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Research article

Determining the relationship between fiber consumption and physical activity and bowel habits in office workers

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Abstract

It is thought that bowel transit time decreases with reduced fiber consumption and physical activity in office workers who lead a sedentary life. The consumption of plant-based diets is decreasing due to technological advances, which leads to a decrease in dietary fiber consumption. Furthermore, officer workers have low physical activity levels. Therefore, the aim of the present study was to determine the relationship between fiber intake, physical activity and bowel habits in office workers. A total of 100 office workers with a mean age of 33.25±7.28 were included in this cross-sectional study. A questionnaire consisting of 29 questions was prepared by the researchers. The questions on bowel habits were prepared based on the Rome III criteria and the Bristol scale was used as the diagnostic criteria of intestinal diseases. It was found that 50% of participants with low fiber consumption and 91.7% of those with high fiber consumption defecate once a day (p<0.05). A significant difference was found in the frequency of defecation according to the water consumption of the participants (p<0.05). It was not found difference between Bristol scale scores and defecation frequency of the participants according to physical activity levels (p>0.05). Further studies should be conducted to increase the knowledge level of individuals about healthy nutrition in order to improve bowel habits and lead a healthier life.

Keywords: *Bowel habits; constipation; dietary fiber; office workers; physical activity*

1. Introduction

Nutrition is one of the most important factors affecting human health and plays a fundamental role in achieving a healthy and long life (Martin et al., 2017). With long working hours and stressful working environment, office workers are at risk of unhealthy diet and insufficient physical activity (Jeong et al., 2013). Healthy nutrition increases the productivity of office workers, strengthens their immune system, and reduces the risk of disease and the rate of occupational diseases (Close et al., 2018).

In the diagnosis of constipation, there are factors that negatively affect the quality of life, such as infrequent and difficult defecation (Song et al., 2019). Although chronic constipation is extremely common among adults, it is difficult to estimate the exact prevalence of constipation due to the lack of a generally accepted definition by doctors and patients. However, population-based studies indicate a global prevalence of 14%. It has been determined that the prevalence increases with age and is almost twice as common in women as in men (Scott et al., 2021). It is stated that the prevalence of functional gastrointestinal diseases in Turkey varies between 15-20% (Dengiz et al., 2022). In a population study conducted on 3214 people from 20 cities, the rate of constipation in Turkey was found to be 8.3% (Kasap and Bor, 2006). Constipation affects people's social lives, performance in daily life, and quality of life (Singh et al., 2007). Studies show that constipation is more common in office workers, who are thought to have more sedentary and stressful occupations (Song et al., 2019). Constipation is associated with low quality of life due to psychosocial effects (Dennison et al., 2005; Mirghafourvand et al., 2016; Li et al., 2021), which is thought to negatively affect

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work efficiency.

Dietary strategies, along with laxatives and faecal bulking agents, are also effective in the treatment of constipation (Aslam et al., 2022). Although lifestyle changes are generally recommended as first-line therapy in the treatment of constipation, data on the effectiveness of these measures are limited. The most recommended treatment in this regard is to increase dietary fiber intake and physical activity (Yang et al., 2012). Dietary fiber, which is resistant to digestive enzymes, is mostly found in grains, fruits and vegetables. Soluble fiber fermented by gut bacteria absorbs water to become a gelatinous, sticky substance. However, insoluble fiber has a bulking effect (Otles and Ozgoz, 2014). In addition, it is believed that exercise facilitates defecation by shortening the transit time in the gastrointestinal tract. Furthermore, the decrease in muscle tone due to sedentary life leads to reduced function of the abdominal and pelvic floor musculature, which is involved in defecation (Gao et al., 2019). Studies in Turkey examining the bowel habits of office workers who are thought to be at risk for constipation are limited. The aim of our study was to determine the relationship between daily fiber intake, physical activity levels and bowel habits of office workers.

2. Materials and methods

2.1. Study design

Our study was conducted between June 2018 and November 2018 with the aim of determining the relationship between daily fiber intake, physical activity levels and bowel habits of office workers. Daily fiber intake was determined with food consumption records. The International Physical Activity Questionnaire (IPAQ) was used to determine the physical activity levels of the participants (Karaca and Turnagol, 2007). Bowel habits were determined by the Rome III Diagnostic Criteria and the Bristol Stool Scale. The sample of this cross-sectional study included 100 volunteer office workers in the province of Istanbul, aged 19-65, without any diagnosed bowel disease. The data collection process of the study was carried out after the approval of the ethics committee (2018-05/04).

2.2. Questionnaire

A questionnaire consisting of 29 questions was created by the researchers in order to determine the demographic characteristics, nutrition and physical activity habits, and bowel habits of the participants. The questions on bowel habits were prepared based on the Rome III criteria, used as the diagnostic criteria of intestinal diseases, and the Bristol Stool Form Scale which was developed in 1990 by Lewis and Heaton. According to this scale, the stool of individuals is classified into 7 groups. The shapes of the stools differ according to their residence time in the colon. For this reason, Bristol Stool Form Scale has been accepted as a reliable and fast indicator of transition time. Low scores (1, 2) represent slow transit, high scores (5-7) represent fast transit and impaired rectal tenderness (Lewis and Heaton, 1997).

According to the activities calculated by the MET-minute score, the participants were divided into 3 activity groups: inactive, minimally active, very active (Gay et al., 2019).

The 24-hour dietary recall method was used to determine the nutritional status of the participants. After agreeing to participate in the research, the participants were asked to keep a food consumption record for three straight days, 2 days on weekdays and 1 day on weekends. Average fiber intakes from food consumption records were grouped according to Recommended Dietary Allowances (RDA) (Food and Nutrition Board, 2002). Household units (such as water glass, thin/thick slice, coffee/teacup, matchbox, meal/tea spoon) were used in the records.

2.3. Data analysis

Statistical evaluation of the data was done with the SPSS (Statistical Package for Social Sciences) 23.0 package program. Chi-square test was used to evaluate the differences between variables. Descriptive statistics were presented as number, percentage, mean and standard deviation. The data obtained from the food consumption records were entered into the Nutrition Information System (BEBIS) version 7.2 and the daily average fiber intake was determined.

3. Results

The general characteristics of the individuals are given in Table 1. The mean age of the participants was 33.25 ± 7.28 years and 73.0% were women. 55.0% of the participants were married. 89.0% of the participants had an educational status of college or above. It was observed that the majority of the participants (88.0%) were physically inactive or minimally active (Table 1).

Table 1
General characteristics of office workers (n=100).

Demographic Characteristics		n	%
Gender	Female	73	73.0
	Male	27	27.0
Marital status	Married	55	55.0
	Single	45	45.0
Educational status	High school	11	11.0
	College and above	89	89.0
Physical activity status	Inactive	30	30.0
	Minimally active	52	52.0
	Very active	18	18.0

The comparison of Bristol scale scores and defecation frequencies according to the activity status of office workers is given in Table 2. According to the Bristol scale, 31.8% of the inactive participants and 27.3% of the very active participants had slow bowel transit (p=0.590). When compared according to the frequency of defecation, it was found 6.7% of the inactive and 5.6% of the very active participants defecated once in three days (p>0.05) (Table 2).

The knowledge levels of the individuals about dietary fiber are shown in Table 3. While 43.0% of the participants answered yes to the question “Is dietary fiber essential for maintaining a healthy life?”, 51.0% of the participants stated that they had no knowledge. Of those who answered yes to this question, 47.9% were women (p<0.05). While 39.0% of the participants answered yes to the question “Does increasing dietary fiber consumption affect defecation frequency?”, no difference was found between men and women (p>0.05). To the question “Which is the natural food group with the highest dietary fiber content?”, the most common answers were vegetables and fruits (60.0%), I do not know (18.0%), and legumes (13.0%), respectively. When the average daily fiber consumption of the individuals participating in the research is examined; it was

Table 2
Comparison of Bristol form and defecation frequency according to physical activity level of office workers.

		Physical Activity						p
		Inactive		Minimally Active		Very Active		
		n	%	n	%	n	%	
Bristol scale	Low scores (1,2)-slow transit	7	31.8	10	40.9	6	27.3	0.590
	Moderate scores (3,4)-normal transit	18	28.6	34	54.0	11	17.5	
	High scores (5-7)-fast transit	5	35.7	8	57.1	1	7.1	
Frequency of defecation	Once a day	16	53.3	23	44.2	6	33.3	0.822
	Twice a day	7	23.3	19	36.5	8	44.4	
	Once in two days	5	16.7	7	13.5	3	16.7	
	Once in three days	2	6.7	3	5.8	1	5.6	

Table 3
Knowledge levels of office workers about dietary fiber and their daily fiber intake.

Knowledge Level About Dietary Fiber		Female		Male		Total		p
		n	%	n	%	n	%	
Is dietary fiber essential for maintaining a healthy life?	Yes	35	47.9	8	29.6	43	43.0	0.039
	No	2	2.7	4	14.8	6	6.0	
	I do not know	36	49.3	15	55.6	51	51.0	
Does increasing dietary fiber intake affect defecation frequency?	Yes	33	45.8	6	22.2	39	39.0	0.092
	No	2	2.8	3	11.1	5	5.0	
	I do not know	38	51.4	18	66.7	56	56.0	
Fiber content Which natural food group has the highest fiber content?	Milk and dairy products	5	6.8	0	0.0	5	5.0	0.162
	Vegetables and fruits	46	63.0	14	51.9	60	60.0	
	Legumes	10	13.7	3	11.1	13	13.0	
	Meat and meat products	1	1.4	0	0.0	1	1.0	
	Grains	1	1.4	2	7.4	3	3.0	
	I do not know	10	13.7	8	29.6	18	18.0	
Daily dietary fiber intake	Insufficient (<20 g)	20	27.4	8	29.6	28	28.0	0.521
	Normal (20-35 g)	44	60.2	16	59.2	60	60.0	

Table 4
Comparison of Bristol form and defecation frequency according to fiber consumption of office workers.

Variables		Fiber						p
		Low		Normal		High		
		n	%	n	%	n	%	
Bristol scale	Low scores (1,2)-slow transit	6	21.4	13	21.7	3	25.0	0.378
	Moderate scores (3,4)-normal	19	67.9	39	65.0	5	41.7	
	High scores (5-7)-fast transit	3	10.7	8	13.3	4	33.3	
Frequency of defecation	Once a day	14	50.0	20	33.3	11	91.7	0.019
	Twice a day	7	25.0	26	43.3	1	8.3	
	Once in two days	5	17.9	10	16.7	0	0.0	
	Once in three days	2	7.1	4	6.7	0	0.0	

Table 5
Bristol form and defecation frequency status of office workers according to water consumption.

		2-3 Glasses		4-6 Glasses		7-9 Glasses		10-12 Glasses		Total		p
		n	%	n	%	n	%	n	%	n	%	
Bristol scale	Low scores (1,2)-slow transit	4	23.5	4	18.2	4	18.2	10	25.0	22	22.0	0.694
	Moderate scores (3,4)-normal transit	11	64.7	13	59.1	16	76.2	23	57.5	63	63.0	
	High scores (5-7)-fast transit	2	11.8	5	22.7	1	4.8	7	17.5	15	15.0	
Frequency of defecation	Once a day	8	8.1	10	10.7	6	6.1	20	20.4	44	44.9	0.025
	Twice a day	6	6.1	5	5.3	8	8.1	14	15.0	33	33.7	
	Once in two days	2	2.1	7	7.5	4	4.2	2	2.1	15	15.3	
	Once in three days	1	1.0	0	0.0	3	3.2	2	2.1	6	6.1	

determined that men consumed an average of 22.5±6.14 g and women consumed an average of 18.6±9.44 g. There was a significant difference between the genders in terms of fiber consumption ($p<0.05$). When fiber intake was evaluated, it was determined that 27.4% of female employees and 29.6% of male employees had insufficient dietary fiber intake (<20 g) ($p>0.05$) (Table 3). Considering the energy and other nutrient intakes of the participants, the daily energy, carbohydrate and protein

intakes of both men and women were lower than the RDA recommendations; it was determined that the fat intake was higher than the RDA recommendations.

The Bristol scale scores and defecation frequency of the office participants according to fiber consumption are shown in Table 4. There was no difference between fiber consumption and Bristol scale scores ($p>0.05$). When defecation frequency was compared, it was found that 50.0% of those with low fiber intake and 91.7% of those with excess fiber intake defecated once a day. The difference between the groups was found to be statistically significant ($p<0.05$) (Table 4). However, no significant differences were found between the Bristol scale and defecation frequency of the participants and daily carbohydrate, protein and fat intakes ($p>0.05$).

The Bristol scale scores and defecation frequency of the participants according to water consumption are shown in Table 5. According to the Bristol scale scores, 23.5% of those who drank 2-3 glasses of water a day had slow transit, 64.7% had normal transit, and 11.8% had fast transit ($p>0.05$). When defecation frequency was compared, it was found that 20.4% of those drank 10-12 glasses of water per day defecated once a day, 15.0% defecated twice a day, 2.1% defecated once in two days, and 2.1% defecated once in three days ($p<0.05$) (Table 5).

4. Discussion

It is thought that intestinal transit rate decreases due to the decrease in fiber consumption and physical activity in office workers who lead a sedentary life. The aim of our study was to examine the relationship between daily fiber intake, which varies depending on the dietary habits, physical activity levels, and bowel habits of office workers and to make recommendations in line with the results obtained.

It has been determined that increased physical activity level is associated with a significant decrease in the prevalence of constipation (Yurtdas et al., 2020). According to the results of a study conducted on women (n=62,500), in which 5.4% of women were diagnosed with constipation, the prevalence of constipation was found to be lower in women who reported doing physical activity every day. The prevalence rate of constipation among women with both high physical activity levels and high fiber intake was found to be 0.32 compared to those with physical activity levels of less than once a week and those in the lowest quantile of fiber intake (Dukas et al., 2003). Surprisingly, in another population-based study, self-reported physical inactivity was not strongly associated with fewer than 3 defecations per week or hard/lumpy stools (Wilson, 2020). Similarly, in the present study, no significant difference was found in the Bristol scale scores and the frequency of defecation according to the physical activity levels of office workers ($p>0.05$). Some studies have shown that exercise can reduce the risk of constipation by stimulating colonic motility and accelerating gastrointestinal transit (Strid et al., 2011; Costa et al., 2017). However, these effects may vary depending on the lifestyle (nutrition, exercise) of the person (Costa et al., 2017). This supports the lack of data showing the effects of physical activity on constipation. There is a need for randomized controlled studies on physical activity and constipation.

Common risk factors of chronic constipation include inadequate fiber and fluid intake. It has been determined that adequate fiber consumption increases stool weight and leads to a decrease in bowel transit time, while inadequate fiber consumption causes constipation (Forootan et al., 2018). However, diets containing soluble fiber may be associated with the improvement of chronic constipation symptoms (Suares and Ford, 2011). Evidences indicated that soluble fiber improves symptoms of constipation in irritable bowel syndrome with varying effects on abdominal pain (Bijkerk et al., 2004). In a study evaluating the effect of dietary fiber supplementation on functional constipation, placebo group, low dose group (LD: 7 g/day insoluble fiber + 1.2 g/day soluble fiber) and high dose group (HD: 14 g/day insoluble fiber + 2.4 g/day soluble fiber) were compared in parameters of constipation. When the subjects were subdivided on the basis of bowel transit time, a significant improvement was observed only in the HD group (Kim et al., 2006). Consistent with the literature, a significant difference was found between the fiber intake and the defecation frequency of the participants in the present study ($p<0.05$). In addition, in our study, it was determined that 27.4% of the female employees and 29.6% of the male employees had insufficient dietary fiber intake (<20 g). In a similar study conducted on office workers (n=58), the average fiber intake of the participants was 7.7 (2.70-37.80) grams. In the study, it was determined that only 3.44% of the participants had adequate dietary fiber intake (Faridahanum et al., 2021).

Considering the proven effects of dietary fiber on bowel habits (McRae, 2020), the knowledge level of people about dietary fiber is important. In our study, while 43% of the participants thought that dietary fiber is essential for a healthy life; 18% could not answer the question of the food with the highest fiber content. In a study with a high number of participants (n=1363), the majority of the participants had sufficient knowledge about the positive effects of dietary fiber-rich foods on obesity (84.3%), cardiovascular diseases (70.5%) and blood sugar regulation (68.9%). However, there was an inconsistency in translating this information into healthy food choices, especially when dining out (Alfawaz et al., 2020). These findings are similar to the fact that although the participants in our study knew the importance of dietary fiber, they did not know about foods containing dietary fiber. This contrasts with some studies that have shown that nutritional information is associated with food choices. Food choices depend not only on nutritional information, but also depends on external factors such as sensory evaluation, packaging, labeling, consumer perceptions, etc.

The number of studies examining the effect of fluid intake on constipation is insufficient (Lindeman et al., 2000; Shen et al., 2019). A study with a large number of participants (n=10.914) indicated that low fluid intake was associated with constipation (Markland et al., 2013). In a cohort of Turkish adults (n=4561), it was determined that decreased fiber intake and insufficient physical activity, as well as decreased fluid intake, were associated with an increased risk of constipation (Yurtdas et al., 2020). The majority of the individuals participating in the present study (78.0%) consume 10-12 glasses of water daily. A significant difference was found in defecation frequency with respect to daily water consumption of the participants ($p<0.05$).

5. Conclusion

Based on the results obtained in the present study, it was determined that dietary fiber intake was insufficient in 28% of office workers. A significant difference was found in bowel habits with respect to dietary fiber intake and fluid intake. It was determined that the participants with low fiber intake defecated

less frequently compared to participants with high fiber intake. There was no significant relationship between bowel habits and physical activity levels of office workers. These findings support studies showing that office workers, who are usually sedentary, have insufficient fiber intake. There is a need for further studies conducted with office workers who are at risk for constipation to elucidate this issue. Our study will be a reference for further studies that will question the dietary fiber intake and bowel habits of office workers. In addition, dietitians should raise awareness of office workers about healthy nutrition with simple practices that can be adapted to daily life in order to improve constipation symptoms and allow officer workers to lead a healthier life.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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Research article

The morpho-physiological responses of a tolerant and sensitive wheat (*Triticum aestivum* L.) cultivar to drought stress and exogenous methyl jasmonate

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Abstract

One of the most significant abiotic factors that has a negative impact on wheat productivity globally is drought. To comprehend the impacts of drought on wheat and propose remedies, numerous studies are carried out on various wheat varieties. In this study, 50 µM of methyl jasmonate (MeJA) was applied to tolerant Gün 91 and sensitive Bezostaja wheat cultivars and they were exposed to drought stress for 15 days. The responses of MeJA application on wheat development and physiology, as indicators of drought tolerance, were investigated comparatively. Wheat's morphology was negatively impacted by drought stress, which also decreased the crop's relative water content (RWC) and protein content while raising its soluble sugar level. Furthermore, Gün 91, a tolerant cultivar, came to the fore as the cultivar with higher shoot-root length, RWC, total soluble sugar and protein contents compared to Bezostaja cultivar as a result of drought application. Exogenous MeJA application, cause to increase in content of osmolytes (total soluble sugar, protein) compared to the drought group and had an improving effect in maintaining the water status of wheat seedlings. Hence, the RWC increased from 48.90% to 66.87% in the tolerant Gün 91 cultivar, but no change was observed in Bezostaja cultivar. Applying 50 µM of MeJA increased the protein by 4.42%, total soluble sugar by 19.92%, and RWC by 36.74% in Gün 91 cultivar while increasing protein by 3.11% and total soluble sugar by 11.02% in Bezostaja cultivar. Moreover, there is not any significant effect of MeJA observed on the shoot-root length of both cultivars and the RWC of Bezostaja cultivar. When all results are evaluated together, exogenous MeJA application may positively affect the response of wheat seedlings, and minimize the damaging effects so we can suggest using MeJA and cultivars that are resistant to drought stress for wheat yield.

Keywords: *Drought; methyl jasmonate; protein; sugar; wheat*

1. Introduction

One of the most extensively cultivated grains is wheat (*Triticum aestivum*) ranging from temperate to subtropical regions (Ahmed et al., 2019). Generally, the basic food of the world's population (approximately one-third of) is wheat and as the first cereal product in most developing countries. It has the potential to be used in numerous fields such as flour, bread, biscuits, cakes, cookies, pasta, noodles, beverages, and biofuel production (Knott et al., 2009). It is very important to increase wheat production for its use in many fields and providing the sufficient food for the rapidly increasing world population. Food and Agriculture Organization (FAO) reported "A further increase in population will lead to inadequate levels of food consumption and put pressure on food resources to increase even more". Based on these predictions, efforts have been made to develop product varieties that can cope with different types of stress and provide higher yields for a long time (FAO, 2023).

Drought has gained relevance because of the effects of recent global climate change, and it is one of the main factors limiting world wheat yield. It is predicted that global warming and climatic fluctuations will lead to significant losses in wheat yield by increasing the frequency of droughts in the coming years (Rijal et al., 2021). Drought stress delays plant growth and

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crop yield by affecting the morphological, biochemical, physiological, and molecular properties of plants. Additionally, it results in a significant decrease in the efficiency of photosynthetic activity, water use, stomatal conductance and leaf area (Farooq et al., 2019). Plants undergo morphological changes that are critical to respond to water deficiency, such as a decrease in growth rate, a deep root system and altered root-to-shoot ratio are used to prevent drying out. Furthermore, plant cells exposed to drought accumulate some organic compounds (proline, glycine-betaine, soluble amino acids, sugars, etc.), in order to maintain their turgor status, reduce their osmotic potential, and facilitate water uptake from the external medium (Vinod, 2012). Methyl jasmonate (MeJA), a naturally occurring phytohormone that is a methyl ester of jasmonic acid, controls plant development and growth by preserving the biochemical, morphological, and physiological process of plants. It functions in some signal transduction systems as a signaling chemical, activating specific enzymes that catalyze biosynthetic events to produce protective substances such polyphenols, alkaloids, and antioxidants. Additionally, it has been shown that these signaling molecules function systemically, causing the activation of several defense genes that have been activated by a stressful environment. As a result, when exposure exogenously, these signaling molecules increase abiotic stress tolerance (Walia et al., 2007; Fahad et al., 2014). Some plant growth regulators synthesis is reduced by abiotic stressors. Therefore, for reducing the detrimental effects of abiotic stress, the exogenous usage of growth regulators can make up for the plant's endogenous shortage and enhance its tolerance (Ashraf and Foolad, 2007). While the exogenous use of methyl jasmonate regulates various plant physiological responses that lead to the development of tolerance to stress, these effects of MeJA vary depending on the tissue, plant species, severity, the exposure time of drought stress, and the application amount (Karami et al., 2013).

The growing demand for wheat and the fact that consumption in sub-Saharan Africa has recently reached around 650 million tons per year have put further pressure on the demand for wheat (Mason et al., 2012). In this manner, creating drought-tolerant wheat cultivars with higher water utilize productivity is of best need, particularly within the setting of food supportability. The using of tolerant cultivars is known as an effective method for increasing yield and operating in arid and semi-arid regions. Finding strategies to boost output under various environmental situations, such as the selection of tolerable cultivars to drought stress, may benefit from additional research on physiological and biochemical features and the exogenous application of suitable growth regulators. The aim of the study is; to investigate the morphological and physiological properties of two different wheat cultivars in various irrigation regimes with the application of methyl jasmonate exogenously.

2. Materials and methods

2.1. Growth conditions and MeJA application

Two wheat cultivars, including drought stress-sensitive Bezostaja and tolerant Gün 91 cultivars, were used in the study. Sodium hypochlorite (5%) was used for surface sterilization. The soil that was composed of peat and perlite (1:1) added to the pots in which the seeds would be planted, and each of them was watered until reaching the field capacity. Fifty of the sterilized seeds were planted in each pot and grown in the plant growth chamber under 4000 lux light intensity, 25°C temperature, and 16/8 hours light/dark photoperiod conditions for 43 days. All pot experiments were irrigated with ¼ Hoagland nutrient solution based on the field water capacity for 28 days, and drought stress applications were initiated after this period. At this stage, while the control group continued to be irrigated, the application groups were left to develop without irrigation for 15 days. On the 14th day after the start of the application, 50 µM MeJA was applied exogenously to the plants under drought stress by spraying it. All plants were harvested 24 hours after the MeJA application, and their root-shoot lengths and RWC were determined. Some fresh material samples from the control and application groups were left to dry in the shade and at room temperature to be used in the analysis of total soluble sugar content.

2.2. Root-shoot length

During the plant harvesting of the cultivars in the control and drought stress-applied groups, the root and shoot lengths were measured by a millimeter ruler in 10 repetitions and expressed as cm plant^{-1}.

2.3. Relative water content (RWC%)

Immediately after the plants were harvested, fresh weights of randomly selected plant samples in the control and application groups were measured and recorded. The plant materials, whose fresh weights were measured, were kept in distilled water for 6 hours so that they would reach osmotic balance, and at the end of this period, their turgor weights were recorded. At the next stage, the seedlings were dried at 50°C, dry weights were recorded by weighing them again. The -RWC of the materials in the control and application groups were calculated according to the formula below, based on these three measured values (Hu et al., 2010).

RWC (%) = [(Fresh Weight-Dry Weight) / (Turgor Weight-Dry Weight)] x 100

2.4. Total soluble sugar content

By using the phenol-sulfuric acid method, the amount of total soluble sugar was measured (Dubois et al., 1956). 50 mg sample was weighed at and ethanol (5 ml) was added before being placed in a bath at 80°C for 60 minutes. Test tubes were centrifuged at 5000 rpm for 20 minutes. Then, 1 ml of supernatant, 1 ml of 5% phenol, and 5 ml of concentrated sulfuric acid (H_2SO_4) were added and mixed by vortex. The total soluble sugar content was then reported as mg g^{-1} dry matter by using a UV-Vis spectrophotometer readings at a wavelength of 490 nm.

2.5. Protein content

0.5 g sample of the fresh plant material was homogenized in 100 mM phosphate buffer (pH 7.0) and centrifuged at 14000 rpm for 20 minutes at +4°C. After adding 480 ml of distilled water and 5000 ml of Bradford solution to 20 µl of the supernatant, UV-Vis spectrophotometer was used to detect the absorbance at a 595 nm wavelength. A standard curve made with bovine serum albumin (BSA) and protein contents were expressed as µg g^{-1} fresh weight (Bradford, 1976).

2.6. Statistical analysis

Three replications of the analysis were conducted using a random design. The data acquired from the analyses were analysed by one-way analysis of variance (ANOVA). Also, Duncan's test using the statistical analysis application SPSS 21.0. Each wheat cultivar was subjected to statistical analysis on its own. Statistics were considered as significant at a *p*-value of ≤ 0.05.

3. Results and discussion

In the present study, tolerant and sensitive wheat cultivars were selected, and their morphological and physiological responses and the effects of MeJA application were determined\ comparatively. Drought stress-sensitive Bezostaja and tolerant Gün 91 cultivars were chosen as the plant materials. The agricultural and climatic information on the two cultivars is available at www.wheatatlas.org (Wheatatlas, 2023). As a result of drought applications, the shoot length in both wheat cultivars increased less compared to the control, whereas the root length increased due to stress. In the control group, the plants continued to develop since irrigation was maintained. However, since there was a slowdown in development due to lack of water in drought-applied plants, the shoot length was shorter. The shoot length of Gün 91 was not statistically significant but showed greater improvement over Bezostaja (Table 1).

Table 1
Effect of MeJA on shoot and root length of wheat cultivars grown under drought stress conditions.

Treatment		Shoot length cm plant^{-1}	Root length cm plant^{-1}
Gün-91	Control	50.95±0.89^{a}	12.70±0.56^{b}
	Drought	44.75±1.35^{b}	16.30±0.21^{a}
	Drought + MeJA	42.10±1.14^{b}	16.10±0.23^{a}
Bezostaja	Control	47.30±1.42^{a}	11.20±0.65^{b}
	Drought	43.10±1.22^{b}	14.30±0.32^{a}
	Drought + MeJA	43.25±0.75^{b}	14.10±0.44^{a}

*All values are given as Mean ± Standard Deviation. The same wheat variety and different character in the same column indicate that the difference between the means is significant ($p \leq 0.05$)

Wheat undergoes a number of morphological changes in response to drought, which are clearly visible at different plant development stages. In general, the shoot part and the root part of the wheat morphological response can be separated. The reduction in leaf size, shape, area, pubescence, and shoot length is included in the shoot component (Denčić et al., 2000). The growth of plants that continue to develop under normal conditions occurs in the presence of cell division, cell expansion, and turgor pressure (Rijal et al., 2021). In this study, it was considered that the water losses resulting from the drought application might lead to insufficient turgor formation and a possible decrease in the amount of auxin/cytokinin hormones adversely affected the plant growth. Our results on the effect of drought stress on growth are parallel with other studies. The responses of drought stress on the wheat reported that water deficiency led to a reduction in shoot length (Abdalla and El-Khoshiban, 2007). Likewise, many other researchers have reported a reduction in shoot growth when wheat is exposed to drought conditions (Azooz and Youssef, 2010; Farooq et al., 2013).

Plant roots penetrate the depths of the soil to absorb water in water shortage. Numerous studies have suggested that plant drought tolerance is correlated with root volume, weight, length, and density. To combat drought stress, wheat uses its roots' osmotic adjustment, greater root penetration and root density into the soil, and increased root-to-shoot ratio (Ali et al., 2020). If water potential decreases, it is ensured that the turgor level is maintained up to a certain level by making osmotic adjustments in the root, and potential gradient of water is rearranged for intaking of water. In our study, drought application promoted the increase in root length in both sensitive and tolerant cultivars. The root length, which increased due to drought stress, was more in tolerant wheat cultivar according to sensitive one (Table 1). As a result; it can be said that root length increased in the wheat cultivars so that plants could reach the water deep in the soil and use this water efficiently. In the comparative study of the standard Hartog and the Seri wheat genotype, which forms denser roots, the Seri genotype had a longer root length and thus contributed to the increase in yield by allowing more water uptake in deeper soil layers (Manschadi et al., 2006). While Ahmed et al. (2019) revelated that root length was longer in drought-tolerant wheat genotypes, Kato et al. (2007) and Kuru et al. (2021) indicated that, root length increased in case of water deficiency in different rice cultivars. Furthermore, it was observed that the MeJA application had no effect on root and shoot length in both wheat cultivars. The morphological changes due to drought occur as a result of a long duration of drought. When plants are exposed to short-term water deficiency, they close their stomata as the first response before the above-mentioned morphological responses and prevent water loss (Mahajan and Tuteja, 2005). Since the MeJA application was performed for a short time (24 hours) in our study, it was normal that there were no morphological changes such as root and shoot length.

The RWC is a useful measurement for estimating the water status of the plant and provides information about a genotype's capacity for absorption of water from the soil. In our study, drought stress reduced the RWC in both cultivars; however, the reduction rate was higher in the drought-sensitive Bezostaja cultivar. Moreover, while MeJA application improved RWC in the tolerant Gün 91 cultivar, it had no positive effect on the sensitive Bezostaja cultivar (Fig. 1). Based on protoplasmic permeability, RWC is a measure of a plant's sensitivity to drought stress, and higher RWC indicates a drought-tolerant plant (Raja et al., 2020). According to Pazirandeh et al. (2015)'s study on barley genotypes, the RWC decreases during drought stress, although the usage of methyl jasmonate improved the decline. Drought-tolerant Sirvan and sensitive Pishtaz wheat cultivars were exposed to drought, and MeJA was applied, and consequently, it was reported that drought-tolerant Sirvan cultivar had a higher RWC rate and low-concentration MeJA application had an improving effect in Sirvan cultivar (Javadipour et al., 2021). These literature data are parallel with the results of our study. Furthermore, according to Ahmad et al. (2017) and Bali et al. (2019), the administration of jasmonic acid enhanced the RWC of tomato and broad bean seedlings during heavy metal stress. By influencing plant stomatal cells, methyl jasmonate raises the RWC of the leaf and improves the water status, membrane stability, and water transport system of stressed plants. Closing the stoma likely causes an increase in RWC since less water is lost from the plant cells as a result (Javadipour et al., 2021).

