

The Prevalence of Complementary and Alternative Medicine among Women with Gynecologic Cancers: Levels of Effectiveness and Satisfaction

Gul Pinar¹, Ali Ayhan²

¹Department of Nursing, Faculty of Heath Science, Ankara Yıldırım Beyazıt Üniversity, Ankara, Turkey, ²Baskent Üniversity Ankara Hospital, Faculty of Medicine, Gynecologic Oncology Clinic, Ankara, Turkey

ABSTRACT

Aim: In this study, it was aimed to evaluate the prevalence of complementary and alternative medicine (CAM) methods, as well as the effectiveness and satisfaction of the CAM method used in women with gynecological cancer. **Methods:** The sample of this descriptive and cross-sectional study consisted of 243 women diagnosed with gynecological cancer. In the study, a questionnaire form consisting of 27 questions was used to determine the sociodemographic characteristics of women, gynecological cancer history, and the use of CAM as a data collection tool. Results: The average age of the patients was 52.6 years (SD = 13.1). Most of them were primary school graduates (40.3%) and married (65.0%). More than half of the women (62.1%) had ovarian cancer, 42.4% of women are in the third stage of cancer, and 55.6% were diagnosed within the 1st year. The prevalence use of CAM method was 68.3%, respectively, body and mind treatments (78.9%), biologicalbased treatments (56.6%), manipulative/body-based treatments (47.0%), and energy therapies (11.4%). Among biologically therapies, most women commonly used therapy was herbal (80.8%) medicine, respectively, black grapes (71.1%), nettle (52.6%), and ginger (43.4%). Satisfaction with CAM use was 5.80 ± 1.43 , and its effectiveness was 5.71 ± 1.48 out of 7. It was determined that the use of CAM was increased among those with advanced stages, those who had a long-term diagnosis, those with chronic diseases, the number of chemotherapy cures, and those who did not receive surgical treatment (P < 0.05). Conclusion: In our study, it was found that the use of CAM is common in women with gynecological cancer, and the satisfaction and effectiveness of these methods are high. In this regard, health professionals within a multidisciplinary team understanding in line with the needs of patients, they should realize the advantages, disadvantages, and limitations of CAM in the consultancy services it provides for CAM based on evidence.

Key words: Complementary and alternative medicine, effectiveness, gynecologic cancer, satisfaction

INTRODUCTION

ynecological cancers are a frequent group of cancer in women worldwide and hence an important public issue that negatively affects women's health. [1-4] Unfortunately, there are currently no screening programs for gynecological cancer, except cervical. Therefore, potentially encouraging women for help-seeking behaviors or providing prompt consultation facilities might have a significant impact on the preventable and treatable conditions. [5-7] According to

GLOBACON 2018 results, 7.9% of female cancer incidence in the world is cervical cancer (570.00 new cases, 311.00 deaths), 4.8% is endometrial cancer (380.00 new cases, 90.000 deaths), and 3.6% is ovarian cancer (295.000 new cases, 185.00 deaths). Endometrial cancer among the most common cancers in Turkey (5.4%), ovarian cancer (9.3%), and cervical cancer (2.4%) are available. Studies show that women with gynecological cancer experience physical, psychosocial, and sexual problems during the treatment process and these problems negatively affect their quality of

Address for correspondence:

Gul Pinar, Department of Nursing, Faculty of Heath Science, Ankara Yıldırım Beyazıt Üniversity, Cankiri sk, Cicek cd. No: 3/2, 06610 Ulus, Ankara, Turkey. Tel.: +9(0)312324155/4556.

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life. [1-7,10] A significant number of women with gynecological cancers prefer complementary and alternative medicine (CAM) methods as an additional therapy to standard medical therapy for the past decades, including our country. [11-20] In a study conducted in fourteen European countries, there has been a steady increase in the use of CAM among cancer patients (range from 14% to 73%). [21] According to the World Health Organization (WHO), in 2016, the use of CAM is 80% in Asia and Africa, 70% in Canada, 90% in Germany, and 50% in Sweden. [22] Undoubtedly CAM has been performed for centuries; nowadays, among modern medical therapies, it has become popular, which is primarily based on holistic and supportive approach to actual medical treatment and is still being accepted as an alternative therapy. [23]

In many countries, numerous studies showed that the use of CAM was common among patient with gynecologic cancer into various categories such as spiritual and relaxation methods, massage, herbal remedies, vitamin nutrient, chiropractic, yoga, meditation, hypnosis, cupping, aromatherapy, reflexology, homeopathy, Reiki, acupuncture, acupressure, osteopaths, mind therapies, and mental imagery to relieve their symptoms of the disease and improve their quality of life. [10-21,24-32] In spite of the widespread use of CAM therapies, results are rarely supported by evidence-based information. There still a need awareness of the efficacy of CAM and their interaction with routine medical therapy. [33]

Aim

This study aimed to evaluate the prevalence of complementary and alternative medicine (CAM) methods, as well as the effectiveness and satisfaction of the CAM method used in women with gynecological cancer.

