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REVIEW

Cancer Patients at Risk of Herb/Food Supplement–Drug Interactions: A Systematic Review

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Herbal medicines and dietary supplements are commonly taken by patients with cancer, leading to concern over interactions with conventional medicines. A literature search was carried out to identify published studies exploring supplement use by patients with a cancer diagnosis. A total of 818 articles were retrieved using the key words, but only 41 are judged to be relevant based on title. Following the review of the abstracts, ten papers were considered to be potentially relevant, but of these, only two met the selection criteria, and three additional papers were identified from published reviews. Of 806 patients surveyed, 433 (53.7%) were reported to be taking combinations of supplements and drugs, and 167 incidents of risk were identified, affecting 60 patients (13.9%). The interactions identified were mainly theoretical and not supported by clinical data. No studies reported any adverse events associated with these combinations; most did not record the actual drug combinations taken, and the risk potential of some supplements appears to have been over-estimated. More effort should be made to investigate supplement use in this vulnerable patient group, based on sound evidence of plausible interaction, not only to avoid harm but also to provide reassurance where appropriate if the patient wishes to take a particular supplement. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: cancer patient; complementary and alternative medicine (CAM); drug interaction; herbal medicine; food supplement; systematic review.

INTRODUCTION

The use of complementary and alternative medicines (CAM) such as herbal medicines and dietary supplements ('supplements') is well documented and is particularly common in patients with chronic diseases such as cancer (Goey *et al*., 2013, 2014; Corner *et al*., 2009; McLay *et al*., 2012). Concern over interactions between these supplements and conventional medicines ('drugs') has substantially increased, especially as there is a paucity of data regarding such interactions, and particularly with chemotherapy drugs, which have a narrow therapeutic index (McCune *et al*., 2004; Goey *et al*., 2013). Some supplements have been shown to affect the metabolism of certain chemotherapy agents; for example, St John's wort (*Hypericum perforatum*), which is considered to be the herb most likely to lead to serious clinical consequences, has shown significant pharmacokinetic interactions with irinotecan and imatinib (Izzo, 2012; Russo *et al*., 2014). This concern is compounded by poor communication between doctors and patients about CAM use and the lack of easily available and accurate information on CAM for healthcare professionals (Cramer *et al*., 2013). The identification of cancer patients who take herbal and dietary supplements and who may be at risk from herb–drug interactions (HDIs) (to include all supplements) is therefore needed to assess the seriousness of the issue and to provide guidelines for the safe use of these products. Several studies have examined the potential for HDIs in cancer patients, documenting the supplements taken and hypothesising the level of risk involved based on theoretical considerations. This is a useful but conservative approach, which is likely to produce a higher level of estimated risk than one based on known HDIs from clinical reports and plausible mechanisms from experimental studies. A recent recommendation has been made that *in vitro* tests should always use conditions that mimic as closely as possible physiological conditions, and also take into account confounding factors such as poor bioavailability, but even then, clinical studies are required to confirm clinical relevance (Goey *et al*., 2013). This review aims to determine the proportion of cancer patients deemed to be at risk from HDIs by systemically examining the published literature for studies reporting the specific herbs and dietary supplements most commonly used alongside conventional medicines, together with the risks for these combinations as assessed by the authors.

The questions that guided the review were as follows:

(1) What proportion of cancer patients is reported to be at risk from HDIs?
(2) Which supplement–drug combinations involve a risk of interaction?
(3) Which supplements are most used by cancer patients and alongside which drugs?

METHODS

Literature search. Medline, Cochrane, PubMed and Web of Knowledge databases were searched to identify published studies exploring supplement use concurrent

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with drug use by patients with a cancer diagnosis. The following key words were entered into the databases: Herb-drug, Herb AND Drug, Interaction. Reference lists of published reviews retrieved by the search were also searched to identify relevant papers.

