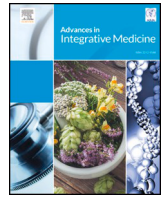




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Original Research Paper

Traditional and complementary medicine use and beliefs during COVID-19 outbreak: A cross-sectional survey among the general population in Turkey



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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19) caused a universal psychosocial impact, with many individuals exposed to threats preferring to try self-care interventions and non-conventional approaches such as traditional and complementary medicine (T&CM) for preventive purposes. This study was conducted to determine the use of and beliefs about T&CM among a subset of the general Turkish population during the COVID-19 outbreak.

Method: A cross-sectional online survey was carried out among the general population (aged ≥ 18 years) of Adana, Turkey during the strict lockdown period (April 11 to April 30, 2020). The survey instrument included details about sociodemographic characteristics, general information, T&CM use and beliefs. It was distributed among eligible participants via social media channels (Instagram, WhatsApp and Facebook accounts).

Results: Out of a total 389 participants, 39.3% ($n = 153$) used T&CM and 60.7% were non-T&CM users during COVID-19. Of those using T&CM, 61 (39.8%) reported the usage of more than one form of T&CM, mostly herbal medicine (30.8%), followed by nutritional supplements/vitamins (23.8%). 33.9% ($n = 52$) of participants using T&CM did not report T&CM use to their medical physicians. A statistically significant difference was observed between T&CM users and non-T&CM users in gender, age, marital status, level of education, income, and prior use of T&CM ($p < 0.05$). Social media ($n = 204$; 52.4%) was the primary source of information for T&CM use. Overall, 33.7%, 54.8% and 39% of participants in this study believed that T&CM therapies are effective, have fewer side-effects/safe and should be used for COVID-19, respectively.

Conclusion: During the outbreak of COVID-19, a significant proportion of the population reported the use of T&CM, with different beliefs about T&CM being observed. Better-structured T&CM-specific educational programs, enhanced physician-patient communication and access to reliable information are needed to ensure appropriate T&CM use during pandemics in Turkey.

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1. Introduction

The recent coronavirus disease-2019 (COVID-19) outbreak has become a major public health issue worldwide, like severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1,2]. COVID-19 has been declared a Public Health Emergency

for International Concern by the World Health Organization (WHO) [3]. COVID-19 is characterized by flu-like symptoms, including cough, fever, severe acute respiratory problems, and death in some cases [1,4]. COVID-19 is a serious threat to human health and as of October 2021, more than 200 million people have been diagnosed globally with over 4.5 million deaths due to COVID-19 [5]. COVID-19 caused a universal psychosocial impact and raised anger, fear and panic among the general population [6–8]. In such circumstances, individuals exposed to threats and uncertainty prefer to try preventive approaches including self-care interventions and adhere to non-conventional

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approaches such as traditional and complementary medicine (T&CM) to demonstrate their control and reduce risk [9,10].

The term T&CM refers to therapeutic products and procedures that are not a part of conventional medical care, and are often used by patients without medical supervision [11]. There are several types of T&CM that are practiced in different regions, which tends to make T&CM a difficult phenomenon to identify and calculate [12]. However, according to the published literature, the reported rate of T&CM use among the general population ranged from 9% to 76% globally [13,14]. T&CM therapeutic methods and preferences vary widely across the globe due to the socio-cultural, historical, traditions, diseases prevalence as well as religious background of the individuals [15,16].

Anatolia, the region where the Republic of Turkey is now centered, has been home for several ancient civilizations and traditional medicine approaches have been developed and influenced throughout the centuries. The use of T&CM for various diseases is widespread in Turkey [17,18], as well as other Middle east countries such as Iran [19], Syria [20], Iraq [21], Lebanon [22], Palestine [23], Saudi Arabia [10,15,16] and Kuwait [24]. The Ministry of Health in Turkey announced the first legal regulation for T&CM use in 2014, with an aim to build a resource center for all T&CM-related matters, to regulate T&CM practices in healthcare facilities and to provide T&CM education [25]. However, there are still legal and institutional problems, including a lack of structured and comprehensive education/training programs existing in Turkey related to T&CM [26].