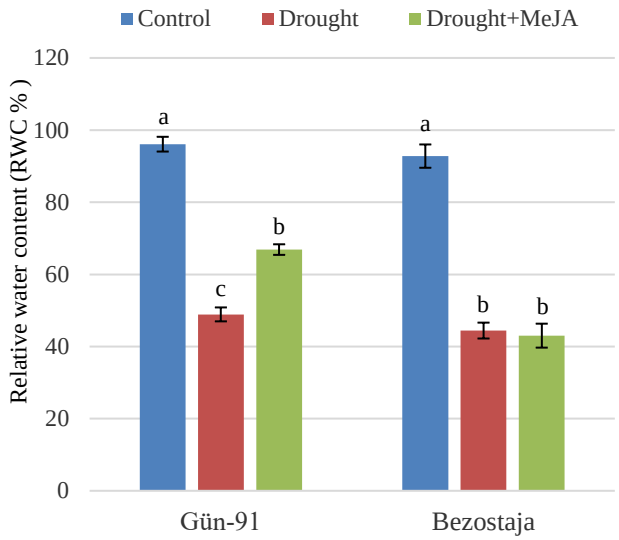

Fig. 1. Effect of MeJA on RWC of wheat cultivars grown drought stress conditions. Vertical bars indicate ±SE.

In general, sugars often function as osmoprotectants and membrane stabilizers in abiotic stress conditions. Furthermore, they also maintain the leaf water content and osmotic compatibility of plants exposed to drought stress conditions (Xu et al., 2007). Under drought stress, glucose causes stomatal closure and improves plant adaptability (Osakabe et al., 2013). In our study, drought stress increased the soluble sugar content in both cultivars, but the rate of increase in the drought-tolerant cultivar was higher. Furthermore, MeJA application increased the soluble sugar content in both cultivars compared to drought application, and the rate of increase was 19.92% in Gün 91 cultivar and 11.02% in Bezostaja cultivar (Fig. 2). In a study, sugar accumulation in the wheat cultivar increased due to drought, which was stated to have contributed to high wheat yield (Shi et al., 2016). Drought stress cause to increase the soluble sugar content of wheat genotypes, Sids 1 and Beni-Suef 5, however jasmonic acid use during drought considerably decreased the soluble carbohydrate content in both cultivars (Abeed et al., 2021). Contrary to these findings, other researches have shown that the exogenous administration of methyl jasmonate raises the soluble sugar concentration (Wu et al., 2012; Tayyab et al., 2020). This difference may be associated with the balance between starch accumulation in plants and sucrose, the transport form of carbohydrate in plants (Xu et al., 2015). The findings of our investigation are in agreement with those of Wu et al. (2012) and Tayyab et al. (2020). It can be said that the MeJA application attempted to preserve the osmotic balance against drought by increasing the accumulation of soluble sugar and, thus, contributed to the more efficient uptake of water from the soil by plants.

Drought, among other environmental stresses, harms proteins, membrane lipids, and other biological components by causing oxidative stress and the formation of free oxygen radicals (Dąbrowski et al., 2019). The results of our study revealed that protein content decreased in wheat cultivars exposed to drought stress. The decrease in protein content due to water deficiency was reported by many researchers (Yang et al., 2015; Faraji and Sepehri, 2020). MeJA applied with drought application cause to an increase in protein content in two cultivars compared to the drought application group (Fig. 3). The rate of increase was found to be 4.42% in Gün 91 cultivar and 3.11% in Bezostaja cultivar. Soaking corn seeds in MeJA may reduce the negative effects of drought stress by increasing antioxidant activities, proline and carbohydrate content as well as total protein. (Abdelgawad et al., 2014). Application of MeJA has been reported to play a protective role against water stress and increase protein levels in many plants (Tayyab et al., 2020; Abeed et al., 2021).

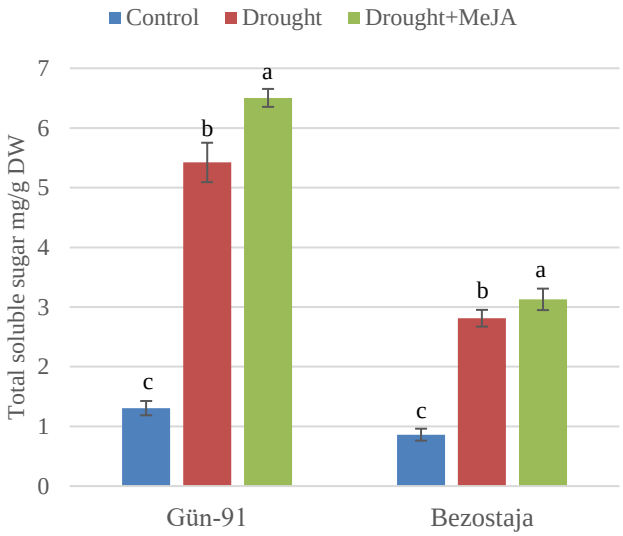

Fig. 2. Effect of MeJA on total soluble sugar of wheat cultivars grown drought stress conditions. Vertical bars indicate ±SE.

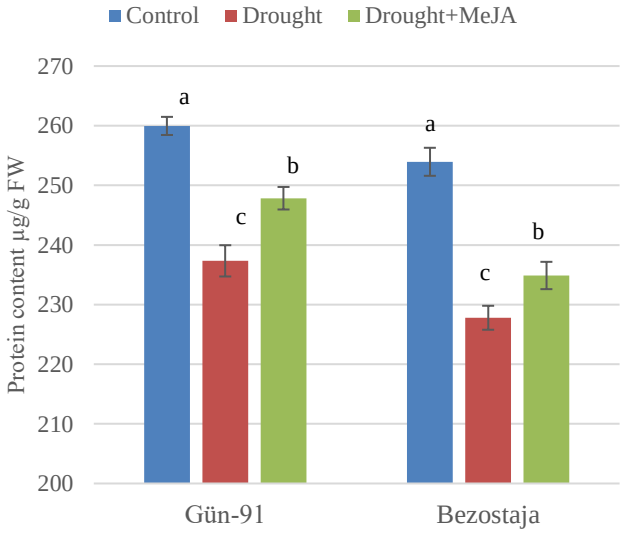

Fig. 3. Effect of MeJA on proteins of wheat cultivars grown drought stress conditions. Vertical bars indicate ±SE.

4. Conclusion

Both wheat cultivars were negatively affected by the lack of irrigation, which also changed the morphological and physiological characteristics. Nevertheless, the methyl jasmonate application had positive effects on the RWC, soluble sugar and protein contents. Exogenous applications of MeJA can mostly avoid the destructive impacts of drought-induced osmotic stress in wheat seedlings by balancing osmolytes such as sugar. Furthermore, they can also increase drought tolerance in wheat by preventing protein denaturation due to stress. The fact that Gün 91 cultivar had higher RWC, soluble sugar and protein contents after the MeJA application revealed that it was

more tolerant compared to Bezostaja cultivar. In conclusion, using MeJA is an alternative to change adverse results of drought stress together with the selection of appropriate cultivars. The results of our study will support research programs that attempt to develop anti-drought stress applications in order to increase the yield of wheat cultivars.

Conflict of interest: The author declares that he has no conflict of interests.

Informed consent: The author declares that this manuscript did not involve human or animal participants and informed consent was not collected.

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Research article

The genus of *Rumex* (Polygonaceae) in Istanbul and the new check-list of Polygonaceae in Türkiye

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Abstract

Rumex is an important genus of the Polygonaceae family. It is represented in Türkiye by 28 species (but two are suspicious) and seven hybrids. There are nine *Rumex* species in Istanbul. *Rumex bucephalophorus* is a rare dune plant and is known from only two places. In contrast, the *R. crispus* species, in particular, has been collected from most areas. All distributions of investigated species are recorded on the maps. In addition, all Polygonaceae members in Türkiye are listed in light of new developments.

Keywords: *Check-list; Istanbul; key; Polygonaceae; Rumex*

1. Introduction

Rumex is a genus belonging to taxonomically problematic Polygonaceae family that is with included about 160 species (Rechinger, 1984).

Identifying of *Rumex* species in the early stages of flowering is difficult, easiest when the nutlets are nearly ripe. Still, it becomes slightly more difficult again as the inflorescences dry and the ripe nutlets are shed (Holyoak, 1998). Ripe fruit is essential for a precise diagnosis. The best fruiting time interval is from March to June. Numerous stems often arise from a robust and thick rootstock, and some species have long rhizomes (perennials) or their rootstock (annuals).

The Polygonaceae family is studied in The Flora of Türkiye and The East Aegean Islands vol. 2 (Coode and Jullen, 1967). Later, there were various additions in vol.10 (Davis et al., 1988) and vol.11 (Ozhatay, 2000). There are 28 species and seven hybrids in Türkiye (Table 1).

There are no systematic publications on *Rumex* in Türkiye. Publications are especially relevant to the genera *Polygonum* and *Persicaria* (Keskin, 2009; Kilic, 2014; Kocyigit et al., 2015; Keskin and Severoglu, 2020; 2021a, 2021b, 2022; Keskin et al., 2021; 2022). Also, a new species, *Rheum telianum* Ilcim, was described (Ilcim and Karahan, 2020), and *Reynoutria* was added as a new genus for Türkiye (Karaer et al., 2020).

Table 1
The development of the Polygonaceae family to the present day in Türkiye.

Cins Adı	The Flora of Türkiye and The East Aegean Islands			Keskin, 2012
	Volume 2	Volume 10	Volume 11	
Atraphaxis	4 species	-	-	4 species
Pteropyrum	1 species	-	-	1 species
Calligonum	1 species	-	-	1 species
Rheum	1 species	-	-	1 species
Oxyria	1 species	-	-	1 species
Polygonum	27 species	6 species	4 species	40 species
Rumex	23 species and 5 hybrids	2 species and 2 hybrids	2 species	28 species and 7 hybrids
Emex	1	-	-	1 species
Fagopyrum	-	-	-	1 species
Fallopia	-	-	-	1 species

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2. Materials and methods

The work is based on field surveys (2019-2022) along various Istanbul districts. The samples were collected and deposited at the herbaria MUFE and NGBB (acronyms, according to Thiers 2022). Moreover, specimens from the Herbaria E, ANK, ISTE, ISTF, ISTO, MUFE, and NGBB were studied, and relevant literature on the genus concerning Türkiye and the neighbouring countries was analysed (Halacsy, 1904; Rechinger, 1964; Snogerup and Snogerup, 1997).

When preparing the maps, only the samples examined in the herbariums and the species collected were considered.

2.1. Study area

Istanbul is a big city between the European and Asian sides of the Bosphorus. A semi-arid Mediterranean climate is dominant in the area, with a local oceanic climate (Altay et al., 2020). Istanbul's property lies in Europe and Asia, between the Marmara and the Black Sea, and in two phytogeographical regions (Euro-Siberian and Mediterranean). Istanbul is a part of the Euro-Siberian region represented by the Euxine sub-region, while the Mediterranean region belongs to the East Mediterranean province (Davis, 1971; Altay et al., 2020).

Such a position manifests in miscellaneous flora and vegetation (Altay et al., 2020). Regarding the flora, Istanbul has a vibrant flora with a total of 2.218 taxa reported by Baytop (2009).

3. Results and discussion

Rumex species detected in Istanbul, according to Flora of Türkiye vol. 2 (Cullen, 1968), are *R. acetosella* L., *R. bucephalophorus* L., *R. conglomeratus* L., *R. crispus* L., *R. pulcher* L., *R. obtusifolius* L. subsp. *subalpinus* (Schur) Celak, *R. sanguineus* L., *R. tuberosus* L. at the end of this study, all these species were confirmed, and *R. cristatus* DC. species were added to the Istanbul flora.

The findings about the species and identification key are listed below.

3.1. Identification key of Rumex in Istanbul

1. Plants dioic; leaves with wide auricles to the sides at the base 2

_ Plants monoic; leaves without auricles at base 3

2. Roots tuberous; the inner tepals have a tubercle in the middle; fruiting tepals much wider than achenes *tuberosus*

_ Roots simple, rhizomatous; the inner tepals without a tubercle; fruiting tepals not enlargement a*cetosella*

3. Fruiting pedicels thick, at most as long as tepals *pulcher*

_ Fruiting pedicels thin, longer than tepals 4

4. Dune plants; flowers 1-2; pedicels completely swollen *bucephalophorus*

_ Land plants; flowers more than 2; pedicels not swollen 5

5. Tubercules large, up to tepal segments; inner tepal at fruit time forward noticeably elongated veinless part 6

_ Tubercules narrower than tepals; inner tepal not elongated forward, but webbed veins usually everywhere 7

6. Tubercule 1, almost spherical, white or reddish; pedicels longer than tepals *sanguineus*

_ Tubercules 3; length longer than width, usually dark-dirty white or rarely red; pedicel at most less long than from tepal *conglomeratus*

7. Tubercle 1; pedicels swollen at the tip, 2-times longer than tepals *obtusifolius* subsp. *subalpinus*

_ Tubercle 3; pedicels no swollen, at most little longer than tepals 9

8. Petiole deeply channelled; fruiting tepal 4-5 mm, circular in outlines *crispus*

_ Petiole terete; fruiting tepal 6-8 mm, length longer than width *cristatus*

3.2. Rumex species in Istanbul

3.2.1. Rumex acetosella L., Sp. Pl. 1: 338 (1753). (Fig. 1&2)

It is perhaps the most well-known species with its unique structure and leaves in the *Rumex* genus. Especially the leaves have a slightly bitter and sour taste. However, its morphology is very variable. The size range is very different. Naturally, many researchers consider these differences as different taxa; therefore, it cannot be said that all taxa are valid. One must admit that this species is highly polymorphic. Scientifically, it would inevitably be more correct to accept this species broadly: *Rumex acetocella* s.l. It probably grows in all districts of Istanbul.

3.2.2. Rumex bucephalophorus L., Sp. Pl. 1: 336 (1753). (Fig. 1&2)

It is a type of *Rumex* with a unique appearance. It is typical with clublike pedicels, which are especially thin on the underside but prominently swollen towards the top. Although all of the Istanbul populations are observed in the dunes, they exist outside the dune area, albeit very little. Therefore, it is possible to say that the population is well developed in the environment where it grows, but the dunes are often open to destruction. For this reason, there is often a decrease in their population. It is usually branched from the base, and the branches bend to the sides and show an upward curling structure. Some specimens are single-bodied and grow in a form that can be considered upright. The body is primarily red. The morphology of this species is variable. Many taxa related to the main species have been identified, but it is impossible to say that there are definite boundaries between them. For this reason, it would be more accurate to examine this species broadly: *Rumex bucephalophorus* s.l.

3.2.3. Rumex conglomeratus Murray, Prod. Gotting. 52 (1770). (Fig. 1&2).

It is a cosmopolitan species in Türkiye. It stands out as a species with a high ability to adapt to both ruderal environments and natural areas. It is a medium-sized species, less than one meter in length. The base leaves dry quickly while the fruit is in the ripening stage. Flower boards are usually in crowded clumps. The ends of the fruiting tepals are elongated tongue-in-cheek forward with typically veinless. Each tepal has a prominent tubercle. It is related to the *R. sanguineus* species. It is easily distinguished from it by the fact that the fruity tepals are 3-tuberculate (not 1-piece). Therefore, diagnoses based on non-fruited samples are always a candidate to be wrong. It probably grows in all districts of Istanbul.

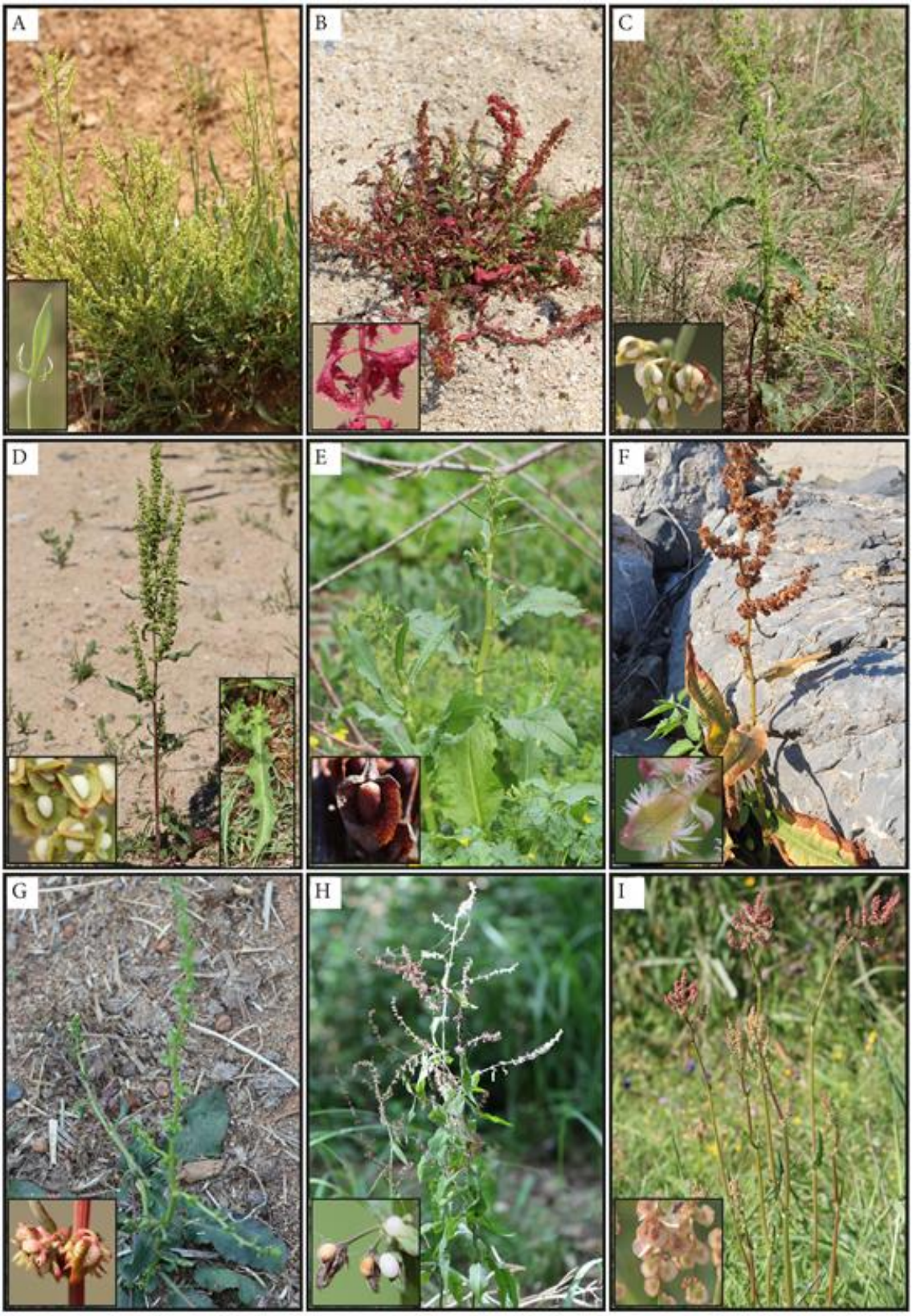

Fig. 1. *Rumex* species of Istanbul: **A.** *R. acetosella*, **B.** *R. bucephalophorus*, **C.** *R. conglomeratus*, **D.** *R. crispus*, **E.** *R. cristatus*, **F.** *R. obtusifolius* subsp. *subalpinus*, **G.** *R. pulcher*, **H.** *R. sanguineus*, **I.** *R. tuberosus*

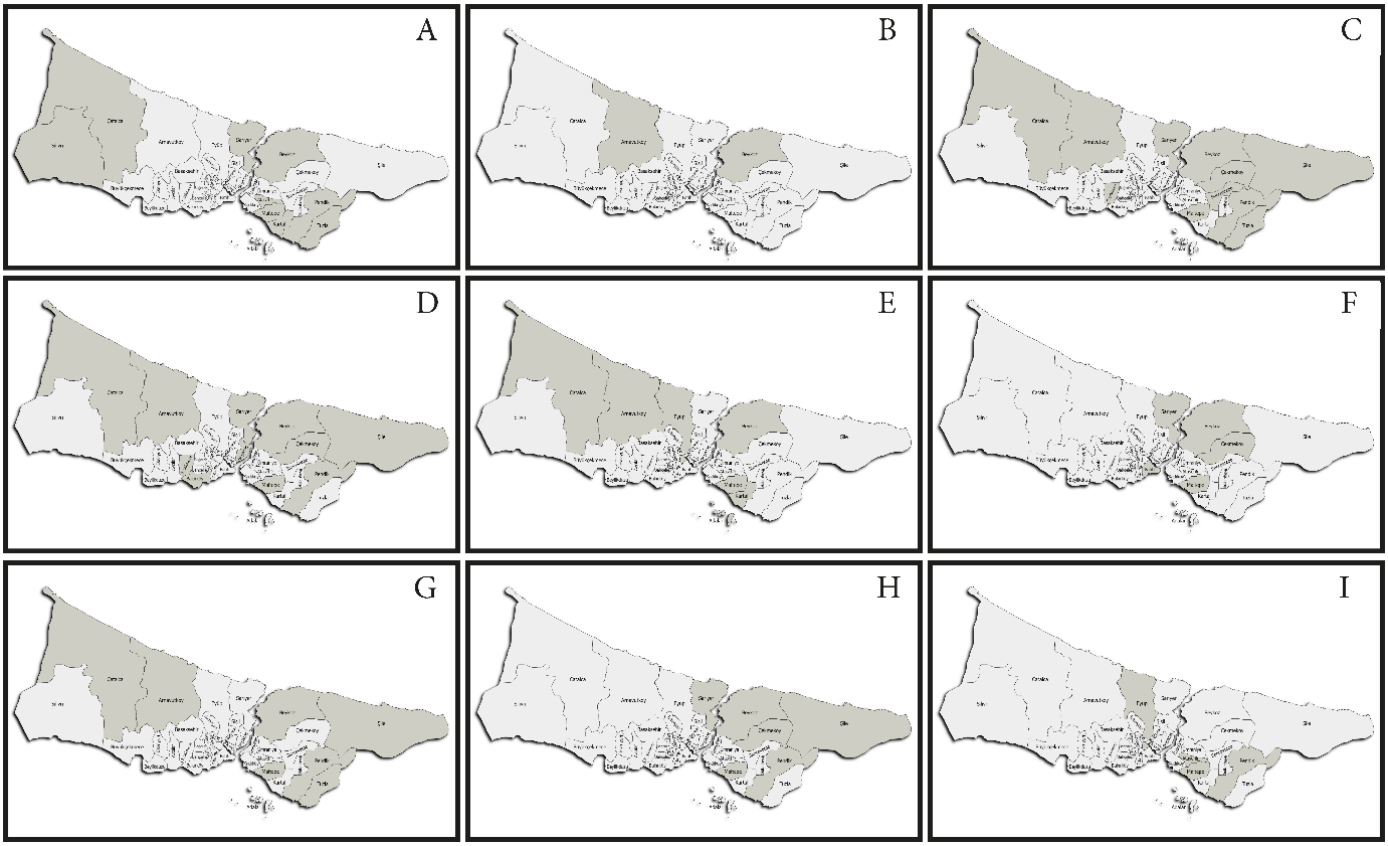

Fig. 2. Distributions maps of *Rumex* species in Istanbul: **A.** *R. acetosella*, **B.** *R. bucephalophorus*, **C.** *R. conglomeratus*, **D.** *R. crispus*, **E.** *R. cristatus*, **F.** *R. obtusifolius subsp. subalpinus*, **G.** *R. pulcher*, **H.** *R. sanguineus*, **I.** *R. tuberosus*.

3.2.4. Rumex crispus L., Sp. Pl. 1: 335 (1753). (Fig. 1&2).

It is one of Istanbul's most common *Rumex* species with long base leaves and wide channeled stems. It can be found in many different habitats. We can explain the fact that it has such variable characteristics with its broad ecological willingness. In addition, the leaves of this species are often collected for cooking purposes. Therefore, it probably grows in all districts of Istanbul.

3.2.5. Rumex cristatus DC., Cat. Pl. Horti Monsp. 139 (1813). (Fig. 1&2).

It is a new record for Istanbul. Although it is a new record, this species has been found in Istanbul's Anatolian and Thrace parts. In addition, various herbarium specimens were examined. A number of publications in the literature emphasize that it has a wide morphological variation. Therefore, more detailed studies should be done on this species in our country. In this way, the boundaries between interpretations can be well defined, and in this case, new taxa can be specified if necessary. It forms a small group of individuals in the living environment. It generally prefers a rich soil structure.

3.2.6. Rumex obtusifolius L. subsp. subalpinus (Schur) Rech. f. in Beih. Bot. Centralbl. 49(2): 61 (1932). (Fig. 1&2).

It is a polymorphic species. In Türkiye, only subsp. *subalpinus* taxon is recorded. Its long and drooping pedicels are distinctive. In addition, the triangular outline of the fruit and only one tubercle on it is a unique feature. This species is collected for cooking. In addition, this type is a forgotten value because the yellow color obtained from its roots was often used in old Turkish carpets and kilims (Eyupoglu et al., 1983; Ugur, 1988).

3.2.7. Rumex pulcher L., Sp. Pl. 1: 336 (1753). (Fig. 1&2).

It is a cosmopolitan species with a unique stance. Pedicels thickened and curved downwards at the fruiting time are very typical. Similarly, the basal leaves' violin-like (pandurate) structure is an excellent distinguishing character. Fruit structure has very variable characteristics. For this reason, many related taxa have been defined. Therefore, this situation reveals a highly controversial problem from a systematic point of view. Similar differences can be seen when examining the population.

For this reason, we think a classification based only on the size of fruit teeth is wrong. Therefore, it would be more accurate to examine this species in a broader sense: *Rumex pulcher* s.l. It probably grows in all districts of Istanbul.

3.2.8. Rumex sanguineus L., Sp. Pl. 1: 334 (1753). (Fig. 1&2).

Table 2
A comparison of *Rumex sanguineus* and *Rumex conglomeratus* species.

	Rumex sanguineus	***Rumex conglomeratus***
Stem	40-100 cm	30-80 cm
Ochrea	5-10 cm	1-3 cm
Petioles	4-5 cm	3-6 cm
Tubercles	1-piece, shorter than tepals	3-piece, as long as tepals
Pedicels	Longer than fruiting tepal	As long as fruiting tepals
Achenes	1-1.5 mm	1.5-2 mm

It is related to the *R. conglomeratus* species and is one of

the most complex species to collect (Table 2). It is distinguished by having a single tubercle in the fruit, red veins on the base leaves, long ocrea, and height. The literature has reported that this species is difficult to find and is most likely an invasive species (Chase, 1926). Considering that it is known from only four provinces in Türkiye, it can easily be said that all records here are invasive.

3.2.9. Rumex tuberosus L., Sp. Pl., ed. 2. 1: 481 (1762). (Fig. 1&2).

It is a typical species with prominent tubers in its underground structure and lanceolate leaves. However, it also has many different forms and shapes. Therefore, other subspecies have been defined. A few of these subspecies can be found in Istanbul (Cullen, 1967). However, the characters used to distinguish them are not very precise.

For this reason, it was concluded that these subspecies are only the morphological differences shown by the species, and it is supposed that it is correct to examine them in a broad sense: *R. tuberosus* s.l. Similarly, this species has been studied by Uotila (2017) in a way we accept. This species primarily inhabits open meadows and forest margins. It is susceptible to environmental factors. In other searches made at the same gathering time in areas where collections were made before, either they could not be found, or the number of individuals was deficient.

4. A new checklist of Polygonaceae in Türkiye

I. *Atraphaxis*

1. *A. angustifolia* Jaub. & Spach, Illustr. Pl. Or. 2: 15 (1844-6).
2. *A. billardieri* Jaub. & Spach, Illustr. Pl. Or. 2: 15 (1844-6) var. *billardieri*
3. *A. billardieri* Jaub. & Spach var. *tournefortii* (Jaub. & Spach) Cullen, Notes Roy. Bot. Gard. Edinburgh 27: 215 (1967).
4. *A. grandiflora* Willd., Sp. Pl. 2: 440 (1799). end.
5. *A. spinosa* L., Sp. Pl. 333 (1753).

II. *Bistorta*

6. *B. officinalis* L., Sp. Pl. 360 (1753).
7. *B. carnea* (K.Koch) Kom., Fl. URSS 5: 682 (1936).

III. *Calligonum*

8. *C. polygonoides* L., Sp. Pl. 530 (1753).

IV. *Emex*

9. *E. spinosa* (L.) Campd., Monogr. des Rumex 58 (1819).

V. *Fagopyrum*

10. *Fa. esculentum* Moench, Methodus 290 (1794).

VI. *Fallopia*

11. *F. aubertii* (L.Henry) Holub, Folia Geobot. Phytotax. 6 (2): 176 (1971).
12. *F. convolvulus* (L.) Á.Löve, Taxon 19: 200 (1970).
13. *F. dumetorum* (L.) Holub, Folia Geobot. Phytotax. 6: 176 (1971).

VII. *Koenigia*

14. *K. alpina* (All.) T.M.Schust. & Reveal, Taxon 64 (6): 1200 (2015).

VIII. *Oxyria*

15. *O. digyna* (L.) Hill, Hort. Kew. 158 (1768).

IX. *Persicaria*

16. *Pe. amphibia* (L.) Delarbre, Fl. Auvergne ed. 2: 519 (1800).
17. *Pe. decipiens* (R.Br.) K.L.Wilson, Telopea 3(2): 178 (1988).
18. *Pe. hydropiper* (L.) Delarbre, Fl. Auvergne (Delarbre) ed. 2: 518 (1800).
19. *Pe. hydropiperoides* Small, Fl. S.E. U.S. 378, 1330 (1903).
20. *Pe. lapathifolia* (L.) Delarbre Fl. Auvergne ed. 2: 519 (1800) subsp. *lapathifolia*
21. *Pe. lapathifolia* (L.) Delarbre subsp. *brittingeri* (Opiz) Soják Preslia 46: 153 (1974).
22. *Pe. lapathifolia* (L.) Delarbre subsp. *nodosa* (Pers.) Á.Löve, Rit Landbú. Atvinnud. Háskólans, B 3: 109 (1948).
23. *Pe. leblebicii* (Yıld.) Raus, Willdenowia 44(2): 293 (2014). end.
24. *Pe. maculosa* Gray, Nat. Arr. Brit. Pl. ii. 269 (1821).
25. *Pe. minor* (Hudson) Opiz, Seznam Rostlin Kvetney Cesk, 72 (1852).
26. *Pe. nepalensis* (Meisn.) H. Gross, Bot. Jahrb. Syst. 49: 277 (1913).
27. *Pe. orientalis* (L.) Spach, Hist. Nat. Vég. (Spach) 10: 537 (1841).
28. *Pe. perfoliata* (L.) H.Gross, Bot. Jahrb. Syst. 49(2): 275 (1913).
29. *Pe. thunbergii* (Siebold & Zucc.) H.Gross, Bot. Jahrb. Syst. 49(2): 275 (1913).

X. *Polygonum*

30. *Po. afyonicum* Leblebici & Gemici, N. Roy. Bot. Gard. Edin. 42(2): 321(1985). end.
31. *Po. arenarium* Waldst. & Kit., Descr. Icon. Pl. Hung. 1: 69 (1801).
32. *Po. arenastrum* Boreau, Fl. Centre France, ed. 3, 2: 559 (1857).
33. *Po. argyrocoleon* Steud. & Kunze, Linnea 20: 17 (1847).
34. *Po. aviculare* L., Sp. Pl. 362 (1753).
35. *Po. bellardii* All., Fl. Pedem. ii. 205. t. 90. f. 2 (1785).
36. *Po. buxiforme* Small, Bull. Torrey Bot. Club 33: 56 (1906).
37. *Po. cappadocicum* Boiss. & Balansa, Diagn. Pl. Orient. ser. 2, 4: 78 (1859). end.
38. *Po. cognatum* Meissn. Monogr. Polyg. 91 (1826).
39. *Po. ekimianum* Leblebici, H.Duman & Aytaç, Willdenowia: 23 (1-2): 163 (1993). end.
40. *Po. equisetiforme* Sibth. & Sm., Fl. Graec. Prodr. 1: 266 (1809).
41. *Po. istanbulicum* M.Keskin, Nordic J. Bot. 27 (1): 11 (2009). end.
42. *Po. karacae* Ziel. & Borat., Willdenowia 21 (1-2): 173 (1991). end.
43. *Po. longipes* Halácsy & Charrel, Oesterr. Bot. Z. 40: 164 (1890).
44. *Po. maritimum* L., Sp. Pl. 1: 361 (1753).
45. *Po. melihae* Gemici & Kit Tan, Nordic J. of Botany 32(5): 540 (2013). end.
46. *Po. mersinicum* M. Keskin, Ann. Bot. Fenn. 59(1): 318 (2022). end.
47. *Po. mesembricum* Chrtek, Preslia 32: 367 (1960).
48. *Po. urnigera* M.Keskin, Phytotaxa 538 (2): 114 (2022). end.
49. *Po. neglectum* Besser, Enum. Pl. 45 (1821).
50. *Po. paronychioides* C.A.Mey., Bull. Soc. Imp.

