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ORIGINAL RESEARCH

Effect of Use of Walnut Leaf Tea on Reduction of Exacerbation Frequency and Quality of Life in Patients with Chronic Obstructive Lung Disease

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Abstract

Objective: This study aims to investigate the effect of tea prepared with walnut leaves on COPD patients' exacerbation frequency, dyspnea score, and life comfort.

Material-Method: 80 patients diagnosed with COPD and selected using the cluster sampling method participated in our study. They were divided into two groups: the first group consumed walnut leaf tea in addition to their treatment, and the second group only received their medical treatment. Both groups were followed up for six-month periods by the researcher and the follow-up was terminated after three interviews. Then, GOLD staging was performed, the mMRC (Modified Medical Research Council Dyspnea Scale), the CAT (COPD Assessment Test), and the Katz daily living activities scale (ADL) were applied, and a combined COPD assessment was made.

Results: The average age of the patients was 67.1±7 years; 57.5 % of them were male, 42.5 % were smokers, and 56.3 % were COPD stage 2. At the end of the year, the rate of hospital admissions in non-tea-drinking participants was 85%, while the rate of tea-drinking participants was 17.5%, and the difference between them was significant, $p<0.001$. The rate of patients who were planned to change treatment due to exacerbation was 7.5% in tea-drinking participants and 40% in non-tea-drinking participants, and the difference between them was significant, $p<0.001$.

Conclusion: Exacerbations, hospital admissions, and hospitalizations were reduced, and the comfort of life was positively affected in COPD patients who consumed walnut leaf tea in addition to treatment.

Keywords: COPD, Walnut Leaf, Quality of Life, Dyspnea, Complementary and Alternative medicine (CAM)

INTRODUCTION

For centuries, people have used various traditional medicine methods like phytotherapy, which has been passed down from generation to generation, to relieve various ailments. Phytotherapy is a method that uses plants whose therapeutic effects have been determined through experience. Walnut leaf (Juglans regia L.) is one of these plants. It has anti-inflammatory, antimicrobial, anthelmintic, antibacterial, keratolytic, and hypoglycemic effects, and its impact in preventing venous insufficiency and hemorrhoid symptoms have been shown.[1] The main compounds found in walnut leaves are phenolic compounds, juglone, flavonoids and vitamin C. Phenolic compounds are defined as 3- and 5-caffeoylquinic acids, 3- and 4-p-coumaroylquinic acids, p-coumaric acid, quercetin 3-galactoside, quercetin 3-pentoside derivatives, quercetin 3-arabinoside, quercetin 3-xyloside and quercetin 3-rhamnoside.[2] It is known that these compounds have radical scavenging activities that reduce oxidative stress.[3]

It has been determined that juglone has antiviral, antibacterial, antifungal, antidiabetic, and antineoplastic effects. It has shown its effects on human tumor types such as glial tumors, melanoma, leukemia, stomach cancer, prostate cancer, and cervical cancer in vitro, with its strong cytotoxic and genotoxic effects by increasing cell membrane damage, inducing oxidative damage and necrotic and apoptotic cell death.

Chronic obstructive pulmonary disease (COPD) is a clinical entity that is usually progressive, characterized by airway abnormalities such as bronchiolitis and/or emphysema and airflow limitation, often accompanied by airway hypersensitivity. It can be characterized by a productive cough for two consecutive years and three months every year after excluding other causes of cough, and sometimes with asthmatic symptoms.[5,6]

It is among the top three causes of death in Turkey and the world and is predicted to cause a disease burden with increasing social and economic aspects,

as well as loss of labor force, as the direct underlying cause of 7.8% of all deaths by 2030.[7]

Chronic respiratory symptoms characterize COPD; patients' hospital admission reasons are often known as dyspnea, cough, hemoptysis, sputum production, wheezing, chest tightness, fatigue, and activity limitation.[8]

Dyspnea is the most prominent symptom in patients whose quality of life is restricted by the current symptoms.[9]

Dyspnea, also known as shortness of breath, can be defined as the subjective respiratory discomfort experienced by the person experiencing it, consisting of uncomfortable or difficult breathing or sensations of varying intensity.[10,11] Subjectively perceived by patients in different ways, such as air hunger, difficulty breathing, feeling of suffocation, heavy breathing due to the influence of cognitive, behavioral and sociocultural factors, these symptoms can affect the patient's quality of life, physical activities, and psychosocial conditions such as sleep quality.[12,13] It is essential to accurately and effectively evaluate the severity of dyspnea, determine the treatment, and plan care and rehabilitation.[14]

Therefore, it is essential to plan the effectiveness of the treatment by evaluating the scores of the CAT scoring and mMRC dyspnea scale commonly used for COPD patients and making a combined COPD assessment. this study aimed to show the effect of walnut leaf tea on dyspnea symptoms and patients' quality of life, as it is thought to positively impact the process of COPD, a chronic progressive disease since it has not been done before.

MATERIALS AND METHOD

Type of study

The structure of this study was planned as a quasi-experimental research.

Universe and sample

The participants consisted of 80 patients diagnosed with COPD who were followed up in the Pulmonary Diseases Department of Atatürk University Faculty of Medicine and accepted to participate. OpenEpi, Version 3, an open-source calculator, and the Gpower 3.1.9.2 program were used to calculate the sample size. 95% confidence (1-α), 95% test power (1-β), d=0.4 effect size, and the number of samples were 80 people were determined. Two groups were created using the cluster sampling method. The first group was selected by the researcher from patients who had previously used walnut leaf tea had no problems, had not consumed it for at least 6 months, and would currently use tea, while the second group was randomly selected from patients who were receiving their medical treatment and did not use any complementary medicine method according to their registration order.

Data collection tools

GOLD staging: For patients diagnosed with COPD, FEV1/FVC < 70% and GOLD stage 1: FEV1 ≥ 80% (of the expected), stage 2: FEV1 50%-79% (of the expected), stage 3: FEV1 30%-49% (of the expected), stage 4: FEV1 < 30% (of the expected).

mMRC (dyspnea) scoring: Four situation assessments can be scored between 0-4; stage 0 is "I only get short of breath during heavy exercise," stage 1 is "I only get short of breath when I walk on a flat road or when I go up a slight hill," stage 2 is "I have to walk slower than my peers on a flat road or stop and rest from time to time due to my shortness of breath," stage 3 is "I get short of breath and stop after walking 100 m or a few minutes on a flat road." Stage 4 is "I cannot leave the house because of my shortness of breath, or I get short of breath when I get dressed or undressed."

CAT scoring calculation was used in which eight situations were questioned and scored between 0 and 5. A scoring system with a two-category evaluation was used: scoring below 10 points and above 10 points.

Katz ADL scale: The scores given with the system where 0-1 points can be provided for six situations were collected and categorized as dependent (0-2), semi-dependent (3-4), and independent (5-6).

A combined COPD assessment was made by evaluating all the results. According to this assessment, Group A: low risk, few symptoms, 0-1 exacerbations/year and no exacerbation-related hospitalization, CAT<10 or mMRC 0-1, Group B: low risk, many symptoms, 0-1 exacerbations/year or no exacerbation causing hospitalization, CAT ≥ 10 or mMRC ≥ 2, Group C: high risk, few symptoms, ≥ two exacerbations/year or ≥ one exacerbation causing hospitalization, CAT< 10 or mMRC 0-1, Group D: high risk, high symptoms, ≥ two exacerbations/year or ≥ one exacerbation leading to hospitalization, CAT ≥ 10 or mMRC ≥ 2.

Inclusion criteria were; agreeing to participate in the study, being between 40-75 years of age, having a diagnosis of COPD,

Exclusion criteria were having a malignancy accompanying COPD, having asthma, having an allergy to walnuts or similar nuts, having another known allergy or being prone to allergy, being pregnant, breastfeeding, receiving chemotherapy,

having an immune deficiency, being hospitalized or needing to be hospitalized due to a different chronic disease.

Data collection process

When all participants came to the study, their complete blood count values, GOLD staging according to spirometry values, Katz ADL scale, mMRC, and CAT scores were evaluated, and their first data was recorded on 01.07.2013. Participants who will consume walnut leaf tea were questioned about the methods and frequency of consumption.

The frequency of tea use was twice a month, brewed with hot water (150-200 ml) for five minutes. It was learned that the tea was prepared with one teaspoon (approximately 1 gram) of dried mechanically crushed walnut leaves, which has no side effects on human health, and that it was an approved product from the Ministry of Agriculture. Participants were not restricted from drinking tea for 6 months, provided that the method and amount would not harm human health.[15]

At the end of the first 6 months, on 01.01.2014, the GOLD staging, ADL scale, mMRC and CAT scores, oxygen saturations, vaccination status, whether they applied to the hospital due to COPD exacerbation, whether they were hospitalized, if they were hospitalized, how many days of treatment they received, and whether their treatment changed in the last 6 months were recorded. In the second 6 months, walnut leaf tea-drinking participants were restricted from consuming walnut leaf tea, and only the evaluations of both groups were made after they received their treatments. At the end of the second 6 months, on 01.07.2014, GOLD staging, ADL scale, mMRC and CAT scores, oxygen saturations, vaccination status, whether or not the patients applied to the hospital due to illness, whether or not they were hospitalized, if they were hospitalized, how many days of treatment they received, and whether or not their treatment changed in the last 6 months were recorded. All data were collected, and a combined COPD assessment was performed.

Statistical analysis

Number and percentage, arithmetic mean, and standard deviation were used as descriptive statistics. The obtained data were analyzed with SPSS version 26, Kolmogorov Smirnov test was used to detect normal distribution, Student- t, Mann-Whitney U, Cochran's q, Friedman test, Marginal Homogeneity test, Chi-square tests were performed to determine the statistical significance level, and the significance value was accepted as $p<0.05$.

Ethical approval: It was approved by the Atatürk University non-drug clinical research ethics committee with decision number B.30.2.ATA.0.01.00/67 and carried out according to the principles of the Declaration of Helsinki.

RESULTS

Table 1 compares the of socio-demographic characteristics and health history of COPD participants. The mean age of patients was 67.1±7 years, and 57.5% were male. 50% of the patients were primary school graduates, 90% were married, 11.3% were smokers and had quit before, 42.5% were still smokers, and 73.8% had another chronic disease. (n=5, 8.5%) had diabetes mellitus, (n=26, 44.1%) had hypertension, (n=17, 28.8%) had both diabetes mellitus and hypertension, (n=4, 6.8%) had thyroid disease, (n=7, 11.9%) had other diseases and 56.3% had COPD stage 2.

At the end of the first 6 months, the hospital admission rate of participants who did not drink walnut leaf tea was 67.5%, while the hospital admission rate of participants who drank tea was 10%, $p<0.001$ (Table 2). While no change was planned in the treatment of participants who drank tea, a change was planned in the treatment of 32.5% of participants who did not drink tea (Table 2). These changes included long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) treatments. At the end of the first 6 months, there was no hospitalization in the tea-drinking group, while 62.5% of the non-tea group was hospitalized, $p<0.001$ (Table 2).

There was no significant difference in mMRC dyspnea scores between the tea-drinking and non-tea-drinking groups at the end of the first 6 months (Table 2). However, the difference between the mMRC scores of the tea-drinking and non-tea-drinking groups at the 6-month and 1-year evaluations was significant. The difference between the mMRC comparisons of the first 0-6 months and the first 1 year in the tea-drinking group was significant ($p=0.004$, $p=0.011$) (Table 3).

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Table 1. Comparison of socio-demographic characteristics and health history of COPD patients

	Overall n (%) 80 (100.0)	**Tea user n (%) 40 (50.0)**	**Non-tea user n (%) 40 (50.0)**	**p- value**
Age (years) mean± SD	67.1± 7	67.2± 8.1	67.1± 5.9	>0.05
Gender				
Male	46 (57.5)	22 (55)	24 (60)	>0.05
Female	34 (42.5)	18 (45)	16 (40)	
Marital status				
Married	72 (90)	33 (82.5)	39 (97.5)	0.025
Single	8 (10)	7 (17.5)	1 (2.5)	
Educational status				
Literate	14 (17.5.)	7 (17.5)	7 (17.5)	>0.05
Primary school	40 (50)	20 (50)	20 (50)	
High school	24 (30)	12 (30)	12 (39)	
University and over	2 (2.5)	1 (2.5)	1 (2.5)	
Working status				
Employed	31 (38.8)	17 (42.5)	14 (35)	>0.05
Unemployed	49 (61.3)	23 (57.5)	26 (65)	
Additional disease				
Yes *	59 (73.8)	24 (60)	35 (87.5)	0.005
No	21 (26.3)	16 (40)	5 (12.5)	
Drug use				
Yes	59 (73.8)	25 (62.5)	34 (85)	0.022
No	21 (26.3)	15 (37.5)	6 (15)	
Surgery history				
Yes	7 (8.8)	4 (10)	3 (7.5)	>0.05
No	73 (91.3)	36 (90)	37 (92.5)	
Smoking status				
Yes	34 (42.5)	12 (30)	22 (55)	
No	37 (46.3)	23 (57.5)	14 (35)	>0.05
Quit smoking	9 (11.3)	5 (12.5)	4 (10)	
gold stage				
Stage 1	15 (18.8)	11 (27.5)	4 (10)	
Stage2	45 (56.3)	20 (50)	25 (62.5)	>0.05
Stage3	19 (23.8)	8 (20)	11 (27.5)	
Stage4	1 (1.3)	1 (2.5)	0	
mMRC scale				
Stage0	4 (5)	4 (10)	0	
Stage1	8 (10)	4 (10)	4 (10)	
Stage2	41 (51.2)	17 (42.5)	24 (60)	>0.05
Stage3	24 (30)	14 (35)	10 (25)	
Stage4	3 (3.8)	1 (2.5)	2 (5)	
CAT scoring				
<10	46 (57.5)	30 (75)	16 (40)	0.003
≥10	34 (42.5)	10 (25)	24 (60)	
adl scale				
Low	57 (71.3)	26 (65)	31 (77.5)	
Moderate	23 (28.7)	14 (35)	9 (22.5)	>0.05
High	-	-	-	
Oxygen saturation mean± SD	89.5± 3.9	90.6± 3.3	88.4± 4.2	0.011
Blood sample analysis means± SD				
Hgb	13.9± 1.9	14.3± 1.7	13.4± 2	0.039
Eos	1.4± 1	1.4± 1	1.4± 1	>0.05
Wbc	7877± 3135	7631± 2503	8123± 3677	>0.05
Influenza vaccine				
Yes	7 (8.8)	7 (17.5)	0	0.012
No	73 (91.3)	33 (82.5)	40 (100)	

*Diabetes mellitus, hypertension, thyroid disease

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Table 2. Comparison of two groups after 6-12 months

	After 6 months *				After 12 months **			
	Overall n (%) 80 (100.0)	Tea user n (%) 40 (50.0)	Non-tea user n (%) 40 (50.0)	p- value	Overall n (%) 80 (100.0)	Tea user n (%) 40 (50.0)	Non-tea user n (%) 40 (50.0)	p- value
Admission to Pulmonary Clinic								
Yes	31 (38.8)	4 (10)	27 (67.5)	<0.001	41 (51.2)	7 (17.5)	34 (85)	<0.001
No	49 (61.3)	36 (90)	13 (32.5)		39 (48.8)	33 (82.5)	6 (15)	
Change of treatment								
Yes	13(16.3)	0	13 (32.5)	0.008	19 (23.8	3 (7.5)	16 (40)	0.001
No	67 (83.8)	40 (100)	27 (67.5)		61 (76.3)	37 (92.5)	24 (60)	
Hospitalization								
Yes	25 (31.8)	0	25 (62.5)	<0.001	31 (38.8)	1 (2.5)	30 (75)	<0.001
No	55 (68.8)	40 (100)	15 (37.5)		49 (61.3)	39 (97.5)	10 (25)	
Hospitalization day								
Mean ± SD	3±5	0	6±5.8	<0.001	4.6±6.2	0.33±2	8.9±6.1	<0.001
CAT scoring								
<10	61 (76.3)	39 (97.5)	22 (55)	<0.001	62 (77.5)	36 (90)	26 (65)	0.007
≥10	19 (23.8)	1 (2.5)	18 (45)		18 (22.5)	4 (10)	14 (35)	
adl scale scoring								
Low	65 (81.3)	31 (77.5)	34 (85)	>0.05	64 (80)	30 (75)	34 (85)	>0.05
Moderate	15 (18.8)	9 (22.5)	6 (15)		16 (20)	10 (25)	6 (15)	
High	-	-	-		-	-	-	
GOLD stage								
Stage 1	16 (20)	12 (30)	4 (10)	>0.05	15 (18.8)	11 (27.5)	4 (10)	>0.05
Stage2	44 (55)	19 (47.5)	25 (62.5)		44 (55)	20 (50)	24 (60)	
Stage3	20 (25)	9 (22.5)	11 (27.5)		21 (26.3)	9 (22.5)	12 (30)	
Stage4	0	0	0		0	0	0	
mMRC scale								
Stage0	5 (6.3)	5 (12.5)	0		6 (7.5)	5 (12.5)	1 (2.5)	
Stage1	9 (11.3)	4 (10)	5 (12.5)	>0.05	7 (8.8)	3 (7.5)	4 (10)	>0.05
Stage2	46 (57.5)	23 (57.5)	23 (57.5)		47 (58.8)	23 (57.5)	24 (60)	
Stage3	18 (22.5)	8 (20)	10 (25)		18 (22.5)	9 (22.5)	9 (22.5)	
Stage4	2 (2.5)	0	2 (5)		2 (2.5)	0	2 (5)	
Oxygen saturation mean± SD	91 ± 3.13	91.6± 2.734	90.4± 3.410	>0.05	92,64± 2.630	92.63± 2.667	92.65± 2.627	>0.05

*LAMA, LABA addition, **LABA, LAMA, theophylline addition

In the tea-drinking group, the rate of patients with a CAT score <10 at the beginning was 75%, while after six months, it was 97.5% (Table 2). When the ADL scale scores were compared for both groups at the end of the first six months, the difference was not significant. However, the rate of patients with a low addiction level in the tea-drinking group was 65% at the beginning, and this rate was determined to be 77.5% at the end of six months p=0.039 (Table 4).

At the end of one year, the hospital admission rate of participants who did not drink walnut-leaf tea was 85%. In contrast, the hospital admission rate of participants who drank tea was 17.5%, and the difference between them was significant p<0.001. In the non-tea-drinking group, the rate of patients who were planned to have a treatment change was 40%, and the difference between the participants in the tea-drinking and non-tea-drinking groups was significant, (p=0.001). Change in the treatments were LAMA, LABA, and theophylline drugs addition (Table 2). When the hospitalizations at the end of one year were evaluated, the difference between the tea-drinking and the non-tea drinking groups was significant (p<0.001). The hospitalization rate in the non-tea-drinking group was 75%, and in the tea-drinking group was 2.5% (Table 2). At the end of one year, there was no significant difference between the groups in terms of dyspnea scores and ADL scores (Table 2).

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Table 3. Comparison of tea-drinking group and non-drinking group after 6 months and 12 months

	Tea user (beginning) n. (%) 40 (50.0)	Tea user (6 months) n. (%) 40 (50.0)	p-value	Tea user (beginning) n. (%) 40 (50.0)	Tea user (12 months) n. (%) 40 (50.0)	p-value	Non-Tea user (beginning) (n.%) 40 (50.0)	Non-Tea user (6 months) (n.%) 40 (50.0)	p-value	Non-Tea user (beginning) (n.%) 40 (50.0)	Non-Tea user (12 months) (n.%) 40 (50.0)	p-value
Gold stage												
Stage 1	11 (27.5)	12 (30)	>0.05	11 (27.5)	11 (27.5)	>0.05	4 (10)	4 (10)	>0.05	4 (10)	4 (10)	>0.05
Stage2	20 (50)	19 47.5)		20 (50)	20 (50)		25 (62.5)	25 (62.5)		25 (62.5)	24 (60)	
Stage3	8 (20)	9 (22.5)		8 (20)	9 (22.5)		11 (27.5)	11 (27.5)		11 (27.5)	12 (30)	
Stage4	1(2.5)	0		1(2.5)	0		0	0		0	0	
Mmrcscale												
Stage0	4 (10)	5 (12.5)	0.004	4 (10)	5 (12.5)	0.011	0	0	>0.05	0	1 (2.5)	>0.05
Stage1	4 (10)	4 (10.)		4 (10)	3 (7.5)		4 (10)	5 (12.5)		4 (10)	4 (10)	
Stage2	17 (42.5)	23(57.5)		17 (42.5)	23 (57.5)		24 (60)	23 (57.5)		24 (60)	24 (60)	
Stage3	14 (35)	8 (20)		14 (35)	9 (22.5)		10 (25)	10 (25)		10 (25)	9 (22.5)	
Stage4	1 (2.5)	0		1 (2.5)	0		2 (5)	2 (5)		2 (5)	2 (5)	

*****Marginal homogeneity test*

Table 4. 12 months follow-up of the walnut leaf tea-drinking and non-drinking group

	Tea user (beginning) n (%) 40 (50.0)	Tea user (6 months) n (%) 40 (50.0)	Tea user (12 months n (%) 40 (50.0)	p-value	Non-Tea user (beginning) n (%) 40 (50.0)	Non-Tea user (6 months) n (%) 40 (50.0)	Non-Tea user (12 months n (%) 40 (50.0)	p-value
CAT scoring								
<10	30 (75)	39 (97.5)	36 (90)	0.001	16 (40)	22 (55)	26 (65)	0.001
≥10	10 (25)	1 (2.5)	4 (10)		24 (60)	18 (45)	14 (35)	
Adl scale								
Low	26 (65)	31 (77.5)	30 (75)	0.039	31 (77.5)	34 (85)	34 (85)	>0.05
Moderate	14 (35)	9 (22.5)	10 (25)		9 (22.5)	6 (15)	6 (15)	
High								
Oxygen saturation mean± SD	90.68 ± 3.331	91.6± 2.73	92.65± 2.62	<0.001	88.45 ± 4.29	90.4± 3.41	92.63± 2.667	<0.001

Cochran's q, * Friedman test.

When the effects of variables on scale scores according to tea drinking status were examined, it was determined that employment status, education status, presence of chronic disease, and medication use (p=0.040, p=0.005, p=0.012, p=0.019) affected the mMRC dyspnea scale in the year-end evaluations of tea drinking participants (Table 5). When the effects of variables on CAT scale scores according to tea-drinking status were examined, it was determined that gender and education affected the relevant score in the year-end evaluations of tea-drinking participants (p=0.020, p=0.015) (Table 6). In participants who did not drink tea, the effects of smoking status, gender, and whether or not they were employed were determined by the CAT score (p=0.031, p=0.020, p=0.007) (Table 6).

