

## Traditional Islamic Medicine Utilization among Adult Patients with Cancer in Saudi Arabia

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Received: August 12, 2017; Published: September 22, 2017

### Abstract

**Introduction:** Traditional Islamic Medicine (TIM) is a diverse of health practice used by patients as an orientation to their own values and beliefs towards good health which might affect the conventional cancer therapy. In this study we aim to determine the utilization of TIM among adult oncology patients in Saudi Arabia and to evaluate the correlations between the variants and each type of TIM used.

**Material and Methods:** A cross sectional descriptive study was conducted. Questionnaires were completed by patients eligible for treatment with chemotherapy. Patients diagnosed with cancer were invited to participate in the study after signing a consent form. The questionnaire is divided into three parts: socio-demographic data, clinical data and TIM utilization data.

**Results:** We collected a total of 104 questionnaires. The mean age of the patients enrolled in the study was 52.5 years. The median age was 45 years. Out of 104 patients 97.1% used TIM. The remedies used with the highest percentage were honey (57.7%), followed by Zamzam water (26%), and followed by Nigella and Fenugreek (25% each). Majority of the patients (91%) used the remedies for religious nature explained by them as "following Quran and Al Sunnah Al Nabawiah for our Prophet Mohamed".

**Conclusions:** TIM usage is highly prevalent among Saudi cancer patients. It indicates the strong influence of religion on people's behavior mainly those diagnosed with cancer. TIM provides a remarkable source of new drug development. They might possess different therapeutic activities. These pharmacological properties need to be further studied on a larger scale.

**Keywords:** Traditional Islamic Medicine; Oncology; Honey; Quraan

### Introduction

Patients diagnosed with cancer suffer from the disease, its symptoms and treatment side effects. Patients and caregivers want to do everything that might combat all these issues including disease treatment and cancer prevention. They want to feel better and to cope with having cancer and its treatment toxicities. Patients might turn to religious approaches including prayer, reading Quraan, drinking Zamzam water and using the prophetic medicine in addition to the conventional standard therapy recommended by the treating oncologist.

Complementary and alternative medicine (CAM) is considered as a leading modality for treatment of patients with cancer in different regions globally as Middle East, Europe, United State and China. Results from the 2002 survey conducted in USA by National Health Information showed that 36% of adults use CAM. The American spent 33.0 billion U.S dollar, accounting for 11.2% of total out of pocket health care expenditure on traditional products. In Saudi Arabia Al-Faris and colleagues, 2008 conducted a survey in Riyadh region and

concluded that 73% of Saudi population had previously used CAM. While Al Bedah and colleagues, 2013 conducted a study in Al-Qassim province in Saudi Arabia and found that 74% of the subjects had visited CAM providers, mainly spiritual healers, herbalists and providers of honeybee products. These subjects spent 350,000 USD on CAM visits and 300,000 USD purchasing CAM products [1-10].

In Arab world, the population uses the Traditional Islamic Medicine (TIM). TIM is defined by Alrawi and colleagues as a system of healing practiced since antiquity in the Arab world within the context of religious influences of Islam and comprised of medicinal herbs, dietary practices, mind-body therapy, spiritual healing and applied therapy. Whereby many of these elements reflect an enduring inter-connectivity between Islamic, medical and prophetic influences as well as regional healing practices emerging from specific geographical and cultural origins [11].

Muslim patients with cancer turn mainly to Quran and Sunnah, which are considered as the main two sources that form the basis of Islam, for guidance in all areas of life including health and medical matters. Narrated Abu Huraira: The Prophet Muhammad Peace Be Upon Him (PBUH) said, "There is no disease that Allah has created, except that He also has created its treatment". Sahih Al Bukhari: Book #71, Hadith #582 [12]. Patients explore and use traditional forms of medicine with faith that any cure is from Allah. According to those beliefs, the uses of traditional Islamic medicine lead to mental wellbeing and spiritual cures. Traditional medicine in Islam is often referred to as the Medicine of the Prophet (PBUH) (al-tibb an-Nabawi) [13]. Examples for TIM are black seed, honey, olive oil, dates, Zamzam Water and siwak [14-17].

