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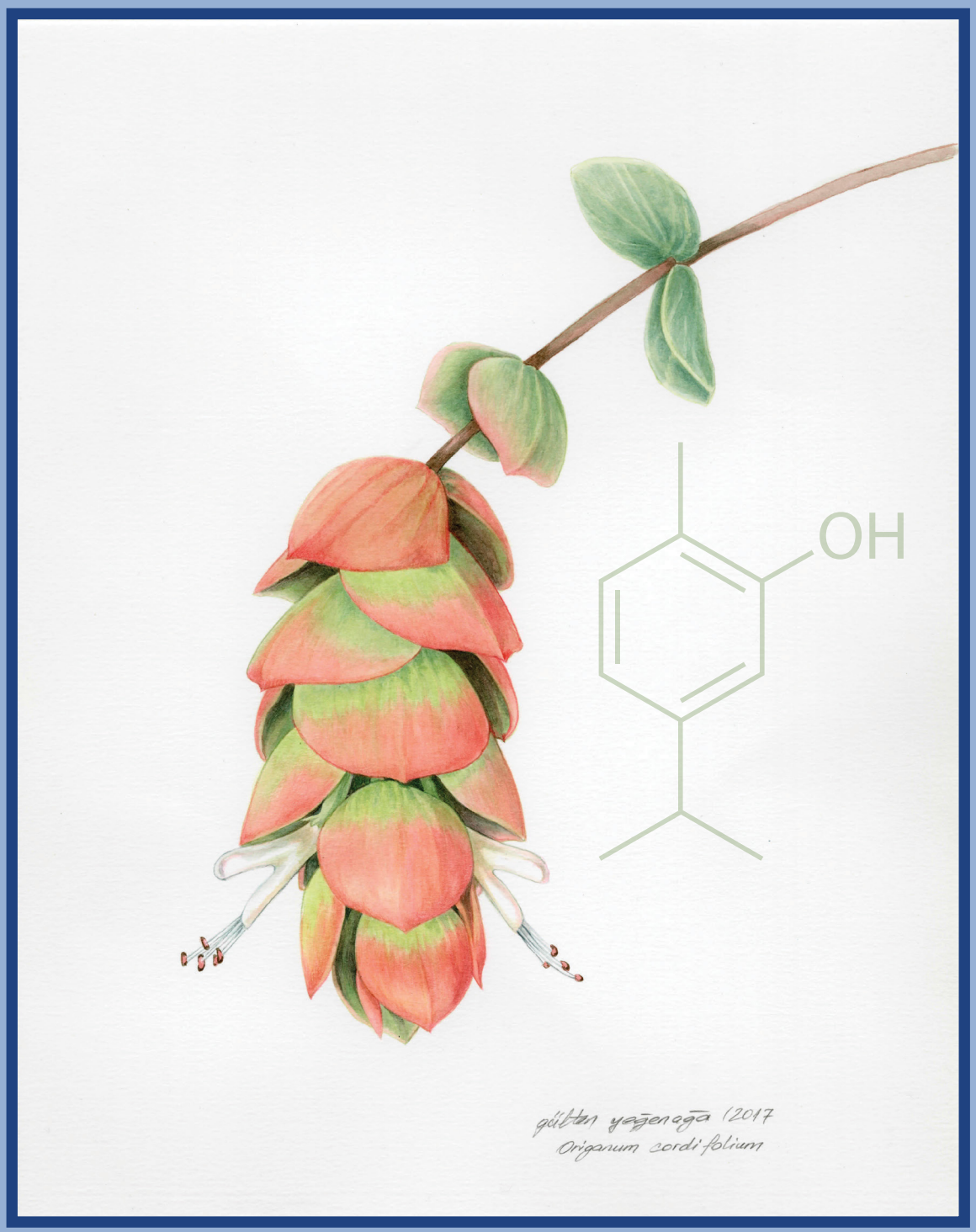

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Reviews

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Comparison of the pharmaceutical properties of paracetamol tablets belonging to different companies in the Northern Cyprus pharmaceutical market

Emine Dilek Ozyilmaz[1*;**], Tansel Comoglu[2**], Roya Nourmohammadi[1]

[1] Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

[2] Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey.

Abstract

Paracetamol (PAR) tablets are commonly used over the counter formulations among the patients as analgesic and antipyretic. Therefore, the determination of the quality of these widely used tablets is important. On Northern Cyprus drug market, paracetamol formulations are provided various by pharmaceutical companies from different countries like Turkey, UK and local companies. In this study, three different brands (A, B, C) of traditional PAR (500 mg) tablets, selected for the evaluation of the pharmaceutical properties, were tested according to United States Pharmacopeia (USP) 32. Similarities and differences between conventional PAR tablets that are available in Northern Cyprus drug market were evaluated.

Keywords

Dissolution profiles, Northern Cyprus pharmaceutical market, paracetamol tablet, quality control.

Article History

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Article Info

***Corresponding author:** Emine Dilek Ozyilmaz **email**: emine.ozyilmaz@emu.edu.tr

**Emine Dilek Ozyilmaz and Tansel Comoglu contributed equally to this manuscript.

Research Article:

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INTRODUCTION

World Health Organization (WHO) describes *'quality control in pharmaceutics'* as "the all necessary procedures to provide the purity of a specific drug formulation". The quality control studies include the controls of all pharmaceutical properties of starting materials and finished product during and after the production to ensure quality (Bhowmik *et al.,* 2014).

According to pharmacopoeias; quality control tests on tablets can be listed as weight variation, hardness, diameter and thickness, friability, dissolution and content uniformity. It is necessary to carry out all these tests on the tablets during production and before blistering (Mathur *et al.,* 2015).

Paracetamol (PAR) is widely used as an antipyretic and analgesic drug in patients of all age groups. It doesn`t show any serious adverse effect but dose is limited for both children and adults; the dose should be arranged as 150 mg and 4 g respectively (Oscier and Milner, 2009). PAR is mostly metabolized by liver and eliminated via the urine. Side effects such as maculopapular rashes on the skin, urticaria, met- hemoglobinemia and some gastrointestinal symptoms can be seen when used at high doses and for a long-term (Yoon *et al.,* 2016).

On the Northern Cyprus drug market, there are conventional paracetamol formulations in the forms of tablet, coated tablet, suspension and suppository manufactures by different companies from different countries.

In this study, the quality control studies have been performed on conventional PAR tablets which are frequently used in the Northern Cyprus pharmaceutical market. Furthermore, difference (f1) and similarity (f2) factors have been calculated for PAR tablets in order to evaluate their dissolution data.

MATERIALS AND METHODS

Materials

PAR was purchased from Rochem, Turkey. Three different brands of PAR tablets (500 mg) were chosen and entitled as PAR A (Batch: 010), PAR B (Batch: 05), PAR C (Batch: 004).

Methods

Stock standard solution of paracetamol

A solution of PAR in 0.1 N HCL at the concentration of 100 µg / mL was prepared as a stock solution. Seven different concentrations of PAR solutions were prepared using the stock solution. The wavelength at which paracetamol showed

maximum absorbance was determined using UV spectroscopy at 243 nm and a calibration line was drawn. (Mathur *et al.,* 2015; TF 2017). Necessary analytical parameters for the assay of PAR were determined by ANOVA test.

LOD and LOQ determination

The limit of detection (LOD) and the limit of quantitation (LOQ) values were calculated using the following equations.

Limit of detection = 3 SD / m

Limit of quantitation = 10 SD / m

Where;

SD: Standard deviation of absorbance

m: Slope of the calibration curve (Nagashree, 2015).

In vitro quality control characteristics of paracetamol tablets

Determination of thickness and diameter: The thickness and the diameter of paracetamol tablets from each brand were measured using Erweka tester.

Hardness test: The test was performed by a hardness tester (Erweka) on 10 PAR tablets for each brand (Gundogan *et al.,* 2008).

Friability Test: 10 PAR tablets were weighed precisely on an analytical balance (initial weight) and placed into the friabilator (Erweka) for 4 minutes at 25 rpm. Then, the tablets were weighed again to calculate the weight difference. Then, the tablets were weighed again to calculate the weight difference and percentage friability was calculated (Comoglu and Gonul 2005). (2005).

Weight variation: Deviation values in the weight of PAR tablets were determined according to United States Pharmacopeia (USP) 32, using the Shimadzu analytical balance (Mathur *et al.,* 2015).

Disintegration test: Disintegration that is the preliminary stage of drug dissolution is a process of breaking the tablet into granules and is defined as the part of in vitro and in vivo correlation. Disintegration time of PAR tablets was determined in distilled water at 37 °C by USP disintegration apparatus (Erweka) (Gundogan *et al.,* 2008).

Content uniformity test: The amount of PAR in each tablet from different brands was detected by using UV spectrophotometry. A standard solution was prepared by using pure PAR and 0.1 N HCl. Sample solutions were prepared using 20 tablets from each brand in 0.1 N HCl. The absorbance values of the prepared solutions were detected spectrophotometrically at 243 nm (Shimadzu 1202 UV-VIS spectrophotometer). The PAR amount in each tablet was calculated using the calibration equation previously determined by Sahle *et al.* (2012). The experiment was conducted as triplicated.

Dissolution tests: Dissolution tests on PAR tablets were performed using USP paddle

method at 50 rpm. 900 ml of 0.1 N HCl solution (at 37 ± 0.5°C) was used as dissolution medium. The samples were withdrawn at specific time intervals and assayed using Shimadzu 1202 UV-VIS spectrophotometer at 243 nm. The percentage of cumulative PAR amounts released from the tablets were calculated. The experiment was conducted as triplicated and cumulative PAR release graph was plotted versus time for each brand of PAR tablet.

Comparison of the dissolution profiles

In this study, difference (*f1*) and similarity (*f2*) factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These factors are useful to calculate the difference between percent drug dissolved per unit time for a test and a reference product. The difference ($f1$) and similarity ($f2$) factors are defined by the following equations (Comoglu and Gonul, 2015).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

RESULTS AND DISCUSSION

Results of assay of paracetamol

The calibration line of paracetamol is shown in Figure 1. Analytical method validation parameters for the determination of paracetamol by UV spectrophotometric method are given in Table 1.

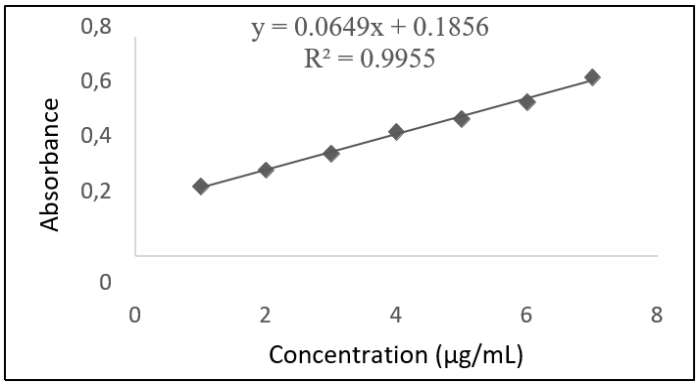

Figure 1: Calibration line of paracetamol.

Table 1: Analytical method validation parameters for the assay of PAR.

Parameters	Results
Linearity range (µg/mL)	1-7
Slope (m)	0.0649
% RSD* of m	0.46
SE* of m	0.03
Intercept (n)	0.1856
RSD* of n (%)	6.5
SE* of n	0.006
Determination coefficient (r^2)	0.995
LOD (µg/mL)	0.0198
LOQ (µg/mL)	0.06
% RSD* for precision	1.81
RSD* for accuracy	0.27

*RSD: Relative Standard Deviation
*SE: Standard Error

Quality control test results

The results obtained from the quality control tests are as shown in Table 2.

Table 2: Quality control test parameters.

PAR tablets	Weight (g) (Mean±SD)	Diameter (cm)	Thickness (cm)	Hardness (kg/cm^2) (Mean±SD)	Friability (%) (Mean±SD)	Disintegration time (min.sec) (Mean±SD)	Content uniformity (%) (Mean±SD)
PAR A	0.563 ± 0.010	1.270	0.397	12.85 ± 1.90	0.366 ± 0.02	1.10 ± 0.0001	99.35 ± 0.52
PAR B	0.452 ± 0.078	1.290	0.523	21.5 ± 3.54	0.316 ± 0.04	2.45 ± 0.0001	98.43 ± 0.43
PAR C	0.664 ± 0.023	0.741	0.520	34.37 ± 2.09	0.222 ± 0.001	1.40 ± 0.0003	95.65 ± 0.48

*SD: Standard Deviation

The results of content uniformity of three different brands of PAR tablets show that amount of PAR drug available in all formulations are between in the range of 90-110%. According to USP 32 PAR tablet criteria, content uniformity of all of the PAR tablets were determined to be optimum.

Tablets require a certain amount of hardness to withstand mechanical strength of handling during manufacturing and packaging. On the other hand, the dissolution time and disintegration of the tablets are two parameters related to their hardness. According to pharmacopoeias, the suggested minimum value for tablet hardness is 4 kg. All PAR tablets included in the study fulfilled the hardness criteria. The percentage friability value that is directly affected by the hardness in tablets should be less than 1. Accordingly, the percentage friability of all tested PAR tablets were found to be less than 1. The difference factor ($f1$) is comparative to the average difference among the three profiles, whereas similarity factor ($f2$) is inversely proportional to the average squared difference among the three profiles with emphasis on the larger difference among the time points. The evaluation of these factors are suggested for the comparison of dissolution profile by FDA

guideline. According to guideline, $f1$ values should be between 0-15, and $f2$ should be vary between 50 -100. The calculated are shown in Table 3.

Table 3: Difference ($f1$) and similarity ($f2$) factors for reference (PAR A) versus test products (PAR B and C).

	PAR B	PAR C
***f*1 values**	6.50	5.93
***f*2 values**	77.63	79.41

For tests (PAR B and PAR C) versus reference (PAR A), $f1$ values revealed that the dissolution profiles of tests were similar to the profile of the reference. Releasing the active material in an expected time explain the basic therapeutic effect of the dosage form. According to USP 32, conventional PAR tablets have to release at least 80% of the labelled amount in 30 minutes. As can be seen in dissolution profiles (Figure 2), all PAR tablets release the active drug as suggested by USP 32.

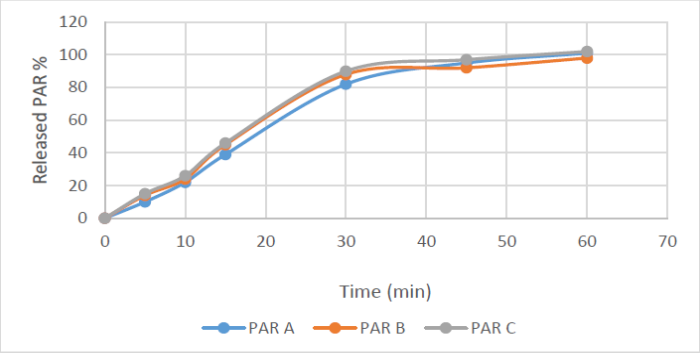

Figure 2: Dissolution profiles of conventional paracetamol tablets.

Zero order, first order and Hixson-Crowell kinetics were applied to the dissolution data of conventional PAR tablets and the results are shown in Table 4. As seen from the table, first order kinetic gives the highest determination constant (R^2).

Table 4: Kinetic parameter results of dissolution data for conventional PAR tablets.

		PAR A	PAR B	PAR C
Zero Order Kinetic	RMS	173.767	423.543	244.229
	k0	0.088	0.283	0.177
	R^2	0.821	0.711	0.638
First Order Kinetic	RMS	1.305	0.915	0.525
	k1	0.066	0.169	0.131
	R^2	0.992	0.997	0.994
Hixson-Crowell	RMS	3.692	4.688	4.527
	k4	0.095	0.099	0.070
	R^2	0.908	0.734	0.806

RMS: Residual Mean Square
k_0: Rate constant of the investigated kinetic
R^2: Determination coefficient

CONCLUSION

As a conclusion, three conventional PAR tablets that were bought from North Cyprus drug market, fulfill all the USP 32 pharmacopeia standards. When the release kinetics of the PAR tablets (PAR A, B and C) were examined, it was detected that the most appropriate kinetics is the first-degree release. This release kinetics is an expected kinetic model for immediate release tablet formulations. According to the results of the study, it can be concluded that all examined PAR tablets display immediate release and are compatible with the data provided by their manufacturers.