The most commonly reported T&CM techniques in previously published studies in Turkey include prayer, herbal teas/ herbal therapies, multi-vitamin/nutritional supplement, acupuncture, cupping, homeopathy, massage and apitherapy [17,18,27,28]. T&CM practices in Turkey are generally related to the consumer's religious values [27,28], and the use of T&CM is also often correlated with several factors such as attitudes and beliefs, socio-demographic, health characteristics and cultural issues of people. Predicting variables such as information about T&CM, gender, age, income, educational and health status, and prior use of T&CM were also highlighted in previous studies [27–29].

The usage of T&CM in infectious diseases has gained in popularity and has been highlighted in previously conducted studies [9,17,18]. Whilst many T&CM are considered to be safe, there are potential direct and indirect risks associated with T&CM use. Direct risks come from the T&CM intervention itself (e.g., poor manufacturing quality, contamination) or its interactions with other therapies (e.g., herb/drug interactions). Examples of indirect risks include opportunity costs when a less effective TC&M is used in place of other effective treatments, delays in seeking medical care and failure to deliver prescribed therapies or T&CM medicines being taken in sub-therapeutic doses [30]. According to the recent study, the use of T&CM medicines has increased significantly among individuals who are afraid of contracting COVID-19, without considering the potential harmful effects of such drugs [10]. Previous literature has documented the use of T&CM products during previous threatening emerging infectious disease outbreaks such as SARS and MERS [9]. In the Middle East region, limited studies have explored the use of T&CM among the general population as preventive measures during the COVID-19 pandemic [10]. Moreover, studies examining the use of T&CM by the general population during COVID in Turkey as well as globally, were not found in literature searches. Therefore, this study was conducted to determine the use and belief about T&CM among a regional Turkish general population (Adana) during the COVID-19 outbreak.

2. Method

2.1. Study design and setting

A cross-sectional online survey was carried out during the COVID-19 outbreak among the general population in Adana, Turkey.

Adana is the 5th largest city in Turkey with a population of just over 1.2 million. This study was conducted during the strict COVID-19 lockdown period from April 11 to April 30, 2020 [31].

2.2. Inclusion and exclusion criteria

Participants aged were ≥ 18 years and currently living in Adana city of Turkey were included, while, respondents below 18 years of age were excluded from this study.

2.3. Ethical consideration

The study was carried out in compliance with the Helsinki Declaration and the research protocols were accepted by the Ethical Review Committee of Cukurova University, Adana, Turkey (Meeting No: 98, Date: April 10, 2020, [Supplementary File 1](#)).

2.4. Sampling method

A convenience sampling technique was used in this study. A self-reported questionnaire was designed for this study, based on a literature search of similar studies [9,10,27,28]. Three researchers reviewed the questionnaire tool to assess the appropriateness, validity, consistency, and adequacy of the questions. A questionnaire was prepared in English and Turkish (the native language of Turkey) using *Google forms* [32], and a survey link was distributed electronically to the eligible participants via social media channels (Instagram, WhatsApp and Facebook). In this work, the online data was collected because a community-based sampling survey was difficult to conduct during this special period due to lockdown restrictions and to prevent potential COVID-19 exposure. A pilot study on 30 participants was also performed prior to the survey being launched. Statistical Package for the Social Sciences (SPSS: Chicago, IL, U.S.A, Version 22.0) was used for the calculation of reliability coefficient *Cronbach alpha* (value: 0.776). The final online survey was launched on April 11, 2020 and the response acceptance was closed on April 30, 2020 when the required sample size was reached.