Naturalistes Moscou: 356 (1838).

51. *Po. patulum* Bieb., Fl. Taur.-Cauc. 1: 304 (1808).
52. *Po. pulchellum* Loisel. Mém. Soc. Linn. Paris 6: 411 (1827).
53. *Po. polycnemoides* Jaub. & Spach, Ill. Pl. Orient. 2: 30 (1844).
54. *Po. praelongum* Coode & Cullen, Notes Roy. Bot. Gard. Edinburgh 27: 215 (1967).
55. *Po. romanum* Jacq., Bserv. Bot. 3: 8, t. 58 (1768).
56. *Po. rottboellioides* Jaub. & Spach, Ill. Pl. Orient. 2: 32 (1845).
57. *Po. rurivagum* Jord. ex Boreau, Fl. Centre France, ed. 3, 2: 560 (1857).
58. *Po. salebrosum* Coode & Cullen, Notes Roy. Bot. Gard. Edinburgh 27: 215 (1967). end.
59. *Po. salsugineum* M.Bieb., Tabl. Provo Casp. 114 (1798).
60. *Po. samsunicum* Yıld. & Leblebici, Willdenowia 19(1): 87 (1989). end.
61. *Po. setosum* Jacq., Obs. 3: 8, t. 57 (1768).
62. *Po. luzuloides* Jaub. & Spach, Ill. Pl. Orient. 2: 37 (1845).
63. *Po. sivasicum* Kit Tan & Yıldız, Notes Roy. Bot. Gard. Edinb. 45: 439 (1988). end.

XI. *Pteropyrum*

64. *Pt. olivierii* Jaub. & Spach, Ill. Pl. Orient. 2: 9 (1846).

XII. *Reynoutria*

65. *Re. japonica* Houtt., Nat. Hist. (Houttuyn) 2(8): 639, t. 640 (1777).

XIII. *Rheum*

66. *Rh. ribes* L., Sp. Pl. 1: 372 (1753).
67. *Rh. telianum* İlçim, Phytotaxa 477(1): 82 (2020). end.

XIV. *Rumex*

68. *Ru. acetosa* L., Sp. Pl. 1: 337 (1753).
69. *Ru. acetosella* L., Sp. Pl. 338 (1753).
70. *Ru. alpestris* Jacq., Enum. Stirp. Vindob. 62 (1762).
71. *Ru. alpinus* L., Sp. Pl. 1: 334 (1753).
72. *Ru. amanus* Rech.f., Candollea 12: 108 (1949). end.
73. *Ru. angustifolius* Campd., Monogr. Rumex 63: 73 (1819). subsp. *angustifolius*
74. *Ru. angustifolius* Campd. Monogr. Rumex 63: 73 (1819). subsp. *macranthus* (Boiss.) Rech.f., Feddes Rep. 353 (1934).
75. *Ru. bithynicus* Rech.f., Pl. Syst. Evol. 148: 317 (1985). end.
76. *Ru. bucephalophorus* L., Sp. Pl. 336 (1753).
77. *Ru. caucasicus* Rech.f., Repert. Spec. Nov. Regni Veg. 31: 258 (1933).
78. *Ru. chalepensis* Mill., Gard. Dict. ed. 8, n. 11 (1768).
79. *Ru. conglomeratus* Murray, Prod. Desig. Stir. Gotting. 52 (1770).
80. *Ru. crispus* L., Sp. Pl. 335 (1753).
81. *Ru. cristatus* DC., Cat. Pl. Horti. Monsp. 139 (1813).
82. *Ru. cyprius* Murb., Acta Univ. Lund. n.s., ii. No. 14, 20 (1907).
83. *Ru. dentatus* L., Mant. Pl. 2: 226 (1771). subsp. *halacsyi* (Rech.) Rech.f., Beih. Bot. Centr. 49(2): 16 (1932).
84. *Ru. gracilescens* Rech.f., Phyton (Horn) 8: 143 (1959). end.
85. *Ru. hydrolapathum* Huds., Fl. Angl., ed. 2, 1: 154 (1778).
86. *Ru. maritimus* L., Sp. Pl. 335 (1753).
87. *Ru. nepalensis* Spreng., Syst. Veg. ed. 16, 2: 159 (1825).
88. *Ru. obtusifolius* L., Sp. Pl. 335 (1753). subsp. *subalpinus* (Schur) Celak., Prodr. Fl. Böhm. 159 (1873).
89. *Ru. olympicus* Boiss., Diagn. Pl. Orient. 1, 5: 45 (1844). end.
90. *Ru. palustris* Sm., Fl. Brit. 1: 394 (1800).
91. *Ru. patientia* L., Sp. Pl. 333 (1753).
92. *Ru. ponticus* E.H.L.Krause, Beih. Bot. Centralbl. 24, 2: 15 (1908). end.
93. *Ru. pulcher* L., Sp. Pl. 336 (1753).
94. *Ru. sanguineus* L., Sp. Pl. 334 (1753).
95. *Ru. scutatus* L., Sp. Pl. 337 (1753).
96. *Ru. thyrsiflorus* Fingerh., Linnaea 4: 380 (1829).
97. *Ru. tmoleus* Boiss., Diagn. Pl. Orient. 1, 12: 101 (1853). end.
98. *Ru. tuberosus* L., Sp. Pl. ed. 2, 481 (1762).
99. *Ru.* x *autranianus* Freyn & Sint. ex Dinsm., Post, Fl. Syria, Palest. & Sinai, ed. 2: 465 (1933). (*R. nepalensis* x *R. obtusifolius*).
100. *Ru.*x *gemlikensis* Rech. f., Pl. Syst. Evol. 148(3-4): 319 (1985). (*R. bithynicus* x *R. pulcher*). end.
101. *Ru.* x *muellneri* Rech.f., Verh. Zool.-Bot. Ges. Wien 49: 243 (1889). (*R. nepalensis* x *R. patientia*).
102. *Ru.* x *prusianus* Rech.f., Pl. Syst. Evol. 148 (3-4): 319 (1985). (*R. bithynicus* x *R. cristatus*). end.
103. *Ru.* x *pseudopatientia* Rech.f., Phyton (Horn) 8: 151 (1959). (*R. gracilescens* x *R. patientia*).
104. *Ru.* x *subtranianus* Freyn & Sint., Bull. Herb. Boiss. 4: 178 (1896). (*R. nepalensis* x *R. obtusifolius*).
105. *Ru.* x *subtrilobus* Boiss., Diagn. Pl. Orient. ser. 1, 5: 46 (1844). (*R. cristatus* x *R. nepalensis*)
106. *Ru.* x *uludaghensis* Rech.f., Phyton (Horn) 8: 151 (1959). (*R. nepalensis* x *R. olympicus*). end.

There are 106 taxa of Polygonaceae in the flora of Türkiye. Of these, 19 taxa (*Atraphaxis* 1, *Persicaria* 1, *Polygonum* 11 and *Rumex* 6) are endemic. *Persicaria* leblebicii (Yıld.) Raus species is a highly suspicious endemic (Keskin and Severoglu, 2020).

Polygonum is the most difficult to diagnose genus. Its characters are close to each other, so it should be examined carefully. Identified from the province of Istanbul, *Po. urnigera* M.Keskin is our newest species and is the best example (Keskin and Severoglu, 2022). Of the species listed above, 3 (*Polygonum romanum* Jacq., *R. alpestris* Jacq., *R. thyrsiflorus* Fingerh) is doubtful of being found in Türkiye. Although these species have been reported by Karamanoglu (1974), they have not yet been collected. Therefore, they are possibly wrong-identified.

Rumex is very suitable for hybridization. Three of these hybrids are endemic. It is predicted that the number of hybrids will increase as a result of detailed field studies.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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Research article

Trends of changing land use dynamics in the Terkos Lake basin between 1980 and 2023 and their impact on natural ecosystems

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Abstract

Anthropogenic processes are one of the main causes of environmental change in this century. As an indicator of man's struggle for dominance over nature, the environment has been directly affected. These changes, which we encounter in every region of the place where we live, on a local and global scale, and which are due to man, cause the natural cycle of ecosystems to be disrupted. As in Türkiye in general, land use changes in the study area under the influence of direct and indirect factors in some regions are very rapid. No matter how much effort are made to control them, factors that have a direct impact on the environment, such as population growth, agriculture, industrial facilities, and the design of transport infrastructure, are the most important causes of change. In this direction, this study aims to identify the trends of land use changes around Lake Terkos and to reveal the deficiencies and fragilities of the relationship networks. It is also an indication of possible changes in the ecological status of the lake and its surroundings in relation to this situation. Terkos Lake's prolonged use as a crucial drinking water source for Istanbul makes it a valuable study site to investigate its ecological state and management practices. Nevertheless, it has recently been under pressure due to transportation (airport, Northern Marmara Motorway, Istanbul Canal and other transport networks), urban sprawl, and industry. In this context, first of all, the dynamics of land use and the rapidly changing areas (hot zones) between 1980 and 2023 have been identified and the extent of the changes over time has been shown. Possible future land use changes were analysed in the light of this data. As a result of the study, the speed of transformation of green areas was revealed. In this direction, especially in the field of the aquatic ecosystem, vulnerable areas were identified, the degree of being affected by future change was revealed and the trend in the dimensions of use and change was analysed.

Keywords: *Flora; land use and land cover change; Lake of Terkos; natural ecosystem*

1. Introduction

Land use and land cover change, which has been a very intensive area of study worldwide in recent years, has been analysed in different areas. These areas include cities (Garipagaoglu and Duman, 2018; Dadashpoor et al., 2019; Ozturk and Gunduz, 2019; Luo et al., 2020; Duran and Dogan, 2022; Karaoglu and Erdel, 2022), coastal areas (Guney and Polat, 2015; Abdullah et al., 2019), natural ecosystems, especially lake and river basins (Gulersoy, 2014; Sun et al., 2018; Peters et al., 2019; Ozcalik et al., 2020; Bahadir and Uzun, 2021; Kacmaz and Doker, 2021; Tas and Akpinar, 2021; Bayrak et al., 2022). People may encoumore than one environmental problem in their living environment. Climate change, the growth of urban areas, and the proliferation of industrial facilities lead to loss of diversity over time, the degradation of soils, the pollution of water, and thus the degradation of ecosystem services (Costanza et al., 2014; Meyfroid et al., 2018). Anthropogenic processes are the main driver of land use change (Lai et al., 2021). Among these changes on Earth, 60% are

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attributed to direct anthropogenic influence, while 40% are due to indirect factors, including climate change (Song et al., 2018).

Owing to the hastening of developmental endeavours in urban and rural regions during recent years, the proximal vicinity of Lake Terkos, located in the northern region of Istanbul, has experienced land use change processes such as the expansion of settlements, the reduction of the effectiveness of agricultural areas and the intensification of transport activities. The urban and rural expansion has had the most significant impact on these changes. Today, the implementation of changes in land use directly related to anthropogenic processes is expressed in terms of welfare and development. However, they remain the main causes of environmental problems. These problems include water and air pollution, erosion, decreasing agricultural area, and decreasing species of wetland ecology (Wei et al., 2017; Wu et al., 2018; Yilmaz et al., 2021).

According to United Nations and World Bank data, the world's population will reach 7,924 million by 2022 and 8,010 million by 2023. Worldwide, 55% of this population lives in urban areas (World Bank, 2019), and 76% of Turks will live in cities by 2020. By 2030, it is estimated that 65% of the world's population will live in cities (CSB, 2019). As the urban population continues to grow, many challenges will be faced. In Istanbul, the population has been growing steadily. This has led to the development of new areas. As a result, new transportation networks and development activities have revealed many different situations, such as loss of vegetation cover and pollution. The most important of these changes are undoubtedly the new airport, the Northern Marmara Motorway, new residential areas, and the planned study of the Istanbul Canal. The existing lake basin is under serious pressure from all these activities (Yalcin et al., 2020; Yilmaz et al., 2021).

Sustainable ecological planning of the Lake Terkos basin is important for the continuity and usefulness of the rapidly developing local economy and urbanization in the region. Non-sustainable practices that fail to serve the interests of the future will hasten the degradation of the basin. Therefore, planning should consider the ecologically important areas. Conservation is the first principle to be considered. In this study, the natural ecosystem of the lake and its surroundings and the changes it has undergone were analysed using satellite images from different years. In this way, periods of change and trends in land cover were identified and compared. The level of the lake was determined from each satellite image and the directions of water level changes were revealed.

1.1. Conceptual framework

Environmental studies are generally carried out in two categories (Johnston and Sidaway, 2016). One of them is to analyze the existing structure and define the natural environment (Detwyler and Marcus, 1972; Berry, 1974; Berry and Horton, 1974; Douglas, 1983; Douglas, 2013), and the second was on the identification of environmental problems (O'Riordan, 1971a; 1971b). Both types of the study tracked and analyzed the traces of changes in the environment.

There have been different definitions of the environment because the environment is an area which is the subject of study in different branches of science. (Daramola and Ibem, 2010). In the view of the sociologist Bain, the environment refers to the external and impersonal conditions that affect people within a region. The environment refers to the external and impersonal conditions that affect people within a region. It is the sum of all conditions surrounding a person at any given time (Bain; 1973).

As obvious from these definitions, the environment is the natural systems that govern the existence and interaction of all the natural elements of the environment and establish a relationship between them (Johnson, 1992; Efobi, 1994; Muoghalu, 2004).

Disruption of the balance established within these systems poses a serious threat to environmental sustainability and ecology (Marcuse, 1998). Today, changes in land use and land cover are very rapid in intensively used urban areas and in the regions where they interact. The increase in the rate of change of these two closely related elements has a negative impact on the carrying capacity of the environment. Therefore, changes in the geographical ecology expand the boundaries of the Ecological Footprint (Stoel, 1999; Luo et al., 2018). As a result of environmental degradation, humans, who are part of the environment, have begun to pollute soil, water and air as a result of urbanization and industrialization. To some extent, the ecological footprint, which shows the need for natural resources, is felt more in urban areas where consumption is intense (Sagir, 2012; Senol, 2012; 2015; 2023).

With the increase in population size, population density has concomitantly risen, particularly in cities. In Istanbul, Türkiye's largest and most important city in many respects, the population is growing faster than the national average each year (Avci, 2010; Ozturk et al., 2017). This situation has brought with it a wide range of problems (Yulu, 2017). According to 2021 data, 18.7% of the country's population lives in Istanbul, Türkiye's most vibrant city, with a population density of 2,900 (TUIK, 2021).

Urban population growth has driven outward expansion, including in Istanbul's Lake Terkos and its urban development zone, notable for its rapid expansion. The transport investments made in the region in the last five years and new projects (Canal Istanbul) have started to put the region in a rapid urbanization process. As one of the places in Istanbul where land use and land cover changes are most pronounced, it has been a place to focus on for years because it is a watershed where the city's drinking water, agricultural and livestock center and oxygen-producing forests are located (Altay et al., 2015; Yilmaz et al., 2021).

1.2. Study area

The Terkos Lake Basin is located in the northeast corner of Istanbul between 28° 5′ 51″-28° 43′ 41″ east longitude and 41° 27′ 29″-41° 13′ 39″ north latitude. The basin lies west of Istanbul, north of the Çatalca peninsula, and on the coast of the Black Sea. While a large part of it is in the Arnavutköy, Çatalca, and Silivri districts of Istanbul, a very small part is in the Saray district of Tekirdağ. The most important streams in the basin are mainly Istranca, Kayınpınar, Kapaklı, Çeşme and their tributaries, which feed Lake Terkos (Durusu). The basin, which has maintained its drinking water quality for years, covers an area of approximately 735 km² within the boundaries formed by the rivers. There are no large settlements in the basin; there are 11 rural settlements in the form of villages, mainly engaged in agriculture and animal husbandry. However, the region is important in terms of attracting major investment and population in 2018 and beyond. The villages, which until now have existed as small settlements, are now attracting large populations. However, it is still one of the least developed regions of Istanbul. Most of the Terkos Lake basin is less than 200 meters above sea level. The western and south-western parts of the basin are

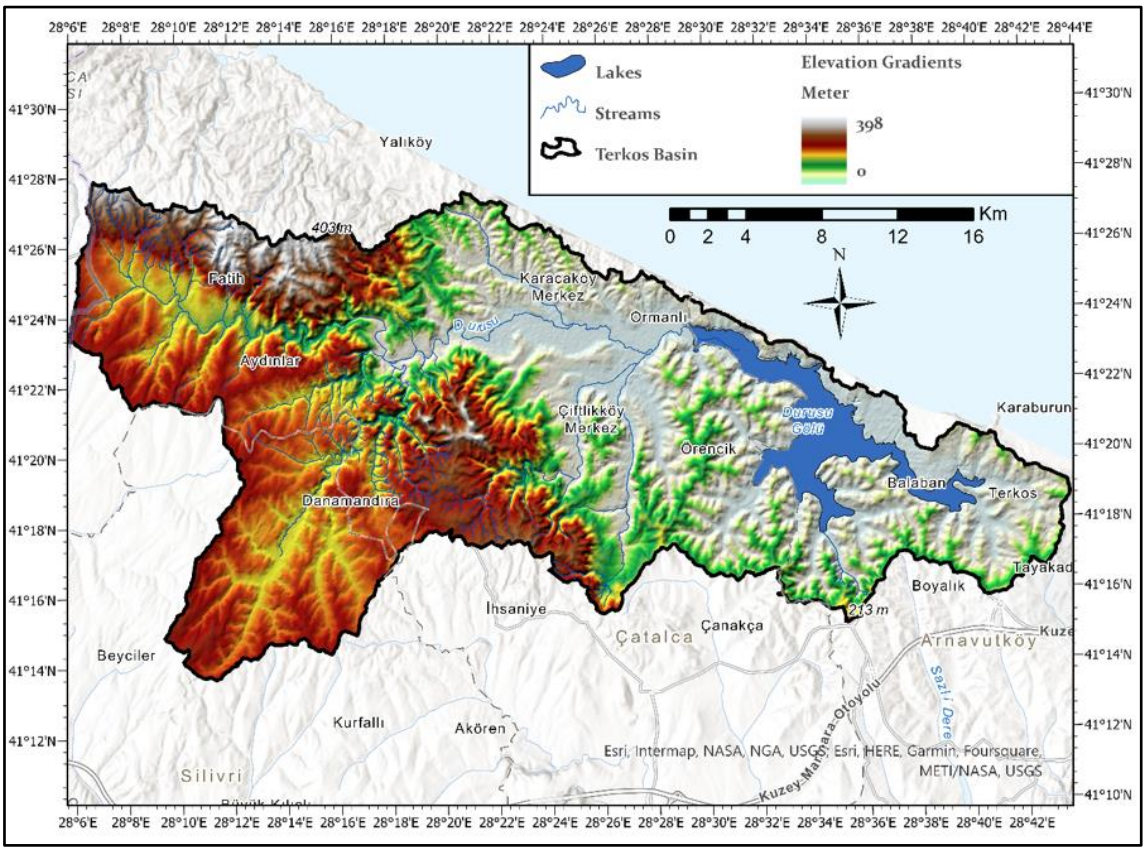


Fig. 1. Map of the Terkos Basin.

higher than other areas. The source of the lake's feeding rivers is in the highlands, which gradually slope towards it. Terkos Lake is fed by Belgrad, Fındık, Kanlı, Deli Yunus, Başköy, Karacaköy and Çiftlikköy Streams. (Fig. 1) (Sozen et al., 2021; Yilmaz et al., 2021; Bozkurt et al., 2023).

2. Material and methods

NDVI, NDWI, Natural Color, and Near Infrared bands were extracted from raw Sentinel 2, Landsat 1-5, Landsat 4-5, Landsat 7, and Landsat 8-9 data using ArcMap Pro software. First, the satellite images were clipped to the study area using the raster clip tool.

Then

- NDVI formula using red and NIR band data for NDVI band: (NIR - Red) / (NIR + Red)
- NDWI formula using Green and NIR band data for NDWI band: (Green - NIR) / (Green + NIR) was used.

The Natural Color and Near Infrared formula and band combinations vary depending on the satellite image. For the Natural Color band in Sentinel 2 satellite imagery, the RGB composite band was created with the combination 4,3,2 using Red, Green, and Blue band data. The Near-Infrared band was also created using the 8,4,3 combination.

NDVI, NDWI, Natural Color, and Near Infrared images were created by combining the bands obtained. The formulae and Python codes required for image acquisition are described in detail in the Results section. As a result, the changes in different satellite images over the years were revealed by remote sensing method and the land use and spatial changes of the basin were analyzed. Finally, the satellite images of different bands obtained in the field were analyzed on a pixel basis using the "Supervised Classification" tool in ArcMap Pro software to measure land use change, and the raster data obtained were converted into vectors and spatial measurements were made using the "Calculate Geometry" tool. Finally, to determine the rate of change, the "Change Detection" tool was used to identify the areas of greatest change around Lake Terkos.

3. Results and discussion

In the study, the changes observed in the land as a result of the analyses of satellite images in 1980-2000-2020 and 2023 were handled in four stages. In this period, the spatial development and change in the Terkos Lake Basin were analyzed as a whole. In the first one, the land use of 1980 was analyzed with different satellite images, and the basic data for this year were compared with 2000. Likewise, the year 2000 was compared with 2020 and the differences between the years were revealed. The image of the year 2023 was also analyzed in order to draw attention to the changes in the land as a result of some new activities and constructions such as the new airport, new transportation network, and developing urban area in the northeast corner of the basin and to reveal the difference of the change. In this direction, the following process steps and findings are presented and the direction and trend of change are revealed.

Satellite sensors can image the Earth in different regions of the electromagnetic spectrum. Each region in the spectrum is called a band. Sentinel-2 has 13 bands. The true color composite uses the red, green, and blue visible light bands in the respective red, green, and blue color channels, resulting in a natural color product that is a good representation of the Earth as people would see it naturally (Sentinelhub Playgraund, 2023). What is meant by true color here is finding the color range closest to natural colors. It means that the colors of the object in the image

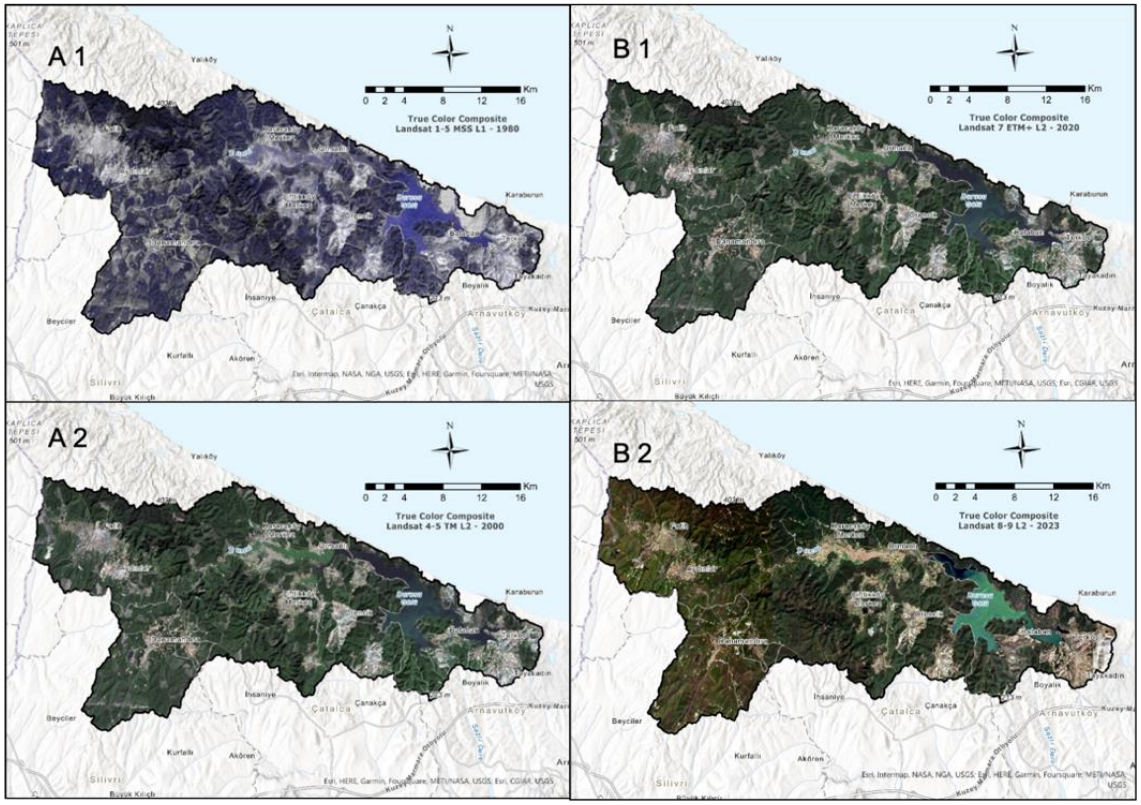


Fig. 2. Terkos Lake Basin 1980-2000 (A 1-2)-2020-2023 (B 1-2) True-color composite.

are displayed in the same color range as they appear in nature when viewed by the human eye. A true-color image shows the area in its true color, for example, vegetation in green, rivers and lakes in blue. It covers the entire visible spectrum, mapped to the image's RGB color space using the satellite's red, green, and blue/green spectral bands (Fig. 2).

In the true color composite, Sentinel-2 maps the band values B04, B03, and B02 to the R, G, and B components, respectively corresponding to the red, green, and blue parts of the spectrum.

In this composite
- For Sentinel-2: BO4, B03, B02
- For Landsat 4-5 TM: B03, B02, B01
- For Landsat 7 ETM: B03, B02, B01
- For Landsat 8: B04, B03, B02
- For MODIS: B01, B04, B03 band combinations are used.

Also sample Python code for Sentinel 2 image;

```
//VERSION=3
function setup() {
  return {
    input: ["B04","B03","B02", "dataMask"],
    output: { bands: 4 }
  };
}
function evaluatePixel(sample) {
    return [2.5* sample.B01, 2.5* sample.B02, 2.5* sample.B03, sample.dataMask];
}
```

(Costum Scripts, 2023; GitHub, 2023; Sentinelhub Playgraund, 2023).

False color compositing uses at least one non-visible wavelength to image the Earth. False-color compositing using the near-infrared, red, and green bands is very popular. A band is a region of the electromagnetic spectrum; a satellite sensor can image the Earth in different bands. False-color imagery is most commonly used to assess plant density and health, as plants absorb red and reflect near-infrared and green light. Cities and exposed soil appear grey or brown, and water appears blue or black (Sentinelhub Playgraund, 2023).

The false-color infrared composite maps the near-infrared spectral band B8 and the red and green bands B4 and B3 directly to the sRGB components. Because plants absorb red and reflect near-infrared and green light, it is most commonly used to assess plant density and health. Areas covered with plants appear dark red because they reflect more near-infrared light than green. The denser plant cover is darker red. Cities and exposed soil appear grey or brown, and water appears blue or black (Fig. 3) (GISGeography, 2023; Sentinelhub Playgraund, 2023).

- For Sentinel-2: B08, B04, B02
- For Landsat 1-5 MSS: B04, B02, B01
- For Landsat 7 ETM+: B04, B03, B02
- For Landsat 4-5 TM: B04, B03, B02
- For Landsat 8: B05, B04, B03
- For MODIS: B02, B01, B04 band combinations are used.

Also, sample Python code for Sentinel 2 for the image;

```
//VERSION=3
function setup() {
  return {
    input: ["B08","B04","B03", "dataMask"],
    output: { bands: 4 }
  };
}
function evaluatePixel(sample) {
    return [2.5* sample.B08, 2.5* sample.B04, 2.5* sample.B03, sample.dataMask];
}
```

(Costum Scripts, 2023; GitHub, 2023; Sentinelhub Playgraund, 2023).

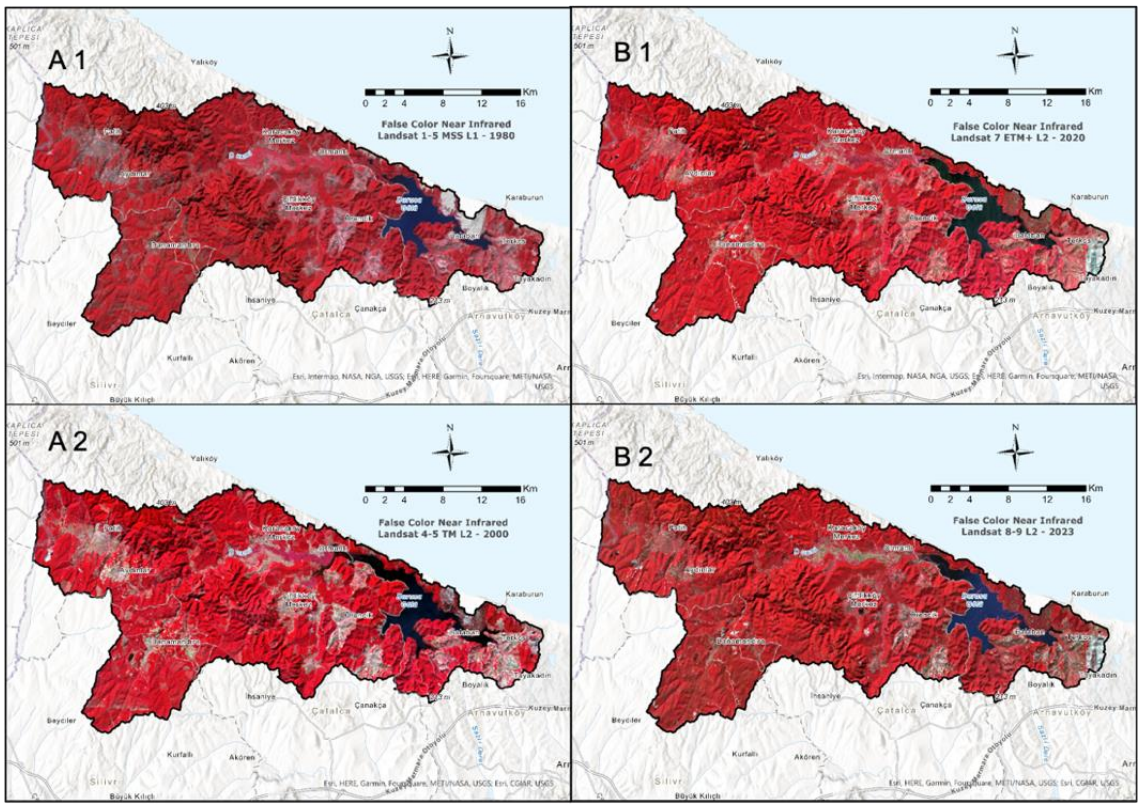


Fig. 3. Terkos Lake Basin 1980-2000 (A 1-2) - 2020-2023 (B 1-2) False colour view in the near infrared.

The normalized difference vegetation index is a simple but effective index for measuring green vegetation cover. It is a measure of the health of vegetation based on how plants reflect light at certain wavelengths. The value range of NDVI is -1 to 1. Negative NDVI values (values approaching -1) correspond to water. Values close to zero (-0.1 to 0.1) correspond to barren areas, usually consisting of rock, sand, or snow. Low, positive values represent shrubland and grassland (about 0.2 to 0.4), while high values indicate temperate and tropical rainforest (Sentinelhub Playgraund, 2023) (Fig. 4). NDVI is obtained from satellite images and different bands are used according to different satellite images.