In this study we aim to determine the utilization of Traditional Islamic Medicine (TIM) among adult patients with cancer in Saudi Arabia and to evaluate the correlations between the variants such as age, sex, level of education and each type of TIM used.

### Materials and Methods

**Study design:** This is a cross sectional descriptive, correlational study.

**Setting:** Tertiary care hospital in Riyadh, Saudi Arabia.

**Ethical consideration:** We had an approval from the local Institutional Review Board (IRB) in the hospital to conduct the study and to access patient's records.

### Research sample

The sample size was calculated by the sample size calculator based on the number of patients with cancer visiting the out-patient chemotherapy day unit, 5% margin of error and 95% confidence level. The significant p value is < 0.05.

**Inclusion criteria:** All patients > 18 years old diagnosed with any type of cancer, at any stage of the disease and eligible for chemotherapy treatment at adult oncology out-patient clinic were approached for possible inclusion in the study.

In this present study a total of 218 patients with cancer were invited to participate in the study and to complete the survey. The number of surveys collected and completed by the participants was 104. The survey response rate is 47.7%.

### Procedures

A structured questionnaire was designed by the oncology clinical pharmacist based on the aim of the study. The questionnaire was developed in Arabic language, reading level of grade 6. We considered the two important psychometric properties, reliability and validity.

The survey consists of three main sections. The first section is the demographic data that includes sex, age, marital status, educational level, employment status, region, smoking status, and other co-morbid diseases. The second section is the clinical characteristics that include the type of cancers, time since diagnosis, and the stage of the disease. The third section is the TIM utilization data that includes the following questions:

1. Are you currently using TIM?
2. What are the TIM products that you are using?
3. What is the purpose of having TIM?
4. How often do you use each product of TIM?
5. How much are you having from each product?
6. Who recommended TIM for you?

The vast majority of the questions had pre-formulated answers.

All participating patients received information from the assigned pharmacist about the study and its purpose. Patients were not paid to take part in the study and were informed that they were free to decline answering any question with which they were not comfortable. Patients were assured that any information they would reveal would strictly remain confidential and would only be used for research purpose. Those who accepted the enrollment in the study signed a consent form.

The questionnaire was anonymous. Patients completed the questionnaire while they were waiting at the chemotherapy day unit to have their prescribed treatment. In case of patients whom are not able to interact, the caregiver completed the questionnaire. The assigned pharmacist was available in the unit to help the patients if there is a need or having questions and then to collect the questionnaires upon completion. Socio-demographic data were assessed by a self-report questionnaire. The clinical data were retrieved from the medical electronic records and from patient's own files. The study took place from January 2012 to August 2012.

### Study validation (pilot study)

To evaluate the questionnaire, validation was performed on 15 patients with cancer selected randomly. We used simple randomization using the daily list of patients based on numbers. The questions were clear for the patients and none were modified. The findings from these surveys were included in the analysis.

### Data analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS) program version 17. Descriptive statistics were calculated with all variables to summarize the data. A  $P < 0.05$  was considered statistically significant.

### Results

A total of 104 surveys were completed and collected. The rest of the surveys were not returned to us. Most of these patients mentioned that they prefer to complete the survey at home, but unfortunately they did not return the surveys to the assigned pharmacist.