Inclusion and exclusion criteria. In order to retrieve all relevant papers, the inclusion criteria were any studies published in any language between 2000 and 2013 that reported herb–supplement–drug interactions with cancer patients, and specifically those that assessed levels of risk from such interactions. Published studies only were searched as they have been subjected to peer-review and thus offer an extra level of reliability in a subject area prone to exaggeration (Williamson *et al*., 2013). The rationale for judging risk, as reported in each study, could not be validated in the absence of robust clinical data and is necessarily subjective; assessments may (and should) change with time as new clinical reports become available to confirm or refute them. Studies that reported HDIs with paediatric populations (who could not freely choose to take supplements themselves), non-cancer patients and purely experimental studies in animals were outside the remit of this review and were excluded.

Selection and recording. Titles were exported into endnote X5. Titles were screened by the first author (SMA) for relevance, and the abstracts of the selected citations were reviewed by the researcher and another author (RLH), and then, where relevant, full text papers were retrieved. Where RLH and SMA agreed that full text papers met the inclusion criteria, the following data were abstracted into Microsoft Excel 2010 by SMA, and data input was double checked by RLH: authors, publication year and country, hospital department, description of methodology, HDI reported (yes/no), potential HDIs assessed (yes/no), number of participants, number of patients taking supplements with conventional medicine, number of such potential HDIs and number of patients taking supplements deemed to be at risk of HDIs.

Data synthesis. Summary data from all included studies were entered into Microsoft Excel (2010) by SMA. The accuracy of data entry was checked by RLH. The following were calculated from the pooled data: percentage of patients taking supplements with conventional medicines, percentage of patients taking supplements deemed to have the potential to interact with conventional medicine, number of potential HDIs and percentage of use of each supplement reported to interact with conventional medicine. In addition, median (range) was calculated for the percentage of patients taking supplements with drugs and the percentage of patients at risk of HDIs.

RESULTS

Studies selected

A total of 818 articles were retrieved from the databases using the keywords; all were in English. Forty-one articles were judged to be relevant based on their titles. Following review of their abstracts for content, ten papers were considered to be potentially relevant. Of these ten papers, only two papers met the inclusion criteria. Three additional papers were identified as relevant from the reference lists of published reviews (Lee *et al*., 2006; McCune *et al*., 2004; Werneke *et al*., 2004). The main reasons for excluding studies are summarised in Fig. 1. Four studies included in this review were cross-sectional questionnaire surveys, and one study was of interviews with patients attending oncology departments. Of the questionnaire-based studies, three were self-administered surveys (McCune *et al*., 2004; Werneke *et al*., 2004; Engdal *et al*., 2009); one was researcher administered (Lee *et al*., 2006), and one study was conducted using interviews with a standardised questionnaire (Zeller *et al*., 2013). Studies were conducted in the USA (2) (Lee *et al*., 2006; McCune *et al*., 2004), UK (1) (Werneke *et al*., 2004), Norway (1) (Engdal *et al*., 2009) and (1) Germany (Zeller *et al*., 2013). Participants in these studies were surveyed and interviewed to determine their use of herbal medicines and dietary supplements and to determine whether they may be at risk from HDIs. A brief description of these studies is presented in Table 1.

Percentage of patients using supplements with conventional medicine

806 participants were included in the five studies which had met the inclusion criteria; of these, 433 (95% CI: ±3.44) were reported using supplements concomitantly with drugs (conventional medicines) (Table 1).

Percentage of cancer patients taking supplements with the potential to interact with conventional medicine

Of the 433 patients taking supplements and drugs concurrently, 167 potential interactions between supplements and drugs were identified by the authors. Of these potential interactions, 60 (13.9%) patients were reported to be at risk of HDIs. The median (range) percentage of patients reported to be at risk from HDIs was 12.2% (0–36.2).