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Table 5. Effect of variables on mMRC dyspnea scale scores of tea-drinking and non-tea drinking group after 12 months

		mMRC Dyspnea scale of the tea-drinking-group					**mMRC Dyspnea scale of non-tea-drinking- group**					
		stage 0 n (%)	stage 1 n (%)	stage 2 n (%)	stage 3 n (%)	p	stage 0 n (%)	stage 1 n (%)	stage 2 n (%)	stage 3 n (%)	stage n (%)	p
Gender	Man	2 (40)	3 (100)	14(60.9)	3 (33.3)	>0.05	0	3 (75)	16 (66.7)	5 (55.6)	0	>0.05
	Women	3 (60)	0	9 (39.1)	6 (66.7)		1 (100)	1 (25)	8 (33.3)	4 (44.4)	2(100)	
Marital status	Single	2 (40)	0	5 (21.7)	0	>0.05	0	0	1 (4.2)	0	0	>0.05
	Married	3 (60)	3 (100)	18 (78.3)	9 (100)		1 (100)	4 (100)	23 (95.8)	9 (100)	2(100)	
Working status	Unemployed	2 (40)	0	13 (56.5)	8 (88.9)	0.040	1 (100)	2 (50)	14 (58.3)	7 (77.8)	2(100)	>0.05
	Employed	3 (60)	3 (100)	10 (43.5)	1 (11.1)		0	2 (50)	10 (41.7)	2 (22.2)	0	
Education	İlliterate	0	0	3 (13)	4 (44.4)	0.005	0	0	3 (12.5)	3 (33.3)	1 (50)	>0.05
	Primary school	3 (60)	0	12 (52.2)	5 (55.6)		1 (100)	2 (50)	13 (54.2)	3 (33.3)	1 (50)	
	High school	2 (40)	2 (66.7)	8 (66.7)	0		0	2 (50)	7 (29.2)	3 (33.3)	0	
	University and more	0	1 (33.3)	0	0		0	0	1 (4.2)	0	0	
Medication	No	4 (80)	3 (100)	6 (26.1)	2 (22.2)	0.012	1 (100)	1 (25)	3 (12.5)	0	1 (50)	0.048
	Yes	1 (20)	0	17 (73.9)	7 (77.8)		0	3 (75)	21 (87.5)	9 (100)	1 (50)	
Additional disease	No	4 (80)	3 (100)	7 (30.4)	2 (22.2)	0.019	0	1 (25)	3 (12.5)	0	1 (50)	>0.05
	yes	1 (20)	0	16 (66.7)	7 (77.8)		1 (100)	3 (75)	21 (87.5)	9 (100)	1 (50)	
Surgery	no	4 (80)	3 (100)	21 (91.3)	8 (88.9)	>0.05	0	4 (100)	22 (91.7)	9 (100)	2 100)	0.009
	yes	1 (20)	0	2 (8.7)	1 (11.1)		1 (100)	0	2 (8.3)	0	0	
Influenza	no	5 (100)	3 (100)	19 (82.6)	6 (66.7)	>0.05	1 (100)	4 (100)	24 (100)	9 (100)	2 (100)	
	yes	0	0	4 (17.4)	3 (33.3)		0	0	0	0	0	
Smoking status	no	4 (80)	0	15 (65.2)	4 (44.49	>0.05	0	1 (25)	8 (33.3)	3 (33.3)	2 100)	0.040
	yes	1 (20)	1 (33.3)	6 (26.1)	4 (44.4)		0	15 (75)	15 (62.5)	4 (44.4)	0	
	quit	0	2 (66.79	2 (8.7)	1 (11.1)		1 (100)	0	1 (4.2)	2 (22.2)	0	

Table 6. Effect of variables on cat score in the tea-drinking and non-tea drinking group after 12 months

		CAT Score of tea drinking group			**CAT Score non-drinking group**		
		<10 n (%)	≥ 10 n (%)	p	<10 n (%)	≥ 10 n (%)	P
Gender	Man	22 (61.1)	0	0.020	19 (73.1)	5 (35.7)	0.021
	Woman	14 (38.9)	4 (100)		7 (26.9)	9 (64.3)	
Marital status	Single	7 (19.4)	0	>0.05	1 (3.8)	0	>0.05
	Married	29 (80.6)	4 (100)		25 (96.2)	14 (100)	
Working status	Unemployed	19 (52.8)	4 (100)	>0.05	13 (50)	13 (92.9)	0.007
	Employed	17 (47.2)	0		13 (50)	1 (7.1)	
Education	illiterate	4 (11.1)	3 (75)	0.015	3 (11.5)	4 (28.6)	>0.05
	Primary school	19 (52.8)	1 (25)		11 (42.3)	9 (64.3)	
	High school	12 (33.3)	0		11 (42.3)	1 (7.1)	
	University and more	1 (2.8)	0		1 (3.8)	0	
Drug use	No	14 (38.9)	1 (25)	>0.05	5 (19.2)	1 (7.1)	>0.05
	Yes	22 (61.1)	3 (75)		21 (80.8)	13 (92.9)	
Additional disease	No	15 (41.7)	1 (25)	>0.05	4 (15.4)	1 (7.1)	>0.05
	Yes	21 (58.3)	3 (75)		22 (84.6)	13 (92.9)	
Surgery	No	33 (91.7)	3 (75)	>0.05	25 (96.2)	12 (85.7)	>0.05
	Yes	3 (8.3)	1 (25)		1 (3.8)	2 (14.3)	
Smoking status	No	21 (58.3)	2 (50)	>0.05	7 (26.9)	7 (50)	0.031
	Yes	11 (30.6)	1 (25)		18 (69.2)	4 (28.6)	
	Quit	4 (11.1)	1 (25)		1 (3.8)	3 (21.4)	

When the effects of variables on ADL scale scores were examined according to tea-drinking status, the year-end evaluations of tea-drinking participants determined that working status and education status affected the ADL scale score (p=0.016, p=0.037) (Table 7). When the combined COPD evaluation was made, no significant difference was found between the comparisons of tea-drinking participants at the end of the first six months and one year (second six months) (Table 8). A significant difference was found between the comparisons of non-tea drinking participants at the end of the first six months and one year (second six months) (p=0.034). It was seen that the non-tea-drinking group was negatively affected.

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Table 7. Effect of variables on ADL scale score in tea-drinking and non-drinking group after 12 months

		ADL scale score of tea drinking group		p	ADL scale score of non-tea drinking group		P
		Semi-dependent n (%)	Independent n (%)		Semi-dependent n (%)	Independent n (%)	
Gender	Man	3 (30)	19 (63.3)	>0.05	1 (16.7)	23 (67.6)	0.019
	Woman	7 (70)	11 (36.7)		5 (83.3)	11 (32.4)	
Marital status	Single	0	7 (23.3)	>0.05	0	1 (2.9)	>0.05
	Married	10 (100)	23 (76.7)		6 (100)	33 (97.1)	
Working status	Unemployed	9 (90)	14 (46.7)	0.016	5 (83.3)	21 (61.8)	>0.05
	Employed	1 (10)	16 (53.3)		1 (16.7)	13 (38.2)	
Education	illiterate	4 (40)	3 (10)	0.037	3 (50)	4 (11.8)	>0.05
	Primary school	6 (60)	14 (46.7)		3 (50)	17 (50)	
	High school	0	12 (40)		0	12 (35.3)	
	University and over	0	1 (3.3)		0	1 (2.9)	
Drug use	No	2 (20)	13 (43.3)	>0.05	0	6 (17.6)	>0.05
	Yes	8 (80)	17 (56.7)		6 (100)	28 (82.4)	
Additional disease	No	2 (20)	14 (46.7)	>0.05	0	5 (14.7)	>0.05
	Yes	8 (80)	16 (53.3)		6 (100)	29 (85.3)	
Surgery	No	9 (90)	27 (90)	>0.05	4 (66.7)	33 (97.1)	>0.05
	Yes	1 (10)	3 (30)		2 (33.3)	1(2.9)	
Smoking status	No	5 (50)	18 (60)	>0.05	5 (83.3)	9 (26.5)	0.026
	Yes	4 (40)	8 (26.7)		1 (16.7)	21 (61.8)	
	Quit	1 (10)	4 (13.3)		0	4 (11.8)	
İnfluenza vaccine	No	7 (70)	26 (86.7)	>0.05	6 (100)	34 (100)	
	Yes	3 (30)	4 (13.3)		0	0	

Table 8. Combined COPD assessment of tea-drinking and non-tea drinking group for 6-12 months

		Tea drinking group			Non-Tea drinking group		
		(6 month) n (%)	(12 month) n (%)	p	(6 month) n (%)	(12 month) n (%)	p
COPD stage	A	8 (20)	7 (17.5)	>0.05	3 (7.5)	1 (2.5)	0.034
	B	30 (75)	30 (75)		8 (20)	4 (10)	
	C	1 (2.5)	2 (5)		2 (5)	4 (10)	
	D	1 (2.5)	1 (2.5)		27 (67.5)	31 (77.5)	

DISCUSSION

This study was conducted to evaluate the effect of walnut leaf tea on disease exacerbation, dyspnea and quality of life in individuals with COPD; the findings obtained to be discussed are; hospital admission, hospitalization and treatment change rates regarding the patient's physical and functional parameters, ADL, mMRC, CAT scale scores. When the participants were evaluated as two groups consuming and not consuming walnut leaf tea, the difference between the groups in terms of hospital admissions, treatment changes, and hospitalizations was significant both in the first 6 months, and at the end of one year. The rates of hospital admission, change in treatment, and hospitalization were relatively low in the tea-drinking group. This is thought to be due to the anti-inflammatory, antimicrobial, and antineoplastic effects of walnut leaf tea, as determined in previous studies.[15]

In our study, when the ADL scale score calculations made during the follow-up period were compared in the non-tea-drinking group the difference between them was not found to be significant, as shown in other studies conducted on COPD patients. However, it was determined that their quality of life was generally low[18].

The difference between the measurements made during the follow-up period in the tea-drinking-group was found to be significant. While the rate of patients with a low dependency level in the tea-drinking group was 65% at the beginning, this rate was determined as 77.5% in the evaluation at the end of the first 6 months and 75% of the assessment at the last 6 months. This significant change may have occurred with decreased severity and frequency of disease symptoms such as cough and dyspnea. Indeed, it is seen that dyspnea and cough constitute serious obstacles to physical activity. In support of our study, it can be thought that the nutritional support given in addition to the treatment in COPD patients in the study conducted by Lobah et al. and the curcumin treatment used by Safari et al. have a positive effect on the anti-inflammatory process[16,17].

In our study, no significant difference was observed between the two groups regarding mMRC dyspnea score at the end of the follow-up periods. Similar to the results of our study, no significant change was found in the mMRC scale in a study with

curcumin[19]. However, in our study, no change was observed in the periodic follow-ups in the non-tea-drinking group. In contrast, the difference between the mMRC scale scores in the periodic follow-ups of the tea-drinking group was significant. A change was observed in the direction of improvement in dyspnea symptoms. It can be thought that the anti-inflammatory process mentioned before reduced the dyspnea level.

When the tea-drinking group was evaluated in terms of CAT score at 6-month follow-ups, the rate of patients with CAT score <10 at the beginning was 75%, 97.5% after 6 months, and 90% after 1 year, and the difference between them was significant. It can be thought that the number of patients with a score below 10 increased due to the changes caused by the anti-inflammatory effect of walnut-leaf tea and its positive impact on dyspnea and cough.

An adverse effect of smoking on the CAT score was detected in non-tea-drinking group, However, it was determined that smoking status did not affect the CAT score in the tea drinking group. It can be thought that walnut-leaf tea acts as a barrier against the harmful effects of smoking.

When the oxygen saturations of the participants in the tea-drinking group were evaluated at the end of one year in 6-month periods, it was determined that there was a tendency for improvement in oxygen saturations. The difference between the initial measurements and the measurements at the end of one year was found to be significant.

At the end of one year, in the evaluation made in terms of GOLD classification according to FEV1 level, it was determined that there was no significant difference between the two groups. The difference between the initial and end-of-year comparisons of the participants in the tea-drinking group tended to improve, although it was not significant. When the studies in the literature were evaluated, the study of Wang et al. also supported the results of our research and showed that there was no significant change in FEV1 value[20].

When the participants were evaluated, it can be thought that the patients with lower levels of education in the tea-drinking group had higher levels of dyspnea, and that as the level of education increases, patients are more conscious, have better access to treatment, and have better compliance with treatment. The results of studies in the literature support our study[21].

Chronic diseases can negatively affect COPD patients due to organ dysfunction, biochemical disorders, and wound healing disorders. In our study, the difference between the dyspnea levels of patients with chronic diseases and those without was significant in tea-drinking patients. When the literature was reviewed, the study results were similar to our study[22].

Limitations

The limitation of the study is that it was conducted in a single hospital. Future studies should be performed in more than one center, with larger sample groups, and for more extended periods.

CONCLUSION

The results show that tea prepared with walnut leaves may be beneficial in a chronic inflammatory disease such as COPD by reducing the severity of symptoms through various mechanisms, reducing hospitalizations, hospitalizations, exacerbations, and polypharmacy, and improving quality of life. It is thought that patients prefer alternative medicine because the drugs used in the treatment of COPD do not provide a definitive treatment. In addition, it can be assumed that patients using walnut leaf tea pay more attention to their health and treatment, but it should not be neglected that conscious information is essential for patients

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ORIGINAL RESEARCH

Investigation of the Relationship Between Health Literacy and Attitude Towards Traditional and Complementary Medicine Among Health Licensor Candidates

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Abstract

Objective: Traditional and complementary medicine has started to gain more place in health services in recent years. The increase in its use makes it necessary to have information about its use. In this study, the relationship between health literacy and attitudes towards traditional and complementary medicine of prospective health license candidates was examined.

Material-Method: In this cross-sectional study, health literacy levels of prospective health license candidates, their attitudes towards traditional and complementary medicine (TCM) and the relationship between them were examined. A questionnaire was administered to students who were selected by stratified sampling method from students studying in six different departments of Kirikkale University Faculty of Health Sciences. The questionnaires were analyzed.

Results: The study included 331 students. Most of the participating students were female (88.5%). The highest score on the health literacy scale was obtained by students from the Department of Social Work and the highest score on the TCM scale was obtained by nursing students. The students who participated in the study had a low level of education about TCM (5.7%), use of TCM products (19%) and a negative attitude towards TCM products (6.3%). There is a significant positive correlation between the scores obtained from the health literacy scale and the scores obtained from the attitude towards traditional and complementary medicine scale. However, this correlation is at a low level ($r=.110$, $p<.05$).

Conclusion: It was found that the number of health license candidates who received training related to TCM was low. It is thought that it would be beneficial to increase health literacy and knowledge about TCM in order for TCM products and methods, whose use has increased due to their inclusion in payment lists, to be beneficial for health.

Keywords: Health Education, Traditional Medicine, Complementary Medicine, Integrative Medicine

INTRODUCTION

Health services is an area where scientific studies are concentrated and new developments are constantly tried to be revealed, as its subject is to increase the quality of human life, improve health and most importantly, human life. Although new technology, drugs and treatment methods are the reason for people's preference, it has been observed that traditional and alternative medicine, which forms the basis of today's practices, has started to be used frequently in addition to modern methods[1]. Both the revival of traditional and complementary medicine (TCM) by the media and experts[2] and the difficulty and expensiveness of accessing health services have increased people's interest in TCM[3].

TCM is described as "a comprehensive body of knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to different cultures, used to maintain health, as well as to diagnose, improve, or treat physical and mental illnesses"[4]. TCM, whose use has partially decreased with the spread of modern medicine, has come to the fore again due to the increase in population, long waiting lines in health institutions, financial obstacles and supply problems such as epidemic periods. In addition, it has become an area of increasing importance and attracting the attention of researchers due to reasons such as social marketing opportunities pioneered by social media, the trust provided by the inclusion of TCM services in the coverage packages, the belief that TCM is the basis of current treatments among the public[5].

TCM is used to strengthen the immune system,

reduce side effects of medications, prevent diseases, and manage illnesses[4,6]. Common TCM practices worldwide include herbal treatments, aromatherapy, acupuncture, cupping therapy, biofeedback, hypnosis, meditation, yoga, Reiki, hirudotherapy, bioenergy, ozone therapy, Ayurveda, balneology, chiropractic, and Tai Chi/QiGong[7]. The increased use of TCM has led to discussions on what these methods are used for and how they should be applied. Without sufficient knowledge, the use of these methods aimed at protecting and improving health may not achieve the desired outcomes and can even worsen health conditions[8]. Therefore, these methods should be applied under the supervision of experts, and individuals participating in these methods should have the competency to find and understand necessary information[9,10]. This is where the concept of health literacy comes into play.

Health literacy is defined as the ability of individuals to access, understand, interpret, and use health-related information to protect, improve, and treat their health and navigate healthcare services[11,12]. The level of this skill affects the decisions individuals make about their health and consequently their health outcomes. Individual differences among people influence their level of health literacy. Therefore, there are differences in how individuals access, understand, interpret, and effectively use health-related information[13-15]. While these differences mostly provide individual benefits, they can sometimes have societal benefits. For example, an individual with an infectious disease who has adequate information about the disease and recognizes the need for treatment can prevent the disease from posing a risk to others[16]. Studies in the literature indicate that individuals with low health literacy levels are less effective in using healthcare services, delay seeking healthcare, fail to adhere to healthcare professionals' recommendations and instructions, are inadequate in self-care, and make mistakes in medication use[17-19].

Issues related to healthcare systems, the accessibility of TCM methods and products, and the increase in service providers and treatment options have heightened the need for health literacy. Despite the scientific evidence supporting the benefits and side effects of many TCM methods and products being limited, they are frequently used by individuals. According to the Institute of Medicine (IOM), there is limited evidence on how knowledgeable individuals are about TCM methods and products, their information sources, and how they evaluate and use this information[20]. Therefore, making decisions about the use of TCM methods and products requires comprehensive health literacy[21].

Studies in Türkiye have examined the relationship between the use of TCM methods and products and health literacy in adults, students enrolled in specific programs, or specialized healthcare professionals[22-25]. However, there is a noticeable lack of studies examining the relationship between the attitudes of students from various health-related programs towards TCM and their levels of health literacy. It is thought that conducting this research on students who will be future health professionals will contribute to the literature. Therefore, this study aims to investigate the attitudes of health license candidates from different programs towards TCM, the relationship between these attitudes and health literacy levels, and personal characteristics.

MATERIALS AND METHODS

The study aims to examine the relationship between health literacy and attitudes towards TCM among health license candidates. The population of the study consists of students enrolled in the Faculty of Health Sciences at Kırıkkale University during the 2022-2023 academic year. A stratified sampling method, which allows for homogeneous selection related to the research problem within a defined population with sub-layers or subunit groups, was used to determine the study group. It was identified that 2219 students were enrolled in six different departments of the Faculty of Health Sciences at Kırıkkale University during the 2022-2023 academic year. According to Altunışık et al., 331 individuals need to be included in the sample to represent a population of 2400[26]. Based on this, 331 individuals determined through stratified sampling by department were included in the study.

The data collection tool used in the study consists of three parts. The first section includes the general information form prepared by the researchers. The second part includes the 47-item health literacy scale (SOYA-EU 47), which was developed by the European Union within the scope of the "European Health Literacy Project 2009-2012" project and whose Turkish validity and reliability study was conducted by Tanrıöver et al.[27]. The third section includes the TCM Attitude Scale, which consists of 27 items, developed by McFadden et al.[28] to

evaluate the attitude towards traditional and complementary medicine, and whose Turkish validity and reliability study was conducted by Köse, Ekerbiçer and Erkorkmaz[29]. The total score is used in the scales, one of which is a five-point Likert-type scale and the other a seven-point Likert-type scale. Necessary permissions were obtained for the use of the scales. In addition, institutional permission was obtained from Kırıkkale University Faculty of Health Sciences and ethical permission dated 11.10.2023-2023.10.12 from Kırıkkale University Non-Interventional Ethics Committee to conduct the study.

The data obtained through questionnaires were examined for normal distribution using skewness and kurtosis coefficients, which were found to be within ±1, indicating normal distribution[30]. Cronbach's α values were used to assess the reliability of the scales, and these values are provided in the findings. One-way ANOVA was used to determine differences in Health Literacy Scale and TCM Attitude Scale scores according to the department of study. Independent Samples t-Test was used to determine differences in scores based on age, gender, education in TCM, use of TCM, and negative experiences with TCM methods. Pearson Correlation Test was conducted to reveal the relationship between health literacy and attitudes towards TCM.

RESULTS

The descriptive characteristics of the participants included in the study are presented in Table 1. Among the participants, 57.4% are 21 years old or older, and 88.5% are women. Among the students selected stratified by department, 94.3% have not received any education on TCM, 81% do not use TCM products, and 93.7% have not experienced any negative situations related to TCM.

Table 1. Descriptive information about the participants

Variables		f	%
Age	20 and under	141	42.6
	21 and older	190	57.4
Sex	Woman	293	88.5
	Man	38	11.5
Educational Status	Nutrition and Dietetics	53	16.0
	Child Development	60	18.1
	Physical Therapy and Rehabilitation	63	19.0
	Nursing	68	20.5
	Social Service	40	12.1
	Healthcare Management	47	14.2
Status of receiving training on TCM	Yes	19	5.7
	No	312	94.3
Status of using TCM products	Yes	63	19.0
	No	268	81.0
A negative situation regarding TCM products	Yes	21	6.3
	No	310	93.7

The health literacy scale used in the study divides participants into four groups based on the score obtained from the scale. A score range of 0-25 is considered inadequate health literacy, 26-33 is considered problematic-limited health literacy, 34-42 is considered adequate health literacy, and 43-50 is considered excellent health literacy. The distribution of participants according to these groups is shown in Table 2. It is observed that 5.7% of the participants have inadequate health literacy, while 56.8% have adequate or excellent literacy levels.

Table 2. Distribution of participants according to their health literacy levels

Score Range	Number of People	Percentage	Cumulative Percentage
0-25 Points	19	5.7	5.7
26-33 Points	124	37.5	43.2
34-42 Points	145	43.8	87.0
43-50 Points	43	13.0	100.0
TOTAL	331	100	

Descriptive statistics for the health literacy and attitudes towards TCM scales used in the study are shown in Table 3. Participants obtained an average score of 143.32 ± 17.40 on the health literacy scale

and an average score of 120.92 ± 13.92 on the attitudes towards TCM scale. On the subdimensions of the health literacy scale, participants scored the lowest on applying health information (33.06 ± 4.31) and the highest on accessing health information (37.54 ± 4.95). On the subdimensions of the attitudes towards TCM scale, they scored the lowest on dissatisfaction with modern medicine (30.92 ± 10.40) and the highest on holistic view of health (48.77 ± 6.67). The reliability coefficients of the scales and subdimensions being above 0.60 indicate that the data are reliable.

Table 3. Statistics on scales and subdimensions.

	Minimum	Maximum	Mean	Standard Deviation	Cronbach alpha
Health Literacy Total	98	188	143.32	17.40	0.947
Access to health information	19	48	37.54	4.95	0.863
Understanding health information	20	44	33.90	4.36	0.821
Evaluating health information	21	48	35.63	5.36	0.851
Applying health information	22	44	33.06	4.31	0.773
TCM Total	80	160	120.92	13.92	0.770
Intellectual perspective on complementary medicine	10	55	34.41	7.41	0.817
Dissatisfaction with modern medicine	10	60	30.92	10.40	0.818
Holistic view of health	24	63	48.77	6.67	0.705

Table 4 presents the examination of scores obtained from the health literacy scale, the attitudes towards TCM scale, and the subdimensions of these scales in terms of the age groups variable. The analysis showed that both health literacy and attitudes towards TCM did not differ by age groups (p=0.117; p=0.224). However, it was determined that there was a statistically significant difference in the health information evaluation subdimension of the health literacy scale and the dissatisfaction with modern medicine subdimension of the attitudes towards TCM scale according to the age variable (p<0.05).

Table 4. Comparison of the scores obtained by the participants from the scales according to age groups

SUBDIMENSIONS	AGE				t	p
	20 and under		21 and older			
	x̄	S.S.	x̄	S.S.		
Health Literacy Total	145.11	19.21	141.99	15.85	1.571	0.117
Access to health information	37.76	5.41	37.37	4.58	.685	0.493
Understanding health information	34.36	4.70	33.56	4.07	1.620	0.106
Evaluating health information	36.45	5.82	35.03	4.92	2.344	**0.020**
Applying health information	33.36	4.70	32.84	4.00	1.087	0.278
TCM Total	122.00	15.03	120.12	13.02	1.219	0.224
Intellectual perspective on complementary medicine	34.68	7.48	34.22	7.42	.555	0.579
Dissatisfaction with modern medicine	32.60	10.58	29.67	10.11	2.549	**0.011**
Holistic view of health	48.36	6.18	49.07	7.01	-.950	0.343

Table 5 presents the examination of scores obtained from the health literacy scale, the attitudes towards TCM scale, and the subdimensions of these scales in terms of the sex variable. The analysis found that the scores from the scales and subdimensions did not differ by sex (p>0.05).

Table 5. Comparison of the scores obtained by the participants from the scales according to sex

SUBDIMENSIONS	SEX				t	p
	Woman		Man			
	x̄	S.S.	x̄	S.S.		
Health Literacy Total	143.00	17.18	145.81	19.08	-.938	0.349
Access to health information	37.51	4.92	37.78	5.21	-.324	0.746
Understanding health information	33.85	4.32	34.34	4.69	-.649	0.517
Evaluating health information	35.53	5.34	36.39	5.55	-.925	0.356
Applying health information	32.92	4.20	34.15	5.00	-1.657	0.099
TCM Total	121.41	13.50	117.10	16.56	1.803	0.072
Intellectual perspective on complementary medicine	34.60	7.22	33.00	8.95	1.249	0.213
Dissatisfaction with modern medicine	30.95	10.51	30.65	9.65	.168	0.867
Holistic view of health	49.01	6.61	46.92	6.95	1.825	0.069

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Table 6 presents the examination of scores obtained from the health literacy scale, the attitudes towards TCM scale, and the subdimensions of these scales in terms of the field of study. The analysis found that the total health literacy score did not vary by field of study (p>0.05), while the health information application subdimension did vary (p<0.05). It was also observed that the scores from the subdimensions of intellectual view of complementary medicine and holistic view of health in the attitudes towards TCM scale varied by field of study (p<0.05). The groups causing these differences are specified under the post-hoc section.

Table 6. Comparison of the scores obtained by the participants from the scales according to the departments in which they were educated

SUBDIMENSIONS	**DEPARMENT**														
	ND		**CD**		**PTR**		**NUR**		**SS**		**HM**		**F**	**p**	**Post-Hoc**
	x̄	**S**	**x̄**	**S**	**x̄**	**S**	**x̄**	**S**	**x̄**	**S**	**x̄**	**S**			
Health Literacy Total	137.62	14.91	144.23	17.24	145.66	16.38	141.94	17.25	147.55	18.71	143.85	19.58	1.994	0.079	
Access to health information	36.26	4.63	37.30	4.75	17.47	5.27	37.33	4.27	38.97	5.59	38.46	5.24	1.777	0117	
Understanding health information	32.52	4.13	34.30	4.26	34.39	4.24	33.73	4.25	34.87	4.40	33.74	4.82	1.762	0.120	
Evaluating health information	34.28	4.42	36.11	5.23	36.65	4.71	35.07	5.46	36.22	5.81	35.51	6.51	1.484	0.195	
Applying health information	31.43	3.59	33.46	4.35	33.88	4.02	32.69	4.36	34.22	4.36	32.87	4.83	2.853	**0.015**	ND-FTR ND-SS p<0.05
TCM Total	120.07	13.17	115.88	14.15	121.31	12.18	125.02	11.72	122.17	13.60	120.78	17.90	2.953	**0.013**	CD-NUR p=0.003
Intellectual perspective on complementary medicine	33.77	5.57	31.78	8.02	35.19	6.86	36.04	7.10	34.72	7.63	34.85	8.86	2.468	**0.033**	CD-NUR p=0.015
Dissatisfaction with modern medicine	30.41	10.66	30.46	10.15	32.60	10.70	30.23	10.01	31.32	11.49	30.48	9.87	.461	0.805	
Holistic view of health	48.00	7.54	46.80	5.81	48.95	6.98	51.27	5.54	49.02	6.53	48.08	7.03	3.343	**0.006**	CD-NUR p=0.002

Table 7 shows the health literacy scale, the attitude scale towards traditional and complementary medicine, and the examination of the scores obtained from the sub-dimensions of the scales in terms of receiving training on traditional and complementary medicine. As a result of the analysis, it was determined that the total score obtained from the health literacy scale and the scores obtained from the sub-dimensions of access to health information and application of health information differed (p <0.05) according to the status of receiving training on traditional and complementary medicine. In addition, it was determined that those who received training in TCM had higher health literacy scores. It was determined that the score obtained from the attitude scale towards TCM did not change according to the education level regarding traditional and complementary medicine, but the dissatisfaction towards modern medicine sub-dimension varied according to the education level regarding TCM (p <0.05). It has been determined that those who received education achieved higher scores in this dimension.