MATERIALS AND METHODS

Study design, setting, period, population, and sample size

This descriptive and cross-sectional study was carried out during April 01, 2015, and July 01, 2015, in a private University Hospital, Gynecology-Oncology Clinic in Turkey. The universe of the study consisted of 900 patients who applied to the gynecology clinic of the relevant hospital for a year. The sample of the study was determined according to the formula "calculating the number of sample in cases of known universe," the sample size was determined as 243 patients with gynecologic cancers. Power calculation was made with G* power 3.1. The power calculation made for the difference of CAM usage rate (0.683) from 0.50 over the study sample was found over 95% (upper of 95%, alpha = 0.05, d = 0.183).

Exclusion and inclusion criteria

The study group consisted of women who were hospitalized and treated for the diagnosis of gynecologic cancer (ovarian, endometrial, cervical, vulvar, and vaginal). The inclusion criteria were: (a) Hospitalized and treated for the diagnosis of gynecologic cancer (ovarian, endometrial, cervical, vulvar, and vaginal) at least 18 years old, (b) able to understand in Turkish language, (c) diagnosed with invasive cancer by pathological examination, (d) to be diagnosed with gynecologic cancer at least 3-month before interview, (e) the patient should be able to understand and respond the asked questions, and (f) to be free of any cognitive dysfunction. Exclusion criteria were significant medical condition that would interfere with study participation.

Instruments

The data were collected using "Questionnaires Form" developed by the researchers by analyzing the literature and contains 27 items^[26,34] (Özçelik and Fadıloğlu, 2009; Amanak *et al.*, 2013)^[13,17,27,35] (Grunienigen *et al.*, 2001). The questionnaires consisted of three parts. The first part included sociodemographic characteristics of participants such as age, education level, marital status, occupation, socioeconomic status, place of residence, husband occupation, and education level. The second part included to determine gynecological cancer of history such as type of malignancy, stage of cancer, treatments type, chronic disease, previous, and present treatments. The third part included CAM use of participants CAM use, CAM methods, information about CAM (source of information about treatment, treatment method, reasons for usage), and satisfactory and effectiveness scale.

CAM methods were used in the study; (i) biologically-based therapies, such as herbs, dietary supplements, or vitamins; (ii) mind-body interventions such as meditation, prayer, meditation, yoga, healing, or support groups; (iii) energy therapies (i.e., Biofield therapies such as Qi Gong, therapeutic touch, and Reiki or bioelectromagnetic-based therapies such as magnetic fields); and (iv) manipulation and body-based methods, such as massage, exercises, acupuncture, chiropractic, or osteopathy (NNCIH, 2014). Those who use at least one of these methods are considered to be "using CAM." Patient satisfaction and effectiveness with CAM use were evaluated on visual analog scale of 1–7 with higher scores indicating more satisfaction and effectiveness (1 = not satisfied at all, 7 = very satisfied). The data collection form was filled face to face by the researchers.

Ethical approval

Ethical approval was obtained for the conduct of this study from Baskent University (No: KA14/29; Tarih: 12/03/14). The researcher introduced the questionnaire to participants and explained the coverage of the material. Participants completed an informed consent form in which they were assured of the confidentiality of their responses, following which they provided informed consent that participation was voluntary and anonymous. Rules specified in the Helsinki Declaration were observed in the data collection phase.

Data analysis

The statistical analyses were performed using SPSS for Windows version 20.0. Descriptive statistics were calculated for all variables. The participants were categorized as either CAM users or nonusers. To estimate the adjusted odds ratios (ORs), a logistic regression model was constructed, with CAM use as the dependent variable. Predictor variables included age, educational status, marital status, economic status, cancer type, cancer stage, treatment modality, chronic disease, and diagnosis time. A stepwise, forward selection process was used to construct the model with variables. Statistical significance was set at P < 0.05.