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Microwave assisted synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate via manganese(III) acetate mediated radical cyclization reaction

Negar Khezri, E. Vildan Burgaz*

Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

Abstract

"Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate" is dihydro-furan-fused monocyclic heterocycles containing dihydrofurocoumarin framework. Compounds that include these core structures are especially important for drug discovery.

Manganese(III) acetate has been used as an efficient oxidizing agent for the preparation of "ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate" by the multi-steps reaction of ethyl 3,3-bis(4-fluorophenyl)acrylate and 4-hydroxycoumarin under microwave irradiation to perform faster heating times, significantly reduce reaction times, and the efficient solubilization of manganese(III) acetate in acetic acid. The cyclization reaction was achieved using reactivity of the carbonyl group within the molecule.

Keywords

Dihydrofuran, manganese(III) acetate, microwave irradiation, radical cyclization reaction.

Article History

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***Corresponding author:** E. Vildan Burgaz **email:** vildan.burgaz@emu.edu.tr

Research Article:

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INTRODUCTION

Heterocycles are generally important in the field of medicinal chemistry for drug discovery. Drugs containing heterocycles are used in a number of therapies, including those for cancer, ulcer, metabolic and cardiovascular diseases, infections, and central nervous system (CNS)-related illnesses. Furan, thiophene, and pyrrole are among the most popular five-membered heterocycles with a single heteroatom and are of great importance for the discovery of novel drugs (Riddell, 1980; Li, 2013).

The salts of transition metal (Mn^{3+}, Co^{3+}, Cu^{2+}, Ce^{4+}) that are capable of transferring single electrons are known to produce α-carbon radicals with enolizable functional groups, which can generate new carbon-carbon bonds when added to unsaturated systems (Iqbal *et al.*, 1994; Ozgur *et al.*, 2019; Akpinar *et al.*, 2018; Aslan *et al.*, 2014; Yilmaz *et al.*, 2008). Manganese(III) acetate, cerium(IV) ammonium nitrate are the most commonly-used types of these metal salts (Bar *et al.*, 2001; Kajikawa *et al.*, 2001).

Reaction mixtures that include manganese(III) acetate are known as suitable candidates for microwave irradiation, despite being considered in a limited number of publications (Mu *et al.,* 2005). Microwave irradiation could potentially facilitate the rapid heating, efficient solubilization, and significantly reduce the reaction time of $Mn(OAc)_3$ in acetic acid (Curti *et al.*, 2009). Consequently, it has widely been used as a controllable, yet powerful method of heating organic reactions. Microwave reactions typically result in higher yields, better selectivities, and shorter reaction times (Larhed and Hallberg, 2001; Larhed *et al.,* 2002; Wathey, 2002; Kappe, 2002; Kappe and Stadler, 2005; Eycken, 2006; Kappe *et al.,* 2009).

MATERIALS AND METHODS

Triethyl phosphonoacetate **(1)**, bis (4-fluorophenyl) methanone **(2)** and 4-hydroxycoumarin **(4)** were obtained from Sigma Aldrich. Because the purity of these compounds was more than % 99, no other purification step was applied.

Synthesis of starting material: "Ethyl 3,3-bis(4-fluorophenyl) acrylate (3)"

As shown in Figure 1, conjugated ester **(3)** was synthesized by using triethyl phosphonoacetate **(1)** and bis (4-fluorophenyl) methanone **(2)** in tetrahydrofuran (THF) and sodium hydride (NaH) (Pinna *et al.*, 2003; Burgaz *et al.*, 2011).

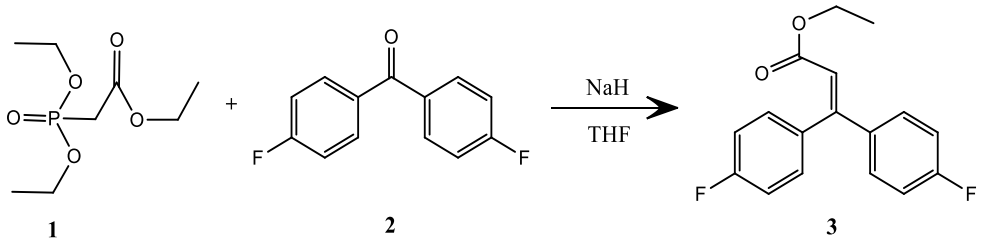

Figure 1: General mechanism for the synthesis of ethyl 3, 3-bis (4-fluorophenyl) acrylate.

A solution of triethyl phosphonoacetate (120 mmol, 21 mL) in THF (50 mL) was added dropwise to a solution of NaH (120 mmol, 60% dispersion in mineral oil, 4.8 g) in THF (200 mL) within ice bath. Half an hour later, the suitable ketone (100 mmol) was added to the reaction mixture and was stirred for 2-3 days at room temperature. When the reaction was finished, THF was subjected to decreased pressure and vaporized. The remainder was extracted with diethyl ether. Afterwards, the organic layer was dried by sodium sulfate and vaporized. The crude product was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5:1).

Synthesis of "ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate"

General mechanism for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate is shown in Figure 2.

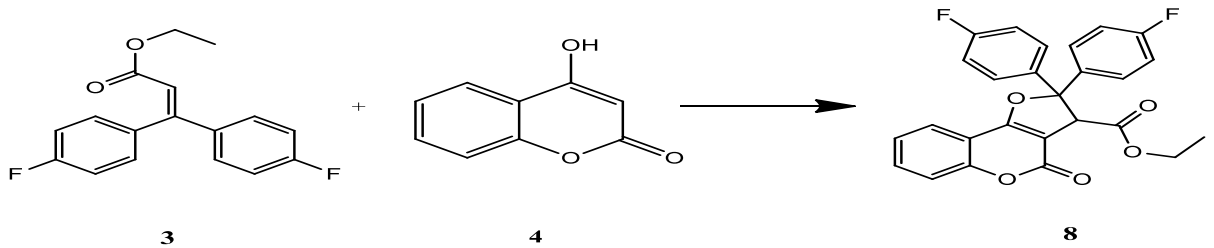

Figure 2: General mechanism for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate.

4-hydroxycoumarin **(4)** (1 mmol, 0.163 g) and subsequently ethyl 3,3-bis(4-fluorophenyl) acrylate **(3)** (0.5 mmol, 0.145 g) were added to a test tube containing manganese(III) acetate dihydrate (3 mmol, 0.804 g) and mixed well. Acetic acid was added into the tube and the mixture was poured into a microwave reaction vial with a magnet inside the vessel for mechanical stirring. The vial was placed inside the microwave machine.

Optimization of the reaction

In order to maximize performance, optimization was carried out. To produce the higher amount of the product with the minimum waste, the percentage yield is

extremely remarkable and is useful as an indicator that the strategy is productive and accurate. Therefore, various factors such as temperature, time, pressure and concentrations were arranged to obtain the highest-yield of the product. Finally, the microwave machine was adjusted at 80˚C for 5 minutes. After the reaction was completed, water was added and extraction was done with chloroform. The organic layer was dried over sodium sulfate and then evaporated. The product was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3:1) to give the product ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate **(8)** (0.124 g, 55 %).

Mechanism of reaction

In the synthesis of the product **(8)**, the very early reaction is the generation of the radical form of 4-hydroxycoumarin **(5)** due to the addition of MAH (Figure 3). The unpaired electrons positioned on secondary radical 4-hydroxycoumarin **(5)** make the compound highly reactive. Thus, the π-bond of 2,3-diene chain belonging to ethyl 3,3-bis(4-fluorophenyl)acrylate **(3)** is captured by the radical during the addition of acetic acid, being broken down forming benzyl radical (because benzyl radical is more stable than secondary radical). Then, the produced intermediate **(6)** is converted to the enol form **(7)** which subsequently undergoes intramolecular reaction with the attack of the oxygen atom on the enol group to the carbocation to form the cyclized product **(8)** (Figure 4).

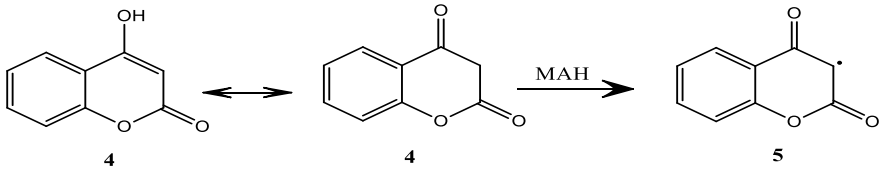

Figure 3: Mechanism of reaction for the radical generation of 4-hydroxycoumarin.

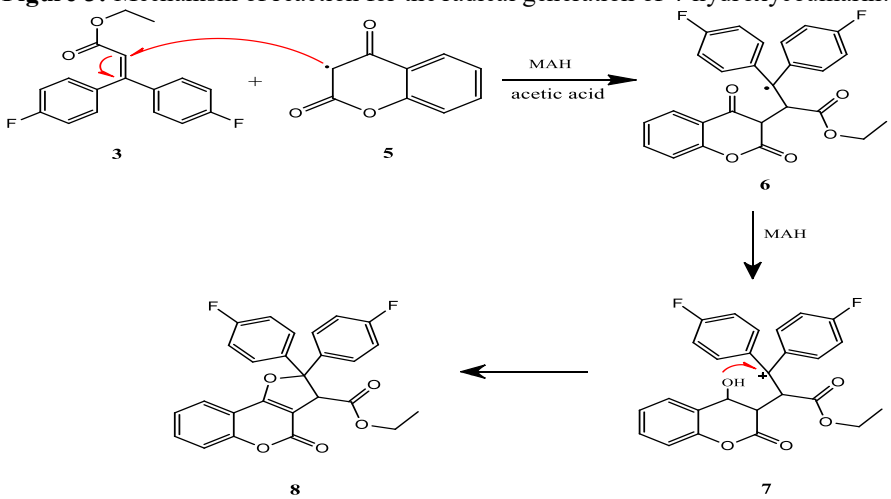

Figure 4: Mechanism of reaction for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate.

RESULTS AND DISCUSSION

In this study, free radical cyclization reaction method was developed under the assistance of microwave irradiation for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate **(8)**. Microwave-assisted heating results in include faster heating times, significantly reduced reaction times, and the efficient solubilization of utilized reagents. Therefore, the method has found a number of different technological applications in drug discovery and medicinal chemistry.

Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate was synthesized successfully. ^{1}H-NMR and ^{13}C-NMR results show that protons and carbon atoms involved in this compound are completely comparable to the structure of product that was expected according to the mechanism of reaction.

Ethyl 3,3-bis(4-fluorophenyl)acrylate (3) : ^{1}H-NMR (CDCl3), δ (ppm): 1.15 (3H, t, J = 7.2 Hz, CH_3), 4.07 (2H, q, J = 7.2 Hz, CH_2), 6.30 (1H, s, alkene H), 7.00- 7.05 (2H, m, ArH), 7.07- 7.10 (2H, m, ArH), 7.16- 7.19 (2H, m, ArH), 7.21- 7.28 (2H, m, ArH).

Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate (8) : **^{1}H-NMR** (CDCl3), δ (ppm): 0.91 (3H, t, J = 7.2 Hz, CH_3), 3.68-3.82 (2H, m, CH_2), 4.96 (1H, t), 6.98 (2H, td, J = 8.4 and 2.0 Hz, ArH), 7.14 (2H, td, J = 8.4 and 2.0 Hz, ArH), 7.22-7.26 (2H, m, ArH), 7.37 (1H, td, J = 8.0 and 0.8 Hz, ArH), 7.42 (1H, d, J = 8.8 Hz, ArH), 7.64 (1H, td, J = 8.8 and 2.0 Hz, ArH), 7.69 (2H, m, ArH), 7.86 (1H, dd, J = 7.6 and 1.6 Hz, ArH). **^{13}C-NMR** ($CDCl_3$), δ (ppm): 13.86 (CH_3), 57.19, 61.92 (CH_2), 98.81, 101.88, 112.29, 115.02, 115.23, 115.88, 116.10, 117.53, 123.21, 124.49, 128.53, 129.01, 133.50, 135.33, 138.12, 155.68, 159.54, 161.62, 161.79, 164.10, 164.28 (C4), 166.10 (C=O), 168.30 (C=O).

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A study on life expectancy in Turkey

Canan Gulcan

Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

Abstract

Life expectancy, in general, is one of the crucial determinants of a country's health status. This is particularly valid for the countries where industrialization has been improving. Turkey is one of the leading countries within this category, and there are limited number of studies about causal relationship between life expectancy and its determinants. Therefore, the aim of this study is to explore causal relationship between life expectancy and its determinants during the period of 1975-2014. In order to analyze the causal relationship between life expectancy at birth and its economic and environmental determinants; gross domestic product per capita, food production index, CO_2 emissions (kt), and urbanization were identified as factors influencing life expectancy at birth. Regarding the data obtained, the causal relationship between life expectancy and its determinants was investigated employing the Granger causality test based on VECM for a sample of Turkey. The results indicated that although the variables used in the model have had a long run relationship (i.e., GDP per capita, food production index, CO_2 (kt), and urbanization), the urbanization is the only Granger cause of life expectancy at birth for Turkey.

Keywords

Cointegration, Granger causality life expectancy, urbanization.

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***Corresponding author:** Canan Gulcan **email**: canan.gulcan@emu.edu.tr

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INTRODUCTION

Life expectancy is the crucial determinant for a country's health status especially for those countries where industrialization improves. As shown in Figure 1, while the life expectancy at birth in the world was 60,987 in 1975, this number increased by 18.68% to 71.7 in 2014. Similarly, in Turkey, life expectancy at birth was 56.1 in 1975, and it reached to 77.1 in 2014 as shown in Figure 2 (OECD, 2019). The determinants of this increase in life expectancy at birth for different countries have always attracted curiosity from different perspectives including economic, health, social, and environmental conditions.

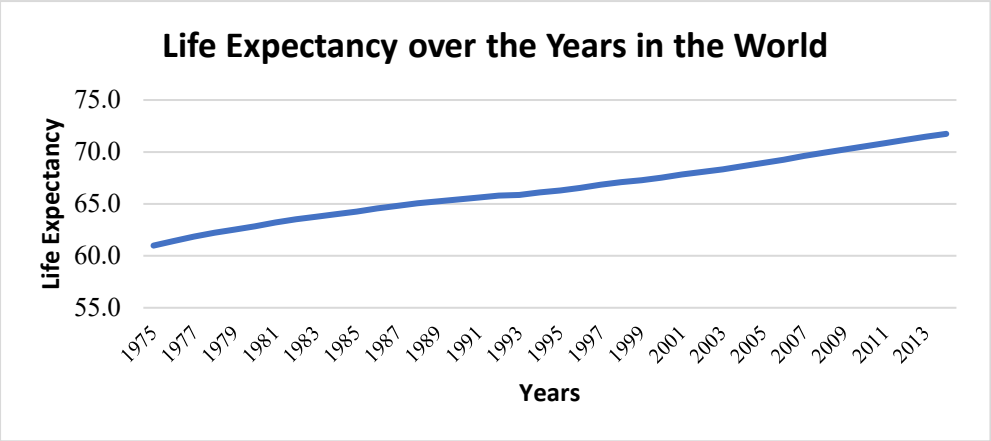

Figure 1: Life expectancy over the years in the world (OECD, 2019).