### Socio-demographic

About 54 patients were female (52%). The majority of participants were above 40 years of age (73%). The median age was 45 years and the mean age was 52.5 years. Around half of the patients (44%) had secondary school education; more than fifty percent (51%) were not employed. Fifty percent (50%) were from the middle region in the Kingdom. Socio-demographic data is presented in (Table 1).

|                              | N (104) | %    |
|------------------------------|---------|------|
| Gender                       |         |      |
| Female                       | 54      | 52   |
| Male                         | 50      | 48   |
| Age                          |         |      |
| 20 - 30                      | 11      | 10.6 |
| > 30 - 40                    | 17      | 16.3 |
| > 40 - 50                    | 25      | 24   |
| > 50 - 60                    | 19      | 18.3 |
| > 60 - 70                    | 19      | 18.3 |
| > 70                         | 13      | 12.5 |
| Marital status               |         |      |
| Married                      | 92      | 88.5 |
| Single/Divorced/widowed      | 12      | 11.5 |
| Education level              |         |      |
| Illiterate                   | 13      | 12.5 |
| Primary education            | 26      | 25   |
| Secondary education          | 46      | 44.2 |
| College/University education | 19      | 18.3 |
| Employment status            |         |      |
| Employed                     | 34      | 32.7 |
| Not employed                 | 53      | 51   |
| Retired                      | 17      | 16.3 |
| Area (region)                |         |      |
| North                        | 15      | 14.4 |
| South                        | 25      | 24   |
| West                         | 4       | 3.85 |
| East                         | 8       | 7.7  |
| Middle                       | 52      | 50   |
| Smoking status               |         |      |
| Smoker                       | 10      | 9.6  |
| Non smoker                   | 94      | 90.4 |
| Other co-morbid diseases     |         |      |
| None                         | 73      | 70.2 |
| Diabetes                     | 23      | 22.1 |
| Hypertension                 | 16      | 15.4 |
| Others                       | 11      | 10.6 |

**Table 1:** Socio-demographic characteristics.

**Clinical characteristics**

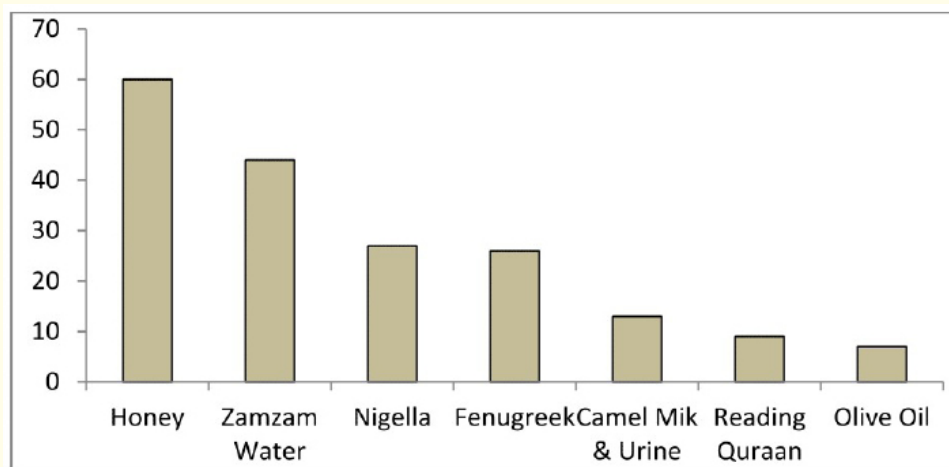
Most of patients were diagnosed with breast cancer (34.6%) followed by colorectal cancer and Non-Hodgkin’s lymphoma (18.3%) each. The duration of medical treatment since diagnosis was 6 months to 2 years in (75%) of patients. About (44.2%) of the patients had Stage 3 tumor. Some patients had other co-morbid diseases (Table 2).

| Clinical data               | N (104) | %    |
|-----------------------------|---------|------|
| <b>Type of cancer</b>       |         |      |
| Breast cancer               | 36      | 34.6 |
| Colorectal cancer           | 19      | 18.3 |
| NHL                         | 19      | 18.3 |
| HL                          | 13      | 12.5 |
| Others                      | 17      | 16.3 |
| <b>Time since diagnosis</b> |         |      |
| < 6 months                  | 15      | 14.4 |
| 6 month - 2 years           | 78      | 75   |
| > 2 years                   | 11      | 10.6 |
| <b>Stage of the disease</b> |         |      |
| S1                          | 0       | 0    |
| S2                          | 18      | 17.3 |
| S3                          | 46      | 44.2 |
| S4                          | 19      | 18.3 |
| Not mentioned               | 21      | 20.2 |