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Table 7. Comparison of the scores obtained by the participants from the scales according to their training status on TCM

SUBDIMENSIONS	RECEIVING TRAINING RELATED TO TCM				t	p
	Yes		No			
	x̄	S.S.	x̄	S.S.		
Health Literacy Total	155.10	23.46	142.60	16.75	2.287	**0.034**
Access to health information	40.42	5.97	37.36	4.84	2.630	**0.009**
Understanding health information	35.73	5.90	33.79	4.23	1.409	0.175
Evaluating health information	38.78	6.90	35.44	5.20	2.074	0.052
Applying health information	36.73	5.66	32.84	4.12	3.896	**0.000**
TCM Total	120.57	18.36	120.94	13.64	-.086	0.933
Intellectual perspective on complementary medicine	34.73	8.98	34.39	7.35	.193	0.847
Dissatisfaction with modern medicine	35.57	12.57	30.64	10.21	2.018	**0.044**
Holistic view of health	47.31	8.18	48.86	6.57	-.980	0.328

Table 8 shows the health literacy scale, the attitude scale towards TCM, and the examination of the scores obtained from the sub-dimensions of the scales in terms of usage of TCM products. As a result of the analysis, it was determined that the scores obtained in both scales and their subscales did not vary according to the use of TCM products ($p>0.05$).

Table 8. Comparison of the scores obtained by the participants from the scales according to their usage of TCM products

SUBDIMENSIONS	TCM PRODUCTS USE STATUS				t	p
	Yes		No			
	x̄	S.S.	x̄	S.S.		
Health Literacy Total	147.22	21.04	142.40	16.34	1.700	0.093
Access to health information	38.73	6.09	37.26	4.61	1.791	0.077
Understanding health information	34.84	5.02	33.69	4.17	1.685	0.096
Evaluating health information	36.47	6.44	35.44	5.07	1.193	0.236
Applying health information	33.84	4.98	32.88	4.13	1.408	0.163
TCM Total	121.58	14.41	120.76	13.58	.419	0.675
Intellectual perspective on complementary medicine	35.82	7.79	34.08	7.33	1.674	0.095
Dissatisfaction with modern medicine	31.38	10.33	30.81	10.43	.387	0.699
Holistic view of health	48.25	8.12	48.89	6.29	-.586	0.559

Table 9 shows the analysis of the scores obtained from the health literacy scale, the attitudes towards TCM scale and the sub-dimensions of the scales in terms of whether there is a negative experience with traditional and complementary medicine. As a result of the analysis, it was determined that only the dimension of holistic view towards holistic medicine, which is a sub-dimension of the attitude towards TCM scale, varied according to whether there was a negative experience with TCM ($p<0.05$) and those who had no negative experience obtained higher scores.

Table 9. Comparison of the scores obtained by the participants from the scales according to negative experiences related to their use of TCM products

SUBDIMENSIONS	A NEGATIVE EXPERIENCE WITH TCM				t	p
	Yes		No			
	x̄	S.S.	x̄	S.S.		
Health Literacy Total	139.23	20.37	143.60	17.19	-1.112	0.267
Access to health information	36.47	6.70	37.61	4.81	-1.020	0.308
Understanding health information	33.52	5.16	33.93	4.31	-.418	0.676
Evaluating health information	33.95	6.18	35.75	5.29	-1.490	0.137
Applying health information	32.09	4.36	33.13	4.31	-1.069	0.286
TCM Total	118.85	14.86	121.06	13.87	-.702	0.483
Intellectual perspective on complementary medicine	35.42	6.42	34.34	7.51	.643	0.521
Dissatisfaction with modern medicine	31.14	8.14	30.97	10.54	.099	0.921
Holistic view of health	45.04	9.23	49.02	6.40	-2.667	**0.008**

Table 10 presents the findings regarding the correlation between health literacy, attitude towards TCM scale and its sub-dimensions. There is a significant positive correlation between the scores

obtained from the health literacy scale and the scores obtained from the attitude towards TCM scale. However, this correlation is at a low level (r=.110, p<.05). There is also a low level of significant correlation between the score obtained from the attitude towards TCM scale and the sub-dimensions of the health literacy scale, namely understanding health information (r=.124, p<.05) and evaluating health information (r=.138, p<.05). There is a low level negative correlation between dissatisfaction with modern medicine, which is a sub-dimension of the attitude towards TCM scale, and both the total score of health literacy (r=-.113, p<.05) and the sub-dimensions of access to health information (r=-.177, p<.01) and understanding health information (r=-.134, p<.05). Another sub-dimension of the attitude towards TCM scale, holistic view of health, has a low level negative correlation with both the total score of health literacy (r=.178, p<.01) and the sub-dimensions of access to health information (r=.182, p<.01), understanding health information (r=.232, p<.01) and evaluation of health information (r=.131, p<.05).

Table 10. Correlation between scales

		Health Literacy Total	Access to health information	Understanding health information	Evaluating health information	Applying health information
TCM Total	r	.110*	.059	.124*	.138*	.070
	p	.046	.282	.024	.012	.206
	n	331	331	331	331	331
Intellectual perspective on complementary medicine	r	.034	.006	.017	.056	.038
	p	.543	.909	.754	.307	.492
	n	331	331	331	331	331
Dissatisfaction with modern medicine	r	-.113*	-.177**	-.134*	-.038	-.073
	p	.040	.001	.014	.494	.185
	n	331	331	331	331	331
Holistic view of health	r	.178**	.182**	.232**	.131*	.102
	p	.001	.001	.000	.017	.065
	n	331	331	331	331	331

DISCUSSION

TCM has recently become one of the concepts on the agenda due to reasons such as the increase in the number of health personnel adopting its use, the inclusion of some practices within the scope of reimbursement, and the declaration of opinions of those who have experienced it both on social media and in society. Although there are applications with scientific validity, some applications may lead to undesirable results due to the lack of a scientific basis or the wrong dose, application method or application area of the users or practitioners. For this reason, the use, application or recommendation of TCM methods that protect, improve or treat health requires a certain level of health literacy. In this regard, the level of knowledge and attitude of healthcare professionals, who have an important position in informing and guiding the society, about TCM becomes important. For this reason, this study aimed to determine the health literacy levels, attitudes towards TCM, the relationship between them and the factors affecting them of health license candidates who will be the health professionals of the future.

Participants obtained an average score of 143.32±23.46 from the health literacy scale. Additionally, 56.8% of the participants were found to have adequate or excellent health literacy levels. Participants obtained an average score of 120.92±18.36 from the TCM scale. It was observed that 94.3% of the participants did not receive any training on TCM, 81% did not use TCM products, and 93.7% did not have a negative experience with TCM products. According to studies, the rate of using traditional/complementary medicine treatment methods at least once is 48% in Australia, 31% in Belgium, 70% in Canada, 49% in France and 42% in the USA[31]. In studies conducted at different times in Turkey, results varying between 12.6% and 76%

were obtained[22, 32-34].

Factors affecting the participants' scores obtained from the health literacy and TCM scales were examined. It was observed that the total score obtained from the health literacy scale did not show a statistically significant difference according to age groups. However, it was observed that participants under the age of 20 obtained higher scores in the "evaluating health information" dimension, which is one of the sub-dimensions of the health literacy scale, and that age constituted a statistically significant difference in this dimension. Contrary to expectations, this result shows that those under the age of 20, that is, those who are in the lower grades of health license education, evaluate health-related information better. It was also observed that the total score obtained by the participants from the TCM scale did not show a statistically significant difference according to age groups. In the dimension of "dissatisfaction with modern medicine", which is one of the sub-dimensions of the TCM scale, it was observed that participants under the age of 20 obtained higher scores and that age constituted a statistically significant difference in this dimension. This result shows that those under the age of 20, that is, those who are in the lower grades of health license education, have more dissatisfaction with modern medicine.

The relationship between the department of education and health literacy and TCM was also examined. It was observed that the department of education had a statistically significant effect only on the health knowledge sub-dimension of the health literacy scale. In this dimension, the low score of nutrition and dietetics department students and the high scores of physical therapy and rehabilitation and social work departments caused the difference to emerge. In the score obtained from the TCM scale, it was seen that there were multiple departments affecting the score. A statistically significant difference was found between the TCM total score and the department of education. The groups that formed this difference were the students of child development department who scored low on this dimension and nursing students who scored high. Statistically significant differences were also found in the sub-dimensions of TCM, namely "intellectual view of complementary medicine" and "holistic view of health". The groups that made up this difference in both dimensions were the students of the department of child development who scored low on this dimension and the nursing students who scored high on this dimension. The fact that nursing students were informed about TCM applications within the scope of their curriculum may have positively affected their attitudes. This result can be considered as an indication that it would be beneficial to include content on basic health information, developing diagnosis and treatment methods in all health-related departments that deal with the health and development of individuals.

The comparison criterion was whether the scores obtained from the health literacy and TCM scales differed according to the status of receiving a training on TCM. As a result of this comparison, it was seen that those who received training obtained higher scores in the total scores of health literacy and the sub-dimensions of access to health information and application of health information, and this difference was statistically significant. It was seen that those who received a TCM-related training obtained higher scores in the sub-dimension of the TCM scale, "dissatisfaction with modern medicine", and this difference was statistically significant. In line with these results, it can be said that TCM-related training increases health literacy in general and decreases the satisfaction of the trainees against modern medicine.

Another comparison criterion was whether the scores obtained from the health literacy and TCM scales differed according to whether they had a negative experience with TCM. In this comparison, it was observed that having or not having a negative experience created a statistically significant difference only in the dimension of holistic view of modern medicine. Those who did not have a negative experience with TCM obtained higher scores in this dimension. The relationship between gender and use of TCM products and the scores obtained from the Health literacy and TCM scales was also examined in the study and it was seen that these variables did not cause any difference.

Finally, the correlation between health literacy, attitude towards TCM scale and its sub-dimensions was examined. It was observed that the correlation between the scores obtained from the health literacy scale and the scores obtained from the attitude towards TCM scale was positively significant but at a low level.

In the study examining the relationship between TCM and health literacy in medical faculty students using the same TCM scale, it was concluded that

students obtained an average score of 104.72±16.46 from the scale and that there was no significant correlation between health literacy and TCM. In addition, it was concluded that the necessity and scope of health literacy is important, considering that the number of students who think they have knowledge about complementary medicine practices is low, they do not receive information from reliable sources of information on this subject, and even medical faculty students have problems in accessing healthy information about complementary medicine[24].

In the study examining the relationship between health literacy and TCM in nursing students and using the same TCM scale, it was found that nursing students obtained a mean score of 110.29±20.13 from the TCM scale. It was stated that there was a significant positive correlation between health literacy and TCM at a moderate level, and as the health literacy level of the students increased, the level of traditional and complementary medicine knowledge also increased. It was also concluded that there was a statistically significant correlation between having subjects related to TCM in the courses and being interested in TCM and the score obtained from the TCM scale[35].

In the study examining the relationship between health literacy and TCM in adults using the same TCM scale, it was concluded that the participants obtained 103.99±22.03 points from the TCM scale and that there was a weak negative relationship between health literacy and TCM scale scores ($r = -19$; $p < .01$)[22].

Some studies conducted in different periods and regions in the literature show that the use of TCM practices increases as the level of health literacy increases[21, 36, 37].

It was observed that there was no common result in the studies analyzed. In addition, there is limited information on how much information the users of TCM practices in the society have about these products and treatment methods, the source of the information they have, the evaluation of the information and when they use it. Users of TCM products and treatment methods may have difficulties in accessing the right information in a diversifying and increasing amount of information. This situation may result in harm while expecting benefit from products and methods. For this reason, users should have comprehensive and critical health literacy[21, 38].

CONCLUSION

Health license candidates are health professionals who will work in health-related fields and guide the society in the future. During their duties, they will not always encounter service recipients who act in line with scientific knowledge, but they will also encounter people who use TCM products and treatment methods that do not yet have scientific validity. In order to protect and improve the health of the society, it is important for these people to guide the society correctly about practices that have a scientific basis and practices that are not yet based on a scientific basis. For this reason, they should have a certain level of health literacy in both practices. In this study, a weak positive relationship was found between health literacy and TCM. Since the participants were health license candidates, it was predicted that this relationship would be higher when the research was planned. However, as a result of the research, it was concluded that this relationship was a weak relationship contrary to expectations. There is no complete unity in the studies examined in the literature and the studies are divided into two as those that find a statistically significant relationship between health literacy and TCM and those that do not. In studies conducted on students studying in health-related departments in Turkey, it was seen that there were opinions that it would be beneficial to add TCM to the curriculum as a stand-alone course. While TCM has been practiced by non-professionals in Turkey for years, it has been practiced by health professionals in the last few years and has been included in the scope of payment. The use of TCM by health authorities will make TCM more widely known and increase its use by professionals and nonprofessionals alike. Considering the studies in the literature, the results of this study and the expected increase in the use of TCM;

-Providing trainings on TCM applications in health education departments,

-To examine health literacy and attitude towards TCM in larger groups of health education students and health professionals,

-Sharing information about scientifically beneficial TCM products and practices and methods applied by health professionals with the public,

-The Ministry of Health should organize a TCM training program for health professionals,

-It is thought and recommended that taking measures against the application of TCM products

and practices by non-professionals may be beneficial in increasing the use of beneficial practices and preventing the damages that may occur as a result of unconscious use.

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ORIGINAL RESEARCH

Traditional and Complementary Medicine Practices Used by Mothers in the Treatment of Acute Upper Respiratory Tract Infections in Children

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Abstract

Objective: The aim of this study was to determine the traditional and complementary medicine methods used by mothers of children with acute upper respiratory tract infection.

Material-Method: We conducted a survey study with questions regarding the traditional and complementary medicine methods used by mothers of 300 children aged 2-12 years who presented to the pediatric outpatient clinic with symptoms of acute upper respiratory tract infections.

Results: Eighty-six point seven percent of mothers reported using traditional and complementary medicine (T&CM) practices at varying frequencies. When asked about the frequency of using non-pharmacological treatment options, 36.4% stated that they always preferred these methods, while 40.6% said they sometimes did. It was observed that 42.3% of mothers started alternative treatments before visiting a doctor, while 40.6% used T&CM after seeing a doctor if they could not get better with the medication prescribed by the doctor. The most common reason for choosing T&CM methods, cited by 50.3% of respondents, was the belief that these treatments are natural and harmless. The most frequently performed practices included giving honey to reduce coughing (36%) and using lukewarm baths to lower fever (74.3%), as well as rinsing nasal congestion with saline or saltwater (48.3%). The information sources regarding these practices were family members (60.6%) and the internet or social media (50.3%). No statistically significance was found between mothers' ages, educational levels, or employment status and the use of T&CM for upper respiratory tract infections.

Conclusion: We found that mothers frequently used various T&CM methods, and that incorrect treatments were common. Families should be informed about what constitutes correct and incorrect treatment practices, and they should be warned about the potential side effects of incorrect treatments.

Key words: Traditional and Complementary Medicine, Mother, Acute Respiratory Tract Infections

INTRODUCTION

According to the World Health Organization (WHO), Traditional medicine is the sum total of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses. The terms “complementary medicine” refer to a broad set of health care practices that are not part of that country’s own tradition or conventional medicine and are not fully integrated into the dominant health-care system. They are used interchangeably with traditional medicine in some countries. [1] Although Traditional and Complementary Medicine (T&CM) practices are predominantly recognized within Eastern medicine, their utilization extends across nearly all societies. Recent studies indicate a growing popularity of T&CM practices in Western societies, including the United States, as well as in our own country. [2,3]

T&CM methods are used to support medical treatments, sometimes applied when there is no response to drug treatment, and sometimes alone. Acute upper respiratory tract infections are the most common infections in children. Approximately 40% of the patients admitted to paediatric outpatient clinics are children with respiratory tract infections.[4] Upper respiratory tract infections such as laryngitis, pharyngitis, nasopharyngitis and rhinitis are among the most common diseases. The most common symptoms of upper respiratory tract infections include cough, sore throat, nasal congestion, fever and headache. In children, upper respiratory tract

infections may progress to lower respiratory tract infections, leading to a worsening clinical condition. [5] Although T&CM treatments are used in various diseases, it has been shown in many studies that they are frequently used in upper respiratory tract infections. [6]

This study investigates the frequency and reasons for the preference of T&CM methods used by mothers of children presenting with upper respiratory tract infections at our outpatient clinic, and also the knowledge and attitudes of the mothers about these methods.

MATERIALS AND METHODS

Between July 2024 and October 2024, mothers of children aged 2-12 years who presented to the Pediatrics Outpatient Clinic of Düzce University Hospital with complaints such as cough, fever, sore throat, nasal congestion, earache and were diagnosed with upper respiratory tract infection constituted the study group. The questionnaire form consisted of seventeen questions covering personal information and questions about T&CM practices. The questionnaire forms were completed through face-to-face interviews with the mothers who consented to participate in the study. The researchers collected information about the circumstances, frequency, timing and reasons of T&CM use; sources of information about them, thoughts about their effectiveness, and whether they would recommend them to others. Ethical approval was obtained from the ethics committee of Düzce University (Date/Number: 10.06.2024/119).

Statistical analysis

The data in the questionnaire forms were uploaded to SPSS 21.0 statistical programme and statistical analyses were performed. Categorical variables were shown as frequency and percentage. Continuous variables with normal distribution were presented as mean ± standard deviation. The Mann-Whitney U test was used to compare two groups of continuous variables with independent samples. The Chi-square test was used for the analysis of categorical data, and the relationship between the significant variables and T&CM use was determined by Spearman correlation analysis. A p-value of $p < 0.05$ was considered significant.

RESULTS

Three hundred children with upper respiratory tract infections and their mothers were included in our study. Among the children, 153 (51%) were girls and 147 (49%) were boys. The mean age of the children was 8.8±4.2 years. It was found that 1% of the mothers included in the study were illiterate, 23% had a university degree, 73% were housewives, and 49.6% were between the ages of 30-40(Table 1). No statistically significant difference was found between the mothers' age (p=0.25), educational status (p=0.89) and employment status (p=0.88) and the use of T&CM for upper respiratory tract infections (p >0.05).

Table 1. Demographic data of the mothers who participated in the study

Age	**n**	**%**
< 20	14	4,6
20-30	51	17
30-40	149	49,6
> 40	86	28,6
Mothers profession		
Housewife	219	73
Civil servant	34	11,3
Worker	43	14,3
Tradespeople	4	1,3
Educational level		
Illiterate	3	1
Primary school	70	23,3
Secondary school	74	24,6
High school	84	28
University	69	23

When we asked the mothers participating in the study what they would do first in cases such as fever, cough, sore throat, earache, nasal congestion and runny nose in their children, 47% answered that they would go to a doctor, 23% said they would try non-pharmaceutical methods at home, and 30% indicated they would use medications available at home. When asked whether they use non-pharmacological methods at home when their children have upper respiratory tract infection symptoms, 13.3% stated that they never use them, 36.4% always, 40.7% sometimes, and 9.6% rarely use T&CM methods.

42.3% of mothers reported using these practices

before visiting a doctor, 40.6% stated that they used them after seeing a doctor, and 17% stated that they started using them before going to a doctor and continued them after the doctor's visit.

50.3% of mothers said that they used T&CM methods because they considered them to be natural and harmless. When asked about the sources from which they learned about T&CM methods for their children, 60.6% stated that they learned them from their close environment (family, friends), 50.3% indicated that they had obtained the information from media tools (internet, TV, social media). Additionally, 39.6% of mothers who used T&CM methods for their children were observed to recommend them to others (Table 2).

Table 2. Distribution of mothers' use of T&CM

Reasons for using T&CM	**n**	**%**
Thinking that it is natural, harmless	151	50,3
Difficulty of finding doctor's appointment	44	14,6
Fear of side effects of medication	37	12,3
Easier and cheaper	15	5
No benefit from medical treatment	14	4,6
Habit	10	3,3
Source from which T&CM is learned		
Close environment (Family, friends)	182	60,6
Media (internet, social media, TV)	151	50,3
Herbalist	3	1
Suggesting the T&CM method		
Yes	119	39,6
No	181	60,3

The study identified various Traditional and Complementary Medicine (T&CM) methods used by mothers whose children exhibited symptoms of respiratory tract infections, such as fever, cough, sore throat, ear pain, and nasal congestion. The methods used are summarised in Table 3.

Table 3. T&CM practices of mothers in upper respiratory tract complaints

Practices to reduce fever	n	%
Lukewarm bath	233	74,3
Putting a cloth soaked in cold water	86	28,6
I do not apply non-medication	40	13,3
Wiping with vinegar water	26	8,6
Wiping with cologne	0	0
Sweating under the duvet	0	0
Practices to alleviate coughing		
I do not apply non-medication	124	41,3
Honey	108	36
Herbal tea (linden, mint, thyme)	72	24
Molasses	48	16
Horseradish-honey	12	4
Onion-honey	7	2,3
Giving garlic	3	1
Practices to reduce sore throat		
I do not apply non-medication	130	43,3
Honey	98	32,6
Soup	69	23
Milk with honey	50	16,6
Herbal tea (linden, mint, thyme)	42	14
Vinegar	39	13
Lemon	21	7
Practices for relieving ear pain		
I do not apply non-medication	271	90,3
Onion juice instillation	13	4,3
Dripping vegetable oils (udi turkey oil, lavender oil, almond oil)	8	2,6
Breast milk instillation	7	2,3
Butter dripping	3	1
Practices to relieve nasal congestion		
Nasal washing (with saline, saline solution)	145	48,3
I do not apply non-medication	137	45,6
Fogging	26	8,6
Dripping vegetable oils (udi turkey oil, lavender oil, almond oil)	7	2,3

The rate of lukewarm bath, which was accepted as the correct method to reduce fever, was found to be

74.3%, while incorrect applications were observed in 37.2% of cases. The most commonly used method to alleviate cough was giving honey (36%) and offering herbal teas such as mint or linden (24%). The most common methods used by mothers to reduce sore throat were giving honey (32.6%) and offering soup(23%) While 90.3% of mothers stated that they did not use any non-pharmaceutical applications for ear pain, the rate of those who used wrong application was 10.3%. When asked about the methods used to alleviate nasal congestion, 48.3% of mothers reported using saline solution or saltwater for nasal irrigation, while 45.6% stated that they did not use any non-pharmacological intervention.

When we asked the mothers whether they would try non-medical methods they first encountered on social media or television for their children, 75.6% said they would never try them, 17% said they would try them if the person recommending was a doctor, 6.3% stated they would try them if they were a herbal product, and 1% said they would try them if they were recommended by a favourite influencer. When asked whether they think every product labelled as "herbal" or "natural" is natural and harmless, 88.6% answered "no", while 11.4% said "yes". When we asked the mothers whether they would use supplements labelled as containing herbal ingredients to prevent their children from getting sick, 57.3% of the mothers said "no", 22.7% said "yes", 20% said "I don't use them, but I am considering whether I should".

DISCUSSION

Studies show that the use of T&CM therapies is becoming increasingly popular all over the world, including European countries and the United States of America. In publications from European countries, the use of T&CM treatment is reported to be 56% (range: 10-90%) in adults and 45% (range: 5-90%) in children. [7]

In a meta-analysis of 17631 children in the UK, the average rate of T&CM use within 1 year was 34% (range: 20-41) and the lifetime use rate was 42% (range: 29-61). 48.3% (range: 14-61) of patients/parents stated that they thought T&CM was useful. [8] In the United States of America, the average rate of T&CM use in children was reported to be 11.6%. [9] Although the frequency varies in our country, it is observed to be practised in all regions. In a review conducted in Turkey, the average rate of T&CM use was found to be 60% (standard deviation±17%, range: 26%-87%).[10] In a study conducted with children with respiratory tract infection and their parents, Topaloğlu et al. found that 93.7% of parents and Aydın et al. found that 69.4% of parents applied T&CM. [11,12]

As a result of our questionnaire study, we determined the rate of T&CM use by mothers who applied to the Pediatrics Outpatient Clinic of our hospital with the complaint of upper respiratory tract infection as 86.7%. Although this rate seems to be considerably higher than the data in Europe and the USA, it is similar to studies conducted in Turkey. We believe that the high proportion of this response is due to the fact that our study only included patients with upper respiratory tract infections.