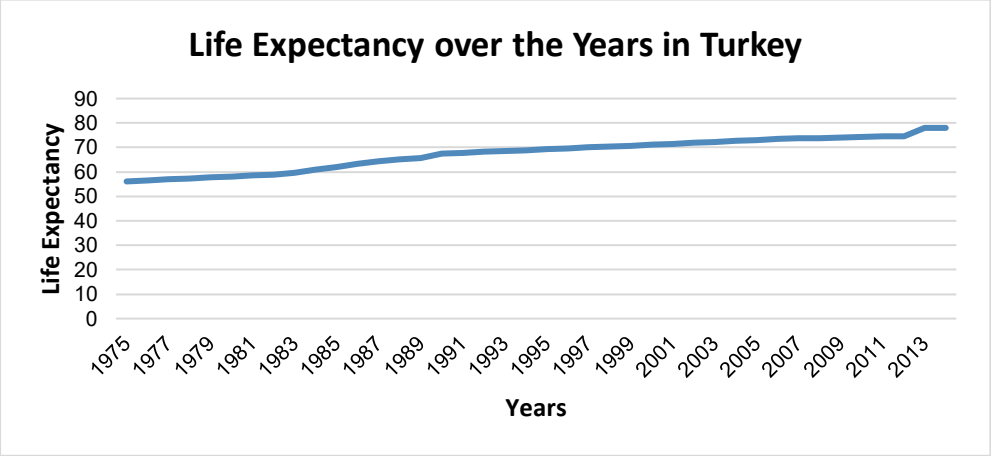

Figure 2: Life expectancy over the years in Turkey (OECD, 2019).

Life expectancy has significant implications on individual and human behavior which affects fertility behavior, human capital and economic growth (Coile *et al.,* 2002; Zhang *et al.,* 2001). There are numerous studies about the determinants of life expectancy from different perspectives (Coile *et al.,* 2002; Zhang *et al.,* 2001; Husain, 2002; Taban, 2006; Shaw *et al.,* 2005). So far, the results obtained regarding

these studies indicated that income, education, illiteracy, urbanization, health expenditures on health care, number of doctors, availability of safe drinking water, nutritional conditions, geographical location, developments in health technology, income inequality, and employment have had statistically significant effects on this increase in life expectancy (Messias, 2003; Taban, 2006; Shaw *et al.,* 2005; Rogot *et al.,* 1992).

Among the economic determinants, income is one of the most frequently investigated factors on life expectancy (Anand and Ravallion, 1993; Grosse and Auffrey, 1989; Kakwani, 1993; Preston, 1980; Rogers and Wofford, 1989; Wilkinson, 1992). In general, many research studies found out a positive relationship (Rogot *et al.,* 1992; Rogers and Wofford, 1989). In other words, the more the income, the higher the average number of life expectancy. According to Preston (1980), the income has an indirect relationship with life expectancy at birth, since it affects the quality of units influencing the health status such as access to food, clean water, education, and health services (Preston, 1980). Messias (2003), on the other hand, investigated the relationship between income inequality and life expectancy in Brazil using simple linear regression, and, accordingly, it has been found that there was a significant and negative relation between them (Messias, 2003). This study showed that an increase by 0.01 in income inequality caused a decrease by 0.6 years in life expectancy (Messias, 2003).

Another economic determinant found to be associated with life expectancy is employment. It has been stated that there exists differences between the life expectancies of employed and unemployed individuals. Therefore, the findings pointed out a positive and significant association between life expectancy and employment (Rogot *et al.,* 1992).

Health spending which measures goods and services related to the health is another determinant for the life expectancy from the economic perspective. A study conducted in Canada investigated the health spending and its outcomes related to health using 15 years of data from the provinces of the country (Crémieux *et al.,* 1999). Accordingly, a positive relationship between health spending and life expectancy was found, that was pointing out a decrease in health spending leading to a decrease in life expectancy. Mohan and Mirmirani (2007) found a positive relationship between life expectancy and health spending for The Organisation for Economic Co-operation and Development (OECD) countries as well (Mohan and Mirmirani, 2007).

Food availability is another concern for life expectancy. The findings supported that an

increase by 1% in food availability led to an increase in life expectancy by 0.13% (Halicioglu, 2011). It has been suggested that economic policies should be implemented to rise spending in health care and food availability (Halicioglu, 2011).

Beside economical determinants, there are also social factors acting on life expectancy. Among them, illiteracy rate is one of the important factors. It has been previously shown that there was a statistically significant and negative relationship between illiteracy and life expectancy (Messias, 2003). Accordingly, among the variables including illiteracy rate, employment and income inequality the strongest factor was found to be illiteracy rateAas the illiteracy rate increases by 10 units, life expectancy decreases by 2.2 years.

Urbanization is one of the environmental factors that affects life expectancy. The work of Halicioglu (2011) pointed out the impact of urbanization, and it was found a negative effect on life expectancy at birth. However, other studies investigated the determinants of life expectancy found out a positive effect of urbanization (Bayati *et al.,* 2013; Delavari *et al.,* 2016; Fayissa and Gutema, 2005; Kabir, 2008; Baltagi *et al.,* 2012; Thornton, 2002). Accordingly, Thornton (2002) stated that the more the urbanization, the less the death rates in the United States of America.

Another determinant factor from environmental perspective for life expectancy at birth is CO_2 emission (kt) including the consumption of solid, gas fuels, and liquid. Previous studies found both positive and negative relationship between CO_2 emission (kt) and life expectancy at birth (Fayissa and Gutema, 2005; Baltagi *et al.,* 2012; Amjad and Ahmad, 2014).

The present study aimed to analyze the causal relationship between life expectancy at birth and some of its economic and environmental determinants (i.e., gross domestic product per capita, food production index, CO_2 emission (kt), and urbanization) during the period of 1975-2014 in Turkey.

METHODS

It has been planned to examine the causal association between life expectancy and its economic (gross domestic product per capita, and food production index), and environmental determinants (CO_2 and urbanization) using Granger causality test for Turkey between 1975 and 2014. The data for life expectancy was obtained from OECD database, and the data for other variables (i.e., gross domestic per capita,

food production index, CO_2, urbanization) was obtained from the World Bank database. Each variable in the model is in its natural logarithmic form. All analyses were conducted using Eviews 9 econometric program.

The model was specified as below:

$lle = \alpha_0 + \alpha_1 lgdppc + \alpha_2 lfpi + \alpha_3 lurb + \alpha_4 lCo_2 + \mu_t$

where, lle is the natural log of life expectancy at birth, lgdppc is the natural log of gross domestic product per capita (constant 2010 US$), lfpi is the natural log of food production index, lurb is the natural log of urbanization, lCo_2 is the natural log of carbon dioxide emission (kt), and μ_t is the error term in the model.

RESULTS

Descriptive statistics

The annual data between 1975 and 2014 for Turkey was obtained from the World Bank and the OECD databases. The summary of descriptive statistics associated with Turkey is presented in Table 1.

Table 1: Descriptive statistics of the variables.

	le	Gdppc ($)	Fpi (%)	Urb (%)	Co_2 (%)
Mean	67.485	7,750.696	85.25175	3.1985	179164.4
median	69.100	7,329.363	82.39000	2.4658	165555.9
Maximum	78.000	13,277.76	129.7300	6.2018	345981.5
Minimum	56.100	4,967.398	52.27000	2.0576	65697.97
Std.dev.	6.5407	2,337.810	20.82720	1.2310	83696.53

le: Life expectancy; gdppc: Gross domestic product per capita; fpi: Food production index; urb: Urbanization; Co_2: Carbondioxide emission.

Accordingly, the mean of the life expectancy at birth was 67.485, the minimum and maximum values during the period 1975-2014 were 56.1 and 78.0, respectively. Additionally, the mean of gross domestic product per capita was $7,751, and it ranged from $4,967 to $13,278. The means of the food production index, urbanization, and CO_2 emission (kt) were 85.25%, 3.19%, and 179164.4 (kt), respectively.

Testing for stationarity

In order to employ the causality test, it is compulsory to examine stationarity of time series data, since estimates with non-stationary data often causes spurious regression (Gujarati, 1995). The common tests in order to check the existence of unit root in the series are Augmented Dickey Fuller (ADF), Phillips Perron (PP), Kwiatkowski–Phillips–Schmidt–Shin KPSS), and Ziwot Andrews tests. However, for this study, Augmented Dickey Fuller, and Phillips Perron tests were employed to check stationarity in the series, respectively

(Dickey and Fuller, 1981; Phillips and Perron, 1988). The results are shown in Table 2. Hence, the findings of the ADF and PP tests showed that life expectancy at birth, GDP per capita (constant US$), food production index, urbanization (% of total population), and CO_2 emission (kt) are not stationary at level, so we failed to reject null hypothesis indicating that the series has unit root. On the other hand, after taking the first differences of the series, they became stationary providing that all the variables used in the model are integrated order (1).

Table 2: Unit root test results.

	Level		1st difference	
ADF	Probabilities		Probabilities	
Series	constant	trend	constant	trend
lle	-1.31	-1.19	-5.82***	-5.93***
lgdppc	0.71	-2.08	-6.05***	-6.37***
lfpi	-0.20	-2.44	-12.39***	-12.22***
lurb	-1.40	-2.50	-4.18***	-8.26***
lCo_2	-0.95	-2.40	-2.40***	-6.20***
	Level		1st difference	
PP	Probabilities		Probabilities	
Series	constant	trend	constant	Trend
lle	-1.25	-1.31	-5.91***	-5.97***
lgdppc	0.81	-2.15	-6.06***	-6.39***
lfpi	-0.85	-3.86	-3.86***	-12.86***
lurb	-1.83	-1.30	-4.18***	-4.12***
lCo_2	-1.09	-2.40	-6.37***	-6.26***

***denotes 0.01 significance level.

The results of the unit root test provide us to employ vector auto-regressive (VAR) and investigate the co-integration relationship among each variable. In order to make accurate predictions, optimal lag length was identified, and the results are shown in Table 3.

Table 3: Lag length selection.

Lag	LogL	LR	FPE	AIC	SC	HQ
0	219.0402	NA	4.71e	-11.89112	-11.67119	-11.81436
1	388.8488	283.0143*	1.54e-15*	-19.93604*	-18.61645*	-.19.47547*
2	410.8594	30.57030	1.97e-15	-19.76997	-17.35070	-18.92558
3	432.9664	24.56327	2.92e-15	-19.60924	-16.09031	-18.38104
4	461.9409	24.14541	3.90e-15	-19.83005	-15.21145	-18.21803

*indicates lag order selected by the criterion
LR: sequential modified LR test statistic (each test at 5% level); FPE: Final prediction error; AIC: Akaike information criterion; SC: Schwarz information criterion; HQ: Hannan-Quinn information criterion.

According to the Table 3, it has been found that Sequential Modified LR test (LR), Final Prediction Error (FPE), Akaike Information Criterion (AIC), Schwarz Information Criterion (SC), and Hannan-Quinn Information Criterion (HQ) suggested lag 1 for the model.

Cointegration test

A cointegration test allows identifying the existence of long run relationship between series. The compulsory condition of cointegration is that the variables included

must be integrated at the same order (Johansen, 1992). The most common tests for cointegration testing are Johansen Cointegration test (Johansen, 1992), Engle-Granger two step methods (Engle *et al*., 1986), and Phillips Ouliaris test (Phillips and Ouliaris, 1988). In the present study, Johansen cointegration test was conducted to check the long run relationship between included variables.

The results of cointegration test are shown in Table 4. Accordingly, the findings showed that Trace tests, and max Eigen indicated 3, and 1 co-integrating equations at 10 percent significance level, respectively.

Table 4: Johansen cointegration test.

Hypotheses	Eigenvalue	Trace Statistic	Critical Value	Probabilities
H_0: r=0 H_1: r≥1	0.576723	87.77710	65.81970	0.0010***
H_0: r≤1 H_1: r≥2	0.470837	55.10741	47.49359	0.0090***
H_0 : r≤2 H_1: r≥3	0.387851	30.92199	27.06695	0.0370**
H_0: r≤3 H_1: r≥4	0.271287	12.27235	13.42878	0.1443
H_0: r≤4 H_1: r≥5	0.006461	0.246305	2.705545	0.6197
Hypotheses	Eigenvalue	Max-Eigen Statistic	Critical Value	Probabilities
H_0: r=0 H_1: r=1	0.576723	32.66969	31.23922	0.0691*
H_0: r≤1 H_1: r=2	0.470837	24.18542	25.12408	0.1284
H_0: r≤2 H_1: r=3	0.387851	18.64963	18.89282	0.1074
H_0: r≤4	0.271287	12.02605	12.29652	0.1097
H_0: r≤5	0.006461	0.246305	2.705545	0.6197

***denotes 0.01 significance level; **denotes 0.05 significance level; *denotes 0.10 significance level.

Additionally, according to the results of the normalized co-integration test shown in Table 5, gross domestic product per capita, and urbanization significantly affect life expectancy at birth negatively in the long run. On the other hand, the results showed that food production index and CO_2 emission (kt) also significantly, affect life expectancy at birth positively in the long run. Finally, it has been concluded that we could employ the Block exogeneity Wald tests based on vector error correction model (VECM) to determine the direction of causality due to the existence of co-integration among variables in the long run.

Table 5: Normalized cointegrating coefficients.

lle	lgdppc	lfpi	lurb	lCo_2
1.000000	0.327965	-0.341322	0.110738	-0.167716
	(0.04354)	(0.08344)	(0.01440)	(0.04266)

Lle: Natural log of life expectancy at birth; lgdppc:the natural log of gross domestic product per capita; lfpi: Natural log of food production index; lCo_2: Natural log of carbondiaoxide emission.

The Granger causality/block exogeneity wald test

Following the co-integration test, a causal relationship between life expectancy and its determinants were examined using the block exogeneity Wald test based on VECM to test on lagged explanatory variables, and the results of Granger block exogeneity are shown in Table 6. Accordingly, the findings have pointed out

that there is a causal relationship between life expectancy and urbanization with a probability of 0.0409 at 5% significance level. On the other hand, other variables (i.e., gross domestic product per capita, food production index, and Co_2 emission (kt)) were found to have no causal effect on life expectancy at birth at 0.01, 0.05 or 0.10 significance levels. Other variables which have causal relationship with each other are gdp per capita and fpi with a probability of 0.0495, Co_2 and gdp per capita with a probability of 0.0810 at 5%, and 10% significance levels, respectively.

Table 6: The Granger causality/block exogeneity wald test.

Dependent variable D(lle)			
Independent Variables:	Chi-sq	df	Prob.
D(lgdp)	0.214375	1	0.6434
D(lfpi)	1.410477	1	0.2350
D(lurb)	4.179525	1	0.0409**
D(lCo_2)	0.153621	1	0.6951
Dependent variable: D(lGDPPC)			
Independent Variables:	Chi-sq	df	Prob.
D(lle)	0.066036	1	0.3674
D(lfpi)	1.564407	1	0.0495**
D(lurb)	0.254774	1	0.4007
D(lCo_2)	1.781793	1	0.1871
Dependent variable: D(lfpi)			
Independent Variables:	Chi-sq	df	Prob.
D(lle)	0.066036	1	0.7972
D(lgdppc)	1.564407	1	0.2110
D(lurb)	0.254774	1	0.6137
D(lCo_2)	1.781793	1	0.1819
Dependent variable: D(lurb)			
Independent Variables:	Chi-sq	df	Prob.
D(lle)	0.606858	1	0.4360
D(lgdppc)	0.151539	1	0.6971
D(lfpi)	2.16413	1	0.1411
D(lCo_2)	0.301960	1	0.5827
Dependent variable: D(lco2)			
Independent Variables:	Chi-sq	df	Prob.
D(lle)	2.285540	1	0.1306
D(lgdppc)	3.045021	1	0.0810*
D(lfpi)	0.173473	1	0.6770
D(lurb)	0.048297	1	0.8261

*denotes 0.10 significance level; **denotes 0.05 significance level.

