of zebrafish. Our observations led us to conclude that the administration of different concentration of quinalphos promotes the concentration of MDA levels in in-vitro 3D tissue culture system.

Figure 2. Lipid peroxidation of QP exposure organotypic tissue culture. Compared to controls lipid peroxidation was increased depending on the exposure time and concentration.



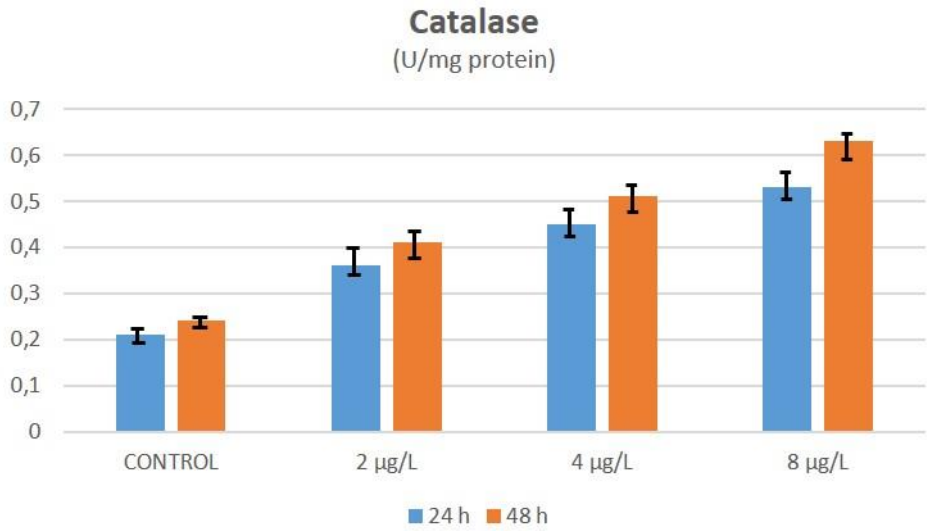
SOD levels of organotypic 3D liver cultures of zebrafish exposed to quinalphos were shown in figure 3. SOD is a group metalloenzymes that plays an important role in cellular defiance against free radical induced damage by catalyzing the dismutation of superoxide and produced in peroxisomes and mitochondria to H_2O and H_2O_2 (33; 34). In our study SOD levels were increased significantly in time and concentration depended. In other studies, performed in vivo techniques, it was observed that SOD activity in the liver of *D. labrax* after 96 h exposure to fenitrothion which is an OP pesticide, was increased (35). Different studies performed with different teleost species and different OP pesticides, it was clear that SOD is a common biomarker for exposure of OP pesticides in vivo. Our study also has shown that in vitro methods such as the organotypic culture of tissues like the liver could be used for assessment of xenobiotics, instead of whole organisms.

Figure 3. Superoxide Dismutase (SOD) activities of QP exposed liver organotypic tissue culture. Enzyme Activities increased significantly depending on increased concentration and exposure time.



CAT has been implicated as essential defiance against the potential toxicity of superoxide anions (36). It is an antioxidant enzyme that acts specifically on H_2O_2, forming oxygen and water. CAT is mainly located in the peroxisomes and it is responsible for the reduction of hydrogen peroxide produced from the metabolism of long-chain fatty acids in peroxisomes (37). In our study exposure of quinalphos in different concentrations and exposure time, CAT activity levels increased significantly depending time and concentration (Figure 4). In related studies hepatic CAT activity was determined to be increased after different OP pesticides such as cypermethrin and malathion in different teleost species such as *O. niloticus* and *L. rohita* (38).

Figure 4. Catalase (CAT) enzyme activities of organotypic liver tissue culture exposed to QP. CAT levels increased meaningfully depending on increased concentration and exposure duration.



The same increase level was observed in GST activities (Fig 5). The enzyme GST is involved in the detoxification of many xenobiotics and this plays an important role in protecting tissues from oxidative stress (38). An increase in GST activity has also been observed in the studies with *C. carpio* after 2,4-D and azinphos-methyl exposure (39). Studies have shown that GST is the one of the biomarker for exposure of OP pesticides and our study conclude that in vitro experimental designs could be used for analysis of GST activity for evaluating the toxicity of OPs.

Figure 5. Glutathione-s-Transferase (GST) enzyme activities of organotypic liver tissue culture exposed to QP. GST levels increased meaningfully depending on increased concentration and exposure duration.

It is clear that quinalphos is not only genotoxic, but also cause lipid peroxidation and oxidative stress. Levels of lipid peroxidation and oxidative stress were elevated by increased concentration and longer exposure duration. These findings are in accordance with the report of Padmanabha et al. (40) who examined acute and chronic exposure of quinalphos on *C. carpio*. As a conclusion, it is clear that 3D tissue culture gives more efficient results when compared with 2D; and organotypic tissue culture is a more efficient and simple method to observe the effects of chemicals when compared to in vivo methods. We have to inform that only seven zebrafishes were sacrificed for his investigation.

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Research Article

PRESERVING THE SPATIAL MEMORY IN HISTORIC BUILDINGS AND SPACES AND ITS CONTRIBUTION TO THE URBAN IDENTITY: A CASE STUDY OF ÇANAKKALE URBAN SITE[1]

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ABSTRACT

In the present study, it is aimed to preserve the place of historic buildings and spaces in the spatial memory together with their images and to investigate its contributions to the urban identity. In this context, an examination was made on eight historic buildings and spaces selected from Çanakkale Urban Site (an avenue, a street, a square, a garden, a courtyard, a religious building, an education building, and a registered old building). Within the scope of this study, a specialist group of 70 people was determined in the survey technique. The aim of the survey technique was to question the spatial memory, urban image, and urban identity cases and their relations with each other through the examples selected from Çanakkale Urban Site.

In this context, when the buildings and spaces which have acquired a place in the urban memory are defined in terms of spatial memory parameters and urban images, this also strengthens their contributions to the urban identity. The buildings and spaces selected as the material in the study are still being used, which strengthens the spatial memory parameters. The spatial memory parameters which affect the places of the buildings and spaces concerned in the urban identity the most are the parameters of "historical and cultural value", "memory value and continuity of use", "originality and rarity value", and "aesthetic and artistic value", respectively. The historic buildings and spaces identified with all these parameters contribute to the city's states as a city of "history", "culture-art", and "tourism" the most. When the buildings and spaces concerned are evaluated in terms of the urban images, they are mostly identified as "districts", "nodes", "paths", and "landmarks", which strengthens their places in the urban identity.

As a result of the study, proposals were made for the preservation of the spatial memory parameters in historic buildings and spaces and for the continuity of the historic buildings and spaces by emphasizing the contribution to the formation of the urban image and the urban identity.

Keywords: *Çanakkale Urban Site, Spatial Memory, Spatial Memory Parameters, Urban Identity, Urban Image, Conservation.*

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1. INTRODUCTION

Cities are social, political, economic, and cultural areas of interaction besides being physical spaces that enable people to coexist and that provide the labor force (Wirth, 2002) and they are gradually standing out in the globalized world (Güler *et al.*, 2016). A city becomes a physical, social, political, and cultural area when the accumulations belonging to different periods and ways of life of history gather (Birol, 2007). Therefore, neither the coexistence of buildings nor the physical plans drawn by the experts who organize the development of a city is enough for the formation of a city. A city is at the same time a social phenomenon and one should first of all take this into consideration in order to read the traces of architecture in the city accurately (Kuban, 2016). Likewise, Calvino (2002) expresses that *"cities, like dreams, are made up of desires and fears"*. Expectations and concerns also shape the living spaces. For instance, in those societies where war was experienced, the cities were enclosed with ramparts and shaped with a planning understanding towards protecting it and those in it.

On the other hand, cities are spaces where societies and individuals coexist and socialize; which are built by thousands of different people with very different characteristics from any sociocultural classes and different ethnic groups; which assume the role of being a meeting place for different sections of the society (Erdönmez and Akı, 2005; Farrelly, 2011); and where events take place and life flows (Farrelly, 2011). With their social and cultural assets besides their spatial importance, cities have an original urban identity and are distinguished from each other so (Güler *et al.*, 2016). Thus, the concepts of city and space cannot be considered separate from each other and spaces make a great contribution to the physical-social formation of a city.

There is also a relationship between a space and a user that is nourished by interaction. A human being is a living thing with physical and spiritual needs. While expecting a space to meet his/her needs, he/she also wants it to be good for his/her soul (Yıldırım Erniş, 2012). In addition, space, time and motion determine the boundary of a city and a city holds on to some time on the space. Thus, the spaces where city dwellers pass their time and the times passed in these spaces make a cultural contribution to a city and also define the ways of life of city dwellers (Kaypak, 2010).

A space is the most important element which forms the basis for an environment built by people; which has not been identified with definite limits; and which develops in line with past experiences and accumulations. While examining the continuity of spaces, the permanence of those assets of theirs which influence the entire society is also scrutinized (Turgay, 2013). In this context, spatial memory is defined as *"the recording of space-related learning, sensations, experiences, perceptions, and memories in the memory during life with not only their own components but also the phenomena taking place in it, the ambient characteristics, and life, in other words, with 'its context' and their association"* by Öymen Özak (2008).

The functioning of the short- and long-term memories is essential in giving meaning to a space and in the formation of the image of that space. The images a person has acquired through his/her past experiences are kept in the long-term memory (Turgay, 2013). This relationship between an image and the physical form creates the spatial perception and the urban image assumes the most important role in the formation of the urban identity (Lynch, 2014). Spaces either are preserved or cannot be preserved in users' memories. Each remembered space takes its place in the memory together with its respective image. Urban images also draw attention as important reference points while defining the place of a city in the spatial memory.

The urban memory results from the coexistence of "space, time, memory, and identity". The processes of formation of the identity and the memory and ensuring/preserving their continuity over time play significant roles in such issues as the spatial perceptions by the

individuals living in cities, their sense of belonging, and their lifestyles (Aslan and Kiper, 2016). The elements which make up the urban identity can be evaluated in terms of the elements caused by the natural, human, and man-made environments (Önem and Kılınçaslan, 2005). The urban identity takes form within a long time span. It shapes the city as a blend of its such qualities as its geographical content, cultural level, architecture, local traditions, and lifestyle (Suher *et al.*, 2004). For the formation of an urban identity, the continuity of these assets should be provided and the material and immaterial assets which convey the messages coming from the past of the city to the future should be conserved. Therefore, one of the most important features which reflect the urban identity is the historical and architectural features of that city and their ways of preservation in the spatial memory (Ayyıldız and Ertürk, 2017). Indeed, the identity of a city which has experienced the surprising periods of economic, cultural, and political history is made up of the visual pieces of evidence of the past that have permanently acquired a place in its spatial memory (Lynch, 2014).

In summary, what distinguishes urban spaces from each other and makes each of them different from another is the events experienced by their society and the traces they have left regarding them. Trailing a society in the space that it belongs to is only possible through the survival of the buildings and spaces that it left behind and transferred its life experiences on up to the present time. These buildings and spaces, the most important witnesses to the societies living in the past, acquire historical value and form a permanent spatial perception in the memories of the city and of city dwellers when they reach the present time.

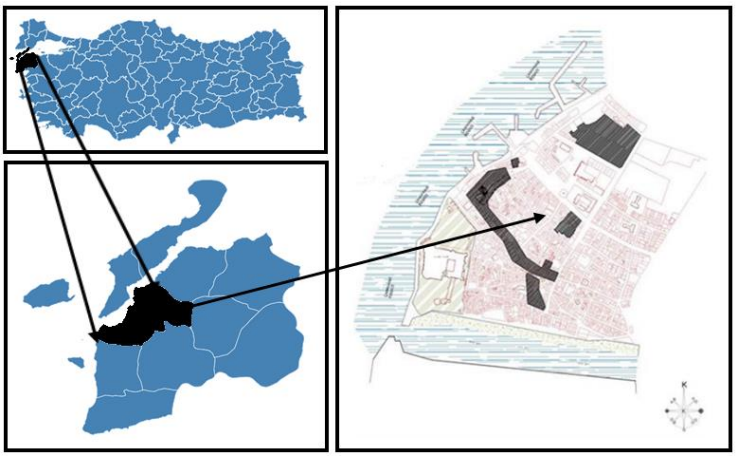
In the study carried out in this context, the eight historic buildings and spaces selected as examples from Çanakkale Urban Site were evaluated in terms of spatial memory parameters, urban identity, and urban images and proposals were made concerning this.

2. MATERIAL AND METHOD

2.1. Material

Çanakkale has significant potential with its location on the coast of the Dardanelles as well as with its rich archaeological and cultural wealth, slightly degraded nature, and climatic diversity (Koç, 2004). According to the population census data of 2018, the population of the central district is 136.002 people (TurkStat, 2018). In the resolution by the Council for the Conservation of Cultural and Natural Properties of Edirne (EKTVKK), dated 26.05.1995, it was decided to register the region between Sarıçay and Calvert Park (Public Garden) and the sea and Atatürk Avenue as "Çanakkale Urban Site" (Figure 1) (Directorate of the Regional Council for the Conservation of Cultural Properties of Çanakkale-ÇKVKBK, 2018). The eight historic buildings and spaces (an avenue, a street, a square, a garden, a courtyard, a religious space, an educational building, and an example of civil architecture) located within Çanakkale Urban Site and selected in line with the purpose of the study define the main material of the study (Figure 2). Such visual and literary data as the reports, maps, photographs, plans, and sketches obtained from the relevant public institutions and organizations as well as the photographs taken and observations made in the study area were each evaluated as a supplementary material within the scope of the study.

Figure 1. The location of the study area in Turkey and in Çanakkale province (created by making use of Turkey ShapeFile, 2019 and the Directorate of the Council for the Conservation of Cultural and Natural Properties of Çanakkale-ÇKTVKK, 1996)



2.2. Method

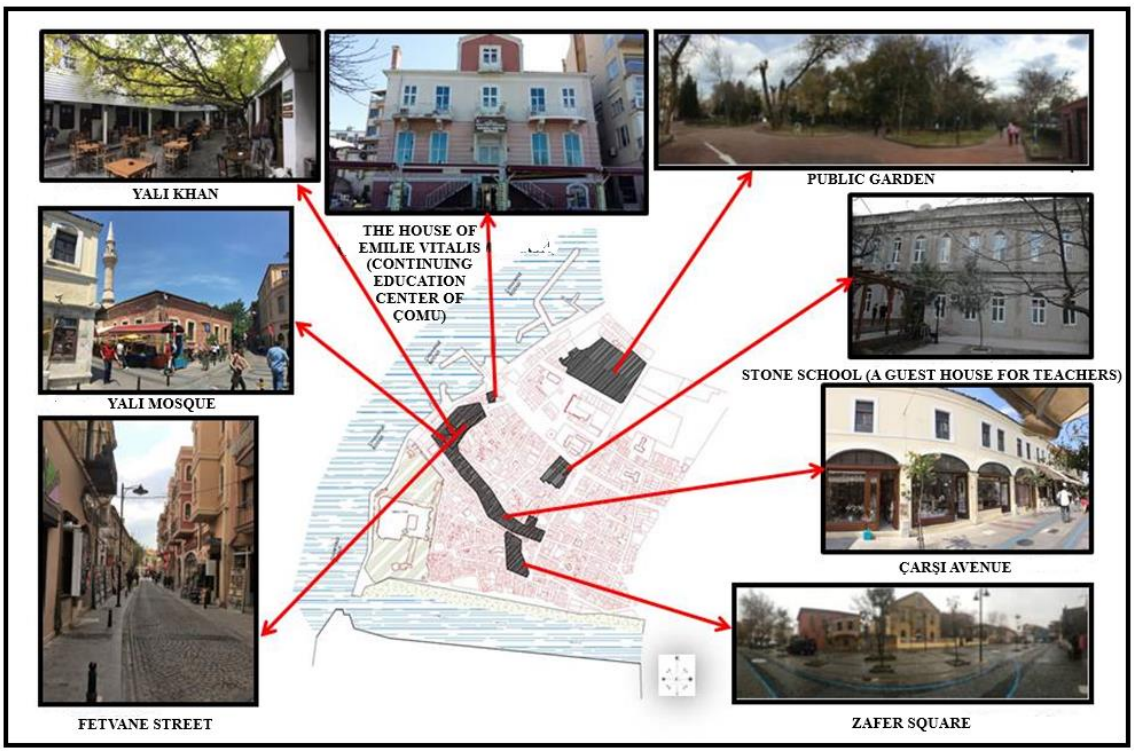
The survey technique was employed in the study in order to question the place of the selected historic buildings and spaces in the spatial memory of the city and to determine their contributions to the urban identity. Moreover, the buildings and spaces concerned were addressed according to Lynch (2014), who determined the formation of an urban image in five different physical elements; which of these elements the buildings and spaces concerned corresponded to was determined; and what kind of a contribution they made to the urban identity of Çanakkale was established. The sample size of the survey study was created with the non-probability and purposive sample techniques and a specialist group of 70 people was determined. This specialist group was selected from the people who lived in Çanakkale for long years, who were responsible for the physical structure of the city, and who took part in the social responsibility projects for the city. People from the employees in the Directorate for Development and Urbanization of Çanakkale Municipality, the Special Provincial Administration of Çanakkale, Çanakkale Archaeology Museum, and the Provincial Directorate for Environment and Urbanization in Çanakkale (e.g. architects, city planners, archaeologists, and engineers) as well as from the academics and the city intellectuals were included in the specialist group.