**Table 2:** Clinical characteristics.

**Pattern of TIM utilization among the participants**

Most of the patients used TIM at different levels (97.1%). The range of TIM products used is one to seven. The mean of TIM was 2.71, std. deviation 1.28, and the average was 1.6 types per patient. The extent of utilization varied according to the demographic data. The most common TIM used are Honey (57.7%), Zamzam Water (42.3%), Nigella (26%), Fenugreek (25%), Camel milk and urine (12.5%) (Figure 1).



**Figure 1:** Types and pattern of TIM utilization.

We asked the patients about the frequency and quantity taken from the most common used TIM. Most of the patients replied that they use honey as 1 - 2 teaspoons in the morning, either alone or dissolved in water, while Nigella was taken by most of the patients as 7 seeds once daily in the morning, Zamzam water was taken instead of the normal water. Fenugreek was used by patients daily after boiling it in water. TIM was used by patients for years during treatment from cancer.

### Sources of TIM utilization recommendations

Most of the patients (87%) reported that they used TIM based on recommendations from Quraan and Al Sunnah of Prophet Mohamed (PBUH), (57%) had recommendations from family members and friends and (22%) had recommendations from other patients.

### Correlations

We evaluated the correlation between the variants and each type of TIM used. We correlated the independent variables which included the age, level of education with the dependent variables such as the use of honey, Zamzam, Nigella, Fenugreek, camel milk and urine and olive oil.

#### Honey

**Education:** We ranked education to 4 ranks (illiterate, primary, secondary and college/university). The correlation between use of honey and level of education college/university, secondary school, primary school, illiterate were ( $p = 0.036$ ,  $r = -0.205$ ), ( $p = 0.911$ ,  $r = -0.011$ ), ( $p = 0.796$ ,  $r = 0.026$ ), ( $p = 0.026$ ,  $r = 0.218$ ) respectively. Results were statistically significant with weak negative correlation in patients with college/university level of education and it was statistically significant with weak positive correlation in illiterate patients.

**Age:** We ranked the age to 2 ranks (< 40 years and > 40 years). The correlation between use of honey and age < 40 years and > 40 years were ( $p = 0.10$ ,  $r = -0.162$ ), ( $p = 0.086$ ,  $r = 0.169$ ) respectively.

**Type of cancer:** No significant correlation.

#### Fenugreek

**Education:** The correlation between use of Fenugreek and level of education college/university, secondary school, primary school, illiterate were ( $p = 0.025$ ,  $r = -0.220$ ), ( $p = 0.302$ ,  $r = 0.102$ ), ( $p = 0.312$ ,  $r = 0.100$ ), ( $p = 0.741$ ,  $r = -0.033$ ) respectively. Results were statistically significant with weak negative correlation in patients with college/university level of education.

**Age:** The correlation between use of Fenugreek and age < 40 years and > 40 years were ( $p = 0.075$ ,  $r = -0.176$ ), ( $p = 0.032$ ,  $r = 0.211$ ) respectively. Results were statistically significant in patients > 40 years.

**Type of cancer:** Use of Fenugreek was positively associated with the type of cancer, mainly colon cancer,  $p = 0.005$ .

#### Nigella

**Education:** The correlation between use of Nigella and level of education college/university, secondary school, primary school, illiterate were ( $p = 0.842$ ,  $r = 0.020$ ), ( $p = 0.727$ ,  $r = -0.035$ ), ( $p = 0.651$ ,  $r = -0.045$ ), ( $p = 0.373$ ,  $r = 0.088$ ) respectively.