DISCUSSION

In the current study, the causal relationship between life expectancy and its determinants were examined during the period 1975-2014 for Turkey. The determinants of life expectancy were classified as the economic and environmental perspectives. Gross domestic product per capita (constant US$) and food production index were included in the economical perspective, while urbanization (% of total population) and CO_2 emission (kt) were included in the

environmental perspective. All variables were examined using Johansen co-integration analysis, and Granger causality test based on VECM. The results of the analyses elicited a long run relationship between included variables in the model. However, only urbanization has a causal relationship with life expectancy, and has a negative effect on it. This result is in parallel to the finding of Halicioglu (2011) indicating that there is a negative relationship between life expectancy and urbanization in Turkey.

A rapid process of urbanization has been experienced in Turkey as a developing country. First of all, it is important to consider the fact that, such a rapid increase in the population in urban areas may also trigger certain disadvantages such as increased criminal rates, insufficient health services, elevated environmental pollution and limited access to clean usable water and. However, there are controversies to these expectations as well. For instance, a study in which the relationship between globalization and life expectancy in 92 countries was investigated, a positive effect of urbanization on life expectancy was found significant (Bergh and Nilsson, 2010). Within this work, urbanization has still been found as the most significant causal determinant for the life expectancy at birth in Turkey. This is in parallel with the study of Halicioglu (2011), which reported that theurbanization was found to possess a negative relationship with life expectancy at birth for the data analyzed during the period of 1965-2005 (Halicioglu, 2011). Therefore, this finding has still been found valid for the period of 1975-2014. It is important to note that this study is specific for Turkey, since there are other studies conducted in various regions of the world stating positive effect of urbanization on life expectancy. Thus, this implies that the effect of urbanization on life expectancy is region-dependent (i.e., changeable from one country to another). Regarding these both positive and negative effects of urbanization displayed previously in different studies, we have also expected to observe a causal relationship between life expectancy at birth and some other determinants used in the model for this study including CO_2 (kt), gross domestic product per capita (constant $), and food production index. However, no causal relationships were found between life expectancy and these determinants within this study for Turkey.

CONCLUSION

In this study, it was shown that Turkey has undergone a rapid urbanization during the period of 1975 to 2014. This resulted in a causal relationship with life expectancy at birth in negative manner. Policy makers should particularly focus on reducing the population intensity and increasing the accessibility to important sources related to health and hygiene. Since it has well been established that urbanization in Turkey grows up fast particularly through metropole cities, the economic investments should particularly focus on increasing the conditions of subsidiaries. From the general perspective, it was observed that the results are not comparable with other countries indicating that such determinants might have variable effects on life expectancy at birth. Therefore, the extrapolation of the results to other developed or developing countries is not possible currently.

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The genus *Persicaria* (Polygonaceae) in Turkey with a new taxon record

Mustafa Keskin[1*], Zeki Severoğlu[2]

[1] Marmara University, Science Institute, Istanbul, Turkey.

[2] Marmara University, Faculty of Arts and Sciences, Department of Biology, Istanbul, Turkey.

Abstract

Polygonaceae family mainly introduces itself with its stipules called ochrea. In Flora of Turkey, this family is indicated by eight genera that include *Atraphaxis*, *Pteropyrum*, *Calligonum*, *Rheum*, *Oxyria*, *Polygonum*, *Rumex*, *Emex*.

This article emphasizes that the genus *Polygonum* and *Persicaria* are utterly different from each other. Full names and distributions of the species of *Persicaria* in Turkey are given in detail. A new *Persicaria* taxon is also reported from Turkey. A diagnostic key for *Persicaria* has been created for the first time. The taxonomic status of the *Persicaria leblebicii* which was recently given as a new species, has been discussed.

Keywords

A new record, *Polygonum*, *Persicaria*, Polygonaceae, Turkey.

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***Corresponding author:** Mustafa Keskin **email**: trifolium@hotmail.com

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INTRODUCTION

The Polygonaceae family is a large family including 43 genera and up to 1,100 species worldwide (Brandbyge, 1993). This family mainly introduces itself with its stipules called ochrea.

In Flora of Turkey, the family is represented by eight genera including *Atraphaxis* L., *Pteropyrum* Jaub. & Spach, *Calligonum* L., *Rheum* L., *Oxyria* Hill., *Polygonum* L., *Rumex* L., *Emex* Neck. ex Campd. (Davis, 1967). The checklist published by Keskin (2012) has exactly accepted the classification in Flora of Turkey, but reported numerous species. *Reynoutria* Houtt. has been published as a new genus for in Turkey (Karaer *et al.,* 2020). In the article, the authors gave a new diagnostic key for the genus in Flora of Turkey. Leblebici (1990) has extensively studied the genus *Polygonum* and published a detailed list of species classified under the genus. Keskin (2009) introduced the new species of *Polygonum istanbulicum* M. Keskin and again published a list of the current species of *Polygonum*. Brandbyge (1993) examined the Polygonaceae family in two subfamilies and seven Tribus. This classification is summarized in table 1.

Table 1: Classification of Polygonaceae by Brandbyge (1993).

Scitienfitical Names	Descriptions
I. Subfam. Erigonuideae Meisner	Shrubs, perennial or annual herbs; leaves without well-defined stipules. Branching often sympodial, inflorescences cymose and specialized with an involucre composed of several to one single bract.
1. Tribe Eriogoneae Benth.	Involucres tubular or reduced to a series of 3 to many involucral bracts (15 genera).
2. Tribe Pteroslegieae Torr. & Gray	Involucre reduced to a single highly modified bisaccate, inflated, and reticulated bract, which encloses the mature achene (2 genera).
II. Subfam. Polygonoideae Jaretzky emend. Haraldson	Trees, shrubs, woody lianas, perennial or annual herbs; leaves with stipular sheats (ocreae), monopodial branching, inflorescences racemose with cymose partial inflorescences.
1. Tribe Triplareae Meisner	Trees or shrubs, often dioecious; perianth segments in two whorls of three; outer tepals often enlarged in fruit (5 genera).
2. Tribe Cocrolobeae Dumortier emend. Haraldson	Trees, shrubs, lianas, climbing or twining vines; perianth pentamerous often accrescent in fruit (5 genera).
3. Tribe Rumiceae Dumortier	Herbs, perennial or annual; perianth segments in two whorls of three (or two whorls of two) (4 genera).
4. Tribe Polygoneae emend. Haraldson	Shrubs, perennial or annual herbs; perianth pentamerous; outer tepals often winged, keeled or angular, smaller or larger than inner (8 genera).
5. Tribe Persicarieae Dumortier	Herbs, perennial or annual; perianth pentamerous: outer tepals rarely winged, keeled or angular, often smaller than inner or absent (3 genera).

As shown in Table 1, *Polygonum* and *Persicaria* are two different genera examined under different Tribus. Because there are fundamental differences in between the two genera, the classification suggested by Brandbyge is accepted.

MATERIALS AND METHODS

Examined materials were collected from the Anatolian part of Istanbul in the field trips by Mustafa Keskin during the Phd thesis (Systematical, Morphological, Chronological, Palynological, and Sociological Features of Polygonaceae Members of İstanbul Province). The collected specimen resembels *Persicaria lapathifolia* at the first glance but has been detected to be different from *Persicaria lapathifolia* mainly due to leaf features. According to the Flora of Turkey, identification was not possible. Investigation was carried out in numerous herbaria (E, EGE, ISTE, ISTF, ISTO, MUFE, ANK, GAZI, HUB, NGBB, VANF) and related articles Davis, 1967; Keskin 2009 and 2012; Leblebici, 1990; Webb and Chater, 1964; Snogerup and Snogerup, 1997; Rechinger and Schiman-Czeika, 1968; Komarov, 1936; Tan and Baytop, 1995) were carried out.

All collected specimens are housed in the Marmara University Faculty of Arts and Sciences Herbarium (MUFE).

RESULTS AND DISCUSSION

A New Record for Turkey; *Persicaria lapathifolia* (L.) Delarbre Fl. Auvergne ed. 2: 519 (1800). subsp. *brittingeri* (Opiz) Soják Preslia 46: 153 (1974). Figure 1, Map 4

Syn.: *Polygonum brittingeri* Opiz, Naturalientausch viii. 74. (1824).

Type: Dnus Britinger, legit prope Liuz in Australia, 1823.

Annual, 40-100 cm, branched from the base; reddish; low striate; loosely hairy. Ochrea 10-nerved, 15-22 mm, especially at the upper part of stem ciliate and hairy. Petiols 5-12 mm, hairy. Leaves broadly ovate-lanceolate, 25-50 x 10-22 mm; lanate at the bottom at least when young, green at upper but sparsely hairy; hirsute-ciliate at edge; blackish mauve spots present. Peduncles 5-25 mm, yellow glands present and hirsute. Inflorescences congested spike, 10-35 mm. Pedicels short and included in ochrea. Perianth pinkish 2-2,5 mm, covered with yellowish glands, veins present. Fruiting perianth enlarged, stillus exceeding tepals. Style 2. Stamens 5-6. Achenes shiny, sunken, 2 mm.

The locality of the examined taxon: İstanbul: Bostancı coast, near scaffolding, rocky openings, 1 m, 17.xi.2019, M.Keskin 7889!.

İstanbul: Tuzla, Akfırat, Against the Formula-1 race ground, meadows and old humid areas, 25.vi.2020, M.Keskin 8019!.

This taxon is distinguished by its type and form of pubescence making it different from the main taxon. Probably, its distribution is more than that is known.

Figure 1: *Persicaria lapathifolia*: subsp. *lapathifolia* (left), from İstanbul, M.Keskin 8004, and subsp. *britingeri* (right), from İstanbul, M.Keskin 7889.

The Examined Specimen for *Persicaria lapathifolia* subsp. *lapathifolia* from İstanbul

İstanbul: Büyükçekmece, Güzelceköy, in field, 11.ix.1970, A.Baytop, G.Ertem, N.Özocak, F.Öktem (ISTE 18479!).

İstanbul: Çatalca, Between Dursunköy and Boyalık, roadside, 90 m, 15.viii.2002, İ.Genç 1469 (ISTE 82277!).

İstanbul: Çatalca, Karaman stream, 28.vii.1967, A.Baytop, G.Atila (ISTE 11599!).

İstanbul: Çekmeköy, entrance to the village of Hüseyinli, 7 m, N 41° 07' 07,5" ve 29° 17, 58,8", 11.vii.2020, M.Keskin 8032!

İstanbul: Küçükçekmece, Levazım-Maliye school, Special Education Center and Rest camp, 18.viii.1986, K.Ergezen (ISTE 57213!).

İstanbul: Maltepe, Başıbüyük district, the forest of Süreyyapaşa Hospital, wet area, 1.xii.2019, M.Keskin 7897!.

İstanbul: Maltepe, Büyükbakkalköy, 26. viii.1950, T.Baytop (ISTE 3782!).

İstanbul: Pendik, Akfırat beldesi, Formula-1 race area, creek circumference, 26.xii.2004, M.Keskin 3625!.

İstanbul: Pendik, Aydos mountain, 17.viii.1950, A.Berk, T.Baytop (ISTE 3783!).

İstanbul: Sancaktepe, Paşaköy, D 020 motorway, roadside, highway, wide roadside opening and green spaces, E 41.025342 ve B 29.27239, 25.vi.2020, M.Keskin 8004!.

İstanbul: Sarıyer, Garipçe, Bird watching, N 41° 11’ 38,7’’ ve E 29° 04’ 34,4’’, in-forest, 18.ix.2016, M.Keskin 6505!, N.Özhatay, E.Özhatay.

İstanbul: Sarıyer, Kemerburgaz-Bahçeköy, 3.ix.1952, A.Berk, T.Baytop (ISTE 3133a!).

İstanbul: Şile, in-center, 24.viii.1952, A.Berk, T.Baytop (ISTE 3134!).

İstanbul: Şile, in-center, wet area,11.viii.1972, H.Argöksel (ISTE 23076!).

İstanbul: Şile, Ömerli creek, 24.viii.1952, A.Berk, T.Baytop (ISTE 3132!).

The New List of *Persicaria* species in Turkey

In Turkey Flora, twelve taxa have been reported to *Persicaria* so far. These taxa are listed below, and distribution maps specify where the taxa are present in Turkey. The distributions reported here are given to the land trips of the first author according to the samples diagnosed in different herbariums.

1. *P. amphibia* (L.) Delarbre, Fl. Auvergne ed. 2: 519 (1800) (Map 1) .
2. *P. decipiens* (R.Br.) K.L.Wilson, Telopea 3(2): 178 (1988) (Map 5) .
3. *P. hydropiper* (L.) Delarbre, Fl. Auvergne (Delarbre) ed. 2: 518(1800) (Map 3)
4. *P. lapathifolia* (L.) Delarbre Fl. Auvergne ed. 2: 519 (1800).
   subsp. *lapathifolia* (Map 4).
   subsp. *brittingeri* (Opiz) Soják Preslia 46: 153 (1974) (Map 4)
5. *P.leblebicii* (Yıld.) Raus, Willdenowia 44(2): 293 (2014) (Map 2).

Dissussion about *P. leblebicii* lalest taxonomic status:

This species have been published by Yildirimli (2011) and then was transferred to *Persicaria* by Raus (2014). The original article is supported by four photos. Although the first one was stated to belong to the living state of the plant, it belongs to the *P. lapathifolia*. The other three photos belong to the herbarium sample. The author distinguished it from *P. hydropiper* and *P. minor*. However, when the description and photos of the plant are examined, it is understood that the new species is primarily matched to *P. minor*. The only difference that can be seen is the achenes types, but when the literature information is examined, it is understood that there is a similar type of achenes in the *P. minor*. Small (1895) explained in his monograph on the North American *Polygonum*, which describes the achenes structure of this species as follows: “achenes lenticular, nearly 2 mm long broadly oblong conspicuously biconvex or triquetrous and narrowly ovoid-oblong, black, smooth and shining”. The feature is also mentioned with detailed drawings. *P. hydropiper* and *P. minor* can quickly become hybridized because they have similar morphological properties. For this reason, it is thought that the *P. leblebicii* may be either *Persicaria* × *ambigua* (Meisn.) B.Bock hybrid or *Persicaria minor* (Hudson) Opiz. The definitive diagnosis can be determined by examining the type of sample.

6. *P. maculosa* Gray, Nat. Arr. Brit. Pl. ii. 269 (1821) (Map 2).
7. *P. minor* (Hudson) Opiz, Seznam Rostlin Kvetney Cesk, 72 (1852) (Map 1).
8. *P. nepalensis* (Meisn.) H. Gross, Bot. Jahrb. Syst. 49: 277 (1913) (Map 5).
9. *P. orientalis* (L.) Spach, Hist. Nat. Vég. (Spach) 10: 537 (1841) (Map 3).

10. *P. perfoliata* (L.) H.Gross, Bot. Jahrb. Syst. 49(2): 275 (1913) (Map 6).

11. *P. thunbergii* (Siebold & Zucc.) H.Gross, Bot. Jahrb. Syst. 49(2): 275 (1913). (Map 6).

