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Complementary and alternative medicine use among cancer patients in Palestine with special reference to safety-related concerns

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ABSTRACT

Ethnopharmacological relevance: The use of CAM including herbal medicine as the most preferred CAM modality, among cancer patients who are taking prescription medications has shown to be highly prevalent worldwide as well as in several Middle Eastern countries, with a high percentage of the patients do not disclose their CAM use to treating physician.

Aim of the study: The current study aimed to evaluate the patterns of CAM use among two cohorts of cancer patients in Palestine over a three-year period, and to identify socio-demographic factors that are associated with CAM use.

Materials and methods: Across-sectional survey of patients attending outpatient cancer clinics. The method was based on a semi-structured questionnaire. In order to identify safety-related concerns associated with the products listed, a literature search was conducted using different databases (PubMed, Micromedex, AltMedDex, and the Natural Medicine Comprehensive Database).

Results: In 472 cancer patients including 372 of the 2011 cohort; and 100 of the 2014 cohort, the overall prevalence of CAM use was 69.5%. CAM users were more likely to be $\leq$65 years old, village resident, being in the midst of chemotherapy, to have high interest spiritual quest, and to have no other chronic diseases. A significant number of CAM users reported using herbal preparations (98.3%, and 89.6% in the two study cohorts, respectively). In the current study, a total of 40 plant taxa belonging to 23 botanical families were reported by $\geq$3 cancer patients in the two cohort groups. The top most commonly used plant in the 2011 cohort group was *Arum palaestinum* (43.5%), while *Ephedra foeminea* emerged as the top most commonly utilized plant (from 0.0% in 2011 to 55.2% in the 2014 cohort), mainly due to a recent publicizing and portraying of the plant in the local media as an effective cancer herbal remedy. Safety-related concerns were associated with 33 (82.5%) herbs, including herb-drug interactions with altered pharmacokinetics (8, 20% herbs), direct toxic effects (16, 40% herbs), and increased in vitro response of cancer cells to chemotherapy (30, 75% herbs).

Conclusions: CAM use, especially herbal medicine in cancer is highly prevalent in Palestine. This study has demonstrated the role of the media on the emergence of new CAM herbal therapies among cancer patients in Palestine, and discussed its potential implications on patients and for oncologists who are treating them. Some of the most widely used herbal medicines by cancer patients in the present work are known to interact with conventional anticancer drugs. Hence, the disclosure of the use of herbal remedies by patients to health professionals with sufficient training in CAM use is important for the later in order to assess whether there are any possible herbal drug interactions and/or harmful drug reactions.

1. Introduction

Cancer is an important public health challenge in Palestine and worldwide (Palestinian Health Information Center, PHIC, 2015; Ferlay et al., 2015). In Palestine, cancer incidence rate was 82.2 per 100,000 of the population in 2014 (PHIC, 2015). After

Abbreviations: PHIC, Palestinian Health Information Center; CAM, Complementary and alternative medicine; CYP, Cytochrome P450; TAPHM, Traditional Arabic Palestinian Herbal Medicine; IRB, Institutional Review Board; BERC, Biodiversity and Environmental Research Center; EF, *Ephedra foeminea*; EGCG, Epigallocatechin gallate; OATP, Organic anion transporting polypeptides; TRAS, Trastuzumab

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cardiovascular diseases (29.5%), cancer was the second most frequent cause of death in Palestine (14.2%) (PHIC, 2015).

The term "complementary and alternative medicine" is used to describe those therapies that are considered to be complementary or alternative to "western" pharmaceuticals and medical practices, natural, or traditional medicine (Pearson and Chesney, 2007). The use of CAM among cancer patients who are taking prescription medications has shown to be highly prevalent worldwide (Ernst and Cassileth, 1998; Leng and Gany , 2014; Tuna et al., 2013; Farooqui et al., 2015; Molassiotis et al., 2006; Ezeome and Anarado, 2007; Sewitch and Rajput, 2010; Can et al., 2009; Davis et al., 2012) as well as in several middle eastern countries, e.g., Jordan (about 100%) (Akhu-Zaheya and Alkhasawneh, 2012), Saudi Arabia (90%) (Jazieh et al., 2012), Turkey (57%) (Yildiz et al., 2013), Israel (51%) (Paltiel et al., 2001), Morocco (46%) (Brahmi et al., 2011), and Iran (35%) (Montazeri et al., 2007). Between 20% and 70% of patients using CAM, including herbal therapies, do not inform their physician about using CAM as a result from an expected negative response (Davis et al., 2012). A similar trend was also found amongst other chronic diseases patients (e.g., diabetes, and hypertension) in Palestine (Ali-Shtayeh et al., 2012, 2013). However, many oncology health care providers admit their lack of competence in the field of herbal medicine (Trimborn et al., 2013).