Supplements with potential to interact with drugs

One hundred eight HDIs were reported; more than half of these interactions involved garlic (16/108; 14.8%), green tea (15/108; 13.9%), mistletoe (10/108; 9.3%), Chinese herbs (9/108; 8.3%), iron (5/108; 4.6%), St John's wort (4/108; 3.7%) and ginger (4/108; 3.7%). All 32 supplements reported to potentially interact with drugs used by oncology patients are presented in Table 2. The drugs most frequently reported to interact with supplements were cyclophosphamide (7; 7.9%), nonsteroidal antiinflammatory drugs (6; 6.7%), irinotecan (6; 6.7%), vinorelbine (6; 6.7%), warfarin (4; 4.5%) and paclitaxel (4; 4.5%). The specific combinations of supplements and drugs reported to potentially interact and the nature of the interaction (as assessed by individual study authors) are detailed in Table 3.

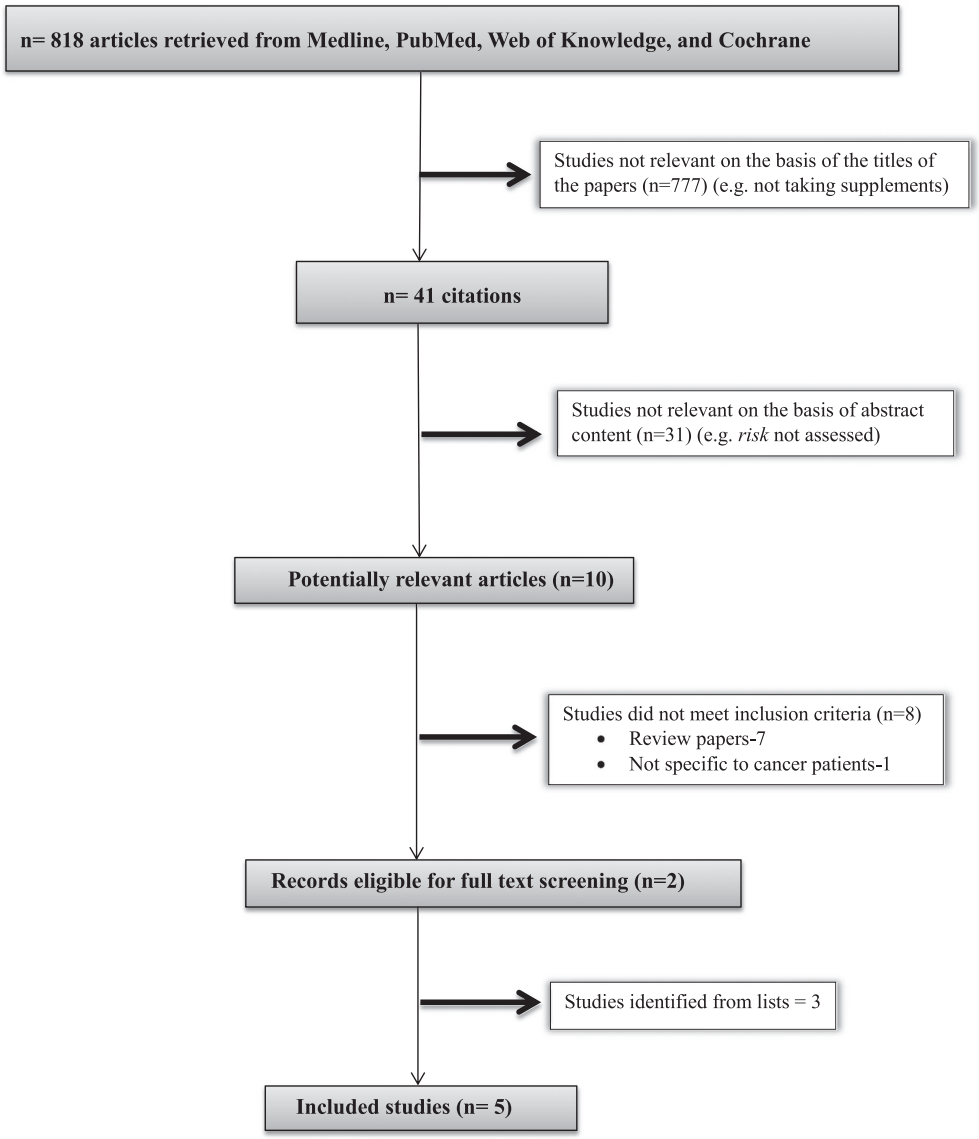

Figure 1. The study selection process.