The survey in the study by Taşçıoğlu and Altunkasa (2018) was taken as the basis when drawing up the survey; however, the different survey examples in various theses and papers on the subject of the study (Topçu, 2011; Asar, 2013; Başaran Uysal, 2013; Er, 2014; Bozdağ, 2015; Kürkçüoğlu and Ocakçı, 2015; Altuğ Turan and Gülgün, 2016; Diker and Çolpan Erkan, 2017; Güneroğlu and Bekar, 2017; Turan and Yalçıner Ercoşkun, 2017) were also examined and an original survey was drawn up in line with the subject and purpose of the study. The survey consisted of two sections. The first section contained questions to categorize the respondents, whereas the respondents were shown photographs (Figure 2) of the selected historic buildings and spaces in the second section. The spatial memory parameters of the historic buildings and spaces in the photographs, their contributions to the urban identity and which urban image(s) they corresponded to were questioned. The 5-point Likert scale was utilized to quantify the spatial memory parameters of the buildings and spaces concerned and their contributions to the urban identity and the results were evaluated in SPSS 24.0 program. Besides the statistical results of the survey, the oral & written expressions of the respondents were also used in the evaluations made.

3. A SHORT HISTORY OF THE HISTORIC BUILDINGS AND SPACES SELECTED

The urban image classes by Lynch (2014) were utilized when selecting the historic buildings and spaces which constituted the main material of the study. Lynch (2014) defined the urban image within the physical elements as paths, edges, districts, nodes, and landmarks. Thus, as a result of the observations and examinations within Çanakkale Urban Site, the historic buildings and spaces where the physical elements could be taken into consideration were examined as examples. The examples selected in this context were Çarşı Avenue, Fetvane Street, Zafer Square, the Public Garden, Yalı Khan, the Yalı Mosque, the Stone School (Taş Mektep)/the Guest House for Teachers, and the House of Emilie Vitalis/the Continuing Education Center of ÇOMU. The buildings and spaces concerned (Figure 2) were also preferred as they acquired a place in the urban memory but did not stand out much, along with their original historical qualities. Some of the buildings and spaces concerned have survived up to the present time as the representatives of a specific period in the urban memory, with some of them maintaining their original function but some of them undergoing change in function.

Figure 2. The historic buildings and spaces selected in the study area (created by making use of the Directorate of the Council for the Conservation of Cultural and Natural Properties of Çanakkale-ÇKTVKK, 1996)



Çarşı Avenue: Commercial life and shops are known to be concentrated along Yalı and Çarşı Avenues in the architectural pattern of Çanakkale (CHVIP-the Historic City Commission, 2016). Especially Çarşı Avenue stood out as a place where the function of trade developed in those periods when the city was established. Upon the establishment of the city in the 14th century, shops began to form for the necessary requirements of the public in this region, which was close to the quay. It is known that the tradesmen in the place concerned generally comprised Muslims, Greeks, Armenians, and Jews (Büberci, 2003). The avenue is intensively maintaining its commercial function today as well. According to the report by the CHVIP-the Historic City Commission (1997), Yalı Avenue, Fetvane Street, Çarşı Avenue, Fatih Mosque Square and Zafer Square as well as the streets leading to these two squares are at the same time spaces where the urban silhouette is good.

Aynalı (Mirrored) Bazaar is located at Çarşı Avenue and has a significant place in the urban memory of Çanakkale and İlya Halyo from the Jewish community had it constructed in 1890 (Eren, 1990). Containing souvenir shops, this bazaar was used as a shopping arcade-bazaar during the early periods of its construction but as a stable by the English soldiers as it was burnt and collapsed during Çanakkale Wars. Repaired in 1967, the bazaar was reintroduced into the city by Çanakkale Municipality with the restoration project drawn in 2004 by Architect and Archaeologist Prof. Dr. Ümit Muzaffer Serdaroğlu (Güleryüz, 2017).

Fetvane Street: Fetvane Street is located between two historic spaces (Muvakkithane [timing room] and the Clock Tower) which announce time in the city (Uralman, 2012). The governor of the city had the Clock Tower constructed in 1897 with the money donated by an Italian named Vitalis, who worked as a consul in Çanakkale for long years. The muvakkithane (timing room) is a two-storey masonry building. The building, the downstairs of which was a shop and the upstairs of which was a muvakkithane, was constructed in 1867, according to its inscription (Kurtman, 1991). Fetvane Street runs perpendicularly to Çarşı Avenue and to the west of it are the City Museum and the Yalı Mosque. Fetvane Street has generally not changed its function since the early dates of its formation. This street, where Greek taverns and depots were generally available initially, also includes buildings which are used as shops, restaurants-cafés, and hotels today besides the spaces for entertainment purposes.

Zafer Square: An Armenian community that arrived in the city in the 1650s created a neighborhood in the Zafer Square (the Old Church) region (Çavuş and Koç, 2004). The Armenian Church constructed in 1873 is located at Zafer Square (Başaran Uysal, 2013). The church was built with hewn stones and preserves its originality as an architectural character (CHVIP-Historic City Commission, 1997). The Fatih Mosque, another important building in the area, is located at the northern endpoint of the area. This mosque was constructed in 1462 and completely renovated between 1862 and 1863 in the reign of Sultan Abdülaziz (Koç, 2006). Apart from it, the Armenian Primary School, the Tıflı Mosque and the Building of Nedime Hanım are located at and around Zafer Square (Başaran Uysal, 2013) and these buildings form a periphery around the square. The Armenian Church, one of the most striking buildings at the square, is now mostly used by the Faculty of Fine Arts of Çanakkale Onsekiz Mart University (ÇOMU). Even though the historic buildings located at and around Zafer Square preserve their own original identities in the general sense (CHVIP-Historic City Commission, 1997), it is seen that many of them have lost their original function today.

The Public Garden: The garden of the mansion located on the side of the strait and owned by the Calvert Family that lived in Çanakkale in the 1840s makes up some of the current Public Garden. Spreading over a vast area, this garden was designed to qualify as an English garden (Allen, 1999; from Erduran Nemutlu *et al.*, 2008). Discovered to house 85 ornamental plants, the Public Garden (Erduran Nemutlu *et al.*, 2008) is an important space which also stands out with its landscape value within the urban site (CHVIP-Historic City Commission, 1997).

Yalı Khan: Yalı Khan, whose date of construction is written as 1889 on the signboard suspended in it, had not changed its initial function and had been used as an accommodation building until the late 1970s (Tolun, 2013). It is mentioned that Yalı Khan, which is known to have functioned as a hotel where those who arrived in Çanakkale to work stayed in the early years of its construction, had a larger, cleaner, and wider courtyard than those of the other khans in Çanakkale and contained a large number of rooms lined up around the courtyard (Algör, 2007). Yalı Khan, which has two gates that lead to Yalı Avenue and Fetvane Street and which houses bookshops, handicraft workshops, and cafés today, is also like a crossing corridor which joins both streets together.

The Yalı Mosque: Although it is known that the first construction of the Yalı Mosque belonged to the early 18th century (Dündar, 2017), the Yalı Mosque and the shops were damaged in the fire that broke out on 6 August 1836 and Tavil Ahmet Ağa had it constructed again. On the other hand, the fire that broke out on 27 January 1854 completely burned the mosque too (Korkmaz, 2010). According to what is written on its inscription, the mosque was last renovated in 1854 following the fires it had suffered from (Dündar, 2017). The fenced graveyard of the mosque renovated by Colonel Halil Bey houses the tomb of Colonel Halil Bey (Eren, 1990). This locality, where Yalı Khan, the Yalı Mosque and Yalı Public Bath are located, is also one of the early cores of the city (Algör, 2007).

The Stone School (Taş Mektep) (A Guest House for Teachers): The school building constructed depending on the modernization initiatives in the Ottoman Period is known to have been the building of "Kale-i Sultaniye Mekteb-i İdadî", which was constructed using the state budget in 1892. Known as "Taş Mektep", this school building is two-storeyed (Uygun, 2015). The school, which took the name "Çanakkale Sultanisi (high school)" in 1913, began to provide education at the high school level, but education was terminated during the First World War. Having begun to be used as a hospital after the city had begun to be controlled by the English following Çanakkale Wars, the Stone School later functioned as barracks (Eren, 1990). The building assumed the mission of being the only secondary school of the city between 1924 and 1949 and took the name "Çanakkale Lisesi (High School)" on 12 September 1949. The İdadî Building (secondary school) served as "the first teacher training school" between 1956 and 1971. Used as a Commercial High School between 1971 and 1998, this building was restored in 2000 and provided with the function of being a "Guest House-Hotel for Teachers" (Uygun, 2015).

The House of Emilie Vitalis (Continuing Education Center of ÇOMU): "Emilie Vitalis", an Italian merchant who lived in Çanakkale, had it constructed in the late 19th century. Belonging to Emilie Vitalis, who worked as the Italian Commercial Attaché and a merchant, this building was designed as both an office (official department) and a house (Tombul, 2015). According to the information in the land office, the building concerned was sold to the Treasury in 1937 by the daughters of Italian Consul Ezir Karalin (Algör, 2007). The building functioned as a house for a while in the early 20th century for Mrs. Milton – the director of English cemeteries. Used as the Directorate of TEKEL from the early years of the Republic to 1992, the building was allocated to Çanakkale Onsekiz Mart University in 1992 and used as the Rectorate Building until 2001 (Tombul, 2015; Algör, 2007). The building is still being used by the university and its upstairs serves as the Continuing Education Center of ÇOMU and its downstairs as a café.

4. FINDINGS

Such basic characteristics of the respondents as gender, age, marital status, educational status, occupation, participation in cultural, artistic, and environmental activities, and membership to a nongovernmental organization were questioned in the first section of the survey study. On the other hand, the questions in the second section of the survey were aimed at determining the selected historic buildings and spaces in terms of spatial memory parameters, urban identity, and urban image. The questions in this section were individually organized for each building and space.

The respondents were shown the photographs in Figure 2 and asked to evaluate the historic buildings and spaces concerned in terms of spatial memory parameters, urban image, and urban identity via their knowledge in their own memory together with these photographs. The spatial memory parameters and the urban identity were questioned with 5 assessment criteria and the 5-point Likert Scale (5-Very Good, 4-Good, 3-Slightly Good/Moderate, 2-Bad,

1-Very Bad). Before that, the reliability degrees of the scales in the survey had been examined and Cronbach's alpha statistics had been used for this purpose. Whether the parameters quantified different views of the respondents was assessed with Hotelling's T^2.

4.1. Çarşı Avenue

The avenue, which is still preserving the architectural structure of the period when it was first constructed, makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.26). This also has positive impacts on the urban identity and the space concerned contributes to the "historical" identity of the city in the first degree with the highest average (4.24%). As also stated by the respondents, Çarşı Avenue is an avenue which has acquired a place in the memories of the city dwellers and of the incomers to the city in terms of "memory value and continuity of use" since the city was first established and this parameter makes the second highest (mean 4.11) contribution to the formation of the spatial memory. The local people and those coming from the surrounding settlements mostly use this avenue for shopping. The avenue is at the same time a triangulation and reference point used for meeting, assembling, and crossing. Çarşı Avenue is a space with "original" qualities since it reflects the architectural character of the period of its construction. Moreover, the rates, colors and forms of the masses are in harmony with each other along the line that makes up the silhouette of the avenue. This distinguishes the avenue from the other avenues and streets, thereby presenting an original structure (Table 1).

Table 1. Reliability of the scales (spatial memory/urban identity) for Çarşı Avenue and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.26**	.928	n	0	4	11	18	37
				%	0	5.7	15.7	25.7	52.9
	Originality and rarity value	**3.73**	.883	n	1	2	27	25	15
				%	1.4	2.9	38.6	35.7	21.4
	Aesthetic and artistic value	**3.50**	1.018	n	2	9	23	24	12
				%	2.9	12.9	32.9	34.3	17.1
	Memory value and continuity of use	**4.11**	1.136	n	3	4	11	16	36
				%	4.3	5.7	15.7	22.9	51.4
	Technical value	**2.57**	1.246	n	17	17	22	7	7
				%	24.3	24.3	31.4	10.0	10.0
	Cronbach's Alpha=0.807, Scale mean=3.63, Hotelling's T^2=162.929, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.81**	1.146	n	3	7	14	22	24
				%	4.3	10.0	20.0	31.4	34.3
	Its contribution to its state as a city of culture/art	**3.51**	1.189	n	4	12	14	24	16
				%	5.7	17.1	20.0	34.3	22.9
	Its contribution to its state as a city of trade	**3.36**	1.341	n	8	11	18	14	19
				%	11.4	15.7	25.7	20.0	27.1
	Its contribution to its state as a city of rent	**2.04**	1.173	n	30	18	16	1	5
				%	42.9	25.7	22.9	1.4	7.1
	Its contribution to its state as a historic city	**4.24**	1.042	n	2	4	7	19	38
				%	2.9	5.7	10.0	27.1	54.3
	Cronbach's Alpha=0.567, Scale mean=3.39, Hotelling's T^2=146.675, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

Besides, as also stated by the CHVIP (Çanakkale Houses Vitalization Project)-the Historic City Commission (2016), magnificent examples of the iron grills making up the façade surfaces of the avenue can be seen together with their circular constructions, which generally develop from a single center. Designed by the then architects or journeymen and masters, these grills are still preserving their originality and rarity. As also stated by the respondents, the avenue therefore gets the third highest contribution (mean 3.73) from "originality and rarity value". Çarşı Avenue is in some order with its attached and single-, two-, and three-storey buildings. The front façades of the buildings that sit on a linear street are directly related to the avenue. These buildings also resemble the arched shop windows. The door and window joinery of the buildings is generally wooden and was decorated with various wrought-iron railings. As also stated by the respondents, these details enhance the "aesthetic and artistic value" of the avenue and this parameter makes a significant contribution (mean 3.50) to the formation of the spatial memory in the fourth degree (Table 1).

Located in the upper section of the avenue, "Aynalı (Mirrored) Bazaar" has been the subject of songs, poems, and books since the period of its construction. It is one of the spaces that come to mind first when Çanakkale is considered and that the tourists coming to the city want to see the most. The studies for the conservation of the historical pattern in the place concerned also contribute to the tourism in the city. Furthermore, this avenue, one of the places with the maximum opportunities for shopping, enlivens both tourism and trade. In this context, as also stated by the respondents (mean 4.24-3.81), the avenue contributes to the state of the city as "a city of history and tourism" (Table 1).

When Çarşı Avenue is evaluated in terms of the urban images, it is seen that the highest rate belongs to the image of "path" (50.0%) because the intensive commercial function of the avenue, its uninterrupted continuation along a line, the fact that it is distinguished from the other streets by its pavement and ground flooring and the continuation of its façade pattern along the path strengthen the image of "path". The respondents secondly indicated the avenue as a "node" (45.7%). The presence of banks, various shops, and cafés at the avenue concerned contributed to its being a "node". Also identified as a district (31.4%), this space is at the same time expressed as a "district" which has the maximum opportunities for shopping and which is distinguished from the other avenues and streets by this aspect (Table 2).

Table 2. The distribution of selection of the urban image for Çarşı Avenue

Urban Image	Respondents	Percentage
Paths	35	50.0
Edges	18	25.7
Districts	22	31.4
Nodes	32	45.7
Landmarks	19	27.1

4.2. Fetvane Street

With its street pattern, which preserves its historical integrity today as well, Fetvane Street makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.56). Besides, Fetvane Street also has a high contribution (mean 4.26) to the parameter of "memory value and continuity of use" as it was formed in the years when the city was established and as it is still used intensively. This narrow street, whose traditional architecture has been preserved, is in integrity with its unique building style and material pattern. The abundance of registered buildings draws attention on the street, where the traditional street pattern has also been preserved. Even though these buildings have

changed their previous functions, they significantly contribute to the unique structure of the street. As also stated by the respondents, Fetvane Street, one of the rare streets in the city with its building characters and street pattern, contributes to the formation of the spatial memory in the second degree (mean 3.97) in the context of the parameter of "originality and rarity value". Fetvane Street is a street which is located between the Clock Tower and the Yalı Mosque as a blend of the Modern Age and the Ottoman Period and to which the buildings used as shops, hotels, waterside mansions, and houses add "artistic value". The buildings with a façade on Fetvane Street are single- two- or three-storey attached historic buildings. The two-storey masonry buildings on the street coexist with their different colors and patterns. The buildings were generally made from stone materials. The solids and voids created on the façades at similar rates provide façade integrity. The cobblestone pavement of Fetvane Street also adds "aesthetic value" to the street. Although those buildings which are used after they have been restored and altered on this historic street, where one can see the previous construction techniques and material pattern, constitute the majority, it is seen that they still preserve their aesthetic appearances. Thus, the parameter of "aesthetic and artistic value" makes a significant contribution (mean 3.84) to the formation of the spatial memory in the third degree (Table 3).

When Fetvane Street was first formed, it drew attention with its such buildings as depots and restaurants, the majority of which belonged to Greeks, as well as with its proximity to the harbor. In time, the shops were monopolized by Muslim families also upon the emigration of the Greek people. Housing many registered buildings, this street was formed in the processes following the early years of the establishment of the city and also contributed to the city's acquisition of a "historical" identity (mean 4.33). Considered to make a substantial (mean 4.21) contribution to the "cultural/artistic identity" of the city as well, this street mostly hosts various cultural/artistic activities. The bookshops where famous writers and poets come, Yalı Khan, where different groups (e.g. CHVIP-Historic City Commission, Local Agenda 21 of Çanakkale, and the City Council of Çanakkale) assemble and organize meetings and the cafés and bars where various musical activities take place are examples of this. This street, the use of which has been continuing to date, has acquired a place in the memory of the respondents with the bookshops lined up along both sides of the street besides its cafés and bars, which predominantly serve the entertainment sector. Located on the street as one of the important spaces, Yalı Khan has become an important symbol of the street for the city dwellers and for those who come from outside. Involving the cultural, artistic, and entertainment activities, Fetvane Street also makes a significant contribution to the city's acquisition of a "touristic" identity (mean 3.90) with all these characteristics of its (Table 3).