Idendification key of Turkish species

1. Perennials, up to 6 m tall; strongly rooting from nodes; usually in water, aquatic, rarely terrestrial or rarely subterrestrial; stamens longer than tepal *P. amphibia*

1. Annuals or perennials with at most 2.5 m tall; usually strict; rarely slightly rooting at the base (*P. thunbergii* and *P. decipiens*); terrestrial; stamens shorter than tepal or equal

2. Barbed plants

3. Stems more and recurved barbed; fruit metallic blue, spheroidal; not rooting at nodes *P. perfoliata*

3. Stems loosely barbed; fruit not metallic colour, trigonous; rooting at nodes *P. thunbergii*

2. No barbed plants

4. Inflorescences congested, capitate

5. Plants strict with 100-250 cm long; ochrea foliaceous flange at upper *P. orientale*

5. Plants slightly strict or somewhat recurved after middle; ochrea not foliaceous flange

6. Ochrea long ciliate, as long as tube; peduncles and leaves non glands *P. maculosa*

6. Ochrea short ciliate, shorter than the tube; peduncles and leaves yellow amber glands

7. Nods area whitish glandular trichomes; inflorescens capitate; nuts biconvex or trigonous *P. nepalensis*

7. Nods area glabrous or a few hairy; inflorescens oblong spike; nuts biconvex with subken in middle *P. lapathifolia*

a.Leaves lanate at the bottom at least when young; little longer than the width subsp. *britingeri*

b.Leaves glabrous or loosely hairy; longer than the width subsp. *lapathifolia*

4. Inflorescences loosely spike, easily seen its axis

8. Perennial plants with rhizomes or roots from nodes; tepals glabrous *P. decipiens*

8. Annuals; tepal glandular

9. Leaves oblong-lanceolate to ovate-lanceolate; stamen 4-6 *P. hydropiper*

9. Leaves linear or linear-lanceolate; stamen 6-8

10. Achenes lenticular, biconvex *P. minor*

10. Achenes trigonous *P. leblebicii*

Map 1. The Distribution map of *Persicaria amphibia* ● and *minör* ●

Map 2. The Distribution map of *Persicaria maculosa* ● and *leblebicii* ●

Map 3. The Distribution map of *Persicaria hydropiper* ● and *orientalis* ●

Map 4. The Distribution map of *Persicaria lapathifolia* subsp.*lapathifolia* ● and *britingeri* ●

Map 5. The Distribution map of *Persicaria decipiens* ● and *nepalensis* ●

Map 6. The Distribution map of *Persicaria perfoliata* ● and *thunbergii* ●

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Lamiaceae in Turkey: Additional taxa 2000-2019

F. Neriman Ozhatay[1], Sukran Kultur[2], Bahar Gurdal[2*]

[1]Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

[2]Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Botany, Istanbul, Turkey.

Abstract

The diversity of vascular plants of Turkey was documented in the Flora of Turkey and the Eastern Aegean Islands edited by Prof. Peter H. Davis and published in nine volumes between 1965 and 1985. The identification of additional taxa has necessitated the publication of the supplementary volumes to the Flora of Turkey volume 10 in 1988, and the second supplemental volume, vol. 11 edited by Turkish scientists published in 2000. Lamiaceae is cited in Flora of Turkey vol. 7 as 523 species, with 2 monotypic genera: *Dorystaechas hastata* Boiss. & Heldr. ex Benth. and *Pentapleura subulifera* Hand.-Mazz. and endemism percentage is 43.60. In the supplementary volumes: 20 species are added to vol. 10 (1988) and 31 more species are added to the vol. 11 (2000). In this present study, after publication of vol.11 additional taxa to the Flora of Turkey are given in a systematic order since the year 2000. In eighteen years the number of additional taxa is 78 of which 53 are new taxa for science and 25 of them is new record for Turkish flora. During this period two genera, *Lophanthus* Adans. and *Perilla* L. are added. As a result the Lamiaceae in Turkey is represented by 653 species and endemism percentage increased to 47.62 according to recent publications.

Keywords

Additional taxa, flora of Turkey, Lamiaceae.

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***Corresponding author**: Bahar Gurdal **email**: bahar.gurdal@istanbul.edu.tr

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INTRODUCTION

Turkey, a large peninsula with a land surface of 779.452 km², is bordered by three seas and extends across both Europe and Asia. The total area of Turkey-in-Europe (Trakya/Turkish Thrace) lying to the north of the Dardanelles and Bosphorus) is 23.500 km². Lying between 36' N and 42' N, Turkey boats three different climates: continental, oceanic and mediterranean.

Turkey falls within three distinctive phytogeographical regions that tie in closely with the three climatic zones, and these are the keys for understanding the floristic richness of Turkey. I. Euro-Siberian Phytogeoraphical Region: This region extends across North Anatolia immediately south of the Black Sea coast from Yıldız Mountains at the Bulgarian border, to Geogria. Within Turkey, the Euro-Siberian region is largely represented by the Euxine sub-region. II. Mediterranean Phytogeographical Region: This phytogeographical region covers western and southern Turkey with all Turkish Mediterranean vegetation belonging to the East Mediterranean province. Maquis, phrygana and garrigue scrub communities typify much of the vegetation at below 1000 m., with a notable abundance of both bulbous and annual therephyte species. III. Irano – Turanian Phytogeoraphical Region: This region occupying Central and East Anatolia in the largest of the three phytogeographical regions in Turkey (Byfield *et al.,* 2010).

Lamiaceae, the sixth largest Angiosperm family, contains more than 245 genera and 7886 species, and distributed worldwide. It includes many economically and medicinally important species (The Plant List, 2013).

Phytogeographic distribution of Lamiaceae taxa in Turkey: According to Celep & Dirmenci (2017), 287 taxa (36.7%) are in the Irano-Turanian phytogeographic region, 293 taxa (37.4%) are in the Mediterranean phytogeographic region, 90 taxa (11.5%) are in the Euro-Siberian phytogeographic region and 112 taxa (14.3%) are unknown or multiregional element in Turkey.

MATERIALS AND METHODS

After the 11th volume (2000), the checklists entitled “Check-list of additional taxa to the supplement flora of Turkey” have been published in a series paper by Ozhatay *et al.,* as Checklist III, IV, V, VI, VII, VIII and IX (Ozhatay and Kultur,

2006; Ozhatay *et al.,* 2009; 2011; 2013; 2015; 2017; 2019). This study is mainly based on these checklists and also recently published paper of Celep & Dirmenci (2017).

In this study, since 2000 after publication vol. 11 additional taxa to the flora of Turkey are examined in a systematic view. Only taxa or species which are known from the mainland of Turkey (Anatolia/Asian part of Turkey & Thrace region/European part of Turkey) are included.

RESULTS

In eighteen years the number of additional taxa is 78 of which 53 are new taxa for science and 25 of them is new record for Turkish flora. During this period two genera, *Lophantus turcicus* Dirmenci, Yıldız & Hedge from Van province and *Perilla frutescens* (L.) Britton from Artvin province, it is naturalized species are added (Dirmenci *et al.,* 2010, Donmez 2002).

78 additional taxa of Lamiaceae family are listed below, arranged in an alphabetical order.

New taxa for science (53 taxa) (in alphabetical order):

Ballota antalyanse F. Tezcan & H. Duman, Türkiye Bitkileri Listesi p. 896 (2012). [Güner (ed.), 2012]

Calamintha pamphylica Boiss. et Heldr. in Diagn. Ser. 1 (12) 52 (1853) subsp. ***alanyense*** S.Alan et Ocak in Ann. Bot. Fennici 44:309 (2007). [Alan et al., 2007]

Clinopodium hakkaricum Dirmenci & Fırat in Ann. Bot. Fenn. 46: 452 (2009). [Fırat & Dirmenci, 2009]

Clinopodium serpyllifolium (M.Bieb.) Kuntze subsp. ***sirnakense*** Fırat & Akçiçek in Phytotaxa 201(2): 132 (2015). [Fırat et al. 2015]

Lamium artvinense Yıldırımlı in Ot Sist. Bot. Dergisi, 19(1): 26 (2012). [Yıldırımlı, 2012a]

Lamium bilgilii Celep in Phytotaxa 312 (2): 264 (2017) [Celep 2017].

Lophanthus turcicus Dirmenci, Yıldız & Hedge in Turk. J. Bot. 34: 125 (2010). [Dirmenci et al., 2010]

Marrubium amasiense Akgül & Ketenoğlu in Ot Sist. Bot. Dergisi 24(2): 39 (2017) [Akgül et al. 2017]

Marrubium cephalanthum Boiss. & Noë subsp. ***montanum*** Akgül & Ketenoğlu in Ot Sist. Bot. Dergisi 21(1): 23 (2014) [Akgül and Ketenoğlu 2014]

Marrubium lanatum Akgül in Ot Sist. Bot. Dergisi 25(2): 25 (2018). [Akgül, 2018]

Marrubium sivasense Aytaç, Akgül & Ekici in Turk J Bot 36: 444 (2012). [Aytaç et al., 2012]

Marrubium yildirimlii Akgül & B. Selvi in Ot Sist. Bot. Dergisi 21(2):17 (2014) [Akgül and Selvi 2014]

Micromeria aybalae H. Duman & T. Dirmenci in Turk J Bot 41: 385 (2017). [Duman & Dirmenci, 2017]

Micromeria maritima Yıldırımlı, Sadıkoğlu et Keskin in Ot Sist. Bot. Dergisi 13: 29 (2006). [Yıldırımlı et al., 2006]

Nepeta dirmencii Yıldırımlı & M.Dinç in Ot Sist. Bot. Dergisi 10(1): 4 (2004). [Yıldırımlı et al., 2004]

Nepeta sibthorpii Benth. subsp. ***tumeniana*** T.Dirmenci in Bot. J. Linn. Soc. 147: 229 (2005). [Dirmenci, 2005]

Origanum × ***adae*** Dirmenci & Yazıcı in Turk J Bot 42: 80 (2018). (*Origanum ayliniae* Dirmenci & Yazıcı × *Origanum sipyleum* L.) [Dirmenci et al. 2018b]

Origanum × ***malyeri*** Dirmenci & Yazıcı in Phytotaxa 371 (3): 148 (2018) (*Origanum vulgare* L. subsp. *hirtum* (Link) A. Terracc. × *Origanum boissieri* Ietsw.) [Dirmenci et al. 2018a].

Origanum × ***sevcaniae*** Dirmenci, Arabacı & Yazıcı in Phytotaxa 371 (3): 150 (2018) (*Origanum vulgare* L. subsp. *hirtum* (Link) A. Terracc. × *Origanum vogelii* Greuter & Burdet) [Dirmenci et al. 2018a].

Origanum ayliniae Dirmenci & Yazıcı in Turk J Bot 42: 78 (2018). [Dirmenci et al. 2018b]

Phlomis dinci Yıld. in Ot Sist. Bot. Dergisi 13: 3 (2006) [Yıldırımlı, 2006]

Phlomis isiliae Yıld. in Ot Sist. Bot. Dergisi 13:3 (2006) [Yıldırımlı, 2006]

Phlomis × ***ekimii*** M.Y.Dadandı & H.Duman in Ann. Bot. Fennici 40(4): 287 (2003). (*Phlomis bruguieri* Desf. × *Phlomis capitata* Boiss.). [Dadandı & Duman, 2003]

Phlomis × ***vuralii*** Dadandı in The Karaca Arboretum Magazine 7(2): 60 (2003). (*Phlomis bourgaei* Boiss. × *Phlomis chimerae* Boissieu). [Dadandı, 2003]

Salvia anatolica Hamzaoğlu et A.Duran in Ann. Bot. Fennici 42: 216 (2005) [Hamzaoğlu et al., 2005]

Salvia brachyantha (Bordz.) Pobed. subsp. ***tankutiana*** Bagherpour, Celep, Kahraman & Doğan in Turk J Bot 35: 345 (2011). [Bagherpour et al., 2011]

Salvia cadmica Boiss**.** var. ***bozkiriensis*** Celep, Kahraman & Doğan in Pl. Ecol. Evol. 144 (1): 113 (2011). [Celep et al., 2011]

Salvia ekimiana Celep & Doğan in Ann. Bot. Fenn. 47: 63 (2010). [Celep & Doğan, 2010]

Salvia ertekinii Yıld. in Ot Sist. Bot. Dergisi 15(1): 5 (2008). [Yıldırımlı & Ertekin, 2008]

Salvia hasankeyfense Dirmenci, Celep & O. Guner in Phytotaxa 227 (3): 290 (2015). [Celep et al. 2015]

Salvia hedgeana Dönmez in Botanical Journal of the Linnean Society, 137(4): 413 (2001). [Dönmez, 2001]

Salvia marashica İlcim, Celep & Doğan in Ann. Bot. Fenn. 46: 76 (2009). [İlcim et al., 2009]

Salvia sericeotomentosa Rechinger f. var. ***hatayica*** Celep & Doğan, in Novon 19: 432 (2009). [Celep et al., 2009a]

Salvia siirtica Kahraman, Celep & Doğan, in Nord J Bot 29: 397 (2011). [Kahraman et al., 2011]

Scutellaria anatolica M. Cicek & O. Ketenoglu in Ann. Bot. Fenn. 48: 277 (2011) [Çiçek & Ketenoğlu, 2011]

Scutellaria* × *ketenoglui M. Çiçek & Yaprak in Phytotaxa 29: 51 (2011). (*Scutellaria tortumensis* (Kit Tan & Sorger) A. P. Khokhr. × *Scutellaria sosnowskyi* Takht. subsp. *sosnowskyi*). [Çiçek & Yaprak, 2011]

Scutellaria yildirimlii M. Çiçek & Yaprak in Phytotaxa 132 (1): 54 (2013). [Çiçek & Yaprak, 2013]

Stachys cretica L. subsp. ***kutahyensis*** Akçiçek in Turk J Bot, 34: 132 (2010). [Akçiçek, 2010]

Stachys gaziantepensis M. Dinç & S. Doğu in Proc. Natl. Acad. Sci. İndia, Sect. B Biol. Sci. 86: 631. [Dinç and Doğu 2016]

Stachys hakkariensis Akçiçek & Fırat in Phytotaxa 257(2): 168 (2016). [Akçiçek et al. 2016]

Stachys ketenoglui Kaynak, Daşkın & Yılmaz, in Nord. J. Bot. 27: 238 (2009). [Daşkın et al., 2009]

Stachys marashica İlcim, Cenet & Dadandı in Ann. Bot. Fenn. 45: 151 (2008). [İlcim et al., 2008]

Stachys namazdaghensis Yıld., in Ot Sist. Bot. Dergisi 17(2): 85 (2010). [Yıldırımlı, 2010]

Stachys pseudobombycina Kaynak, Daşkın & Yılmaz in Nord. J. Bot. 28: 341 (2010). [Yılmaz et al., 2010]

Stachys vuralii Yıldız, Dirmenci & Akçiçek in Ann. Bot. Fenn 48: 403 (2011). [Dirmenci et al., 2011]

Stachys yildirimlii M.Dinç in Ann. Bot. Fennici 43: 143 (2006) [Dinç & Doğan, 2006]

Teucrium aladagense Vural & H.Duman in Turk J Bot 39: 319 (2015). [Vural et al. 2015]

Teucrium microphyllum Desf. in Ann. Mus. Par. x. 300 (1807). [Greuter & Raus, 2006]

Teucrium pruinosum Boiss. var. ***aksarayense*** M. Dinç & S. Doğu in Modern Phytomorphology 9: 15 (2016). [Dinç and Doğu 2016]

Teucrium pseudaroanium Parolly, Erdağ et Nordt in Willdenowia 37: 252 (2007). [Parolly & Eren, 2007]

Teucrium sirnakense Özcan & Dirmenci in Turk J Bot 39: 312 (2015). [Özcan et al. 2015]

Thymus ekimi Yıldırımlı in Ot Sist. Bot. Dergisi, 19(2): 30 (2012). [Yıldırımlı, 2012b]

Thymus turkmenii Yıldırımlı in Ot Sist. Bot. Dergisi, 19(1): 30 (2012). [Yıldırımlı, 2012a]

New records for Flora of Turkey (25 taxa) (in alphabetical order):

Lamium garganicum L. subsp. ***striatum*** (Sm.) Hayek in Prodr. Fl. Balc. 2: 275 (1929). [Tuzlacı & Bulut, 2012]

Marrubium eriocephalum Seybold in Stuttgarter Beitr. Naturk., A 310: 25 (1978) [Fırat 2016]

Mentha × ***villosa-nervata*** Opiz in Nomencl. Bot. 60 (1831). (*M. longifolia* (L.) Hudson × *M. spicata* L.) [Tarımcılar & Kaynak, 1997]

Micromeria persica Boiss. in Diagn. Pl. Or. Nov. Ser. 1, 7: 48 (1846) [Keskin & Sadıkoğlu, 2007]

Perilla frutescens (L.) Britton in Mem. Torrey Bot. Club 5: 277 (1894). [Dönmez, 2002]

Phlomis × ***praetervisa*** Rech. f. Öst. Bot. Zeitschr. 89: 296 (1940). (*Phlomis bruguieri* Desf. × *Phlomis kurdica* Rech. f.), [Kaya & Ertekin, 2012]

Salvia aristata Aucher ex Benth. in DC. Prodr. 12: 270 (1848). [Behcet & Avlamaz, 2009]

Salvia macrosiphon Boiss Diagn. Pl. Or. Nov. Ser. 1, 5: 11 (1844). [Kahraman et al., 2009]

Salvia sylvestris L. in Sp. Pl. 24 (1753). [Greuter & Rous, 2002]

Salvia viscosa Jacq. in Misc. 2: 328 (1781). [Celep et al., 2009b]

Satureja avromanica Maroofi in Iranian J. Bot. 16: 79 (2010). [Fırat 2015]

Satureja icarica P.H. Davis in Notes R.B.G. Edinb. 38: 51 (1980). [Tumen et al., 2000]

Satureja pilosa Velen. in Sitzungsber. Konigl. Bohm. Ges. Wiss. Prag, Math.-Naturwiss. cl. 899(40): 6 (1899). [Tümen et al., 2000]

Stachys cretica L. subsp. ***cretica*** in Sp. Pl. 2: 581 (1753). [Akçiçek et al., 2012].