These are

- Landsat 8 NDVI{:target="_blank"} = (B05 - B04) / (B05 + B04)
- Landsat 5 and 7 NDVI = (B04 - B03) / (B04 + B03)
- MODIS NDVI = (B02 - B01) / (B02 + B01)
- ENVISAT MERIS NDVI = (B13 - B07) / (B13 + B07)
- Landsat 1-5 MSS NDVI = (B04 - B02) / (B04 + B02)
- Landsat 4-5 TM = (B04 - B03) / (B04 + B03)
- Landsat 7 ETM+ NDVI = (B04 - B03) / (B04 + B03) (GitHub, 2023).

NDVI formula is;

NDVI = (NIR-RED)/(NIR+RED)

NIR - reflected light in the near infrared spectrum

RED - reflected light in the red range of the spectrum

According to this formula, the density of vegetation at a given point in the image (NDVI) is equal to the difference of the reflected light intensities in the red and infrared range divided by the sum of these intensities (EOS Data Analiytics, 2023).

Also the image's sample Python code for Sentinel 2;

```
//VERSION=3
const colorRamp = [[0,0x000000],[1,0xffffff]]
let viz = new ColorRampVisualizer(colorRamp);
function setup() {
  return {
    input: ["B08","B04", "dataMask"],
    output: [
      { id:"default", bands: 4 },
      { id: "index", bands: 1, sampleType: 'FLOAT32' }
    ]
  };
```

}(GitHub, 2023; Costum Scripts, 2023; Sentinelhub Playgraund, 2023).

NDWI stands for Normalized Difference Water Index and is an index used to identify and map areas of standing water in satellite imagery. NDWI is calculated by dividing the difference between the green and near infrared (NIR) bands of an image by their sum. It is based on the idea that water strongly absorbs NIR light and reflects green light (Sentinelhub Playgraund, 2023).

In areas of standing water, the NDWI value will be positive, indicating a high difference between the green and NIR values. In other areas, such as vegetation or bare ground, the NDWI will be negative, indicating a small difference between the green and NIR values. NDWI can be used to detect water bodies in a variety of landscapes, including wetlands, rivers, lakes, and even urban areas with built infrastructure (Fig. 5).

NDWI is obtained from satellite images and different bands are used according to different satellite images.

These are

- Sentinel-2 NDWI = (B03 - B08) / (B03 + B08)
- Landsat 1-5 MSS NDWI = (B01 - B04) / (B01 + B04)
- Landsat 4-5 TM NDWI = (B03 - B05) / (B03 + B05)
- Landsat 7 ETM+ NDWI = (B02 - B04) / (B02 + B04)
- Landsat 8 NDWI = (B03 - B05) / (B03 + B05)

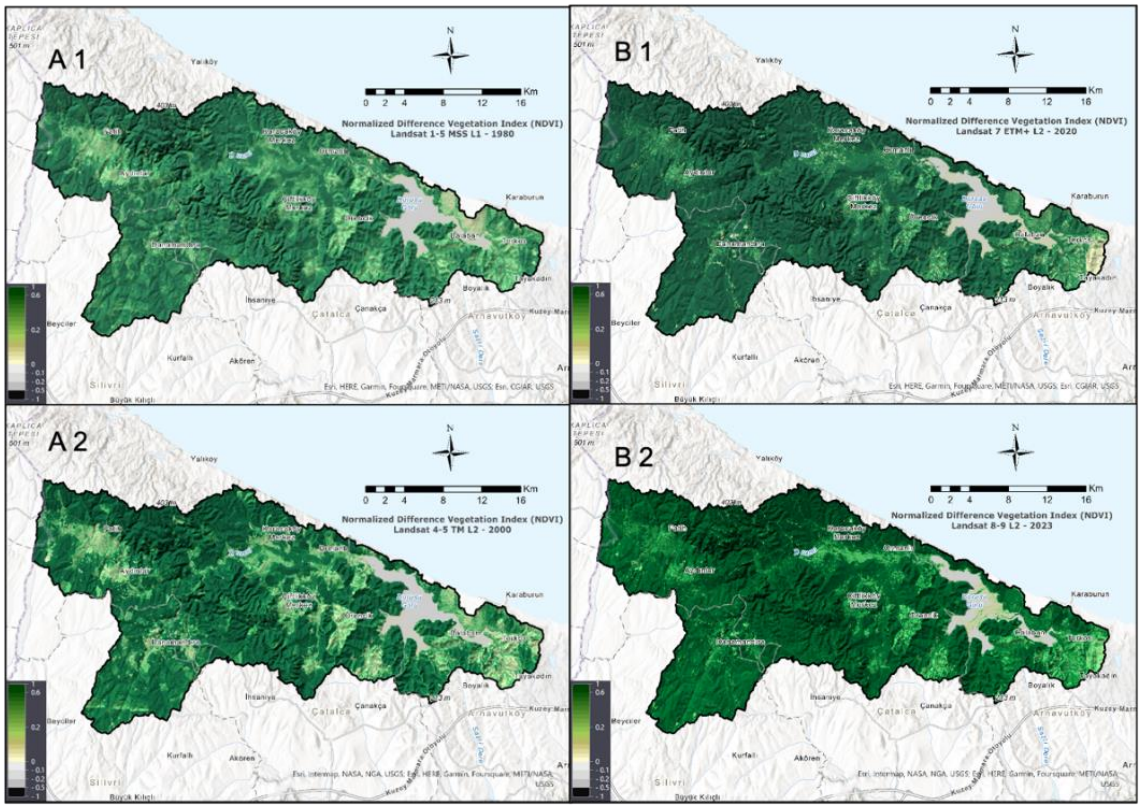


Fig. 4. Terkos Lake Basin 1980-2000 (A 1-2)-2020-2023 (B 1-2) NDVI view.

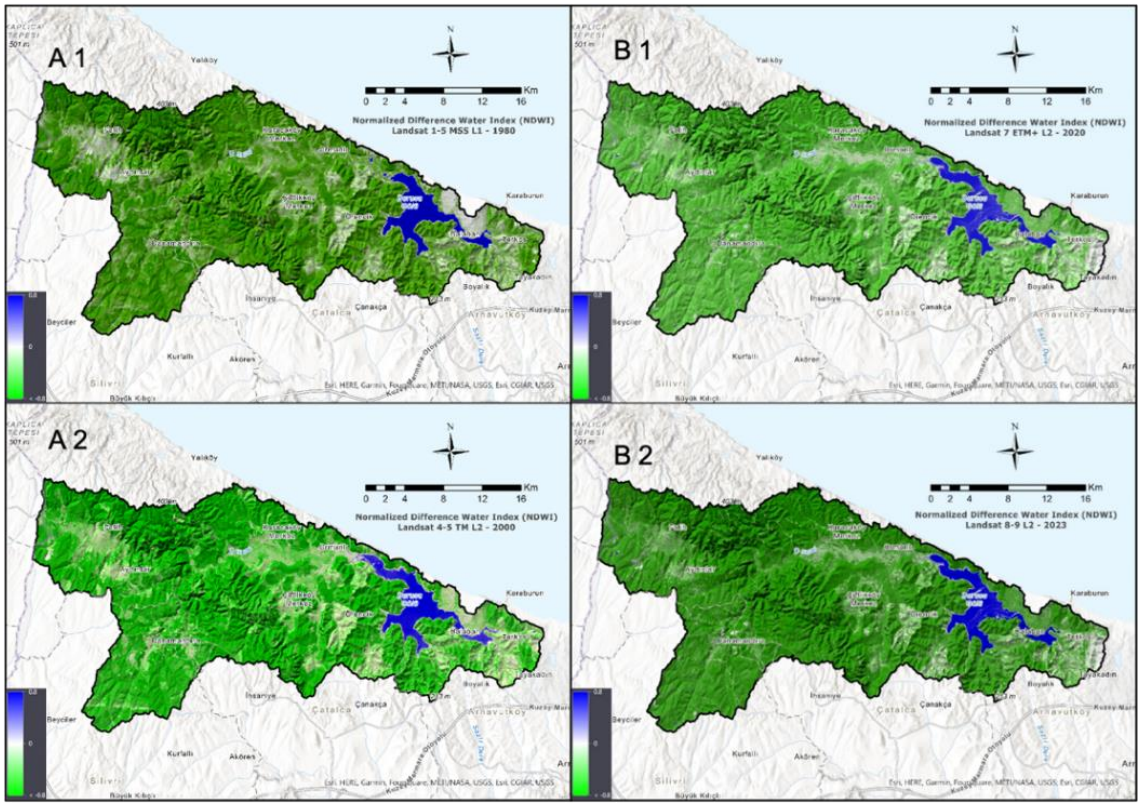


Fig. 5. Terkos Lake Basins 1980-2000 (A 1-2)-2020-2023 (B 1-2) NDWI View.

- MODIS NDWI = (B04 - B02) / (B04 + B02)

The formula for the Normalized Difference Water Index (NDWI) is as follows

NDWI = (GREEN - NIR) / (GREEN + NIR)

Where Green is the green band and NIR is the near infrared band. This formula is used to calculate the NDWI value for each pixel in the image. The resulting NDWI values range from -0.8 to 0.8, with positive values indicating the presence of water. The exact bands used for green and NIR can vary depending on the satellite sensor and data processing method, but the bands commonly used for Sentinel-2 are B03 (green) and B08 (NIR).

```
Also the image's sample Python code for Sentinel 2;
//VERSION=3
const colorRamp = [[0,0xffffff],[1,0x005824]]
let viz = new ColorRampVisualizer(colorRamp);
function setup() {
  return {
    input: ["B03","B08", "dataMask"],
    output: [
      { id:"default", bands: 4 },
      { id: "index", bands: 1, sampleType: 'FLOAT32' }
    ]
  };
}
```

(Costum Scripts, 2023; GitHub, 2023; Sentinelhub Playgraund, 2023).

The rapid increase in population in Istanbul has accelerated the process of change in urban and forest areas. The rapid and uncontrolled expansion of cities in urban areas affects forest and water areas. Although the extent of the impact varies, the result is economic and social problems such as pollution, inadequate infrastructure, and land management (Deniz, 2009).

The expansion of human settlements leads to a decrease in green areas and a deterioration of biodiversity and ecological balance. Istanbul's population initially concentrated in coastal areas and near transport routes, began to expand towards the north of the city with the construction of bridges. After the second bridge, illegal settlements grew rapidly in Arnavutköy, Sultançiftliği, and Habipler. During this period, settlement accelerated and began to threaten forests and water basins (Kılıçaslan, 1981; Terzi and Bolen, 2010). The process experienced after the rapid population growth has entered a new process with the third bridge. In this process, Istanbul has entered a process of expansion toward the urban periphery (Kanbak, 2013). The most important and most affected area within this area is undoubtedly the Terkos Lake basin. The fact that it is Istanbul's main source of drinking water makes it even more important.

Land use and lake level changes in the Terkos Lake Basin were analyzed in two periods, 1980 and 2023. The 1980 satellite image was generated using Landsat 1-5 MSS L1 data from the SentinelHub Explorer module. The land use status in 2023 was generated using Landsat 8-9 L2 data from the SentinelHub Explorer module (Sentinelhub Playgraund, 2023).

ArcMap Pro software was used for both image analyses. In the software, digitization was performed using the supervised classification module of the Image Classification Wizard tool. This method used natural color, infrared, NDVI, or NDWI color bands for detection and pixel sampling. Hundreds of pixel samples were taken in different categories such as water bodies, bare land, agricultural land, settlements, and forest areas and these were categorized according to pixel colors by considering maximum similarity. Calculations were then performed on these digitized areas using the Calculate Geometry tool to determine land use change.

To measure the accuracy of land use, the 2023 satellite image was verified with Google Earth by assigning more than 500 points. A high accuracy of 92% was obtained. The 1980 image of the land was verified with the Landsat 1-5 MSS L1 image and an accuracy rate of 90.7% was achieved. Although such margins of error exist in pixel-based land use change analysis due to similar colors, a very high accuracy rate was achieved (Fig. 6).

When analyzing the land use of the Terkos Lake Basin in 1980, it can be seen that rivers and lakes occupy 2% of the land with 13.3 km². This ratio is the lowest lake level in the study period, and in the following periods, the amount of water in the basin first increased slightly and then decreased again. However, despite the decrease, as seen in the 2023 data, it still has more than twice the water mass compared to 1980, covering 4% of the area with an area of 28.7 km² (Fig. 6-7, Table).

Another category is non-green land. These areas are divided into bare rocky land, non-agricultural land, roads, residential areas and other buildings (facilities). However, these areas are grouped together as non-green areas, both because it is difficult to distinguish between them in such a large area due to the similarity of pixel colors, and to avoid going beyond the purpose of the study. For example, non-green areas, which accounted for 210.8 km² and 29% of land use in 1980, decreased to 26% and 193.6 km² in 2023. In this process, settlement and construction, various afforestation activities around the lake, which has a sensitive ecosystem, and the expansion of the agricultural area, as well as the increase in the water level and the expansion of its area, have led to a slight decrease (Fig. 6-7, Table).

As a result of the analysis, there is an increase in non-green areas and water levels. One of the main reasons for this increase is primarily the human activities in the basin. The airport built in the east of the basin and the intensification of transportation

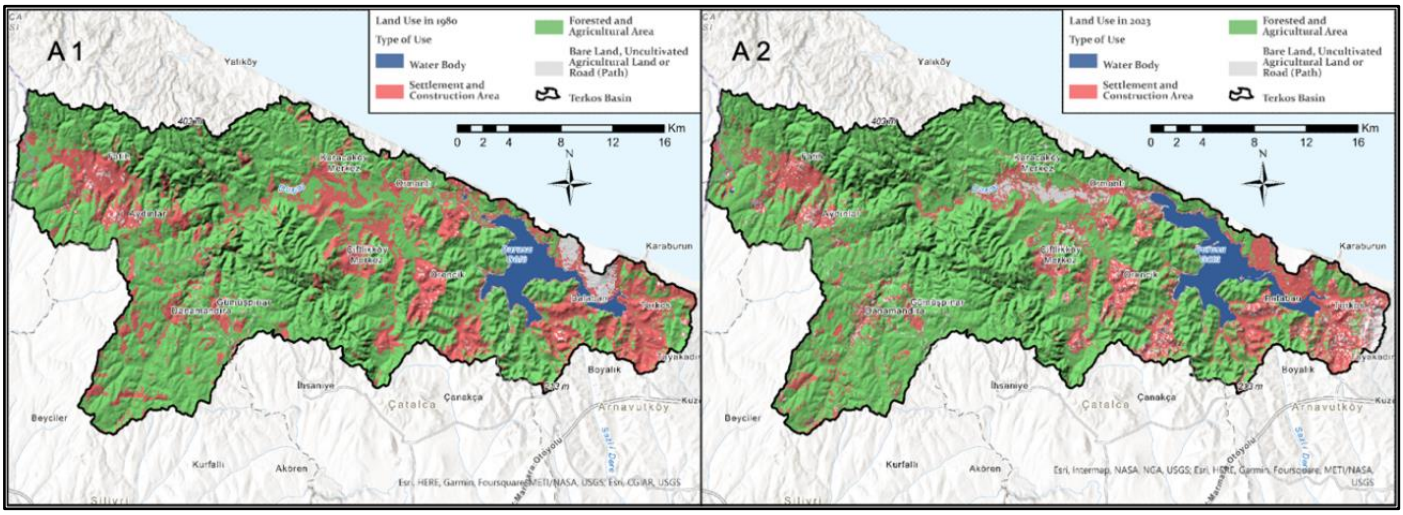


Fig. 6. Land use in Lake Terkos between 1980 (A 1) and 2023 (B 2)

Table
Land use in Lake Terkos between 1980 and 2023.

Class Name	Subclass Name	Subclass Area (Km²)		Class Area (Km²)		Area (%)	
		1980	2023	1980	2023	1980	2023
Water	Water body	13.33	28.72	13.33	28.72	2	4
Non-green area	Bare land, uncultivated agricultural land or road (path)	24.84	40.14	210.85	193.69	29	26
	Settlement and construction area	186.02	153.55				
Green area	Forested and agricultural area	511.31	513.18	511.31	513.18	69	70

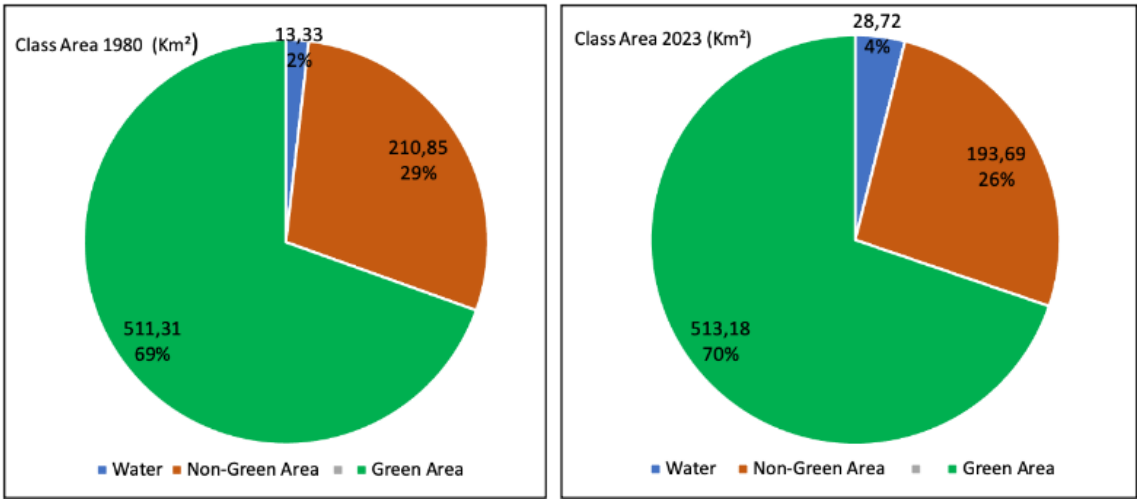


Fig. 7. Land use in Terkos Lake in between 1980 and 2023.

networks in the region have led to an increase in non-green areas. The increase in the water level is based on the principle of protecting and even raising its level in terms of being a drinking water basin. There has been a slight increase in forest and agricultural lands in the area and this is due to the expansion of agricultural areas in the basin and afforestation in the lake basin.

Finally, when analyzing the category of green and agricultural areas, these areas, which covered 69% of the basin in 1980 with 511.3 km², have slightly increased by 1% to 513.1 km² and 70% in 2023. This is due to the reforestation work carried out, in particular around the lake (dune reforestation) and the restriction of agriculture in ecologically sensitive areas by increasing the agricultural area, as mentioned above (Fig. 6-7, Table).

As can be seen from the data, ¾ of the catchment consists of green areas and lakes. These areas have been protected by the measures taken in the period 1980-2023 and the change has been relatively small. However, the facilities that have been built in the lake and its immediate surroundings in recent years, as well as the major projects that are planned, could disrupt the lake's ecosystem if the necessary measures are not taken. In particular, Istanbul Airport, which will be operational in 2019, is expected to destroy green areas in a relatively large area (about 8 km²) in the eastern part of the basin (Fig. 7-9). Moreover, the fact that it encourages the spread of structures like settlements, housing or roads is a major pressure.

When analyzing the changes in the area covered by Lake Terkos, it was found that there were increases and decreases depending on the time period. NDWI images of the lake surface were obtained from Landsat 1-5, Landsat 7 and Landsat 8-9 satellite images taken in 1980, 2000 and 2023. These images, which stand for Normalized Difference Water Index (NDWI), are a relatively accurate index used to determine or map standing water areas.

According to these images; The surface area of Lake Terkos in 1980 was approximately 24.8 km². This was the lowest surface area recorded during the measurement period. After this period, the area of the lake started to increase, especially after 1994. The most important reasons for this are the modernization of the regulation system built around the lake during this period and the controlled change of the water level. As a result, the surface area of the lake increased by about 36% to 39.1 km² in 2000. After this period, dune reforestation work was carried out around the lake in the 2000s to protect and raise the lake level. However, despite these efforts, the lake has been shrinking in recent years. In the last 15 years in particular, the use of the lake's water has reached its maximum level, due to factors such as the spread of settlements, increasing agricultural activity and rapid population growth. As a result, the water surface has shrunk considerably.

According to the latest measurement, in 2023, the lake area decreased by 28.3% compared to the previous period, shrinking to 30.5 km² (Fig. 10). The level of the lake waters, which flow into the Black Sea through a narrow and deep valley with a lake pillar in the eastern part of the lake, is controlled through regulators by building embankments in front of it. The regulator has the duty of regulating the level and water quality. Here, the gates of the regulator are set at a certain level and when the level is exceeded, the water continues to flow over the gates.

The lake is currently not at its natural level (the natural level is 4.5 meters), but its level has been raised. The natural depth can vary between 8-16 m over time. The locks here play a role during these level changes. In periods when the level rises too high, the dune afforestation area is in danger of being flooded, so the gates are opened, and discharges are made. This is important as it is part of protecting the lake area (Fig. 11). Another measure to protect the lake area is to create grove areas. Protection zones have been established around Terkos Lake at certain intervals (such as 100-300-700-900 m) from the shoreline. These protection areas are implemented within the framework of the regulation and are restricted in terms of a settlement.

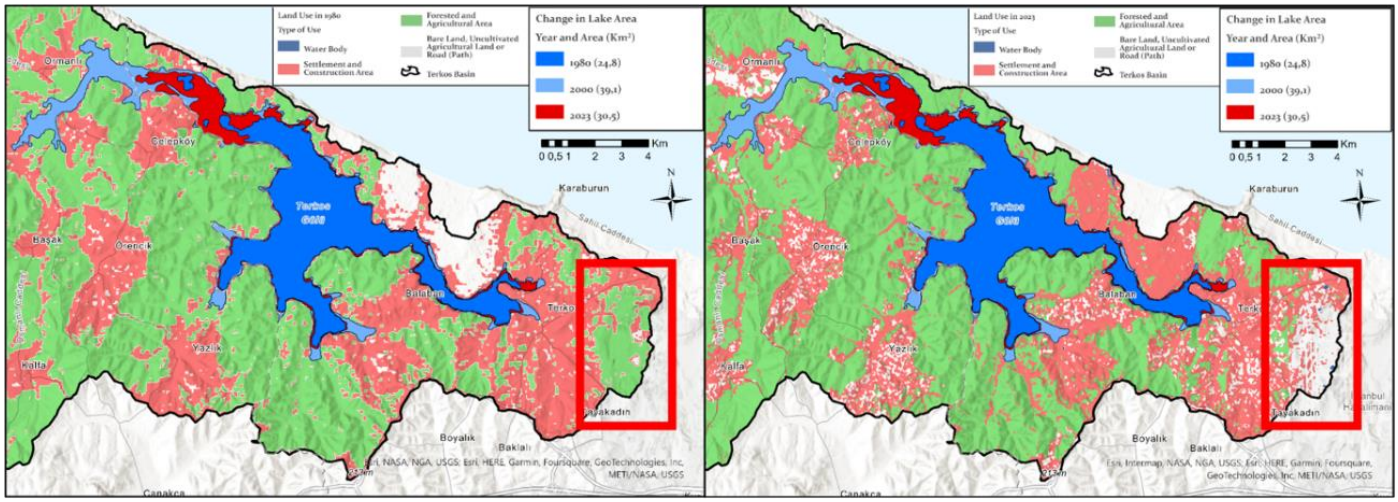


Fig. 8. Changes in land use and lake area around Terkos Lake.

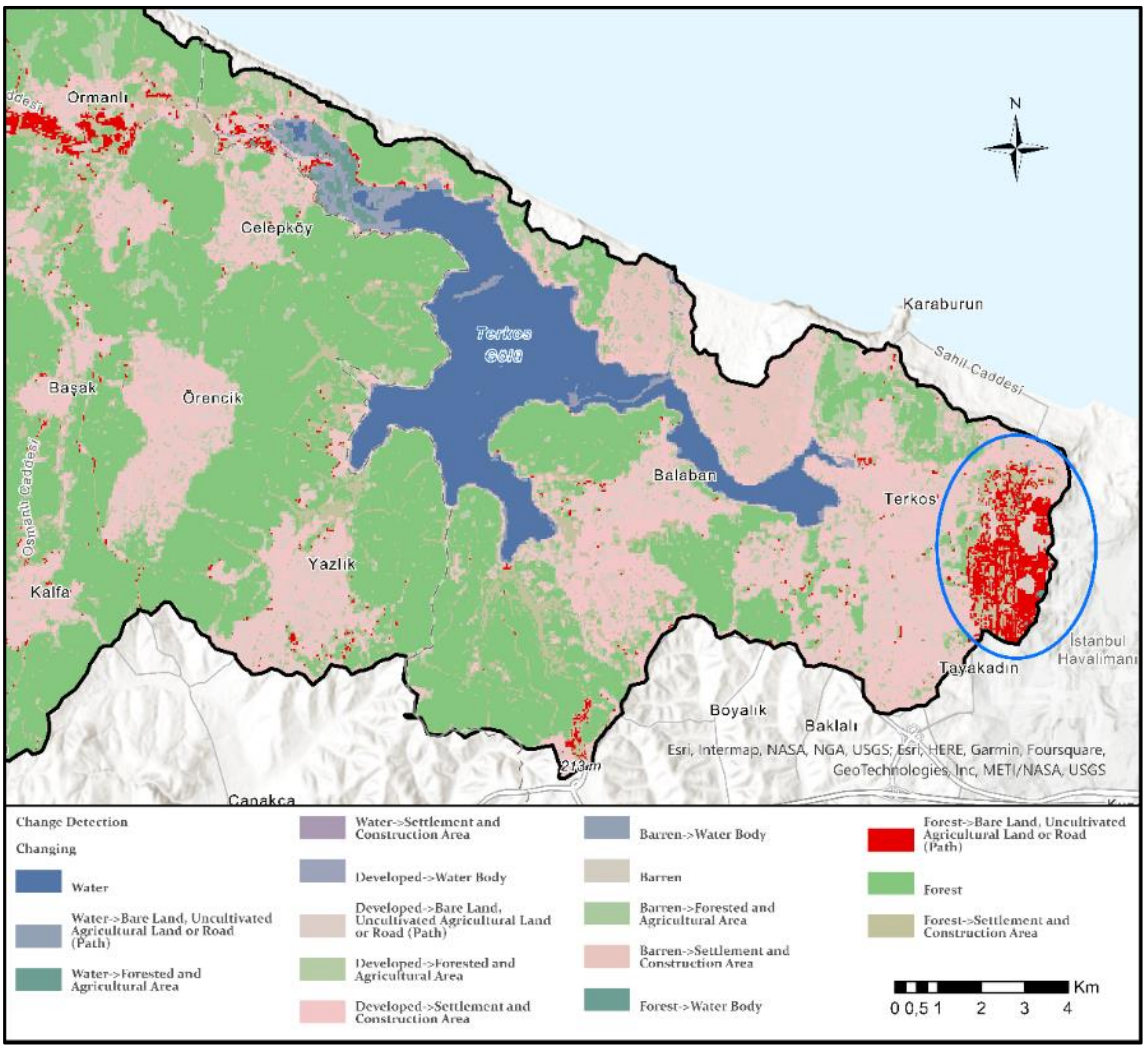


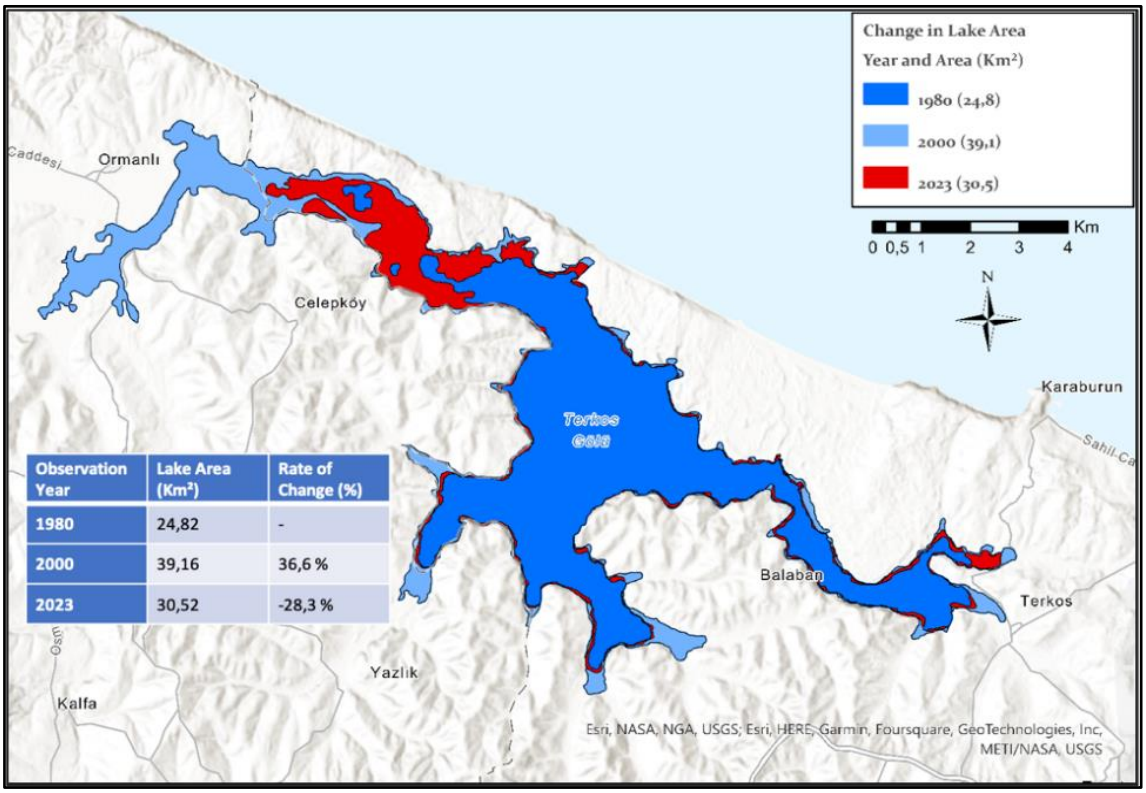
Fig. 9. Changes caused by Istanbul Airport in the eastern basin of Lake Terkos.

The world-famous dune afforestation area was established as one of the most important protection measures in Lake Terkos. It is the first dune afforestation area in Türkiye. Many delegations from England and other countries come here to see the afforestation, do research, and write reports. Two gates, situated 16 km apart, control access to the region housing water treatment plants, dune afforestation, and the lake. Security personnel are present to safeguard the dune afforestation system and the lake against potential harm (Fig. 12).

4. Conclusion

It is very important to protect the ecological environment of Lake Terkos, which is one of the 135 wetlands of international importance designated in Türkiye by the RAMSAR Convention. A small mistake here can damage the entire ecosystem of the lake. For this reason, the dune reforestation area in particular is being protected very carefully.

If the trees disappear, the lake will be in danger. This would



Observation Year	Lake Area (Km²)	Rate of Change (%)
1980	24,82	-
2000	39,16	36,6 %
2023	30,52	-28,3 %

Fig. 10. Changes in the area of Lake Terkos between 1980-2000-2023.