There are differences in the demographic characteristics and health status of T&CM users. Health-related and sociodemographic determinants of T&CM treatments were analysed in Europe and it has been found that the use of T&CM is more prevalent among women, individuals with higher levels of education, those with higher income levels, and people with long-standing health issues.[13,14] In some studies conducted in Turkey, it was determined that the frequency of T&CM use decreased as the educational level of parents increased. [11,15,16] However, in the study by Bozkaya et al. it was observed that the use of T&CM was less in older parents and no significant difference was found between education level and T&CM usage. [17] In our study, we did not find any relationship between maternal age, maternal employment and maternal education level and T&CM use.

In our study, 86.7% of mothers reported using T&CM practices with varying frequencies when their children experienced upper respiratory tract infections. When asked about the frequency of T&CM applications, 36.4% stated they always used them and 40.6% sometimes preferred them; Additionally 42.3% used these applications before going to a doctor. In contrast, In the study by Aydın et al. it was found that 100% of mothers used T&CM methods for respiratory tract infections, 38.2% sometimes used them, and 43.6% used these practices before drug treatment, similar to our study. [12]

In the study by Topaloğlu et al., the sources of information for T&CM methods were found to be 71.3% from close social circles (family and friends) and 11% from media outlets (TV, internet, social media). In the study of Bozkaya et al. 56% of the participants said that they learnt about alternative treatment methods from family and 37.6% from

media organs. Similarly, Hepokur et al. found that the information sources of the mothers were 38.9% close environment (relatives, friends, neighbours, etc.), 24.8% media (TV, Internet, etc.), 22.2% health professionals (doctor, pharmacist, nurse, etc.). In our study, when the mothers who used T&CM methods in their children were asked where they had learned about these methods, 60.6% stated learning from their close environment (family, friends) and 50.3% from media tools (internet, TV, social media). This increase in the proportion of media tools in our study may be due to the more widespread use of social media and the internet over the years and which has a greater influence on people. This shows that social media, internet and television are tools that should be used more frequently by health professionals to convey accurate information about T&CM methods to the public. [11,17,18]

In previous studies, it has been found that the frequency of alternative treatment use in people with chronic diseases is higher than the normal population. Although our study was not conducted in patients with chronic diseases, it is meaningful in terms of showing that the use of T&CM is quite common in acute diseases with a usage rate of 87.6%. [19]

When their children had fever, 74.3% of the mothers used warm shower, which is accepted as the correct practice to reduce fever, while the rate of incorrect practices (wiping with vinegar water 8.6%, putting a cloth soaked with cold water 28.6%) was found to be 37.2%. Wiping with vinegar water had previously been reported in studies from earlier years at rates of 27.5% and 25.4%. The reduction in the proportion of incorrect practices in our study, along with the absence of practices such as wiping with cologne or inducing sweating by covering with heavy blankets, and the increase in the frequency of correct practices, is encouraging. [16,20]

Cough in children is the most common symptom after fever in upper respiratory tract infections. It is known that many applications such as giving honey, molasses, lemon, herbal tea, giving horseradish-honey, onion-honey mixtures, putting hot towel, wool on the chest, applying butter on the chest, applying batikon are used to reduce cough. Among these alternative applications, giving honey is accepted as a correct application. In meta-analyses, honey has been shown to reduce symptoms of upper respiratory tract infections and cough. [21] In the study of Büyük et al, 72.8% of mothers gave teas prepared from herbs such as linden and mint to relieve cough, 73.3% of mothers increase the consumption of fruits like tangerine, orange and lemon to alleviate cough of the child and 19.4% of the mothers tried to relieve cough by giving the child milk with honey. The rate of mothers applying vicks to the body of a coughing child and using steam inhalation at home was found to be 15%. No mothers in the study were reported to have not used T&CM methods. [22] In our study, the most commonly used method to reduce cough was giving honey with a rate of 36% and giving herbal tea such as mint and linden with a rate of 24%, again similar to the studies. However, in our study, the rate of mothers not using any T&CM method for cough was 41.3% which is higher compared to the data available in the literature.

It is known that various non-drug applications are used in sore throat, ear pain and nasal congestion, which are other findings of upper respiratory tract infection. In the study published by Aydın et al. in 2015, 60.1% of the non-pharmacological applications used to relieve sore throat were determined as drinking herbal tea, 25.5% honey, 8.6% gargling with apple cider vinegar, 5.9% black cumin. [12] In the study conducted by Ozyazicioglu et al. in Kars in 2010, when ear pain was observed in children, mothers used harmful practices such as giving aspirin or ear drops to their children 41.1%, using evil eye beads 9.9%, blowing cigarette smoke or a few drops of breast milk, dripping olive oil 4. 8%, pouring salt or sugar into the ear and then dripping garlic juice on it 4.5%, covering the ear with cotton or soil or putting cooked onion wrapped in cloth in the ear 4.3%. [23] In the study conducted by Efe et al. in Antalya, the practices performed by mothers to their children when their children had ear pain were as follows: taking them to a health institution 41.8%, dripping breast milk 30.3%, dripping the juice of plants and different substances (fig, apple, onion, garlic juice, cologne-lemon juice, oxygenated water, salty water) 7. 2%, doing nothing, waiting for it to pass 13.3%, dripping olive oil, glycerin, putting cotton wool with vaseline 2.9%, putting cotton wool with urine, putting house dust 0.4% shouting in the ear, blowing cigarette smoke, putting a hot cloth, lying on the aching side 1.8%.[24] In a study conducted by Yaman et al. in Erzurum in 1994, it was found that 21.1% of mothers applied butter mixed with sugar to the nose to relieve nasal congestion, 6.7% dripped breast milk into the nose and 5.9% dripped butter into the nose.[25] In our study, the most common methods used by mothers to reduce sore throat were giving honey (32.6%) and giving soup (23%). While 90.3%

of mothers stated that they did not use any non-pharmaceutical application to reduce earache, the rate of those who used wrong application was 9.7%. When asked about the methods used to reduce nasal congestion, 48.3% of mothers stated that they washed their nose with saline or saline solution, and 45.6% stated that they did not use non-pharmaceutical applications. Only 2.3% of the participants said that they dripped herbal oils (udi turkey oil, lavender oil, almond oil). In our study, we observed that the frequency of misapplication decreased compared to the studies conducted in previous years. This may be due to both the increase in the level of knowledge over the years and the geographical regions, cultural and demographic characteristics of the regions where the studies were conducted.

In our study, 50.3% of mothers said that they used the T&CM methods because they found them natural and harmless. When we asked mothers whether they believed that every product labeled as 'herbal' or 'natural' is truly natural and harmless, 88.6% answered 'no,' while 11.4% responded 'yes.' When we asked mothers whether they use supplements with herbal ingredients to prevent their children from getting sick, 57.3% of mothers said "no", 22.7% said "yes", 20% responded "I don't use them, but I am considering whether I should." Herbal medicines are often considered safe treatment options because they are perceived as "natural". However, this belief can lead to the oversight of potential side effects and harmful effects that these treatments may have. However, studies have shown that not all of them are safe for direct human use, especially in paediatric patients.[26] Studies have shown that it can have a strong toxic effect, which may lead to complications such as treatment delays, drug interactions when used with medications, poisoning, nausea, vomiting, headache, dermatitis, even more severe results like respiratory failure, chronic liver damage and renal failure. [27]

CONCLUSION

When all these results are combined, we found that the use of T&CM in our study was more deliberate, with fewer incorrect applications compared to previous studies. We think that this may be due to the socio-economic and cultural differences of the region where we conducted our study as well as the increasing use of the internet and media outlets. However, harmful and wrong non-medical practices were still being used. Therefore, in order to inform families about the use of T&CM and to eliminate the negative effects that may be experienced by choosing the right T&CM methods, it would be useful for the Ministry of Health to make informative shares and public spots through mass media and to increase the level of knowledge of physicians and healthcare professionals about T&CM.

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ORIGINAL RESEARCH

The Relationship Between the Use of Apitherapy Products and the Frequency of Constipation in Adults

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Abstract

Objective: This study aims to reveal the effectiveness of apitherapy products on constipation, as well as other possible risk factors, in individuals with functional constipation.

Material-Method: This cross-sectional study was conducted with 652 adults (460 men and 192 women) between the ages of 18-65 in Turkey. Constipation was defined as defecation frequency of less than 3 times a week. Dietary fluid and fiber intake was assessed by the 62-item food consumption frequency (FFQ). The use of bee products was questioned in terms of quantity and frequency. Physical activity status was questioned with a 3-question short form.

Results: It was determined that 17.8% of the cohort (19.1% males, 14.6% females) had constipation. The percentage of constipation was higher in underweight individuals (28.5%) compared to other Body Mass Index (BMI) groups. Individuals with chronic diseases have a higher percentage of constipation (22.4%) than those without the disease. A significant relationship was found between constipation and fiber intake ($p = 0.001$). Honey ($p=0.013$) and royal jelly ($p=0.030$) intake was significantly higher in individuals without constipation than in individuals with constipation.

Conclusion: The rate of functional constipation is high in Turkish adults. Fiber intake, presence of chronic disease and BMI affect constipation. Constipation is lower in those who consume honey and royal jelly from bee products. Interventional studies are needed on the use of bee products to reduce the symptoms and frequency of constipation.

Keywords: Apitherapy, Constipation, Fiber, Physical Activity

INTRODUCTION

Constipation is one of the most common gastrointestinal problems. Constipation is generally defined as infrequent, hard, painful defecation and incomplete emptying of the rectum. The term functional constipation describes constipation that is not based on any organic etiology and accounts for 90% of constipation cases in early ages.[1-4] It is known that conditions such as abdominal discomfort, abdominal pain, and fecal incontinence due to chronic constipation cause emotional, behavioral and social problems in individuals and negatively affect the quality of life. This situation has led to new searches for treatment options. Today, emphasis is placed on dietary fiber, probiotics, family and individual education, and regulation of toilet habits in the treatment of constipation.[1,5,6]

The complex communities of microorganisms that colonize the gastrointestinal tract play an important role in human health. Intestinal microbiota plays an important role in many metabolic, physiological and immunological events in humans, especially nutrition. Due to all these features, the intestinal system microbiota has become the focus of attention and has been the subject of many studies in recent years. As these studies increase, it is important to identify nutritional treatments that have positive effects on the intestinal microbiota and reveal their positive effects.[7,8] Some herbal formulas for the treatment of constipation are supported by limited evidence, but the lack of a safe dose determination is a potential concern.

Apitherapy is the science of using honeybee products to maintain health and help the individual regain health in case of illness. Pollen, a bee product, is the male reproductive unit formed in the

antennae of higher flowering plants. It is transferred to the stigma of a flower by wind, water, and various animals. One of the animals that provide this transfer is bees.[9] Bees add nectar and honeybee enzymes secreted from salivary glands (e.g., catalase, amylase) to flower pollen to create pollen loads known as bee pollen.[10] Metabolites found in bee pollen show antioxidant,[11] anti-inflammatories,[12] antibacterial[13] and liver protective[14] properties. Bee bread is formed by the adding digestive enzymes and honey and the fermentation of lactic acid during the storage of pollen in the honeycomb.[15] Bee bread has antimicrobial and antioxidant properties.[16] Royal jelly is a secretion produced by the hypopharyngeal and mandibular salivary glands of young worker bees (bees aged 5-14 days), with a white-yellowish, gelatinous-viscous sour taste and a slight phenol odor.[17] It is recommended for the treatment of osteoporosis, wounds, immune disorders and as a preventive measure against cancer.[9] Bee venom is a transparent liquid used in the defense of the hive. Its composition includes biologically active molecules such as melittin, apamin, phospholipase 2, histamine, dopamine, norepinephrine and others.[18] Honey is a natural with many medicinal effects, including antibacterial, liver-protective, antihypertensive and antioxidant.[19] Propolis is a resinous substance collected from the buds of plants and created by bees by mixing them with enzymes, pollen and wax from their secretions. It is stated to be effective in antioxidant activity, antiviral effects, radiation protection and wound treatment.[9]

Natural products are promising for discovering new pharmaceuticals in gut health. However, few studies have investigated the effects of apitherapy products on constipation. Therefore, this study aimed to contribute to dietary treatment approaches in constipation by examining the effects of apitherapy on constipation.

MATERIALS AND METHODS

Study populations

This cross-sectional study was conducted using a random sampling method with 652 adult individuals between the ages of 18-65 who applied to a health center in Turkey between January 2023 and December 2023. Before starting the study, volunteer participants were informed about the study and had to sign a "Voluntary Consent Form" in compliance with the Declaration of Helsinki protocols (World Medical Association). Fırat University Non-Interventional Research Ethics Committee reviewed and approved the study (2022/03-45). Study data was generated through a survey using face-to-face interview method. Individuals under 19 years of age and over 55 years of age, those with chronic health problems, individuals with disabilities, participants diagnosed with irritable bowel syndrome, those using products that affect bowel movements (laxatives, antidepressants, calcium channel blockers, opioids, pre- and probiotics and magnesium tablets), and pregnant/breastfeeding women were excluded from the study.

Assessment of constipation status

Constipation status was determined with a single question. Constipation was considered if the frequency of defecation was less than 3 times a week.[20]

Dietary fiber, fluid, water and bee products intake

Semi-quantitative food frequency questionnaire (FFQ) has been validated for assessment of dietary intake in Turkish adults.[21] Water (mL/d), fluid (mL/d), and dietary fiber (g/d) intake were assessed with a 62-item FFQ. FFQ modified to assess constipation-related habits.[22,23] FFQ was also modified in line with the most commonly used foods in Turkey. Additionally, the use of bee products has been questioned.

Participants were asked how much and how often they consumed certain food groups (bread, whole-grain foods, pasta/rice, fruit, vegetables, potatoes, legumes, bee products, coffee, tea, kefir (fermented milk), ayran (yogurt-water), milk, alcoholic beverages and non-carbonated beverage) in the last month. The "Food and Nutrition Photo Catalog" was used so that the participants could accurately remember the quantities and measurements of the drinks and foods they consumed. Food consumption status and constipation status in the last month were evaluated together. Fiber intake was evaluated with the US Department of Agriculture (USDA) (National Nutrient Database for Standard Reference, Release 25 Software v.1.2.2) database. Water, fluid and fiber intake was evaluated in quartile ranges.

Anthropometric measurements

Body weights (kg) were measured with a Tanita BC 545N portable body analyzer. Leicester brand stadiometer was used for height measurement. While the head was in the Frankford plane and the individual was in an upright position, the measurement was recorded with a sensitivity of 0.1 cm by taking deep breaths. Students' Body Mass Index (BMI) was calculated by dividing their body weight by the square of their height (body

weight/height (kg/ m^2)).[24] BMI values are classified as normal weight (<25 kg/ m^2), overweight (25–29.9 kg/ m^2), and obese (≥30 kg/ m^2) according to the World Health Organization (WHO) classifications.[25]

Physical activity

To evaluate the physical activity status of individuals, the 3-question short form used by Marshall et al. (2005) was used. The first question asks about regular physical activity status. In the second question, "3 or more activities a week" is 4 points, "1-2 times a week" is 2 points, "never" is 0 points; In the third question, “5 or more times a week” is evaluated as 4 points, “3-4 times a week” is evaluated as 2 points, “1-2 times a week” is evaluated as 1 point, and “never” is evaluated as 0 points. If the score obtained by adding the second and third questions is ≥4, it indicates that sufficient physical activity is performed.[26]

Statistical analysis

Evaluation of the data was done with Statistical Package for the Social Sciences 25.0, SPSS 25.0. Fisher exact tests or Chi-square tests determined constipation status in men and women according to BMI, age, education level, chronic disease status, smoking consumption and physical activity status. Data with normal distribution are shown as mean±standard deviation (X±SD) value. When using descriptive data, number and percentage (%) distribution was used. Statistically significant values are expressed as $p<0.05$.

RESULTS

This study was conducted with a total of 652 participants, 460 (70.6%) men and 192 (29.4%) women (Table 1). The average age of the participants was 25.8 ± 9.53 years. Of the total cohort, 17.8% were diagnosed with constipation (19.1% of males, 14.6% of females). No statistically significant difference was found between constipation status and gender ($p>0.05$).

Table 1. Comparision of constipation prevalence by gender

	Male (n = 460)		Female (n = 192)		Total (n = 652)		
Stool frequency (per week)	n	%	N	%	n	%	*p* value
Constipated (<3)	88	19.1	28	14.6	116	17.8	0.166
Non-constipated (≥3)	192	80.9	164	85.4	536	82.2	

p was calculated by chi-square test. *$p < 0.05$

The characteristics of the participants according to constipation status are shown in Table 2. A statistically significant relationship was found between constipation and age, BMI, education level and presence of chronic disease ($p < 0.05$). However, no significant relationship was found between constipation and smoking and physical activity status ($p > 0.05$). The percentage of constipation in the 18-29 age range (20.0%) was found to be higher than other age groups ($p < 0.05$). The constipation percentage of participants with low BMI (28.5%) was higher than the constipation percentage of normal (17.8%), overweight (12.1%) and obese (12.5%) participants (Table 2). The constipation percentage of high school graduates (30.6%) was found to be higher than that of university graduates (16.3%) and master's degree graduates (19.2%) (Table 2).

Table 2. The characteristics of the participants according to their constipation status.

		Constipated (n = 116)	Non-constipated (n = 536)	Prevalence of constipation (%)	*p* value
Age (years)	18-29	98 (84.5%)	392 (73.1%)	20.0	**0.022**
	30-39	6 (5.2%)	86 (16.0%)	6.5	
	40-49	8 (6.9%)	38 (7.1%)	17.3	
	50-59	4 (3.4%)	20 (3.7%)	16.6	
BMI (kg/m^2)	Underweight	24 (20.7%)	60 (11.2%)	28.5	**0.017**
	Normal	72 (62.1%)	332 (61.9%)	17.8	
	Overweight	14 (12.1%)	102 (19.0%)	12.1	
	Obese	6 (5.2%)	42 (7.8%)	12.5	
Educational Level	Primary School	-	10 (1.9%)	-	**0.022**
	Secondary School	-	2 (0.4%)	-	
	High School	22 (19.0%)	50 (9.3%)	30.6	
	University	84 (72.4%)	432 (80.6%)	16.3	
	Master’s degree	10 (8.6%)	42 (7.8%)	19.2	
Chronic Disease	Yes	22 (19.0%)	76 (14.2%)	22.4	**0.013**
	No	94 (81.0%)	460 (85.8%)	17.0	
Smoking	Yes	20 (17.2%)	102 (19%)	16.4	0.809
	No/Quit	96 (82.8%)	434 (81%)	18.1	
Physical Activity	Inactive	90 (77.6%)	394 (73.5%)	18.6	0.362
	Active	26 (22.4%)	142 (26.5%)	15.5	

p was calculated by chi-square test. BMI: Body mass index. Significant values are shown in bold ($p < 0.05$)

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The participants' use of bee products is shown in Table 3. The bee products most used by the participants were honey (87.1%), followed by propolis (33.1%), pollen (18.1%) and royal jelly (10.7%). 33.1% of the participants think that the use of bee products is good for the disease.

Table 3. Participants' use of bee products

		n	**%**
Being knowledgeable about bee products	*Yes*	*404*	62.0%
	No	*248*	38.0%
Bee products consumption status	*Yes*	*440*	67.5%
	No	*212*	32.5%
Honey consumption status	*Yes*	*568*	87.1%
	No	*84*	12.9%
Propolis consumption status	*Yes*	*216*	33.1%
	No	*436*	66.9%
Pollen consumption status	*Yes*	*118*	18.1%
	No	*534*	81.9%
Bee bread consumption status	*Yes*	*25*	3.8%
	No	*627*	96.2%
Royal jelly consumption status	*Yes*	*70*	10.7%
	No	*582*	89.3%
Bee wax consumption status	*Yes*	*25*	3.8%
	No	*627*	96.2%
When choosing bee products, be careful whether they are water-based or alcohol-based	*Yes*	*282*	43.3%
	No	*370*	56.7%
Using bee products because they are good for your illness	***Yes***	***216***	**33.1%**
	No	***436***	**66.9%**

p was calculated by chi-square test. Significant values are shown in bold ($p < 0.05$).

Dietary water, fluid and fiber intake of participants with and without constipation is shown in Table 4. A statistically significant relationship was found between constipation and fiber intake. The constipation percentage of fiber intake in the low quartile (24.7%) was found to be higher compared to fiber intake in the other quartile.

Intake of dietary fiber, water, liquid and apitherapy products according to constipation status is shown in Table 5.

Table 4. Dietary water, fluid, and fiber intake of the participants with and without constipation.

	Constipated (n = 116)	Non-constipated (n = 536)	Prevalence of constipation (%)	*p* value
Water intake				
Lowest quartile (<800 mL/d)	16 (13.8%)	90 (16.8%)	15.1	
Middle lower quartile (800-1200 mL/d)	34 (29.3%)	134 (25.0%)	20.2	0.677
Middle upper quartile (1200-1600 mL/d)	26 (22.4%)	134 (25.0%)	16.3	
Highest quartile (>1600 mL/d)	40 (34.5%)	178 (33.2%)	18.3	
Total dietary fluid intake				
Lowest quartile (<1612 mL/d)	30 (25.9%)	132 (24.6%)	18.5	
Middle lower quartile (1612-2145 mL/d)	24 (20.7%)	140 (26.1%)	14.6	
Middle upper quartile (2145-2696 mL/d)	28 (24.1%)	136 (25.4%)	17.1	0.500
Highest quartile (>2696 mL/d)	34 (29.3%)	128 (23.9%)	21.0	
Dietary fiber intake				
Lowest quartile (<12.2163 g/d)	40 (34.5%)	122 (22.8%)	24.7	
Middle lower quartile (12.2163-22.4081 g/d)	16 (13.8%)	148 (27.6%)	9.8	
Middle upper quartile (22.4081-37.1407 g/d)	36 (31.0%)	126 (23.5%)	22.2	**0.001**
Highest quartile (>37.1407 g/d)	24 (20.7%)	140 (26.1%)	14.6	

Table 5. Amount of dietary fiber, water, fluid and apitherapy products intake of the participants with and without constipation.

	Constipated (n = 58)	Non-constipated (n= 268)	*p* value
Total dietary fiber (g)	23.9±18.66	26.5±17.88	0.174
Total fluid intake (mL)	2273.9±876.56	2194.17±1024.27	0.436
Water intake (mL)	1274.1±610.02	1323.2±888.88	0.408
Honey (g)	3.5±3.71	5.4±3.78	**0.013**
Propolis (g)	0.1±0.22	0.1±0.24	0.869
Pollen (g)	0.2±1.34	0.3±1.00	0.283
Bee bread (g)	0.1±0.30	0.1±0.87	0.133
Bee milk (g)	0.0±0.14	0.1±0.43	**0.030**
Bee wax (g)	0.0±0.14	0.0±0.40	0.056

Date are shown as the mean±standard deviation. p value was calculated by independent t-test. Significant values are shown in bold ($p<0.05$)

Honey and royal jelly intake in the non-constipation group was found to be statistically significantly higher compared to the constipation group ($p < 0.05$). No statistically significant relationship was found between participants with and without constipation in terms of dietary fiber, fluid intake, water intake, propolis, pollen, bee bread and bee wax intake ($p > 0.05$).

DISCUSSION

Bees produce many products containing bioactive ingredients such as honey, propolis, royal jelly, bee pollen, beeswax and bee venom, which have been used in the treatment of various diseases by different civilizations for centuries.[27] In this study, we investigated the relationship of apitherapy products with constipation and the results we found were remarkable.

Constipation is a functional gastrointestinal disease that is common worldwide and can cause serious damage to quality of life as well as impose large socioeconomic burdens on both individuals and national health insurance.[28,29] The 652 participants in this study were 70.6% male and 29.4% female, with an average age of 25.8 ± 9.53 years. Of the total cohort, 17.8% were diagnosed with constipation (19.1% of males, 14.6% of females). According to the results obtained in this study, no statistically significant difference was found between gender, smoking and physical activity status and constipation status ($p>0.05$). A statistically significant relationship was found between constipation and age, BMI, education level and presence of chronic disease ($p < 0.05$).

It is reported that honey has effects in the prevention and treatment of gastrointestinal disorders such as peptic ulcer, gastritis and gastroenteritis. Regular consumption of honey increases the population of normal flora called bifidobacteria; Components of honey have been found to produce a prebiotic effect similar to the effect of fructooligosaccharides.[30-32] A study has shown that intestinal microbiota plays a role in alleviating loperamide-induced constipation in BALB/c mice with honey supplementation and can be considered as an evaluation parameter in constipation treatment strategies.[33] Another study found that participants using Sidr Honey had no recurrence of constipation during a one-year follow-up.[34] In another case, people diagnosed with inflammatory bowel syndrome (IBS) who experienced severe diarrhea or constipation, bloating, and stomach upset were shown to be successfully treated with raw Manuka honey on an empty stomach.[35] In this study, similar to other studies, it was observed that individuals who consumed honey, the bee product most preferred by the participants, had statistically significantly less constipation ($p = 0.013$). Royal jelly contains a number of bioactive substances, including 10 hydroxy-trans-2-decenoic acid (10H2DA; "royal jelly acid"), which exerts an immunomodulatory effect.[36] In this study, individuals consuming royal jelly had statistically significantly less constipation ($p=0.030$). The fact that individuals who consume honey and royal jelly experience less constipation suggests that consuming these foods may be beneficial in the treatment of constipation.