**Age:** The correlation between use of Nigella and age < 40 years and > 40 years were ( $p = 0.483$ ,  $r = -0.070$ ), ( $p = 0.843$ ,  $r = 0.020$ ) respectively.

**Type of cancer:** Use of Nigella was positively associated with type of cancer, mainly HL,  $p = 0.036$ .

#### Camel milk and urine

**Education:** The correlation between use of Camel milk and urine and level of education college/university, secondary school, primary school, illiterate were ( $p = 0.561$ ,  $r = 0.058$ ), ( $p = 0.606$ ,  $r = -0.051$ ), ( $p = 0.612$ ,  $r = 0.050$ ), ( $p = 0.580$ ,  $r = -0.055$ ) respectively.

**Age:** The correlation between use of Camel milk and urine and age < 40 years and > 40 years were (p = 0.311, r = -0.100), (p = 0.075, r = 0.175) respectively.

**Type of cancer:** Use of Camel milk and urine was negatively associated with type of cancer, mainly breast cancer, p = 0.005.

**Olive oil**

**Education:** The correlation between use of Olive oil and level of education college/university, secondary school, primary school, illiterate were (p = 0.214, r = -0.123), (p = 0.515, r = 0.065), (p = 0.823, r = 0.022), (p = 0.884, r = 0.015) respectively.

**Age:** The correlation between use of Olive oil and age < 40 years and > 40 years were (p = 0.502, r = -0.067), (p = 0.405, r = -0.083) respectively.

**Type of cancer:** Use of olive oil was positively associated with type of cancer, mainly breast cancer, p = 0.003.

Patients were interviewed for the purpose of using the TIM. The highest percentage of patients said that they use TIM to treat cancer 86.5%, followed by 55.8% to improve general health, 41.3% to improve the immunity, 13.5% to improve bone pain and 10.5% to improve the treatment side effects (Table 3).

| Purpose of using TIM              | %    |
|-----------------------------------|------|
| To treat cancer                   | 86.5 |
| To improve general health         | 55.8 |
| To improve immunity               | 41.3 |
| To improve bone                   | 13.5 |
| To improve treatment side effects | 10.5 |

**Table 3:** Purpose of using TIM.

**Discussion**

**Prevalence of TIM use**

In this cross sectional descriptive correlational study, 104 surveys were completed and collected. We surveyed the patients diagnosed with cancer about the use of TIM. The prevalence of TIM use in our study was (97.1%) which is higher than the reports from different countries in Middle East. Use of CAM percentage was reported by different authors in Arab countries as follows: Farah Naja., *et al.* 2015 from Lebanon as 40%, Ali-Shtayeh., *et al.* 2011 from Palestine as 60.9%, Afifi., *et al.* 2010 from Jordan as 35.5%. Our results were almost similar to the report from Saudi by Jazieh AR., *et al.* 2012 (90.5%). The variation in prevalence of TIM use could be explained by differences in socio-cultural perception [21-25].

The most common TIM used in Middle East were honey, Zamzam Water, Nigella, Fenugreek and Camel milk and urine but with different percentages.

Our study is the first research limited to the TIM utilization. Previous studies included the TIM with CAM use. Accordingly, the comparison between our study results and other published researches results are not comparable.

Most of our results were statistically not significant. This might be related to the small sample size.

**Use of TIM and possible drug interaction**

Most of anticancer drugs have narrow therapeutic window. This might lead to drug interaction with CAM including TIM. Drug interactions are responsible for unpleasant toxicities of chemotherapeutic agents that might lead to delay of treatment. One of the mechanisms

of interactions between CAM and oncology drugs is the induction of drug metabolizing enzymes and ATP-binding cassette drug transporters. This type of interaction lower plasma levels of the anticancer drugs and might lead to treatment failure. Some of the drug interactions have been identified such as St. John's wort with irinotecan and imatinib. However, evidently, more research is necessary to prevent possible therapeutic failure or toxicity in cancer patients [26].