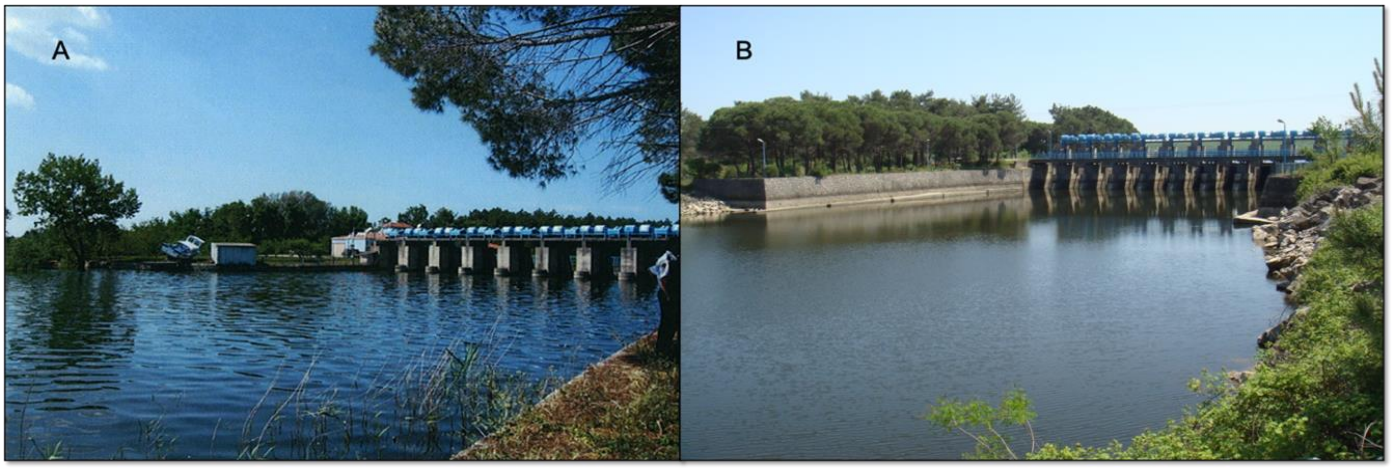


Fig. 11. Regulators for the regulation of the water level in the lake of Terkos (Durusu).

Fig. 12. Red pine and black pine trees in the dune afforestation area, protecting the lake ecosystem from the dunes.

mean the loss of about 150-300 million m^3 of water, about 1/3 of Istanbul's annual water needs. The reservoir here is fed by dams built on the streams that flow from Istranca, which keeps the water fresh. This reduces pollution and preserves the lake's water.

It has also been found that the water is better than other reservoirs in terms of freshness and drinkability. So much so that the water can be drunk with a glass immersed in the lake. To protect the water quality and maintain the productivity of the lake ecosystem, activities such as fishing, hunting, picnicking, camping, etc. should not be allowed in the area. Tourist and educational trips should be carried out in a controlled manner by professionals.

In addition, projects have been carried out in recent years, and some are still in the planning stage, which can put a lot of pressure on the lake's ecosystem. These projects include large and complex construction elements that have very high economic returns but need to be carried out very carefully in terms of their negative impacts. The project with the highest impact is currently the Istanbul Airport project. The airport, whose construction has been completed, has resulted in the destruction of approximately 8 km^2 of green space in the eastern part of the lake. In addition, the motorway projects that followed the construction of the airport and the attractive environment created by the bridge threaten the basin by increasing the number of new settlements or illegal constructions around the lake. Another major project, the Istanbul Canal, has not yet been realized and its possible effects are still being debated. It is believed that the project's impact on groundwater or aquifers could affect the lake's water quality, increasing salinity and reducing the quality of drinking water. It is also estimated that the project will intensify settlement around the basin, increase the amount of drinking water to be abstracted from the lake, and cause imbalances in the lake's water level. In addition, the project can be expected to cause air pollution, landslides, corrosion, liquefaction, or ground collapse and indirectly affect the lake.

On the other hand, important projects have been initiated to protect the lake ecosystem. Projects such as Taşoluk Drinking Water Treatment Plants, Terkos İkitelli Transmission Line, Terkos Advanced Biological Wastewater Treatment Plant are important initiatives that have been launched in recent years to make the most efficient use of the lake's water and to protect the lake's ecosystem. The increase of these and similar initiatives should be encouraged, the opening of new settlements in the lake and its immediate vicinity should be strictly prevented, and the basin planners should be among the planning stakeholders by revealing various risk factors through multidisciplinary academic studies.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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Research article

The effect of radiotherapy on neurogenic speech and language disorders of patients with primary brain tumour in the early period

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Abstract

Within the scope of the study, it is aimed to reveal the effect of radiotherapy applied to neurogenic speech and language disorder patients diagnosed with primary brain tumour in the early period. The participants of the study consist of 35 patients selected among those with primary brain tumour who applied to the Radiation Oncology Unit of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital. Within the scope of the research, Gülhane Aphasia Test 2 (GAT-2) and Standardized Mini Mental Test (MMT) were applied to the participants before they received radiotherapy. GAT-2 and MMT were reapplied to the patients 30 days after they had received radiotherapy as part of the treatment process. Results of the study indicated that, before radiotherapy, tumours formed in the frontal and temporal lobes, including the dominant language centers, had a negative effect on the cognitive performance of the patients, as well as their speech and language skills. However, after radiotherapy was applied, two patients with tumours in the left parietal lobe had a decrease in their speech and language skills, while no deterioration was observed in the speech and language skills of the other participants. This may be due to the early phase of radiotherapy.

Keywords: *Brain tumour; neurolinguistics; radiotherapy; speech and language disorders*

1. Introduction

Cancer is one of the most important health problems of the modern world; it is at the top of the list of human deaths due to disease, and its incidence is increasing day by day. Although there are many subtypes, only 2% of cancer diseases and 3% of cancer-related deaths are due to brain tumours. Glioblastoma (GB) is the most common high-grade malignant brain tumour in the adult age (Fig. 1) group with a poor prognosis, constituting approximately 35-40% of primary brain tumours (Stupp et al., 2005; Savci, 2006; Noone et al., 2015).

Tumour localization, volume, and respectability are among the prognostic factors that affect the survival of GB patients. In addition to wide surgical resection, the most ideal standard and effective treatment approach in glioblastoma is simultaneous radiotherapy (RT) and adjuvant chemotherapy (Cho et al., 2010).

Although the tumour is surgically removed with the help of radiological imaging, these glial tumour cells spread within the healthy brain tissue, and it is often accepted that microscopic tumour cells are left behind after the surgical procedure (Fig. 2 and 3). Therefore, radiotherapy is recommended after surgery to destroy the gross tumour volume, whether it is microscopic or macroscopic in size. If the tumour is in a region where critical

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and healthy organs are located and the risk of surgery is high, RT and/or chemotherapy alone can be applied (Walker et al., 1978).

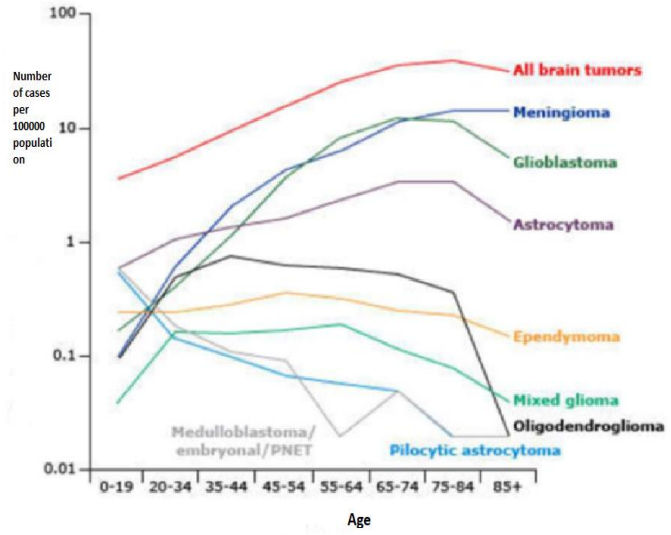

Fig. 1. Incidence rates of primary brain tumours (Michaud et al., 2017).

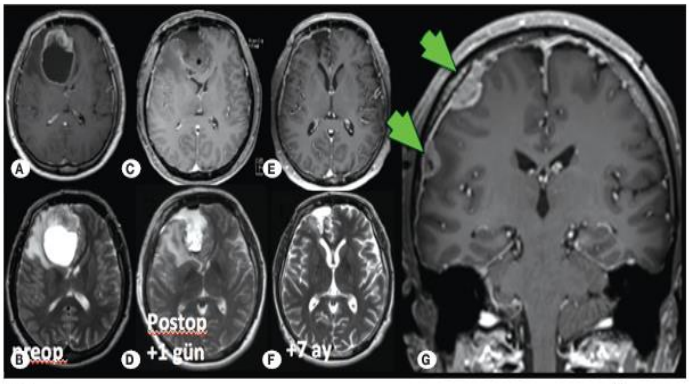

Fig. 2. Unexpected recurrence patterns are frequently observed in glioblastomas that do not have typical molecular genetic features. In the example, preoperative (A, B), early postoperative (C, D) and postoperative 7th month MR images (E, F, G) of a glioma patient without TERT mutation, chromosome 7 or chromosome 10 copy number changes are presented. It is observed that the resection cavity of the patient remained stable after radio-chemotherapy, but the patient developed distant, multifocal, supratentorial leptomeningeal recurrences, which are rarely observed in glioblastoma (gün=day; ay=month) (Ozduman et al., 2019).

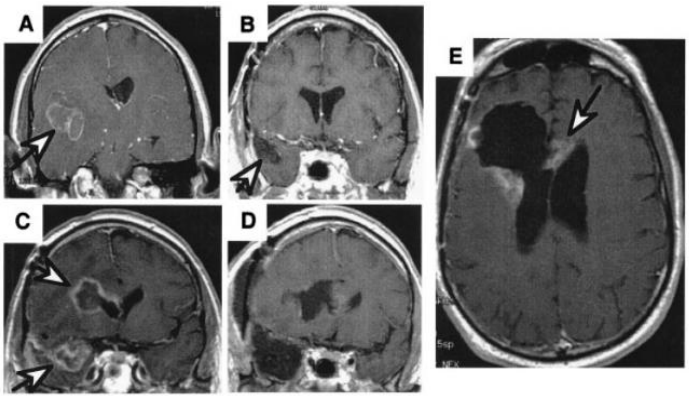

Fig. 3. Post-operative and 6-month computed tomography image obtained in temporal section of a GB patient (https://giemsa.net/korkulu-ruya-glioblastoma-gbm/).

In GB radiotherapy, while the healthy organs are protected at the highest level, the planned target volume is treated with high-energy ionized X-rays. With the recent developments in radiotherapy treatment techniques, the survival rate in GB has increased, especially for curative patients. However, radiotherapy-induced necrosis and late radiation toxicity are frequently encountered in these patients. Therefore, it is very important to investigate radiotherapy techniques and developments that will minimize the harmful effects of irradiation in GB radiotherapy in terms of patient dose and quality of life.

Depending on the developing technology, different models of commercial linear accelerators are frequently used in radiotherapy cancer treatments. In particular, modern techniques with high technological features can be preferred in the radiotherapy of head and neck cancers. Thanks to these modern techniques, it is aimed to protect the surrounding organs at risk while giving the prescribed dose to the tumour tissue by changing the intensity of ionized X-rays. These modern techniques are frequently used in GB radiotherapy because of the desired dose distributions over the target volume and the high degree protection of critical organs. The advantages and disadvantages of these different radiotherapy techniques in parameters such as target volume and dose distribution on healthy tissues and treatment times have been shown in many studies (Hess et al., 1994).

Aphasia is defined as an acquired language disorder that occurs as a result of brain damage in the hemisphere that is dominant in language processing, and causes problems in understanding and/or producing language in people. An individual with aphasia usually has relatively stronger non-linguistic cognitive skills such as memory, attention, and executive functions. However, problems in cognitive skills can sometimes occur with aphasia (Spreen and Risser, 2003; ASHA, 2023).

According to the National Aphasia Association, aphasia is observed in approximately 25-40% of people who have had a stroke. About 35-40% of adults who apply to hospitals with a stroke are diagnosed with aphasia when they are discharged (Pedersen, 1995; Dickey et al., 2010; NAA, 2023).

With the increase in studies and findings related to aphasia, many aphasia classifications have been included in the literature. The most frequently used classification in scientific research and clinics is the "Boston Classification System" which is based on impaired language skills. According to this classification system, aphasia is initially classified as fluent and halting (non-fluent) according to the characteristics of spoken language features. Types of aphasia in the Boston system are Broca's aphasia, Wernicke's aphasia, anomic aphasia, conduction aphasia, global aphasia, and the less common transcortical aphasia. There are also aphasia types in the literature that do not fully meet the clinical features of this widely used classification system. These aphasias consist of Primary Progressive Aphasia (PPA), Crossed Aphasia, and Subcortical Aphasia (Helm-Estabrooks et al., 2004; Davis, 2007; ASHA, 2023).

PPA is a syndrome caused by a neurodegenerative disease and characterized by the progressive deterioration of language skills despite the relative preservation of cognitive skills. It is similar to other types of aphasia in the sense that it leads to loss of language skills due to a neurological cause, while it is similar to neurodegenerative dementia types in terms of its progressive nature. While PPA is caused by a neurodegenerative condition, other types of aphasia are mostly caused by a stoppage of blood

flow, mainly due to stroke (Mesulam, 2001; Hallowell, 2017). Furthermore, PPA has an insidious onset and occurs frequently before the age of 65, and its symptoms tend to get worse over time (Ardila, 2014). The first symptoms of PPA to be recognized are characterized by linguistic impairments, particularly word-finding problems, although cognitive skills are relatively intact. Over time, people with PPA often develop mild cognitive impairment followed by dementia (Ceccaldi et al., 1996; Hallowell, 2017).

Crossed aphasia is a rare type of aphasia that occurs with language impairment in a person as a result of damage to the dominant side of the body. For example, crossed aphasia may occur in a right-handed person who develops aphasia after right hemisphere damage. Many people with crossed aphasia also have accompanying symptoms such as left visual neglect and visuospatial problems typically associated with right hemisphere lesions (Fischer et al., 1991; Hund-Georgiadis et al., 2001).

Subcortical aphasia is a condition characterized by a partial or complete loss of verbal communication ability that develops as a result of damage to subcortical brain regions without loss of cortical function in Broca's or Wernicke's zones (Table 1). Subcortical aphasia can be caused by lesions in the basal ganglia, thalamus, or cerebellum (Hallowell, 2017; Kang et al., 2017). As a function of the affected subcortical brain region, various language disorders may occur after a stroke (Mega and Alexander, 1994).

Speech disorders of neurological origin include, but are not limited to, dysarthria, apraxia of speech, acquired neurogenic stuttering, palilalia, echolalia, forms of mutism, foreign accent syndrome, and aprosody associated with right hemisphere dysfunction (Duffy, 2013). Dysarthria is a neurogenic-based motor speech disorder characterized by abnormalities in the strength, speed, rate, range, stability, tone, or accuracy of movements required for some or all of the respiration, articulation, phonation, resonation, and prosodic components of speech due to neuromotor damage in the peripheral or central nervous system (Freed, 2011; Duffy, 2013; ASHA, 2023).

Among the causes of dysarthria are congenital disorders (e.g. cerebral palsy), neurodegenerative diseases (e.g. Parkinson's disease, ALS), vascular diseases (e.g. stroke), infectious diseases, demyelinating diseases (e.g. multiple sclerosis), toxic/metabolic diseases, neoplastic diseases (e.g. brain tumour), trauma, encephalitis, and many other conditions. The differences in the nature and location of the pathology give rise to different types of dysarthria (Roseberry-McKibbin and Hegde, 2006; Duffy, 2013; Hegde and Freed, 2016). Common lesion zones associated with dysarthria include the lower motor neuron, unilateral or bilateral upper motor neuron, cerebellum, and basal ganglia (Rampello et al., 2016; ASHA, 2023).

Apraxia of speech is a disorder in the timing-sequencing ability of motor commands required to properly position the articulators during voluntary speech production (Freed, 2011; Roth and Worthington, 2015). Although it is a neurologically based motor speech disorder similar to dysarthria, there is no muscle weakness or paralysis in apraxia, and there is a problem with motor planning and programming of speech movements (Freed, 2011; Duffy, 2013). This problem can affect any system that requires the purposeful sequencing of muscle movement (Roth and Worthington, 2015). Thus, a problem arises in the ability to perform articulatory movements at the right time and in the correct ordering of phonemes. Therefore, impairments in articulation and prosody usually occur. Although it is a result of damage to the central nervous system, the movement problem in apraxia of speech is not caused by muscle weakness or slowness (Freed, 2011).

Table 1
Clinical characteristics and classification of aphasia (Goodglass and Kaplan, 1972; Davis, 2007).

Non-fluent Aphasia		**Fluent Aphasia**	
Speech production is static and effortful. Grammar is poor; content vocabulary can be preserved.		The person can produce coherent speech. Sentence structure is relatively preserved, but there are distortions in meaning.	
Auditory comprehension skills are relatively better.	Auditory comprehension skills are poor.	Auditory comprehension skills are relatively better.	Auditory comprehension skills are poor.
Broca's aphasia; repetition of words and sentences is poor.	**Global aphasia;** severe expressive and receptive language disorder is available. Communication can be established using facial expression, intonation and gestures.	**Conductive aphasia;** there are difficulties in finding words and repetition of words and sentences is poor.	**Wernicke's aphasia;** repetition of words/sentences is poor.
Transcortical motor aphasia; repetition skills are preserved.		**Anomic aphasia;** repetition of words/sentences is good; word finding difficulties are present.	**Transcortical sensory aphasia;** repetition of words/sentences is preserved; may repeat questions instead of answering them.

Apraxia of speech is considered in two subtypes: developmental and acquired apraxia of speech (ASHA, 2023). Developmental apraxia of speech may be idiopathic or of neurological origin, whereas acquired apraxia of speech results from damage to the motor programming areas of speech in the left cerebral hemisphere. Generally, Broca and supplementary motor areas are affected. Among some types of pathology, vascular lesions that cause strokes particularly affect speech programming structures and pathways (Roseberry-McKibbin and Hegde, 2006; Hegde and Freed, 2016). The most common causes of acquired apraxia of speech include stroke, traumatic brain injury, tumours of the left hemisphere usually involving the frontal lobe, surgical trauma (for example, tumour resection), or degenerative diseases (Duffy, 2006; 2013). Apraxia of speech is sometimes referred to as primary progressive apraxia of speech in the literature because it is a symptom of degenerative conditions (Duffy et al., 2020).

The key characteristics of apraxia of speech include errors in the production of consonant and/or vowel sounds, substitutions or additions of sounds, inconsistent sound errors, decreased speech speed, use of equal stress on adjacent syllables, error awareness, searching behavior, error correction effort, and often failure of this effort. (McNeil et al., 2009; Duffy, 2013; Hegde and Freed, 2016; Allison et al., 2020).

This study aims to determine the effect of radiotherapy on neurogenic speech and language disorders in the early period in patients diagnosed with a primary brain tumour and receiving radiotherapy.

2. Materials and methods

In this multidisciplinary study, a descriptive research design was used. The ethics committee approval of our research was obtained from the University of Health Sciences Hamidiye

Scientific Research Ethics Committee, with the decision dated May 27, 2022, and numbered 22/301. The study aims to reveal the effect of radiotherapy applied to patients diagnosed with a primary brain tumour on neurogenic speech and language disorders in the early period.

The participants of the study consist of 35 patients selected among patients diagnosed with a primary brain tumour who applied to the Radiation Oncology Unit of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital. The selection and exclusion criteria for the participants included in the study are as follows:

1) Having been diagnosed with a primary brain tumour,

2) Radiotherapy will be applied as part of the treatment processes,

3) Being age ranging from 20 to 85 years,

4) Not having any speech and language disorders before the disease,

5) Not having severe intelligibility and hearing problems.

For the data collection part of the study, consent was obtained from the participants/proxies by filling out the consent form; an anamnesis file was created for each participant, and they were informed that they could withdraw from the study at any time. Within the scope of the research, Gülhane Aphasia Test 2 (GAT-2) and Standardized Mini Mental Test (MMT) were applied to the participants before they received radiotherapy. GAT-2 and MMT were reapplied to the patients 30 days after they had received radiotherapy as part of the treatment process. The purpose of using GAT-2 is to determine the speech and language skills of patients with brain tumor before and after radiotherapy. Likewise, the purpose of using MMT is to determine patients' mental status before and after radiotherapy. At the end of the study, the GAT-2 and MMT scores of the participants obtained before and in the early period after radiotherapy application were interpreted, and the results were obtained.

3. Results and discussion

A total of 35 participants, 21 male and 14 female, diagnosed with primary brain tumour were included in the study. The mean age of the patients is 55. 17 of the participants are primary school graduates, 10 are high school graduates, and 8 are university graduates. 30 patients are right-handed, and 5 patients are left-handed. Of the primary brain tumours detected in the patients, 21 are located in the right hemisphere and 14 in the left hemisphere, predominantly in the frontal, temporal, and parietal lobes.

GAT-2 was applied to the patients before radiotherapy. While 28 patients showed normal results, low scores were obtained in 7 cases with brain tumours localized in the frontal and temporal lobes. Similar results were obtained in the MMT part of the application. While the MMT results of 28 patients are normal, the MMT scores of 7 patients with low GAT-2 scores also show a low course.

The patients were called to the hospital on the 30th day after the RT application, and GAT-2 and MMT were applied again. While 26 of the 28 patients with high scores in the GAT-2 application before RT achieved similar high scores, 2 patients with the tumour localized in the left parietal lobe achieved lower scores than before the GAT-2 test applied after RT. It is seen that 7 cases with low GAT-2 scores before RT had similarly low scores after RT. When the MMT results were examined, 28 patients who received MMT before RT and got high scores had similar scores at the repetition of the test, while patients with low MMT results in the first application were able to obtain low scores after RT.

4. Conclusion

Primary brain tumours show a progressive course in the disease process and cause different accompanying health problems in patients depending on the areas they are localized in the brain. Neurogenic speech and language disorders are also diseases that can occur due to brain tumours. In brain tumour treatments, radiotherapy is applied in addition to wide surgical resection, and together with adjuvant chemotherapy that, also affects the patient's survival. Necrosis and late radiation toxicity that may occur in brain tumour radiotherapy applications can also cause various types of damage to the brain after the application.

This study aims to determine the effect of radiotherapy on neurogenic speech and language disorders in the early period in patients diagnosed with a primary brain tumour and receiving radiotherapy. In this context, 35 patients diagnosed with a primary brain tumour and receiving radiotherapy were studied. GAT-2 and MMT were applied to the patients before and after radiotherapy in the early period and evaluated according to the localization of the tumour in the brain.

When the data obtained after the applications were interpreted, it was determined that tumours formed in the frontal and temporal lobes, including the dominant language centers, before radiotherapy had a negative effect on the cognitive performance of the patients, as well as their speech and language skills. After radiotherapy was applied to the patients during the treatment process, two patients with tumours in the left parietal lobe had a decrease in their speech and language skills, and no deterioration was observed in the speech and language skills of the other participants. We think that this may be due to the early phase of radiotherapy.

In other studies, especially considering the effects of radiotherapy on cancer and healthy tissues, it is predicted that the difference in scores between these test scores for the late effects of 6 months and above may increase in cases before and after irradiation.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The ethics committee approval of our research was obtained from the University of Health Sciences Hamidiye Scientific Research Ethics Committee, with the decision dated May 27, 2022, and numbered 22/301.

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Research article

Phenolic and carotenoid composition of *Rhododendron luteum* Sweet and *Ferula communis* L. subsp. *communis* flowers

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Abstract

The biologically important potential of polyphenols and carotenoids from plants motivates the exploration of new natural sources and medicinal uses for these chemicals. Plants with colorful flowers are used not only for the benefits of bioactive compounds but also for smart textile materials and as colorants. In this study, quantification of phenolic compounds and carotenoids in *Rhododendron luteum* Sweet and *Ferula communis* L. subsp. *communis* flowers were determined. The flowers of these plants were analysed for the first time in Türkiye. While catechin (297.36±3.42 µg/g), 4-OH benzoic acid (179.28±2.87 µg/g) and salicylic acid (178.98±2.42 µg/g) are found to be relatively higher in *R. luteum* Sweet flowers compared to other phenolic compounds, relatively higher amounts of rutin (335.95±4.32 µg/g) and ferulic acid (367.10±4.11 µg/g) were found in *F. communis* L. subsp. *communis* flowers. On the other hand, lutein and β-carotene were detected in both species, whereas astaxanthin (4.46±0.21 µg/g) was found only in *R. luteum*. This phytochemical information may be important for the proper utilization of these plants as sources of phenolic compounds and carotenoids for a variety of possible commercial applications.

Keywords: *Carotenoids; extraction; Ferula communis* L. subsp. *communis; phenolic compounds; Rhododendron luteum* Sweet

1. Introduction

More than 850 species of *Rhododendron* (Ericaceae) are endemic to Europe, North America, Southeast Asia, China, Japan, and Australia (Heywood, 1993). *Rhododendron luteum* Sweet (Yellow-flowered Rhododendron), which is frequently used as an ornamental plant and in floriculture because of its cold hardiness, is native to Eastern Europe (Caucasus area), north-eastern Lithuania, and Poland (Sawidis et al., 2011). In Türkiye, it is found in the north, particularly along the coast of the Eastern Black Sea, in the North Anatolian Mountains, in a few locations south of the Marmara Sea, and in the southeast Taurus Mountains (Alan et al., 2010; Marin et al., 2014).

The fragrant, funnel-shaped, 1-4 m tall shrub, deciduous plant, with yellow blooms grow in spring alongside or before the leaves and contain poisonous nectar (Marin et al., 2014). The flowers and leaves of *R. luteum* and *R. ponticum* contain a toxic substance called andromedotoxin. The honey produced by bees from these is called mad honey. (Alan et al., 2010). Despite the fact that these two species are toxic to people and animals, they have medical applications (Parfionov, 1987; Alan et al., 2010; Lyko et al., 2022). As a result of research conducted in Türkiye on samples of *R. luteum* leaves, it was determined that the produced extracts exhibited a variety of activities, including suppression of bacterial growth and cytotoxicity. *R. luteum* is well-known for its pharmacological properties and has been discovered to contain a substantial number of polyphenols. (Mahomoodally et al., 2020; Olech et al., 2020). In Turkish traditional medicine, it has been used to cure inflammation and rheumatic discomfort; when used topically, and proven to be effective in treating fungal infections (Popescu and Kopp, 2013). According to another work, Turkish and Chinese traditional

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medicine employ *R. luteum* to treat acute and chronic bronchitis, rheumatism, arthritis, asthma, pain, inflammation, hypertension, and muscular and metabolic problems (Erdemoglu et al., 2008; Jaiswal et al., 2012; Lin et al., 2014). Chronic inflammation and oxidative stress are linked to several disorders, including cancer, cognitive dysfunctions, rheumatoid arthritis, and heart disease. While anti-inflammatory drugs can cause problems such as damage to the gastric mucosa, a decrease in gastric acid production, diarrhea or nausea, or painful side effects (Bindu et al., 2020), on the contrary, secondary metabolites derived from plant-based medicines have been demonstrated to possess either directly or indirectly anti-inflammatory and antioxidant properties without causing significant adverse effects (Pietta, 2000; González et al., 2015). Numerous studies demonstrate that polyphenols, such as flavonoids, have powerful antioxidant and anti-inflammatory properties (Olech et al., 2020). Antioxidants such as ascorbic acid, carotenoids, and phenolic compounds are chemicals generated by medicinal plants that help inhibit lipid peroxidation (Ceylan et al., 2019). Therefore, analysing the contents of herbal medications appears to be a potential option for determining the levels of secondary metabolites present in their composition and for discovering new natural and safe agents.

Due to the presence of polyphenolic compounds, carotenoids, and antioxidant properties, the flowers of *R. luteum* exhibit anti-inflammatory, antiviral, antibacterial, anticancer, anti-diabetic, immunomodulatory, cardioprotective, and hepatoprotective effects. (Demir et al., 2016). In tests with extracts of its leaves and flowers, it was shown that the extract showed specific cytotoxicity against colon and liver cancer cells relative to normal fibroblast cells (Demir et al., 2016; 2018). According to the study findings, *R. luteum* can be an excellent source of antioxidant and anticancer natural agents owing to their potential to inhibit the multiplication of cancer cells (Demir et al., 2018).

It has been utilized historically as an antidysenteric agent in the treatment of anti-hysteria and dysentery (Gunther, 1959; Heywood, 1972). *Ferula communis* L. (Giant fennel) is one of the most well-known ancient medicinal herbs. (Miski, 1986; Akaberi, 2015). *Ferula*, which is a member of the *Apiaceae* family, contains around 170 species (Rahali et al., 2019) that are scattered from Central Asia westward and through the Mediterranean area to northern Africa. *F. communis* is a 1-2.5 m tall, thickly rooted, hairless, latex-containing perennial aromatic plant with fragrant leaves (Rahali, 2021). The pharmacological properties of the genus *Ferula* are well-documented in both human and veterinary medicine. Its use as traditional medicine is preferred to treat a number of diseases (Singh, 1998). As medicinal applications of the genus *Ferula,* several studies have documented anti-carcinogenic (Saleem et al., 2001), anti-diabetic (Iranshahy and Iranshahi, 2011), anti-bacterial, anti-ulcerative, and anti-inflammatory benefits (Li et al., 2015; Rahali, 2021). However, reports indicate that *F. communis* is a highly dangerous and hazardous plant for people and animals (Rahali, 2021; Marchi, 2003). This is because *F. communis* exists in nature with two distinct chemical structures (chemotypes). Chemically hazardous *F. communis* and non-toxic *F. communis* are often found in distinct geographic locations (Akaberi et al., 2015). According to published research, the secondary metabolites of *F. communis* vary substantially based on regional conditions (Maggi et al., 2016).

According to classical medical texts such as Dioscorides, this plant has a wide variety of medicinal uses. For instance, crushed fresh seeds have been used to evacuate bloody contents from the mouth, relieve diarrheal stomach discomfort, and cure snake bites (Akaberi et al., 2015). For instance, it is utilized locally as a traditional cure to treat skin problems in Saudi Arabia, whilst roasted flower buds are employed to treat fever and diarrhea (Collenette, 1985). In general, polyphenols have significant anti-carcinogenic, anti-inflammatory, anti-diabetic, anti-osteoporotic, and anti-degenerative activities against the development of malignancies, cardiovascular diseases, diabetes, and osteoporosis (Graf et al., 2005). It is important to investigate the contents of plants used for therapeutic purposes in different regions. In this study, the contents of some phenolics and carotenoids in the flowers of *R. luteum* Sweet and *F. communis* L. subsp. *communis* plants were investigated. The secondary metabolite contents of these flowers were detected for the first time in Türkiye.

2. Materials and methods

2.1. Chemicals and reagents

Catechin, taxifolin, epicatechin, gallic acid, caffeic acid, ferulic acid, ellagic acid, protocatechuic acid, protocatechuic aldehyde, vanillin, p-coumaric acid, resveratrol, salicylic acid, rutin, 4-OH-benzoic acid, rosmarinic acid, oleuropein standards, and HPLC grade methanol used during extraction was purchased from Merck (Darmstadt, Germany) from Sigma Aldrich (Steinheim, Germany). The carotenoid standards (lutein, β-carotene and astaxanthin) in this study were obtained from CaroteNature (Switzerland).

2.2. Sampling area

The flowers of *Rhododendron luteum* Sweet and *Ferula communis* L. subsp. *communis* plants were collected from Şebinkarahisar district of Giresun. The identification of these species was made by Dr. Rena Hüseyinoğlu. The flowers obtained from these plants were dried in an oven at 40°C for 48 hours (Fig. 1).

Fig. 1. Photographs of dried plant flowers (A) *Rhododendron luteum* Sweet and (B) *Ferula communis* L. subsp. *communis*.

2.3. Extraction of phenolic compounds and carotenoids

The extraction of phenolic compounds was performed via Soxhlet extraction. For this purpose, 5 g of each sample was ground in a blender and placed in a Soxhlet cartridge. Methanol (150 ml) was added to the apparatus and extraction was carried

out. After this process, the resulting mixture was filtered, and the solvent was evaporated with a rotary evaporator at 40°C and 175 mbar. After, the samples were dissolved in 25% methanol-water and stored at -20°C until LC-MS/MS analysis.

For the extraction of carotenoids, a modified protocol was applied to the plant samples reported in a previous study (Erdogan et al., 2020). Each sample was weighed (1 g) and $CaCO_3$ (1 g) was added to each. The mixture was extracted using 20 ml of ethanol containing 0.01 percent pyrogallol in an ultrasonic bath (Elmasonic S80H) for 15 minutes at 30 degrees Celsius. The solution was subsequently centrifuged at 5000 rpm for two minutes. After separating the filtrate, the residual biomass was re-extracted with new ethanol until its discoloration.