RESULTS

Two hundred forty-three patients were asked to complete this study. The average age of patients was 52.65 ± 13.13 years. Most of the women were primary school graduates (40.3%), married (65.0%), and their economic income was moderate (58.4%). About 62.1% of women suffered from ovarian cancer, 42.4% are in the third stage of cancer, and 55.6% are in the first year of cancer diagnosis. Chemotherapy was applied to 90.9% of the women and surgical treatment was applied to 80.1% [Table 1].

The percentage of CAM usage in our study is 68.3%. For women using CAM; 62.6% family, friends, and patients; 22.2% internet, newspaper, magazine, and television; 14.5% self; and 8.4% physician or nurse were effective. However, only 18.1% of the women using CAM were in cooperation with the healthcare team. CAM methods preferred by women, respectively, body and mind treatments (78.9%), biologicaltreatments (56.6%),manipulative/body-based treatments (47.0%), and energy therapies (11.4%). Among the body and mind treatments, the most used methods are "praying" (87.0%), "herbal" in biological-based treatments (80.8%), "massage" in manipulative – body-based therapies (69.2%) and "creative imagery" in energy treatments was determined (64.8%). In the present study, while general satisfaction with CAM use was determined as 5.8 ± 1.43 over 7 points, the effectiveness score was 5.71 ± 1.48 . The level of satisfaction and effectiveness in using CAM; energy treatments (satisfaction: 6.31 ± 1.60 ; effectiveness: $6.42 \pm$ 1.26) were found to be at the highest level. Manipulative and body-based treatments (satisfaction: 5.93 ± 1.31; effectiveness: 5.93 ± 1.28), body and mind treatments (satisfaction: 5.87 ± 1.26 ; effectiveness: 5.78 ± 1.36), and biologically-based treatments (satisfaction: 5.33 ± 1.55 ; effectiveness: 5.28 ± 1.57) followed [Table 2]. Participants stated that they are mostly used to improve the quality of life and to prevent cancer recurrence.

As a result of univariate logistic regression analysis; CAM use in women with chronic disease was 1.96 times (CI = 1.128; 3.407) compared to those without chronic disease, 3.76

times (CI = 1.017; 13.923) in patients with cancer in the fourth stage of cancer, 28.77 times (CI = 6.520; 126,958), it was 2.68 times more (CI = 1.504; 4.803) in patients with cancer duration of one year or <1 year, and 4.58 times more (CI = 1.1342; 15.639) in those who did not undergo surgical treatment (P < 0.05). In the multivariate model, "chemotherapy application," "having chronic disease," and "no surgical treatment" were associated with CAM use (P < 0.05). Other significant covariates are shown in Table 1.

In the present study, mostly herbal supplements (80.8%) were used in biological-based treatments. Among herbal supplements, respectively, black grapes (71.1%), nettle (52.6%), ginger (43.4%), green tea (34.2%), black cumin (27.6%), black mulberry (25.0%), carob (22.3%), reishi mushroom (21.6%), sage (21.6%), blueberry (19.7%), thyme (19.7%), green lentil (18.4%), mistletoe (17.1%), pomegranate (17.1%), and red beet (13.1%) [Table 3].

DISCUSSION

The use of CAM is increasing in the world and gynecology patients are frequently affected by this increase. [1-7] In various studies covering Europe and the Middle East, the percentage of CAM use in women with gynecological cancer ranges between 40% and 67%. [1-8,13,16-18] In studies conducted in Turkey and that this is why the show changes or recalculations between 31.6% and 84.1% (3.610–15.19). Similarly, in our study, the percentage of using CAM in women with gynecological cancer was 68.3%. These findings show that the use of CAM is common in gynecological cancer.

Studies show that women using CAM use this method with the suggestions of media, internet, friends, and families, and most CAM users do not inform their healthcare workers.^[14,15,28,36] In our study, the majority of women specified their family, friends, and other treated patients as a source of information in the choice of CAM method. At the same time, only 18.1% of the women using CAM have collaborated with healthcare professionals while using CAM. This shows that women using CAM receive information from scientifically unreliable sources. It is emphasized in the literature that the unconscious use of CAM may delay treatment and recovery in patients with cancer. Therefore, it is important for healthcare professionals to question the individual practices of cancer patients in the treatment process.[36-38] However, in the studies conducted, it is emphasized that the knowledge level of health professionals about CAM is not sufficient. For this reason, it is important to organize the education curriculum of health professionals to cover CAM applications and provide CAM consultancy based on evidence. [39,40]