DISCUSSION

To our knowledge, this is the first systematic review conducted to identify the percentage of adult cancer patients reported to be at risk from HDIs based on specific drug regimens. This review identified five studies, which met our inclusion criteria and found that about half of the cancer patients who participated were taking herb/dietary supplements at the same time as conventional medicines. This is not contentious: the problem arises when trying to estimate the risk of potential harm of such combinations, retrospectively, and in the absence of robust clinical data, and this is the most serious limitation of all such studies, including this systematic review. There are also other more common considerations concerning terminology, bias and response rates, which apply to all such studies. Firstly, definitions and inclusion criteria chosen to define CAM are not uniform (Bishop *et al*., 2010; Werneke *et al*., 2004); for example, some patients do not consider vitamin supplements purchased on their own initiative to be CAM, whereas others consider food supplements prescribed by their doctors, and needed for basic nutrition, to be CAM. Homoeopathic products are often confused with herbal medicines and described as such; although due to unmeasurably low concentrations of any possible active constituents, they are unable to interact with drugs. Terminology issues are likely to affect the response rate because patients self-report CAM use: a UK study that invited 500 cancer patients to participate in a questionnaire-based survey about their CAM use included 182 individuals who did not take part as they 'were not taking any CAMs' (Werneke *et al*., 2004). Secondly, response rates for survey studies are notoriously low (Chiu and Brennan, 1990), and responders may self-select, thus introducing bias from CAM enthusiasts, which may account for a greater proportion of positive responses than would be reflected in the patient population as a whole. Thirdly, the evidence for retrospectively categorising a combination as 'likely to produce an interaction' is generally weak, in that the interaction was not actually identified (or reported) if it had. Finally, the 'grey literature' (unpublished reports) was not surveyed. These may contain useful data, but in the absence of peer-review and concerns

Table 1. Details of the papers included in the review

Study	Lee *et al.*, 2006	McCune *et al.*, 2004	Werneke *et al.*, 2004	Engdal *et al.*, 2009	Zeller *et al.*, 2013	Combined data for all studies	Median percentage (range)
Country	USA	USA	UK	Norway	Germany	—	—
Hospital department	Oncology	Oncology	Oncology	Oncology	Oncology	—	—
Methodology	Researcher administered questionnaire	Self-administered questionnaire	Self-administered questionnaire	Self-administered questionnaire	Interview	—	—
Herb/dietary supplement + conventional medicines recorded	Yes	Yes	Yes	Yes	Yes	—	—
Potential herb–drug interactions assessed	Yes	Yes	Yes	Yes	Yes	—	—
Participants surveyed/interviewed (number)	200	76	318	112	100	806	—
Participants taking supplements with drugs (number (%))	121 (60.5%)	58 (76.3%)	164 (51.6%)	42 (37.5%)	48 (48%)	433 (53.7%)	58% (37.5, 763)
Potential interactions between supplements and drugs (number)	14	45	30	47	31	167	—
Participants at risk of supplements–drugs interactions [number (%)]	3 (2.5%)	21 (36.2)	20 (12.2%)	0	16 (33.3%)	60 (13.9%)	12.2% (0–36.2)

Table 2. Incidence of potential herb–drug interactions as assessed and reported by study authors