After vacuum filtering using 47 mm 0.20 m nylon filter paper, the mixed filtrates were finally collected (Sartorius). In the dark, the resulting extracts were saponified for two hours with 10% methanolic KOH. To halt the saponification process, 10.0 ml of 10% (w/v) Na_2SO_4 was added. The carotenoids were then extracted using 10.0 ml of diethyl ether.

This procedure was repeated until no yellow/red hue was noticed in the supernatant. The mixture was then treated with $CaCl_2$ to eliminate any leftover water, filtered using nylon filter paper, and evaporated to dryness at 40°C and 400 mbar using a rotary evaporator (Stuart RE 400). The residue was subsequently diluted in 5 ml of methanol and kept at -20°C for LC-MS/MS analysis.

2.4. Analysis of phenolic compounds and carotenoids by LC-MS/MS

LC-MS/MS analysis of phenolic compounds using C_{18} column (ODS Hypersil, 4.6 x 250mm 5µm) at 30°C and flow rate of 0.7 ml min^{-1} (Seker et al., 2021). The mobile phase information and operating conditions of the LC-MS/MS are given in Table 1.

Table 1
LC-MS/MS conditions for the analysis of phenolic compounds in plants.

	Solvent program		
LC-MS/MS parameters	Time (Min.)	A % (Water) containing % 0.1 Formic acid	B % (Methanol)
	0	100	0
	1	100	0
	22	5	95
	25	5	95
	30	0	100
Flow rate	0.7 ml/min		
Column oven temperature	30°C		
Column specifications	ODS HYPERSİL C_{18} 4,6*250 mm 5um		
Injection volume	20 µl		
Analysis time	34 min		
Ionization source	ESI		

For the quantification of carotenoids, C_{30} carotenoid column was used (YMC, 4.6 x 250mm 5µm) at 25°C and flow rate of 1.0 ml/min (Erdogan et al., 2022). The mobile phase information and operating conditions of the LC-MS/MS are given in Table 2.

3. Results and discussion

Ferula communis L. subsp. c*ommunis* is widely used in traditional medicine for a wide variety of ailments. Fresh plant materials, raw extracts, and isolated components of *F. communis* are reported to exhibit many antidiabetics, antimicrobial, antiproliferative and cytotoxic properties (Akaberi et al., 2015). There is a similar study on phenolic component analysis in *F. communis* flowers realized by Rahali et al. (2019). In the study, a total of 11 phenolic compounds were analyzed. These; tannic, gallic, syringic acid, ferulic, chlorogenic acids and catechin, catechin hydrate, resorcinol, coumarin, quercetin and flavone. Among them, catechin, gallic acid and ferulic acid were analyzed. While catechin could not be detected in this study, the amounts of gallic acid and ferulic acid were found to be 6.99 µg/g and 63.70 µg/g, respectively. The highest amount found was resorcinol with 148.02 µg/g. Gallic acid and catechin could not be detected in our study. The amount of ferulic acid was determined as 367.10 µg/g. This result is approximately 5.76 times more than the flowers collected from Tunisia. *Ferula* flowers are characterized by the presence of ferulic acid. Apart from these, unlike the studies in the literature, in *Ferula* flowers; protocatechuic acid, protocatechuic aldehyde, caffeic acid, vanillin, taxifolin, oleuropein and 4-OH-benzoic acid, salicylic acid and rutin were detected. The major phenolic compounds determined in *F. communis* flowers were ferulic acid and rutin with content of 367.10 µg/g and 335.95 µg/g, respectively. Apart from these, the amounts of salicylic acid and 4-OH-benzoic acid in the flowers were found to be higher than the other phenolic compounds.

Table 2
LC-MS/MS conditions for the analysis of carotenoids in plants.

	Solvent program			
LC-MS/MS parameters	Time (Min.)	A % (Methanol)	B % (Water)	C % (tert- butyl-methyl ether)
	0	70	5	25
	5	60	5	35
	10	45	0	55
	154	25	0	75
Flow rate	1.0 ml/min			
Column oven temperature	25°C			
Column specifications	YMC C_{30} carotenoid column 4.6*250 mm 5um column			
Injection volume	20 µl			
Analysis time	15 min			
Ionization source	APCI			

The abovementioned is the first study to detect phenolic compounds in *F. communis* flowers. In this context, our study is the first for *F. communis* in Türkiye and the second for *F. communis* flowers in the world. Also, many different phenolic compounds analyzed in this study. These polyphenols in flowers are known to effectively inhibit the oxidation process due to their hydroxyl groups and cyclic structures. It is also reported that various parts of this plant show antibacterial and cytotoxic activities (Akaberi et al., 2015). Another plant collected from Şebinkarahisar region is *Geranium ibericum* subsp. *jubatum.* When compared to *Geranium* flowers, it is seen that compounds other than catechin, gallic acid, and protocatechuic acid are quite high in *Ferula* flowers (Seker et al., 2021).

Due to its antioxidant effects and low toxicity, ferulic acid is currently widely employed in the food and cosmetics industry (Goleniowski et al., 2013). It has been observed that rutin, which has a combination of antioxidant activity from radical scavenging, xanthine oxidase inhibition, and chain-breaking effects (Itagaki et al., 2010), protects several types of cancer via a variety of pathways and performs a number of essential biological functions. Studies have demonstrated that rutin reduces the initiation and progression of several forms of cancer by inhibiting the development of numerous diseases (Nouri et al., 2020).

When literature studies regarding *Rhododendron luteum* Sweet are examined, the studies on the leaves of this plant are present, but there is no study on the phenolic component content of the flowers. For this reason, there is no study in which the obtained results can be compared. The results obtained can only be compared with the results obtained from the leaves of *R. luteum* or the phenolic component contents found in the flowers of *R. ponticum* or other plants.

Accordingly, the results of the investigation of phenolic compounds in *R. luteum* flowers will be the first in the literature. Among these results, the highest amount belongs to catechin with 297.36 µg/g. Apart from that, 4-OH-benzoic acid 179.28 µg/g and salicylic acid 178.98 µg/g were determined in *R. luteum* flowers. Protocatechuic acid, p-coumaric acid and gallic acid were also detected in the extracts. When we look at the studies on *R. luteum* leaves in the literature, it is seen that these values are 4-5 times lower than the amounts found in the leaves (Łyko et al., 2022). These values seem low when compared to another *Rhododendron* species, *R. ponticium* (Malkoc et al., 2016).

When compared to *Ferula communis*, the highest number of phenolic components determined in *Ferula* flowers was rutin and ferulic acid, while no ferulic acid was detected in *R. luteum* and the amount of rutin was found to be at a very low level of 4.35 µg/g. On the contrary, while catechin, epicatechin, *p*-coumaric acid and gallic acid were not found in *Ferula*, these amounts were found relatively high in *R. luteum* flowers. It is known that catechin has protective properties for human health due to its antioxidant properties (Zanwar et al., 2014). Although the amounts of catechin, gallic acid and ellagic acid were lower in *R. luteum* compared to *Geranium* flowers with high antioxidant properties, the amounts of all other phenolic compounds determined were higher than *Geranium* flowers (Seker et al., 2021).

In addition to phenolic compounds, the flowers/leaves of many plants may contain various carotenoids. In fact, various flowers of the same species might have varied quantities of total carotenoids. These may be the result of soil qualities, production conditions, and other variables, such as floral parts or analytical parameters. The majority of carotenoids in published research on various flowers are xanthophylls such as lutein and zeaxanthin. Various amounts of lutein may be found in the following plants: Chrysanthemum (11.78-307.22 g/g dry weight), snapdragon (14.1 g/g dry weight), garden nasturtium (350-450 g/g fresh weight), Mexican marigold (1062 g/g fresh weight), and pansies (51.1 g/g dry weight). It has also been observed that edible flowers, leafy greens, and root vegetables have significant levels of carotene. For instance, spinach (4 mg/100 g) in summer sun (358.1 mg/100 g fw), Mexican marigold (8.55 mg/100 g fw), and squash blossoms (1.01-13.35 mg/100 g fw) have greater carotene concentrations than carrots (0.3 mg/100 g fw) (Singh et al., 2001). However, related plants have not been shown to contain astaxanthin. In a research, *Cucurbita maxima* was shown to have trace quantities of astaxanthin (Seroczyńska et al., 2006). According to the findings of our investigation, the acquired carotenoid levels are quite high. Specifically, the lutein levels reported from both species are astonishingly high. On the other hand, a rather significant level of astaxanthin, which was exclusively detected in *R. luteum*, was discovered. Table 4 presents a summary of the outcomes.

Table 3
Quantitative results of phenolic compounds in plant flowers (µg g^{-1}).

Phenolic compounds	*F. communis*	*R. luteum*
Gallic acid	ND	59.98±0.60
Protocatechuic acid	16.50±0.24	88.26±0.73
Protocatechuic aldehyde	7.59±0.12	5.34±0.06
Catechin	ND	297.36±3.42
Epicatechin	ND	16.62±0.37
Caffeic acid	5.55±0.06	3.60±0.05
Vanilin	31.05±0.45	22.44±0.30
Taxifolin	10.35±0.18	4.14±0.06
p-Coumaric acid	ND	78.97±1.14
Ferulic acid	367.10±4.11	ND
Rosmarinic acid	ND	ND
Oleuropein	0.20±0.01	ND
4-OH-Benzoic acid	58.14±0.42	179.28±2.87
Salicyclic acid	59.40±0.68	178.98±2.42
Rutin	335.95±4.32	4.35±0.07
Resveratrol	ND	ND
Ellagic acid	ND	0.44±0.01

ND: Not detected
Data are represented as the mean ±SD (standard deviation) of three measurements

Table 4
Quantitative results of carotenoid in plant flowers (µg g^{-1}).

Carotenoids	*F. communis*	*R. luteum*
Lutein	633.72±12.20	207.63±3.58
Astaxanthin	ND	4.46±0.21
β-carotene	23.16±0.69	36.57±1.34

ND: Not detected
Data are represented as the mean ±SD (standard deviation) of three measurements

4. Conclusion

According to the findings of this study, some of the reported therapeutic benefits of *Rhododendron luteum* and *Ferula communis* flowers may be attributable to the phenolic compounds and carotenoids that were identified. The first detailed description of the flowers of these plants will make a significant contribution to the literature. Even though both blooms are yellow, the phenolic and carotenoid contents of the two plants differ greatly.

The phenolic and carotenoid contents of these plants may contribute to their anti-inflammatory, antiviral, antibacterial, anticancer, anti-diabetic, immunomodulatory, cardioprotective, and hepatoprotective medicinal properties. To better comprehend the origins of these effects, it is necessary to identify the many secondary metabolites present in the structure of these plants. Additionally, at subsequent phases, the amount of essential oil in the flowers of these plants and the amount of phenolic components in the leaves can be investigated and published.

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Research article

Comparison of main metal industry sub-business lines from occupational health and safety perspective using CIRITIC and EDAS methods

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Abstract

The basic metal industry is one of the most economically important business lines in the manufacturing industry. According to the Social Security Institution (SSI) 2020 data, the basic metal industry in Türkiye is represented by 16 sub-businesses lines. In this study, it is aimed to evaluate the risk levels of the sub-business lines of the basic metal industry class, which is included in the SSI economic activity classification. Occupational Health and Safety data included in the 2020 SSI statistics were used to determine risk levels. The number of employees who have an occupational disease, the number of deaths because of work accidents, the period of temporary incapacity for work (inpatient), the period of temporary incapacity for work (outpatient), and the number of employees who have had a work accident are the criteria selected from these data. In the evaluation made according to these criteria, Multi-Criteria Decision-Making methods were used. Criteria Importance Through Intercriteria Correlation (CRITIC) and Evaluation Based on Distance from Average Solution (EDAS) methods were used to determine and classify the importance levels of the criteria determined for 16 sectors. As a result of the analysis, it has been determined that the riskiest sector among the main metal industry sub-business lines is the "Manufacture of basic iron and steel products and ferrous alloys" and the most important criterion is the number of insured persons with occupational diseases.

Keywords: *Base metal industry; CRITIC; EDAS; occupational health and safety*

1. Introduction

The manufacturing industry has a large share among the income sources of the countries and is one of the most important sectors in terms of economic growth. One of the most economically important business lines in the manufacturing industry is the basic metal industry. The basic metal industry plays an important role in the manufacturing sector when the areas in which it is used in the industry are considered (Sengul, 2020).

One of the most important sectors contributing to the development of Türkiye both economically and as a workforce is the basic metal industry sector. This sector provides important inputs to many fields in Türkiye thanks to its productions with 16 different business lines (Eyuboglu and Bayraktar, 2019).

As seen in Fig. 1, when analyzed in terms of production according to TUIK's 2020 statistics, monthly production indices of manufacturing industry and basic metal industry show a parallel performance.

In an increasingly competitive environment, it has become

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an important issue to protect, maintain and improve the status of businesses. Due to the information shared instantly with the technological developments experienced, businesses have entered a competition obligation not only across the country but also on a global scale. To keep up with the global competitive environment, it is of great importance for businesses to ensure the continuity of efficiency and quality in their activities and increase their performance (Uygurturk and Korkmaz, 2012). In addition, this competition forces businesses to act by considering the developments in global rival businesses as well as their own activities. (Yildirim et al., 2019). For this reason, determining their performance according to the future can be shown among the plans that businesses will make in order to maintain their existence and increase their efficiency (Bakirci et al., 2014).

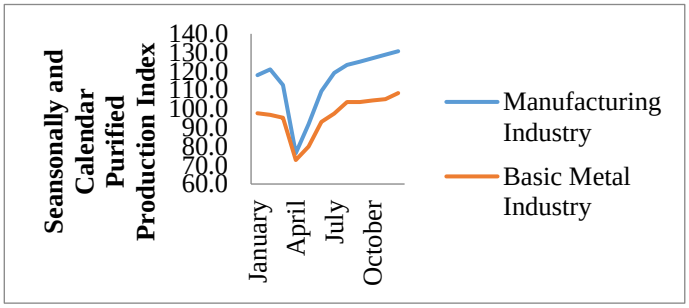

Fig. 1. Production indices (TUIK 2020).

According to the Social Security Institution (SSI) 2020 data, the basic metal industry in Türkiye is represented by 16 sub-business lines and there are 6,803 workplaces operating in this field and 175,994 employees working in these workplaces. This sector is a very risky sector due to the high need for manpower in the activities carried out and being in the very dangerous class in terms of working conditions. If the dangers and risks in the working environment cannot be reduced to reasonable levels, losses will occur because of accidents that may occur, and both the sector and the country will have to bear the consequences. For this reason, it is necessary for business managers to exhibit rational behaviors in the plans they will carry out according to the results of the risk assessments to be made. These behaviors should include adopting a proactive approach to any accident that may occur in workplace environments and providing the necessary occupational safety conditions by taking the necessary precautions. Thus, because of creating safe working environments in enterprises, a great step will be taken to ensure and maintain continuity and increase productivity.

Occupational Health and Safety (OHS) is a phenomenon that has emerged not only for the needs of employees and working environments, but also to increase social welfare and to protect and observe all segments. For this reason, Occupational Health and Safety Law No. 6331 came into force to improve health and safety conditions for all segments and to overcome existing problems. Thus, a new era has started for the studies to be carried out in the field of OHS, and the activities to be carried out have been desired to have a holistic structure. With this Law, great importance was attached to risk assessment as a proactive approach to prevent negative situations that may occur in workplaces (Can and Kargi, 2019).

Work-related accidents attract attention in the global context, among the deaths that occur because of occupational accidents. The high number of deaths because of work accidents in Türkiye is an indication that the activities carried out within the scope of OHS are insufficient and the problems continue. To prevent these problems, it is important to determine the existing or potential risks in the working environment and to decide on the measures to be taken.

In this study, it is aimed to determine the riskiest sector among these sectors by examining the OHS indicators in the SSI 2020 statistical yearbook of 16 different sectors, which are sub-branches of the Basic Metal Industry sector, which is in the very dangerous business line. In this context, two methods were used from Multi-Criteria Decision-Making (MCDM) approaches: Diakoulaki et al. (1995) CRITIC (Criteria Importance Through Intercriteria Correlation) and Ghorabaee et al. (2015) EDAS (Evaluation Based on Distance from Average Solution).

2. Materials and methods

The CRITIC method used in the study was developed by Diakoulaki et al. (1995). Through CRITIC, one of the MCDM methods, the degree of importance of the problems is shown objectively according to the determined criteria. The weights of the criteria are derived from the concentration of contradiction and contrast, which is the basis of all decision-making situations. Correlation analysis is used to determine the contrast of the criteria determined in this method (Zardari et al., 2015). Therefore, first, it is necessary to create the correlation matrix for weighting. There is a directly proportional relationship in the matrix created between the degree of accordance with the determined criteria and the correlation value. In other words, the higher the accordance between the two criteria, the higher the correlation of these criteria will be. In this method, in order to obtain the value of the decision criteria, the standard deviation and correlation of all decision criteria should be taken into account (Wang and Luo, 2010). The application steps of the CRITIC method are listed below (Wu et al., 2020; Maruf and Ozdemir, 2021; Omurbek et al., 2021; Ozkan and Ag, 2021; Dogan, 2022).

Step 1. Generating the decision matrix:

In this step, the decision matrix *X* is created, which includes criteria corresponding to different alternative situations. The decision matrix X, consisting of "n" criteria and "m" alternatives, prepared with the help of the data in the decision problem, is as follows (Alp and Engin, 2011):

$$X = \left\lfloor x_{ij} \right\rfloor_{m \times n} = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1n} \\ x_{21} & x_{22} & \cdots & x_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ x_{m1} & x_{m2} & \cdots & x_{mn} \end{bmatrix} \quad (1)$$

Step 2. Generating the normalized decision matrix:

In the second step, normalization process is performed to convert the criteria values to common values. In this way, criteria with different measurement values will be made dimensionless. In this step, the criteria are determined as cost-oriented or benefit-oriented criteria in terms of their purposes. While the equation given in Equality (2) is used for benefit-oriented criteria, the equation given in Equality (3) is used to

calculate values for cost-oriented criteria (Bulgurcu, 2019).

$$r_{ij} = \frac{x_{ij} - x_j^{\min}}{x_j^{\max} - x_j^{\min}} \quad (2)$$

$$r_{ij} = \frac{x_j^{\max} - x_{ij}}{x_j^{\max} - x_j^{\min}} \quad (3)$$

Step 3. Calculation of multiple correlation (ρjk):

The relationship between the criteria is obtained by calculating with the help of correlation coefficients. The amount of information in the criteria shows the relative importance of the criteria (Vujicic et al., 2017). By means of the r_{ij} value obtained because of the normalization process, the ρ_{jk} correlation value between the "*j*" and "*k*" criteria is calculated using Equality (4) (Akcakanat et al., 2018).

$$\rho_{jk} = \frac{\sum_{i=1}^{m}(r_{ij} - \bar{r}_j) * (r_{ik} - \bar{r}_k)}{\sqrt{\sum_{i=1}^{m}(r_{ij} - \bar{r}_j)^2 * (r_{ik} - \bar{r}_k)^2}} \quad \text{j,k=1,2…,n} \quad (4)$$

Step 4. Calculation of relationship density (Cj) value:

In the first stage of the fourth step, the standard deviation values of the criteria are obtained with the help of Equality (5). Then, the *Cj* value, which is the total amount of information belonging to the criteria, is obtained with the help of Equality (6).

$$\sigma_j = \sqrt{\frac{\sum_{i=1}^{m}(r_{ij} - \bar{r}_j)^2}{m-1}} \quad (5)$$

$$C_j = \sigma_j \sum_{k=1}^{n}(1 - \rho_{jk}) \qquad \text{j=1,2,…,n} \quad (6)$$

The criteria with low correlation and high standard deviation among the criteria are the criteria with high total amount of information and have the greatest importance (Madic and Radovanovic, 2015).

Step 5. Calculation of criterion significance weights (Wj):

In this step, Equality (7), which is the method of dividing the "*Cj*" value of each "*j*" criterion by the sum of all criteria values, is used to calculate the criterion weights. The objective critical weight shows the conflict and contrast intensity of the criteria (Jahan et al. 2012).

$$w_j = \frac{C_j}{\sum_{k=1}^{n} C_j} \quad (7)$$

Step 6. Calculation of score value (ski):

In the last step, necessary calculations are made by using Equality (8) to determine criterion weights.

$$sk_i = \sum_{j=1}^{n} w_j \times x_{ij} \quad (8)$$

Another method utilized in the study is the EDAS method which is one of the MCDM methods and was developed by Ghorabaee et al. (2015). The logic of this method is basically like the Technique for Order Preference by Similarity to Ideal Solution (TOPSIS) method, but there is a fundamental difference. This difference is that, unlike VIKOR and TOPSIS methods, in this method, analyses are made according to their proximity to the positive and negative ideal solution. In other words, the analysis in the EDAS method is not with the ideal solution approach; is performed with an average solution with negative and positive distance values.

There are two different values in the EDAS method: (1) the negative distance to the average solution and (2) the positive distance to the average solution. These values are the values that guide the existing alternatives. As a result of the analyzes made, it is desired that the positive distance value is the highest and the negative distance value is the lowest for the most appropriate result (Trinkūnienė et al., 2017).

EDAS method analyzes are performed in seven steps. These steps are listed below (Ghorabaee et al., 2015; Ulutas, 2017; Trinkūnienė et al., 2017):

Step 1. Generating the decision matrix (X):

In the first step of this method, the initial decision matrix for the decision problem is generated as in Equality (9).

$$X = \left[X_{ij}\right]_{m \times n} = \begin{bmatrix} x_{11} & x_{12} & \cdots & x_{1m} \\ x_{21} & x_{22} & \cdots & x_{2m} \\ \cdots & \cdots & \cdots & \cdots \\ x_{m1} & x_{m2} & \cdots & x_{nm} \end{bmatrix} \quad (9)$$

Step 2. Generating the average values matrix (AVj):

In the second step, a matrix of average values is generated for the criteria determined with the help of Equality (10).

$$AV_j = \frac{\sum_{i=1}^{n} X_{ij}}{m} \quad (10)$$

Step 3. Obtaining positive and negative distance matrices from the average:

In the third step of the method, a matrix of positive and negative distances from the average is generated. For the determined criteria, the average positive distance matrix (*PDA*) is formed by means of Equality (11) and the average negative distance matrix (*NDA*) by means of Equality (12). It is resolved by Equality (13) and (14) if the criteria determined are benefit-oriented, and by Equality (15) and (16) if the criteria are cost-oriented.

$$PDA = \lfloor PDA_{ij} \rfloor_{mxn} \tag{11}$$

$$NDA = \lfloor NDA_{ij} \rfloor_{mxn} \tag{12}$$

$$PDA_{ij} = \frac{\max(0,(X_{ij} - AV_j))}{AV_j} \quad j \in \text{benefit criterion} \tag{13}$$

$$NDA_{ij} = \frac{\max(0,(AV_j - X_{ij}))}{AV_j} \quad j \in \text{benefit criterion} \tag{14}$$

$$PDA_{ij} = \frac{\max(0,(AV_j - X_{ij}))}{AV_j} \quad j \in \text{cost kriteri} \tag{15}$$

$$NDA_{ij} = \frac{\max(0,(X_{ij} - AV_j))}{AV_j} \quad j \in \text{cost kriteri} \tag{16}$$

In the equalities given above, the cost criterion expresses the criteria that are desired to be minimum, and the benefit criterion expresses the criteria that are desired to be maximum.

Step 4. Calculation of weighted total values:

In the fourth step of the method, the weighted total positive distances (SP_i) and negative distances (SN_i) are calculated using Equality (17) and (18) by means of the positive and negative distance matrices obtained from the previous step. The w_j value given in the equalities indicates the importance weight of each evaluation criterion.

$$SP_i = \sum_{j=1}^{m} w_j PDA_{ij} \tag{17}$$

$$SN_i = \sum_{j=1}^{m} w_j NDA_{ij} \tag{18}$$

An increase in the SP_i value and a decrease in the SN_i value indicate that the alternatives are at the desired level. In other words, in this step, the highest SP_i value and the lowest SN_i value will show that the alternative is the alternative that is suitable.

Step 5. Normalizing weighted total distances:

In the fifth step of the method, the weighted total values of SP_i and SN_i obtained in the previous step are normalized with the help of Equality (19) and (20).

$$NSP_i = \frac{SP_i}{\max_i (SP)_i} \tag{19}$$

$$NSN_i = 1 - \frac{SN_i}{\max_i (SN_i)} \tag{20}$$

Step 6. Calculation of evaluation scores of alternatives:

In the sixth and last stage of the method, the average of the NSP_i and NSN_i values obtained in the fifth step is taken and performance evaluation is made for each alternative. Success values are obtained by means of AS_i Equality (21). Among the obtained results, it is decided that the alternative with the highest AS_i value is the best alternative.

$$AS_i = \frac{1}{2}(NSP_i + NSN_i) \tag{21}$$

AS_i value, it must be ensured $0 \le AS_i \le 1$ condition.

3. Results and discussion

According to the SSI 2020 data used in the analyzes, the list of sub-activity branches of the Basic Metal Industry is given in Table 1.

Table 1
Business lines included in the evaluation.

Manufacturing of main iron and steel products and ferrous alloys	X_1
Manufacturing of steel tubes, pipes, hollow profiles, and similar fittings	X_2
Cold drawing of bars	X_3
Cold rolling of narrow strips	X_4
Cold forming or folding	X_5
Cold drawing of wires	X_6
Precious metal production	X_7
Production of aluminum	X_8
Lead, zinc and tin production	X_9
Production of copper	X_{10}
Production of other non-ferrous metals	X_{11}
Processing of nuclear fuels	X_{12}
Iron casting	X_{13}
Steel casting	X_{14}
Casting of light metals	X_{15}
Casting of other non-ferrous metals	X_{16}

Table 2
Evaluated criteria.

Number of insured persons with work accidents by incapacity for work (days)	C_1
Total temporary incapacity for work (outpatient)	C_2
Total temporary incapacity for work (inpatient)	C_3
Number of insured persons with occupational diseases	C_4
Number of insured deaths because of work accident	C_5

The list of criteria determined for the sub-activity branches of the Basic Metal Industry is given in Table 2.

3.1. CRITIC method analysis

3.1.1. Generating the decision matrix

The first step to be taken to solve the decision problem is to generate the decision matrix that the determined criteria and alternatives take together. A decision matrix is generated in which 16 alternatives and 5 selected criteria are included together. 16 different business lines (alternative) belonging to the basic metal industry and the "Number of Insured Persons with Work Accidents by Incapacity for Work (days)" (C1), "Total Temporary Incapacity for Work (Outpatient)" (C2), "Total Temporary Incapacity for Work (Inpatient)" (C3), "Number of Insured Persons with Occupational Diseases" (C4), and "Number of Insured Deaths as a result of Work Accident" (C5) (five different Cj, j=1,…) were evaluated according to 5 criteria.

Within the framework of the evaluations because of the analysis performed with the CRITIC method, the initial decision matrix was created as in Equality (1) and presented in Table 3.

Table 3
Initial decision matrix.

	Number of Insured Persons with Work Accidents by Incapacity for Work (days) C_1	Total Temporary Incapacity for Work (Outpatient) C_2	Total Temporary Incapacity for Work (Inpatient) C_3	Number of Insured Persons with Occupational Diseases C_4	Number of Insured Deaths because of Work Accident C_5
X1	5267	70200	1349	11	11
X2	2177	29182	378	4	6
X3	174	2153	16	0	0
X4	44	421	1	0	0
X5	447	6539	151	2	0
X6	458	6733	80	2	0
X7	26	272	7	0	0
X8	1906	21228	380	1	1
X9	38	557	34	2	0
X10	367	4729	69	1	0
X11	146	2317	115	0	2
X12	2	172	2	0	0
X13	2758	35459	686	20	8
X14	921	9892	175	2	1
X15	756	8621	89	2	1
X16	295	4579	113	1	2

3.1.2. Normalized decision matrix (r_{ij})

To carry out the objective weighting process, the second step was generated according to the benefit/cost orientation of the normalized decision matrix criteria. Since all the criteria determined at this stage are cost-oriented, the necessary procedures were carried out using Equality (3) and the results obtained are shown in Table 4. Since all calculated values affect the cost situation, the minimization process has been carried out.

3.1.3. Calculating multi-correlation (ρjk)

Table 4
Normalized decision matrix.

Criteria / Alternative Criteria	C1 min	C2 min	C3 min	C4 min	C5 min
X1	0,000	0,000	0,000	0,450	0,000
X2	0,587	0,586	0,720	0,800	0,455
X3	0,967	0,972	0,989	1,000	1,000
X4	0,992	0,996	1,000	1,000	1,000
X5	0,915	0,909	0,889	0,900	1,000
X6	0,913	0,906	0,941	0,900	1,000
X7	0,995	0,999	0,996	1,000	1,000
X8	0,638	0,699	0,719	0,950	0,909
X9	0,993	0,995	0,976	0,900	1,000
X10	0,931	0,935	0,950	0,950	1,000
X11	0,973	0,969	0,915	1,000	0,818
X12	1,000	1,000	0,999	1,000	1,000
X13	0,477	0,496	0,492	0,000	0,273
X14	0,825	0,861	0,871	0,900	0,909
X15	0,857	0,879	0,935	0,900	0,909
X16	0,944	0,937	0,917	0,950	0,818

After the normalization process performed in the third step of the application, the multi-correlation matrix showing the correlation levels between the criteria was calculated by means of Equality (4) and given in Table 5.

Table 5
Relationship coefficient matrix.

Criteria	C1	C2	C3	C4	C5
C1	1,000	0,998	0,985	0,733	0,925
C2	0,998	1,000	0,988	0,735	0,938
C3	0,985	0,988	1,000	0,749	0,931
C4	0,733	0,735	0,749	1,000	0,817
C5	0,925	0,938	0,931	0,817	1,000

3.1.4. Calculating correlation density (C_j)

At this stage, the *1-ρjk* value presented in Table 6 was calculated by using the data in Table 5 to calculate the *Cj* value. Then, using the normalized values calculated in Table 4 for the standard deviation values of the criteria, the calculation was made by means of Equality (5) and presented in Table 7. Finally, using the standard deviation values, the correlation density (*Cj*) values of the criteria were calculated by means of Equality (6) and the results are given in Table 8.

Table 6
(1-ρjk).

Criteria	C1	C2	C3	C4	C5
C1	1,000	0,998	0,985	0,733	0,925
C2	0,998	1,000	0,988	0,735	0,938
C3	0,985	0,988	1,000	0,749	0,931
C4	0,733	0,735	0,749	1,000	0,817
C5	0,925	0,938	0,931	0,817	1,000

Table 7
Standard deviation values for criteria.

Standard deviation sj, j=1,….,5				
s_1	s_2	s_3	s_4	s_5
0,2698	0,2665	0,2603	0,2633	0,3042

3.1.5. Calculating criterion importance weights (W_j)

Table 8
Correlation density.

Business Line	C_j
Number of insured persons with work accidents by incapacity for work (days) (C_1)	0,0969
Total temporary incapacity for work (outpatient) (C_2)	0,0910
Total temporary incapacity for work (inpatient) (C_3)	0,0905
Number of insured persons with occupational diseases (C_4)	0,2542
Number of insured deaths because of work accident (C_5)	0,1183

The importance weights (W_j) calculated by Equality (7) in the penultimate step of the CRITIC method are given in Table 9.

Table 9
Importance weight values.

Business Line	W_j
Number of insured persons with work accidents by incapacity for work (days) (C_1)	0,148
Total temporary incapacity for work (outpatient) (C_2)	0,139
Total temporary incapacity for work (inpatient) (C_3)	0,139
Number of insured persons with occupational diseases (C_4)	0,390
Number of insured deaths because of work accident (C_5)	0,181

When the findings in Table 9 are examined, it has been determined that the importance weights of the criteria determined for the basic metal industry vary between 0.139 and 0.390. According to these results, it has been concluded that the most important performance criterion for the basic metal industry is "Number of Insured Persons with Occupational Diseases". The criterion of "Total Temporary Incapacity for Work (Inpatient)" is the lowest performance criterion in terms of importance weight.

3.1.6. Calculating the score value (sk_i)

In the last step of the application, using the values obtained from the alternatives, the score value (sk_i) was calculated by means of Equality (8) and given in Table 10.