Stachys cretica L. subsp. ***salviifolia*** (Ten.) Rech.f. in Ann. Naturhist. Mus. Wien 48: 170 (1937). [Akçiçek et al., 2012].

Stachys megalodonta Hausskn. & Bornm. ex P.H.Davis subsp. ***megalodonta*** in Notes Roy. Bot. Gard. Edinburgh 21: 46 (1951). [Güner and Akçiçek 2015]

Stachys thracica Davidov in in Spisan. B'lghar. Akad. Nauk. xii. 109 (1915). [Akçiçek et al., 2012].

Stachys tymphaea Hausskn. in Mitt. Bot. Ver. Jena v. 70 (1887). [Akçiçek et al., 2012].

Teucrium chasmophyticum Rech.f. in Pl. Syst. Evol. 134: 287 (1980) [Dönmez, 2006]

Teucrium krymense Juz. in Bot. Mater. Gerb. Bot. Inst. Komarova Akad. Nauk S.S.S.R. 14: 19 (1951). [Ocakverdi, 1986]

Teucrium melissoides Boiss. & Hausskn. ex Boiss. in Flora Orientalis 4: 813 (1879). [Dönmez et al., 2010]

Ziziphora clinopodioides Lam. subsp. ***elbursensis*** (Rech.f.) Rech.f. in Fl. Iranica 150: 487 (1982) [Fırat 2017]

Ziziphora clinopodioides Lam. subsp. ***filicaulis*** (Rech.f.) Rech.f. in Fl. Iranica 150: 486 (1982) [Fırat 2017]

Ziziphora clinopodioides Lam. subsp. ***kurdica*** (Rech.f.) Rech.f. in Fl. Iranica 150: 487 (1982) [Fırat 2017]

Ziziphora clinopodioides Lam. subsp. ***rigida*** (Boiss.) Rech.f. in Fl. Iranica 150: 483 (1982) [Fırat 2017]

DISCUSSION AND CONCLUSION

The results proven that Turkey is one of the centers of diversity for Lamiaceae in the Old World. In addition, Turkey has about 10% of all Lamiaceae members in the World. The largest five genera in the country based on the taxon number are *Stachys* (118 taxa), *Salvia* (107 taxa), *Sideritis* (54 taxa), *Phlomis* (53 taxa) and *Teucrium* (49 taxa). According to taxon number, five genera with the highest endemism ratio are *Dorystaechas* (1 taxon, 100%), *Lophantus* (1 taxon, 100%), *Sideritis* (54 taxa, 74%), *Drymosiphon* (9 taxa, 67%), and *Marrubium* (27 taxa, 63%).

In this review, we have updated the latest taxonomic status of genera and species in the family for Turkish Lamiaceae members.

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Akgul G, Ketenoglu O (2014). A new subspecies for the flora of Turkey, *Marrubium cephalanthum* Boiss &Noë subsp. *montanum* Akgül & Ketenoğlu (Lamiaceae). *Ot Sist. Bot. Dergisi* **21**(1): 21-28.

Akgul G, Ketenoglu O, Dogan M (2017). A new species of *Marrubium* L. (Lamiaceae) from Turkey. *Ot Sist. Bot. Dergisi* **24**: 37-46.

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Donmez AA (2006). *Teucrium chasmophyticum* Rech.f. (Lamiaceae): A new record for the flora of Turkey. *Turk J Bot* **30**: 1-4.

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Urolithins and their antimicrobial activity: A short review

Omar Mohamed Aboelftouh Ammar, Mehmet Ilktac*, Hayrettin Ozan Gulcan

Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

Abstract

In the last few decades, the rate of the production of new antibiotic has declined significantly. This is mainly due to the high costs needed for both research and development processes. On the other hand, antibacterial resistance developed by bacteria against the already present antibiotics has been increasing extensively. Thus, finding alternatives to synthesize new antimicrobial molecules is now a priority to fight against resistant bacteria. One of these alternatives that can be used as precursors for new antimicrobial molecules is secondary metabolites. Ellagitannins, abundantly found in walnut, pomegranate, and berries, are known as precursors of ellagic acid which possess antimicrobial, anticancer, and antioxidant activities. Ellagic acid is metabolized in mammalian gastrointestinal system via gut microbiota to form dibenzo [b, d] pyran-6-one metabolites, which are known as urolithins. Urolithins are the metabolites of ellagic acid which are responsible for its biological activities. There are many types of urolithins such as urolithin A, urolithin B, urolithin C and urolithin D that were detected in mammalian gastrointestinal tract. Urolithins were shown to possess antimicrobial activity against bacteria, viruses and fungi. In this article, it was aimed to review the antimicrobial activities of various natural and synthetic urolithins concomitant to their chemistry.

Keywords

Antimicrobial activity, ellagic acid, ellagitannins, gut microbiota, urolithins.

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***Corresponding author:** Mehmet Ilktac **email:** mehmet.ilktac@emu.edu.tr

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INTRODUCTION

The discovery of antibiotics was one of the greatest achievements in the history of medicine (Gaynes, 2017). However, nowadays, the spread of antibiotic-resistant pathogens has become a major public health problem. The period in between 1960 and 1980 is known as the golden age of the antibiotic discovery because majority of the antibiotics which are currently available was discovered during this period. However, during the 21st century, the antibiotic drug discovery could not continue at the same frequency as the golden age. Famous pharmaceutical companies such as; Novartis, AstraZeneca, Sanofi, Bristol-Myers Squibb, and Allergan started to drop their antibiotic researches and turning away from any participation in the development of new antibiotics. The reason of this turning away can be estimated as economic because the costs needed for both research and development process, as well as the organization of clinical trials carries a big financial risk irrespective of the drug candidate. Moreover, antibacterial drugs can only offer modest returns in investments compared to other classes of drugs. Morever, the increase in the rate of antibiotic resistant bacteria resulted in the difficulty of the treatment of the infectious diseases (Junaid *et al.,* 2018; Gajdács, 2019).

Secondary metabolites are low molecular weight molecules that can be extracted from various plant species with numerous pharmaceutical activities. These phytochemicals turned out to be an important area for research due to their abilities to offer larger scale structural diversities and less adverse effects those of synthetic compounds. This direction toward phytochemicals led to the discovery of new sources of antimicrobials, which is essential to overcome the constant evolution of the microorganisms' resistance against existing antimicrobials (Simões *et al.,* 2009).

There are various mechanisms that can result in the development of antibiotic resistance mechanisms. These mechanisms include the modification of the antibiotics by chemical alterations of the antibiotic, destruction of the antibiotic molecule, decrease in the penetration of antibiotic via the change in the permeability, efflux of the antibiotics by cellular pumps, change in the target sites by the protection of targets, modification/mutation (Smith, 2017).

One of the phytochemicals which possess obvious antimicrobial activity is polyphenols or phenolic compounds that include ellagitannins (Figure 1). Ellagitannins are complex chemical structures which are able to release hexahydroxydiphenoic acid (HHDP), the

precursor of ellagic acid, by spontaneous lactonization. Ellagitannins exhibit antioxidant, antimicrobial, anti-inflammatory, and anticancer activities. Morever, they have beneficial effects on health and protective effects against various chronic cardiovascular diseases (Clifford, 2000).

Ellagitannins and ellagic acid in nature

Ellagitannins and ellagic acid are known as polyphenolic structures which are present in some seeds, fruits, and nuts such as; walnuts, almonds, pomegranates, strawberries, and black raspberries. Thus, ellagitannins and ellagic acid are present in daily human dietary intake with various beneficial activities. Studies related with their metabolism within body were performed to understand their mechanism of action (Landete, 2011). Ellagic acid is converted to urolithins in the gastrointestinal tract via gut microflora by the conversion of free ellagic acid to dimethylated ellagic acid glucuronide, which is then converted via colon microbiota into hydroxy derivatives of dibenzopyran-6H-6- one, which are known as urolithins (Tomás-Barberan *et al.,* 2009). Urolithins are chemically known as dibenzo [b, d] pyran-6-ones, or 3,4-benzocoumarins, dibenzo-α-pyrones, and benzo[c]chromen-6-ones. These compounds were initially isolated from natural sources followed by sheep renal calculus and called urolithin A, and urolithin B. Urolithins are produced within the gastrointestinal tract via intestinal microbiota through the opening and decarboxylation of one of the two lactones in ellagic acid and subsequent removal of hydroxyls from various positions. Decarboxylation of ellagic acid forms the first metabolite which is urolithin M-5 that can be metabolized to urolithin D, and urolithin M-6 by the removal of a hydroxyl group from different positions. Urolithin C and urolithin M-7 can be formed by removal of second phenol hydroxyl, whereas urolithin A and isourolithin A are formed via removal of third hydroxyl. On the other hand, urolithin B, and isourolithin B were detected as a result of dehydroxylation of urolithin A, and isourolithin A, respectively (Figure 2). According to the number of hydroxyl groups on the structure, urolithins are categorized into pentahydroxyurolithin as urolithin M-5, tetrahydroxyurolithin as urolithin D, and urolithin M-6, trihydroxyurolithins as urolithin C, and urolithin M-7, dihydroxyurolithins as urolithin A, and isourolithin A, and monohydroxyurolithin as urolithin B, and isourolithin B (Garazd and Garazd 2016).

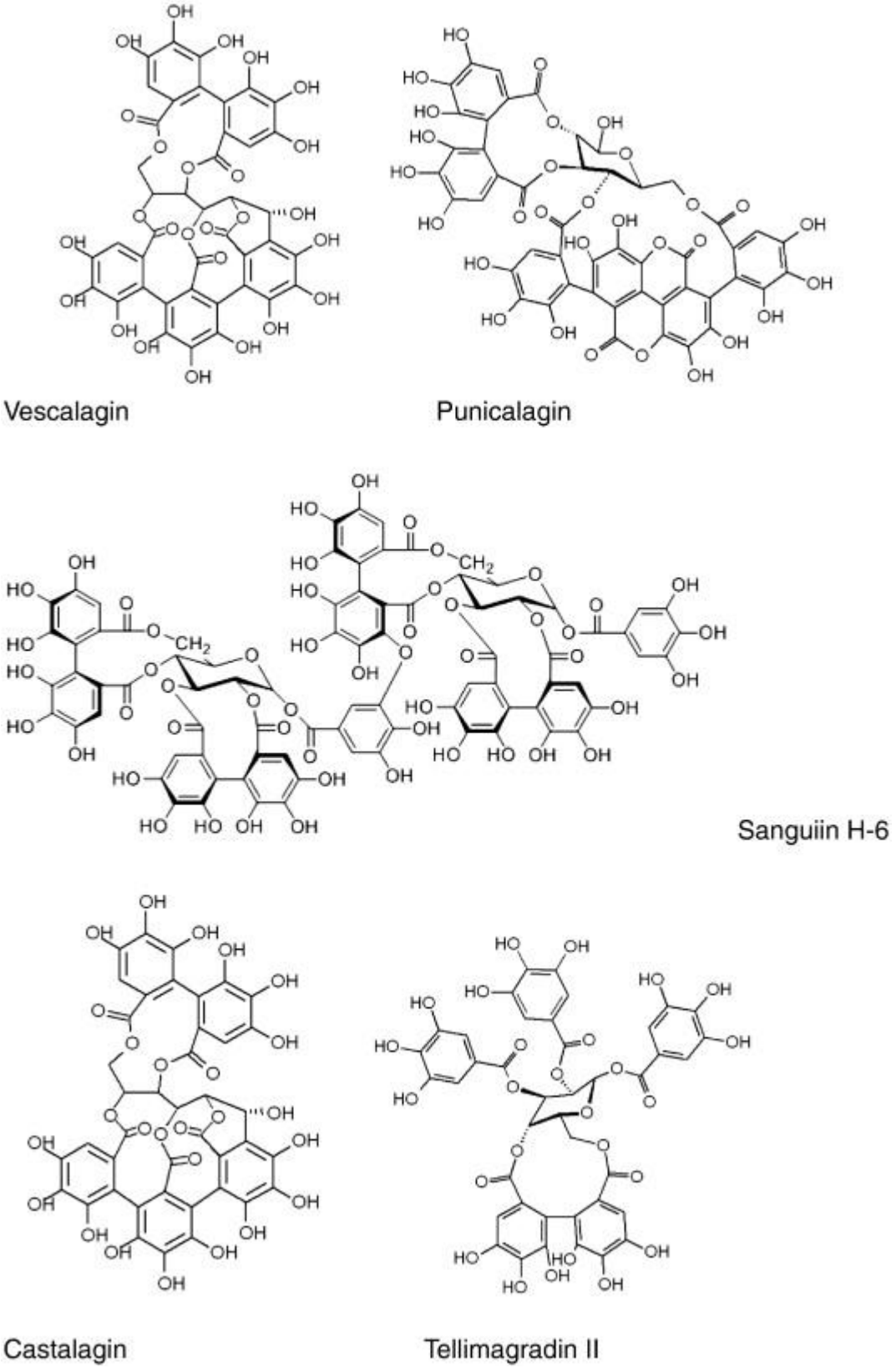

Figure 1: The main structure of ellagitannins (Landete, 2011).