Herb/dietary Supplement	Number (%) potential interactions cited
Garlic	16 (14.8)
Green tea	15 (13.9)
Mistletoe	10 (9.3)
Chinese herbal tea	9 (8.3)
Iron	5 (4.6)
St John's wort	4 (3.7)
Ginger	4 (3.7)
Ginseng	4 (3.7)
Echinacea	3 (2.8)
Evening primrose	3 (2.8)
Cod liver oil	3 (2.8)
Ginkgo	3 (2.8)
Centrum multivitamin	2 (1.9)
Potassium	2 (1.9)
Magnesium	2 (1.9)
Parsley	2 (1.9)
Goldenseal	2 (1.9)
Kava kava	2 (1.9)
Milk thistle	2 (1.9)
Soy	2 (1.9)
Aloe vera	2 (1.9)
Germanium	1 (0.9)
Wild yam	1 (0.9)
Fish oil	1 (0.9)
Coenzyme Q10	1 (0.9)
Calcium	1 (0.9)
Laetrile/apricot kernel	1 (0.9)
Valerian	1 (0.9)
Golden root	1 (0.9)
Medicinal mushrooms	1 (0.9)
Agaricus	1 (0.9)
Rooibos	1 (0.9)
Total	108

about impartiality, their relevance cannot be guaranteed. All of these factors will contribute to the wide variety of estimations of CAM use in cancer patients, which was reported by Ernst to vary between 7% and 64% (Ernst, 1998).

The studies included in our review show that most cancer patients did not discuss their CAM use with healthcare professionals, confirming many previous studies (Williamson *et al*., 2013; Bishop *et al*., 2010). Only five studies were found to fit the inclusion criteria by assessing risk based on actual supplement–drug combinations being taken, suggesting that more detail of drug regimens needs to be included and that speculation based purely on numbers of combinations recorded should be reduced. Patients certainly need more education about the benefits and harms of CAM, especially their use in conjunction with other medication. There are legitimate concerns about some types of CAM: for example, patients should know that many supplements have not been proven to be effective but that manufacturers are allowed to make claims on the basis of a 30-year history of safe traditional use; that some herbs have dose limitations associated with their use; that antioxidant supplements that bind to free radicals may interfere with radiotherapy (Ernst, 1998), although this has not been clinically confirmed; and most importantly, that supplements may alter the metabolism of concurrent

Table 3. Types of potential herb–drug interactions, as assessed and described by study authors

Supplement	Drug	Description of interaction
Garlic	Glyburide	Increased hypoglycaemia
	Aspirin	May increase INR and risk of gastrointestinal haemorrhage
	Omeprazole	May increase INR and risk of gastrointestinal haemorrhage
	Paclitaxel	Altered drug metabolism
	Vincristine	Altered drug metabolism
	Vinorelbine	Altered drug metabolism
	Docetaxel	Not reported
	Doxorubicin	Not reported
	Irinotecan	Not reported
	Cyclophosphamide	Altered drug metabolism
Green tea	Cyclophosphamide	Not reported in the study
	Vinorelbine	Not reported in the study
	Etoposide	Not reported in the study
	Doxorubicin	Not reported in the study
	Epirubicin	Not reported in the study
	Cisplatin	Not reported in the study
	Irinotecan	Not reported in the study
Iron	Levofloxacin	Decreased absorption
	Tetracycline	Decreased absorption
	Lisinopril	Decreased absorption
	Levothyroxine	Decreased absorption
Mistletoe	Vinorelbine	Not reported in the study
	Irinotecan	Not reported in the study
	Trastuzumab	Hypersensitivity to antibodies
	Bevacizumab	Hypersensitivity to antibodies
	Lapatinib	Hypersensitivity
St John's wort	Cyclophosphamide	Altered drug metabolism
	Vincristine	Altered drug metabolism
	Vinorelbine	Altered drug metabolism
	Paclitaxel	Altered drug metabolism
Ginseng	Warfarin	Increased anticoagulation
	Bendrofluazide	Ginseng may increase or decrease blood pressure
	Antihypertensives (unspecified)	Ginseng may increase or decrease blood pressure
Echinacea	Rituximab	Stimulation of immune system, especially B lymphocytes which monoclonal antibodies target
	Corticosteroids	Unwanted stimulation of immune system
	Monoclonal antibodies	Not reported in the study
	Cyclophosphamide	Not reported in the study
Evening primrose oil	Sodium valproate	Evening primrose oil: decrease of seizure threshold; reduction in effectiveness of antiepileptic medication
	Naproxen	Increase INR
Centrum multivitamins	Warfarin	Decreased anticoagulation
Potassium	Lisinopril	Decreased absorption
Ginkgo biloba	Diclofenac	Antiplatelet, increases INR
	Aspirin	May increase INR
Parsley	Atenolol	Increased hypotension
	Nifedipine	Increased hypotension
Goldenseal	Antihypertensives (unspecified)	Increase in blood pressure
	Paclitaxel	Potential decrease in paclitaxel metabolism
Kava kava	Ibuprofen	Increases INR in high doses
Milk thistle	Paclitaxel	Potential decrease in paclitaxel metabolism
	Doxorubicin	Potential decrease in doxorubicin metabolism

