

The prevalence and predictors of herb-drug interactions among Iranian cancer patients during chemotherapy courses

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June 3, 2022

Abstract

Abstract Background: The concurrent usage of herbal medicines with conventional therapies is an important concern in cancer treatment which can lead to unexpected consequences like herb-drug interactions. The aim of this study was to determine the prevalence of potential herb-drug interactions and to predict factors associated with herb-drug interactions for cancer patients. **Methods:** This cross-sectional study was conducted among a convenience sample of 315 cancer patients referring to the oncology clinics of Kerman in 2018. Data were collected via comprehensive face-to-face interviews and medical chart reviews. A drug interaction checker was used to determine herb-drug interactions. The information of patients was compared based on herb-drug interactions by using bivariable logistic regression models and predictors were determined by the multivariable logistic regression model. All analyses were performed by Stata software version 16. **Results:** Of 262 patients who used herbal medicines, 209 patients [79.8% (95% CI: 75.2 – 85.1)] had potential herb-drug interactions. Chamomile was the most popular herbal medicine (n=163, 78%), and minor and moderate herb-drug interactions were caused by green tea (n=34, 16.3%) and peppermint (n=78, 37.5%). The number of chemotherapeutic agents (OR: 1.92, 95% CI: 1.43–2.58; P-value<0.0001) and the experience of pain during chemotherapy courses (OR=2.22, 95%CI:1.00–4.94; P-value=0.04) were some of the predictors of herb-drug interactions among cancer patients. **Conclusion:** The majority of cancer patients used herbal medicines during chemotherapy courses and physicians could reduce the odds of herb-drug interactions with proper education, monitor the side effects of chemotherapy, and prevent patients from self-medication with herbal medicines.

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Methods: This cross-sectional study was conducted among a convenience sample of 315 cancer patients referring to the oncology clinics of Kerman in 2018. Data were collected via comprehensive face-to-face interviews and medical chart reviews. A drug interaction checker was used to determine herb-drug interactions. The information of patients was compared based on herb-drug interactions using bivariable logistic regression models and predictors were determined by the multivariable logistic regression model. All analyses were performed by Stata software version 16.

Results: Of 262 patients who used herbal medicines, 209 patients [79.8% (95% CI: 75.2 – 85.1)] had potential herb-drug interactions. Chamomile was the most popular herbal medicine (n=163, 78%), and minor and moderate herb-drug interactions were caused by green tea (n=34, 16.3%) and peppermint (n=78, 37.5%). The number of chemotherapeutic agents (OR: 1.92, 95% CI: 1.43–2.58; P-value<0.0001) and the experience of pain during chemotherapy courses (OR=2.22, 95%CI:1.00–4.94; P-value=0.04) were some of the predictors of herb-drug interactions among cancer patients.

Conclusion: The majority of cancer patients used herbal medicines during chemotherapy courses and physicians could reduce the odds of herb-drug interactions with proper education, monitor the side effects of chemotherapy, and prevent patients from self-medication with herbal medicines.

Keywords: Cancer, Chemotherapy, Herbal medicine, Food/Herbal drug interactions

1. Introduction

Cancer is one of the major leading causes of death worldwide (1). According to World Health Organization (WHO) reports, breast, colorectal, lung, and liver cancers had the highest incidence and mortality rate in the Eastern Mediterranean Region (EMR) in 2020 (2). These types of cancers with similar incidence and mortality are also observed in Iran and there is an increment trend in incidence and mortality rate for most cancers (3). Surgery, radiation therapy, and systemic treatment are the main cancer treatment protocols that are applied separately or in combination for cancer patients (4). Chemotherapy, as a systemic treatment of cancer, has many side effects (5) such as nausea and vomiting, diarrhea, mucositis, fatigue, and hair loss (6, 7).

For reducing the short-term and long-lasting side effects of chemotherapy, a great proportion of cancer patients used the Complementary and Alternative Medicines (CAM) (8-10); this usage is commonly without the consultation provided by physicians and health care workers (11). Among CAM therapies, herbal medicines are more popular among patients. Current reports show a remarkable and variable prevalence of using herbal medicine by cancer patients from 14% to 66.7% (12-15), especially during conventional treatments or palliative care and chemotherapy (37% -38%) (16, 17). In fact, the concurrent usage of herbal medicines with conventional therapies is one of the most important concerns in cancer treatment which can lead to unexpected consequences (18, 19).