Recent research has shown that propolis not only has antioxidant effects due to the unique diversity of its components (especiall y polyphenols), but can also modulate inflammatory pathways, immune system function, intestinal microbiota, and GI permeability.[37,38] In this study, propolis was found to be the second most consumed apitherapy product by the participants. Protective effects of the anti-inflammatory effect of bee venom on pathological mechanisms involved in liver injury[39] and airway inflammation[40] have been reported. Due to the way pollen is processed by bees, it becomes a product rich in enzymes and probiotics, making it beneficial for intestinal disorders such as ulcerative colitis, constipation and diarrhea, reducing inflammation and intestinal permeability. Bee bread is absorbed by the human body more efficiently than pollen, because the pollen envelope dissolves during processing, enhancing the absorption of vitamins.[41] According to Bogdanov (2020), bee bread can improve digestion and intestinal disorders, as it is a source of probiotics that helps restore the intestinal microbiome, especially in patients undergoing colonoscopy or antibiotic treatment.[42] Beeswax mainly contains hydrocarbons, free fatty acids, fatty acid esters and fatty alcohol, as well as exogenous substances such as pollen, propolis and flower components. Bee wax composition may vary between bees depending on genetic factors and diet.[17] In this study, it was found that the consumption of propolis, bee venom, pollen, bee bread and bee wax did not significantly affect constipation. Low and irregular consumption of these products may also be effective in achieving this result.

The strength of the study is that there is no other study comparing the consumption of apitherapy products with constipation in Turkey. The limitation of the study may be the small sample size and the

exclusion of confounding factors more broadly.

CONCLUSION

The traditional knowledge provided by different civilizations regarding the application of bee products is extremely valuable and gives clues about their usefulness and preparation methods in the treatment and prevention of many diseases. While studies involving in vitro analyzes have revealed important findings regarding the biological properties and mechanisms of action of bee products, in vivo analyzes have also provided information about the pharmacological activities of bee products. In addition to in vitro and in vivo analyses, such studies are used as an important approach to question the usage areas of apitherapy products and investigate their effects on health. Clinical trials have shown that bee products are effective in treating a variety of diseases, both internal and external, but few articles have described the mechanisms of action of apitherapy products on constipation.

Apitherapy is practiced in some parts of the world. As a result of comprehensive information research, it has been concluded that there is insufficient data regarding the prevalence of apitherapy or the use of bee products in treatment across different world regions. In order to make further progress in our knowledge of bee products, the acquired knowledge must be more easily accessible for the benefit of humanity. Therefore, in order to benefit from bee products and their potential and standardize their use, it is of great importance to strengthen the exchange of information between beekeepers, researchers, apitherapists, nutritionists, doctors, sellers and consumers, and to share the results in scientific and alternative activities.

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ORIGINAL RESEARCH

Effect of the Music Intervention on the Anxiety of Patients Receiving Mechanical Ventilation

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Abstract
Objective: Anxiety is very common in patients receiving mechanical ventilation. There are lots of methods to reduce anxiety such as sedatives, and analgesics. However, these methods have some adverse effects. Previous studies show that music interventions have a positive impact on anxiety. In this study, it was aimed to study the effect of music intervention on anxiety in patients receiving mechanical ventilation.
Material-Method: The data were collected by using a patient sociodemographic form, patient monitoring form, Ramsey Sedation Scale, Glasgow Coma Scale, Face Anxiety Scale, and State Anxiety Inventory. Music was played to the patients in the experience group for 60 minutes using a Mp3 player and earphones. Data were collected before listening to the music, at the 30. minutes, at the 60. minutes of listening and 30 minutes after listening. State Anxiety Inventory was assessed before listening to the music and 30 minutes after the music session ended. (90. minutes).
Results: It was found that music positively affected the anxiety symptoms of the patients. Diastolic blood pressure, pulse rate, State anxiety, and facial anxiety scores decreased, indicating a positive influence from the intervention.
Conclusion: It was concluded that music intervention can be used as a useful intervention in the management of anxiety in patients who receiving mechanical ventilation.
Keywords: Mechanical Ventilation, Music Therapy, Anxiety, Psychiatrie

INTRODUCTION

Mechanical ventilation is one of the most frequently used treatment modalities to promote sufficient respiration for patients in intensive care units (ICU).[1] Despite its lifesaving nature, stress caused by mechanical ventilation increases the anxiety felt by patients.[2] According to the literature, the majority of patients who are on mechanical ventilation support experience anxiety.[2.3] Increased anxiety stimulates the sympathetic nervous system, as manifested by an increased heart rate, blood pressure, respiratory rate, and neurohumoral responses.[4] Most of the time, pharmacological therapy, involving such medications as sedatives and anxiolytic agents, is used to control the distress arising from mechanical ventilation.[5] However, the drugs used to control the distress are expensive, both directly and indirectly, in terms of complications during administration.[4,5,6] On the other hand, the inability to speak, the inability to express feelings, thoughts, and wishes, and the dependence on a machine cause anxiety in patients who are dependent on mechanical ventilation.[5.6] It was reported that 70%-80% of patients n the ICU have anxiety, especially in patients receiving mechanical ventilator support.[6,7,8,9] When psychiatric consultations regarding patients on mechanical ventilator support were evaluated, it was found that 80% of the patients had symptomatic depression, delirium, and anxiety.[6] Anxiety in intensive care patients is known to cause many undesirable results such as pain, delayed wound healing, and weaning from the mechanical ventilator.[9,10,11,12]

It is already known that sedation employed in the treatment of anxiety in patients who are dependent on mechanical ventilation increases the cost of care and prolongs the hospital stays, which, then makes it necessary to search for alternative non-pharmacological treatments for ventilator-dependent patients.[6,12,13] According to the literature data, non-pharmacological methods in patient care appear to have positive impacts on the management of pain, sleep quality, anxiety, and delirium.[14.15]

As one of the non-pharmacological methods, music interventions are employed to cope with anxiety in our present day. Studies report that music may be employed to reduce anxiety[16,17] with an effect on patients' physiological and psychological responses to anxiety. Chlan et al. (2001) defined music therapy as the therapeutic use of music to promote the health and well-being of patients.[18] Critical Care Medicine Society 2013 Guideline recommends non-pharmacological interventions such as music on pain, tension, and delirium management in the intensive care units.[19] Because music intervention is a low-cost, easy-to-access, and safe intervention, reducing the need for sedation and helping patients recover faster.[16,17,18,19] The characteristics of anxiety-reducing music include simple repetitive rhythms, predictable dynamics, low pitch, slow tempos, the consonance of harmony, a lack of percussive instrumentals, and vocal timbres.[20]

Music intervention is a nonpharmacologic nursing intervention that can be employed as a complementary adjunct in the care of patients supported by mechanical ventilation. In studies conducted with ICU patients, it was reported that the use of music reduces the psychological and physiological impacts of patients' anxiety.[18,21] It was found that the intervention of music in patients who were dependent on mechanical ventilation in Intensive Care Units (ICUs) reduced the anxiety levels of patients.[22] Previous studies reported that the music applied between 25-90 minutes was effective in reducing the physiological impacts of anxiety.[20.21]

Music intervention can be employed for the care of mechanically ventilated patients because it is not expensive, accessible, and does not harm the patient. However, limited studies were detected that measure the effectiveness of music intervention in mechanically ventilated patients.[5,6,7,8,18,22,23] For this reason, the study was conducted to examine the effects of music intervention on the patient's anxiety level in patients who depend on mechanical ventilation. The following six hypotheses were tested in the study.

H_1: The systolic and diastolic blood pressures of the individuals who undergo music intervention are lower than the control group.

H_2: The heart rate of the individuals who undergo music intervention is lower than the control group.

H_3: The respiratory rate of the individuals who undergo music intervention is lower than the control group.

H_4: The oxygen saturation of the individuals who undergo music intervention is higher than the control group.

H_5: The state anxiety scores of the individuals who undergo music intervention are lower than the control group.

H_6: The facial expression anxiety scores of the individuals who undergo music intervention are lower than those of the control group.

MATERIALS AND METHODS

Materials

A semi-experimental design with a repeated measures approach was employed to determine the impacts of music intervention on systolic/diastolic blood pressure, respiratory rate, oxygen saturation, and self-reported measures of anxiety in patients receiving mechanical ventilation. Subjects were assigned to either intervention or control groups by having a case nurse draw lots.

Participants

The present study was conducted with patients who were on mechanical ventilation in the Intensive Care Unit (ICU) of a university hospital. The inclusion criteria for both the experimental and control groups were to be 18 years of age or older, not to use psychotropic drugs and not to have pain. Among these patients, those who were dependent on mechanical ventilation on the postoperative first day scored 1 or 2 on the Ramsay Sedation Scale (RSS), scored above 9 on the Glasgow Coma Scale (GCS), were not on high-dose inotropic support (dopamine and/or dobutamine; not exceeding 10 mcg/kg/hour), patients with O_2 saturation above 90 were included in the study. Before the data of the study were collected, the patients and their relatives were informed about the procedures to be applied by the researcher, and verbal and written consent was obtained.

Sampling

In the present study, the similarity of individual characteristics such as age and gender was taken into account in the selection of the sample. The sample size was determined statistically by Power Analysis. The power of the study was expressed as 1-β (β =Type II error probability). In the calculation made, considering the parameters of the groups, the effect size (d) was 1.037 in case of an error of α=0.05 to obtain 90% power. The sample size was determined as 15 for each group and a total of 30 individuals, 15 of which were experiment-experimental and 15 were control, were taken into the sample. The inclusion criteria and flowchart of the study are given in Figure 1.

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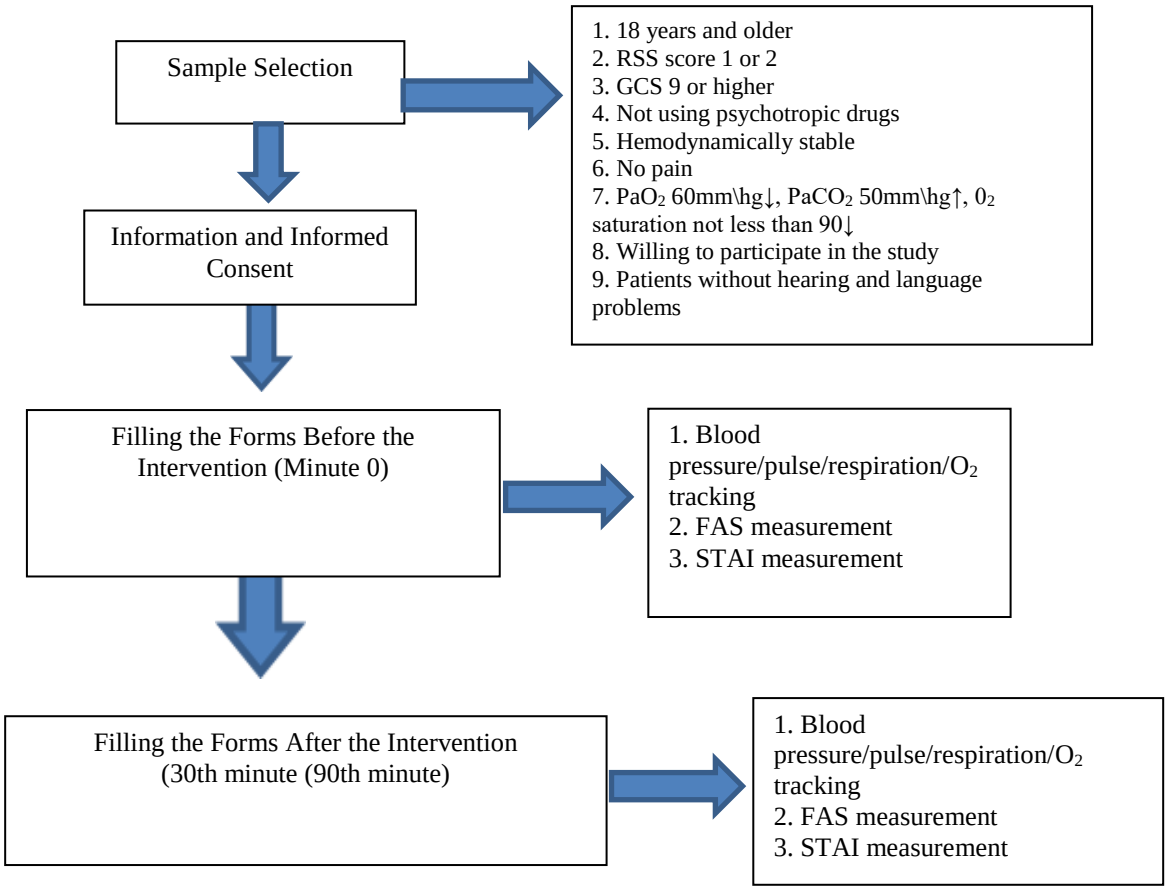

Figure 1. The Flowchart of Sampling and Data Collection Process

Methods

Measurement

Six data collection forms were employed by the researchers before and after the intervention. The first was the sociodemographic characteristics form that included data on age, gender, and educational status. In the second form, the systolic and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation of the patients on the monitor were recorded at 0, 15, 30, 60, and 90 minutes before and after the intervention. In the third and fourth forms, GCS and Ramsey Sedation Scale RSS were noted, which enabled the patient's consciousness and neurological assessment to be made. GCS was developed by Teasdale and Jennet in 1974[24]. GCS is an international scale used to directly determine the level of consciousness and coma of patients. It has been used by physicians and nurses in intensive care and neurology clinics for many years because it reflects the changes in the state of consciousness of patients quickly and reliably. On the scale, 13-15 points indicate that the patient is awake, 8-12 points are considered as precoma, and 8 and below is considered coma. RSS was developed by Ramsey et al. (1974) to determine the sedation level of patients.[25] The RSS was developed and started to be used in intensive care units about 30 years ago and is the most frequently used scale by intensive care workers to date. An increase in the score on the scale, which consists of a total of six items, indicates an increase in the level of sedation. As the fifth form, the Face Anxiety Scale (FAS) was employed to determine the patient's anxiety status.[26] This form is filled with observation in mechanically ventilated patients and is scored between "0" and "10". As the score increases, the severity of anxiety increases.[26] As the sixth form, the STAI-1 State Anxiety Form was employed to determine the presence of anxiety.[27] The STAI Form, which consists of 20 items, is one of the most widely employed tests in medicine to measure anxiety. The STAI is the most frequently used measure of state and trait non-disorder-specific anxiety, with a citation index over 16,000 since its first publication. The questionnaire was has been translated into 48 languages as of 2011. The STAI has been shown to have excellent psychometric

properties with good reliability and validity. Internal consistency coefficients for the scale ranged from .86 to .95 (Spielberger et al., 1983). In this form developed by Spielberg, the highest score that can be obtained from the scale is 80, and the lowest score is 20. The higher the calculated total anxiety score, the higher the anxiety level of the person.[28]

Procedures

To prevent the patients in the intensive care unit from being affected by external stimuli, the music to be employed in the intervention was played with the help of headphones and Mp3. Participants in the control group continued to receive mechanical ventilation support in their rooms while the participants in the experimental group listened to music. During this period, room temperature, lighting and noise level were maintained before and after the measurement to prevent the stressor effect on the control group.The music employed in the intervention was prepared by the TUMATA Music Therapy Association.[29] It has long been known that Turkish music maqams have physical and psychological effects on humans. The type of music used in the research was decided in line with the opinions and suggestions of an expert academician. This type of music was selected from classical Turkish music with specific melodies that reduce anxiety and provide peace. These melodies are especially the "Rast Maqam" in classical Turkish music, which stimulates feelings of joy and peace. After the music selection was decided, a 60-minute recording was prepared in the rast melody in line with the opinions of an expert academician. According to the literature on the subject, the duration of music playback can be between 25-90 minutes.[22] Therefore, the patients in the experimental group were exposed to music for 60 minutes.

Data collection

The systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate, oxygen saturation, and FAS scores of the patients in the experimental group were measured and recorded at the 30th minute of the music intervention, the 60th minute after the end of the music intervention and 30 minutes after the end of the music intervention (90th minute). After the intervention was completed, the researcher removed the individual's earphones and filled out the post-intervention forms. In the literature, anxiety is classified into state and trait anxiety[27]. State anxiety constitutes an acute and transient psychological response to a stimulus, whereas trait anxiety reflects a chronic, enduring, anxious disposition commonly observed in generalized anxiety and panic disorders. Since the aim of this study was to investigate state anxiety in patients, the STAI form was completed only once, 30 minutes after the end of the music intervention (at 90 minutes). To ensure objectivity, data with FAS were collected by a nurse who cares for both groups, apart from the researchers. The same nurse who collected data with FAS before the music intervention collected data again with FAS after the intervention. Systolic and diastolic blood pressure, heart rate and respiratory rate, oxygen saturation, FAS, and STAI scores of the patients in the control group were also measured and recorded by paying attention to the same durations and rules.[6,.23]

Ethical consideration

To conduct the study, permission was obtained from the Uskudar University Ethics Committee with the number No: B.08.6.YOK.2.US.0.05.06.2017/89. Also, written consent from the patients and their relatives was obtained before the intervention. The 30 patients included in the sample, comprising both the experimental and control groups, read the informed consent form and signed to indicate their acceptance. After music intervention, a CD containing the music used in the study was given to the control group too. All methods were carried out in accordance with relevant guidelines and regulations in Ethics declaration section.

Statistical analysis

The SPSS 21.0 program was employed for statistical analysis. One-sample Kolmogorov Smirnov test was used to determine whether the data conformed to normal distribution. In evaluating the study data, also to descriptive statistical methods, the Student's *t*-Test was employed for two-group comparisons of normally distributed variables, and the Mann-Whitney U Test was employed for two-group comparisons of non-normally distributed variables. The Paired Sample ***t***-Test was employed for intra-group comparisons of normally distributed variables, and the Wilcoxon Signed Ranks Test was employed for intra-group comparisons of non-normally distributed variables. The Repeated Measures Test was used in the evaluation of the follow-up of the variables with normal distribution and Bonferroni Test was used in pairwise comparisons. The Friedman Test was employed for the evaluation of the follow-up of the variables that did not show normal distribution, and Dunn's Test was employed for pairwise comparisons. The Pearson Chi-Square Test and the Fisher-Freeman-Halton Test were employed to compare the

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qualitative data. Significance was evaluated at the $p<0.05$ level at least.

RESULTS

The study was conducted with a total of 30 patients (15 in the experimental group and 15 in the control group). Although H_1, H_2, H_5, and H^6 hypotheses were partially accepted in the study, it was found that H_3 and H_4 hypotheses were not accepted.

When the descriptive characteristics of the patients were evaluated, it was found that their ages ranged from 41 to 68 years, and when their gender was examined, 46.7% (n=14) were female and 53.3% (n=16) were male. When the duration of the groups spent on the ventilator was evaluated, the average number of days was found to be 4.80±2.25 days. When the length of stay in the Intensive Care Unit was evaluated, it was found that the average was 12.07±3.86 days. The mean GCS of the patients was 9.83±0.38; RSS mean was found to be 1.17±0.38. A statistically significant difference was found between the duration of the experimental group being attached to the ventilator and the control group's duration of being attached to the ventilator ($p<0.05$). According to these results, the duration of being attached to the ventilator of the experimental group (3.80±1.82) was found to be lower than the duration of being attached to the ventilator (5.80±2.24) of the control group (Table 1).

Table 1. The descriptive characteristics of the patients on mechanical ventilation

Descriptive Characteristics		Experimental Group (n=15)	Control Group (n=15)	Test Value
Age (years)	Median (Min-Max)	63 (41-66)	56 (51-68)	t=1.565
	Mean±SD	60.20±6.65	56.87±4.88	p= 0.129 *
Gender	Female	7 (46.7)	7 (46.7)	x^2 =0.001
	Male	8 (53.3)	8 (53.3)	p=1,000**
Education level	Illiterate	3 (20.0)	3 (20.0)	
	Primary school	3 (20.0)	6 (40.0)	x^2 = 1,846
	Middle school	5 (33.3)	4 (26.7)	p=0.701***
	High school	4 (26.7)	2 (13.3)	
	College	3 (20.0)	3 (20.0)	
Length of stay on the ventilator (days)	Median (Min-Max)	4 (1-8)	6 (2-10)	t=-2.682
	Mean±SD	3.80±1.82	5.80±2.24	**p= 0.012***
Length of stay in Intensive Care Unit (days)	Median (Min-Max)	10 (5-16)	16 (8-18)	t=-1,986
	Mean±SD	10.73±3.37	13.40±3.96	p= 0.057*
GCS scores	Median (Min-Max)	9-10 (10)	9-10 (10)	Z= -0.482
	Mean±SD	9.87±0.35	9.80±0.41	p= 0.630****
RSS scores	Median (Min-Max)	1-2 (1)	1-2 (1)	Z= -0.482
	Mean±SD	1.13±0.35	1.20±0.41	p= 0.630****
	Awake, anxious, restless, or both	13 (86.7)	12 (80.0)	
	Awake; cooperative, oriented, calm	2 (13.3)	3 (20.0)	

Student **t-Test; **Pearson Chi-Square Test; ***Fisher-Freeman-Halton Test; ****Mann Whitney U-Test*

No statistically significant differences were detected in the systolic blood pressure, respiratory rate, and oxygen saturation values of the patient groups before, at the 30th, 60th, and 30th minutes after the music intervention. ($p>0.05$) (Table 2) However, for diastolic blood pressure, statistically significant differences were observed between the experimental and control groups at the 30th minute of the intervention ($p<0.05$). According to these results, the diastolic blood pressure of the experimental group before the intervention (82.07±7.71) and the 30th minute of the intervention (79.60±6.94), the diastolic blood pressure of the control group before the intervention (73.40±7.33) and it was found to be higher than the 30th minute of the intervention (73.60±8.54). (Table 2). In this case, the H1 hypothesis can be partially accepted as the diastolic blood pressure changes.

Regarding the heart rates, no statistically significant differences were detected between the experimental and control groups' values before the intervention, at the 30th and 60th minute, and 30 minutes after the intervention (90 minutes) in the experimental and control groups ($p<0.05$). According to these results, the diastolic heart rate of the experimental group was found to be lower both before the intervention (82.07 ± 7.71) and at the 30th minute of the intervention (79.60±6.94) compared to the diastolic heart rate of the control group before the intervention (73.40±7.33), and at the 30th minute of the intervention (73.60±8.54) (Table 2). In this case, the H_1 Hypothesis was partially accepted because diastolic heart pressure was changed.

Regarding the heart rates, statistically significant differences were detected between the experimental and control groups' values at the 60th minute, 30 minutes after the application (90 minutes) of the experiment, and control groups ($p<0.05$). According

to these results, the heart rate of the experimental group at the 60th minute of the application (83.67±13.05) and the value after the 30th minute of the application (90 minutes) (82.53±13.59), the heart rate of the control group at the 60th minute of the application and the value after the 30th minute of the application (95.00±15.69). In this case, Hypothesis H_2 was partially accepted and Hypotheses H_3 and H4 were not accepted (Table 2).

Table 2. The Effect of Music Intervention on Vital Findings

Systolic Blood Pressure (mmHg)		**Pre-MI**	**30th min of MI**	**60th min of MI**	**Post-MI**
Experimental Group (n=15)	Min-Max-(Med.) Mean±SD	120-180-(146) 149.93±17.21	125-177-(142) 146.73±16.70	107-159-(126) 130.13±15.56	100-160-(125) / 125.33±18.01
Control group (n=15)	Min-Max-(Med.) Mean±SD	102-169-(140) 137.73±18.22	118-160-(145) 140.80±12.34	116-160-(142) 138.93±12.78	112-165-(140) 136.73±13.80
		t= 1.885 p= 0.070	t= 1.107 p= 0.278	t= -1.693 p= 0.102	t= -1.946 p= 0.062
Diastolic Blood Pressure (mmHg)					
Experimental Group (n=15)	Min-Max-(Med.) Mean±SD	70-96-(85) 82.07±7.71	69-88-(82) 79.60±6.94	65-86-(76) / 75.40±5.79	58-80-(70) 70.67±6.22
Control group (n=15)	Min-Max-(Med.) Mean±SD	56-84-(74) 73.40±7.33	52-90 (72) 73.60±8.54	62-84-(76) / 75.33±7.01	58-85-(78) 73.67±8.72
		t= 3.155 **p= 0.004***	t= 2.112 **p= 0.044***	t= 0.028 p= 0.978	t= -1.085 p= 0.287
Heart Rates (times/min)					
Experimental Group (n=15)	Min-Max-(Med.) Mean±SD	60-130-(87) 89.20±18.19	60-128-(87) 87.60±16.80	58-110-(86) / 83.67±13.05	59-118-(80) 82.53±13.59
Control group (n=15)	Min-Max-(Med.) Mean±SD	52-124-(100) 99.47±19.06	46-120-(100) 97.60±18.09	59-116-(100) / 95.67±15.27	54-113-(97) 95.00±15.69
		t= -1.509 p= 0.142	t= -1.569 p= 0.128	t= -2.314 **p= 0.028***	t= -2.326 **p= 0.027***
Respiration Rate (min)					
Experimental Group (n=15)	Min-Max-(Med.) Mean±SD	16-32-(27) 24.87±6.01	16-30 (24) 23.60±5.03	16-28-(22) / 22.13±3.81	16-24-(22) 21.07±2.49
Control group (n=15)	Min-Max-(Med.) Mean±SD	12-32 (22) 22.73±5.51 t= 1.013 p= 0.320	12-78-(24) 26.60±15.14 t= -0.728 p= 0.472	18-32-(26) / 24.53±5.00 t= -1.478 p= 0.150	16-32-(24) 24.00±5.24 t= -1.959 p= 0.060
Oxygen Saturation (%)					
Experimental Group (n=15)	Min-Max-(Med.) Mean±SD	94-100-(98) 98.13±2.00	95-100-(99) 98.33±1.91	94-100-(99) / 98.13±1.96	95-100-(98) 98.13±1.81
Control group (n=15)	Min-Max-(Med.) Mean±SD	93-100- (99) 98.53±1.92	94-100-(99) 98.53±1.85	94-100-(99) / 98.53±1.73	94-100-(99) 98.60±1.80
		t= -.559 p= 0.581	t= -.291 p= 0.773	t= -.593 p= 0.558	t= -.708 p= 0.485

**Student t-Test*

In the experimental group, the STAI scores after 30 minutes (90 minutes) were statistically lower than before the application (p=0.001; p<0.01). The change in STAI scores 30 minutes after the application (90th min) compared to the pre-application was not statistically different in the control group (p=0.378; p>0.05). In this case, Hypothesis H5 was partially accepted.