(Continues)

Table 3. (Continued)

Supplement	Drug	Description of interaction
Cod liver oil	Warfarin	Increase of INR with high or changing doses
	Diclofenac	Antithrombotic effect, increases INR
	Aspirin	Increases INR
Soy	Cyclophosphamide	Not reported in the study
	Epirubicin	Not reported in the study
Aloe vera	Irinotecten	Not reported in the study
Germanium	Antihypertensives (unspecified)	Renal failure, anaemia, neurological and muscular problems
Wild yam	Naproxen	Oestrogenic effect (not an interaction but reported by authors)
Chinese herbs (unspecified)	Chemotherapy (unspecified)	Unspecified interaction
	Endocrine therapy (unspecified)	Unspecified interaction
	Antibodies (unspecified)	Unspecified interaction
Medicinal mushrooms unspecified	Antibodies (unspecified)	Medicinal mushrooms are reported to non-specifically activate the immune system; thus hypersensitivity may be induced
Fish oil	Naproxen	Increases INR
Coenzyme Q10 (ubiquinone)	Warfarin	Reduces anticoagulant properties of warfarin, has vitamin K like effects
Laetrile/apricot kernels	Doxorubicin	Potentially decreases doxorubicin metabolism
Calcium	Felodipine	Decreased therapeutic effect
Valerian	Irinotecan	Not reported in the study
Golden root/Rhodiola	Cyclophosphamide	Not reported in the study
Agaricus	Irinotecan	Not reported in the study
Rooibos	Irinotecan	Not reported in the study

INR, International Normalised Ratio.

drugs (even otherwise innocuous substances such as grapefruit). It is crucial that patients are encouraged to disclose their CAM use so that clinical evidence can be gathered, then risk can be assessed more accurately, which will lead to more realistic warnings of potential harm, but also in some cases, reassurance that a combination appears to be safe.

This review finds that garlic, green tea, mistletoe, iron, Chinese herbal tea, St John's wort, ginseng, ginger, echinacea, evening primrose, ginkgo, parsley, goldenseal and kava kava are the most frequently used herbs, which were reported to have the potential to interact with conventional medicine although patient numbers are small. Garlic was the herb most frequently mentioned, and the authors of the included studies suggested that garlic may alter drug metabolism when given with cyclophosphamide, vinca alkaloids and paclitaxel; however, these interactions are mainly theoretical and are not confirmed by clinical reports. Goey *et al*. (2014) now suggest that garlic is likely to be safe with docetaxel therapy based in *in vitro* studies.

More recent assessments of interaction potential do not support these assessments. For example, garlic is reported to increase the risk of gastrointestinal haemorrhage when combined with aspirin and omeprazole, and a study on HDIs in non-cancer patients has indeed shown that garlic may have antiplatelet or anticoagulant effects, potentially exacerbating the risk of gastrointestinal bleeding, which is consistent with the findings of this review (Thomsen *et al*., 2005; Abebe, 2002), but in fact, no clinical adverse events have been published to date (May 2014). In a study identifying potential interactions between herbal medicines and conventional drug therapies used by older adults attending a memory clinic, garlic (reported as one of the most frequently used herbs) had potential to interact with conventional medicines, but again, no clinical reports are available (Dergal *et al*., 2002). Because garlic is also eaten frequently and in great quantities by very many people, without ill-effect, such theoretical reports must be interpreted cautiously.