In Palestine, as well as in many countries including Jordan, Turkey, and USA, several population-based studies, have shown extensive use of medicinal plants use as the most favored CAM modality (Ali-Shtayeh et al., 2011, 2012, 2013; Afifi et al., 2010; Akyol and Öz, 2011; Grover et al., 2002; Ezeome and Anarado, 2007; Gratus et al., 2009; Algier et al., 2005; Ali-Shtayeh et al., 2000). Herbal medicine contains pharmacologically active components, some of which might interact with conventional drugs (Ernst, 2000) which, in turn, could threaten the health of patients (Ernst et al., 2006; Izzo and Ernst, 2009). When pharmaceutical drugs are simultaneously used with herbal therapies, interactions may decrease or increase the toxicological or pharmaceutical effects of either ingredient (Ernst, 2000; Hardy, 2008; De Smet, 2004; Zhang et al., 2009). A potential risk to human health could be the concurrent use of multiple conventional therapies and herbal medicines (Werneke et al., 2004).

Herb-drug interactions can take place at the pharmaceutical, pharmacodynamic, or pharmacokinetics levels (Beijnen and Schellens, 2004). Interactions at the pharmacokinetic level involve changes in the metabolic pathway (absorption, distribution, metabolism, or excretion) of the chemotherapeutic drug. At the level of metabolism of anticancer drugs, almost all pharmacokinetic interactions involve cytochrome P450 (CYP) metabolizing enzymes, of which CYP3A4 is the most important enzyme in the metabolism of chemotherapeutic drugs (Lau et al., 2013). This problem may be aggravated by the emergence of new herbal therapies with unknown toxicity.

Traditional Arabic Palestinian Herbal Medicine (TAPHM) is closely related to patients' health belief models and is an integral part of the socio-medical landscape among the Palestinian population (Ali-Shtayeh and Jamous, 2006; 2008; Ali-Shtayeh et al., 2014). Lower cost and acceptability of medicinal herbal use in Palestine, encourage patients to believe in their healing potentials (Ali-Shtayeh and Jamous, 2006; 2008).

In Palestine, little is known on the use of CAM by cancer patients. The current study aimed to evaluate the patterns of CAM use among two cohorts of cancer patients in Palestine over a three-year period. In addition, the study focused on the information-seeking behavior and CAM use disclosure to health professionals. The study was also aimed to identify demographic and socio-economic factors that are associated with CAM use. Another aim was to search the literature for potentially harmful herb-drug interactions. To our knowledge, no previously published study has investigated the pattern of CAM use among Palestinian patients living with cancer.

2. Methods

2.1. Subjects and recruitment

The study used a cross-sectional survey of patients attending the Tumors Outpatient Department at Alwattani Governmental Hospital in Nablus, in Palestine. To ensure a representative sample, the interviews were conducted on different days and at different times. The study included patients of both sexes across different age groups. Ethical approval was obtained prior to the study from the Institutional Review Board (IRB) at the Ministry of Health in Nablus. The interviews were carried out by researchers from the Biodiversity and Environmental Research Center (BERC), Nablus. Prior to proceeding with the interview, the patients were informed about the purpose of this study and confirmed that all information would remain confidential and be used for research purposes only. If the patients were younger than 16 years of age or unable to interact, the next of kin were interviewed.

2.2. Study questionnaire

The study patients were asked a series of questions regarding demographic details of the patient; disease details; information about use of CAM; source of information; purpose of the use of CAM and outcomes; extent of CAM therapy effect on the treatment of cancer; patients' objections or misgivings about seeking CAM for the treatment of patient's cancer, seeking out CAM if it were provided as part of the oncological service; consultation with healthcare professional about using CAM in the treatment of cancer; main expectations of CAM consultation and treatment integrated in the Tumors Outpatient Department; most troublesome problems which the patient would like to improve as a result of CAM treatment; phase in the oncological treatment was the patient at the time of the study; and extent of interest in spiritual or religious quest. The majority of the questions had pre-prepared answers, and the main themes addressed by the questionnaire are represented in Table 1. To evaluate the questionnaire, a pilot study was conducted with 50 randomly selected patients. The results from the pilot study have not been included in the analysis of data for this study.

2.3. Research cohorts

In this study, 472 patients diagnosed with cancer were randomly selected at the Tumors Outpatient Department, Alwattani Hospital, Nablus and participated in the study. The study took place on two periods, the first from April - July 2011 (2011 cohort group), and the second from Aug – Oct 2014 (2014 cohort group). A total of 372 patients, and 100 patients participated in the two periods, respectively.

2.4. Review of the literature on the risk of herb-drug interactions

An extensive review focusing on simultaneous use of CAM herbal medicine and conventional therapies in cancer care among Palestinian patients was performed. The search was based on various databases (PubMed, Google scholar, Micromedex, AltMedDex, and The Comprehensive Natural Databases published between January 2011 and Dec 2015 (Natural Medicines Comprehensive Database Home page, 2015)). The scientific and English common names of the identified herbs were used to carry out a Medical Subject Headings (MeSH) search. The search included the