In the pharmacokinetic interactions, herbal medicines due to their pharmacokinetic properties interact with chemical agents and affect the absorption, distribution, metabolism, and excretion of chemotherapeutic agents when orally used. The pharmacodynamics interactions often are lower clinically significant than pharmacokinetic interactions (20-22). The herb-drug interactions in cancer patients are more important, however, the prevalence of this event among cancer patients is not known and limited studies reported only a proportion of patients who were at risk for herb-drug interactions (19, 23, 24). Along with the unclear prevalence of herb-drug interactions in cancer patients, the epidemiological predictors of it are also unknown and several studies have only reported the mechanisms of some herb-drug interactions (19, 25, 26). As regards a great proportion of Iranian cancer patients use herbal medicine in combination with a chemotherapeutic agent (27), and according to the lack of updated studies on this issue, the aim of this study was to determine the prevalence of potential herb-drug interactions among these patients and also identify the epidemiological predicting factors of herb-drug interactions for Iranian cancer patients.

2. Material and methods

2.1 subject and setting

The present cross-sectional study was conducted among 315 cancer patients who referred to the oncology clinics of Kerman (one private and two governmental clinics) during February to June 2018. These patients were selected via convenience sampling method and sampling was not restricted to sex, cancer site and clinical stage of cancer. The inclusion criteria were age above 18 years and receiving at least one chemotherapy courses through infusion, injection or oral route. Patients who had completed the chemotherapy course one month before the survey were also eligible for the study.

2.2 Data collection

In this study data were collected via comprehensive face to face interviews and also medical chart reviews. For interview, we designed an interview form consisting of three separated parts. In the first part age, sex, marital status, place of residence and educational level of patients were collected as demographic information. The second part included the common name of herbal medicines which patients used them in oral route during chemotherapy courses. In the last part of the interview form, common side effects of chemotherapy such as constipation and diarrhea, nausea and vomiting, pain, skin and oral lesions were asked. In this part, the status of other comorbidity illnesses was recorded. The first author interviewed all patients in waiting rooms of clinics before the start of chemotherapy course or after its completion. Other clinical information was obtained through medical chart review. The cancer site, clinical stage, metastatic status and recurrence status were in clinical information category. To protect patients' privacy, this part of the data collection was done by the staff of the oncology clinics.

2.3 herb-drug interaction assessment

For checking herb-drug interactions, we used a drug interaction checker supported by natural medicine collaboration (URL: <https://naturalmedicines.therapeuticresearch.com/>). The scientific names of herbal medicines and the generic name of chemotherapeutic agents as pair of herb-drug check together. In this part, the scientific name of herbal medicines was determined and approved by two herbalists. According to the results, interactions were stratified in three levels: minor, moderate and major based on the evidence (anecdotal evidence, theoretically based on pharmacology, vitro studies, randomized and non-randomized clinical trials).

2.4 Ethical approval

The protocol of the study was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences (ethics no: IR.KMU.REC.1396.1278). In this study, oral informed consent was obtained prior to interviews by the first author of the study.

2.5 Data analysis

Data were described using mean $\pm$ Standard Deviation (SD), frequency, its percentage and 95% Confidence Intervals (CIs). Demographic and clinical information of patients were compared based on herb-drug interactions by bivariable logistic regression models. Every variable with a P-value <0.2 in bivariable models was selected and entered into the multivariable logistic regression model using backward elimination. In every step of multivariable models, variables with great P-value were continuously removed from the model set until all remaining variables in the model were significant (P-value <0.05). All descriptive and analytical analyses were performed by using Stata software version 16.

3. Results

3.1 Demographic and clinical information of cancer patients with herbal medicines

Of 315 cancer patients recruited for the study, 262 patients (83.2%; 95% CI: 78.6, 87.1) used at least one herbal medicine during chemotherapy courses and were included in this analysis. The mean $\pm$ SD age of cancer patients who used herbal medicines was 51.1 ± 14.0 years (age range: 18 to 92). More than 70% of the patients were females (n=188, 71.8%) and urban residents (n=204, 77.9%). The majority of cancer patients were married (n=248, 94.7%). More than half of the patients were under diploma (n=152, 58.0%). Breast was the most prevalent cancer site among patients (n=98, 37.4%). Almost nearly half of the patients had metastatic cancers (n=117, 44.7%), but recurrence was not frequent among them (n=45, 17.2%). More than half of the patients suffered from comorbidities (n=138, 52.7%). Common complications among patients were nausea and vomiting (n=186, 71.0%), constipation and diarrhea (n=169, 64.5%) and pain (n=160, 61.1%) (Table 1).

3.2 Prevalence of herb-drug interactions

Of 262 patients with herbal medicine, 209 patients [79.8% (95% CI: 75.2 – 85.1)] had potential herb-drug interaction. The prevalence of herb-drug interactions based on demographic and clinical information is shown in Table 1.