2.5. Data collection instrument

A short introduction to the context, purpose, procedures, anonymity and confidentiality statements, as well as notes for the completion of the questionnaire, were included in the final one-page questionnaire. A yes-no question had to be answered by participants to approve their desire to participate. The participants were directed to complete the self-reporting questionnaire after approval. There were four parts of the questionnaire: sociodemographic characteristics, general information, T&CM use and beliefs related items. Sociodemographic variables included age, gender, marital status, educational level and monthly income. General information included 5 questions related to the presence of any disease, knowing about COVID-19, previous use of T&CM and source of information for T&CM and COVID-19. The third part consisted of 3 items related T&CM use, types of T&CM modalities and sharing T&CM information with their family physicians. The last part of the survey consisted of five questions regarding the T&CM recommendation to others, effectiveness, side effects, safety and use of T&CM for COVID-19 and was answered on a yes/no/ uncertain basis.

2.6. Sample size

Using the Raosoft sample size calculator [33], the minimum required calculated sample size was 385. The response distribution was assumed to be 50%, the margin of error 5% and the confidence level of 95% were selected for the estimation of sample.

$$n = N \frac{x}{(N - 1)E^2 + x}$$

Where x is a confidence interval, N is the size of population and E is the margin of error.

2.7. Statistical analysis

Statistical analysis was carried out via SPSS (version 22.0). Descriptive statistics for categorical variables were calculated as frequencies and percentages. A Chi-square test was used to check the difference in the characteristics of the participants. A p-value (<0.05) was considered as a statistically significant.

3. Results

A total of 401 respondents completed the questionnaire (n = 12; 3% of responses were omitted due to missing information and errors in the filling of the questionnaire). 389 participants were ultimately included in this study. Females (n = 254; 65.3%) were more present than males (n = 135; 34.7%), with an average age of 42.7 years across all participants. The majority of participants were married (79.9%), had a university level of education (n = 300; 77.1%) and had monthly incomes of more than 4000 Turkish liras (approximately USD 600) (49.4%). Approximately 61.2% of participants reported absence of any illness and 21.6% reported heart disease, followed by diabetes (14.4%). The majority (n = 376; 96.7%) of the respondents were aware of COVID-19% and 31.6% reported the use of T&CM prior to COVID-19. (Table 1).

Overall, 39.3% (n = 153) of the participants were using T&CM (using at least one T&CM) and 60.7% were non-T&CM users for COVID-19 prevention in this study. Additionally, 61 (39.8%) participants reported the usage of more than one form of T&CM. Herbal medicines (30.8%; n = 66/214) were the T&CM most commonly used by respondents, followed by nutritional supplements/vitamins (23.8%; n = 51/214) and prayer/faith healing (17.7%; 38/214).

Table 1
Sociodemographic characteristics of the participants (n = 389).

Variable	Number (n)	Percentage (%)
Gender		
Male	135	34.7
Female	254	65.3
Age		
≤40 years	137	35.2
≥40 years	252	64.8
Marital status		
Married	311	79.9
Single	78	20.1
Education level		
Primary School	11	2.8
Secondary School	21	5.4
High school	57	14.7
University	300	77.1
None	0	0
Monthly income		
Less than 2000 Turkish Lira (TL)	56	14.4
2000–4000 Turkish Lira (TL)	141	36.2
More than 4000	192	49.4
Any illness (Disease)		
Heart disease	84	21.6
Diabetes	56	14.4
Asthma	11	2.8
None	238	61.2
Know about COVID-19		
Yes	376	96.7
No	13	3.3
Any T&CM Usage prior to the COVID-19		
Yes	123	31.6
No	266	68.4
Total	389	100

Table 2

Types of traditional and complementary medicine modalities (at least one or more than one form of T&CM) used among the general population during the COVID-19 outbreak (n = 214).