Cultural and sociodemographic factors can affect the use of CAM. Different studies showed that increasing the level of income, being a woman, being married, having religious

	Table 1: Characteristics of users and non-users of CAM (n=166)						
Characteristic	Total	CAM User		Univ. logistics regression			
	n (%	Yes (n=166) n (%)	No (<i>n</i> =77) <i>n</i> (%)	OR (95% CI)	P value		
Age groups							
49 years and over	88 (36.2)	56 (33.7)	32 (41.6)		0,201		
50-64 years	106 (43.6)	83 (50.0)	29 (37.7)	1,635 (0.892; 2.998)	0,112		
65 years and over	49 (20.2)	27 (16.3)	16 (20.8)	0,964 (0.453; 2.053)	0,925		
Educational status							
Illiterate	32 (13.2)	22 (13.3)	10 (13.0)		0.623		
Primary school	98 (40.3)	70 (42.2)	28 (36.4)	1.136 (0.478; 2.703)	0.772		
Senior high school	59 (24.3)	41 (24.7)	18 (23.4)	1.035 (0.408; 2.625)	0.942		
University	54 (22.2)	33 (19.9)	21 (27.3)	0.714 (0.283; 1.804)	0.477		
Marital status							
Single	43 (17.7)	29 (17.5)	14 (18.2)		0.045		
Married	158 (65.0)	115 (69.3)	43 (55.8)	1.291 (0.624; 2.673)	0.491		
Husband died	42 (17.3)	22 (13.3)	20 (26.0)	0.531(0.220; 1.280)	0.158		
Economic status							
Income <expenditure< td=""><td>56 (23.0)</td><td>43 (25.9)</td><td>13 (16.9)</td><td></td><td>0.207</td></expenditure<>	56 (23.0)	43 (25.9)	13 (16.9)		0.207		
Income=expenditure	142 (58.4)	91 (54.8)	51 (66.2)	0.725 (0.349; 1.504)	0.388		
Income>expenditure	45 (18.5)	32 (19.3)	13 (16.9)	1.344 (0.549; 3.287)	0.517		
Cancer type							
Ovarian	151 (62.1)	105 (63.3)	46 (59.7)	0.978 (0.416; 2.299)	0.960		
Endometrial	58 (23.9)	38 (22.9)	20 (26.0)	0.814 (0.315; 2.106)	0.672		
Cervical	30 (12.3)	21 (12.7)	9 (11.7)		0.815		
Vagen/Vulvar	4 (1.6)	2 (1.2)	2 (2.6)	0.429 (0.052; 3.534)	0.431		
Stages							
1	20 (8.2)	11 (6.6)	9 (11.7)		0.031		
II	92 (37.9)	55 (33.1)	37 (48.1)	1.216 (0.459; 3.223)	0.694		
III	103 (42.4)	77 (46.4)	26 (33.8)	2.243 (0.903; 6.500)	0.079		
IV	28 (11.5)	23 (13.9)	5 (6.5)	3.764 (1.017; 13.923)	0.047		
Treatment modality ^b							
Chemotherapy	221 (90.9)	164 (98.8)	57 (74.0)	28.772 (6.520; 126.958)	0.001		
Surgical treatment	214 (80.1)	140 (84.3)	74 (96.1)	4.581 (1.1342; 15.639)	0.015		
Radiotherapy	10 (4.1)	8 (4.8)	2 (2.6)	1.899 (0.394; 9.160)	0.425		
Chronic disease							
Yes	118 (48.9)	90 (54.2)	29 (37.7)	1.960 (1.128; 3.407)	0.017		
No	124 (51.1)	76 (45.8)	48 (62.3)		0.013		
Time after diagnosis							
1-12 months	135 (55.6)	80 (48.1)	55 (71.4)		0.32		
13 months and longer	108 (44.4)	86 (51.9)	22 (28.6)	2.687 (1.504; 4.803)	0.001		

^aUniv. logistics regression analysis, ^bLine percent was calculated and number (n) was multiplied since patients could have taken combined treatments.

beliefs and cultural features increase the use of CAM in patients. [11-14,17,18] However, in the study of Akyüz *et al.* [35] and Molassiotis *et al.*,[21] it is stated that the use of CAM increases as the age decreases and the education level increases. In

some studies, it is emphasized that the lower the education level^[6,14] and the higher the age,^[40,41] the higher the use of CAM. In our study, it was determined that there was no significant relationship between the use of CAM according