3.3 Properties of chemotherapy regimens of cancer patients with interaction

Thirty-three different chemotherapeutic agents were prescribed for cancer patients. The mean $\pm$ SD of prescribed medications was 4.0 ± 1.8 per patient (medication range: 1 to 10). Cyclophosphamide was the most frequent chemotherapeutic agent (n=105, 50.2%). Arsenic Trioxide, Flutamide, Nivolumab, and Thalidomide (n=1, 0.48%) were the least prescribed chemotherapeutic agents. The common chemotherapeutic agents are presented in Fig 1.

3.4 Properties of herbal medicines used by cancer patients with potential interaction

Cancer patients with potential herb-drug interaction reported 78 different herbal medicines used during chemotherapy courses. The mean $\pm$ SD number of herbal medicines among these patients was 12.6 ± 5.5 per patient (range: 2 to 29). The *Matricaria chamomilla* L.(chamomile) was the most popular herbal medicine among cancer patients. The most frequent herbal medicines used by a significant percentage of cancer patients are depicted in Fig 1.

3.5 Frequency and types of herb-drug interactions

Based on the findings, 128 pairs of herbs and drugs can lead to potential herb-drug interactions. Of them, 19 and 116 pairs of herbs and drugs caused potential minor and moderate herb-drug interactions among cancer patients. In this study no major herb-drug interaction was found. Potential moderate herb-drug interactions occurred in all patients (n=209, 100%), while potential minor herb-drug interactions happened in less than a third of the patients (n=67, 32.1%). The frequent potential minor and moderate herb-drug interaction was caused by *Camellia sinensis* L. (green tea) (n=34, 16.3%) and *Mentha piperita* L. (peppermint) (n=78, 37.5%), respectively when used in combination with Cyclophosphamide. Among herbal medicines, *Camellia sinensis* L. (green tea), *Matricaria chamomilla* L.(chamomile), *Curcuma longa* L. (Turmeric) and *Silybum marianum* L.Gaertn (milk thistle) caused both potential minor and moderate herb-drug interactions. Potential minor and moderate herb-drug interactions are detailed in Appendix A.

3.6 Frequency of confirmed evidence for herb-drug interactions

In this study, the considerable number of herb-drug interactions was determined or confirmed with vitro (66 studies) and clinical studies (46 studies, randomized and non-randomized clinical trials) and only 4 herb-drug interactions were based on anecdotal evidence (Fig 2). All herb-drug interactions were confirmed by one evidence except nine herb-drug interactions which were confirmed by two evidences. These pairs were “Cyclophosphamide and *Mentha piperita* L.” (Vitro and randomized clinical trial), “Cyclophosphamide and *Glycyrrhiza glabra* L.” (Vitro and randomized clinical trial), “Docetaxel and *Glycyrrhiza glabra* L.” (Vitro and randomized clinical trial), “Doxorubicin and *Valeriana officinalis* L.” (Vitro and non-randomized clinical trial), “Paclitaxel and *Glycyrrhiza glabra* L.” (Vitro and randomized clinical trial), “Tamoxifen and *Mentha piperita* L.” (Vitro and randomized clinical trial), “Tamoxifen and *Foeniculum vulgare* Mill” (Vitro and theoretically based on pharmacology), “Tamoxifen and *Valeriana officinalis* L.” (Vitro and non-randomized clinical trial) and “Tamoxifen and *Glycyrrhiza glabra* L.” (Vitro and randomized clinical trial). The type of evidence for other herb-drug interactions is presented in Appendix A.

3.7 Mechanisms of actions of herb-drug interactions

Based on the reported evidences, in the most drug interactions, induction or inhibition of hepatic and intestinal Cytochrome P450 3A4 (CYP3A4) were occurred (139 cases; 69.8%). Results showed that the first phase of metabolism of chemotherapeutic agents which mostly depend on CYP3A4 was impaired. Other frequent mechanisms of herb-drug interactions were the dip of GI transit time (11 cases) and the plunge of hepatotoxicity of chemotherapeutic agents (8 cases) (table 2).