T&CM modalities	Number (n)	Percentage (%)*
*Herbal medicines	66	30.8
**Nutritional supplements/vitamins	51	23.8
Prayer/faith healing	38	17.7
Hajama (Cupping)	21	9.8
Massage	18	8.4
Apitherapy (royal jelly, bee pollen etc.)	11	5.1
Acupuncture	8	3.7
Leech therapy	1	0.5
Chinese traditional medicines	0	0
Homeopathy	0	0
Aromatherapy	0	0
Hypnotherapy	0	0

Abbreviation: * Percentage (%) explaining that more than once response was allowed. T&CM: traditional and complementary medicine, n: frequency, %: percentage, COVID-19: Coronavirus disease-2019.*Herbal medicines: includes *Aloe vera, Garlic, Ginkgo biloba, Senna, Ginseng, Cranberry, herbal tea, Glucosamine, Soy, others.* **Nutritional supplements/vitamins: include different multi vitamins and minerals like calcium and iron etc.

Additionally, in our study, the use of T&CM including prayer/faith healing was 39.3% and excluding prayer/faith healing was 29.5%. Furthermore, 33.9% (n = 52 out of 153 T&CM user) of participants did not notify their conventional physicians about their T&CM use for COVID-19 (Table 2).

There was also a statistically significant difference in gender, age, marital status, educational level, income and previous use of T&CM (p < 0.05) between T&CM users and non-T&CM users (Table 3).

In this study, social media (n = 204; 52.4%), relatives/neighbor/friends (n = 107; 27.5%) and television/radio (n = 67; 17.2%) were the primary source of information for T&CM use during COVID-19 (Fig. 1).

Mixed responses were obtained for belief-related items. Overall, 28% (n = 109) of the 389 participants had recommended T&CM to others for COVID-19. About one third (33.7%) of participants indicated that they believed that T&CM was effective for COVID-19%, and 60.7% did not agree with this statement. However, the majority of respondents (91.5%) perceived that T&CM should be tested for side effects prior to use in COVID-19 therapy. More than half (54.8%) of the respondents believed that T&CM treatments have fewer side effects and safer than modern/conventional medications. About one third (39%) of participants believed that T&CM remedies are more natural and should be used for the treatment of COVID-19 (Table 4).

4. Discussion

To the author's knowledge, this research is the first attempt to evaluate the T&CM use and beliefs among a regional Turkish population during the outbreak of COVID-19. In this study, a significant proportion of the population (39.3%) reported the use of T&CM for COVID-19 during the April 2020 COVID-19 lockdown period in Turkey. Recently published studies in Saudi Arabia (22.1%) [10] and South Korea (76.1%) [9] also reported significant levels of T&CM use during COVID-19 and MERS outbreak. Previously conducted studies in Turkey also reported general T&CM use and prevalence ranging from 7.1% to 38.8% [17,18,27]. The prevalence of T&CM practices varies widely between different regions, countries and throughout the globe, largely due to social, traditional and religious differences [15–17].

The most commonly recorded T&CM approaches for COVID-19 in this study were herbal medicines and nutritional supplements/vitamins. Similar findings were also reported by the study regarding the use of herbal products during the COVID-19 in Saudi Arabia [10]. Herbal medicines and nutritional supplements/vitamins usage were

Table 3
Socio-demographic and T&CM use characteristics (n = 389).