Table 2: Effectiveness and satisfaction status of the participants according to the CAM method (n=166) Characteristics^a CAM User n (%) Satisfactory level Mean±SDb Effectiveness level Mean±SDb Total score 5.80±1.43 5.71±1.48 166 (100.0) Biologically-based of therapies 94 (56.6) 5.33±1.55 5.28±1.57 Herbs 76 (80.8) Vitamins 21 (22.3) Nutrition-diet 20 (21.2) Animal-derived extracts 20 (21.2) Minerals 8 (8.5) Mind-body interventions 131 (78.9) 5.87±1.26 5.78±1.36 Praying 114 (87.0) Music therapy 32 (24.4) Dreaming 12 (9.1) Meditation 5 (3.8) Support group 2 (1.5) Manipulative and body-based 78 (47.0) 5.93±1.31 5.93±1.28 Massage 54 (69.2) **Exercises** 30 (38.4) Hydrotherapy 2 (1.5) Reflexology 1 (1.2) Acupuncture 1 (1.2) **Energy therapies** 6.31±1.60 6.42±1.26 19 (11.4) Creative imagery 13 (68.4) Reiki 5 (26.3) Therapeutic touch 1 (5.2)

^aLine percent was calculated and number (n) was multiplied since patients could have taken combined treatments.

Table 3: Distributions of preferred herbal supplements among CAM methods						
Biologically-based therapies- herbs (<i>n</i> =76)	n*	%				
Black grapes	54	71.1				
Nettle	40	52.6				
Ginger	33	43.4				
Green tea	26	34.2				
Black cumin	21	27.6				
Black mulberry	19	25.0				
Carob	17	22.3				
Reishi mushroom	16	21.6				
Sage	16	21.6				
Blueberry	15	19.7				
Thyme tea	15	19.7				
Green lentil	14	18.4				
Mistletoe	13	17.1				
Pomegranate	13	17.1				
Red beet	10	13.1				

^{*}n number increased due to multiple answering to these questions

to the age, education, income status, and marital status of the women (P > 0.05) [Table 1].

In addition, in our study, factors associated with cancer and disease processes were found to affect the use of CAM. Among them, it was determined that the use of CAM increased especially with the increase in the fourth stage of cancer, having a chronic disease, the number of chemotherapy cycles, and the duration of cancer diagnosis (P < 0.0.5) [Table 1]. In studies conducted similar to our study finding, it has been determined that as the duration of cancer increases and the stage of cancer increases, the use of CAM increases. [13,14,27,34] This can be explained by the fact that patients diagnosed with advanced-stage cancer have more expectations from the CAM method. At the same time, as surgical treatments are applied more limitedly in patients in this period, treatment options are decreasing, and it is thought that this situation leads patients to CAM applications.

When the CAM methods preferred in our study are examined, it was determined that body and mind treatments were used frequently. The second most preferred method was biological-based treatments, followed by manipulative/body-based

therapies [Table 2]. Similar to the studies conducted, it has been determined that the method frequently preferred by patients using CAM is body and mind treatments, followed by biological-based treatments and manipulative/body-based treatments. [4,15,26,35] In addition, different from our study findings, in some studies, bio-based therapies are used in the first place.[14,15,18,26,41,42] However, when the subtitles of CAM methods are examined in our study, praying (87.0%) took the first place, followed by herbal therapy (80.8%), massage (69.2%), and creative imagination (68.4%) [Table 2]. In the study of Supoken et al., [26] when the methods of using CAM in women with gynecological cancer were examined; praying (92.5%), herbal treatments (40.3%), exercises (37.3%), dietary treatments (23.9%), and massage (17.9%) were reported. In the study of Chase et al., [43] in the use of CAM in women diagnosed with early ovarian cancer, praying (79.3%) took the first place; in patients diagnosed with cervical cancer, vitamin supplements (80.3%) were used first. In the study of Nazik et al.,[15] while it was emphasized that herbal treatments (90.2%) are frequently preferred in the use of CAM; in the study of Akyüz et al., [35] it is seen that praying (94.7%) is preferred. Our study findings are consistent with the researches; especially praying, herbal and dietary treatments, massage, and creative imagery seem to be the preferred CAM methods among patients.