Table 10
Score weights.

Business Line	sk_i
X1	10790,59
X2	4458,40
X3	329,08
X4	65,54
X5	1002,35
X6	1021,24
X7	42,86
X8	3304,43
X9	89,02
X10	725,65
X11	361,96
X12	24,62
X13	5471,73
X14	1545,12
X15	1330,94
X16	700,44

When Table 11 is examined, it is seen that the "Manufacturing of main iron and steel products and ferrous alloys" sector is the business line with the highest risk level among the main metal industry sub-business lines, within the framework of the evaluation criteria considered. This sector is followed by the manufacture of cast iron, machine and steel tubes, pipes, hollow profiles, and similar fittings, respectively.

Table 11
Ranking of score weights.

Business Line	sk_i	Ranking
Manufacturing of main iron and steel products and ferrous alloys	10790,59	1
Iron casting	5471,73	2
Manufacturing of steel tubes, pipes, hollow profiles and similar fittings	4458,40	3
Production of aluminum	3304,43	4
Steel casting	1545,12	5
Casting of light metals	1330,94	6
Cold drawing of wires	1021,24	7
Cold forming or folding	1002,35	8
Production of copper	725,65	9
Casting of other non-ferrous metals	700,44	10
Production of other non-ferrous metals	361,96	11
Cold drawing of bars	329,08	12
Lead, zinc, and tin production	89,02	13
Cold rolling of narrow strips	65,54	14
Precious metal production	42,86	15
Processing of nuclear fuels	24,62	16

3.1.7. EDAS method analysis

Table 12
Decision matrix.

	Number of Insured Persons with Work Accidents by Incapacity for Work (Days) C_1	Total Temporary Incapacity for Work (Outpatient) C_2	Total Temporary Incapacity for Work (Inpatient) C_3	Number of Insured Persons with Occupational Diseases C_4	Number of Insured Deaths as a result of Work Accident C_5
	0,1489	0,1398	0,1390	0,3906	0,1818
X1	5267	70200	1349	11	11
X2	2177	29182	378	4	6
X3	174	2153	16	0	0
X4	44	421	1	0	0
X5	447	6539	151	2	0
X6	458	6733	80	2	0
X7	26	272	7	0	0
X8	1906	21228	380	1	1
X9	38	557	34	2	0
X10	367	4729	69	1	0
X11	146	2317	115	0	2
X12	2	172	2	0	0
X13	2758	35459	686	20	8
X14	921	9892	175	2	1
X15	756	8621	89	2	1
X16	295	4579	113	1	2
AVj	986	12691	228	3	2

In the first step of the method, the decision matrix was generated with the help of Equality (9) by using the data belonging to the Basic Metal Industry sub-business lines from the SSI 2020 data and shown in Table 12. The average values (*AVj*) obtained for the criteria determined in the second step of

the analysis were calculated with the help of Equality (10) and given in Table 12.

After the decision matrix and the average weight calculation, the average positive and negative distance matrices were calculated by means of Equality (11) and (12). It has been taken into account whether the criteria determined in the creation of these matrices are benefit-oriented or cost-oriented. Since the criteria are benefit-oriented, matrices for positive and negative distances were generated using Equality (13) and (14) and presented in Tables 13 and 14.

Table 13
Average positive distance matrix.

	C1	C2	C3	C4	C5
X1	4,34	4,53	4,92	2,67	4,50
X2	1,21	1,30	0,66	0,33	2,00
X3	0,00	0,00	0,00	0,00	0,00
X4	0,00	0,00	0,00	0,00	0,00
X5	0,00	0,00	0,00	0,00	0,00
X6	0,00	0,00	0,00	0,00	0,00
X7	0,00	0,00	0,00	0,00	0,00
X8	0,93	0,67	0,67	0,00	0,00
X9	0,00	0,00	0,00	0,00	0,00
X10	0,00	0,00	0,00	0,00	0,00
X11	0,00	0,00	0,00	0,00	0,00
X12	0,00	0,00	0,00	0,00	0,00
X13	1,80	1,79	2,01	5,67	3,00
X14	0,00	0,00	0,00	0,00	0,00
X15	0,00	0,00	0,00	0,00	0,00
X16	0,00	0,00	0,00	0,00	0,00

Table 14
Average negative distance matrix.

	C1	C2	C3	C4	C5
X1	0,00	0,00	0,00	0,00	0,00
X2	0,00	0,00	0,00	0,00	0,00
X3	0,82	0,83	0,93	1,00	1,00
X4	0,96	0,97	1,00	1,00	1,00
X5	0,55	0,48	0,34	0,33	1,00
X6	0,54	0,47	0,65	0,33	1,00
X7	0,97	0,98	0,97	1,00	1,00
X8	0,00	0,00	0,00	0,67	0,50
X9	0,96	0,96	0,85	0,33	1,00
X10	0,63	0,63	0,70	0,67	1,00
X11	0,85	0,82	0,50	1,00	0,00
X12	1,00	0,99	0,99	1,00	1,00
X13	0,00	0,00	0,00	0,00	0,00
X14	0,07	0,22	0,23	0,33	0,50
X15	0,23	0,32	0,61	0,33	0,50
X16	0,70	0,64	0,50	0,67	0,00

In the next step, the weighted total negative distances (SN_i) and positive distances (SP_i) are calculated with the help of Equality (17) and (18). In this study, EDAS and CRITIC methods were preferred and the weights of the criteria reached in the CRITIC method were used in the weighting process performed in Equality (17) and (18). After calculating the weighted total distances, the (NSP_i) and (NSN_i) values were obtained by normalizing the (SP_i) and (SN_i) values by means of Equality (19) and (20).

As the last step of this method, scores were obtained by evaluating the performance of the alternatives determined. Evaluation score of the criteria (AS_i) is calculated by Equality (21) and given in Table 15. The alternative with the highest (AS_i) value is accepted as the optimal state.

The results obtained when the relevant steps were performed using the EDAS method are given in Table 15.

Table 15
Results.

	SP_i	SN_i	NSP_i	NSN_i	AS_i	Ranking
X1	3,823	0,000	1,000	0,000	0,500	1
X2	0,947	0,000	0,248	0,000	0,124	16
X3	0,000	0,940	0,000	0,943	0,472	5
X4	0,000	0,988	0,000	0,991	0,496	4
X5	0,000	0,508	0,000	0,510	0,255	12
X6	0,000	0,548	0,000	0,549	0,275	10
X7	0,000	0,989	0,000	0,992	0,496	3
X8	0,326	0,351	0,085	0,352	0,219	13
X9	0,000	0,707	0,000	0,709	0,355	8
X10	0,000	0,720	0,000	0,723	0,361	7
X11	0,000	0,700	0,000	0,703	0,351	9
X12	0,000	0,997	0,000	1,000	0,500	2
X13	3,556	0,000	0,930	0,000	0,465	6
X14	0,000	0,294	0,000	0,295	0,148	15
X15	0,000	0,385	0,000	0,387	0,193	14
X16	0,000	0,524	0,000	0,526	0,263	11

When Table 15 is examined, as in the CIRITC method, within the framework of the analyzed evaluation criteria, it has been determined that "Manufacturing of main iron and steel products and iron alloys" has the highest risk level among the main metal industry sub-business lines in the EDAS method.

According to the findings obtained as a result of the analysis, the "occupational disease", which is the riskiest criterion, overlaps with the findings obtained as a result of the study in which Can and Kargı (2019) evaluated the OHS risk levels of 17 different sectors with the EDAS and CRITIC methods. In their research, Ayrim and Can (2017) examined 14 different business lines and aimed to determine the one with the highest risk using the CRITIC method. As a result of their studies, they concluded that the textile manufacturing sector is the riskiest sector. Although the criteria examined are the same, this study differs in terms of the business line examined in our study because the determined business lines are different.

Elmas-Atay and Yildirim (2022) considered 7 different OHS indicators as criteria in their study and determined 88 different sectors as alternatives. As a result of the study carried out with the CIRITIC method, the authors concluded that the riskiest sector is the construction sector. In this study, "death numbers due to occupational diseases" were excluded because they were considered low. In this respect, this study also differs from our study.

4. Conclusion

Despite the developing technology, labor-intensive human workforce studies are still carried out in the basic metal industry. This situation requires the basic metal industry to be included in the very dangerous workplace classification. This requirement also necessitates that the basic metal industry sector should be taken very seriously in terms of occupational safety. When the sector is examined, there are many risks arising from chemical and physical hazards. Due to the existence of these risks and the fact that it is a very dangerous business line, the measures to be taken in terms of OHS will prevent great material and moral

losses.

Within the SSI workplace classification, the basic metal industry is represented by 16 sub-business lines. According to SSI 2020 statistics, there are 6803 workplaces operating in the basic metal industry and 175.994 employees working in these workplaces. In this study, the basic metal industry was handled, and its sub-business lines were examined by CRITIC and EDAS methods.

As a result of the examination made with the CRITIC method, it was determined that the weight of importance was the highest in the criterion of "Number of insured persons with occupational diseases" with 39%. In other words, the most important criterion when evaluating business lines is the number of insured persons with occupational diseases. This criterion was followed by the number of insured deaths because of work accidents (18%), the number of insured persons with work accidents by an incapacity for work (14%), total temporary incapacity for work (inpatient) (13%) and total temporary incapacity for work (outpatient) (13%).

Since EDAS and CRITIC integrated methods were used in the study, the weights of the criteria reached in the CRITIC method were used in the weighting process. In both methods, it was concluded that the riskiest business line among the basic metal industry business lines is "Manufacturing of main iron and steel products and iron alloys".

When the deaths occurring in the world are examined, work-related deaths come to the fore. According to SSI 2020 data, 384,262 work accidents, and 908 occupational diseases have occurred in Türkiye. As a result of these incidents, 1231 employees died because of work accidents and 5 employees died because of occupational disease. In order to eliminate or minimize these accidents and the resulting deaths, the riskiest business lines should be identified, and necessary measures should be taken for these business lines. The measures to be taken are a necessity for employees, employers, and countries. With the study, the basic metal industry sub-branches, which are among the riskiest sectors, were examined and it was aimed to draw attention to minimizing the deaths and injuries caused by the results achieved.

In this context, providing the necessary training on accidents and injuries to the basic metal industry workers, applying collective protection methods, and following up on the personal protective methods will greatly contribute to the reduction of the cases that will occur. In addition, employees should be taught that the training provided, the measures taken, and the planned practices are not a necessity. For this, it is of great importance to make safe behaviors a culture in workplace environments. Considering that work accidents are caused by the unsafe working environment and unsafe employee behaviors (Sadullah, 2021), it can be suggested to examine in detail the characteristics of workplaces, working environments, and the size of workplaces (Alli, 2008) in the prevention of work accidents and occupational diseases.

There are some limitations in the study. One of these limitations is that the criteria considered in terms of occupational health and safety of the examined sectors are not similar for each sector. Another limitation is that the study only belongs to a business line in Türkiye, this business line is not evaluated globally, and the necessary comparisons cannot be made.

As a result, in this study, 16 different sectors, which are sub-business lines of the basic metal industry, which is one of the SSI business lines, were evaluated by considering 5 different criteria. Examining the different criteria that cause work accidents and occupational diseases belonging to these sectors and using different criteria such as working environment and safety culture will make a more comprehensive contribution to the solution of the problem.

Conflict of interest: The authors declare that they have no conflict of interests.

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Derleme makalesi / Review article

Beta-blokerlerin yeniden konumlandırılması: Meme kanseri uygulamaları

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Öz

Adrenerjik reseptörlerin yanıtını (aktivasyonunu) engelleyen beta-adrenerjik reseptör antagonistleri, beta-blokerler olarak adlandırılır. Beta-blokerler hipertansiyon, infatil hemanjiyom anormal stres, iskemik kalp yetmezliği gibi kardiyovasküler durumların tedavisi için yaygın olarak kullanılan ilaçları kapsamaktadır. Tümör mikroçevresindeki tümör ve stromal hücrelerin β-AR uyarımı, tümör büyümesini ve metastatik yayılımı teşvik etmekte ve sağkalımı olumsuz etkilemektedir. İlaçları yeniden yapılandırma, yönlendirme, profillendirme veya konumlandırma olarak adlandırılan strateji, klinik kullanımda var olan bir ilacı olduğu gibi ya da yapısal modifikasyona uğratarak yeni bir endikasyona uyarlamak ya da kullanmak olarak tanımlanmaktadır. Artan kanser vakaları nedeniyle kanser tedavisinin maliyeti artmaktadır. Günümüzde bu maliyetin düşürülmesi ve kanser tedavisinin etkinliğinin artırılması amaçlanmaktadır. Beta-blokerlerın, β-AR uyarımı engelleyerek sinyal yolağında bulunan alt efektörlerin aktivasyonunu ve bunlar ile uyarılan diğer yolakları engellediği bilinmektedir. Ek olarak, beta-blokerlerin hücrelerde proliferasyonu engelleyerek apoptozu uyardığı ile ilgili veriler de mevcuttur. Propranololün meme kanseri hastalarında yeniden konumlandırma çalışmaları, umut vadeden verilerin elde edilmesini sağlamıştır. Bu derlemede, yeniden konumlandırılmış ilaçlar, beta-blokerlerin kanser hücreleri üzerindeki etki mekanizmaları ile bu ilaçların meme kanseri tedavisinde kullanımını konu alan çalışmaların değerlendirilemesi yapılmıştır. Beta-blokerler dahil olmak üzere meme kanseri tedavisi için yeniden konumlandırılan ilaçlar ile ilgili klinik öncesi ve klinik çalışmaların arttırılması, kanser tedavi stratejilerinin çeşitlendirilmesi ve maliyetlerin düşürülmesi açısından kritik öneme sahiptir.

Anahtar kelimeler: *Adrenerjik reseptör; ilaç yeniden konumlandırma; kardiyovasküler ilaçlar; katekolamin; meme kanseri; propranolol*

Repurposing of beta-blockers: Applications in breast cancer

Abstract

Beta-adrenergic receptor (β-AR) antagonists inhibiting receptor activation are called beta-blockers. Beta-blockers are commonly used to treat hypertension, infantile hemangioma, abnormal stress, and ischemic heart failure. β-AR stimulation of tumor and stromal cells in the tumor microenvironment promotes tumor growth and metastasis and adversely affects survival. Drug repurposing or repositioning is defined as adapting or using an existing drug for a new indication in clinical use as it is or by making structural modifications. As cancer incidence increases worldwide, cancer treatment costs are also increasing. The focus of global cancer control is to reduce this cost and increase the effectiveness of cancer treatment. Beta-blockers inhibit the activation of downstream effectors and signaling pathways stimulated by β-AR stimulation. In addition, there is evidence of the anti-proliferative and apoptotic effects of beta-blockers on cancer cells. So far, repurposing studies of propranolol for breast cancer have yielded promising data. In this review, studies on repurposing drugs for cancer treatment, the mechanisms of action of beta-blockers on cancer cells, and use of these drugs in breast cancer treatment were evaluated. Increasing preclinical and clinical studies of

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repurposing drugs for breast cancer treatment, including beta-blockers, is critical to diversifying cancer treatment strategies and reducing costs.

Keywords: *Adrenergic receptor; breast cancer; cardiovascular drugs; catecholamine; drug repurposing; propranolol*

1. Giriş / Introduction

1.1. β-adrenerjik reseptörler ve beta-blokerler / β-adrenergic receptors and beta-blockers

G-protein bağımlı reseptörler, (G-protein coupled receptors; GPCR) hücre zarını yedi kez geçen ve heterotrimerik G proteinleri ile birlikte çalışan reseptör süper ailesidir. Beta-adrenerjik reseptörler (β-adrenoreseptörler; β-AR), G-proteinine bağlı adrenerjik reseptör ailesinin üyeleridir. Adrenerjik reseptörler, yapı ve fonksiyonlarına göre "α- ve β-reseptörler" olarak iki ana gruba ayrılır. α-reseptörler kendi içlerinde α1 ve α2; β-reseptörler ise kendi içlerinde β1, β2 ve β3 olmak üzere alt tiplere ayrılır. α- ve β-reseptörleri, hücre içi yolakları, G-proteinleri, sekonder mesajcıları, uyarılma sonucu hücresel ve fizyolojik cevapları bakımından farklılık gösterirler. Reseptör yanıtının moleküler uyarıcıları α- ve β-adrenerjik reseptör agonistleri olarak adlandırılır (Safi ve ark., 2022).

Adrenerjik reseptörler katekolamin grubu agonistler (noradrenalin, adrenalini, dopamin) ya da kotakalamin olmayan agonistler tarafından uyarılmakla birlikte α- ve β- reseptörlerin farklı dokularda uyarımı farklı fizyolojik cevaplar ile sonuçlanır. Örneğin, α1-AR uyarılması vasküler düz kaslarda kasılma ile vazokonstriktif etkiyle sonuçlanırken, β2-AR uyarılması vasküler düz kaslarda gevşeme ile vazodilasyona neden olur. Genel olarak, çevresel adaptasyon ile ilişkili ve strese cevap olarak artan katekolaminler organizmanın savaş-kaç mekanizmasından sorumludur (Tilan ve Kitlinska, 2010). Temel olarak, β1-AR, kalp, göz, damarlardaki düz kaslar, akciğer ve pankreasta bulunur. β2-AR damar sisteminde, β3-AR ise kahverengi yağ dokusunda bulunur (Hoffmann ve ark., 2004; Forooshani ve ark., 2022).

1.2. Beta-blokerler / Beta-blockers

Adrenerjik reseptörlerin yanıtını (aktivasyonunu) engelleyen beta-adrenerjik reseptör antagonistleri, beta-blokerler olarak adlandırılır. Beta-blokerler, β1-AR ve β2-AR yolaklarını baskılayarak aktivasyonlarını engeller (Lashen ve ark., 2021). Günümüzde carvedilol ve labetalol gibi bazı beta-blokerlerin ise hem α-AR hem de β-AR antagonisti olduğu bilinmektedir (Fang ve ark., 2020). Emorine ve ark. (1989) ilk kez β3-AR'ı ve yapısını, beta-blokerlere duyarsız bir alt tip olarak tanımlamışlardır. Beta-blokerler hipertansiyon, infatil hemanjiyom, anormal stres, iskemik kalp yetmezliği gibi kardiyovasküler durumların tedavisi için yaygın olarak kullanılan ilaçları kapsamaktadır (Bohm ve ark., 2023).

Farmakolojik özelliklerine göre sınıflandırılan üç nesil β-AR antagonisti bulunmaktadır. Beta-blokerler β-AR seçici ve seçici olmayan blokerler olarak sınıflandırılır. Bunlar arasında, birinci nesil β-AR antagonistleri, seçici olmayan β1-β2 blokerlerini oluşturur. Seçici olmayan blokerler β1 ve β2 reseptörlerine bağlanırlar (Rehsia ve Dhalla, 2010; Machackova ve ark., 2011; Do Vale ve ark., 2019). β2 ve β3 seçici antagonistler de bulunmasına rağmen bu antagonistlerin klinikte kullanımı bulunmamaktadır. Klinik kullanımda olan beta-blokerlerler ile ilgili bilgiler Tablo 1'de verilmiştir. Beta-blokerlerin ilk geliştirilen ve en yaygın kullanılan ilacı propranololdur. 1964 yılında geliştirilen bu ilaç, yaygın ve öncelikli olarak hipertansiyon tedavisinde kullanılmaktadır. Fazlasıyla lipofilik olan propranolol, kan-beyin bariyerini geçebilmektedir. Propranolol aynı zamanda en çok klinik veri birikime sahip ilaçtır (Brodde, 2007). İnfatil hemanjiyom tedavisi için FDA (Food and Drug Administration) ve EMA (European Medicines Agency) tarafından onaylanmış bir ilaç sınıfı olmanın yanında, birçok hastalığın tedavisi için endikedir (Mandana ve ark., 2009). Hipertansiyonun yanı sıra koroner arter hastalığı gibi kalp hastalıkları, migren, sepsis, hipermetabolik sendrom ve Alzheimer ile ilişkili akatizi gibi tanımlanan endikasyonlar dışındaki tedaviler için de kullanılabilmektedir (Greendyke ve ark., 1986; Peskind ve ark., 2005; Ali ve ark., 2015).

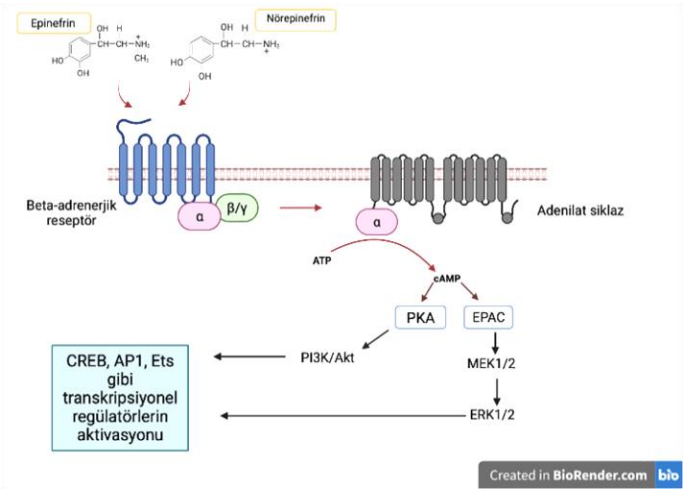
Tablo 1 / Table 1
Beta-blokerler / Beta-blockers (Reiter, 2004; Yang ve ark., 2007; Ripley ve Saseen, 2014; Do Vale ve ark., 2019).

Beta Bloker	Kimyasal Formül	Seçicilik	Yağda Çözünürlük
Atenolol	$C_{14}H_{22}N_2O_3$	β_1 Seçici	Düşük
Bisoprolol	$C_{18}H_{31}NO_4$	β_1 Seçici	Evet
Karvedilol	$C_{24}H_{26}N_2O_4$	Seçici değil	Evet
Seliprolol	$C_{19}H_{24}N_2O_3$	β_1 Seçici	Düşük
Metoprolol	$C_{15}H_{25}NO_3$	β_1 Seçici	Evet
Nebivolol	$C_{22}H_{25}F_2NO_4$	β_1 Seçici	Evet
Nadolol	$C_{17}H_{27}NO_4$	Seçici değil	Düşük
Labetalol	$C_{19}H_{24}N_2O_3$	Seçici değil	Evet
Sotalol	$C_{12}H_{20}N_2O_3S$	Seçici değil	Düşük
Propranolol	$C_{16}H_{21}NO_2$	Seçici değil	Evet
Pindolol	$C_{14}H_{20}N_2O_2$	Seçici değil	Evet
Oksprenolol	$C_{15}H_{23}NO_3$	Seçici değil	Düşük
Asebutanolol	$C_{18}H_{28}N_2O_4$	Kardiyoselektif	Evet
Betaoksolol	$C_{18}H_{29}NO_3$	β_1 Seçici	Evet
Karteolol	$C_{16}H_{24}N_2O_3$	Seçici değil	Düşük
Timolol	$C_{13}H_{24}N_4O_3S$	Seçici değil	Evet
Esmolol	$C_{16}H_{25}NO_4$	Kardiyoselektif	Düşük

1.3. Beta-blokerlerin etki mekanizmaları / Mechanism of action of beta-blockers

Beta-adrenerjik reseptörlere kotekolamin grubu β-AR agonistlerinin bağlanması ile Gα ve Gβγ alt birimleri birbirinden ayrılır (Şekil 1). Gα alt birimi adenilat siklaza bağlanarak ATP'nin sekonder mesajcı siklik adenozin monofosfat (cAMP) dönüşümünü sağlar. cAMP, protein kinaz A'nın (PKA) aktivasyonu için gereklidir. PKA aktivasyonu ile CREB/ATF, STAT, FAK ve GATA gibi önemli transkripsiyonel düzenleyicilerin de yer aldığı alt sinyal yolakları aktive edilir. Bu kinazların aktivasyonu, hücre iskelet dinamikleri aracılığıyla hücre trafiğini, hareketliliğini ve apoptoza karşı direnci düzenler. Bir başka yolda cAMP, cAMP tarafından doğrudan

aktive edilen değişim proteininin (the exchange protein directly activated by cAMP; EPAC) aktivasyonunu sağlayarak hücre büyümesini düzenler (Şekil 1). Beta blokerler, β-AR sinyal yolağında bulunan efektör kinazların aktivasyonunu ve bu kinazlar ile uyarılan diğer yolakları da engeller (Cui ve ark., 2023).



Şekil 1 / Figure 1. β-AR reseptörlerin sinyal yolağı / Signal transduction via β-AR receptors (Modified from Nilsson ve ark., 2020).

Böbrek üstü bezi medullasında üretilen hormon grubu olan katekolaminler β1-AR bağlanarak kalpte kasılma hızı ve gücünde artışa neden olur. β1-AR böbrekten salgılanan renin salınımını indükler. Renin, anjiyotensinojenin anjiyotensin I'e ve sonrasında anjiyotensin I'in anjiyotensin dönüştürücü enzim (angiotensin-converting enzyme; ACE) ile anjiyotensin II'ye çevrimini sağlayarak kan basıncını artırır. Buna karşılık, β2-AR'e bağlanma sonucu solunum yolları, uterus ve vasküler düz kaslar gevşer (Kraboth ve Kalman, 2023).

Beta-blokerler afinite ve etkinliklerine göre adrenoreseptörlere bağlanırlar. Beta-blokerler farklı adrenoreseptör alt tiplerine karşı farklı bağlanma afinitesine sahiptir (Peixoto ve ark., 2020). Afinite, bir ilacın reseptöre bağlanma yeteneği, etkinlik ise bir yanıtı indükleme özelliğidir. İlaç afinitesi ve etkinliğine bağlı olarak ortaya çıkan hücresel ve fizyolojik cevaplar, bloke edilen reseptör ve organ sistemiyle ilişkilidir (Gorre ve Vandekerckhove, 2010). Örneğin, kalpte beta-bloker bağlanması sonucunda kalp kasılma kuvvetini etkileyen inotropik etki ve kalp hızını etkileyen kronotropik etki engellenir ve oksijen ihtiyacı azalır. Aynı zamanda böbrekten salgılanan renin miktarının düşüşü de kan basıncının azalmasına neden olur (Şekil 1). Öte yandan, β1-AR agonist etki kalp kasılmasını ve kronotropisini artırdığından yüksek kan basıncı ve kalp hızında artışa yol açar. Carvedilol ve labetolol gibi seçici olmayan beta-blokerler hem β-AR hem de α-AR antagonistleridir. Bu nedenle, fizyolojik cevap olarak kalp kasılması ve gücünde azalmayla birlikte α1-AR uyarımının inhibisyonu ile vasküler düz kaslardaki gevşeme de gerçekleşir (Oliver ve ark., 2019). Bu etki hipertansiyonun klinik tedavisinde yararlı bir özelliktir (Weir, 2009). Beta-blokerlerın melatonin hormonunun salgılanmasını azaltması nedeniyle tedavi sürecinde hastalarda uykusuzluk veya uyku değişimi olduğu rapor edilmiştir (Fares, 2011).

1.4. β-adrenerjik reseptörler ve kanser / β-adrenergic receptors and cancer

Kronik stres, adrenal medulladan ve sempatik nöronlardan katekolaminlerin salgılanmasını artırır. Birçok çalışmada, kanserin ilerlemesinde strese bağlı olarak çevresel, yaşam tarzı ile ilgili ve sosyoekonomik faktörlerin etkili olduğu ileri sürülmektedir (Jardim ve ark., 2023). Tümör mikro çevresindeki tümör ve stromal hücrelerin β-AR uyarımının, tümör büyümesini ve metastatik yayılımı teşvik ettiği ve sağkalımı olumsuz etkilediği ile ilgili çalışmalar bulunmaktadır. Örneğin, fare meme kanseri modeli üzerinde yapılan bir çalışmada, β-AR aktivasyonunun M2 makrofaj infiltrasyonu yoluyla metastazı 30 kat artırdığını gösterilmiştir (Sloan ve ark., 2010). Nörepinefrin ve epinefrinin kemotaktik ve kemokinetik etkileri, meme kanseri hücrelerinin göçünü artırmıştır (Sood ve ark., 2006). Ek olarak, beta-adrenerjik uyarım meme kanseri metastazı ile ilişkilendirilmiştir (Campbell ve ark., 2012).

Beta-adrenerjik reseptör uyarımının ve beraberinde çalışan alt sinyal yolaklarının aktivasyonunun hücresel bağışıklık cevabı, anjiyogenez, apoptoz, hücre mobilitesi, ekstasellüler matriksin yeniden düzenlenmesi, invazyon, onkoviral aktivasyon ve DNA hasar onarımı dahil olmak üzere kanserle ilişkili birçok hücresel yolağı düzenlemede rol oynadığı bilinmektedir. Ek olarak, Bcl-2 regülatör protein ailesinin bir üyesi olan BAD'ın PKA'ya bağlı aktivasyonu ile hücrelerin apoptotik eğilimi azalır (Cole ve ark., 2012). Nörepinefrin ve epinefrin adenilat siklazın aktivasyonunu sağlar. Hücre içinde cAMP sentezi PKA ve EPAC aktivasyonuna neden olur. Bu aktivasyon ile hücresel sağkalım yolaklarının önemli transkripsiyonel düzenleyicilerinin (CREB, AP-1, ve ETS gibi) pozitif düzenlenmesi gerçekleşir ve inflamasyon, anjiyogenez süreçleri etkilenir (Montminy, 1997; Thaker ve ark., 2006).

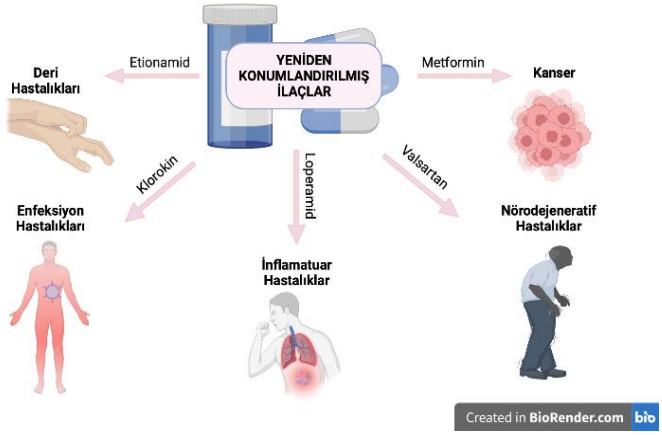
Katekolaminler, β-adrenerjik uyarım ile tümör büyümesini, kanser hücrelerini göçünü ve proliferasyonunu sağlayan VEGF, IL-6, IL-8 gibi büyüme faktörleri ve sitokinler ile matriks metalloproteinazların düzeyini artırır (Chin ve ark., 2016). β-AR uyarımı ile cAMP/PKA, MAPK/ERK1/2, PI3K/AKT, Src/STAT, p38/MAPK ve araşidonik asit kaskadları dahil olmak üzere birçok sinyal yolağı aktive olabilir (Wallukat, 2002). Tümör hücrelerinde β-AR'lerin uyarılması, araşidonik asit (AA) kaskadı ve özellikle siklooksijenaz-2'nin (COX-2) aktivasyonu yoluyla kanser hücre büyümesini ve invazyonunu indükler (Wang ve ark., 2007; Finetti ve ark., 2023). β1 seçici blokerler, temel olarak cAMP/PKA yoluyla kanser invazyonunu engellerken, buna ek olarak β2 seçici blokerlere bağlı invazyonun engellenmesinde RAS, MAPK, NF-κB ve AP-1 yolakları birlikte etki ederler. Bu yolakların akış aşağı efektörlerinin ve/veya akış yukarı düzenleyici proteinlerin engellenmesi, hücre proliferasyonunun ve invaziv karakterlerin azalmasına, hücre döngüsünün durmasına ve apoptoza neden olabilir. VEGF gibi büyüme faktörlerinin nörepinefrin aracılı β-AR uyarımı yoluyla MMP-2 ve MMP-9 ifadelenmelerinin artmasının kanser hücrelerinin göçünü ve invazyonunu arttırdığı farklı hücre hatlarında gösterilmiştir (Schuller ve Cole 1989; Masur ve ark., 2001; Sood ve ark., 2006; Yang ve ark., 2006). Klinik öncesi çalışmalar, nörepinefrin uyarısının propranolol ile baskılanmasının akciğer adenokarsinom, kolon karsinom, yumurtalık ve pankreas kanser hücreleri üzerinde sitotoksik, proliferasyonu ve hücre göçünü engelleyici etkilerinin olduğunu göstermiştir (Schuller ve Cole 1989; Masur ve ark., 2001; Sood ve ark., 2006; Limbu ve ark., 2022).