Variable	T&CM user (n = 153) n (%)	T&CM non-user (n = 236) n (%)	Total (n = 389) n (%)	*p-value
Gender				0.002
Male	52 (34.0)	83 (35.1)	135 (34.7)	
Female	101 (64.0)	153 (64.9)	254 (65.3)	
Age				0.001
≤40 years	34 (22.2)	103 (43.6)	137 (35.2)	
≥40 years	119 (77.8)	133 (56.4)	252 (64.8)	
Marital status				0.042
Married	124 (81.0)	187 (79.2)	311 (79.9)	
Single	29 (19.0)	49 (20.8)	78 (20.1)	
Education level				0.001
Primary school	9 (5.8)	2 (0.8)	11 (2.8)	
Secondary school	15 (9.8)	6 (2.5)	21 (5.4)	
High school	24 (15.7)	33 (13.9)	57 (14.7)	
University	105 (68.6)	195 (82.6)	300 (77.1)	
None	0 (0)	0 (0)	0 (0)	
Monthly income				0.001
Less than 2000 Turkish Lira (TL)	15 (9.8)	41 (17.4)	56 (14.4)	
2000–4000 Turkish Lira (TL)	38 (24.8)	103 (43.6)	141 (36.2)	
More than 4000	100 (65.4)	92 (39.0)	192 (49.4)	
Any illness (Disease)				0.048
Heart disease	21 (13.7)	63 (26.7)	84 (21.6)	
Diabetes	37 (24.2)	19 (8.0)	56 (14.4)	
Asthma	8 (5.2)	3 (1.3)	11 (2.8)	
None	87 (56.8)	151 (64.0)	238 (61.2)	
Know about COVID-19				0.003
Yes	145 (94.8)	231 (97.9)	376 (96.7)	
No	8 (5.2)	5 (2.1)	13 (3.3)	
Any T&CM Usage prior to the COVID-19				0.001
Yes	89 (58.2)	34 (14.4)	123 (31.6)	
No	64 (41.8)	202 (85.6)	266 (68.4)	

Abbreviation: Traditional and Complementary Medicine; Complementary and alternative medicines, n: frequency, %: percentage, COVID-19: Coronavirus disease-2019, TL: Turkish lira.

* p-value < 0.05 was considered as a statistically significant.

also reported as popular T&CM modalities in general studies in the Eastern Mediterranean Region countries [10,16,24,34] and in Turkey [17,27,28].

Globally, herbal products and dietary supplements are used either to promote wellbeing or to assist with health-related issues [10]. The rapid spread of the recent outbreak of the COVID-19 pandemic has increased fear, panic and anger among the general population [7,8,10]. As might be predicted, peoples vulnerable to the risks of such infections appear to be searching for self-care strategies and use unconventional treatments such as herbal products and nutritional supplements to minimize the health-related problems and to develop a greater sense of control in the condition. Prayer/faith healing was also another popular T&CM therapy observed in this study, similar to findings with previous studies in Saudi Arabia [15], Palestine [23] and Turkey [18,29]. Similarities in the cultural environment in Turkey like other Muslim middle east countries may partly explain this. Patients may believe in spiritual power and try to handle the disease in the best possible way by adapting to health care. This can be clarified by the fact that prayer has a significant position and peoples are attached to religious values in Turkish society [17,18]. It is reported that many national surveys of T&CM use do not ask about prayer/faith based practice, but when they do the rates are often quite substantial. Indeed, whether prayer should be classified as a T&CM is contentious and can even be confusing for survey respondents, with subsequent measurement errors. As a result, in future this problem should be addressed to avoid potential misunderstandings and measurement inaccuracies around the levels and impacts of T&CM use [35].

The participants with higher age groups (over 40 years of age), female gender, married, tertiary education, higher monthly income and previous use of T&CM were more likely to use T&CM in this study. A study conducted during the MERS outbreak documented gender, marital status, smoking status, alcohol consumption, and prior use of T&CM as a possible predictor of T&CM use [9]. Another study carried out in Iraq reported that the use of T&CM was associated with patient's educational level and marital status [21]. A Turkish study revealed that T&CM use was more common in women with higher age and primary school graduates [18]. Other studies reported that younger age was also associated with T&CM use [36,37]. The inconsistency in the findings may be due to differences in the sample size of the studies, population and the disease characteristics [9].