Table 3. Reliability of the scales (spatial memory/urban identity) for Fetvane Street and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.56**	.651	n			6	19	45
				%			8.6	27.1	64.3
	Originality and rarity value	**3.97**	.851	n		3	17	29	21
				%		4.3	24.3	41.4	30.0
	Aesthetic and artistic value	**3.84**	.879	n		4	21	27	18
				%		5.7	30.0	38.6	25.7
	Memory value and continuity of use	**4.26**	.811	n		2	10	26	32
				%		2.9	14.3	37.1	45.7
	Technical value	**2.46**	1.236	n	19	19	19	7	6
				%	27.1	27.1	27.1	10.0	8.6
	Cronbach's Alpha=0.707, Scale mean=3.817, Hotelling's T^2=191.7, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.90**	1.144	n	3	6	13	21	27
				%	4.3	8.6	18.6	30.0	38.6
	Its contribution to its state as a city of culture/art	**4.21**	1.048	n		8	8	15	39
				%		11.4	11.4	21.4	55.7
	Its contribution to its state as a city of trade	**3.24**	1.388	n	9	14	17	11	19
				%	12.9	20.0	24.3	15.7	27.1
	Its contribution to its state as a city of rent	**2.11**	1.123	n	26	21	15	5	3
				%	37.1	30.0	21.4	7.1	4.3
	Its contribution to its state as a historic city	**4.33**	.959	n	1	3	9	16	41
				%	1.4	4.3	12.9	22.9	58.6
	Cronbach's Alpha=0.529, Scale mean=3.56, Hotelling's T^2=191.576, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

When Fetvane Street is evaluated in terms of the urban images, it is seen that it corresponds to the image of "path" with the largest percentage (52.9%). Besides, it was called a "district" (34.3%) by the respondents due to the high density of traditional buildings (Table 4). Moreover, the important historic buildings on the street also enable the street to be perceived as a "node" (42.9%) (Table 4).

Table 4. The distribution of selection of the urban image for Fetvane Street

Urban Image	Respondents	Percentage
Paths	37	52.9
Edges	18	25.7
Districts	24	34.3
Nodes	30	42.9
Landmarks	22	31.4

4.3. Zafer Square

In the memories of the respondents, Zafer Square is perceived together with its historic buildings with original qualities, which are located on its periphery and which date back to very ancient times. Therefore, Zafer Square makes more contributions to the formation of the spatial memory in terms of the parameters of "historical and cultural value" (mean 4.56) and "originality and rarity value" (mean 4.23) (Table 5). Even though the space has failed to acquire a place in the memory of the city dwellers as "Zafer Square", it contributes to the city's acquisition of a "historical" identity at a high rate (mean 4.20) with all these characteristics of its and as "the Old Church Square" (Table 5).

Table 5. Reliability of the scales (spatial memory/urban identity) for Zafer Square and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.56**	.715	n		2	3	19	46
				%		2.9	4.3	27.1	65.7
	Originality and rarity value	**4.23**	.935	n	2	1	9	25	33
				%	2.9	1.4	12.9	35.9	47.1
	Aesthetic and artistic value	**3.87**	1.089	n	2	7	13	24	24
				%	2.9	10.0	18.6	34.3	34.3
	Memory value and continuity of use	**3.30**	1.267	n	8	11	16	22	13
				%	11.4	15.7	22.9	31.4	18.6
	Technical value	**2.31**	1.246	n	24	17	17	7	5
				%	34.3	24.3	24.3	10.0	7.1
	Cronbach's Alpha=0.727, Scale mean=3.654, Hotelling's T^2=229.256, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**2.99**	1.479	n	15	14	15	9	17
				%	21.4	20.0	21.4	12.9	24.3
	Its contribution to its state as a city of culture/art	**3.80**	1.258	n	6	6	9	24	25
				%	8.6	8.6	12.9	34.3	35.7
	Its contribution to its state as a city of trade	**1.84**	1.044	n	33	23	9	2	3
				%	47.1	32.9	12.9	2.9	4.3
	Its contribution to its state as a city of rent	**1.61**	.889	n	40	21	7		2
				%	57.1	30.0	10.0		2.9
	Its contribution to its state as a historic city	**4.20**	.987	n	1	3	13	17	36
				%	1.4	4.3	18.6	24.3	51.4
	Cronbach's Alpha=0.685, Scale mean=2.889, Hotelling's T^2=342.319, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

When Zafer Square is evaluated in terms of the urban images, it is seen that especially the Armenian Church, the Tıflı Mosque and the Korfmann Library cause the square to be identified as both a separate "district" and a "node" owing to the presence of each building. The presence of the mosque and the church at the same square also contributes to cultural diversity. Besides, the respondents thinking that the square is merely used as a crossing route think that regulations supporting the historic structure should be made for the square. The Armenian

Church has acquired a place in the memory as the most important building of the square; however, it has frequently undergone adaptive reuse, which weakens its place in the memories of both the city dwellers and the city (Table 6).

Table 6. The distribution of selection of the urban image for Zafer Square

Urban Image	Respondents	Percentage
Paths	14	20.0
Edges	11	15.7
Districts	35	50.0
Nodes	42	60.0
Landmarks	28	40.0

4.4. The Public Garden

With the quality of being one of the oldest open-green areas in the city, the Public Garden makes more contributions to the formation of the spatial memory in the context of the parameter of "memory value and continuity of use" (mean 4.09). Formed after the Calvert Family had organized the backyard of their own house and stated to have been established on a much wider area, the Public Garden is also of historical importance for the city. Thus, the parameter of "historical and cultural value" also has a high rate (mean 3.64). Generally used as a space for crossing by the respondents, the garden remains among the Governor's Office Building, the Old State Hospital, the Municipality Office Building, and partially the City Stadium. This urban space, which has been used since its formation, is also used alternately as an exhibition and festival area from time to time. The "originality and rarity value" (mean 3.63) of this garden, which has acquired a place as a green area in the memories of the respondents, was also found high. The respondents also stated that they thought that this space should be used more productively. It is also particularly stressed that this garden, which is also used as a meeting point, does not serve the purpose of recreation – the most fundamental feature that an open-green area should possess – much (Table 7).

Most of the respondents stating that the Public Garden hardly contributes to the urban identity express that the space makes more contributions to the state of the city as "a city of culture/art" in the context of some cultural-artistic activities carried out in the garden (Table 7).

Table 7. Reliability of the scales (spatial memory/urban identity) for the Public Garden and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**3.64**	1.240	n	6	5	19	18	22
				%	8.6	7.1	27.1	25.1	31.4
	Originality and rarity value	**3.63**	1.182	n	4	7	21	17	21
				%	5.7	10.0	30.0	24.3	30.0
	Aesthetic and artistic value	**3.30**	1.172	n	5	12	23	17	13
				%	7.1	17.1	32.9	24.3	18.6
	Memory value and continuity of use	**4.09**	1.004	n	2	3	11	25	29
				%	2.9	4.3	15.7	35.7	41.4
	Technical value	**2.20**	1.137	n	22	25	14	5	4
				%	31.4	35.7	20.0	7.1	5.7
	Cronbach's Alpha=0.728, Scale mean=3.371, Hotelling's T^2= 157.638, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.04**	1.469	n	14	14	14	11	17
				%	20.0	20.0	20.0	15.7	24.3
	Its contribution to its state as a city of culture/art	**3.46**	1.369	n	7	13	13	15	22
				%	10.0	18.6	18.6	21.4	31.4
	Its contribution to its state as a city of trade	**2.00**	1.204	n	32	18	14	6	
				%	45.7	25.7	20.0	8.6	
	Its contribution to its state as a city of rent	**1.69**	1.057	n	43	13	10	1	3
				%	61.4	18.6	14.3	1.4	4.3
	Its contribution to its state as a historic city	**3.20**	1.314	n	8	14	20	12	16
				%	11.4	20.0	28.6	17.1	22.9
	Cronbach's Alpha=0.681, Scale mean=2.68, Hotelling's T^2=112.608, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

When the Public Garden was evaluated in terms of the urban images, it was identified as a "district" at a high rate (71.4%) by the respondents because the boundaries of the garden are specific and sharp. The green pattern of the garden forms a border with the concrete pattern of the city. The identification of this area mostly as a meeting point by the respondents and the different form of the area from that of the city in general also strengthen its perception as a "node" (50.0%) at a high rate (Table 8).

Table 8. The distribution of selection of the urban image for the Public Garden

Urban Image	Respondents	Percentage
Paths	21	30.0
Edges	11	15.7
Districts	50	71.4
Nodes	35	50.0
Landmarks	20	28.6

4.5. Yalı Khan

Maintaining its use since 1889, Yalı Khan makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.60). The parameter of "memory value and continuity of use" (mean 4.34) has the second highest average. Yalı Khan is a space which has been used since the first day when it was constructed. The space hosts the memories of those people who were in the khan for accommodation purposes in the past as well as mostly the city dwellers, university students, and many visitors who come from outside today. One gate of Yalı Khan leads to Fetvane Street and one gate of it to Yalı Avenue. While this facilitates the access of the city dwellers to the space, the khan is also called 'yolgeçen hanı' (a place where many people are always coming and going) owing to this feature of its. Besides, it is also identified as an area for crossing and a shopping arcade (Table 9).

Table 9. Reliability of the scales (spatial memory/urban identity) for Yalı Khan and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.60**	.730	n	1		4	16	49
				%	1.4		5.7	22.9	70.0
	Originality and rarity value	**4.31**	.877	n		3	10	19	38
				%		4.3	14.3	27.1	54.3
	Aesthetic and artistic value	**4.13**	.900	n	2	1	9	32	26
				%	2.9	1.4	12.9	45.7	37.1
	Memory value and continuity of use	**4.34**	1.006	n	2	3	6	17	42
				%	2.9	4.3	8.6	24.3	60.0
	Technical value	**2.40**	1.172	n	19	20	19	8	4
				%	27.1	28.6	27.1	11.4	5.7
	Cronbach's Alpha=0.751, Scale mean=3.397, Hotelling's T^2= 252.067, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.97**	1.274	n	4	8	9	14	35
				%	5.7	11.4	12.9	20.0	50.0
	Its contribution to its state as a city of culture/art	**4.24**	1.096	n	3	4	5	19	39
				%	4.3	5.7	7.1	27.1	55.7
	Its contribution to its state as a city of trade	**3.20**	1.292	n	9	11	21	15	14
				%	12.9	15.7	30.0	21.4	20.0
	Its contribution to its state as a city of rent	**1.94**	1.102	n	33	18	10	8	1
				%	47.1	25.7	14.3	11.4	1.4
	Its contribution to its state as a historic city	**4.19**	1.183	n	3	5	10	10	42
				%	4.3	7.1	14.3	14.3	60.0
	Cronbach's Alpha=0.582, Scale mean=3.509, Hotelling's T^2=188.307, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

By possessing an inner courtyard and with its potential of being private, the space concerned has the qualities of both being a strong urban fragment and being distinguished from the dynamic part of the city. Thus, some respondents stated that they did not use the space

much, whereas some others stated that they socialized in this area, which was protected from extrinsic effects. Yalı Khan and its courtyard go on protecting themselves as being isolated from the extrinsic factors behind stone walls today as well. The khan preserves its originality with its structure concerned and its rarity as it is the only khan in the city. Therefore, it is observed that the space concerned also makes great contributions to the formation of the spatial memory in the context of the parameter of "originality and rarity value" (mean 4.31) (Table 9).

This historic khan, one of the most important haunts on Fetvane Street, is essential as a space for assembling and socialization where handicraft workshops and cafés are available today, as also stated by the respondents. When identifying the khan, the respondents predominantly drew attention to the wisteria in its garden and underlined that it was a space for relaxing and sitting for the city dwellers. Additionally, it is a space where different cultural and artistic activities are performed and where different social groups can coexist. Thus, it contributes to the "cultural/artistic identity" of the city with the highest average (mean 4.24) (Table 9).

When Yalı Khan is evaluated in terms of the urban images, it is identified as a "node" at the highest rate (62.9%) (Table 10). One of the reasons for this is that it is located on Fetvane Street – one of the busiest streets of the city. The other one is its natural stone walls, ground flooring, and different architectural form.

Table 10. The distribution of selection of the urban image for Yalı Khan

Urban Image	Respondents	Percentage
Paths	13	18.6
Edges	17	24.3
Districts	18	25.7
Nodes	44	62.9
Landmarks	31	44.3

4.6. The Yalı Mosque

The Yalı Mosque makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.59) as it is one of the oldest worshipping buildings of the city and with its striking historical pattern. Even though the use of the Yalı Mosque was restricted for a short time due to the fires it suffered from in different periods, the continuity of its use has been taking place since the date of its construction. At the same time, it is one of the important religious spaces which have witnessed the important events in the city. Thus, the parameter of "memory value and continuity of use" has the second highest average (mean 4.26) (Table 11).

In their views, the respondents particularly emphasized the original architectural form of its minaret. The traditional stone material used in the construction of the mosque substantially distinguishes the building from the other mosques. For these reasons, the average of "originality and rarity value" of the Yalı Mosque (mean 4.03) was also found high in the context of the spatial memory parameters (Table 11).

The Yalı Mosque is within the early establishment core of the city; furthermore, its garden houses both the muvakkithane building and tombs. In this respect, the building concerned contributes to the "historic city" identity of the city with a high average (mean 4.39) (Table 11).

Table 11. Reliability of the scales (spatial memory/urban identity) for Yalı Mosque and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.59**	.670	n			7	15	48
				%			10.0	21.4	68.6
	Originality and rarity value	**4.03**	.916	n		4	16	24	26
				%		5.7	22.9	34.3	37.1
	Aesthetic and artistic value	**3.99**	.909	n		2	23	19	26
				%		2.9	32.9	27.1	37.1
	Memory value and continuity of use	**4.26**	.846	n		2	12	22	34
				%		2.9	17.1	31.4	48.6
	Technical value	**2.39**	1.231	n	21	19	17	8	5
				%	30.0	27.1	24.3	11.4	7.1
	Cronbach's Alpha=0.823, Scale mean=3.849, Hotelling's T^2= 225.417, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.44**	1.293	n	8	8	16	21	17
				%	11.4	11.4	22.9	30.0	24.3
	Its contribution to its state as a city of culture/art	**3.63**	1.374	n	8	8	11	18	25
				%	11.4	11.4	15.7	25.7	35.7
	Its contribution to its state as a city of trade	**2.16**	1.187	n	25	23	13	4	5
				%	35.7	23.9	18.6	5.7	7.1
	Its contribution to its state as a city of rent	**1.66**	.991	n	42	16	8	2	2
				%	60.0	22.9	11.4	2.9	2.9
	Its contribution to its state as a historic city	**4.39**	.952	n	1	1	14	8	46
				%	1.4	1.4	20.0	11.4	65.7
	Cronbach's Alpha=0.562, Scale mean=3.054, Hotelling's T^2=263.349, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

When the Yalı Mosque is evaluated in terms of the urban images, it is identified as a "node" (67.1%) as it is at the intersection point of Çarşı Avenue and Fetvane Street and as it is located at one of the most important avenues of the city (Table 12). Besides, the respondents also stated that the mosque had a striking color and that they therefore preferred this historic building as a meeting point.

Table 12. The distribution of selection of the urban image for Yalı Mosque

Urban Image	Respondents	Percentage
Paths	16	22.9
Edges	16	22.9
Districts	21	30.0
Nodes	47	67.1
Landmarks	31	44.3

4.7. The Stone School (A Guest House for Teachers)

Even though the Stone School (a Guest House for Teachers) has undergone change in function, it goes on existing as "the old school building" in the memory of the city dwellers. Thus, the Stone School makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.20). Since the use of the building, which had earlier been used as a school building, is continuing today as well due to a change in function, it also has a high average (mean 3.77) concerning the parameter of "memory value and continuity of use". Regarding the features of the building, its long façade, symmetrical form, inter-floor-window molding and stone material were indicated as featured by the respondents. Thus, it gets a high value (mean 3.51) from the parameter of "aesthetic and artistic value" (Table 13).

The Stone School is an important building which was constructed in the early years of the Republic. The architectural form, material and plan typology of the building show that it is an old building. Therefore, it contributes to the historical identity of the city with a high average (mean 3.73). Besides, the building concerned and its garden serve as an exhibition area and for accommodation purposes today. This contributes to both the "touristic" (mean 3.23) and "cultural/artistic" (mean 3.23) identities of the city (Table 13).

Table 13. Reliability of the scales (spatial memory/urban identity) for the Stone School and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.20**	.844	n		2	13	24	31
				%		2.9	18.6	34.3	44.3
	Originality and rarity value	**3.47**	1.018	n	1	11	25	20	13
				%	1.4	15.7	35.7	28.6	18.6
	Aesthetic and artistic value	**3.51**	.897	n		8	29	22	11
				%		11.4	41.4	31.4	15.7
	Memory value and continuity of use	**3.77**	1.024	n	2	6	16	28	18
				%	2.9	8.6	22.9	40	25.7
	Technical value	**2.34**	1.226	n	22	19	17	7	5
				%	31.4	27.1	24.3	10.0	7.1
	Cronbach's Alpha=0.751, Scale mean=3.46, Hotelling's T^2= 147.931, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.23**	1.299	n	8	14	16	18	14
				%	11.4	20.0	22.9	25.7	20.0
	Its contribution to its state as a city of culture/art	**3.23**	1.353	n	10	13	12	21	14
				%	14.3	18.6	17.1	30.0	20.0
	Its contribution to its state as a city of trade	**2.30**	1.147	n	22	17	23	4	4
				%	31.4	24.3	32.9	5.7	5.7
	Its contribution to its state as a city of rent	**1.70**	1.012	n	41	15	10	2	2
				%	58.6	21.4	14.3	2.9	2.9
	Its contribution to its state as a historic city	**3.73**	1.262	n	5	7	16	16	26
				%	7.1	10.0	22.9	22.9	37.1
	Cronbach's Alpha=0.673, Scale mean=2.837, Hotelling's T^2=145.416, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

When the Stone School was evaluated in terms of the urban images, it was identified as a "landmark" at a high rate (51.4%), for the imposing appearance of the building is quite great for the street where it is located and the trees in its garden are each perceived as a landmark. Moreover, the space is also identified as a "node" (42.9%) (Table 14) because its courtyard, which serves as a tea garden today owing to adaptive reuse, is at the same time an area for meeting/assembling and relaxing.