Green tea was reported to be the second most frequently used herb involved in potential HDIs. Interactions between green tea supplements were deemed possible with cyclophosphamide, vinorelbine, etoposide, doxorubicin, epirubicin, cisplatin and irinotecan. However, the study did not provide any evidence for them (Engdal *et al*., 2009); no clinical cases have been reported to date, and again, green tea is consumed widely with no apparent harmful effects. A more recent assessment of the potential for both garlic and green tea to interact does not suggest any serious potential for HDIs based on normal intake in food or recommended doses of supplements (Williamson *et al*., 2013), but at the time of analysis, the assessment was reasonable. About a third of the reported 'interactions' involved either garlic or green tea (31/108; 28.7%), and if these studies were removed from the analysis, the number of patients deemed to be at risk and the potential interactions involved would be considerably reduced.

The lack of data regarding possible HDIs in cancer patients and the various complex mechanisms, which may be involved in these interactions, make the estimation of risk of adverse HDIs challenging. The literature shows that CAM is very commonly used in cancer patients (McCune *et al*., 2004) and especially in breast cancer patients (McLay *et al*., 2012), and chemotherapy regimens require accurate dosing and careful blood monitoring of highly toxic drugs. In our review, four potential interactions were identified involving St John's

wort, one of the most frequently used herbal supplements in Europe and in the US. St John's wort is known to alter drug metabolism when combined with cyclophosphamide, vinca alkaloids and paclitaxel, and there have been numerous reports of HDIs involving this herb with many drugs (Williamson *et al*., 2013). Because it is used to treat mild to moderate depression, cancer patients may be expected to consider St John's wort an attractive option. However, it should be avoided by those on cancer drug therapy as a precaution, as it is by far the most likely herb to give rise to HDIs (Izzo, 2012; Russo *et al*., 2014).

CONCLUSIONS

There are many studies that identify possible interactions between herbs and conventional medicines in the general population, but few studies have investigated this in cancer populations. This review found only five papers reporting the percentage of potential HDIs in cancer patients; therefore, it is difficult to draw confirm conclusions about the proportion of cancer patients at risk from herb/dietary-conventional medicines. Furthermore, the reported interactions were mainly theoretical and not supported by clinical data. None of the studies reported any adverse events associated with these combinations, despite the risk being assessed retrospectively, and no actual reports of interaction were recorded.

The current evidence shows that cancer patients may be at risk from HDIs although there appears to have been an over-estimation of the risk from some nutritional supplements such as garlic and green tea, in the light of information available because some of these reviews were carried out. This is not a criticism of the original assessment; it is simply a question of using the information available at the time in the best interests of those patients who wish to take herbal and nutritional products to enhance their general health.

Several recommendations supporting the conclusions of the authors of the individual studies have come out of this review, despite the limitations of the studies and especially the variability of assessment of potential HDIs. The most important is probably that health care professionals should actively discuss CAM with their patients, and should improve their knowledge and awareness of CAM therapies. They should also record CAM use for later appraisal and be able to access authentic CAM references and databases easily, or obtain advice from information services centres quickly. Pharmacists, who may be selling herbal and nutritional supplements to cancer patients, have a clear responsibility to share information gathered from these patients regarding CAM with other healthcare professionals (Klepser and Klepser, 1999). More effort should be made to investigate the use of CAM in this highly vulnerable patient group, to assess the potential for HDIs in a clinically significant manner based on plausible evidence, and using *in vitro* experiments with caution (Goey *et al*., 2013) and to provide reassurance where appropriate that certain combinations are unlikely to cause adverse events.

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Conflict of Interest

The authors report no conflict of interest connected to this study.

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