### Types of TIM used (religious and scientific prospective)

TIM includes Quraan, honey, black seeds, zamzam water, fenugreek, olive oil and camel milk and urine due to religious culture. Patients participated in this study admitted using TIM for different purposes such as to improve general health, treat cancer, increase immunity, and reduce the side effects related to cancer therapy [27]. Most of patients and care givers referred to Quraan and Hadith of Prophet (PBUH) in their beliefs and behaviors. Accordingly, I will present some of the related Hadiths in addition to the scientific views that justify and explain the cultural behaviors.

Narrated Abu Huraira: The Prophet Muhammad (PBUH) said, "There is no disease that Allah has created, except that He also has created its treatment". Sahih Al Bukhari: Book #71, Hadith #582 [27]. Jaber reported the Prophet Muhammad (PBUH) said: "There is a remedy for every malady, and when the remedy is applied to the disease it is cured with the permission of Allah, the Exalted and Glorious" Sahih Muslim Book #26, Hadith #5466 [28,29]. Some of the remedies mentioned in the Holy Quran and Hadith by the Prophet (PBUH) are black seeds, olive oil, dates, honey and Nigella.

Black seeds (*Nigella Sativa*) are a widely used medicinal plant in the treatment of different diseases and ailments. It has two main ingredients Nigella and melatin and two volatile oils nigellone and thymoquinone. Nigellone plays a key role in daily health and wellness. Narrated Khalid Bin Sad that Aisha has narrated that the Prophet (PBUH) said "This black cumin is healing for all diseases except As-Sam". Aisha said, "What is As-Sam?" He said, "Death", Sahih Al Bukhari, Book #71, Hadith #591 [30,31]. Reports from different studies indicate that *Nigella Sativa* has an important role in cancer prevention through the activation of molecular cell signaling pathways [32,33].

Honey is made up of glucose, fructose, and minerals. The slightly acidic pH of honey helps prevent the growth of bacteria, while the antioxidant constitutes clean up free radicals. Narrated Ibn Umar, "In our holy battles, we used to get honey and grapes, as war booty which we would eat and would not store", Sahih Al Bukhari, Vol. 4, Book #53, Hadith # 382 [34]. Honey has medicinal properties as antibacterial activities and possible therapeutic potential against several health disorders of human [35,36].

The well of Zamzam Water is located within the Masjid al-Haram in Mecca, Saudi Arabia. Zamzam Water is considered as a miracle. Narrated by Ibn Abbas 'The Prophet (PBUH) drank Zamzam (water) while standing', Sahih Al Bukhari Vol. 7, Book #69, Hadith #521 [37]. Abdullah Bamosa and colleagues, 2013 carried a study in type 2 diabetic patients to evaluate the effect of Zamzam Water on their antioxidant status, glycemic control and lipid profile. Results showed a significant increase in the serum levels of total antioxidant capacity, Catalase, Superoxide dismutase in Zamzam group patients [38]. Ali Farid and colleagues, 2009 explored the onco preventive action of zamzam water due to the stimulation of Bikunin, Lunasin, and Bowman Birk inhibitor [39].

Sound therapy has been used in dealing with various health problems. Listening to the melodious Qur'anic recitation is known to have therapeutic effects even on individuals who do not understand the meaning of the verses being read. Quran could function as a sound therapy [40]. Zulkumaini and colleagues, 2012 conducted a study to compare between listening to Al Quran and listening to classical music on the brainwave signals for the alpha band. They concluded that listening to Al-Quran recitation increases the alpha band more than listening to classical music. Accordingly, listening to Al-Quran in particular can result in a more relaxing and alert condition compared to classical music [41]. Sadeghi H, 2011 did a review of performed studies in Iran about the voice of Quran and health. He concluded that the influence of Quran lit especially in the area of mental health which were obvious and clear [42].