Table 14. The distribution of selection of the urban image for the Stone School

Urban Image	Respondents	Percentage
Paths	12	17.1
Edges	19	27.1
Districts	21	30.0
Nodes	30	42.9
Landmarks	36	51.4

4.8. The House of Emilie Vitalis (Continuing Education Center of ÇOMU)

The House of Emilie Vitalis, an old and important building of civil architecture in the city, makes more contributions to the formation of the spatial memory in the context of the parameter of "historical and cultural value" (mean 4.41). The building has hosted many cultures and memories also because it has frequently changed function (the Old TEKEL Building, the Old Rectorate Building, the Old Levantine Building, Attaché's Office, the Cultural House of Emilie Vitalis, the Continuing Education Center of ÇOMU, and Vitalis Café). Therefore, it also gets a high value (mean 3.63) from the parameter of "memory value and continuity of use". The two-way entrance staircase, inter-floor plaster and window molding and plaster-decorated balcony shores are striking on the external façade of the building, which is used as the Continuing Education Center of ÇOMU. It is expressed that the motifs of the wrought-iron railings of the ground floor doors and windows of the building are extremely original. Containing original qualities concerning the architectural design criteria, this building also has a high contribution in terms of the parameters of "originality and rarity value" (mean 4.13) and "aesthetic and artistic value" (mean 4.03) (Table 15).

The survival of the House of Emilie Vitalis through conservation to date contributes to the "historical" identity of the city (mean 4.09); its hosting of many cultural/artistic activities contributes to its "cultural/artistic" identity (mean 3.80); and the strategic point where it is located and the continuity of its use contribute to its "touristic" identity (mean 3.53) (Table 15).

Table 15. Reliability of the scales (spatial memory/urban identity) for the House of Emilie Vitalis and their mean values

	Spatial Memory Parameters	Mean	Std. Deviation		1*	2*	3*	4*	5*
Spatial Memory	Historical and cultural value	**4.41**	.789	n	1		7	23	39
				%	1.4		10.0	32.9	55.7
	Originality and rarity value	**4.13**	.850	n		3	12	28	27
				%		4.3	17.1	40.0	38.6
	Aesthetic and artistic value	**4.03**	.900	n		3	18	23	26
				%		4.3	25.7	32.9	37.1
	Memory value and continuity of use	**3.63**	1.194	n	4	10	13	24	19
				%	5.7	14.3	18.6	34.3	27.1
	Technical value	**2.46**	1.282	n	19	21	17	5	8
				%	27.1	30.0	24.3	7.1	11.4
	Cronbach's Alpha=0.753, Scale mean=3.731, Hotelling's T^2= 131.70, P=0.0001								
Urban Identity	Its contribution to its state as a city of tourism	**3.53**	1.380	n	5	16	12	11	26
				%	7.1	22.9	17.1	15.7	37.1
	Its contribution to its state as a city of culture/art	**3.80**	1.281	n	5	9	8	21	27
				%	7.1	12.9	11.4	30.0	38.6
	Its contribution to its state as a city of trade	**2.70**	1.334	n	17	15	19	10	9
				%	24.3	21.4	27.1	14.3	12.9
	Its contribution to its state as a city of rent	**2.04**	1.301	n	33	18	9	3	7
				%	47.1	25.7	12.9	4.3	10.0
	Its contribution to its state as a historic city	**4.09**	1.151	n	2	7	10	15	36
				%	2.9	10.0	14.3	21.4	51.4
	Cronbach's Alpha=0.582, Scale mean=3.23, Hotelling's T^2=97.422, P=0.0001								

*1-Very bad, 2-Bad, 3-Slightly good/moderate, 4-Good, 5-Very good

The House of Emilie Vitalis is at a valuable location thanks to its proximity to Kordon (Promenade), Quay Square, Clock Tower Square, and Çarşı Avenue. Thus, when the building is evaluated in terms of the urban images, it is identified as a "node" (51.4%) and a "landmark" (51.4%) at equal rates by the respondents (Table 16). Besides, its proximity to Quay Square and the easy perception of its plan diagram in different geometry strengthen its perception as a "node" and a "landmark".

Table 16. The distribution of selection of the urban image for the House of Emilie Vitalis

Urban Image	Respondents	Percentage
Paths	8	11.4
Edges	23	32.9
Districts	22	31.4
Nodes	36	51.4
Landmarks	36	51.4

5. DISCUSSION AND CONCLUSION

Permanent memory in space is defined as *"the recording of space-related sensations, perceptions, learning, experiences, and memories in the memory during life with not only their own components but also the phenomena taking place in it, the ambient characteristics, and life, in other words, with 'its context' and their association"* (Özak and Gökmen, 2009). Therefore, with all components of a city, the identity components in particular should be clear and defined.

In fact, the urban identity can be summarized as the whole of those features which distinguish a city from the others (Suher *et al.*, 2004; Ayyıldız and Ertürk, 2017) and forms upon the gathering of many different components. The geography on which every city is established and the human community that lived/lives on it are different. Thus, as also stated by Birol (2007), the identity of a city is shaped by its cultural and natural assets. For the formation of the urban identity, the continuity of these assets should be provided and those material and immaterial assets which convey the messages coming from the past of the city to the future should be conserved. Especially the buildings and spaces which have witnessed different periods of a city join the life of city dwellers, thereby being in a privileged position among the assets concerned. Therefore, the conservation of those buildings in a city which contribute to the original identity of that city and which carry noteworthy architectural and vital features of the period they belong to plays a significant role in providing cultural continuity in that city, in the formation of the urban identity, and in carrying it to the future.

Buildings and spaces, one of the components which make up the urban identity, cast light on the human components – another component – thanks to their casting light on the social, political, cultural, and economic components of the period when they exist. The buildings and spaces of cities further become meaningful and acquire a place in the social memory with the memories of the society that has lived in that city to date. Thus, these buildings and spaces should be conserved and handed down to future generations together with their life experiences and a sustainable identity should be provided (Ayyıldız and Ertürk, 2017).

Today the identities of all cities undergo change owing to the changing requirements of the age and the expectations of the society. The most important phenomenon which preserves the cultural accumulation is the preservation of the traces of those buildings and spaces which make up the urban area in the urban memory. Unfortunately, the historical process and the cultural accumulation are not taken into consideration in the urban planning studies carried out to adapt to the changing conditions. In such studies, the identity of a city should first of all be defined accurately and planning studies which respect its past should be carried out. In this context, one of the most important studies required to be performed is to ensure that the buildings and spaces of historical value accurately acquire a place in the memory of the city dwellers. Therefore, as also stated by Taşçıoğlu and Altunkasa (2018), the urban identity elements resulting from many cultural experiences in the process that has elapsed since its establishment should be acknowledged as leading actors in the shaping of the city.

In the present study, the preservation of the places of the historic buildings and spaces in the spatial memory together with their images and its contributions to the urban identity were evaluated via the eight historic buildings and spaces selected. In this context, when the buildings and spaces which have acquired a place in the urban memory are defined in terms of spatial memory parameters and urban images, this also strengthens their contributions to the urban identity. The buildings and spaces selected as the material in the study are still being used, which strengthens the spatial memory parameters. The spatial memory parameters which affect the places of the buildings and spaces concerned in the urban identity the most are the parameters of "historical and cultural value", "memory value and continuity of use",

"originality and rarity value", and "aesthetic and artistic value", respectively. The historic buildings and spaces identified with all these parameters contribute to the city's states as a city of "history", "culture-art", and "tourism" the most. When the buildings and spaces concerned are evaluated in terms of the urban images, they are mostly identified as "districts", "nodes", "paths", and "landmarks", which strengthens their places in the urban identity.

On the other hand, some evaluations on the buildings and spaces selected as examples were made in the section of the survey which was assessed on the basis of the quantitative observation. Selected as an avenue example, Çarşı Avenue was evaluated as a commercial and cultural core, whereas it was stated that the resulting avenue pattern was defined and guiding. This avenue at the same time has a significant place in the memories of the city and of the city dwellers with its historic buildings and spaces. These spaces are expressed as Aynalı Bazaar, the Yalı Mosque, and the City Museum. Selected as a street example, Fetvane Street was particularly addressed with its building characters as well as with the features of its use. It was stressed that the street concerned relatively reflected the original and historic urban pattern of Çanakkale. Selected as a square example, Zafer Square is identified as a whole together with the buildings of high historical value on its periphery. This demonstrates that the historic buildings maintaining their existence singly also help with the definition and perception of a public area when they are altogether. Selected as a garden example, the Public Garden is identified with the presence of wide walking tracks and a dense vegetation pattern and shows that the ways of design also influence the perception of the space. Selected as a courtyard example, Yalı Khan is mostly identified with its natural stone ground flooring-wall covering and the plant "*Wisteria sinensis* (wisteria)", which turns it into an attraction particularly in spring months. This also reveals the relationship of the spatial memory perception at the same time with the sensory perception. Selected as a religious space example, the Yalı Mosque was only identified as a religious building, while it was also indicated as an intersection point. The identification of the mosque with its original function emphasizes that the continuity of the function of a historic building or space strengthens its place in the spatial memory. It is expressed that the characteristic point of the Stone School, selected as a building example, is its courtyard and that this space is at the same time an area for assembling, meeting, and relaxing. It is also intensively observed that the place of this educational building, which is of extreme importance for the urban memory, in the memories of the city and of the city dwellers due to its changed function has not become clear. Finally, selected as a building section/fragment example, the House of Emilie Vitalis has had different functions to date, as the Stone School has. Besides, it is stressed that its exterior façade features are distinctive. In this context, it is understood that the architectural characteristics of a historic building or space are also of profound importance in the spatial memory perception.

Cities are not merely man-made built environments. Since cities have different spirits, they contain reflections concerning the political power, ideologies, and cultural assets of the period. In this context, avenue, street and square names have a significant place in understanding a city (Turan and Yalçıner Ercoşkun, 2017). Of the buildings and spaces selected in this context, Zafer Square, the Stone School and the House of Emilie Vitalis acquired a place in the memory of the city dwellers with different names from time to time, which also weakens the perception of the examples concerned in the spatial memory and their contribution to the urban identity.

Whilst historic buildings and spaces are integrated with the current modern urban pattern, the changes in function which do not agree with their original structure weaken the spatial perception. Functional change/adaptive reuse is an extremely appropriate practice to conserve and preserve historic patterns in the modern urbanization understanding. Nevertheless, one should avoid those functional changes which will alter or weaken the spatial

perception as much as possible. Thus, the House of Emilie Vitalis and the Stone School do not have a very efficient place in the spatial memory of the city and in the formation of its identity owing to the functional changes they have undergone. At this point, for the accuracy and appropriateness of conservation studies, it is inevitable for property owners, city planners, architects, landscape architects, technical staff members and all other individuals working in institutions to carry out an interdisciplinary study.

It is also extremely important that all individuals living in the society be accurately trained and informed about historic assets so that the social consciousness of this matter will also be enhanced in the same line. Raising social consciousness of this matter also contributes to the formation of the urban memory. The preservation of a building or a space is possible through preserving its original assets and its acquisition of a place in the urban memory. Every building or space which has acquired a correct place in the memory also plays an efficient role in the shaping of the identity of a city.

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Research Article

RESEARCH ABOUT VISITOR PERCEPTIONS OF ÇANAKKALE MARTYRS' MEMORIAL

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ABSTRACT

The Martyrs' Memorial and historical area, located within the boundaries of Çanakkale province and scene of historically important events, is important for all time with significant domestic and foreign visitor potential from Turkey and many other countries. Due to visitor numbers reaching significant amounts, especially in the summer months, the necessity to renovate, develop and ensure sustainability of landscaping infrastructure and furnishings was revealed in line with visitor perceptions. The study applied face-to-face surveys to 100 individuals over the age of 18 years visiting the area. Data obtained from the survey were evaluated with linear regression analysis in the SPSS 15.0 statistical program. The results of the analysis found an R2 value of 0.516, showing that the independent variables of "open and enclosed viewing terraces, car park, furnishings (like pergolas, seating groups, waste bins, digital information panels) and planting" explained 52% of the variation in the dependent variable of "satisfaction rate". With the ANOVA test, the "p" value of "0.000" was found, indicating that the regression model was significant for the whole study. The VIF value was 3 and above showing no correlations between independent variables and emphasizing that four variables should remain in the model (open and enclosed viewing terraces, furnishings, car park). In conclusion, in line with visitor perceptions, the necessity to include landscaping in the area especially the role of planting as shade and windbreaks, car park, furnishings like pergola, waste bins, digital information panels and seating groups, and open and enclosed viewing terraces was determined. Applications of these appropriate to the day's conditions and visitor requirements will contribute to visitor satisfaction.

Keywords: *Çanakkale, planning, Martyrs' Memorial, visitor perceptions*

1. INTRODUCTION

Historical areas have an important place in the identity of a town (Göçer et al., 2018). As distinctive places in terms of natural, historical and cultural aspects, these areas may form a distinction on an individual basis, just as much as for the town (Kelkit, 2003). The landscape planning and design, apart from architectural structures, are very important, especially for areas with excessive visitor potential such as the Çanakkale Martyrs' Memorial (Willis et al., 2001; Çukurçayır, 2002; Jim, 2004; Alkan and Uzun, 2016). This importance is directly related to the duration spent in the area. As a result, the duration spent in the area may reveal differences in satisfaction rates, just as mentally and psychologically (Sherman et al., 2005; Cheng et al., 2010; Sağlık et al., 2016). This study aiming to determine landscape infrastructure and furnishings as factors in the duration spent in the historical area and satisfaction was completed at Çanakkale Martyrs' Memorial. For this, the perceptions of 100 randomly-chosen individuals aged over 18 years visiting the historical area were researched. Finally, an attempt was made to reveal the visitor perceptions and linked variable and developing satisfaction rates (Külekçi and Irmak, 2019).

2. METHODOLOGY

The study was completed at Çanakkale Martyrs' Memorial located at the point where 40° 3' 0.00" latitude and 26° 13' 8.00" longitude intersect, in an area of nearly 26 decares. Field measurements were calculated using Google Earth (Figure 1).

Figure 1. Geographical location of Çanakkale Martyrs' Memorial (adapted from Google Earth (2019)).

With intense visitor potential in the summer months, an attempt was made to evaluate the landscape infrastructure and furnishings of the "Martyrs' Memorial" based on visitor perceptions. For this, surveys were applied to 100 randomly-chosen individuals aged over 18 years visiting the area with face-to-face interviews. Firstly, the demographic characteristics of survey participants were determined. Then visitor perceptions about furnishings like pergola, boundary elements, waste bins, and digital information panels, planting, open and enclosed viewing terraces, and car park landscape elements were researched. The effect of these elements on visitor satisfaction and statistical correlations between them were evaluated with linear regression analysis using the SPSS 15.0 statistical program.

3. RESULTS AND DISCUSSION

The landscape components that may contribute to visitor satisfaction linked to visitor perceptions are explained below.

- Within the scope of planting, landscape furnishings like green belts and green paths were included and are important for the identity and image of the area. The application of this element is based on broad-leaved or coniferous plant groups with dense and large crowns forming a transition corridor (Hıyaban).
- Tree species and plants included in planting should have functions such acting as windbreaks and creating shade. Tree species being evergreen has additional

importance in terms of preventing leaf drop in the area in fall and winter (preventing labor and costs).

- Additionally, another result obtained in the study is that especially in areas with visitor density, maintenance operations such as grass facilities, transfer of grass in local areas, and ensuring continuity should be completed without delay.
- The inclusion of digital panels to inform visitors about topics such as directions to the area, visitor numbers and capacity, and vehicle information was among furnishings in line with visitor perceptions.
- The study by Erten and Gündüz (2011) recommended instantaneously updateable digital panels with the aim of informing visitors about the area and use as part of the protective use system for Uludağ National Park based on regeneration in landscape planning and design.

The linear regression analysis results and interpretations based on survey data obtained in the study are given below.

On Table 1, it appears the independent variable increasing "satisfaction rate" most is "furnishings" with value of 0.326, followed by "planting" and "car park". The coefficients for the "enclosed and open viewing terraces" were negative, meaning they had a negative effect on "satisfaction rate", which was not a desired outcome in this analysis. However, the degree of significance was "0.000" requiring they remain in the model; in other words, showing the model is significant.