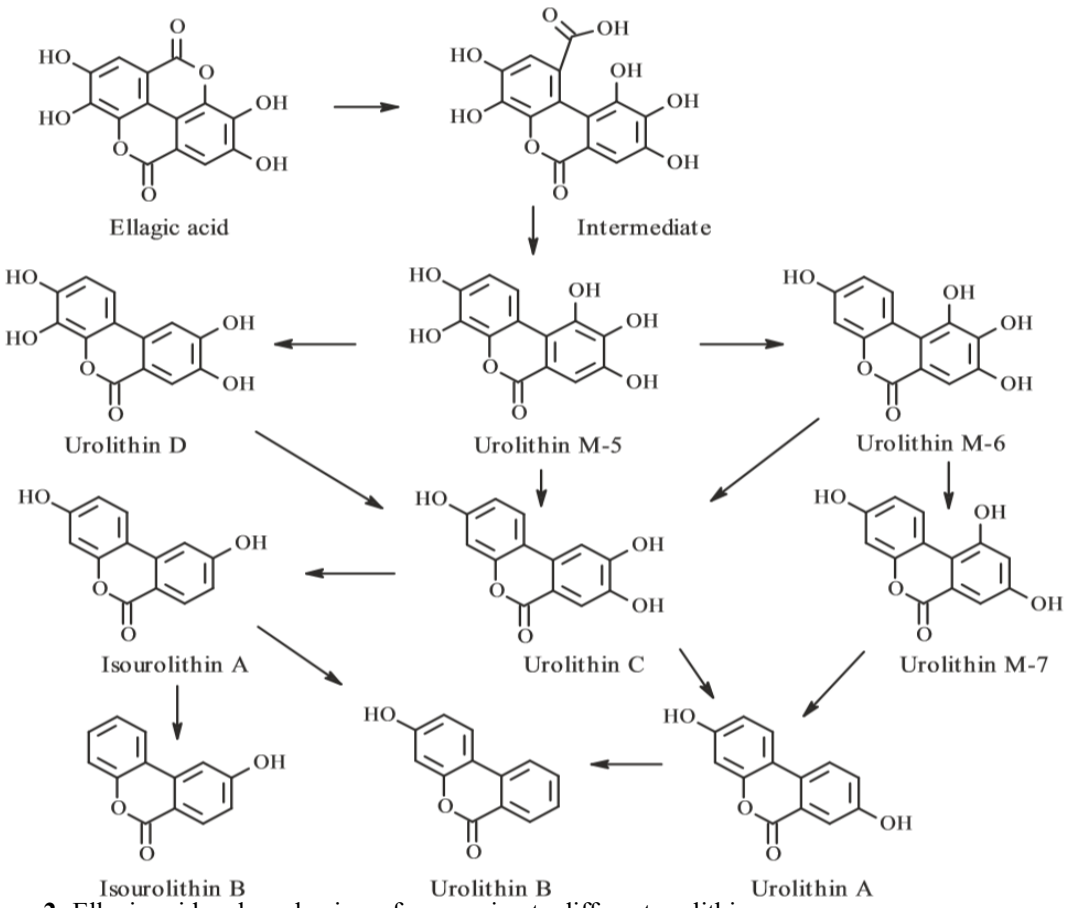

Figure 2: Ellagic acid and mechanism of conversion to different urolithins.

Urolithin production in different mammalian species

The production of urolithin from ellagitannins has been reported in different animal species. In the rumen of ruminants such as; cattle and sheep, the most observable urolithin derivatives are isourolithin A, and urolithin B. On the other hand, urolithin A was the most frequently detected urolithin derivative in the intestine. In monogastric animals such as; rat, mouse, and pig, the main urolithin derivative is urolithin A, its glucuronide, and sulfate conjugates, followed by urolithin B, urolithin C, and isourolithin A. Human being shows the same behavior as monogastric animals after eating ellagitannin-containing foods. These results are reflection of the fact that generally mammals can produce urolithins after ellagitannin-containing food intake. However, there are inter-individual variations because of the difference in the composition of gut microflora (Espín *et al.,* 2013).

Pharmacokinetic studies

In vitro studies indicate that ellagitannins show high stability under the acidic conditions of the gastric environment. Moreover, they are stable in the presence of

gastric enzymes such as pepsin, rennin and gastric lipase without any degradation or hydrolysis to free ellagic acid. Ellagitannins can be absorbed none or little amounts in the stomach can be absorbed because of their complex structures. Similarly, free ellagic acid molecules can be absorbed at very low percentage. During the following stages of digestion, ellagitannins and ellagic acid are metabolized via the intestinal microbiota to urolithin derivatives; especially to urolithin A and urolithin B. Afterwards, they are absorbed through the intestinal epithelia and undergo glucuronidation in liver (Lipińska *et al.,* 2014). Metabolism studies of urolithins showed that urolithin tends to undergo particularly phase II conjugation reactions forming glucuronide and the sulfate metabolites. Moreover, methyl ether metabolites catalyzed by catechol-O-methyl transferase (COMT) enzyme are observed (Yuzugulen *et al.,* 2019).

Antimicrobial activity of urolithins

Ellagitannins and ellagic acid have been investigated in many studies in order to understand their antimicrobial activities. These compunds exhibit antibacterial activities against both Gram positive and Gram negative bacteria, some viruses and fungi. It was shown that ellagic acid bears antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and some clostridia species (Bialonska et al., 2010). Moreover, dose-dependent antimicrobial activity of urolithins against *Helicobacter pylori* isolated from a peptic ulcer patients was observed (Chung, 1998).

It was reported that ellagitannin extracts can inhibit the growth of *Vibrio cholera*, *Shigella dysenteriae*, and *Campylobacter* species (Scalbert, 1991). In a study that was conducted on *Yersinia enterocolitica*, the antibacterial activity of urolithin A, and urolithin B were investigated related to their anti-Qorum Sensing (QS) effects. As a result, it was reported that urolithin A and B possess antimicrobial effect at the concentration of 4 μM via three mechanisms which are growth inhibition, a significant reduction in biofilm biomass, and a notable reduction in the bacterial motility. These effects were found to occur due to the reduction of the level of acylated homoserine lactone (AHL) autoinducers, especially 3-oxo-C6-HSL and C6-HSL, which are essential for lactone and flagella synthesis (Giménez-Bastida *et al.,* 2012). It was also reported that ellagitannins have bactericidal effect against antibiotic-resistant bacteria such as; methicillin-resistant *S. aureus* (MRSA) and carbapenem-resistant *Acinetobacter baumanii*. Inhibitory effects on the growth of some fungi such as; *Candida albicans* and *Cryptococcus neoformans* were also reported (Yoshida *et al.,* 2009).

Urolithins were also reported to have potent antibacterial effect against *Bacillus subtilis*, *E. coli*, *Bacillus cereus* and *Bacillus polymyxa* with minimum inhibitory concentration (MIC) of 20 ppm. Moreover, these compounds were also shown to exhibit strong antibacterial activities against *Salmonella* Paratyphi, *Salmonella* Choleraesuis, and *Salmonella* Enteritidis with MICs of 20 ppm, 10 ppm and 15 ppm, respectively (Hayriye, 2011).

CONCLUSION

Finding new alternatives of secondary metabolites is a priority nowadays because they can be used as precursors for the design of new antibiotic agents. Ellagitannins and ellagic acid have been shown to possess antimicrobial activity in many studies. Clarifying the mechanism of the antimicrobial activity is essential. Urolithins, which are produced via gut microbiota, have been demonstrated to be one of the main metabolites of ellagic acid in the gastrointestinal system of mammals. There are several types of urolithins such as; urolithin A, urolithin B, urolithin C, urolithin M5, urolithin M6, and urolithin M7. Especially urolithin A and urolithin B were reported to possess antimicrobial activity against *Vibrio cholera*, *S. dysenteriae*, *Campylobacter* species, MRSA and carbapenem-resistant *A. baumanii* via inhibiting QS system, a communication system that is essential for the virulence of bacteria.

As a conclusion, urolithin A and B are thought to be attractive precursors for the discovery of new antibacterial agents.

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Evaluation of the recommended treatment and preventive measures of COVID-19

Hananeh Kordbacheh[1,2], Ahmet Aydin[1,2], Sonia Sanajou[2*], Gonul Sahin[1]

[1]Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus, Mersin 10 Turkey.

[2]Yeditepe University, Faculty of Pharmacy, Istanbul, Turkey.

Abstract

The COVID-19 pandemic is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that is continuing to spread around the world threatens the human health and has an impact on global economic crisis.

As of 26th July 2020, no dedicated FDA-approved treatment and vaccine strategies have been confirmed for the treatment and prevention of COVID-19 patients. Many ongoing clinical trials are in progress, and varieties of possible treatments are being tested around the globe.

As a vital part of the healthcare system, doctors, nurses and pharmacists play an important role in providing guidelines of protection to the public not only to prevent and control the infection but also to develop treatment strategies and discover vaccine during the pandemic. Several countries around the world are in rush to discover a new and safe therapy and vaccine for novel coronavirus.

This review highlights current knowledge about the possible therapies, their mechanisms, safety considerations based on interventional trials, clinical data of *in vitro* studies and a patient response.

Keywords

COVID-19, *in vitro* studies, SARS-CoV-2.

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***Corresponding author:** Sonia Sanajou **email:** sonia.sanajou@emu.edu.tr

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INTRODUCTION

As of 26th July, 2020, more than 16 million cases of coronavirus disease 2019 (COVID-19) have been reported around the world, with no proven effective therapies (Wang *et al.*, 2020). The outbreak was first identified in Wuhan, China, in December 2019, rapidly spread to all provinces in China and eventually throughout the world. The earliest sign of the virus was reported as severe respiratory failure, which was confused with regular flu and thought to be caused by the normal seasonal influenza virus. Later on, due to the increasing severity of symptoms and the number of infected cases, this virus was declared novel. The virus was identified as a novel coronavirus and named initially as 2019-n CoV (WHO, 2020a).

Severe acute respiratory syndrome-2 (SARS-CoV-2) is the official name given to the 2019-nCoV and COVID-19 is the disease associated with the virus. The infection was declared as a pandemic on 11th March (WHO, 2020a). The virus represents a unique global challenge due to its contagiousness and lethality. It has been believed that the SARV-CoV-2, similar to other coronaviruses, Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV) emerged in 2002 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) emerged a decade later in 2012, has a zoonotic source. SARS-CoV-2 has infected more people than other coronaviruses and continues to spread rapidly through worldwide (Zheng, 2020).

The close genetic relations of SARS-CoV-1, MERS-CoV, and SARS-CoV-2, suggest that they all have the same origin in bat, but with a different intermediate animals in other to adopt to humans. The virus can transmit from bat to other animal species and mutate in these animals infect humans who are in close contact (Zhao *et al.*, 2004). Genetic analysis showed that coronavirus genomes have 85.5 to 92.4% sequence similarity to pangolin coronaviruses (Lam, 2020).

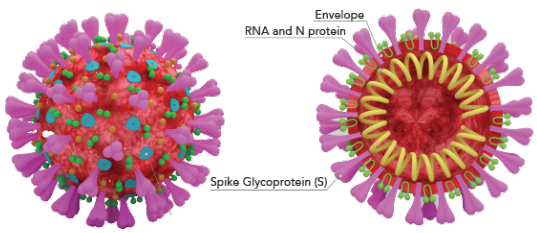

Figure 1: Structure of coronaviruses (Lam, 2020).

SARS-CoV-2 is an enveloped, single-stranded RNA virus that causes lethal respiratory tract infection.

Transmission

There is a preliminary evidence suggesting that the virus can be transmitted from person to person via direct or indirect contact. It has been long accepted that coughing and sneezing can transmit respiratory viruses through droplets. Coronavirus can remain in the air for nearly three hours, and airborne transmission is suspected to be one of the potential routes for the spreading of the disease (Dietz *et al.*, 2020). Coronavirus has been found in the feces of some COVID-19 patients; however, there has not been any confirmed report of the virus spreading from feces to person (Tang *et al.,* 2020).

Pathogenesis

Preliminary evidence suggests that inhaled virus-bearing droplets can deposit directly into the human respiratory tract. Once this virus penetrates deeply into the lower airways of the lung, it recognizes angiotensin-converting enzyme 2 (ACE II) receptor on the surface of alveolar epithelial cells called type II pneumocytes (Sriram and Insel, 2020). The spike (S) protein found on the surface of coronavirus facilitates viral attachment followed by receptor mediated endocytosis. Once the virus enters the host cell, it hijacks the host cell machinery to promote its replication and infects nearby cells. Understanding the mechanism of SARS-CoV-2 could help to identify therapeutic targets and discover a potential treatment (Astuti and Ysrafil, 2020). The virus infects the cell via binding its spike protein to the ACE II receptor, followed by cell membrane fusion. The coronavirus multiples throughout the body and cause more damage and destruction to the lung wall as well as other organs. The body tries to respond to the foreign invader by activating humoral and cellular branches of immune system, which are mediated by B cells and T cells, respectively (Takayama, 2020).

B cells produce antibodies like immunoglobulin M (IgM) and later on, immunoglobulin G (IgG). In the case of COVID-19 infection, B cells first produce IgM and then IgG after 7-14 days (Jacofsky *et al.*, 2020).

Natural killer cells, macrophage and neutrophils are also the main cells involved in viral detection and elimination. SARS-CoV-2 stimulates macrophages to increase their production of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) as a response to the viral infection. The production of pro-inflammatory cytokines can lead to the production of reactive oxygen species (ROS). ROS damages type I and II pneumocytes, which are responsible for gas exchange and production of surfactants,

respectively. This process leads to the acute alveolar damage, reduction of the gas exchange and inability of the production of surfactant (Costela-Ruiz *et al.,* 2020).

Uncontrolled and excessive immune responses may cause immune damage and lead to a hyperinflammatory state, so-called cytokine storm, which is associated with worsening of symptoms and the promotion of lung damage (Ayala *et al.,* 2003).

Accumulating evidence suggests that severly affected patients are more likely to develop cytokine storm syndrome than patients with mild to moderate disease. In cytokine storm syndrome, a large number of cytokines are released in the bloodstream. Cytokine storm is considered to be one of the major causes of acute respiratory distress syndrome (ARDS) and multiple organ failure (Mehta *et al.,* 2020).

Symptoms

The main symptoms of infection by coronavirus are fever above 37.8 °C, dry cough and dyspnea (Table 1). Somehow, some patients never develop any symptoms, whereas some healthy people have severe or even fatal pneumonia. Some main factors and underlying medical conditions like severe lung or heart conditions, diabetes, conditions that trigger their immune system, cigarette smoking, and the elderly are at higher risk of severe illness from COVID-19 (Singhal, 2020).

The chest computed tomography (CT) findings in COVID-19 cases show consolidation and peripheral ground glass opacities, which means that the lung is filled up with inflammation and fluid rather than air. The patient may have abnormalities on chest imaging before the onset of symptoms. Thereby, a CT scan can be used for the diagnosis of COVID-19 patient and monitoring patient response to treatment (Kalra, 2020).

The sign and symptoms of COVID-19 patients can differ according to the severity of the disease. A large proportion of COVID-19 patients may be asymptomatic, but the risk of virus transmission is still high (Bikdeli *et al.,* 2020). Signs and symptoms of coronavirus disease have been classified under three groups as mild, moderate and severe. In Table 1 the symptoms of COVID-19 in mild, moderate and severe cases are shown (Garg, 2020).

Table 1: Signs and symptoms of COVID-19 disease in mild, moderate and severe cases of disease (Garg, 2020).

Mild	Moderate	Severe
Fever (90% of cases)	Dyspnea	Severe pneumoniae
Dry cough (70%)	Increased heart rate	ARDS
Tiredness (49%)	Soreness from cough	Cytokine storm
Muscle pain (15%)	Dry mouth	Multiorgan failure
Headache		
Sore throat		

Control and prevention measures of COVID-19

Informing the public about the early symptoms and preventive measures of COVID-19 to prevent and slow the spread and transmission of the virus. Personal protection, public health and social measures are necessary in order to fight against the pandemic all around the world. Especially high-risk group, including older people, people with chronic health conditions and severe illness, should take in to account the precautions in order to prevent getting infected by COVID-19. To decrease the risk of person-person transmission, it is strictly recommended that mouth and nose should be covered by a mask in public and crowded places, wash hands regularly with soap and water or alcohol-based hand rub. Cover mouth and nose with the flexed elbow or use disposable tissue during coughing and/or sneezing. Keeping social distance and staying at home as much as possible are critical for decreasing the risk of person-to-person transmission (CDC, 2020b; Murthy *et al.*, 2020).

Pharmacists play critical roles in providing guidelines, directing people to reliable resources and educating people about the prevention of infection and management of symptoms during COVID-19 pandemic (Murthy *et al.*, 2020). SARS-CoV-2 outbreak is unique and displays differences when compared to other viral infections. There is still no approved therapies and vaccine for COVID-19. Majority (80%) of the infected individuals recover from the disease without needing special treatment. Self-isolation and quarantine for a while and a regular follow-up by doctor and healthcare provider via the telephone, email and video visits are generally enough for mild cases. Nevertheless, ventilatory support and hospitalization in intensive care unit (ICU) are required, in the case of ARDS and critical ill cases (CDC, 2020a).