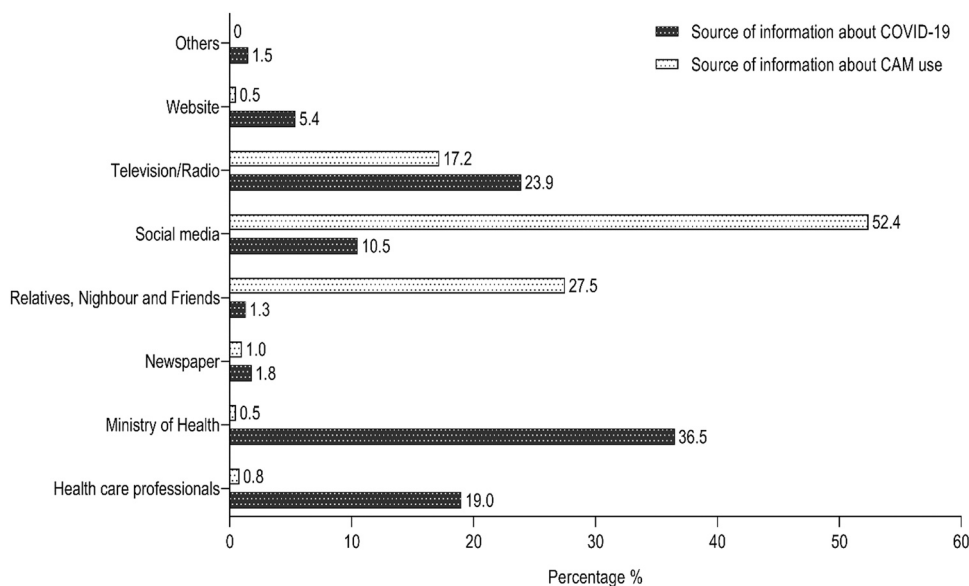


Fig. 1. Source of information for T&CM use during COVID-19.

Table 4
Belief of general population about traditional and complementary medicine (T&CM) use during the COVID-19 outbreak (n = 389).

Variables (Questions)	Response n (%)		
	Yes	No	Uncertain
Did you recommend T&CM therapies to others (friend, neighbor, family or relatives) for COVID-19?	109 (28)	213 (54.8)	67 (17.2)
Do you think T&CM therapies are effective for COVID-19?	131 (33.7)	236 (60.7)	22 (5.6)
Do you think T&CM should be tested for side effects before used in COVID-19 treatment?	356 (91.5)	20 (5.1)	13 (3.3)
Do you think T&CM therapies have fewer side effects and safe than the modern medication?	213 (54.8)	152 (39)	24 (6.2)
Do you think T&CM modalities are natural and should be used for the treatment of COVID-19?	151 (38.8)	224 (57.6)	14 (3.6)

Abbreviation: T&CM: Complementary and alternative medicines, n: frequency, %: percentage, COVID-19: Coronavirus disease-2019.

In the current study, approximately one-third (33.9%) of the participants using T&CM did not share information about their T&CM use for COVID-19 with their physicians. Comparable findings were also reported by another study conducted in Turkey which reported that less than half (45.7%) of T&CM users shared their use with the physician in a health institution in Turkey [28]. Turkish health care authorities should build an effective platform and enhanced physician-patient communication to provide validated and accurate information to protect the safety of people during public health emergencies. Differences in the method of obtaining T&CM information were also observed during COVID-19 among participants in this study. In this study, social media (52.4%) followed by relatives/neighbor and friends (27.5%) were the primary sources for T&CM related information. These results were also supported by the Saudi Arabian study of T&CM for COVID-19 which also reported that the most common source for information regarding T&CM was via social media [10]. However, the majority of respondents in the South Korean of T&CM for COVID-19 stated the mass media as the main source for the T&CM information during MERS outbreak [9]. Previously conducted general studies in Turkey reported that, relatives and friends (50.9%) were the most primary source of information regarding T&CM methods [17]. According to the recent 2020 report, there were 54 million social media users in Turkey, and this level of use may be a probable reason why so many respondents obtained information via social media about T&CM use in our study [38]. Generally, the information provided by the Ministry of Health of any country is reliable and more accurate, but social media sites may be a more easily accessible source of information, even if there is a possible risk of misinformation [39].