Fenugreek is a seed crop. Its scientific name is *Trigonella Foenum Graecum*. The seeds and leaves are used to cure many health problems. Its constituents include protein, vitamin C, fiber, iron, potassium, L-tryptophan and alkaloids. Feyzi S and colleagues, 2014 investigated fenugreek as a source of protein. They concluded that it could be used as a protein source with remarkable functional properties [43]. Rahmati-Yamchi M and colleagues, 2014 reported that fenugreek leaves and seeds have been widely used for therapeutic purposes and recognized to show anti-diabetic, anti-nociceptive properties, anti-cancer and hypocholesterolaemic effects. Diosgenin is a steroidal saponin extracted from fenugreek and known to have anti-cancer properties. Telomerase illustrates a promising cancer therapeutic target. Diosgenin has an inhibitory effect on human telomerase expressed on carcinogenic cells [44].

Olive oil consists of 75% heart-healthy monounsaturated fat and only 13% saturated fat. It contains active compounds such as oleocanthal, which has a strong anti-inflammatory action to fight heart disease and cancer. It also contains the natural antioxidants polyphenols, which has the beneficial effects of lowering cholesterol, blood pressure and the risk of coronary heart disease. Di Francesco A and colleagues, 2014 investigated the effects of extravirgin olive oil (EVOO) and its phenolic compounds on endocannabinoid system gene expression via epigenetic regulation in both human colon cells and rats exposed to short and long term dietary EVOO. They concluded that EVOO and its phenolic compounds may provide a new therapeutic avenue for the treatment and/or prevention of colon cancer [45].

Anti-cancer action of camel products such as milk and urine was studied by different researchers. Recent experiments by A.A. Alhaider and colleagues, 2014 demonstrated that both camel urine and milk, each on its own, inhibited inflammatory angiogenesis in the murine sponge implant angiogenesis model. In addition to the significant inhibition of the expression of the gene encoding carcinogen activating enzyme Cyp1a1 and the mRNA level in cancerous liver cells and the apoptotic anti-cancer action demonstrated in camel milk. The exact mechanism of the anti-malignant constituents in camel urine and milk is not well understood, but it might be related to the iron binding, multi-tasking and multi-functional protein lactoferrin [46-48].

Sayed Amin Tabish, 2008 discussed if CAM (including TIM) is evidence based. He concluded that most of the alternative medicines are rejected because its efficacy has not been demonstrated through double blind randomized controlled trials. Evidence is required to justify and explore the benefit of CAM [49].

The strong correlation between using TIM and the religious beliefs is obvious. Unfortunately, there is still a lack of well-designed human researches that prove the therapeutic benefits of using the remedies mentioned in the Prophetic Medicine. TIM is considered as a very rich field for research to treat many diseases. TIM safety and efficacy needs to be further investigated.

### Limitations

We acknowledge the limitations of the study as we are considering TIM (prophetic medicine) only as it is more related to the Islamic culture. CAM utilization was not included. Sample size is small giving the number of population having cancer in Saudi Arabia. In addition, impact of these products on cancer patients was not studied as well as the possible drug interactions that might lead to negative outcomes. We recommend the conduction of another study that addresses these important points.

### Conclusion

Traditional Islamic medicine utilization is considered very high among the cancer patients in Saudi Arabia. This contributes mainly to the religious beliefs mentioned in the Quraan and Hadith of Prophet Mohammed (PBUH). TIM provides a remarkable source of new drug development. They might possess different therapeutic activities. These pharmacological properties need to be further studied on a large scale of patients through well designed research to prove the scientific evidence for safety and effectiveness. In addition, the possibility of interaction between CAM and cancer therapy as well as possible toxicities needs to be studied to avoid treatment delay and/or failure. Clinical pharmacists have a vital role in patient's education to ensure the best clinical outcome and patient pharmaceutical care.

### Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

### Funding

We did not have any fund for this project.

### Acknowledgment

We acknowledge the help of Hazza Al Otaibi and HalaJoharji during their internship rotation.

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