The FAS score of the experimental group after the 30th minute (90th minute) of the application was found to be statistically significantly lower than the control group (p=0.005; p<0.01). The decrease in anxiety levels in the experimental group in the period up to 30 minutes after the application (90th minute) compared to before the application was statistically significant (p=0.001; p<0.01). The change in anxiety levels in the control group during the period up to 30 minutes after the application (90th minute) compared to the pre-application was statistically significant (p=0.392; p>0.05). In this case, Hypothesis H_6 was accepted (Table 3).

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Table 3. The changes in STAI and Facial Anxiety Scale Scores with Music Intervention

STAI-Form Total Scores		**Experimental group (n=15)**	**Control group (n=15)**	***Test value* *p**
Before the music intervention	Median (Min-Max	63(50-72)	37-70 (64)	t= 0.184
	Mean±SD	61.73±7.21	61.2±8.58	p= 0.855
30 min after the music intervention	Median (Min-Max	42(34-72)	37-72 (66)	t=-5.620
	Mean±SD	43.73±8.43	62.33±9.66	**p= 0.001**
		t=8.058	t=-0.910	
	****p**	**0.001**	0.378	
FAS Scores		**Experimental group (n=15)**	**Control group (n=15)**	**Test value ***p**
Before the music intervention	Mild anxiety	1 (6.7)	1 (6.7)	
	Moderate anxiety	4 (26.7)	8 (53.3)	
	A lot of anxiety	3 (20.0)	4 (26.7)	χ^2=4.372
	Severe anxiety	7 (46.7)	2 (13.3)	p= 0.207
	Median (Min-Max	6 (2-8)	4 (2-8)	
	Mean±SD	6.13±2.07	4.93±1.67	
30^{th} min during the music intervention	Mild anxiety	1 (6.7)	1 (6.7)	
	Moderate anxiety	4 (26.7)	7 (46.7)	
	A lot of anxiety	7 (46.7)	5 (33.3)	χ^2 = 1.642
	Severe anxiety	3 (20.0)	2 (13.3)	p = 0.795
	Median (Min-Max	6 (2-8)	4 (2-8)	
	Mean±SD	5.60±1.72	5.07±1.67	
At the 60th min during the music intervention	Mild anxiety	4 (26.7)	2 (13.3)	
	Moderate anxiety	6 (40.0)	3 (20.0)	
	A lot of anxiety	5 (33.3)	8 (53.3)	χ^2=3.921
	Severe anxiety	0 (0)	2 (13.3)	p= 0.280
	Median (Min-Max	4 (2-6)	6 (2-8)	
	Mean±SD	4.13±1.60	5.33±1.80	
At the 30th min during the music intervention	Mild anxiety	8 (53.3)	2 (13.3)	
	Moderate anxiety	6 (40.0)	3 (20.0)	
	A lot of anxiety	1 (6.7)	8 (53.3)	χ^2=11.506
	Severe anxiety	0 (0)	2 (13.3)	**p= 0.005****
	Median (Min-Max	2 (2-6)	6 (2-8)	
	Mean±SD	3.07±1.28	5.33±1.80	
		χ^2=37,235	χ^2=3,000	
	******p**	**0.001****	0.392	

Student **t-Test; **Paired Samples **t**-Test; ***Fisher-Freeman-Halton Test; ****Friedman*

DISCUSSION

No differences were detected between the groups in terms of age, gender, and education level, and it was found that both groups had similar characteristics (p>0.05). Also, no statistically significant differences were detected between the duration of the groups in the intensive care unit (p>0.05), a statistically significant difference was found in the duration of being attached to the ventilator (p<0.05). Diastolic blood pressure measurement results between the experimental and control groups before the intervention (p=0.004) and at the 30th minute of the intervention (p=0.044) were found to be statistically significantly higher than the control group (p<0.05). In the further analysis made to uncover the difference between diastolic blood pressure measurement results, the change in diastolic blood pressure measurement results was found to be statistically significant (p<0.01). Although the change in the measurement results at the 30th minute of the intervention when compared to the pre-intervention was not significant (p=0.067; p>0.05); The decrease in the measurement results at the 60th minute of the intervention (p=0.002) and half an hour (90 minutes) after the intervention (p=0.001) was found to be significant (p<0.01). In the control group; The change in diastolic blood pressure measurement results was not found to be statistically significant (p=0.167; p>0.05). It was found that the diastolic blood pressure and heart rate of the experimental group were lower than the control group at the 60th minute and half an hour (90th minute) after the music intervention (Table 2). It was found that the effect continues during and after listening to music, and it can be argued that listening to music reduces blood pressure and heart rate. Similarly, Chlan et al. (2001) reported that music applied to patients on mechanical ventilators causes a decrease in blood pressure and heart rate of patients.[18] In some studies on the subject, it was found that the blood pressure and pulse rate values of the experimental group patients decreased in all values measured during the music intervention, but increased after the music intervention ended.[5,6,22] In another study by Akın (2007), it was found that

music intervention decreased blood pressure but did not cause a change in heart rate.[12] In the study conducted by Wong et al. (2001), similar to these studies, a decrease in diastolic blood pressure values of the patients was found as a result of music therapy applied to the intervention group, but no statistically significant difference was found between the diastolic blood pressure values of the patients in the intervention and control groups. [7]

In the present study, it was found that the heart rate was lower in the experimental group than in the control group at the 60th minute (p= 0.028) of the music intervention and 30 minutes after the end of the intervention (p= 0.027). It was found in the study conducted by Wong et al. (2001) that the heart rate in the experimental group was lower than the control group during seven different periods during the music intervention.[7] In the study by Angela et al. (2005), it was reported that the heart rate values of the patients in the intervention group were measured 5 times during the 30-minute music therapy period, and heart rate values decreased in all the measured values.[5] As a result of the evaluation of heart rate values with four different measurement results in our study, the decrease in measurement results half an hour after music therapy (90th min) compared to before (0 min) music therapy was found to be significant (p=0.04; p<0.05). The results of the present study are partially compatible with the results of other studies. Our findings show that the effect of music is not short-lived and continues after the music performance is over.

In many studies in the literature, it was reported that listening to music causes a decrease in the respiratory rate of patients.[6.7] However, no statistically significant differences were detected between the experimental and control groups in terms of respiratory rate and oxygen saturation of the patients in the study (p>0.05) (see Table 2). This result is consistent with Akın's (2007) study result and can be explained by the fact that the respiratory frequency adjusted in ventilation ensures that there is no change in the respiratory rate of the patients.[12] Mechanical ventilation is the mechanical provision of adequate ventilation and reduction of respiratory work in order to maintain gas exchange, which is the main task of the respiratory system, under optimal conditions. Mechanical ventilation is performed in two ways, assisted and controlled, according to whether ventilation is maintained partially or completely artificially. Controlled ventilation is the maintenance of breathing completely artificially, i.e. with a ventilation device, in patients without spontaneous breathing. Therefore, respiratory rate and oxygen saturation are regulated by a ventilator. Therefore, there was no significant change in the respiratory rate and oxygen saturation of the patients after music application.

It was predicted in another hypothesis of the study that music listening would show effects differently in terms of STAI and FAS scores. In this context, no statistically significant differences were detected in the level of anxiety before the music intervention (p=0.207), at the 30th minute of the intervention (p=0.795), and at the 60th minute of the intervention (p=0.280) in the groups (p>0.05). When compared to the patients in the control group, the facial anxiety score levels (FAS) at the 30th minute (90th minute) after the intervention were found to be statistically and significantly lower than the control group, which shows that music has positive effects on patients to reduce their anxiety (p=0.005; p<0.01). In a previous study examining the effects of listening to music on anxiety and pain in ICU patients, it was reported that there was a statistically significant decrease in the facial scale anxiety scores of the patients after listening to music.[10,26] Also, in another study conducted by Lee et al. (2004) investigating the impacts of music and therapy on anxiety with patients on mechanical ventilation support, it was stated that facial anxiety scores of patients decreased after music.[30] Also, it was determined in the study that the STAI scores of the individuals in the experimental and control groups were 61.73±7.21 in the experimental group before the music intervention, although it decreased to 43.73±8.43 after the music intervention (p=0.001; p<0.01). On the other hand, no difference was detected in the STAI scores of the control group in the same period (p=0.378; p>0.05). In line with this result, it can be argued that listening to music reduces patients' anxiety scores, and this finding is similar to the literature data.[5,6,7,8,18,22,23]

This study has several limitations. These limitations are the small number of patients included in the sample, the fact that it was conducted in a single center and that the music intervention was applied only once. The first limitation is that the sample is not large enough to test some hypotheses even though power analysis was performed in the study. For this reason, it is recommended to work with a larger sample in future studies. The second limitation is that's: the study was conducted in a single center. Intensive care units are classified as level 1, level 2 and level 3 according to their location, diagnosis and treatment facilities. The first

level is a center affiliated to a small hospital and the second level is intensive care units affiliated to a large general hospital. The third level is the units where clinical and scientific studies are carried out by a professional healthcare team. They are services where there are specialist doctors serving 24 hours a day, 24-hour laboratory and radiology services, and multidisciplinary work equipped with advanced technology [12]. The intensive care unit in which the study was conducted is the second level, and it is recommended that the study be applied and its effectiveness evaluated in patients receiving treatment in the first and third level intensive care units. In the sample in which the study was conducted, patients listened to structured classical Turkish music in the application. In future studies, it is recommended that semi-structured music applications consisting of different music genres should be realized with patient selection. Since the effect of music on state anxiety was examined in this study, the music application was performed only once. In future studies, it is recommended to examine the effect of structured music performances on trait anxiety of patients from admission to the clinic until discharge.

CONCLUSION

The present study provides results for the use of music as a therapeutic intervention for reducing anxiety. The benefits of preventing physiological reactions to anxiety were demonstrated, particularly in those patients who had received mechanical ventilation. For this reason, music can provide a simple, safe, and effective method of reducing potentially harmful physiological and psychological responses arising from anxiety. In clinical studies conducted to date, the effect of music therapy on reducing anxiety in intensive care patients is well known. At the same time, music reduces anxiety, eliminating the need for sedation and allowing the patient to recover faster. In this study, the effect of music on anxiety management in intensive care patients receiving mechanical ventilation treatment was demonstrated. In addition, music application is more advantageous than other pharmacologic treatments in terms of side effects, risk and cost. Therefore, it is recommended that music applications should be clinically applied to patients by healthcare professionals trained in this field. As shown by the results of this study, music application can be used as an effective complementary application to manage anxiety in patients receiving mechanical ventilation.

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ORIGINAL RESEARCH

Effects of Resveratrol, Caffeic Acid Phenethyl Ester and Silibinin on Isolated Human Umbilical Artery

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Abstract

Objective: The aim of this study was to compare the vasoactive effects of resveratrol, CAPE and silibinin on the basal tone and serotonin (5-HT)-induced contractile responses of isolated human umbilical arteries.

Material-Method: This study was approved by the Non-Drug and Medical Device Research Ethics Committee (Decision No: 2022/3994). The study used umbilical cord samples separated as medical waste in the Department of Gynaecology and Obstetrics. The umbilical cords taken from the middle 1/3 part were brought to the laboratory in cold Krebs-Henseleit Solution (KHS). The arteries isolated from the umbilical cords were cleaned from the surrounding tissues and spirally cut into 2-3x10 mm strips. The strips were suspended in isolated tissue baths filled with 10 ml KHS continuously bubbled with a mixture of 95% O_2 and 5% CO_2 at 37°C. At the beginning of the experiment, the strips were stretched to an initial tension of 1.5 g and allowed to equilibrate for 60 min in KHS, which was changed every 15 min. At the end of the rest period, responses to the applied agents were recorded isometrically (Commat, Ankara, TURKEY) using a transducer (BIOPAC MP36, California, USA). The first group investigated the effects of resveratrol, CAPE and silibinin on basal tonus in the umbilical artery strips. After control contraction with 10^{-6} M 5-HT, the tissues were washed until resting tone was re-established. Concentration-response curves for resveratrol (10^{-9} M -10^{-4} M), CAPE (10^{-9} M -10^{-4} M) and silibinin (10^{-9} M -10^{-4} M) were obtained by cumulative addition to the organ bath. To evaluate the effects of resveratrol, CAPE and silibinin on 5-HT-induced contraction, the strips were contracted with 10^{-6} M 5-HT. After maximal contractile response was achieved, increasing concentrations of resveratrol (10^{-9} M -10^{-4} M), CAPE (10^{-9} M -10^{-4} M) or silibinin (10^{-9} M -10^{-4} M) were added cumulatively to the bath.

Results: Resveratrol, CAPE and silibinin did not affect the basal tone of umbilical arteries. 5-HT is a potent vasoconstrictor endogenous agent in umbilical arteries. Antioxidants used in the study produced relaxation responses in arteries precontracted with 5-HT. When the sensitivity of tissues to these agents and their maximum relaxant effects were evaluated together, silibinin was found to be more effective than the others.

Conclusion: The use of antioxidants to support or treat complications due to oxidative stress in pregnant women is being investigated. The vasoactive effects of exogenous and endogenous agents are important in regulating umbilical vascular tone. Resveratrol, CAPE and silibinin are polyphenol-derived natural antioxidants that have potential use in pregnant women. Our study investigated the vasoactive effects of these agents on umbilical arteries.

Keywords: CAPE, In Vitro, Resveratrol, Silibinin, Umbilical Artery

INTRODUCTION

Increased placental oxidative stress is an effective factor in the development of complications such as preeclampsia, fetal growth restriction and gestational diabetes in pregnant women. Antioxidant supplementation has been recommended to prevent the development of these complications by reducing oxidative stress in pregnant women. Resveratrol, caffeic acid phenethyl ester and silibinin are polyphenol derivative natural antioxidants. Phenolic compounds have been reported to neutralize reactive oxygen species and have therapeutic effects in diseases associated with oxidative damage, such as inflammatory disorders and neurodegenerative diseases. In clinical studies conducted in pregnant women, the therapeutic effects of resveratrol on inflammation, preeclampsia and gestational diabetes

have been shown.[1] Studies are being conducted on the use of CAPE and silibinin for the treatment or support of oxidative stress-related disorders in pregnant women.

The umbilical cord is the structure that connects the fetus to the placenta. There is no autonomic innervation of the umbilical vessels. In the regulation of umbilical placental circulation, endogenous vasoactive mediators such as 5-HT, histamine and PGF are effective. 5-HT is the most potent vasoconstrictor mediator in umbilical arteries.[2] Furthermore, increased plasma free 5-HT levels and vascular sensitivity to 5-HT have been reported in pregnancy-related complications such as preeclampsia.[3, 4]

Resveratrol, caffeic acid phenethyl ester, and silibinin have been shown to have vasoactive effects. However, there is not enough information about the effects of these drugs, which can be used in pregnant women, on the umbilical vessels. The aim of our study was to compare the vasoactive effects of resveratrol, CAPE and silibinin on the basal tone and serotonin induced contractile responses of isolated human umbilical arteries.

MATERIALS AND METHODS

General

This study was approved by the Non-Drug and Medical Device Research Ethics Committee (Decision No: 2022/ 3994). In the study, umbilical cord samples separated as medical waste in the Department of Gynaecology and Obstetrics were used. The umbilical cords taken from the middle 1/3 part were brought to the laboratory in cold KHS. The arteries isolated from the umbilical cords were cleaned from the surrounding tissues and spirally cut into 2-3x10 mm strips. The strips were suspended in isolated tissue baths filled with 10 ml KHS continuously bubbled with a mixture of 95% O_2 and 5% CO_2 at 37°C. At the beginning of the experiment, the strips were stretched to an initial tension of 1.5 g and allowed to equilibrate for 60 min in KHS, which was changed every 15 min. At the end of the rest period, responses to the applied agents were recorded isometrically (Commat, Ankara, TURKEY) using a transducer (BIOPAC MP36, California USA).

Experimental procedure

Effects of resveratrol, CAPE and silibinin on basal tonus in the umbilical artery strips were investigated in first group. After control contraction with 10^{-6} M 5-HT, the tissues were washed until resting tone was re-established. Concentration-response curves for resveratrol (10^{-9} M -10^{-4} M), CAPE (10^{-9} M -10^{-4} M) and silibinin (10^{-9} M -10^{-4} M) were obtained by cumulative addition to the organ bath. To evaluate the effects of resveratrol, CAPE and silibinin on 5-HT-induced contraction, the strips were contracted with 10^{-6} M 5-HT. After maximal contractile response was achieved, increasing concentrations of resveratrol (10^{-9} M -10^{-4} M), CAPE (10^{-9} M -10^{-4} M) or silibinin (10^{-9} M -10^{-4} M) were added cumulatively to the bath.

Drugs and solutions

5-HT (Sigma); Resveratrol (Sigma); CAPE (Sigma); Silibinin (Sigma). Krebs-Henseleit Solution [mM]: NaCl 118.3; KCl 4.69; KH2PO4 1.18; CaCl2 1.25; MgSO4 1.17; NaHCO3 25.0; Glucose 11.1. Serotonin was dissolved in distilled water, CAPE in 70% alcohol, resveratrol in DMSO and silibinin in a mixture of DMSO and distilled water. The solvent mixtures used in preliminary experiments were found to be ineffective.

Statistical analysis

Responses to the agents applied in the study were evaluated as the percentage (%) of the maximum contraction response obtained with 10^{-6} M 5-HT. The data were expressed as mean±standard deviation (SD). Analyses were conducted on a computer using the SPSS 29.0 (Armonk, NY: IBM Corp.) package program. Maximum relaxation (E_{max}) and pD_2 (negative log value of molar concentration producing contraction by 50%) values calculated from the concentration-response curves obtained with resveratrol, CAPE and silibinin were compared. The Shapiro-Wilk's test was applied to the E_{max} and pD_2 values obtained from all groups to check that assumptions of normality were met for continuous numerical data. According to outcomes of the Shapiro-Wilk's test, it was seen that all the data, which were obtained from groups, were normally distributed. So, one-way ANOVA test was used to compare the E_{max} and pD_2 values for the three groups (resveratrol, CAPE, silibinin) followed by the post hoc procedure Tukey HSD. Results were considered statistically significant if $p<0.05$ in all analyzes.

RESULTS

5-HT (10^{-6} M) produced sustained contraction in umbilical artery strips. These contractions were reproducible and time-dependent changes were not observed. Resveratrol (10^{-9} M -10^{-4} M), CAPE (10^{-9} M -10^{-4} M) and silibinin (10^{-9} M -10^{-4} M) added cumulatively to the bath did not affect the basal tone of the tissues. Relaxing effects of resveratrol, CAPE

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and silibinin on the umbilical cord strips were studied in the other group. The supplements used in the study produced dose-dependent relaxation in 5-HT-contracted umbilical artery strips. The maximum relaxant effect of silibinin was higher than the other two drugs in Figure 1 ($p<0.05$). The E_{max} value of resveratrol was also higher than that of CAPE in Figure 1($p<0.05$).

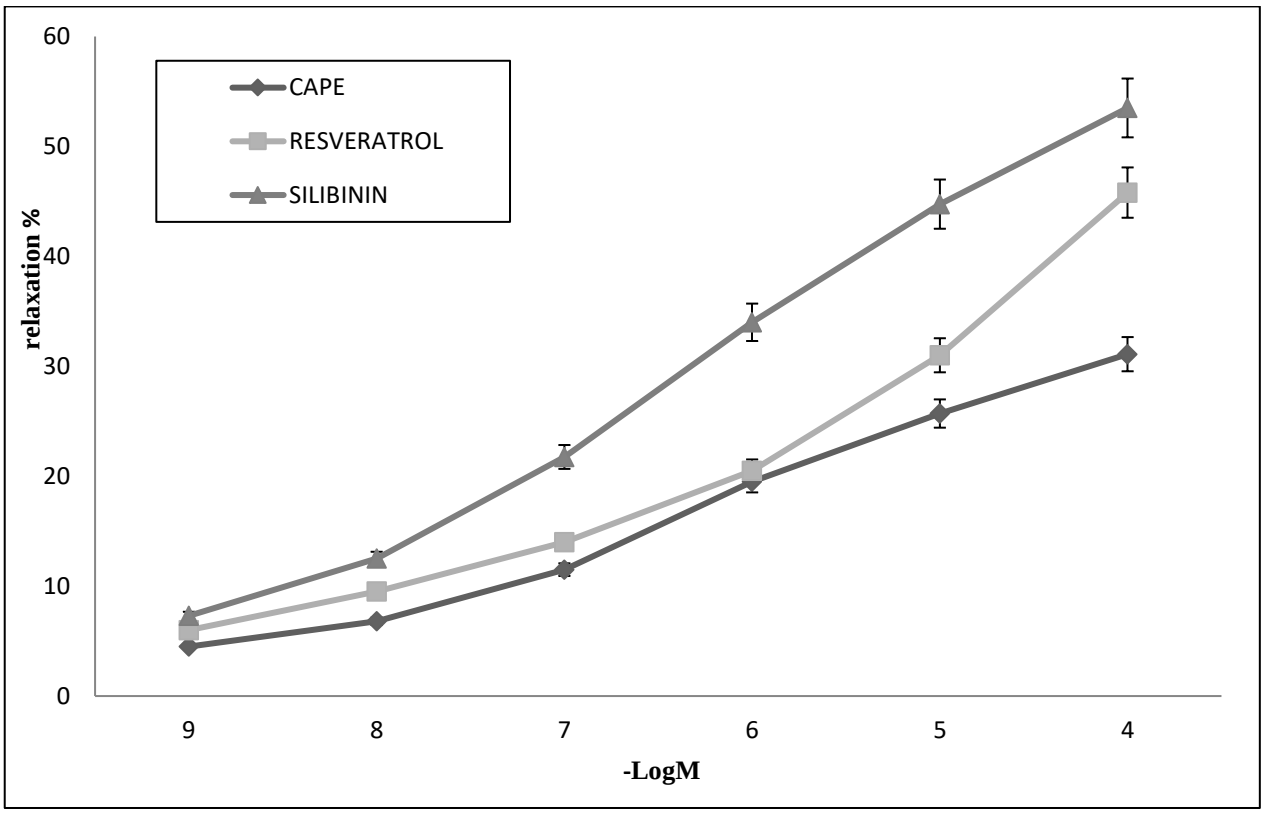

Figure 1. Concentration-response curves of CAPE, resveratrol and silibinin in human umbilical artery contracted with 5-HT (10^{-6} M)

: Relaxation responses to resveratrol were calculated as % of contraction responses obtained with 5-HT (10^{-6} M) and the results were expressed as mean±standard deviation (n=8).

: Relaxation responses to CAPE were calculated as % of contraction responses obtained with 5-HT (10^{-6} M) and the results were expressed as mean±standard deviation (n=8).

: Relaxation responses to silibinin were calculated as % of contraction responses obtained with 5-HT (10^{-6} M) and the results were expressed as mean±standard deviation (n=8).

Our study evaluated the potency of these drugs in the umbilical artery. The pD_2 value of resveratrol was higher than other drugs ($p<0.05$). No significant difference was found between the potencies of CAPE and silibinin ($p>0.05$). E_{max} and pD_2 values calculated for resveratrol, CAPE and silibinin are summarised in Table 1.

Current study showed that the antioxidants, resveratrol, CAPE and silibinin produced significant relaxation in umbilical arteries precontracted with serotonin.