Furthermore, a considerable proportion of the participants in our study (28%) recommended T&CM remedies to others for COVID-19. Willingness to recommend T&CM for epidemic outbreaks was higher in both the South Korean (72.6% for MERS) [9] and Saudi Arabian studies (37% for COVID-19) [10]. According to the Turkish study of general populations, over half (59.4%) of the participants who used T&CM have recommended to others, so recommendations appear lower among this study [28]. Around one-third of participants in this study perceived that T&CM therapies were effective and should be used for the treatment of COVID-19. These results deviated from the South Korean study, which reported higher (73.4%) belief in the efficacy of T&CM for MERS [9]. Perceived effectiveness of T&CM among users was often the most reported reason for T&CM use [29]. In addition, more than half (54.8%) of the participants in this study believed that T&CM modalities had less side effects than modern/conventional medicines and 38.8% advocated the use of T&CM modalities for the COVID-19 treatment. The general population and patients may not know about potential drug-T&CM interactions, and this may be why they are considered such low risk. The interaction of T&CM remedies with medically approved medicines raised the issue of safety [40]. There is urgent need for the implementation of T&CM regulation act, enhanced physician-patients communication and educational programs for the general population about T&CM. Such interventions may be helpful to prevent unwanted effects of inappropriate T&CM use, and guide more effective T&CM use.

Like any other study, this research had also limitations. This was an online survey in which responses depended primarily on honesty and were affected by recall ability, indicating that there could be a chance of bias. There are few studies that examined the use of T&CM worldwide and primarily in the Middle East and Turkey during the COVID-19 pandemic, which limited our ability to compare our results with similar studies of a similar population and socioeconomic level, thus our data may not be able to be generalized, particularly as this study was from a convenience sample from one region of Turkey that were recruited via social media channels rather than a representative sample from the whole country. This may have biased the results for example over or underestimation of total T&CM use, the types of T&CM used, information sources. This study did not question about the reasons for T&CM use, therefore we do not know if participants were using T&CM to prevent or treat COVID-19, to manage other health problems that have arisen or been exacerbated during the pandemic or lockdown, or for the ongoing management of pre-existing conditions. We also do not know if during the lockdown there was reduced access to conventional medical care and T&CM was being used because it was the only option or was more readily available, or if the reverse was true. Finally, we did not explore information about whether T&CM was self-prescribed, prescribed or delivered by a T&CM practitioner, or prescribed or delivered by a conventional medicine practitioner. Despite these limitations, our study will provide important data for health authorities to take appropriate and informed control measures concerning the quality and safety of medical practices regarding T&CM. The study will also provide baseline data for researchers to further investigate the determinants of T&CM use in different health care settings and populations.

5. Conclusion

This study contributes information about the current use of T&CM among a regional Turkish population during COVID-19. A significant proportion of the population reported using T&CM and different beliefs among participants about T&CM was also observed. Herbal medicine and nutritional supplements/vitamins were the most common T&CM modalities used for COVID-19. Further multi-regional studies are needed to explore the reasons for T&CM use and source of T&CM prescribing (self-prescribed, prescribed by a T&CM practitioner, or prescribed or delivered by a conventional medicine practitioner). Given the significant use in serious conditions, efforts to support research in the field of T&CM are also needed, as well as better-structured T&CM-specific educational programs, enhanced physician-patient communication, access to reliable information by authentic sources (qualified medical practitioners, national health authority etc.), collaboration among the local T&CM regulatory authorities, T&CM practitioners and users are crucial for appropriate use T&CM during pandemics in Turkey and beyond.

Ethical statement

The study was carried out in compliance with the Helsinki Declaration and the research protocols were accepted by the Ethical Review Committee of Cukurova University, Adana, Turkey (Meeting No: 98, Date: April 10, 2020, [Supplementary File 1](#)).

Authors statement

The author (s) declared no conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. All authors disclose no competing financial or conflict of interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.aimed.2021.09.002](https://doi.org/10.1016/j.aimed.2021.09.002).

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