3.8 Demographic and clinical correlates of herb-drug interaction among cancer patients

The bivariable logistic regression models showed that herb-drug interactions were related to sex, cancer site, recurrence status, experience pain as chemotherapy complication, and the number of chemotherapeutic agents and herbal medicines. Based on the results, females (OR: 2.28, 95% CI: 1.22–4.26; P-value=0.01), and patients with the experience of pain during chemotherapy (OR: 3.16, 95% CI: 1.70–5.87; P-value<0.0001) had greater odds of herb-drug interactions. By increasing the number of chemotherapeutic agents (OR: 1.75, 95% CI: 1.40–2.19; P-value<0.0001) and herbal medicines (OR: 1.12, 95% CI: 1.05–1.20, P-value<0.0001) the odds of herb-drug interactions increased for cancer patients. In contrast, patients with gastrointestinal cancers (OR: 0.09, 95% CI: 0.03–0.24, P-value<0.0001) and other types pf cancers (OR: 0.20, 95% CI: 0.04–0.95, P-value=0.04) versus patients with breast cancer had a lower odd of herb-drug interactions. Also, cancer patients with unclear recurrence status had lower odds of herb-drug interaction in comparison to patients with negative recurrence status (OR: 0.19, 95% CI: 0.04–0.89, P-value: 0.03) (Table 3).

3.9 Predictors of herb-drug interactions

According to the results of the multivariable logistic regression model, the number of chemotherapeutic agents (OR: 1.92, 95% CI: 1.43–2.58; P-value<0.0001), number of herbal medicines (OR: 1.15, 95% CI: 1.06–1.24, P-value<0.0001), gastrointestinal cancers (OR: 0.08, 95% CI: 0.02–0.30, P-value<0.0001), thorax cancers (OR: 0.10, 95% CI: 0.01–0.61, P-value= 0.01), IV clinical stage (OR: 8.42, 95% CI: 1.10–64.04, P-value= 0.04), unclear recurrence status (OR: 0.06, 95% CI: 0.005–0.67, P-value= 0.02) and the experience of pain during chemotherapy (OR=2.22, 95%CI:1.00–4.94; P-value=0.04) were determined as the predictors of herb-drug interactions among cancer patients (Table 4).

4. Discussion

In this study, more than eight among ten of cancer patients used herbal medicines during chemotherapy courses and eight patients out of ten patients with the history of herbal medicine consumption had potential herb-drug interactions. Potential moderate herb-drug interactions occurred in all patients, while potential minor herb-drug interactions happened in a third of patients. Based on the findings, chamomile is the most popular herbal medicine and green tea leads to frequent potential minor and moderate herb-drug interactions. The number of chemotherapeutic agents, number of herbal medicines, gastrointestinal cancers, thorax cancers, IV clinical stage, unclear recurrence status and the experience of pain during chemotherapy courses were determined as the predictors of herb-drug interactions among cancer patients.

High prevalence of using herbal medicines in combination with conventional treatments is an important issue which has been addressed in many studies with different population (28-31), a finding that has also been discussed in our study. The majority of cancer patients used herbal medicines during chemotherapy courses and according to our previous study, this consumption was also hidden from physicians' view (32). Patients, regardless of current treatments, use herbal medicines for a variety of reasons. For example, patients believe that they can use herbal medicines without trouble, because they are natural, effective in treating diseases and they can reduce cancer symptoms, and they have no side effects (33, 34). These patients have mistaken beliefs about herbal medicines, because herbs when used in combination with drugs have an influence on induction and inhibition of metabolic enzymes and finally on drug absorption (35). Herb-drug interaction is the consequence of this combination and may lead to unexpected adverse clinical outcomes (36, 37) such as hepatotoxicity (38). According to related studies, the prevalence of herb-drug interactions among cancer patients is considerable (39) and it varies from 2.3% (40) to 25% (41) and 46% (42). The findings of our study showed that more than three quarters of cancer patients had herb-drug interactions and this prevalence was higher in comparison to other studies. Some of the reasons for this discrepancy was related to more consumption of herbal medicines by our patients, consumption herbal medicines which lead to herb-drug interaction such as garlic, green tea (43) and chamomile (44) and identification of new pairs of herb and drugs which resulted to interactions over time.

An important issue in Drug Related Problems (RDPs) such as drug interactions is related to Narrow Therapeutic Window (NTW) of some drugs such as chemotherapeutic agents (45, 46). These drugs with a small difference between the minimum effective range and the minimum toxic range have steep dose-response relationship and they must be monitored carefully (47, 48), because small changes in their dose or plasma concentration can lead to life-threatening toxicity or sub-optimal therapy and under treatment of cancer (48, 49). But how dose herbal medicines interact with these drugs? The drug clearance is the key point in this story and the metabolic modification of some enzymes such as CYP and UGT and drug uptake and efflux transporter are involved in this cycle (50, 51). The clearance of 70% of drugs depend on CYP enzyme and the most important drug interactions caused by inhibition and induction of this enzyme as well as UGT in the first and second phases of drug metabolism especially chemotherapeutic agents (52, 53). The results of our study are consistent with similar related studies (54, 55) indicating that most of herb-drug interactions are caused by inhibition or induction of CYP3A4 enzyme. As regards, the metabolized of many drugs depend on this enzyme, induction or inhibition of it can lead to unexpected toxicity and under treatment of cancer. In this regard, physicians and other health workers must pay more attention and had better prevent patients from using herbal medicines in combination with other drugs.