2. İlaç yeniden konumlandırma / Drug repurposing

İlaçları yeniden yapılandırma, yönlendirme, profillendirme veya konumlandırma olarak adlandırılan strateji, klinik kullanımda var olan bir ilacı olduğu gibi ya da yapısal modifikasyona uğratarak yeni bir endikasyona uyarlamak ya da kullanmak olarak tanımlanır. Mevcut, ruhsatlı bir ilacın, yaygın olarak ruhsatsız bir tedavi olarak kullanıldığı yeni bir hastalığa uygulanması olarak da tanımlanabilmektedir (Langedijk ve ark., 2015; Pantziarka ve ark., 2020). Aggarwal ve ark. (2021) tarafından yayınlanan bir makalede ilacın yeniden konumlandırılması, "yeni savaş için eski silah" olarak tanımlanmıştır.

Yeni bir ilaç geliştirilmesi (*de novo*) süreci uzun zaman ve yüksek maliyet gerektirir. İlaçların araştırma-geliştirilmesi, onaylanması ve güvenilirlik profillerinin oluşturması 10-18 yıl sürebilen bir süreçtir. Bununla birlikte, süreç resmi ve ekonomik açıdan da zor bir süreçtir. Yeni bir ilaç geliştirmenin maliyetinin yaklaşık 2-3 milyar dolar olduğu düşünülmektedir (Prasad ve ark., 2016). İlaçların yeniden konumlandırılmasının amacı potansiyel olarak ucuz ve hızlı alternatif ilaç kullanım stratejilerinin geliştirilmesidir. Piyasada bulunan ve kullanılan ilaçların içerikleri ve modaliteleri uyarlanarak ya da genişletilerek başka hastalıkların tedavisinde yeniden kullanılır. Yeniden konumlandırılan ilaçların maliyetinin 300 milyon dolara kadar düşebildiği ve ruhsatlandırma sürecinin 3-12 yıl arasında olabildiği düşünülmektedir. Bu durumun temel olarak üç saç ayağı bulunmaktadır: İlk olarak, yeniden konumlandırılan ilaçlar önceden klinik çalışmaları geçtiği için yeni bir ilaç geliştirme sürecinde karşılaşılabilen başarısızlıkların riski oldukça azalmaktadır. İkinci olarak, formülasyon geliştirme, farmakokinetik ve toksisite profillerinin oluşturulması basamakları geçildiği ve/veya kısaldığı için ilaç geliştirme süresi 3-7 yıldan 1-3 yıla düşebilir (Malik ve ark., 2022). Yeniden konumlandırılabilecek ilaçlar halihazırda çok sayıda klinik çalışmaya tabii tutulmuş ve yan ya da bilinmeyen etkileri araştırılmıştır. Mevcut ilaçların bilgi birikimi sayesinde erken faz deneyleri ve hayvan deneyleri yapma zorunluluğu olmadan ilaç geliştirmenin daha kolay olduğu ve bu stratejinin ilerleyebileceği düşüncesi ortaya konulmuştur (Talevi ve Bellera, 2020). Bir diğer yandan, yeniden konumlandırılmış bazı ilaçlar için Faz I denemelerinin gerekli olabileceği de belirtilmiştir (Pantziarka ve ark., 2020). Üçüncü olarak, sıfırdan bir molekülün geliştirme süreci bulunmamakta ve hücre içi moleküler bağlantı ve etkinlik haritaları *in silico* stratejiler ile oluşturulmaktadır (Ramesh ve ark., 2021). *In silico* moleküler bağlantı ve etkinlik haritalarının çıkarılması sonucunda molekülün yapısal modifikasyona gereksinim duyması sonucunda ise ilacın yeniden yapılandırılması ile konumlandırma çalışmaları yapılmaktadır. Bu avantajların yanında ilaçlar hakkında kapsamlı klinik deneyimin ve moleküler mekanizmaları da kapsayan geniş literatür havuzunun bulunması, ilaç kombinasyonları için de önemli ön verilerin bulunmasını sağlamaktadır (Muratov ve ark., 2021; Li ve ark., 2022).

İlaçların yeniden konumlandırılması ile ilgili çalışmalar son yıllarda ivme kazanmıştır. İlaç maliyetinin düşük olması nedeniyle yeniden konumlandırılan ilaçların erişilebilirlikleri fazla olmaktadır. Bu nedenle, ilaç yeniden konumlandırma düşük ve orta gelişmiş ülkeler için özellikle önem arz etmektedir (Anselmino ve ark., 2021). Birçok ilaç yeniden konumlandırılarak deri hastalıklarının, nörodejeneratif hastalıkların, inflamatuar hastalıkların ve kanserin tedavisinde kullanılır (Şekil 2). Tüberküloz tedavisinde kullanılan etionamid, yeniden konumlandırılarak melanoma tedavisinde tirozinaz inhibitörü olarak kullanılmaktadır (Choi ve ark., 2015). COVID-19 pandemisinde yeniden konumlandırma çalışmaları tedavi protokollerinin geliştirilmesi açısından önemli rol üstelenmiş ve COVID-19'un tedavisinde eski sıtma ilaçları olan klorokin ve hidroksiklorokinin tedavi potansiyeli büyük ölçüde dikkat çekmiştir. Pandemi öncesinde klorokin, MERS-CoV tedavisi için yeniden konumlandırılmıştır (Madrid ve ark., 2013). Ek olarak, ishal sıklığını azaltmak için kullanılan loperamid de MERS-CoV tedavisinde kullanılmaktadır (Regnard ve ark., 2011). Hipertansiyon tedavisinde kullanılan valsartan, yeniden konumlandırılarak nörodejeneratif bir hastalık olan Alzheimer hastalığının tedavisinde kullanılmıştır (Wang ve ark., 2007). Bunların yanında birçok farklı hastalığın tedavisinde kullanılan aspirin, metformin, talidomid, rapamisin, iburufen gibi ilaçlar da yeniden konumlandırılması ve kanser tedavisinde kullanılması ile ilgili farklı çalışmalar bulunmaktadır (Sillaber ve ark., 2008; Lee ve ark., 2011; Akrami ve ark., 2015; Elwood ve ark., 2018; Hiramatsu ve ark., 2018) (Şekil 2).



Şekil 2 / Figure 2. Yeniden konumlandırılan ilaçlar / Repurposed drugs (Modified from Pillaiyar ve ark., 2020).

Kanser tedavisinde kullanılmayan ilaçların kanser tedavisinde kullanılması, sürece farklı bir bakış açısı kazandırarak çalışmaların artmasına katkıda bulunmuştur. Farklı kanserlerin tedavisi için eski ilaçların yeni potansiyel hedeflerinin ve sinyal yolaklarının araştırılması ile ilgili çok sayıda çalışma bulunmaktadır (Fu ve ark., 2022). Kardiyovasküler ilaçların yeniden konumlandırılması bu bağlamda önemli ve öncül sonuçlar sunmuştur (Sardana ve ark., 2011). Ek olarak, kanser tedavisi için tasarlanmamış ve klinik öncesi denemelerde test edilen ve edilecek olan çok sayıda *de novo* ilacın *in vitro* anti-kanser aktiviteleri test edilmekte ve umut verici sonuçlar alınmaktadır (Hua ve ark., 2022; Wang ve ark., 2023).

İlaçların yeniden konumlandırma stratejisinde en çok tercih edilen ilaç grubu kardiyovasküler ilaçlar olmuştur. Kardiyovasküler hastalıkların ve hipertansif hastalıkların tedavisinde kullanılan beta-blokerler da bu strateji içinde bulunur ve kullanılır (Naicker ve ark., 2022).

3. Beta-blokerların meme kanseri tedavisi için yeniden konumlandırılması / Repurposing beta-blockers for breast cancer

3.1. Meme kanseri tedavisi ve yeniden konumlandırma çalışmaları / Breast cancer therapy and repurposing studies

Meme kanseri tedavisinde tümörün büyüklüğü, evresi, derecesi, metastatik özellikleri ve agresifliği dikkate alınmaktadır. Ek olarak, hastanın yaşı, menapoz durumu ve genel sağlık durumu da tedavi süreçlerinde önem arz etmektedir. Meme kanseri farmakoterapisinde sitotoksik kemoterapi, hormon tedavisi, immünoterapi ve endokrin tedaviyi içeren sistemik rejimenler kullanılmaktadır (Khan ve ark., 2020). Birincil, tedavilere ek olarak uygulanan adjuvan tedavi ile kalan kanser hücrelerinin elimine edilmesi ve kanser nüksünü önlemek amaçlanır. Hormon veya hedefe yönelik ajanların kullanıldığı bu tedaviler, hormon reseptör statüsüne göre uygulanır (Maughan ve ark., 2010; Miyahara ve ark., 2022).

Kombinasyon kemoterapi hastaya birden fazla ilaç reçete edilmesidir. Kombinasyon kemoterapide aditif ya da sinerjistik etkiye sahip iki farklı ilaç, tek ve yüksek doz uygulamaya kıyasla daha küçük dozlarda, aynı anda uygulanır. Kombinasyon tedavisinde, farklı etki mekanizmalarına anti-kanser ilaçlar tercih edilerek tekli kullanıma göre daha etkili sonuçlar da elde edilebilmektedir. Daha düşük dozlar daha etkin tedavi ile sonuçlandığından yan etkiler de önemli ölçüde azalmaktadır. Konvansiyonel anti-kanser ajanlarının yeniden konumlandırılmış ilaçlarla kombinasyonu, terapötik etkinliği artırmaya yardımcı olabilir. Ancak, farklı sonuçlara yol açabilen kombinasyon terapileri tasarlanmadan önce ilaç-ilaç etkileşimleri iyi tanımlanmalıdır (Rodrigues ve ark., 2022).

Antidiyabetik, antihipertansif, antabus, antiviral, anti-inflamatuar, antimikrobiyal ilaçların ve antibiyotiklerin antikanser etkileri çalışılmış ve meme kanseri tedavisi için yeniden konumlandırma için değerlendirilmiştir (Tablo 2). Antidiyabetik grupta bulunan metformin, Tip II diyabetin birinci basamak tedavisi için kullanılmaktadır. Yapılan çalışmalarda metforminin meme, prostat, pankreas ve yumurtalık dahil olmak üzere birçok kanser tipinde anti-kanser aktivitesi gösterilmiştir (Gotlieb ve ark., 2008; Alimova ve ark., 2009; Kisfalvi ve ark., 2009; Ben Sahra ve ark., 2010; Garcia ve Tisman, 2010). Metformin, adjuvan tedavi olarak farklı ilaçlarla kombinasyon kullanımı ile ilgili çalışmalar bulunmaktadır. 2020 yılında yapılan bir çalışmada, antidiyabetik ajan olarak metformin kullanan meme kanseri hastalarında, proliferatif bir belirteç olan Ki-67 proteininin belirgin şekilde azaldığı gösterilmiştir (Rahmani ve ark., 2020).

Tablo 2 / Table 2

Meme kanseri tedavisinde kullanılan yeniden konumlandırılmış ilaçlar ve ruhsatlı endikasyonları / Repurposed drugs for breast cancer therapy, and their original licensed indications (Aggarwal ve ark., 2021; Correia ve ark., 2021; Rodrigues ve ark., 2022).

İlaç Adı	Endikasyon
Metformin	Diyabet
Disülfiram	Alkol bağımlılığı
Propranolol	Hipertansiyon
Ritonavir	AIDS/HIV
Partaprevir	Hepatit C
Dasabuvir	Hepatit C
Ombitasvir	Hepatit C
Mebendazole	Parazit solucan enfeksiyonu
Artemisinin	Sıtma

Antabus ilaç sınıfında bulunan disülfiram, alkol bağımlılığı tedavisinde kullanılmaktadır. Yapılan *in vitro* ve *in vivo* çalışmalarda disülfiramın anti-kanser aktivitesi gösterilmiştir (Chen ve ark., 2006). Disülfiramın kanser hücrelerinde apoptozu indüklediği ve yüksek riskli meme kanseri hastalarının sağ kalımını artırdığı gösterilmiştir (Liu ve ark., 2013). Bu özelliklerinin yanında, disülfiram ve metabolitlerinin anti-kanser ilaçların hücre dışına atımını sağlayan P-gp pompasının nükleotid bağlama bölgesindeki sisteinleri kovalent olarak değiştirdiği ve P-gp aktivitesini kalıcı olarak engellediği de rapor edilmiştir (Loo ve ark., 2004). Bu nedenle, disülfiramın çoklu ilaç direncini geri çevirme potansiyeli de değerlendirilmektedir (Kim ve ark., 2017).

Antiretroviral sınıfında bulunan ritonavir, AIDS tedavisinde kullanılan bir ilaçtır. Bir proteaz inhibitörü olan ritonavir, HIV virüsünün proteazına bağlanarak viral gag-pol proteinlerin kesilmesini ve viral kopyaların oluşmasını engeller. Anti-kanser ilaçlarının ritonavir ile kombinasyon tedavisi, akış faktörlerinin aşırı ekspresyonunu inhibe eder. Buna ek olarak bu kombinasyon tedavisinin, enzimleri metabolize etme yeteneği olduğundan, ilaç dirençliliğinin üstesinden gelebileceği düşünülmüş ve buna dair çalışmalar yapılmıştır (Vadlapatla ve ark., 2014). Antiviral ilaçlardan viral proteaz inhibitörü paritaprevir, polimeraz inhibitörü dasabuvir ve viral protein inhibitörü ombitasvirin de anti-kanser özellikleri bulunmaktadır (Karuppasamy ve ark., 2017).

Antihelmitik ilaç sınıfında bulunan mebedazol, parazit solucan enfeksiyonunun tedavisinde kullanılmaktadır. Mebedazolun üçlü negatif meme kanseri (TNBC) hücreler üzerinde yüksek sitotoksik etkisi olduğu *in vitro* olarak gösterilmiştir. Yapılan klinik çalışmalar sonucunda TNBC tedavisi için kullanımı ABD'de FDA tarafından onaylanmıştır. Mebedazolun uzun süreli yüksek doz kullanımlarında bile insanlarda çok uygun bir toksisite profiline sahip olduğu bilinmektedir (Pantziarka ve ark., 2014).

Artemisinin ve yarı sentetik türevleri sıtma tedavisinde kullanılmaktadır. Artemisinin meme kanseri hücrelerinde CDK2 ve CDK4 siklin bağımlı kinazları, siklin E, siklin D1 ve E2F1 transkripsiyon faktörünün ekspresyon düzeylerini azaltarak hücre proliferasyonunu inhibe ettiği ve hücre döngüsünde tutuklanmaya neden olduğu bildirilmiştir (Tin ve ark., 2012). Aynı çalışmada, artemisinin hücre göçü ve invazyonunu azalttığı ve apoptozu indüklediği de gösterilmiştir. Nöroblastom hücrelerinde yapılan bir çalışmada ise artemisinin AMP kinazı aktive ederek mTOR/p70S6K/pS6 sinyal yolağını baskıladığı ve hücre çoğalmasını engellediği rapor edilmiştir (Tan ve ark., 2014).

Kemoterapi başarısını kısıtlayan önemli faktörlerden olan çoklu ilaç direnci (ÇİD), tümör hücrelerinde yapısal olarak farklı anti-kanser ajanlara karşı direnç gelişmesi durumudur. Kemoterapötik ajanların farklı etki mekanizmaları çoklu ilaç dirençliliğine sebep olan hücresel mekanizmaların da farklı ve değişken olmasını gerektirir. Çoklu ilaç dirençliliğinin mekanizmalarından olan artan ilaç atımına bağlı azalan hücre içi ilaç konsantrasyondan sorumlu olan ABC taşıyıcı proteinler substrat seçicidir. Diğer ilaç özgül mekanizmalar, hedef enzim ya da reseptördeki değişim, ilacın hedef enzim ya da reseptöre bağlanma eğilimindeki azalma ve ilaç hedeflerinin değişmesidir (Bodó ve ark., 2003; Vavilis ve ark., 2023). Hücrelerin direnç geliştirdiği etki mekanizmalarından farklı etki mekanizmalarına sahip yeniden konumlandırılan ilaçları içeren kombinasyonlar, dirençli hücrelerin elimine edilmesinde etkin olabilir. Ek olarak, yeniden konumlandırılan ilaçlar P-gp inhibitör etkisi bulunan artemisin örneğinde olduğu gibi ÇİD fenotipinin geri çevrilmesinde de rol oynayabilirler. Dirençli MCF-7/Dox meme kanseri hücrelerinde ve meme kanseri ksenograft modelinde metformin kullanılması, P-gp/MDR1/ABCB1 ve HIF-lα'nın doksorubisin kaynaklı ekspresyonunu azaltmıştır (Davies ve

ark., 2017). Başka bir çalışmada, aynı hücre modeli üzerinde doksorubisinin sitotoksisitesinin arttığı gösterilmiştir (Shafiei-Irannejad ve ark., 2018a, b). Metforminin, bir başka çalışmada dirençli MCF-7-ADR hücrelerinde, P-gp/MDR1/ABCB1 ekspresyonunu da azalttığı gösterilmiştir (Kim ve ark., 2017). Niklosamid, sisplatin ile kombine kullanıldığında sisplatin dirençli üçlü negatif meme kanseri hücrelerinde, epitelyal-mezenkimal geçişi ve tümör büyümesini engellemiştir (Liu ve ark., 2016). Salinomisin meme kanseri kök hücrelerine karşı anti-kanser özelliklere sahip olmakla birlikte (Passeri ve ark., 2023), ÇİD meme kanser hücre hatlarında da güçlü bir P-gp inhibitörü olarak rapor edilmiştir (Riccioni ve ark., 2010).

3.2. Beta-blokerlerin anti-karsinojenik etkisi / Anti-carcinogenic action of beta-blockers

Beta-blokerlerin, kanser hücresinin proliferasyonu ve göçü/invazivliğinde düzenleyici rol alıp almadığı sorusu üzerine çalışmalar seçici olmayan bloker propranolol ile başlamıştır. 1960'larda geliştirilen propranolol hipertansiyon, migren ve anksiyete bozukluğu tedavisinde kullanılmaktadır. Şiddetli infantil hemanjiyomların tedavisinde propranololün etkinliği ve kullanımına dair artan klinik veriler bulunmaktadır (Léauté-Labrèze ve ark., 2008) Hemanjiyom ve kanser gelişiminde β-AR uyarımının rolü ile ilgili veriler, β-AR blokerlerin kanser hücreleri üzerinde anti-proliferatif ve hücre göçünü engelleme etkilerinin çalışılmasını gündeme getirmiştir. Hemanjiyom ve nadir vasküler hastalık modelinde propranololün SOX18 transkripsiyon faktörünün adrenoreseptör yolağından bağımsız olarak küçük moleküler inhibitörü olarak etki ettiği de gösterilmiştir (Overman ve ark., 2019). Propranolol kullanan hastalarda mide, kolon, meme ve prostat kanseri riskinde azalma olduğu bildirilmiştir (Chang ve ark., 2015). *In vitro* çalışmalar ile propranololün prostat kanseri başta olmak üzere akciğer adenokarsinomu, kolon karsinomu, yumurtalık ve pankreas kanseri hücreleri üzerinde anti-proliferatif etkileri gösterilmiştir (Brohée ve ark., 2018). Kullanıldığı diğer ilaçların toksisitesini, anti-anjiyogenik, pro-apoptotik özelliklerini güçlendirerek tümör büyümesini yavaşlattığı ile ilgili çalışmalar bulunmaktadır (Pasquier ve ark., 2013). Propranololün güçlü anti-karsinojenik etkileri olduğuna dair *in vitro, in vivo* ve klinik veriler vardır. COX2/PGE2 inhibitörleri ve kemoterapatik ilaçlar dahil olmak üzere diğer ilaçlarla sinerjik etkisi gösterilmiş ve yeniden konumlandırma ile daha etkili kombinasyon tedavilerinin geliştirilmesinde yer alma potansiyeli bulunmaktadır. Özellikle propranolol gibi seçici olmayan ve β2-AR antagonistler apoptozun indüklenmesinde de etkilidir (Benish ve ark., 2008; Zhang ve ark., 2010). Buna ek olarak propranololün kansere karşı kullanılması konusunda devam eden Faz I, Faz II ve Faz III çalışmaları da bulunmaktadır.

3.3. Meme kanseri tedavisinde beta-blokerlerin kullanılması / Use of beta-blockers fort he treatment of breast cancer

Beta-blokerler tümör büyümesi ve kanser hücresi göçünü azaltır ve tümörigenezi, anjiyogenezi ve metastazı tetikleyen mekanizmaları bloke eder. Kardiyovasküler hastalıkların tedavisinde kullanılan geniş spektrumdaki beta-blokerlerin de dahil olduğu ilaçlar klinik çalışmalarda kanser tedavisi için kullanılmakta ve yeni tedavi modalitelerinin geliştirilmesi açsısından umut vaat etmektedir (Ishida ve ark., 2016; Huang ve ark., 2021). Meme, pankreas, nazofarengeal ve yumurtalık kanseri hastalarında beta-bloker kullanımının tümör boyunu küçülttüğü ve ileri evrelerde prognostik olarak olumlu etkileri ortaya konulmuştur (Barron ve ark., 2012; Diaz ve ark., 2012; Pérez Piñero ve ark., 2012). Üçlü negatif meme kanserinde uygulanan hormon tedavisi gibi yöntemlerin tedavi yanıtı düşüktür (Aggarwal ve ark., 2021). Bu nedenle, özellikle üçlü negatif meme kanseri tedavisi için kullanılan mevcut ilaçlardan daha etkin yeni ilaçların geliştirilmesine ihtiyaç vardır (Malik ve ark., 2022).

Beta-blokerler, meme kanseri prognozunda, tümör büyümesinde ve metastazında yer alan hücresel süreçleri engellemektedir (Powe ve Entschladen, 2011). Meme kanserinde ilk araştırılan beta-bloker anti-anjiyogenik özellikte olan propranololdür. Meme kanseri hücrelerinde propranololün PI3K/AKT ve p38/MAPK yolakları üzerinden etki ettiği ve HIF-1α ve VEGF-A aracılığıyla da β-AR'lerden bağımsız bir şekilde hareket edebileceği de bildirilmiştir (Park ve ark., 2011). Hipertansiyon tedavisi için kullanılan seçici olmayan beta-bloker karvedilol de kanser hücreleri üzerinde proliferasyonu ve hücre göçünü engelleyici etki gösterir. Meme kanseri fare modelinde yapılan bir çalışmada, karvedilolün metastaz ve invazyonu engellediği bildirilmiştir (Gillis ve ark., 2021) Meme kanserinde imatinib ve trastuzumab ile kullanıldığında sinerjistik etki gösteren karvedilolün, bu ilaçlar ile kombine kullanıldığında ilaç bağımlı kardiyotoksisiteyi azalttığı klinik çalışmalarda gösterilmiştir (Erguven ve ark., 2010; Guglin ve ark., 2019). Ek olarak, karvedilol, üçlü negatif meme kanseri Hs578T-Dox hücrelerinde P-gp aktivitesini azaltarak doksorubisin birikimini ve toksisitesini artırmıştır (Jonsson ve ark., 1999).

Yaptığımız bir çalışmada, β1- ve β2-AR ifade eden MCF-7 insan meme kanseri, HT-29 kolon kanseri ve HepG2 hepatosellüler kanseri hücre hatlarında propranolol, β1 seçici atenolol ve β2 seçici ICI118,551'in doz ve süre bağımlı etkilerini izoproterenol aracılı β-AR uyarımı olan ve olmayan koşullarda karşılaştırmalı olarak inceledik (Iseri ve ark., 2014). MCF-7 hücrelerinde, β2 seçici ICI118,551'in 24 saatlik uygulamada diğer beta-blokerlerden daha yüksek sitotoksisiteye sahip olduğunu, blokerlerin uygulama süresi arttıkça sitotoksik etkinin de arttığını ve 72 saatlik uygulama sonrasında propranolol ve ICI118,551'in sitotoksisitelerinin mikromolar düzeyinde ve yakın olduğunu gösterdik. 100µM 48 ve 72 saatlik propranolol ve ICI118,551 uygulamaları MCF-7 hücrelerinin göçünü azaltmada yeterli olurken, 200µM atenolol 24-72 saat uygulama aralığında hücre göçünü azaltmıştır. Meme kanseri hücrelerinde invazyon ve hücre göçünü engellemede propranolol ve ICI118,551 atenololden daha etkili olmuştur. Ek olarak, tüm hücre hatlarında ICI118,551'in sitotoksisitesi en yüksek ve invazyonun ve hücre göçünün en güçlü inhibitör ajanı olduğu ve izoproterenol aracılı β-AR uyarımının MCF-7 invazyonu ve hücre göçü üzerinde önemli bir etkisinin olmadığı belirlenmiştir. Benzer şekilde, pankreas kanseri hücreleri ile yapılan bir çalışma hücre göçünün engellenmesinde ICI118,551'in β1 seçici metaprololden daha etkin olduğunu ve CREB, NF-κB ve AP-1 sinyal yolakları üzerinde etki ettiğini göstermiştir (Zhang ve ark., 2010). Buna karşılık, Lang ve ark. (2004), ICI118,551 ve atenololün uyarılmamış meme ve prostat kanserinde invazyonu engellemediğini göstermiş olmakla birlikte bu çalışmada uygulama konsantrasyonları ve süreleri önemli ölçüde düşüktür. Atenololün propranolol ile benzer yolaklar üzerinden apoptozu indüklediği, proliferasyonu, inflamatuar hücre tepkilerini ve hücre göçünü engellediği ile ilgili çalışmalar bulunmaktadır (Regulska ve ark., 2019).

Epidemiyolojik çalışmalar, beta-bloker kullanımını tümör büyümesinin yavaşlamasıyla ilişkilendirmiştir. Beta-bloker tedavisi alan meme kanseri hastalarının relaps oranının azaldığı ve sağkalım oranının arttığını bildiren klinik çalışmalar bulunmaktadır (Schuller, 2010). Meme kanseri tedavisinde beta-blokelerin adjuvan tedavi olarak kullanılmasını destekleyen veriler yeni tedavi stratejilerine zemin hazırlamaktadır (Yap ve ark., 2018).

4. Sonuç ve öneriler / Conclusion and recommendations

Beta-blokerler hipertansiyon, infatil hemanjiyom anormal stres, iskemik kalp yetmezliği gibi kardiyovasküler durumların tedavisi için yaygın olarak kullanılan ilaçları kapsamaktadırlar. Böbrek üstü medullasından salgılanan nörepinefrin ve epinefrin uyarılması ile hücre içerisinde hücresel sağkalım yolaklarının önemli transkripsiyonel düzenleyicilerinin (CREB, AP-1 ve ETS gibi) aktivasyonu gerçekleşir. Nörepinefrin aracılı β-AR uyarımı ile kanser hücre proliferasyonu, ESM ve tümör mikroçevresinin gelişimi ve metastazı etkileyen inflamasyon, anjiyogenez, invazyon ve hücre göçü düzenlenir. Beta-blokerler, β-AR uyarımı engelleyerek sinyal yolağında bulunan alt efektörlerin aktivasyonunu ve bunlar ile uyarılan diğer yolakları engellerler. Ek olarak, beta-blokerlerin hücrelerde proliferasyonu engelleyerek apoptozu uyardığı ile ilgili veriler de mevcuttur. Yeniden konumlandırılmış ilaçlar, yeni bir endikasyon için kullanım adayı olan ilaçlardır. Yeniden konumlandırma, *de novo* ilaç geliştirmeye kıyasla zaman ve ekonomik açıdan avantaj sağlayan ve güvenilir tedavi stratejileri geliştirilmesini sağlar. Beta-blokerlerin klinik öncesi ve klinik çalışmalarda gösterilen anti-tümör etkileri, güvenilirlik profillerinin bilinmesi ve inflamatuar yanıta neden olmamaları bu gruptaki ilaçların kanser tedavisinde de değerlendirilmesini sağlamıştır. Meme kanseri hücre hatlarında yapılan çalışmalarda beta-blokerlerin hücre proliferasyonunu, metastazını ve invazyonunu azalttığı gösterilmiştir. Propranololün meme kanseri hastalarında yeniden konumlandırma çalışmaları, umut vadeden verilerin elde edilmesini sağlamıştır. Geleneksel tedaviye direnç kazanmış kanser hücrelerine umut olabilecek bu yeni kombinasyon tedavi yöntemi ile meme kanseri hücrelerinin büyümesinin ve yayılmasının durdurulması amaçlanır. Her geçen gün artan kanser vakaları nedeniyle kanser tedavisinin küresel ölçekte maliyeti artmaktadır. Ek olarak, geleneksel tedavilere karşı gelişen direnç, yeni stratejilerin geliştirilmesinin gerekliliğini arttırmaktadır. Bu nedenle, kanser kemoterapisinde yeni hücresel hedefler ve bu hedeflere karşı geliştirilen düşük maliyetli moleküller ile ilgili çalışmalar kanser tedavisine yönelik araştırmaların önemli bir bölümünü oluşturmaktadır. Ancak, yeni stratejilerin hayata geçmesi ve uygun hedefler bulunması için moleküler modifikasyonlar ve klinik denemeler gerekir. Bu denemeler uzun zaman alan ve ekonomik açıdan yüksek maliyetli süreçlerdir. Ek olarak, yeni bir tedavi seçeneği ortaya konulsa da az gelişmiş ya da gelişmekte olan ülkelerde çoğu hasta tarafından ulaşılabilirliği ülkelerin sağlık politikalarına bağımlıdır. Bu nedenle, piyasada mevcut olan, eski, güvenilirlik profilleri belli ve onaylı ilaçların yeniden konumlandırılarak uzun süreli ve maliyetli primer ilaç geliştirme sürecinden kaçınmak pek çok açıdan tercih edilebilir bir yaklaşım olarak ortaya konulmuştur. Kemoterapide yeniden konumlandırılmış ilaç kombinasyonlarının değerlendirilmesi ve sinerjik etkiye sahip çok hedefli ajanların kullanıldığı tedavi yaklaşımları, klinik öncesi çalışmalarda umut verici sonuçlar göstermiştir. Yeniden konumlandırma çalışmalarında göz önünde tutulması gereken bir diğer bileşen de çoklu ilaç dirençliliğidir. Anti-kanser etkilere bulunan ilaçların ÇİD fenotipine olan etkilerinin tanımlanması da alternatif tedavi rejimlerinin oluşturulması açısından önem arz etmektedir. Hücrelerin direnç geliştirdiği etki mekanizmalarından farklı etki mekanizmalarına sahip yeniden konumlandırılan ilaçlar ve bu ilaçları içeren kombinasyonlar, dirençli hücrelerin elimine edilmesinde etkin olabilir. Aday ilaçların özellikle P-gp inhibitör etkisinin ve sitotoksik ilaçlar ile sinerjik veya aditiv etkilerinin bulunması bu ilaçların kombine tedavilerde yeniden konumlandırılmasını sağlayacaktır.

Bu derlemede, yeniden konumlandırılmış ilaçlar, beta-blokerlerin kanser hücreleri üzerindeki etki mekanizmaları ile bu ilaçların meme kanseri tedavisinde kullanımını konu alan çalışmaların değerlendirilmesi yapılmıştır. Beta-blokerler dahil olmak üzere meme kanseri tedavisi için yeniden konumlandırılan ilaçlar ile ilgili klinik öncesi ve klinik çalışmaların arttırılması kanser tedavi stratejilerinin çeşitlendirilmesi ve maliyetlerin düşürülmesi açısından kritik öneme sahiptir. Kanser hücrelerinin karmaşık moleküler mekanizmaları ile ilgili biriken veriler de, gelecekte onkolojik olmayan birçok ilacın bu yönden irdelenmesine ve yeniden konumlandırılmasına fayda sağlayacaktır.

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