Table 1. Correlations

		Satisfaction Rate	Planting	Furnishings	Car park	Enclosed viewing terrace	Open viewing terrace
Pearson Correlation	Satisfaction Rate	1.000	.152	.326	.112	-.434	-.428
	Planting	.152	1.000	-.545	-367	.087	-.172
	Furnishings	.326	-.545	1.000	.217	-.333	-.223
	Car park	.112	-.367	-.217	1.000	-.343	-.010
	Enclosed viewing terrace	.434	.087	-.333	-343	1.000	-.285
	Open viewing terrace	.428	-.172	-.223	-010	-.285	1.000
Sig. (1-tailed)	Satisfaction Rate	.	.066	.000	.135	.000	.000
	Planting	.066	.	.000	.000	.193	.043
	Furnishings	.000	.000	.	.015	.000	.013
	Car park	.135	.000	.015	.	.000	.461
	Enclosed viewing terrace	.000	.193	.000	.000	.	.002
	Open viewing terrace	.000	.043	.013	.461	.002	.

For multiple regression in the study, the adjusted R^2 value in Table 2 should be noted. This value was calculated as 0.516. In other words, this means the independent variables (open and enclosed viewing terrace, car park, furnishings) explained 52% of the variance in the dependent variable (satisfaction rate). This value is above the mean and is satisfactory. The Durbin Watson statistic was calculated as 2.262. This value is close to 2, an indicator that there is no autocorrelation.

Table 2. Model Summary(b)

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics					Durbin-Watson
	R Square Change	F Change	df1	df2	Sig. F Change	Square Change	F Change	df1	df2	Sig. F Change
1	.732(a)	.536	**.516**	8.38461	.536	27.432	4	95	.000	**2.269**

a Predictors: (Constant), Open viewing terrace, Car park, Furnishings, Enclosed viewing terrace; b Dependent Variable: Satisfaction rate

According to Table 3, the "p" value for the ANOVA test was significant with a value of "0.00". Stated differently, the analysis results were significant at the 1% level for the logarithmic function type. In other words, the regression model is significant as a whole. The F value was 27.43%, which is important to confirm the significance of the model. Özdemir and Vural (2015) found statistical correlations significant at the 5% level in a study targeting the effect of landscaping and furnishings on individual and social satisfaction evaluated in terms of rural-urban audiences.

Table 3. ANOVA(b)

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	7714.093	4	1928.523	27.432	.000(a)
	Residual	6678.657	95	70.302		
	Total	14392.750	99			

a Predictors: (Constant), Open viewing terrace, Car park, Furnishings, Enclosed viewing terrace; b Dependent Variable: Satisfaction rate

The coefficients and significance for the regression model are given in Table 4. The coefficient for the constant term was calculated as 133.165 and the p value was 0.000. In this situation the constant term is significant. The regression model coefficients for the independent variables were calculated to be negative.

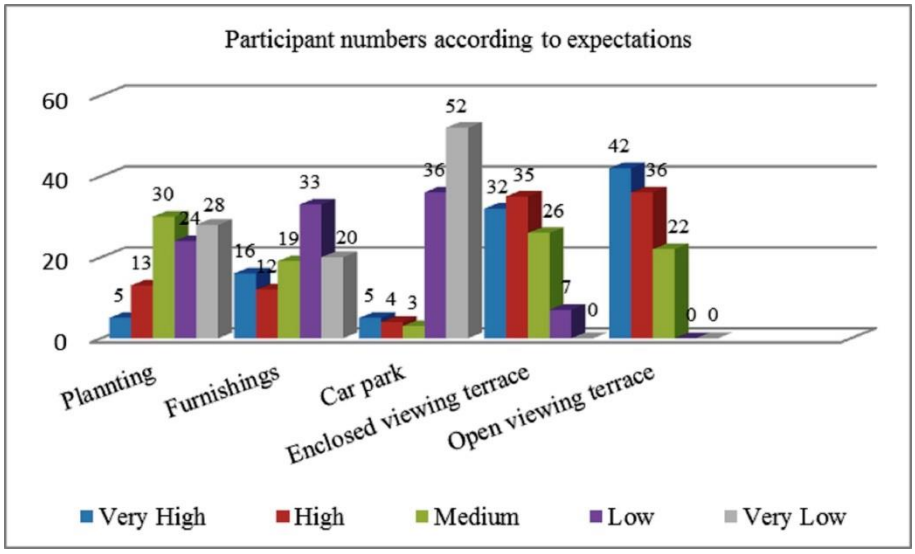
Table 4. Model Coefficients(a)

Model	Unstandardized Coefficients		Standardized Coefficients	t	SSig.	95% Confidence Interval for B		Correlations			Collinearity Statistics	
	B	Std. Error	Beta	Lower Bound	Upper Bound	Zero-order	Partial	Part	Tolerance	VIF	B	Std. Error
(Constant)	**133.165**	8.908		14.949	**.000**	115.481	150.849					
Furnishings	-.747	.790	-.084	-.945	.347	-2.316	.822	.326	-.096	**-.066**	.623	1.605
Car park	**-1.748**	.962	-.152	-1.817	**.072**	-3.657	.162	.112	-.183	**-.127**	.696	1.437
Enclosed viewing terrace	**-9.068**	1.221	-.698	-7.426	**.000**	-11.492	-6.644	-.434	-.606	**-.519**	.552	1.811
Open viewing terrace	**-10.029**	1.260	-.648	-7.959	**.000**	-12.530	-7.527	-.428	-.632	**-.556**	.738	1.355

However, the T test results calculated the significance level as smaller than 0.01 and 0.1, apart from "furnishings". As a result, the significance degrees were found to be 1% and 10%. However, as can be seen there is an inverse correlation between the independent variables and satisfaction rates because the regression model coefficients are negative. Collinearity statistics (VIF values) were not 3 or above, showing there is no correlation between independent variables and may be interpreted to show that it is appropriate for four variables to remain in the model.

The demographic results obtained from the survey are given below. The expectations determined based on perceptions of individuals participating in the survey for the independent variables remaining in the model according to the linear regression model in the statistical analysis results are given in Figure 2.

Figure 2. Expectations of survey participants about landscape planning and design



Accordingly, it was emphasized that planting in the visitor area should mainly include species that act as windbreaks and create shade. Nearly 80% of participants stated they had expectations of low to moderate levels of planting in the area. Contrary to these expectations, the low level may be explained by the inclusion of the open viewing terrace, pergola and climbing decorative plants in the questions. It was determined that nearly 1/3 of participants believed in the necessity to include furnishings like pergola, waste bins, seating groups and digital information panels in the area. Nearly 90% of participants stated the "car park" area should be at "very low" and "low" levels in the area. More that 2/3 of participants had expectations of "very high" and "high" levels for the "open and enclosed viewing terrace" variables. As seen on Figure 3, 44% of visitors to the Martyrs' Memorial were religiously motivated (spiritual). The remaining 56 individuals were understood to come to the area to learn, for trip-observation and recreation, from most to least.

Figure 3. Distribution of reasons for visiting the Martyr's Memorial

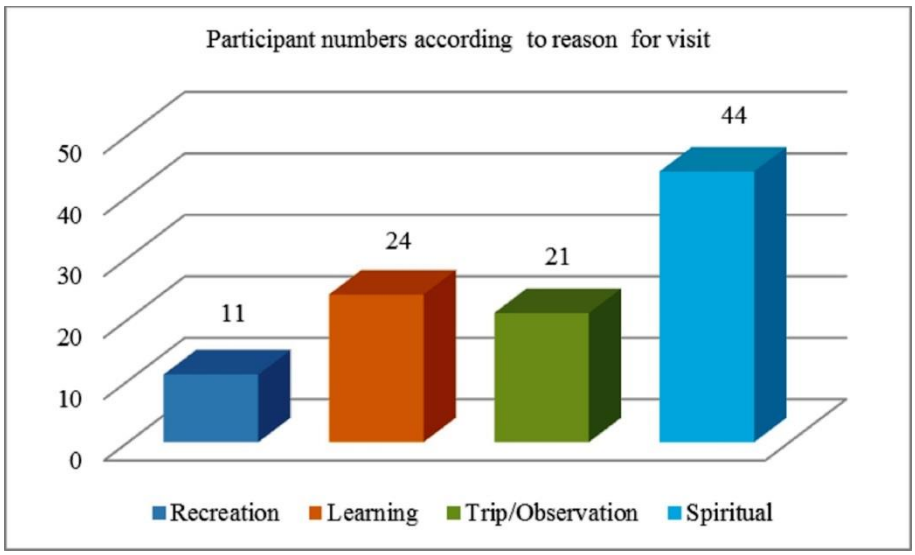
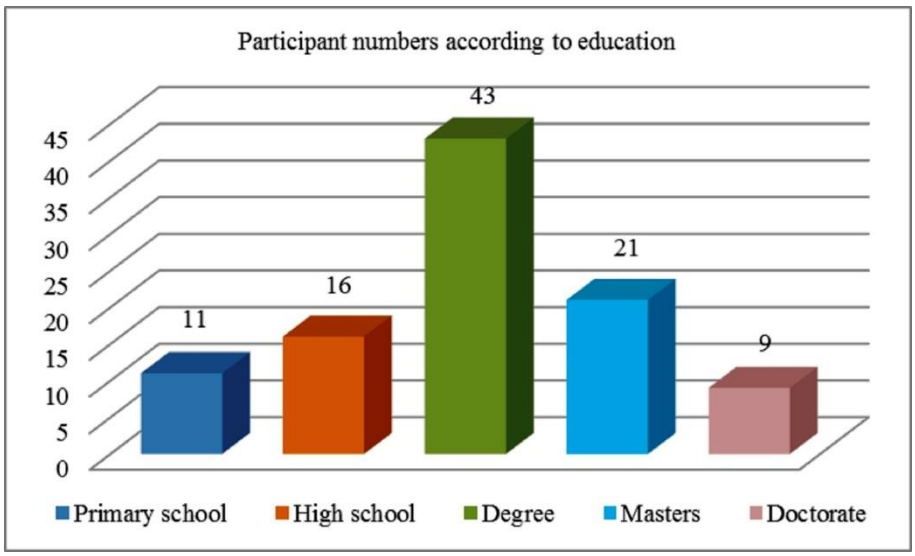


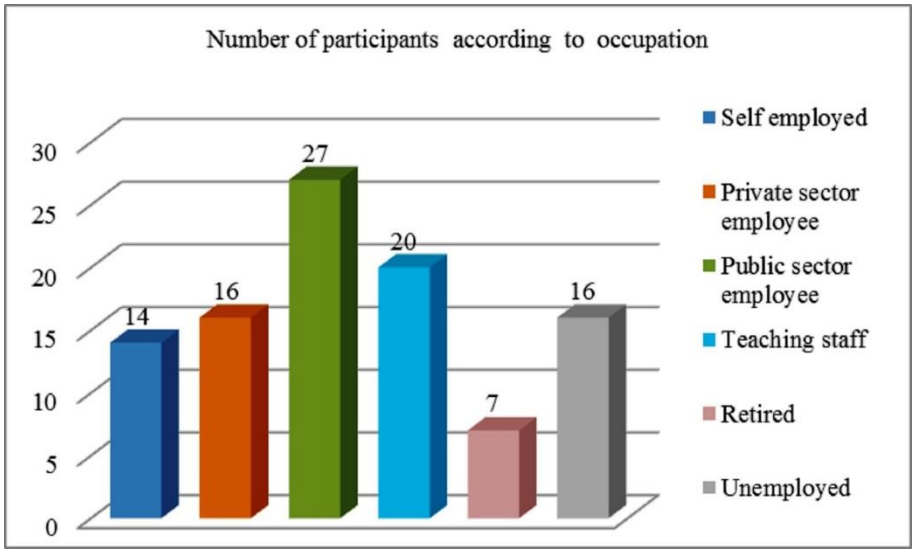
Figure 4 shows that nearly half of visitors participating in the survey had undergraduate "degrees". Thirty individuals had masters and doctorate degrees, with 27% being "primary school" and "high school" graduates. A study by Özdemir and Vural (2015), identified that nearly 1/5 of survey participants were not literate, 1/3 were literate and 1/3 were primary school graduates. A study by Yılmaz et al. (2016) stated that nearly 1/3 of participants were primary school graduates, 1/7 were middle school graduates, 1/3 were high school graduates, and 1/15 were university graduates. The sample in a survey study applied by Akpınar (2019) comprised 44.4% with associate degree and degree level education. Doğan et al. (2015) in a study researching the satisfaction of visitors to the Hasankeyf region observed 49.3% had masters and doctoral degrees when the educational level of visitors was examined.

Figure 4. Educational level of survey participants visiting the Martyr's Memorial



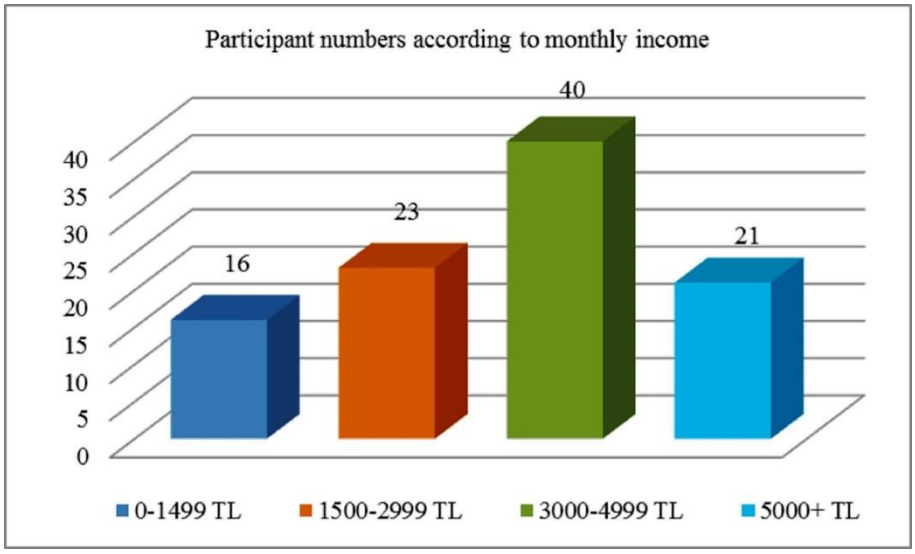
According to Figure 5, 27% of participants were "public sector employees", 20% were "teaching staff", 16% were "private sector employees" and 14% were "self-employed". The study by Özdemir and Vural (2015) found 40.9% of participants were retired. Yılmaz et al. (2016) found 86.7% were unemployed and 13.3% were employed within the scope of the survey participants in their study. In the study by Akpınar (2019), 46.2% of participating individuals were employed.

Figure 5. Distribution of occupation of survey participants visiting the Martyr's Memorial.



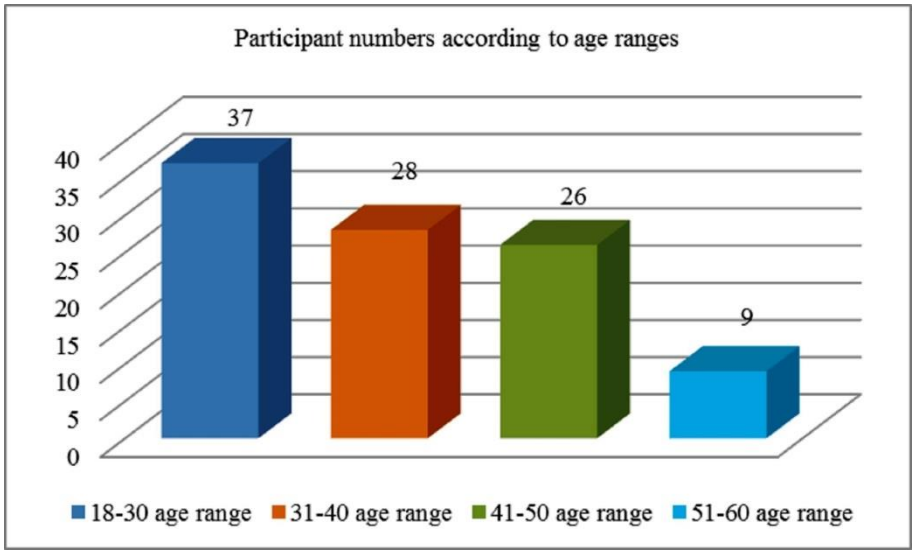
Of the survey participants, 40 individuals were determined to have monthly income from 3000-5000 TL. This was followed by 23 individuals with monthly income of 1500-3000 TL, 21 individuals with income of 5000 TL or more, and 16 individuals with income from 0-1500 TL (Figure 6).

Figure 6. Distribution of monthly income of survey participants.



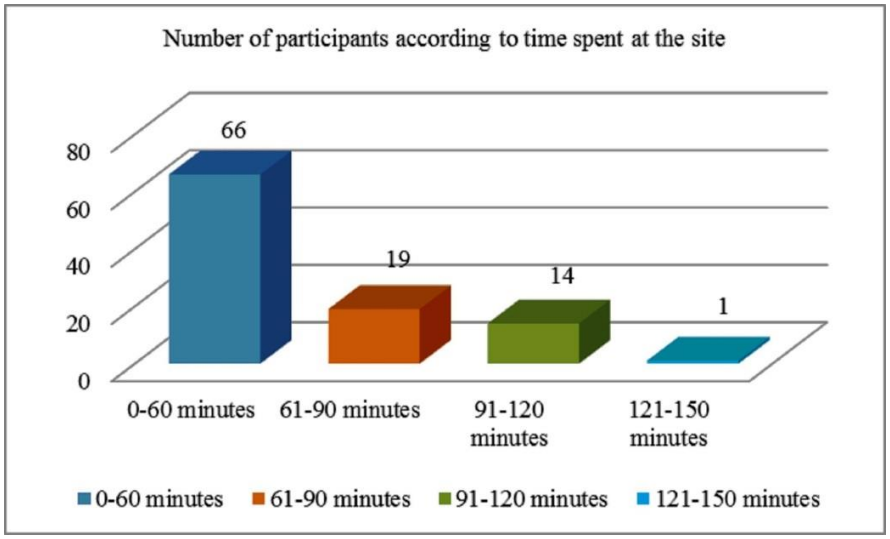
According to the survey results of Akpınar (2019), 39.3% of participants had monthly income from 1000-1999 TL. In the study by Doğan et al. (2015), 24.2% of individuals replying to the survey had monthly incomes from 4000-5000 TL. According to Figure 7, there were 37 visitors participating in the survey aged from 18-30 years, 28 people from 31-40 years, 26 people from 41-50 years and 9 people from 51-60 years of age. Of individuals included in the survey application in the study by Doğan et al. (2015), 45.7% were in the 16-29 year age group.