We also found that the number of herbal medicines and also chemotherapeutic agents as predictors increased the odds of herb-drug interactions among cancer patients. This result is in line with the study conducted by Levy et al. (2017) on hospitalized patients (56) and the study by Chi et al. (2020) on community-dwelling older adults (57). The reason for this event is clear and by increasing the number of each drug (herbal or chemotherapy), the odds of herb-drug interaction subsequently increased. Another predicting factor was experiencing pain during chemotherapy which was associated with increased odds of herb-drug interactions. The results of related studies show that considerable proportion of patients with chronic pain used CAM (58, 59). Licorice (60), chamomile (61) and peppermint (62) as analgesic, are popular herbal medicines and interact with chemotherapeutic agents. As a result, the experience of pain causes the use of herbal medicines and the herb-drug interaction is the potential outcome of this usage.

Type of cancer and advanced cancers were the other predictors of herb-drug interactions in this study. According to the results, patients with gastrointestinal cancers and thorax cancers had lower odds of herb-drug interactions versus patients with breast cancer. This difference can be justified by two reasons. First, the majority of patients with breast cancers are females and females are more likely to use herbal medicines in combination with other drugs (63, 64). Therefore, the odds of herb-drug interactions for females are more than males which was confirmed by results of bivariable logistic regression in our study. The second reason was related to the type of drugs used for patients with breast cancers. Tamoxifen, Letrozole and Exemestane are common drugs which are usually prescribed for postmenopausal breast cancer patients. These patients used specific herbal medicines to reduce complications of menopause such as licorice, fennel and valerian, the supplement estrogenic activity which interact with chemotherapeutic agents (65, 66). In contrast, patients with advanced cancers had greater odds of herb-drug interaction versus other patients. The results of one study showed that patients with advanced cancers were inclined to use CAM and the prevalence of using herbal medicines among these patients were considerable (67). There are several reasons for these patients to use herbal medicines. They look for a way to reduce severe symptoms of cancer and also side effects of chemotherapy courses. Also, they hope to live longer.

Limitations

The main limitation in this study was related to determining scientific names of herbal medicines because some of the herbal medicines with one common name have several scientific names which are different in therapeutic properties. For this issue, the herbalists selected the prevalent species of herbal medicines in our country (Iran). The other limitation was underestimation of herbal medicines which patients used. Because they used some herbal medicines but did not remember the name of them due to recall bias. The other limitation of this study is related to the design of the study. As this was a cross-sectional study, we could not confirm the causation of the predictor variables with the potential herb-drug interaction as the outcome.

4.1 Conclusion

The results of our study revealed that the majority of cancer patients used herbal medicines during chemotherapy courses and all of them who used herbal medicines had potential herb-drug interactions. As regards, the consequences of herb-drug interactions may be life-threatening or change the treatment process of cancer patients. In addition, as the interactions of many herbal medicines with chemotherapeutic agents are not clear, physicians and health care workers should pay more attention to these patients and avoid them to take herbal medicines in combination with chemotherapeutic agents. The risk of herb-drug interactions will remarkably decrease with proper patient education and the training of their families, monitoring the side effects of chemotherapy in patients and consulting patients to prevent them from self-medication with herbal medicines by involving traditional medicine specialists in the treatment process of cancer patients. Extensive studies are recommended to determine the interactions between herbal medicines and chemotherapeutic agents.

Acknowledgement

We thank cancer patients and their families for their participation in this study and also, we are particularly grateful to the staff of oncology clinics for helping us in data collection. We greatly appreciate Professor Mir

Tajadini, Sharifi Far and Rameshk for all the helpful advice in identifying medicinal plant species used as herbal medicines.

Conflicts of interest

None

Funding

This study was funded by the research deputy of Kerman University of Medical Sciences. (Grant number, 95000567).

Availability of Data

“Data sharing not applicable”

Author contribution

All authors contributed to the conceptualization of the study and its methodology. H.S., A.B., S.A., B.K.K. and H.T. was responsible for data curation. Formal analysis and validation were conducted M.S.B, S.M. and A.P. also validated the study. H.S. was the project administrator and wrote the original draft. S.A., S.G.P. and S.H supervised the project. All authors reviews and edited the final version.

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