Oxygenation and ventilation techniques in COVID-19 patients

In COVID-19 patients with respiratory failure, mechanical ventilation should be applied. The duration of mechanical ventilation is adjusted based on the patient's oxygen saturation level (optimum is 95 to 100%). If oxygen saturation does not increase, low flow and high flow nasal cannula non-invasive respiratory support such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) ventilators that both work via a tube into face mask, can be used. If non-invasive devices, do not boost oxygen levels to optimum level; a tube is inserted into the patient's trachea (endotracheal intubation) with long-lasting sedation to achieve more oxygen delivery (Meng *et al.,* 2020; Yang *et al.,* 2020). Extracorporeal membrane oxygenation (ECMO) can be

reserved as the last choice after the failure of other strategies in patients with COVID-19 respiratory failure. During ECMO, blood is removed from the body and passed through an oxygenator known as an artificial lung and then returned to the bloodstream (Pittman MA, 2020). Although ventilation can be lifesaving in COVID-19 patients, there is a chance for virus transmission to healthcare workers during the ventilation procedure. Ventilation is an aerosol-generating procedure and a high concentration of infectious respiratory aerosol can be exhaled from the patient and the virus stays viable in the airborne particles for about three hours. It is crucial to avoid unnecessary invasive ventilation procedures to the patients with COVID-19 and if necessary this procedures requires the use of appropriate personal protective equipments such as gown, face shield, N95 mask by health care provider and surgical mask by patients who are receiving oxygen by nasal cannula. Such patients should stay isolated in a room with negative airflow. Altogether these strategies can reduce the risk of transmission of the virus (Singhal, 2020).

Inhaled nitric oxide therapy

Nitric oxide (NO) is a powerful molecule that is produced by lung endothelial cells and acts as a selective pulmonary vasodilator. NO targets the vascular smooth muscle cells that surround the small arteries in the lung. The United States Food and Drug Administration (FDA) previously has approved the use of NO gas for patients with hypoxic respiratory failure associated with pulmonary hypertension. Based on the previously published findings, inhaled nitric oxide was used by a face mask or mechanical ventilator to treat a limited number of patients with pulmonary complications during the 2003 SARS-CoV outbreak. At that time, inhaled NO helped to improve lung function in severely hypoxemic patients and shortened the length of ventilatory support compared with matched control SARS-CoV patients (Tonelli *et al.,* 2013). Coronavirus can destroy the blood vessels in the lungs, which results in the failure of the production of NO. When NO is deficient, blood vessels constrict and the risk of blood clotting and thrombosis increases. There is a hypothesis that inhaling NO may cure severely ill COVID-19 patients who are already on a ventilator and may help them to get off the ventilator quickly or even prevent people and health care workers from being infected (Poyiadji *et al.,* 2020). Apart from its respiratory effects, NO is believed to have an antiviral activity, which can result in potential benefit against coronavirus infection via preventing viral replication. So far, reported adverse events associated with inhaled NO include the formation of methemoglobin and decrease in the blood

oxygenation level, which is primarily dose-dependent (dose higher than 20 part per million) (de Abajo and Francisco, 2020; Martel *et al.,* 2020).

Renin-Angiotensin-Aldosterone system inhibitors

Animal studies suggested that the renin-angiotensin-aldosterone system (RAAS) inhibitor drugs like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase the expression of ACE II. The same receptor, which is known as an entry point for the SARS-CoV-2 virus, thereby may result in more severe infection and adverse outcomes during the COVID-19 pandemic (Ingraham, 2020). In contrast, other researches have suggested that ACE inhibitor may enhance the vasodilatory and anti-inflammatory properties by converting more angiotensin II to angiotensin 1-7. RAAS inhibitors are a group of drugs that are prescribed worldwide for managing hypertension and heart failure. ACE inhibitors such as enalapril and captopril act by inhibiting the production of angiotensin II. Angiotensin II increases blood pressure and vascular permeability and also has a strong vasoconstriction effect (Herman *et al.*, 2020). ARBs like losartan and valsartan act through blocking the angiotensin I receptors. Hence, they inhibit the binding of angiotensin II to its receptor. ACE II receptor is a key regulatory protein that can degrade angiotensin II to angiotensin 1-7. Angiotensin 1-7 is a vasodilator agent and has hypotensive and anti-inflammatory effects. SARS-CoV-2 downregulates the level of ACE II receptor by binding to it. Therefore, ACE II is unable to exert a protective effect for the body. This situation can result in the production of more angiotensin II and less angiotensin 1-7 that leads to endothelial cell dysfunction. Based on observational database among hospitalized patients with COVID-19 who have underlying cardiovascular diseases and are on medications like ACE and RAAS inhibitors, death rates are unrelated to medications and the relationship between ACE inhibitors or ARBs and death have not been comfirmed yet. The latest data support not to discontinue of ACE inhibitors and ARB medicines during the COVID-19 pandemic (de Abajo and Francisco, 2020).

Anticoagulant agents in patients infected with SARS-CoV-2

It has been reported worldwide that individuals can respond differently to the virus. One third of hospitalized patients develop complications related with clotting, in small vessels, deep vein thromboses in the leg, clots in the lung and stroke (Levi *et al.,* 2020). The reason for blood clotting is still unclear. One possibility is that the virus can enter endothelial cells because ACE II receptor is found on the surface of endothelial cells that line the blood vessels.

As a result, the virus damages the endothelial cells by increasing angiotensin II and decreasing angiotensin 1-7 function and activating platelets. The second possible reason can be the overactivation of the immune system, which leads to an imbalance in clotting factors, that can cause clotting or bleeding. Another theory is that patients in ICU are more likely to develop clots, particularly because of being immobile for a while. Blood tests in COVID-19 patients show an elevated level of D-dimer, which is a by-product of blood clotting. An increase in D-dimer level indicates the presence of blood clot and body inflammation (Li *et al.,* 2020).

Multiple studies so far have shown that the use of a prophylactic dose of low-molecular-weight-heparin (LMWH) is associated with a decreased rate of mortality. LMWH is currently being prescribed for COVID-19 patients with coagulopathy in the absence of any contraindication such as active bleeding and platelet count less than 25 x 10^9 / L. The recommended daily dose is IV 40-60 mg and LMWH is continued until the lab result of a patient turns to normal and the patients is discharged from the hospital. LMWH is preferable over unfractionated heparin due to its more predictable pharmacokinetic characteristic and the lower risk of bleeding. However, LMWH is contraindicated in patients with kidney dysfunction and those whom creatinine clearance is 30 mL/min or less because the decrease in its excretion leads to an increase in the anticoagulation effects (Polderman, 2012).

Because of the risk of venous thromboembolism, pulmonary embolism and renal insufficiency, unfractionated heparin may be a better choice of anticoagulant in COVID-19 patiens because it is extensively cleared by the hepatobiliary system, and protamine sulfate can be given as an antidote in case of bleeding (Kow and Syed 2020; Millar and Laffan, 2017). Thus far, no studies have identified a beneficial effect of aspirin in COVID-19 cases.

Systemic corticosteroid

Patients with severe COVID-19 pneumoniae had markedly increased inflammatory markers such as C-reactive protein, IL-6 and may have cytokine storm syndrome. It is well-known that corticosteroids have potent anti-inflammatory action. In the past, steroid administration did not improve the outcome and reduce the risk of death in patients with SARS-CoV and MERS-CoV but also delayed and impaired viral clearance and increased the risk of secondary infection (Hadjadj, 2020).

In June 2020, Oxford University published a randomized clinical trial to test the potential beneficial use of corticosteroid in

COVID-19 patients. They declared that dexamethasone is the first drug shown to save the lives of critically ill COVID-19 patients on ventilators. In this clinical trial, patients received dexamethasone 6 mg per day either orally or intravenously for ten days and the outcome was compared with that of control group. The researchers concluded that the death rate was reduced by one-third in ventilated patients and by one-fifth in patient, who received oxygen only. There was no benefit among those patients who did not require respiratory support. In people with COVID-19, corticosteroids may theoretically modulate the inflammatory response and reduce the risk of developing ARDS. However, there is currently limited evidence on the topic and clinical trials have still being carried out (Brotherton *et al.,* 2020).

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are FDA approved drugs for the treatment of malaria and lupus rheumatoid arthritis. Researches have suggested that these drugs could possibly be effective in the treatment of COVID-19. FDA issued an Emergency Use Authorization on 27 March 2020, allowed the use of these drugs, under careful heart monitoring, in COVID-19 patients who are admitted to hospitals with evidence of pneumoniae. HCQ and CQ are alkaline compounds. I*n vitro* studies show that CQ and HCQ increase the pH of the lysosome and endosome inhibiting SARS-CoV-2 replication. An interesting new finding demonstrated that HCQ acts as a zinc ionophore that allows the influx of zinc into cells and lysosomes. There is a hypothesis that HCQ or CQ plus zinc supplementation may be more effective in reducing COVID-19 morbidity and mortality. However, on 15th of June 2020, FDA stated that according to ongoing analyses and recent results from a large, randomized clinical trial in hospital, these two drugs resulted in little or no reduction in the likelihood of death or recovery time but prolonged QT interval and led to ventricular arrhythmias and torsades de pointes that leads to sudden cardiac death. Therefore, the potential benefits of CQ and HCQ no longer outweigh their risks (Mehra *et al.,* 2020).

Lopinavir/ ritonavir

The combination of lopinavir and ritonavir is used to treat Human Immunodeficiency Virus (HIV). Lopinavir/ritonavir is classified under protease inhibitors. Lopinavir is an antiretroviral agent given together with ritonavir, which is a potent CYP3A4 inhibitor that helps to increase the level of lopinavir in serum (Chandwani and Shuter, 2008).

There was a hope that these medicines could be effective in the treatment of SARS-CoV-2. On 4th July 2020, WHO announced that hydroxychloroquine and

lopinavir/ritonavir had little or no reduction in the mortality of hospitalized patients when compared to standard care protocols (WHO, 2020b).

The common side effects of lopinavir/ritonavir include gastrointestinal disturbance and diarrhea. Drug interactions with ritonavir are common due to the inhibition of CYP3A4 enzyme activity that leads to an increased level of co-administrated drug which is metabolized by the enzyme (Chandwani and Shuter, 2008).

Remdesivir

Remdesivir is an antiviral drug that is still under investigation and has not been approved by the FDA for any use. It was developed in 2009 as a possible treatment for Hepatitis C and tested for Ebola virus in 2015. During the Ebola epidemic it was not found to be effective enough. In May 2020, FDA issued an emergency use authorization for remdesivir in the treatment of COVID-19 in adults and children with severe disease. FDA defined severe disease as a patient with low blood oxygen levels who needs oxygen therapy or more intensive breathing support such as mechanical ventilation. Remdesivir is a prodrug and turns to its active form called GS-441524, which is known as a adenosine nucleoside analog (FDA, 2020). *In vitro* study shows that remdesivir prevents further replication of viral RNA once it gets incorporated leaving the RNA strand incomplete. A literature review concluded that remdesivir treated patients had shortened recovery time and improvement in the lower respiratory tract infection when compared to the placebo group. Observational studies revealed that remdesivir should be used in the early stage of the disease and the treatment should start with a 200 mg intravenous infusion on the first day, followed by 100-mg a day for at least four consecutive days and not more than nine days for the intubated patient (David Norrie 2020; Wang *et al.,* 2020).

The common side effects of remdesivir are reported to be anemia, decreased hemoglobin, hyperglycemia and transaminitis (Fan *et al.,* 2020).

Favipiravir

Favipiravir is a broad spectrum antiviral prodrug that has been approved in Japan for the treatment of influenza virus infections. The mechanism of action of this drug is to selectively inhibit RNA polymerase and prevent the replication of the viral genome. Favipiravir has a similar mechanism of action to remdesivir but is orally administrated (Wang *et al.,* 2020). Clinical trials have been performed all over the world to assess the efficacy of favipiravir in the treatment of COVID-19 infection. Researches showed that the high concentrations of favipiravir shorten the viral clearance and lead to improvement in

chest imaging of mild and moderate cases. Similar to other antiviral drugs, favipiravir should be admimistered early after the onset of symptoms in order to be effective to reduce the viral load in blood. Diarrhea, liver toxicity and hyperuricemia were reported as adverse effects in some patients. Thus, the concerns related with the safety of favipiravir is still under investigation (Singhal, 2020).

Interleukin-6 inhibitors

Cytokine storm which is which is marked by an elevated level of various chemokines such as IL-1, IL-6 and IFN in serum is associated with high mortality and increased death rates among severe cases of COVID-19. It has been suggested that targeting the inflammatory mediators such as IL-6 may help decrease the inflammatory response, thus reducing the severity of disease such as acute respiratory syndrome. Tocilizumab is an immunosuppressive drug that targets chemokines by binding to IL-6 receptors (Costela-Ruiz *et al.,* 2020). The drug has FDA approval for the treatment of rheumatoid arthritis and cytokine release syndrome. Tocilizumab is an option in patients with severe respiratory symptoms associated with COVID-19. Many clinical trials are undertaken to evaluate the safety and efficacy of the treatment. However, there is still no evidence for the appropriate time to begin the drug. If tocilizumab is administered in the early stage of infection, it can supress the immune system, which is responsible for fighting against the virus. On the other hand, the treatment strategy should be done as early as possible before IL-6 gives the damage (Atal and Fatima, 2020). Tocilizumab consumption poses a risk of severe infections such as upper respiratory tract bacterial infections, skin and soft tissue infections and is not recommended for COVID-19 patients with bacterial pneumonia (Zhang *et al.,* 2020).

Convalescent plasma therapy

After exposure to an infectious agent, the body's immune system response against the agent by producing IgM antibodies within the first week of symptom onset. IgM then gradually decreases where as the level of IgG antibodies increases after 12-17 days following the infection. IgG persists for a relatively longer period than IgM. Antibodies are crucial for the body to fight against infection. These antibodies are found in blood plasma. Convalescent plasma therapy is an experimental treatment and has not been approved for any use by the FDA (FDA, 2020). Through the process, healthcare providers collect the plasma that contain antibodies from COVID-19 patients who have recovered and meet all donor eligibility requirements by FDA. The plasma is then administered to patients who have been infected with SARS-CoV-2 so that the antibodies already

present in the plasma neutralizes the viruses and prevent the entry of the virus in to new cells. Researchers hope that convalescent plasma can be helpful in severe COVID-19 patients. However, this investigational treatment has not yet been confirmed to be safe and effective (Jacofsky *et al.*, 2020).
The possible risks for this therapy are allergic reactions, lung damage, difficulty breathing and transmission of other blood-borne infection such as HIV, hepatitis B and Hepatits C. In order to rpeevent to transmission of blood-borne pathogens, donated blood must be screened for safety as outlined by FDA (Rajendran *et al.,* 2020).

CONCLUSION

In addition to the public health crisis, which results in large-scale loss of life, the COVID-19 pandemic has negatively been affecting the social life, economic and financial markets across the globe. Although seven months have passed, there are still questions and mysteries about how SARS-CoV-2 causes severe disease, how it leads to death in some patients and whether a vaccine or an antiviral drug can be developed to end the pandemic (Murphy *et al.,* 2020). The benefits of some of the potentially effective treatments that are listed in the present review are likely outweigh the adverse events in a short course of treatment. However, the evidence remains unfinished and new information replace the old one day by day. Careful consideration should be given and effective prevention measures should be taken in order to minimize the risk of the transmission of the virus (Burki, 2020). It is recommended strictly by the Center of Disease Control and Prevention (CDC) wearing a medical or cloth face mask in public settings, maintaining physical distance of at least one meter, washing hands regularly, performing alcohol-based hand rubbing, avoiding touching eyes, nose and mouth (CDC, 2020b). Following these simple behaviors can limit the spread of the virus. Governments should increase the rate of diagnostic testing in order to follow up the spread of the virus accurately. It has already been shown that the rate of recovery is higher than the rate of death rate. However, it is not yet definite that people who have recovered from COVID-19 will be protected from reinfections. Overwhelming efforts of healthcare providers including doctors, nurses and pharmacists to manage and care for the health crisis is noble and appreciable to keep people safe and provide supportive care for COVID-19 way (CDC, 2020b; Rosenbaum, 2020)

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