Figure 7. Distribution of age ranges for survey participants.



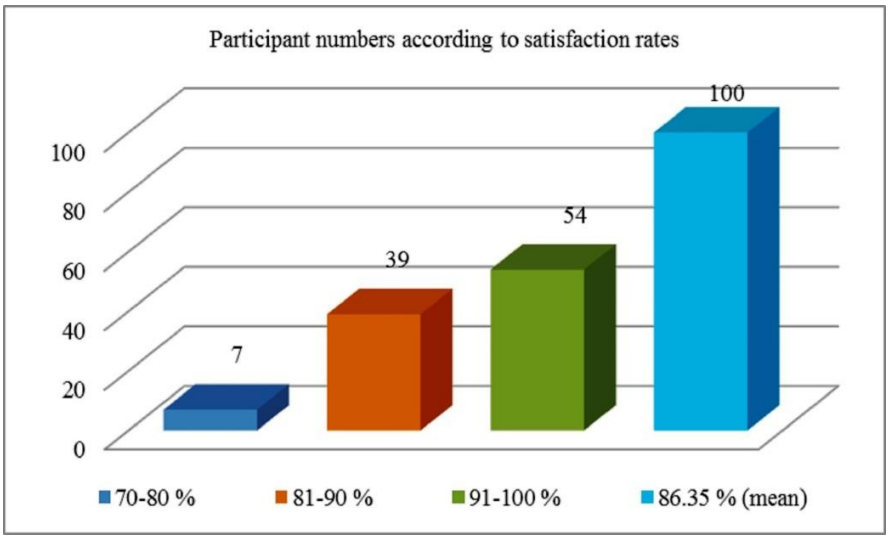
On Figure 8, it was identified that of the 100 individuals randomly chosen from visitors to the Martyrs' Memorial and included in the survey to determine perceptions, 66 spent from 0-60 minutes in the area for their visit. Information was reached that 19 individuals spent from 1 to 1.5 hours for their visit.

Figure 8. Distribution of length of visit for survey participants.



Based on the current situation, when the rates of visitors who completed a satisfactory visit to the area are examined, a mean of 86.35% of the 100 survey participants were satisfied as seen on Figure 9. In the study by Akpınar (2019), it was identified that the mental status of 13.2% of individuals was very positively affected by the quality of the green space.

Figure 9. Distribution of satisfaction rates for survey participants



4. CONCLUSIONS

The study focused on the perceptions of the visitor potential of Çanakkale Martyrs' Memorial, the landscape infrastructure and sufficiency of furnishings within the scope of the area and effect on satisfaction. Data obtained in the study were determined by applying a survey to a randomly-selected target group of volunteers. The study concluded that the landscape infrastructure and furnishings of Çanakkale Martyrs' Memorial are insufficient. Important conclusions reached in line with the aim of the study included the lack or insufficiency of planting of windbreak and shade trees, furnishings like pergola and seating groups, and open and enclosed viewing terraces. When the daily increasing numbers of visitors are considered, the necessity to renovate the historical area in parallel to varying needs was revealed. An area plan for this structure, with continuing change and development, including visitor perceptions will positively contribute to visitor satisfaction (Özdemir, 2019; Sherman et al., 2005; Cheng et al., 2010). With this mandate, it is important not to ignore the perceptions and thoughts of visitors to the historical area in studies about area planning, design and applications.

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Research Article

SEED STRUCTURE AND EMBRYO DEVELOPMENT OF SESELI RESINOSUM (APIACEAE)

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ABSTRACT

The male and female gametophyte development in Seseli resinosum Freyn et Sint were studied with a-light microscope. In order to study the embryology of Seseli resinosum Freyn & Synth that an endemic plant spreading in Zonguldak-Bartin region development of the seed and embryo have been examined. Embryo development of Seseli resinosum was solanad type. In the sections taken zygote, proembryo, 4-cell embryo, 8-cell embryo, spherical embryo, heart-shaped embryo stages were observed. There are differences in the participation of the integument in the formation of the testa. In Apiaceae, only the epidermis of the outer integument forms the seed coat. Since the fruit type is a schizocarp, the testa and the pericarp are inseparable. Testa was seen as 3 or 6 layers. The layers consist of thin-walled cells. The outermost layer is single row and its thickness is less than the other layers.

Keywords: *Seseli resinosum, Apiaceae, Seed structure, Embryo development*

1. INTRODUCTION

The genus *Seseli* L., which belongs to the Apiaceae family, has economic importance. Dried base leaves are used as animal food, and the plant itself is used an ornamental plant in gardens and parks. *Seseli* chemicals are used in medicine[1-2].

Seseli resinosum Freyn et Sint is an endemic species that is widely distributed in the Western Black Sea region of Turkey [3-4]. The environments that harbor the species are quite healthy. However, both the province of Zonguldak, Bartın and tourist destinations with / their sprawling communities represent a danger to which the species is vulnerable (VU) [5].

The author's previous study of the Apiaceae species, including *Aegopodium podagraria* L., *Bupleurum mucronatum* Wight et Arn., *Cuminum cyminum* L.,*Coriandrum sativum* L., *Daucus carota* L., *Daucus muricatus* L., *Eryngium yuccifolium* Michx., *Ferula sinkiangensis* KM. Shen, *Foeniculum vulgare* Mill., *Hydrocotyle americana* L., *Osmorhiza longistylis* (Torr.) DC., *Pastica sativa* L., *Pimpinella diversifolia* D.C., *P. Candolleana* Wight etArn., *P. heyneana* Wall., *P. bracteata* Haines, *P. monoica* Dallz., *Trachyspermum ammi* L. (Sprague), and *Zizia aurea* (L.) W.D.J. Koch., revealed that the embryogeny was Solanad type and that the embryo development was Polygonum type. The embryo sac may be mono-, bi- or tetrasporic, although the first type is predominant [6,7]

Since the fruit type is a schizocarp fruit, pericarp with testa inseparable. Testa was seen as 3 or 6 layers.

Testa consists of the outer / most layer of integument in the Umbelliferae family [8]

The purpose of this work is a detailed investigation of the seed structure and embryo development of *S. resinosum*.

2. MATERIALS AND METHODS

In July and August of 2007-2009, 300 flower buds and 100 flowers in bloom were collected from plants that grew in the rocky fields of Bartın-İnkumu and Zonguldak (Figure 1). The Seseli resinosum flower stems from compound umbels and hermaphrodite. Embriyo and seed devolopment in different stages of development were fixed in formaldehyde, acetic acid, ethanol solution (FAA, 5:5:90), stored in 70% ethanol, embedded in paraffin, serially sectioned (7-8 µm thick) with a Thermo-Shandon Finesse 325 rotary microtome and stained with hematoxylin [9-10].

For the development of embryos, longitudinal sections of flower bud samples are preferred [11].

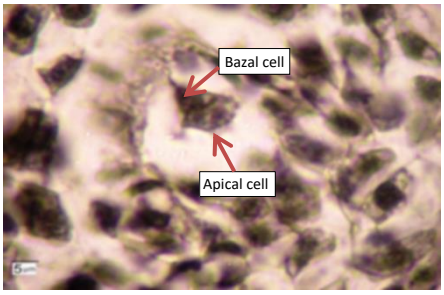
Photomicrographs taken with a Nicon Eclips 200 and a Leica DFC microscope. Photomicrographs of the embriyo and sees devolopment.

Figure 1. Photograph of the upper stem of *Seseli resinosum* showing flower buds.

3. RESULTS

3.1. Solanad type embryo development

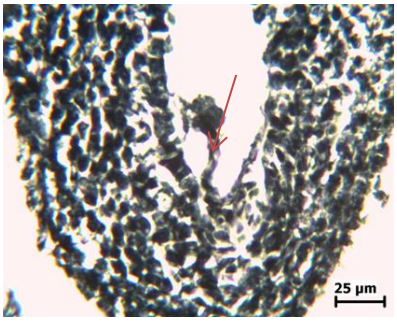
Figure 2. Proembryo, basal and apical cell



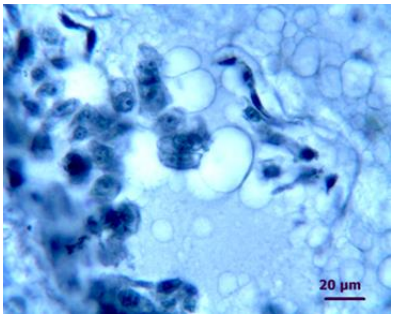
In angiosperms, the zygote is attached to the micropyl end of the embryo sac [12]. Zygote spends a short rest period and it is then divided into a transverse plane to form the basal and apical cell. The basal part and the embryo attach to the sac, and the apical part is located inside the sac (Figure 2).

The basal cell forms the suspensor as a result of successive mitotic divisions. The suspensor binds the embryo to the embryo sac and pushes it into the endosperma [12]. In *Seseli resinosum*, single-stranded filament suspensors were distinguished (Figure 3A).

Figure 3.(A-D).
A. Suspensor, 4-cell proembriyo.
B. 8-cell proembriyo.
C. spherical embryo.
D. Heart shaped embriyo



A



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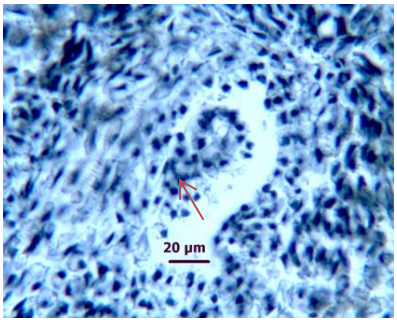

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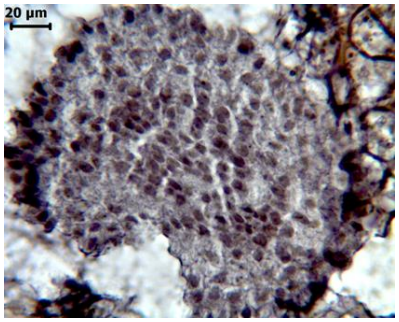


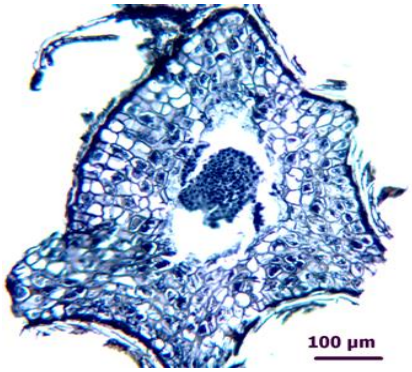
D

In most angiosperms, the zygote is transversely divided and an apical cell into the embryo sac and a large basal cell into the micropile. Depending on the transverse and length division of the apical and basal cells, 8-cell proembryo formation is also observed. (Figure 3B).

3.2. Structure of testa

The fruit is a schizocarp fruit, the testa and the pericarp are inseparable (Figure 4). The testa is 3-6 layered. The layers consist of thin-walled cells. The outer / most layer is single-row and its thickness is less than the other layers. Testa consists of the outer / most layer of the integument in the Umbelliferae family [8]

Figure 4. Testa



4. DISCUSSION

Our findings show some similarities between the embryology of the studied Apiaceae species.

Embryo development in *Seseli resinosum* is solanad type.

Zygote proembryo, 4-cell embryo (Figure 3A)., 8-cell embryo (Figure 3B). spherical embryo (Figure 3C)., heart-shaped embryo stages (Figure 3D).were observed in the sections taken. In *Seseli resinosum*, a single-row filament-like suspensor, which connects the embryo to the embryo sac and has a suitable medium, is distinguished.

There are differences in the participation of the integument in the formation of the testa. In Umbelliferae only the epidermis of the outer integument forms the seed shell [8]. The fruit is a schizocarp fruit, the testa and the pericarp are inseparable.

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Research Article

EFFECTS OF SOME OF HEAVY METALS ON TOTAL PROTEIN AMOUNT AND PEROXIDASE ACTIVITY IN SOLANUM LYCOPERSICUM MILL

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ABSTRACT

In this research, different concentrations of cadmium, nickel, copper heavy metals applied on 10 weeks old Solanum lycopersicum Mill. cv. invictus seedlings by irrigation water. As a result of heavy metal applications total protein amount and peroxidase [EC 1.11.1.7] enzyme activity has been determined by spectrophotometrically. Changing in total protein amount and peroxidase activity in S. lycopersicum seedlings after heavy metal applications has been compared with control group. Depending the application of heavy metals on S. lycopersicum seedlings total protein amount decreased as 57% in 100 ppm of copper application and 10,9% increased in 10 ppm nickel application. The highest increases in peroxidase activity 100 ppm of copper applied and in proportion as 536,03% and treated group with 10 ppm nickel in proportion as 5.97%were determined.

Keywords: *Solanum lycopersicum, cadmium, nickel, copper, total protein, peroxidase.*

1. INTRODUCTION

Solanum lycopersicum Mill. is the member of Solanaceae family and one of the most important vegatable crop grown at the different part of the world (Manawadu et al., 2014).It contains a lof of nutrients and antioxidants (lycopene, phenol, flavonoid, vitamin C) which are quite important as food and for the the human health (Periago et al., 2009). However, heavy metal impacts on food production and human health have become a global concern all over the world. The main reasons of heavy metal pollution are generally urbanisation and industrialisaiton with severe long-term consequences (Rai et al., 2019). The decline in environmental quality as a result of pollution is evidenced by loss of biological diversity, vegetation, harmful chemicals in food grains and atmosphere threats to life support systems (Rai, 2016). It is well known that, some of metals such as copper (Cu), iron (Fe), boron (B), nickel (Ni), manganese (Mn), zinc (Zn) and molybdenum (Mo) are needed in smaller amounts which are called micronutrients or trace elements (DalCorso et al., 2014). These metals can have adverse effect on crop agriculture and human health, when they reach high concentration (Wang et al., 2009; Chaves et al., 2011; DalCorso et al., 2014). Copper is the essential micronutrient and involved in numerous important for the physiological and biochemical functions (Sharma and Agrawal, 2005). Ni is recognized an essential micronutrient for plant growth and it is a component of the enzyme urease which is essential for nitrogen metabolism in higher plants (Bhalerao et al., 2015). Furthermore, some of metals (non essential elements) may potentially harmful effect such as cadmium which is the highest in terms of damage to human health and plant growth (Chaves et al., 2011). Heavy metal's effects can resulted in breaks on DNA strands, mutations of genetic materials, oxidative stress and damage by reactive oxygen species (ROS) and free radicals, structural and functional membrane disintegration (Rai et al., 2019). In many different plant species, oxidative stress has been involved in toxicity of heavy metals. Exposure to metal ions may increase the production of ROS such as hydroxyl radicals, superoxide radicals, or hydrogen peroxide which may react with proteins, lipids nucleic acids and resulted in lipid peroxidation, membrane damage and inactivation of enzyme. Therefore, heavy metals have adverse affect on many physiological processes and also cell viability. Plants have an important mechanism to maintain low ROS level and prevent from the harmful effects of excess level of ROS concentrations. This antioxidant mechanism consists of numerous soluble (glutathione, ascorbate) and membrane (tocopherol) compounds and enzymes to ROS scavenging such as catalase, ascorbate peroxidase, superoxide dismutase, peroxidase (Jomova and Morovıc, 2009; Rucińska-Sobkowiak, 2010). Another important factor in plant defense system under stress conditions is variation in total protein level (Çördük et al., 2016). Exposure to heavy metal stress can cause protein degradation (Emamverdian et al., 2015).

In this study, specific aim was to investigate effects of different concentrations of cadmium, copper and nickel heavy metals on the peroxidase activity and total protein content in *S. lycopersicum.*

2. MATERIAL AND METHODS

2.1. Experimental Plant Material

Seeds were used in this study were obtained from agricultural store. Seeds of *S. lycopersicum* were planted in plastic pots which contain mixture of perlite and torf (1:3). Seedlings were grown in a growth chamber condition at 25±2 °C and 16/8 h photoperiod.

2.2. Heavy Metal Treatment

Ten weeks old seedlings were treated with $CuCI_2$ (12.5 ppm, 25 ppm, 50 ppm, 100 ppm), Cd $(NO_3)_2 4H_2O$ and $NiCI_2.6H_2O$ (10 ppm, 20 ppm, 30 ppm, 40 ppm) by irrigating with water.

All of the experiments have been repeated for three times. Each group has ten tomato seedlings and one group was selected as a control group in each treatment.

2.3. Preperation of Leaf Extracts

Approximately 0.5 g healthy fresh tomato leaves were harvested and grinded in cold 0.05 M sodium acetate buffer (pH 6.5). Homogenates transfered to the eppendorf tubes which were centrifugated at 13.000 rpm for 15 min at 4°C. The supernatants were used for determination of the enzyme activity and total protein content.

2.4. Determination of Total Protein Amount and Peroxidase Enzyme Activity

Total protein content has been analyzed according to Bradford (1976) using BSA as a standard. Amount of total protein was measured spectrophotometrically at 595 nm. Peroxidase activity in the leaf extracts were assayed spectrophotometrically at 300nm according to Kanner and Kinsella (1983).The kinetic enzyme reaction was monitored over 120 sec. and peroxidase measurements were taken in every approximately between 10-15 s. Peroxidase enzyme activity was defined as μmol/mgprot/min.