Table 1. Maximum relaxation (E_{max}) found for resveratrol, CAPE and silibinin in human umbilical artery -$logEC_{50}$ (pD_2) values

	E_{max}	pD_2
Resveratrol	45.88±4.12*	5.68±0.256**
CAPE	31.13±3.13	6.56±0.230
Silibinin	54.75±3.69#	6.46±0.087

*$p<0.05$ according to the E_{max} value obtained with CAPE
#$p<0.05$ compared to the E_{max} value obtained with CAPE and resveratrol
**$p<0.05$ according to pD_2 value obtained with CAPE and silibinin
E_{max} values were calculated as % of 10^{-6} M 5-HT contractions. Expressed as mean±standard deviation (n=8).

DISCUSSION

In this study, resveratrol, CAPE and silibinin did not affect the basal tone of the umbilical arteries, but significantly reduced 5-HT-dependent contractile responses. The maximum relaxant effect of silibinin was significantly higher than that of the other two agents. Resveratrol produced more relaxation than CAPE. The potencies of silibinin and CAPE were found to be higher than resveratrol.

The umbilical vessels mediate the transport of oxygen and nutrients between the mother and the foetus. Umbilical blood flow is important for fetal development and health. These vessels do not have autonomic innervation. Therefore, endogenous or exogenous substances affecting umbilical artery tone are essential for regulating umbilical-placental circulation and the development of the fetus. Resveratrol, CAPE, and silibinin, which are known to have vasoactive effects, are widely used by the public due to their antioxidant effects. Clinical and experimental studies are being conducted on the use of these substances in oxidative stress-related complications in pregnant women.

Resveratrol supplementation has been suggested to have potential in preventing and/or treating oxidative stress-related complications in pregnant women.[1] In one study, it was found that supplementation of the maternal diet with resveratrol in hypoxic pregnancies prevented fetal death.[5] A rodent study found that resveratrol prevented embryonic oxidative stress and apoptosis and improved glucose and lipid profiles in diabetic mothers. Researchers have suggested that resveratrol may be helpful in diabetic pregnant women.[6] In a randomised, double-blind, placebo-controlled trial of 400 patients with pre-eclampsia carrying a singleton pregnancy, aged 21 to 32 years, patients were divided into two groups: the first group received nifedipine and resveratrol, and the second group received nifedipine and placebo. Compared to the nifedipine and placebo group, the time to control blood pressure was significantly reduced in the nifedipine and resveratrol group. In addition, the time between hypertensive crises was longer in the nifedipine-resveratrol group than in the control group. No side effects were observed when the mothers and babies were examined after delivery. It was suggested that resveratrol could be complementary to nifedipine treatment.[7] According to the European Food Safety Authority EFSA data in 2016, the safe dose of resveratrol is 150 mg per day.[8] Relaxant effects of resveratrol have been demonstrated in human saphenous vein and mammary artery.[9] Similarly, in this study, resveratrol induced relaxation in umbilical artery strips. The maximum relaxant effect and potency of resveratrol was lower than that of silibinin.

CAPE is the active component of propolis. In the study by Usman et al.[10], propolis showed a protective effect against oxidative stress in diabetic pregnant rats. In another study, propolis was found to have a maternal protective effect in pregnant mice.[11] When compared with the other agents used in the study, the maximal relaxant effect of CAPE on the umbilical artery was found to be significantly less than that of resveratrol and silibinin. However, its potency was higher than that of resveratrol and similar to the potency of silibinin. In our previous study, CAPE relaxed umbilical arteries contracted by endothelin-1 and prostaglandin F2α more than in this study.[12] In a study conducted in 5-HT-contracted uterine tissue, CAPE was found to cause almost complete relaxation.[13] These results show that the vasodilator effect of CAPE varies depending on the contracting agent and the tissue used.

Silimarin from the plant Silybum marianum and its active component silibinin are known to have antioxidant and hepatoprotective effects. Silibinin is included in the antidote list of the National Poison Advisory Centre as an antidote for mushroom poisoning.[14] The effects of treatment with silimarin and silibinin have been studied in pregnant women and experimental animals. In a randomised clinical trial, silimarin treatment was reported to improve liver function in women with pre-eclampsia.[15] In another clinical trial, silimarin treatment of 150 mg drug twice daily in pregnant women was shown to cause no abnormalities or other adverse effects.[16] In blood mononuclear cells from women with pre-eclampsia, silibinin was found to have a potent anti-inflammatory effect by reducing inflammatory cytokines.[17] In a study in rats with a pre-eclampsia model, silibinin treatment reduced blood pressure and proteinuria and had a protective effect on liver damage.[18] There are few studies on the effects of silibinin on vascular preparations in vitro. In one study, the relaxant effect of silibinin was observed in rat aortic rings contracted with phenylephrine.[19] In our study, silibinin produced greater relaxation than CAPE and resveratrol in the umbilical artery contracted with 5-HT. In addition to causing more relaxation in the umbilical artery than other agents, the sensitivity of tissues to silibinin was found to be high.

CONCLUSION

The use of antioxidants for support or treatment of complications due to oxidative stress in pregnant women is being investigated. The vasoactive effects of exogenous and endogenous agents are essential in regulating umbilical vascular tone. Resveratrol, CAPE and silibinin are polyphenol-derived natural antioxidants that have potential use in pregnant women. In our study, the vasoactive effects of these agents on umbilical arteries were investigated. Resveratrol, CAPE and silibinin did not affect the basal tone of umbilical arteries. 5-HT is a potent vasoconstrictor endogenous agent in umbilical arteries. Antioxidants used in the study produced relaxation responses in arteries precontracted with 5-HT. When the sensitivity of tissues to these agents and their maximum relaxant effects were evaluated together, silibinin was found to be more effective than the others.

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ORIGINAL RESEARCH

Initial Safety and Physiological Impacts of Propolis Inhalation as a Key Component of Apiair Therapy

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Abstract

Objective: Interest in beehive air inhalation therapy, known as Apiair, has grown significantly in recent years. However, clinical studies examining its effects remain limited. Propolis, a key component found in hive air, has been identified as playing an important role in potential therapeutic benefits. This study aims to evaluate the initial safety and physiological impacts of propolis-water extract inhalation in healthy individuals.

Materials and Methods: A total of 20 healthy volunteers were randomly assigned to one of two groups in a double-blind trial. The first group inhaled a saline solution, while the second group received a propolis-water extract. All participants underwent assessments before and after inhalation, including pulmonary function testing, vital signs monitoring, venous blood gas analysis, and electrocardiogram (ECG) recording.

Results: Physiological parameters—including pulmonary function, vital signs, blood gas values, and ECG measurements—remained within clinically normal limits in both groups. No adverse events were observed during the study period.

Conclusion: Propolis-water extract inhalation was found to be safe in healthy individuals. These findings support the safety of propolis inhalation and provide a foundation for further research into its therapeutic potential in respiratory health, contributing to a broader understanding of Apiair applications. Further research is necessary to fully evaluate the long-term efficacy and safety of propolis inhalation.

Keywords: Apiair, Beehive Air, Propolis, Inhalation, Safety

INTRODUCTION

The World Health Organization (WHO) developed a strategy on traditional medicine under the title of the "2014–2023 Traditional Medicine Strategy." A primary goal of this strategy is to facilitate the integration of traditional medicine into national healthcare systems, particularly into primary healthcare services [1].

In Turkiye, the Regulation on Traditional and Complementary Medicine Practices came into force in 2014. Within this framework, apitherapy is defined as the use of bees and bee products to provide protective effects on the human body and as a complementary method for the treatment of certain diseases [2].

One of the application areas of apitherapy is "apiair," also known as "hive air inhalation". Apiair refers to a practice that aims to utilize the air inside the beehive. The harmonious composition of various bee products such as royal jelly, propolis, honey, and pollen found inside the hive contains many compounds. The core concept of the Apiair system relies on inhaling volatile active compounds derived from bee products within the hive[3].

Apiair therapy is considered a potential

complementary method in the treatment of various respiratory tract diseases. This therapeutic approach is widely used, particularly in Germany, Hungary, Slovenia, and Austria [4].

The beehive contains components such as honey, pollen, propolis, beeswax, etc. Therefore, the inhaled hive air is rich in volatile compounds, mainly fatty acids and phenolic acids. Compounds from honey, beeswax, pollen, and propolis have been identified in hive air, with approximately 56 volatile compounds, most of which are short-chain fatty acids [5]. Bee products, especially propolis, exhibit strong antimicrobial, antiviral, antitumor, and anti-inflammatory bioactivities [6].

Propolis is a natural substance produced by honeybees from resins they collect[7]. Honeybees gather these resins from trees such as pine, oak, birch, eucalyptus, poplar, chestnut, and some herbaceous plants [8]. Bees use propolis within the hive for various purposes, including preventing microbial growth, coating the hive walls, sealing cracks and fissures, maintaining the hive's humidity and temperature, and mummifying insects or animals too large to remove from the hive, thus preventing decomposition [7].

Natural composition of propolis generally includes resin and plant balsam, beeswax, essential and aromatic oils, and pollen and various organic substances [9]. Honeybees collect propolis by scraping protective resins from flowers and buds with their mandibles [10,11]. Literature reports indicate that over 300 compounds have been identified in propolis samples from various geographical regions [12–15].

The oral use of propolis has been reported to have beneficial effects in the treatment of certain respiratory diseases, as reported in previous studies[16–19]. However, the efficacy of oral propolis administration in respiratory diseases has been evaluated in only a limited number of studies[19]. Furthermore, none of these investigations have explored the effects of propolis inhalation—a potentially more direct method for targeting respiratory function—through clinical trials.

The purpose of this study is to investigate the initial safety and physiological impacts of propolis inhalation on respiratory functions in healthy individuals, with a particular focus on understanding how this method compares to other forms of propolis administration.

MATERIALS AND METHODS

Participant recruitment

Participants were recruited from the healthy individuals working at the Esenler Health Practice and Research Center of Istanbul Medipol University Hospital. An announcement was made to recruit a group of healthy volunteers from the hospital's staff. The eligibility of participants was evaluated based on specific inclusion and exclusion criteria in coordination with a pulmonologist.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: participants must be between the ages of 18 and 45 years, have a Body Mass Index (BMI) ranging from 18.5 to 24.9 kg/m², and exhibit normal pulmonary function test (PFT) values. Additionally, all participants were required to provide written informed consent.

The exclusion criteria included individuals with a history of febrile illness prior to the study, any history of pulmonary disease, recurrent bronchitis, non-allergic drug reactions affecting the bronchial or pulmonary system, or multiple drug allergies. Smoking was also considered an exclusion factor for this study.

The evaluation criteria and reference value ranges used in the study are presented in Table 1.

Table 1. Reference Ranges Used in Evaluation Criteria.

Evaluation Criteria	Reference Value
Venous blood gas measurement [20]	pH 7.32–7.42, HCO_3^- 23 – 27 mmol/L, pCO_2 36–49 mmHg (female), pCO_2 39–52 mmHg (male) and pO_2 43–68 mmHg HCO_3: 24-28 mmol/L
Pulmonary Function Test (Spirometry) [21]	FVC, FEV1, FEV1/FVC, PEF values should be 70-100% of the expected range
Electrocardiogram (ECG) Measurement [22,23]	Heart rhythm should be regular, and all P-wave values should have the same morphological characteristics
Body Mass Index (BMI) [24]	18.5-24.9 kg/m²
Heart Rate [25]	60-100 beats/min
Blood Pressure [25]	Systolic blood pressure: 120-130 mmHg, Diastolic blood pressure: 70-90 mmHg
Body Temperature [26]	36.5°C ± 5°C
Respiratory Rate [26]	12-20 breaths/min

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Randomization and grouping

The study was carried out as a double-blind trial. To ensure proper administration of either propolis or saline inhalation, nurses from the hospital's emergency department randomly assigned volunteers to use inhaler mask sets containing either propolis or saline solution, delivered via a nebulizer. The number on the medication chamber of the inhaler mask set was recorded on the participant's case report form. Neither the nurses nor the participants were aware of the contents of the numbered medication chambers, ensuring double blinding. Volunteers inhaling the propolis solution were assigned to the experimental group, while those inhaling the saline solution were assigned to the control group (Figure 1).

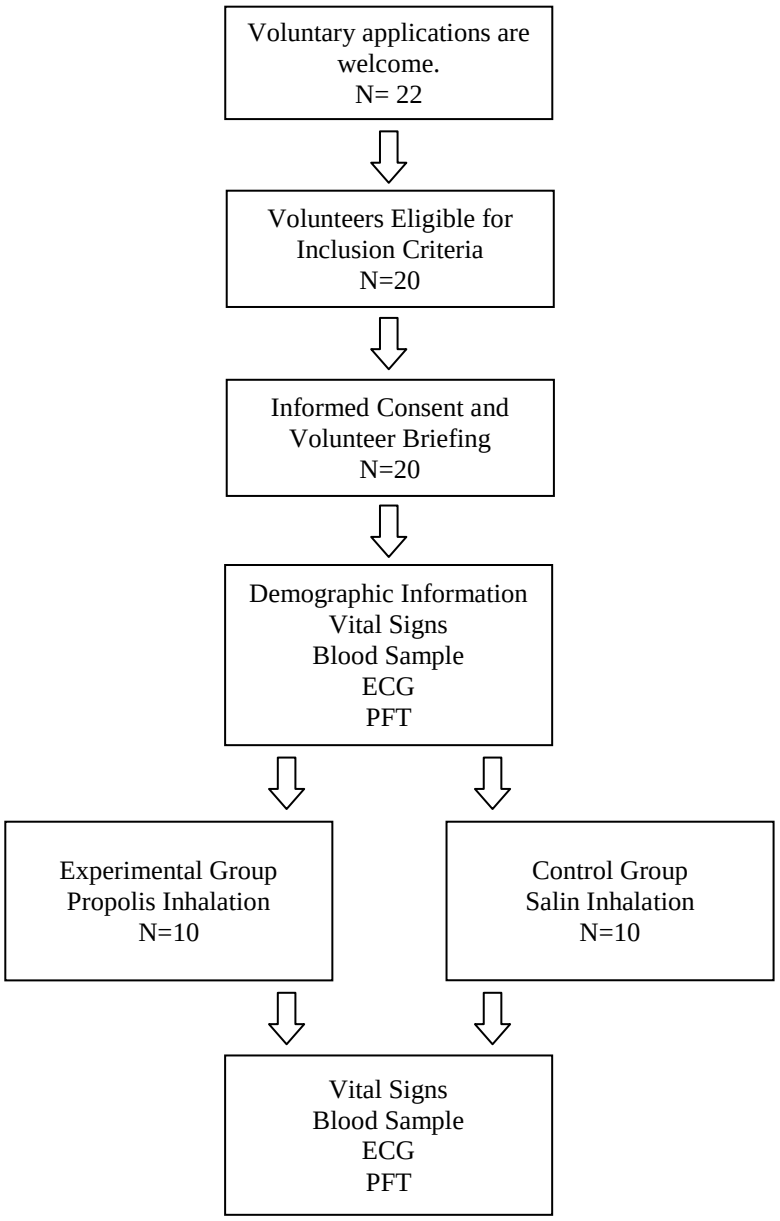

Figure 1. Trial flow-chart.

Chemical composition of propolis by HPLC-DAD

A 10% water-based organic propolis solution was provided by the company, Fanus Food and Organic Products Industry and Trade Ltd. Co. Figure 2 presents the HPLC-DAD chromatograms [27].

Table 2 presents the qualitative and quantitative analysis of the identified compounds in the water-based organic propolis. The amounts of caffeoylquinic acids in propolis are expressed as mg

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of polyphenol or caffeoylquinic acid in the propolis extract. HPLC-DAD analysis revealed that the most abundant compound in propolis was caffeic acid, with a concentration of 204.00 mg/mL Additionally, caffeic acid and trans-cinnamic acid were identified as common compounds in the propolis. Caffeic acid was found in much higher amounts compared to other compounds in the propolis [27].

The HPLC-DAD method was validated by performing replicate analyses and confirming the reproducibility of the results. The linearity and precision of the HPLC method were assessed with multiple samples.

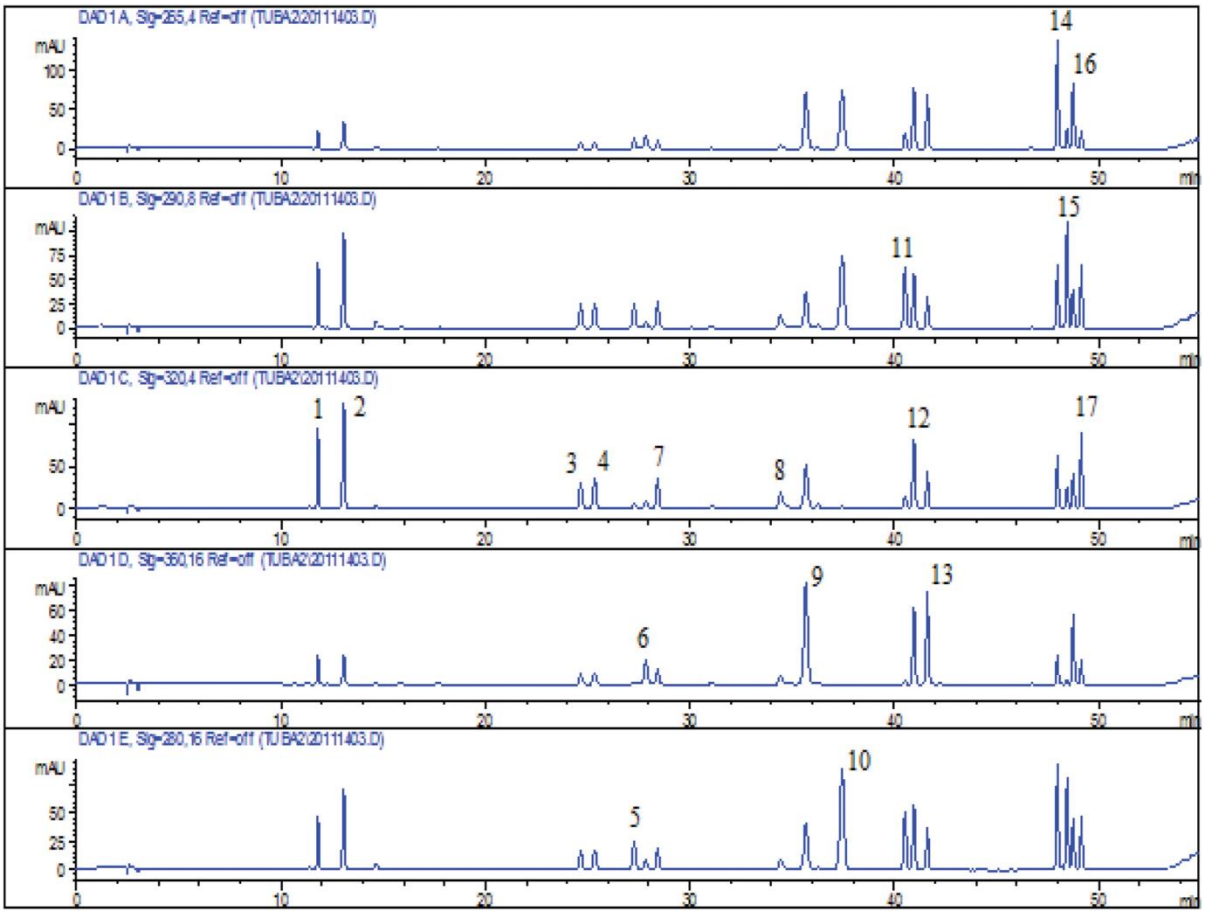

Figure 2. HPLC-DAD chromatograms of a standard solution recorded at wavelengths of 265, 290, 320, 360, and 280 nm [27].

Table 2. HPLC-DAD analysis of water extract of propolis [27].

Number	Compounds	Wavelength (nm)	Retention time (RT)	Concentration (mg/mL)
1	*Chlorogenic acid*	320	*12.484*	*10.20*
2	*Caffeic acid*	320	*13.954*	*204.00*
8	*3,4,5-tri-O-caffeoylquinic acid*	320	*39.694*	*7.75*
11	*Naringenin*	290	*41.309*	*28.90*

Preparation of inhalation products

For the control group, 4 mL of saline solution was added to the medication chamber of the inhalation device using a syringe. The content of the medication chamber was sealed with adhesive tape to prevent visibility, and odd numbers were written on the chamber. For the experimental group, 3 mL of saline solution and 1 mL of 10% water-based organic propolis solution were added to the medication chamber of the inhaler mask set using a syringe. The medication chamber was sealed with adhesive tape to prevent visibility, and even numbers were written on the chamber. The number and content information were documented in an external file.

Pre-inhalation assessment

Volunteers included in the study arrived at the emergency department 30 minutes before inhalation. The informed consent form was signed by the participants, demographic information was recorded by the emergency department nurse, vital signs were measured, an ECG was performed, and a venous blood sample was taken. Then, pulmonary function tests were performed by a pulmonologist using a Spirolab III S/N manual device, and the WinspiroPRO 8.2.0 - Mod.C11 version was used for programming the measurements. Each volunteer was evaluated individually. To obtain expected values, parameters such as age, height, weight, gender, ethnicity, smoking status, and disease groups were entered into the program. Each volunteer was provided with a personal mouthpiece and asked to sit in a chair. Volunteers were instructed to place the mouthpiece between their teeth, take a deep breath, and then exhale forcefully. Measurements were repeated up to three times at the discretion of the specialist based on the expected values.

Application of inhalation protocols

In the experimental group, 3 mL of saline solution and 1 mL of 10% water-based propolis extract, totaling 4 mL of solution, were added to the medication chamber of the inhaler mask set. The chamber was sealed with adhesive tape to obscure the color of the solution. The Omron Compressor Nebulizer (CompAir NE-C28-P) was used for inhalation. Volunteers inhaled the solution for an average of 7 minutes. In the control group, saline solutions were also sealed with adhesive tape to hide the solution's color. The Omron Compressor Nebulizer (CompAir NE-C28-P) was used, and volunteers inhaled for an average of 7 minutes.

Post-inhalation evaluation

After inhalation, volunteers' vital signs were recorded on the case report form by the nurse, an ECG was performed, and a venous blood sample was taken. For pulmonary function testing, the same pulmonologist used the Spirolab III S/N manual device, with measurements programmed using the WinspiroPRO 8.2.0 - Mod.C11 version. Each volunteer was evaluated individually. To obtain expected values, parameters such as age, height, weight, gender, ethnicity, smoking status, and disease groups were entered into the program. Each volunteer was provided with a personal mouthpiece and asked to sit in a chair. Volunteers were instructed to place the mouthpiece between their teeth, take a deep breath, and then exhale forcefully. Measurements were repeated up to three times at the discretion of the specialist, based on expected value ratios.

Statistical analysis

The data obtained in the study were analyzed using the SPSS (Statistical Package for Social Sciences) Windows 22.0 software. Descriptive statistical methods such as number, percentage, mean, and standard deviation were used to evaluate the data. Differences in the proportions of categorical variables between independent groups were analyzed using the Chi-square test. Continuous quantitative variables were compared between two independent groups using the independent samples t-test, while within-group comparisons were conducted using the paired samples t-test.

Ethical approval

This study was conducted following ethical guidelines, with approval from the Istanbul Medipol University Traditional and Complementary Medicine Clinical Research Ethics Committee, dated 19/08/2021, and numbered E-95961207-604.01.01-3898, in accordance with the Declaration of Helsinki.

RESULTS

In the study, 20 healthy individuals were included as participants. No statistically significant difference was observed in gender distribution across the groups ($p=0.763$). The age and BMI scores of the volunteers did not show significant differences between the groups ($p>0.05$) (Table 3).

The pre-inhalation and post-inhalation respiratory rate measurements did not show a significant difference between the groups ($p>0.05$). In the control group, the increase in respiratory rate from the pre-inhalation value ($\bar{x}=19.100$) to the post-inhalation value ($\bar{x}=19.400$) was not found to be significant ($p>0.05$). In the experimental group, however, the increase in respiratory rate from the pre-inhalation value ($\bar{x}=18.800$) to the post-inhalation value ($\bar{x}=19.500$) was found to be significant ($p=0.045$) (Table 4).

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Table 3. Sociodemographic characteristics of the participants (n=20).

		Control Group		Experimental Group		Total		p*
		n	%	n	%	n	%	
Gender	**Male**	1	10.0	1	10.0	2	10.0	X^2=0.000
	Female	9	90.0	9	90.0	18	90.0	p=0.763
		Mean	**SD**	**Mean**	**SD**	**t**	**SD**	**p***
Year		24.800	2.936	27.100	6.757	-0,987	18	0.337
BMI		22.744	2.166	21.670	2.472	1,033	18	0.315

*Chi-square test; SD: Standard Deviation

Table 4. Differences in pre- and post- inhalation respiratory rate measurements between groups (n=20).

Groups	Control Group (n=10)		Experimental Group (n=10)		t[a]	p
	Mean	SD	Mean	SD		
Pre-inhalation respiratory rate	19.100	0.994	18.800	0.919	0.701	0.492
Post-inhalation respiratory rate	19.400	0.843	19.500	0.527	-0.318	0.754
t[b]	-0.709		-2.333			
P	0.496		**0.045**			

[a]Independent samples t-test; [b]Paired samples t-test; SD: Standard Deviation

There were no significant differences between the pre- and post-inhalation values for body temperature, systolic and diastolic blood pressure, pO2, pCO2, SaO2, and HCO3 between the two groups (p>0.05). In the experimental group, a significant increase in heart rate was observed from the pre-inhalation value ($\bar{x}$=77.000) to the post-inhalation value ($\bar{x}$=83.500) (p=0.026), but this increase remained within physiological limits.