In our study, it was determined that herbal methods varied from biological-based treatments. It was determined that black grapes, nettle, ginger, green tea, black cumin, black mulberry, carob, and reishi mushroom were frequently used as herbal methods [Table 3]. In studies conducted in Turkey, the most widely used herbal treatment in cancer patients; it is emphasized that it is nettle, grape juice/seed, green tea, aloe, ginger, saffron, and flax seed.^[5,14,35,41,44] In international studies, it has been stated that herbal products such as mistletoe, ginseng, black cumin, green tea, and garlic are frequently used.^[16,21,24,29,31] When the study results are compared with our research findings, it can be said that the herbal methods preferred by the patients show cultural differences.

In our study, it was determined that black grape seed was the most preferred herbal method. Black grape seed is frequently used by women; it was found that it was used to increase the quality of life, to strengthen the immune system, and to cope with the side effects of treatment. It is stated in the literature that the effect of black grape seed is not known exactly, and when used with high doses, it should not be used with chemotherapeutic agents because it interacts with drugs.^[30,31,34,36] Considering that black grape seed is widely used in our study, it is worrisome in terms of herb-drug interactions. In the literature, it is emphasized that nettle has an antioxidant effect and is used to strengthen the immune system.^[23,36] In our study, nettle was preferred as the second herbal treatment method. This result is similar

to the literature.[15] It was found that this product was used to increase the quality of life, to strengthen the immune system, and to cope with the side effects of treatment, and to support treatment [Table 3]. In the study of Akyüz et al. [35] and Avcı et al., [45] it was determined that nettle was among the most commonly used herbal products. However, it is stated in the literature that ginger is especially benefited from its antiemetic effect[32,46] and it is emphasized that it is also used in cancer treatment and to strengthen the immune system.^[45] In our study, it was determined that it was used to increase the quality of life in addition to the research results [Table 3]. In the randomized controlled study of Alparslan et al., [46] ginger capsule (2 × 400 mg/day) was given to 15 patients in the experimental group who received chemotherapy treatment, while only antiemetic treatment was applied to the control group. As a result of this study, it was reported that the ginger capsule was effective in preventing nausea and vomiting caused by chemotherapy. However, in the systematic review and meta-analysis study conducted by Lee and Oh,[32] it was found that ginger was not effective and did not contribute to the prevention of nausea and vomiting due to chemotherapy. In addition, it is stated in studies that some herbs (feverfew, garlic, ginger, gingko, etc.), including ginger, can cause lifethreatening bleeding when used alone or in combination with anticoagulants. Therefore, in terms of drug-herb interactions, it is important for CAM users to seek counseling from authorized health professionals.[20,21,28,30]

When the level of satisfaction and effectiveness with CAM use is examined in our study, the overall satisfaction score was 5.80 ± 1.43 out of 7, and the effectiveness score was 5.71 \pm 1.48 [Table 2]. In the study of Kav et al., [14] in which scoring was made similar to our study, while the general satisfaction (2.86 ± 1.57) and effectiveness (2.86 ± 1.63) levels of women with gynecological cancer about CAM methods were found to be lower than our study, when compared with the study of Molassiotis et al., [21] the level of satisfaction (5.27 \pm 1.52) was found to be similar to our study. At the same time, although energy treatments, one of the CAM methods, were used at a limited level (11.4%) in our study, satisfaction and efficiency were evaluated as the highest by the patients. This was followed by manipulative and body-based therapies, body and mind treatments, and biological-based treatments. When the literature was examined, no study was found in which satisfaction and effectiveness levels were evaluated according to CAM methods.

CONCLUSIONS

In our study, it was determined that approximately six out of ten women diagnosed with gynecological cancer use CAM, the use of CAM varies due to sociodemographic and diseasespecific factors, the satisfaction and effectiveness level of CAM use is high, and the majority of CAM users do not cooperate with healthcare professionals. It is observed that "prayer" and "herbal product" CAM methods are frequently used to increase the quality of life, strengthen the immune system, and cope with the side effects of treatment. According to our study results, first of all, CAM methods should be integrated into the medical education curriculum and the competence of all health professionals should be increased. The efficiency, advantages, disadvantages, and limitations of applications for CAM methods should be demonstrated with evidence-based studies.

Limitation of the study

The results of the study are limited to the research group and generalizations cannot be made.

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AUTHORS' CONTRIBUTIONS

Study concept and design: Pinar G and Ayhan A. Analysis, interpretation of data and preparation of manuscript: Pinar G. All authors have read and approved the final version of the manuscript.

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