3. RESULTS AND DISCUSSION

In this research, different concentrations of cadmium, nickel, copper heavy metals applied on ten weeks old *S. lycopersicum* cv. invictus seedlings with irrigation water that is being growth under in vivo conditions. Physiological responses were determined as total protein and POX enzyme activity by spectrophotometrically. After exposuring to different heavy metals and concentrations, changing of peroxidase activity levels and total protein content in *S. lycopersicum* cv. invictus seedlings were compared with control group.

3.1. Total Protein Amount Results

Our research results showed that total protein content decreased with the increasing of heavy metal concentration comparing with the control group (Fig. 1,2,3), except 10 ppm nickel concentration (Fig 1).The most important reduction as 57% was observed in plants which were treated with 100 ppm $CuCI_2$ (Fig. 3).

Figure 1. Effects of Nickel on Total Protein Content in *S. lycopersicum*

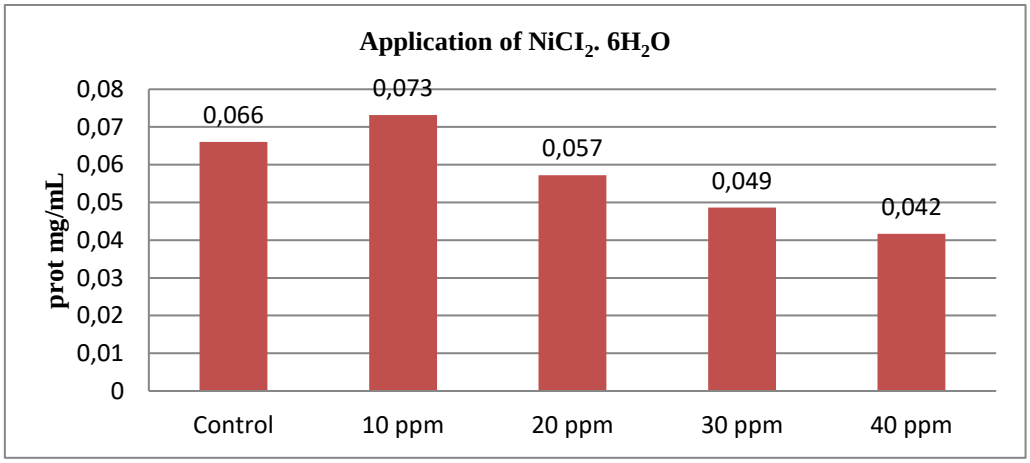


Figure 2. Effects of Cadmium on Total Protein Content in *S. lycopersicum*

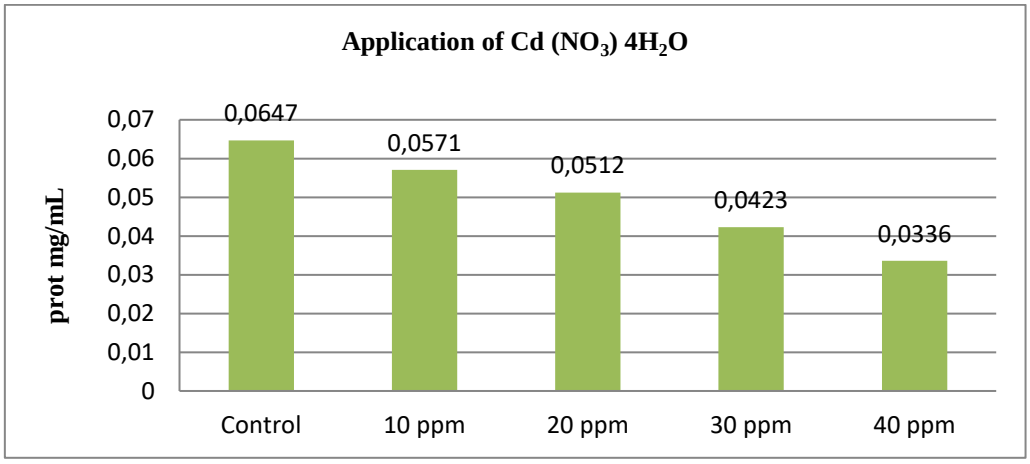
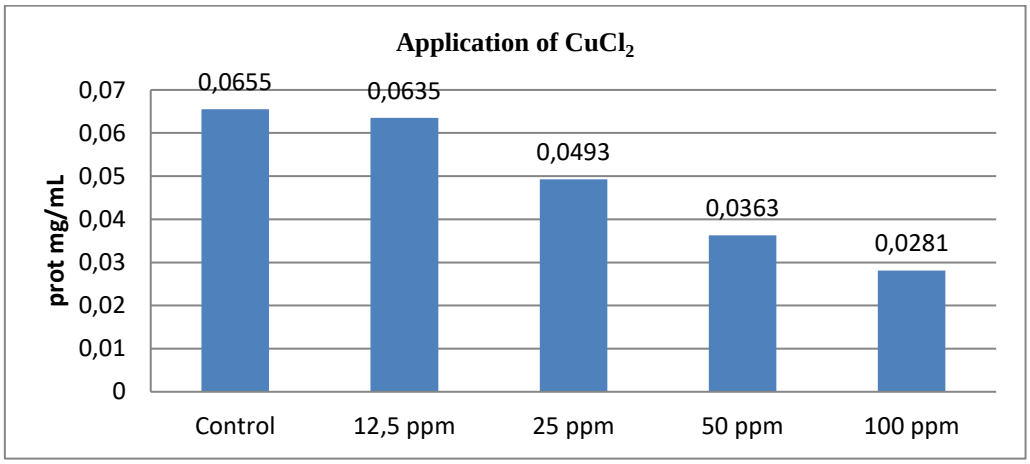


Figure 3. Effects of Copper on Total Protein Content in *S. lycopersicum*



3.2. Peroxidase Activity Results

In all treatments, peroxidase enzyme activities were increased in S. *lycopersicum* when compared with the control groups. Peroxidase activity increased with the increasing heavy metal concentration for three different heavy metals (Fig 4,5,6). The highest increase in peroxidase activity was measured as 536.03% in 100 ppm copper application (Fig. 6) and lowest increase was measured as 5.96% in 10 ppm nickel application (Fig. 4).

Figure 4. Effects of Nickel on Peroxidase Enzyme Activity in *S. lycopersicum*

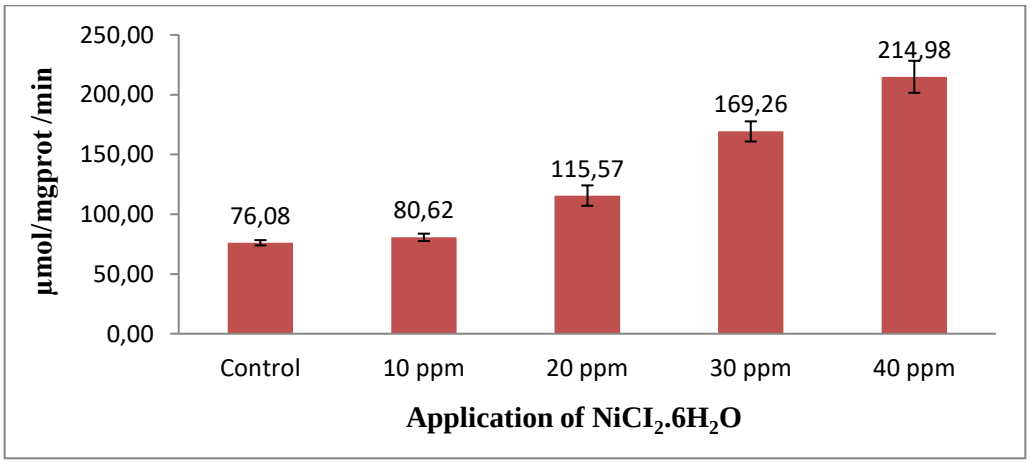


Figure 5. Effects of Cadmium on Peroxidase Enzyme Activity in *S. lycopersicum*

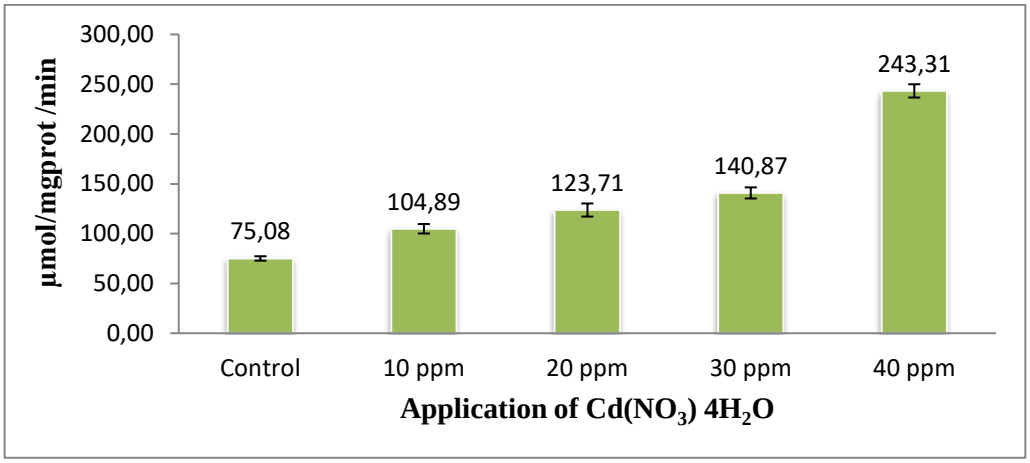
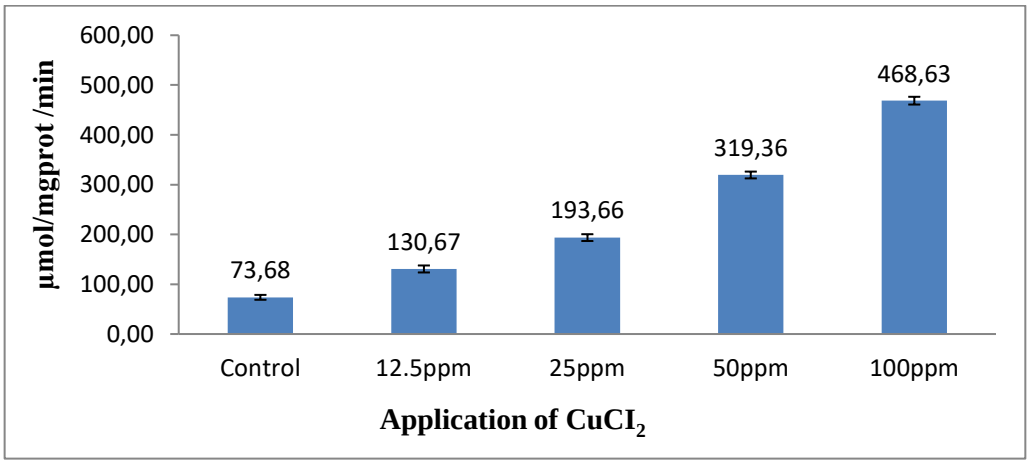


Figure 6. Effects of Copper on Peroxidase Enzyme Activity in *S. lycopersicum*



In our research, peroxidase enzyme activity increased with the increasing heavy metal concentration whereas protein concentration mostly showed reduction. The change in the total protein content may be associated with inhibition of protein synthesis and protein degradation (Çördük et al., 2016).

In parallel with our work research reported that peroxidase activity and proline content increased with the increasing concentration for nickel in water lettuce whereas total protein amount and other carotenoids started to show reduction at higher concentrations (Singh and Pandey, 2011).

In another research was observed remarkably reduction in chlorophyll and total protein content as copper concentration increased in *Helianthus annus* L. seedlings (Kirbag Zengin and Kirbag, 2007).

In pea plants, protein content decreased especially in the presence of higher cadmium concentrations (Bavi et al., 2011). Cd resulted in a decrease in total protein content which can be consequences of increase in protein degradation, a decrease in protein synthesis (Balestrasse et al., 2003).

Similar to our results it was reported that increasing concentrations of Cu treatments resulted in a reduction of total protein concentration and Cu stressed had the most detrimental effects while Ni stress showed less damaging in *Ocimum basilicum* L. following a combined, biochemical, analytical, and physiological approach (Georgiadou et al., 2018).

In another research, it was observed that APX, POD, and SOD were shown remarkable induction with the treatment of Cd, Cu (10, 20 and 50 ppm) in the leaves of tomato when compared to control group (Kısa, 2017). Although high $CdCl_2$ concentrations effect on plants defense mechanism was substantially high, peroxidase activity in both shoots and roots were higher at low $CdCl_2$ concentrations. Protein sythesis was reduced excessively and thus no peroxidase enzyme is synthesized (Bavi et al., 2011).

4. CONCLUSION

In conclusion, the present investigation showed that Cd, Cu and Ni at higher concentrations had adverse effect on *S. lycopersicum*. Our results generally showed that exposure to different concentrations of heavy metals caused increasing of POX acitivity and reduction of total protein level.

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Research Article

INVESTIGATION OF BIOLOGICAL ACTIVITIES OF 4-HYDROXY-3-(2-HYDROXY-5-METHYLBENZYLIDEAMINO) BENZENESULPHONIC ACID

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ABSTRACT

In this study, the antimicrobial activity, DNA cleavage, DNA binding and antioxidant properties of a sulfonic acid-based imine compound were investigated. The antimicrobial activity of the compound was investigated for minimum inhibitory concentration (MIC) against some bacteria and yeast cultures. The DNA cleavage activity of the compound was investigated as hydrolytic and oxidative with the gel electrophoresis method. H2O2 was used as an oxidizing agent for detection of the cleavage activity mechanism. The Ultraviolet-Visible (UV-Vis) field absorption spectroscopy method was used to determine the binding effect to DNA. The sulfonic acid-based imine compound reacted with Calf Thymus DNA (CT-DNA) which was examined by UV-Vis absorption spectroscopy. The free radical scavenging activity was determined using the 2,2-Diphenyl-1-picrylhydrazyl (DPPH) method.

The studied compound was found to be effective on yeast and bacteria at different concentrations. The compound was found to be more effective on Staphylococcus aureus ATCC 25923 and Enterococcus faecalis ATCC 29212 bacteria. DNA cleavage study showed that the compound cleaved DNA without any external agents in hydrolytic and oxidative manner. UV-Vis spectroscopy studies of the interactions between the compound and CT-DNA showed that the compound interacts with CT-DNA via electrostatic binding. The compound to be tested was compared with the butylated hydroxytoluene (BHT) solution used as standard. It was found that the compound exhibits good antioxidant activity.

Keywords: *Sulfonic acid, antimicrobial activity, antioxidant activity, DNA cleavage, DNA binding.*

1. INTRODUCTION

Imine compounds (Schiff base) are highly studied chemicals due to their biological and structural importance. They are used extensively as pigments in dye industry, catalysts and polymer stabilizers in organic synthesis (Branchaud, 1983; Silva *et al*., 2011). Nowadays, in studies their use in biological research in the pharmaceutical industry and medicine has increased the interest in these bases due to being reported as having antibacterial, antifungal, antiulcer, antimalarial, and antitumoral activities (Akocak *et al*., 2019; *Sridhar et al*., 2001; Panneerselvam *et al.,* 2005; Gupta *et al.,* 2015; Akocak *et al*., 2017; Sarıkaya *et al.,* 2014).

Infectious diseases cause deaths around the world. In particular, the fact that some bacteria are more resistant to antibiotics and the increase in this effect seriously affects human health (Taşkın, 2012). However, despite the need for new antimicrobial drugs, the development of antimicrobial agents is unfortunately decreasing gradually (Yıldırım, 2016).

Cancer is an significant important public health problem that ranks second after cardiovascular diseases as known cause of death in the world and in our country (Global Burden of Disease Cancer Collaboration, 2015). For this reason, scientists are conducting extensive studies about the identification or synthesis of new drug molecules that can be effective against cancer and at the same time do not harm human health (Göçmen, 2014).

Compounds targeting deoxyribonucleic acid (DNA) have significant theoretical and application value in the field of biology, chemistry and medicine (Li *et al*., 2011). DNA has become the primary target for many therapeutic agents ranging from anticancer drugs to antibiotics since the clarification of its structure (Sobha *et al*., 2012).

Sulfonic acids are used in the synthesis of organic materials, and salts of sulfonic acids are used as components of phenol compounds, detergents, ion exchangers, rust inhibitors, various dyes and sulfonamide drugs.

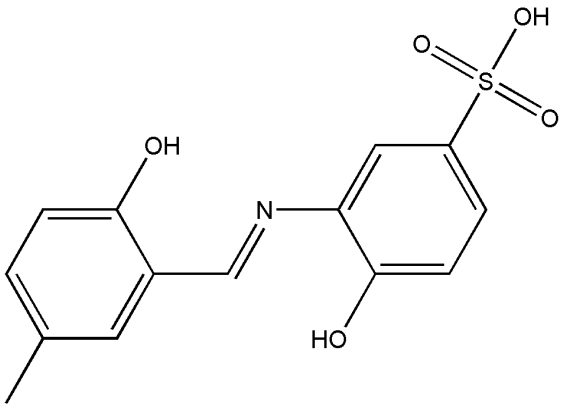
In this study, the sulfonic acid-based imine compound was firstly synthesized by the reaction of 3-amino-4-hydroxybenzenesulfonic with 2-hydroxy-5-methylbenzaldehyde. The structure of the compound was investigated for biological activities such as antimicrobial activity, DNA cleavage, DNA binding and antioxidant activity.