The pre- and post-inhalation FVC measurements did not show significant differences between the groups (p>0.05; 95% CI [L/U]=-0.852/16.052). Similarly, the pre- and post-inhalation FEV1 measurements did not show significant differences between the groups (p>0.05).

However, post-inhalation FEV1/FVC measurements showed a significant difference between the groups (p=0.012). The post-inhalation FEV1/FVC measurements in the experimental group ($\bar{x}$=89.970) were higher than those in the control group ($\bar{x}$=86.460). Pre-inhalation FEV1/FVC measurements did not show significant differences between the groups (p>0.05). In the control group, the decrease in FEV1/FVC from the pre-inhalation value ($\bar{x}$=87.730) to the post-inhalation value ($\bar{x}$=86.460) was not significant (p>0.05). In the experimental group, the increase in FEV1/FVC from the pre-inhalation value ($\bar{x}$=88.790) to the post-inhalation value ($\bar{x}$=89.970) was also not significant (p>0.05) (Table 5).

Pre-inhalation blood pH measurements did not show significant differences between the groups (p>0.05) (Table 6).

Table 5. Differences in FEV_1/FVC Measurements Between Groups (n=20).

Groups	Control Group (n=10)		Experimental Group (n=10)		t[a]	p
	Mean	SD	Mean	SD		
Pre-inhalation FEV_1/FVC	87.730	3.164	88.790	4.408	-0.618	0.544
Post-inhalation FEV_1/FVC	86.460	1.490	89.970	3.691	-2.789	**0.012**
t[b]	1.563		-1.807			
P	0.152		0.104			

[a]Independent samples t-test; [b]Paired samples t-test; SD: Standard Deviation

Table 6. Differences in pH Measurements Between Groups (n=20).

Groups	Control Group (n=10)		Experimental Group (n=10)		t[a]	p
	Mean	SD	Mean	SD		
Pre-inhalation blood pH	7.351	0.034	7.336	0.023	1.167	0.258
Post-inhalation blood pH	7.377	0.030	7.348	0.025	2.281	**0.035**
t[b]	-2.082		-1.213			
p	0.067		0.256			

[a]Independent samples t-test; [b]Paired samples t-test; SD: Standard Deviation

DISCUSSION

In our study, no significant differences were found between the control and experimental groups in terms of vital signs, including body temperature, systolic and diastolic blood pressure, and ECG values. However, in the experimental group, the increase in respiratory rate from pre-inhalation to post-inhalation, as well as the similar increase observed in the control group, remained within clinically normal limits. Additionally, the increase in heart rate remained within normal clinical ranges.

Changes in key parameters, such as FEV1/FVC are clinically significant, as they provide insight into the balance between forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). A decrease in the FEV1/FVC ratio may indicate obstructive lung conditions, while a normal or increased ratio suggests preserved lung function. In this study, the observed changes in these parameters could reflect the potential effects of the inhaled treatments on pulmonary function, warranting further investigation. These findings highlight the importance of monitoring these ratios in evaluating the clinical efficacy of inhalation therapies. When analyzing the PFT values, an increase in the FEV1/FVC ratio was observed in the experimental group after inhalation compared to before inhalation. This finding is promising, as it suggests the potential for water-based propolis inhalation to positively impact the FEV1/FVC ratio in future studies targeting diseases such as COPD and asthma. Additionally, blood parameters such as pH, pCO2, pO2, and HCO3 did not show significant changes between pre- and post-inhalation measurements in either group.

Among the bioactive properties of propolis, its antioxidant effect is particularly notable[28,29]. In addition, propolis is known to exhibit anti-inflammatory [6,12], antimicrobial [30], and anticancer [31] properties. Studies have shown that these bioactivities are particularly related to the flavonoid content of propolis [32,33]. Propolis has also been used in the prevention of respiratory infections in children [34].

Studies on hive air are quite limited. The few existing studies have focused on the composition, potential bioactivity, and safety of hive air [4,35]. In one study, the volatile compounds in hive air were identified and categorized as fatty acids, alcohols, aldehydes, esters, ethers, hydrocarbons, phenols, ketones, nitrogen-containing compounds, and terpenes. They were found to be abundant and closely associated with anti-inflammatory, anti-asthmatic, and antimicrobial effects [4,35]. These data support the potential efficacy of hive air inhalation in the treatment of respiratory conditions such as asthma, bronchitis, and pulmonary fibrosis. Apiair therapy has been utilized to promote relaxation, enhance sleep quality and continuity, and facilitate easier breathing. However, given the limited research on this topic in the existing literature, our study aims to be the pioneering clinical trial in this field.

The limitations of this study include its mall sample size, short duration, and focus on immediate effects. Additionally, the absence of a comparative treatment group, lack of control for environmental factors, and limited scope of measurements restrict the generalizability and comprehensiveness of the findings.

CONCLUSION

This study provides evidence that propolis inhalation is safe in the short term, with no significant adverse effects observed on vital signs, venous blood gas parameters, or ECG results. Notably, it also demonstrates a positive influence on pulmonary function test values, suggesting its potential therapeutic benefits. Given the limited existing research on propolis inhalation, particularly in healthy volunteers, these findings contribute valuable insights into the safety and initial effects of propolis inhalation, as a key component of Apiair therapy, pioneering in this field. However, further research with larger sample sizes and longer durations is necessary to fully understand the efficacy and long-term safety of propolis inhalation.

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REVIEW

Unveiling the Therapeutic Wonders of Curcumin: A Comprehensive Review of Its Impact on Human Health

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Abstract
Curcumin, a vital culinary spice, is the biphenolic active compound of turmeric and has a rich history of use in ancient therapeutic medicine. It has long been used for hundreds of years to treat various ailments such as cancer and neurodegenerative diseases. This review will show an overview of the plant of curcuma and the history of curcumin. In addition, its chemical composition will be discussed to clarify the chemical component essential for its biological activity. Recently, the biological activities of curcumin have been inve stigated. The studies mainly focused on their antitumor, antioxidant, anti-inflammatory, hepatoprotective, neuroprotective, and cardioprotective impacts. This review aims to provide a discussion about curcumin use and its effect on human health and disease prevention.
Keywords: Curcumin, Traditional Medicine, Chemical Composition, Biological and Therapeutic Properties

INTRODUCTION

Curcumin originates from the turmeric plant (*Curcuma Longa*), which is a sacred spice in India, where it has had an important place in social, culinary, and medicinal tradition. Turmeric is one of the main components of traditional Indian medicine, Ayurvedic medicine, which is probably the oldest medicinal tradition of humanity. In Chinese medicine, turmeric is used to treat abdominal pain. In the East, it was traditionally used for its anti-inflammatory action [1]. The therapeutic effects of curcumin have been confirmed by scientific studies, including antioxidant properties, anti-inflammatory, anticarcinogenic, anti-microbial, thrombolytic, cardiovascular (protection against myocardial infarction), hypoglycemic, and anti-arthritic [2,3]. Turmeric's antioxidant properties are associated with its composition of phenolic compounds, grouped under the name of curcuminoids, the main one being curcumin [4].

In this review, the essential impact of curcumin and its medicinal uses will be presented. First, a brief description of the curcuma plant, curcumin's history, and its chemical composition will be provided. In the second part, curcumin, the active compound derived from turmeric, possesses a range of biological properties that contribute to its potential therapeutic effects.

Description of Curcuma plant:

Curcuma longa L. is a species of perennial, rhizomatous, herbaceous plants of the genus Curcuma (family Zingiberaceae) native to south or southeast Asia. **(Figure 1).**

The main ovoid-shaped rhizomes provide round turmeric, and the secondary ones provide long turmeric. Thick, scaly, and wrinkled by desiccation, these rhizomes are orange yellow in section and brownish gray on the surface. An aromatic odor is released after sectioning the rhizome [5]. Its leaves, very long, oblong to elliptical, sheathing, have a powerful axial vein and parallel secondary veins. Within the leaves rises the inflorescence consisting of a cylindrical spike up to 20 cm long. **(Figure 2).**

It is composed of dark green and sterile imbricated bracts, in the axils of which white or yellowish flowers are born, one for each bract. Only the upper bracts, pink, are more beautiful [6].

The flowers have a short, tubular calyx with unequal teeth, a tubular corolla at its base, then divided into

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3 unequal yellow lobes and stamens, including only one fertile, bifid, the anther presenting a large, curved spur at the base. Turmeric is valued for its medical properties. Turmeric root has an active compound such as curcumin, which gives the plant antioxidant, anti-inflammatory, and anti-cancer properties [7].

Figure 1. Curcuma Plant [2]

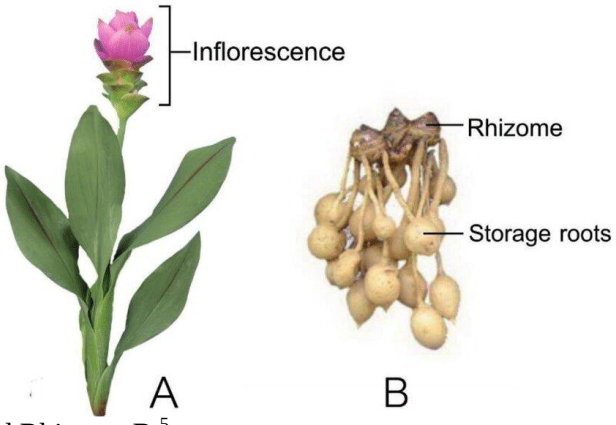

Figure 2. Inflorescence A - and Rhizome B [5]

HISTORY

Turmeric has been cultivated through the centuries in India. Although it was already appreciated there more than 3000 years ago, it is still very present in many Hindu mixtures, such as the masala mixture. It is also still used in rituals to symbolize the sun. It was introduced to Europe in the Middle Ages by Ottoman merchants, where it was widely used as a cheap saffron [8]. In the 18th century, turmeric, under its name Terra merita or Indian saffron, was imported to Europe by the great naval powers (Holland, the United Kingdom, Portugal, and France). If it is used as a spice, it is also used for its medicinal properties. Turmeric is a plant derived from the ginger family that has been used for centuries in Asia. Due to its antioxidant properties, it has long been used as a natural food preservative.

Turmeric powder is the main ingredient in curry, which gives it its intense yellow color. India, where it is believed to have originated, accounts for 90% of the world's turmeric production. It is also produced in other Asian countries such as China, Thailand, Cambodia, and Malaysia [8].

Using of curcumin in traditional medicine:

Curcuma Longa is a plant that grows wild in the forests of Southern Asia, including Indonesia, India, Indochina, nearby Asian countries, and some Pacific Islands. All of these areas have medicinal uses and traditional culinary practices going back to prehistory. In the Indian Ayurveda system of herbal medicine, turmeric is known as warming and strengthening for the entire body[9]. Traditional uses in India include improving intestinal flora, improving digestion, eliminating worms, cleansing the liver and gallbladder, relieving gas, normalizing menstruation, warming, and promoting proper metabolism, correcting both deficiencies and excesses, local application on cuts, sprains, burns, and bruises, providing soothing action in cough and asthma, acting as an antibacterial and anti-fungus, and in any condition of debility or weakness.

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The ancient Hawaiians used curcuma for many things, including ear infections and gastrointestinal ulcers, the prevention and treatment of sinus infections (it is very astringent and appears to pull mucus out). Turmeric is consumed as food, both in its raw and cooked forms, across Asia.

Another traditional use of turmeric is as a dye for cloth and a food colorant—in both cases a cheaper alternative to saffron. It was and is used in religious ceremonies—often representing purity, life, and prosperity. The rhizome is the part of the plant that is most largely used. It can be prepared in different ways and is reputed to alleviate coughs and asthma[10,11].

Chemical composition of curcumin:

Curcumin, or diferuloyl-methane, is the main pigment of turmeric (Curcuma longa), also called Indian saffron. It is a polyphenolic pigment (curcumoid) that gives a yellow color [12]. **(Figure 3).**

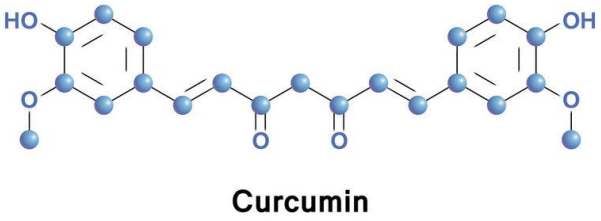

Figure 3: Turmeric and Chemical Structure of Curcumin [12]

The rhizomes can produce 2 to 7% essential oil, which is orange-red and slightly fluorescent. Its main constituents are a sesquiterpene, zingiberene (25%), and its ketone derivatives: turmerone (35%) and ar-turmerone (dehydroturmerone) (12%). **(Figure 4).**

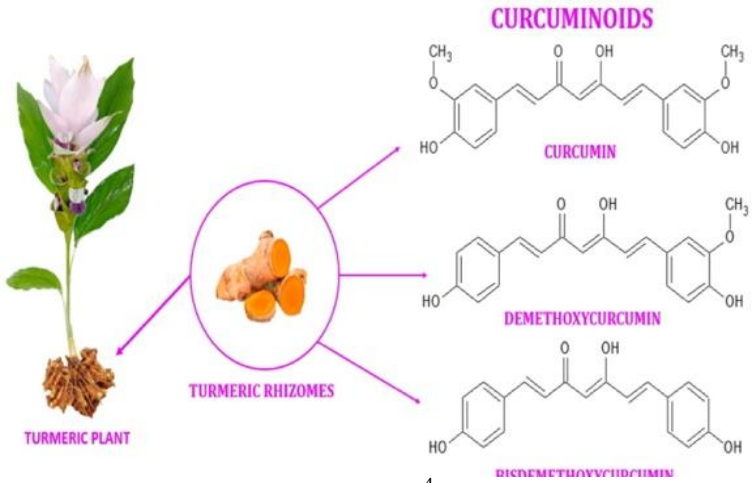

Figure 4: Curcuminoids Found in the Rhizomes of Turmeric [4]

Turmeric is mainly composed of carbohydrates, almost 65%. The carbohydrates present are simple sugars, such as fructose, glucose, and sucrose. There are approximately 10% lipids in turmeric. These include an omega-9, linoleic acid, an omega-6, and steroids (cholesterol, campesterol, and stigmasterol) [13].

A little less than 5% of turmeric powder is composed of minerals, such as calcium, magnesium, potassium, iron, or zinc. Some traces (<1%) of vitamins are found in turmeric, such as vitamins B1, B2, B3, B9, C, and E [13].

BIOLOGICAL AND THERAPEUTIC PROPERTIES OF CURCUMIN

Anti-inflammatory effect:

Inflammation is a cascade of chemical reactions following an attack on the body, which causes swelling (edema), heat (increased local blood circulation), and pain. Regardless of the type of inflammation, it is always comfortable to alleviate the pain. However, taking conventional anti-inflammatories such as NSAIDs (non-steroidal anti-inflammatory drugs), such as ibuprofen, aspirin, etc., leads to numerous side effects linked to the mechanism of action of these synthetic molecules:

digestive disorders, kidney problems, musculoskeletal changes, skin disorders, etc. [14,15].
Turmeric is particularly known for fighting inflammation. More than 6 studies have shown an anti-inflammatory effect of turmeric without toxic effects. The anti-inflammatory effect of curcumin is induced by its ability to stop the production of pro-inflammatory mediators. Indeed, curcumin acts directly on the enzymes responsible for producing inflammatory molecules, also called cyclooxygenase (Cox-2) and 5-lipoxygenase (Lox-5)[16]. Curcumin thus inhibits the production of prostaglandins, leukotrienes, thromboxanes, and cytokines. Osteoarthritis is a common complication among older individuals, and many treatments aim to reduce symptoms using anti-inflammatories. The need for new therapeutic approaches has led to the development of anti-arthritic drugs (e.g., Chondrosulf®, Art 50®), which are not without risks and can cause undesirable effects. Curcumin is considered an alternative to these treatments. In the first clinical study on the effectiveness of curcumin as an anti-rheumatic drug, researchers compared its anti-rheumatic power to that of phenylbutazone in 18 people. Each person received a daily dose of either 1200 mg of curcumin or 300 mg of phenylbutazone for 2 weeks. Curcumin was well tolerated at this dose and exerted activity comparable to phenylbutazone. Curcumin has also been shown to suppress inflammation by many different mechanisms and acts as a potential anti-inflammatory agent [17].

Anti-cancer effect:

Curcumin has shown considerable anticancer effects against several different types of cancer, including breast cancer, prostate cancer, colon cancer, bone cancer, melanoma, etc **(Figure 5).**

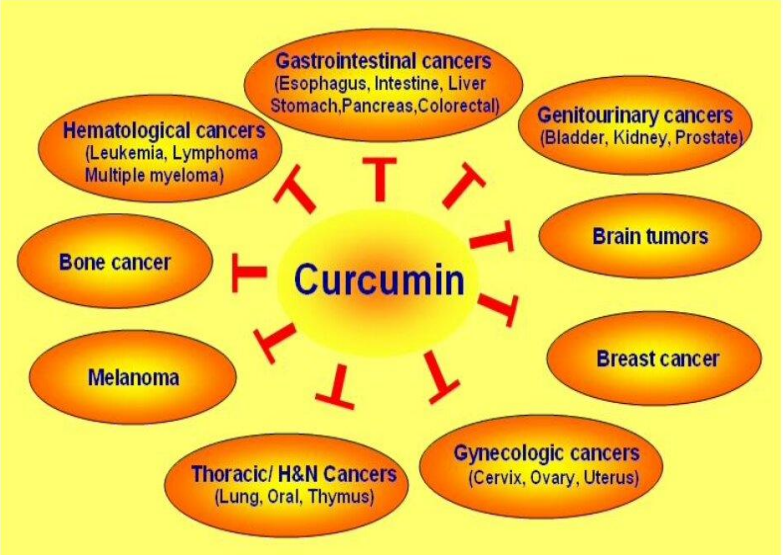

Figure 5: Anti-Cancer Effects of Curcumin[2]

Using highly advanced X-ray crystallography methods, a Chinese American research team demonstrated that active component in turmeric, curcumin, blocks the activity of an enzyme essential for tumor growth.
Preclinical studies performed indicate that curcumin's anticancer action is due to its ability to inhibit several key enzymes involved in tumor progression, including various tyrosine kinases that are already targeted by chemotherapy drugs, as well as certain oncogenes like Her2, another major target of chemotherapy [18].
To clarify curcumin's mechanism, the scientists have studied its inhibitory effect on a very broad range of kinases, a family of ATP-binding enzymes that are known to play crucial roles in tumor growth. They observed that very low concentrations of curcumin (picomoles per milliliter) led to the specific inhibition of an enzyme called dual-specificity tyrosine-regulated kinase 2 (DYRK2).
By blocking the activity of DYRK2, curcumin therefore promotes an accumulation of abnormal proteins, which ultimately cause the death of the cancer cell by intoxicating it. This is particularly true in the case of certain types of cancer that rely heavily on the presence of a functional proteasome, such as triple-negative breast cancer and multiple myeloma. This action of curcumin could even explain certain spectacular results that have been obtained during clinical trials [19].

In terms of cancer prevention, the positive action of curcumin on very advanced cancers, which no longer respond to chemotherapy in several cases, strongly suggests that this action will be even more effective against tumors in their early stages, which are indeed much more sensitive to the presence of anticancer agents. For this reason, regular consumption of turmeric can prevent cancer: Due to its anti-inflammatory action and its multiple anti-cancer properties, curcumin creates an inhospitable environment for microtumors that develop spontaneously during our lives, depriving the resources necessary for their progression into mature cancer [20].

Neuro-protective effect:

Many neurodegenerative illnesses of aging involve the accumulation of protein aggregates, inflammation, and oxidative damage. Curcumin has multiple characteristics for a neuroprotective drug, including antioxidant, anti-protein-aggregate activities, and anti-inflammatory.

Because of its oral safety, pluripotency, long history of use, and low cost, curcumin has high potential for the prevention of multiple neurological conditions for which current therapeutics are suboptimal. Examples reviewed include Parkinson's, Huntington's, Alzheimer's, head trauma, stroke, and aging [21].

i) Antioxidant properties:

The antioxidant property of curcumin prevents the alteration caused by exposure to fatal factors such as drugs, alcohol, heavy metals, and radiation. Because it is a hydrogen donor and a good free radical scavenger.

Curcumin is not very toxic and has limited bioavailability. Protects DNA from oxidative damage due to its ability to capture free radical [22].

ii) Neurotransmitter modulation:

Curcumin modulates the level of various neurotransmitters such as norepinephrine, serotonin, and dopamine in the brain. Norepinephrine is a neurotransmitter involved in emotions, sleeping, learning, and dreaming. Dopamine is involved in emotion, pleasure, and regulating locomotion, while serotonin plays an essential role in neurovegetative functions of the body, such as sleep, appetite, memory and learning, mood, behavior (including sexual behavior), cardiovascular functions, endocrine regulation, and muscle contraction [23].

iii) Amyloid-beta plaque disruption:

Alzheimer's disease promotes a regression in thinking, memory, learning, and organizing skills over time.

An abnormal accumulation of proteins in brain causes Alzheimer's disease. The build-up of these proteins, tau protein and amyloid protein, causes the death of brain cells. Scientists believe that amyloid protein accumulates in brain cells, forming larger masses called plaques.

Recent research on curcumin and amyloid-β has revealed that curcumin prevents amyloid-β aggregation, reaches brain cells, and protects neurons from multiple toxic insults of aging and amyloid-β in humans [24].

Cardioprotective effects:

Cardiovascular diseases (CVDs), disorders of the heart and blood vessels, are the most common cause of death worldwide and a major health problem worldwide. Individuals at risk for CVDs may present weight issues, high blood pressure, and lipid levels or altered glucose. Great progress in research has been made to study the pathogenesis mechanism of CVDs, but the mortality and morbidity of CVDs are still very high. For this reason, there is urgently a need for drugs to prevent and treat these diseases. Compared to traditional drugs, natural drugs have many benefits, such as low long-term toxicity, fewer side effects, and variable bioavailability [25].

Some studies have shown that pleiotropic effects of curcumin in CVDs propose that it is a promising drug candidate.

Specifically, curcumin can significantly inhibit foam cell formation, mitigate vascular endothelial dysfunction, reduce vascular smooth muscle cells (VSMCs) proliferation, protect cardiomyocyte injury after hypoxia and ischemia, inhibit myocardial hypertrophy and fibrosis, and reduce drug-induced myocardial injury [26].

On the other hand, endothelial progenitor cells (EPCs) have an important role in wound healing. Clinical studies have shown that curcumin promoted angiogenesis and migration and reversed the number of aging EPCs by up-regulation of angiotensin I (Ang I) and vascular endothelial growth factor (VEGF)-A4.

Finally, curcumin has a positive and protective effect on CVDs. It is important to note that curcumin is an alternative or complementary medicine, not a replacement for the main treatment, and should be used under the guidance of a doctor [27].

CONCLUSION

We have seen that the major active ingredient in turmeric, curcumin, acts on many targets and has the potential to treat various diseases. The exact

mechanisms by which curcumin produces its therapeutic effects have not yet been fully elucidated, but they are likely mediated through its its antioxidant and anti-inflammatory activity. Indeed, curcumin curcumin has been shown to offer protection against cancer, cardiovascular diseases, Alzheimer's disease, cystic fibrosis, pancreatitis, rheumatoid arthritis, and numerous other pathologies. However, at present, data regarding turmeric and curcumin are mostly based on laboratory studies on animals. Its effectiveness in humans remains to be proven. This will require years of research, as the the number of pathologies that this molecule can potentially treat is considerable. Thus, larger clinical trials are needed to fully evaluate its potential in terms of optimal dose, route of administration, and target diseases. In addition, all the studies performed have focused on the medical applications of curcumin, but none have been developed as a drug. One of the main obstacles to its use is its low bioavailability. For this reason, to benefit well from all its advantages, it is recommended for daily use to combine it with a fatty substance and pepper. A teaspoon of turmeric powder per day in the diet is sufficient to achieve a preventive effect. A lot of research has also been launched to improve its bioavailability. Turmeric, through its ancestral use in cooking as a spice and then in traditional medicine, has proven its safety and its health benefits.

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Erratum

The corrections made in the article titled "Protecting Spermatogenesis from Doxorubicin-Induced Damage: The Effects of Prunus laurocerasus on Oxidative Stress in an Animal Model" in the 2024, 5th Volume, 3rd issue of the International Journal of Traditional and Complementary Medicine Research are as follows:

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Corrected Version: We acknowledge the financial support from the Ordu University Scientific Research Projects Office (Project Number: A2122). Special thanks to Sedat Çökeli for his invaluable assistance with Python analysis.

Correction Explanation: "Kabartan Çökeli, E., Cırrık, S., Güleç Peker, E. G., Hacıoğlu, G. (2024). Protecting Spermatogenesis from Doxorubicin-Induced Damage: The Effects of Prunus laurocerasus on Oxidative Stress in an Animal Model. International Journal of Traditional and Complementary Medicine Research, 5(3), 166-176. In the article with the reference 'https://doi.org/10.53811/ijtcmr.1531515', the project code is misspelled and entered incorrectly as A2006 when it should be A2122. The authors apologise to the readers for this error. This correction text is provided to correct the error in the article.

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