2. MATERIAL AND METHODS

2.1. Material

The sulfonic acid based imin compound used in this study is given below (Figure 1).

Figure 1. The chemical formula of 4-Hydroxy-3-(2-hydroxy-5-methylbenzylideamino)benzenesulphonic acid.



2.2. Methods

2.2.1. Biological activities of compound

2.2.1.1. Determination of antimicrobial activity

In vitro antimicrobial activity was examined for the compound. The antibacterial activities of the compound were tested against two gram-negative *Pseudomonas aeruginosa* (ATCC 27853) and *Proteus vulgaris* (ATCC 13315) bacteria and three gram-positive *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), and *Bacillus subtilis* (ATCC 6633) bacteria. The antifungal activities were examined for *Candida albicans* (ATCC 60193) and *Candida tropicalis* (ATCC 13803) yeasts. Antimicrobial activity studies were performed by the microdilution method according to the procedure shown in Essential Procedures for Clinical Microbiology (Isenberg, 1998). The minimum inhibitory concentration (MIC) value in which the antimicrobial effects of compound was determined.

2.2.1.2. DNA interactions of compound

The agarose gel electrophoresis and Ultraviolet-Visible (UV-Vis) field absorption spectroscopy method were used to determine if there was any damage caused by binding of sulfonic acid based imine compound to DNA.

2.2.1.2.1 Agarose gel electrophoresis method

The agarose gel electrophoresis method was used to identify DNA cleavage products. When the original supercoiled form of plasmid DNA is opened with damage, an open circular loose form is formed, and more fractures may occur and the linear form may also be present. When gel electrophoresis is carried out for DNA, Form I proceeds relatively faster than others, while Form II proceeds more slowly. If both strands are cleaved, Form III which migrates between Forms I and II is found.

Within the scope of the study, plasmid pBR322 DNA was placed in Tris-HCl buffer (10mM, pH=7.4), treated with compound and prepared samples were incubated at 37 $^{\circ}$C for 3 hours, then a loading buffer was added to the mixture, loaded onto 1% agarose gel and run for 1 hour, at 60 V in tris-acetic acid-EDTA (TAE) buffer (400mM Tris-200 mM acetate, 10 mM EDTA, pH=8.2). Then, the bands were visualized under a UV illuminator and photographed (Quantum ST4 gel imagining system, Vilbar Lourmat) (Qiao *et al*., 2011).

2.2.1.2.2. UV-Visible field absorption titration spectroscopy

Binding of the compound to DNA causes changes in its spectroscopic properties. These changes may be in the form of decreased or increased absorption (hypochromicity and hyperchromicity). This causes higher or lower wavelength shifts (shift to blue or red).

Electrostatic interactions cover almost all interactions with groups on the outer surface of DNA. Because the phosphate groups on the outer surface of DNA are negatively charged, they may interact with metal cations such as Na^{+2} or Mg^{+2} in the intracellular environment. This interaction of metal ions with DNA neutralizes the negative charge of the phosphate groups, and the counter ions are released. This may result in changes in the structure of DNA. As a general rule, an electrostatic component must be present in the molecular structure for the design of a molecule capable of binding strongly to DNA. Other types of interaction with DNA may also involve electrostatic interactions (Strekowski and Wilson, 2007).

In this way, whether the compound binds to DNA was determined by observing the change of absorption in the absence and presence of DNA. For this purpose, Calf-Thymus DNA (CT-DNA) was used. The CT-DNA and studied compound were placed in TNE buffer (10 mM Tris-HCl, 50 mM NaCl and 1 mM EDTA at pH: 7.4). The DNA solution was prepared and

DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient at 260 nm. UV-Vis field spectrum titrations were performed by adding equal amounts of DNA to both the compound and control solution to eliminate the absorbance of DNA itself. After each DNA addition, the measurements were recorded after waiting for 5 minutes at room temperature. UV-Vis measurements were then taken between 200-600 nm.

2.2.1.3. Free radical scavenging activity (DPPH)

The free radical scavenging activity was determined using the 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical according to the Blois (1958) method with some modifications. In this method, the DPPH molecule is reduced by donating H^+ to the antioxidant molecules present in the medium, which leads to a decrease in absorbance. The lower the absorbance value, the greater the free radical removal activity of the substance being tested.

DPPH solution was prepared in methanol and 1 mL of the prepared DPPH solution was added to the compound at different concentrations (10, 20, 40, 60, 80 and 100 µg/mL). The reaction mixture was stirred vigorously and incubated in the dark for 30 min. at room temperature. The color of DPPH changed from purple to yellow. BHT was used for the positive control and a solvent (methanol) was used as a negative control. Then, the absorbance was measured at 517 nm by using a spectrophotometer (Spectro UV-Vis Dual Beam-Labomed, Inc.).

The free radical scavenging activity was calculated using the following formula, the results being determined as % inhibition.

Inhibition (%) = $[(A_0-A_1)/A_0] \times 100$

Where A_0 is absorbance of control and A_1 is the absorbance of compound or standard.

3. RESULTS AND DISCUSSION

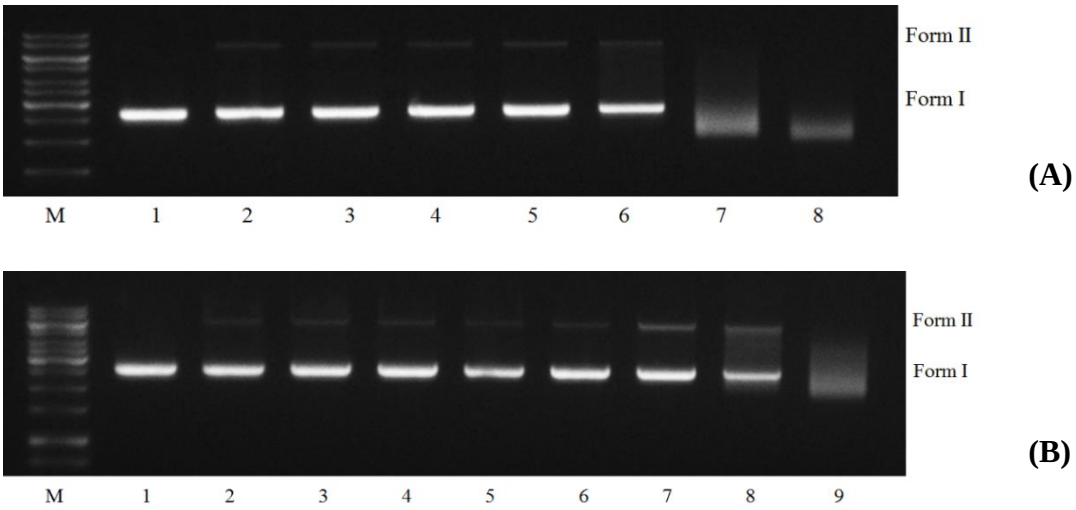
3.1. Antimicrobial activity

MIC values were measured against microorganisms with the microdilution method. The compound was found to be effective on yeast and bacteria. The values were read as the smallest concentration of the compound in the series that prevents visible growth of the test organism. Ampicillin, gentamicin and fluconazole antibiotics were used as positive controls. The antimicrobial activities of the compound varied between the concentrations of 64-256 µg/mL. The compound was found to be especially effective on *S. aureus* (ATCC 25923) and *E. faecalis* (ATCC 29212) bacteria (64 µg/mL). The compound showed the same antifungal activities (128 µg/mL) for both *C. albicans* (ATCC 60193) and *C. tropicalis* (ATCC 13803) yeasts, while it had a low effect on *P. aerouginosa* (ATCC 27853) bacteria (256 µg/mL).

3.2. DNA cleavage activity

Seven different concentrations (6.25, 12.5, 25, 50, 100, 200 and 400 µM) were prepared to determine the DNA cleavage activity of the compound used in the study. As a result of hydrolytic cleavage, it was observed that pBR322 plasmid DNA was cleaved by the compound at increasing concentrations and DNA was completely denatured at concentrations of 200 and 400 µM (Figure 2A). In the presence of an oxidizing agent (H_2O_2), the compound cleaved DNA at all concentrations and completely denatured DNA at a concentration of 400 µM (Figure 2B).

Figure 2. M: Marker, 1. Plasmid DNA, (A): Hydorlytic: 2. DNA+6,25 µM compound, 3. DNA+12,5 µM compound, 4. DNA+25 µM compound, 5. DNA+50 µM compound, 6. DNA+100 µM compound, 7. DNA+200 µM compound, 8. DNA+400 µM compound, (B): Oxidative: 2. DNA+6,25 µM compound+H_2O_2, 3. DNA+12,5 µM compound+H_2O_2, 4. DNA+25 µM compound+H_2O_2, 5. DNA+50 µM compound+H_2O_2, 6. DNA+100 µM compound+H_2O_2, 7. DNA+200 µM compound+H_2O_2, 8. DNA+400 µM compound+H_2O_2.

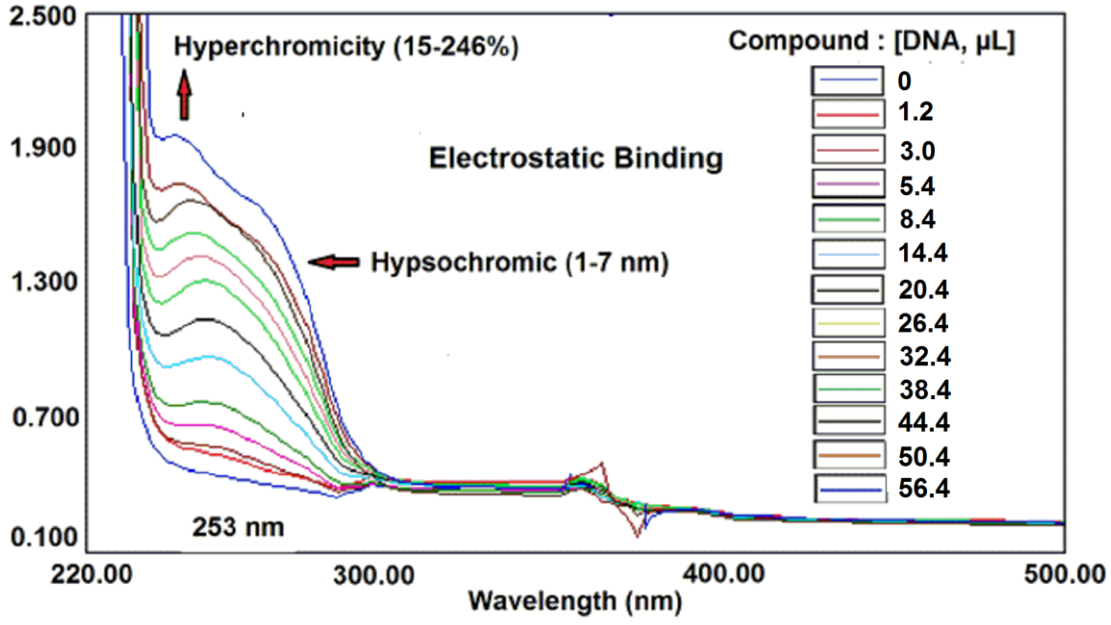


3.3. UV-Visible field absorption spectroscopy

The reactions of the compound with CT-DNA were examined by UV-Vis absorption spectroscopy. Differences in maximum absorbance of the free molecule and the molecule bound to DNA were compared to determine changes after interactions between the compound and DNA.

When the UV-Vis spectra of the compound are examined, it was observed that the change in absorbance intensity was increased in the direction of hyperchromism by gradually increasing the concentration of CT-DNA applied. 15-246% hyperchromism in the compound and 1-7 nm hypsochromism was observed with absorption at 253 nm (Figure 3).

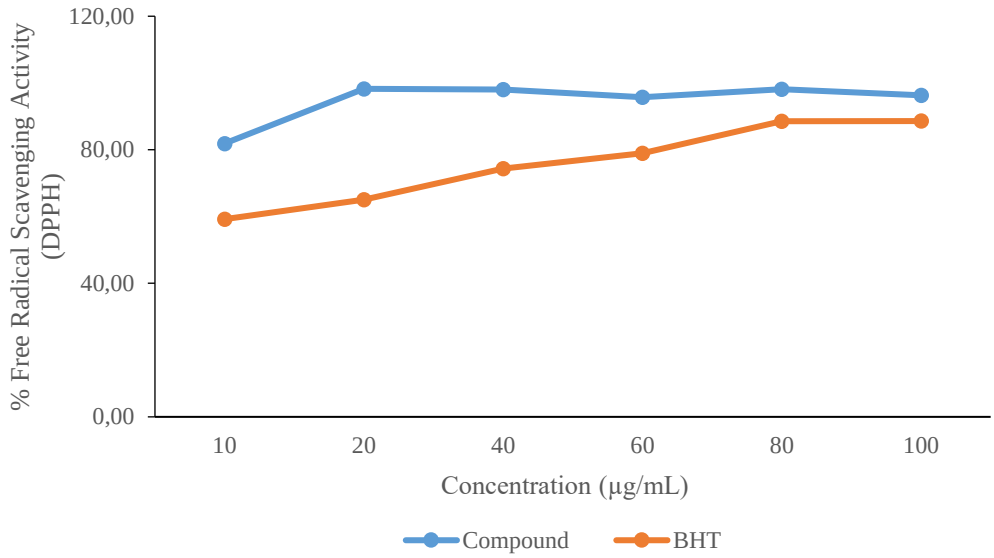
Figure 3. Absorption spectra trace of the compound with CT-DNA.



3.4. Free radical scavenging activity (DPPH method)

The antioxidant activity of the compound was investigated with the DPPH method which is commonly used. Results were compared against BHT control. The antioxidant activity data revealed that the compound exhibited good antioxidant activity as concentrations increased in the DPPH method (Figure 4).

Figure 4. Free radical scavenging activity of the compound.



DNA is considered to be the primary intracellular target of drugs developed for the treatment of many diseases due to its role in regulating cell viability and function. Therefore, there is increasing interest in the search for new molecules that can interact with DNA (Erkkila *et al*., 1999; Chouai *et al*., 2005; Liu *et al*., 2010). It is known that compounds capable of interacting with DNA have potential biological and pharmacological activities, and that this activity is closely related to the binding affinity and mode of binding of the compound to DNA.

Schiff bases and metal complexes are an important classes of compounds that attract attention with their diverse biological and pharmaceutical effects. Many Schiff base ligands are reported to have antibacterial, antifungal and antitumor activity (Wang *et al*., 2006; Quiao *et al*., 2011; Tabassum *et al*., 2013; Alizadeh *et al*., 2015). Considering all these properties, it is thought that newly synthesized Schiff bases and complexes may have similar properties. Therefore, the investigation of the interactions and biological activities of Schiff bases and complexes with DNA is very important for disease prevention and design of new chemotherapeutic drugs. DNA binding is particularly important for development of new chemotherapy drugs. Basically, the complex binds to DNA through three non-covalent modes: electrostatic, groove and intercalation binding (Rambabu *et al*., 2019).

Mermer *et al*. (2019) investigated the antimicrobial and antioxidant activities of synthesized Schiff base derivatives. They studied antimicrobial activity by using *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ATCC 13883, and *Acinetobacter haemolyticus* ATCC 1900. Antioxidant activity was investigated using DPPH (2,2-diphenyl-1-picrilhydrazil) radical. As a result, they found that all synthesized compounds had antioxidant and antimicrobial activities against tested microorganisms.

Alizadeh *et al*. (2014) in their study examined the in vitro DNA binding and pBR322 plasmid DNA cleavage activities of benzothiazole Schiff-base complexes. They found that the DNA binds electrostatically or to grooves and breaks down oxidatively.

Tadavi *et al*. (2018) studied the biological activities of a new Schiff base and complexes derived from the condensation of 2-hydroxy-6-isopropyl-3-methyl benzaldehyde and 1,2-diaminopropane. They investigated the antioxidant, antimicrobial and DNA cleavage activities of all compounds. Antibacterial activities were determined against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*. Antifungal activities were examined against *C. albicans, A. flavus, A. niger* and *C. neoformans* yeasts. Antioxidant activities were tested with 2,2-diphenyl-1-picrilhydrazil using the free radical scavenging method (DPPH). DNA cleavage activity was examined using plasmid DNA pBR322 in the presence of H_2O_2. As a result, they found an increase in antibacterial activity of complex compounds and showed low antifungal activity. They also indicated that all compounds exhibited antioxidant activity and the DNA cleavage occurred only with the Co complex.

4. CONCLUSIONS

In this study, the newly synthesized and characterized sulfonic acid-based imine compound was investigated for antimicrobial activity, DNA binding, DNA cleavage and antioxidant activity. The sulfonic acid-based imine compound was shown to have high antibacterial activity against *S. aureus* and *E. faecalis* bacteria. The interaction of the compound with CT-DNA was studied with UV-Vis absorption spectroscopy. It was revealed that the compound bind to CT-DNA through the electrostatic mode. When DNA cleavage activity results are analyzed, it was determined that the compound cleaved pBR322 plasmid DNA both hydrolytically and oxidatively depending on concentration. The free radical scavenging activity against DPPH was found to have good antioxidant properties. Also, the compound exhibited higher activity than the standard BHT.

Due to specific binding properties of Schiff bases and their various applications in cancer therapy, these compounds were reported as suitable candidates for antimicrobial, artificial nuclease, DNA probe, and antitumor drugs (Kiran *et al*., 2015). Research and design of new molecules that can interact with DNA is one of the most promising ways to discover new DNA- targeting anticancer drugs to be used in chemotherapy (Qiao *et al*., 2011). Therefore, it is very important to investigate the interaction of molecules with DNA in order to develop effective chemotherapeutic agents and better anticancer and antibacterial drugs.

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