INTERACTION BETWEEN COMPLEMENTARY AND ALTERNATIVE MEDICINE WITH CONVENTIONAL ANTI-CANCER MEDICINE

Stephen J Clarke[1] and Andrew J McLachlan[2]
1. Faculty of Medicine, University of Sydney, New South Wales and Cancer Pharmacology Research Group, Concord Hospital, New South Wales.
2. Faculty of Pharmacy, University of Sydney, New South Wales and Centre for Education and Research on Ageing, Concord Hospital, New South Wales.
Email: stephen.clarke@sydney.edu.au

Abstract

An increasing proportion of the population use complementary and alternative medicine including herbal medicine. This use is frequently undertaken in addition to their prescribed treatments, often without their physician's knowledge. For many types of complementary and alternative medicine, this concomitant use of treatments is without significant risk of adverse effects. However, for systemically administered complementary and alternative medicine, such as herbal medicine, there are significant risks of adverse drug interactions between herbal medicine and conventional treatments, which may result in either increased drug toxicity or therapeutic failure. It is clear that certain combinations of herbal medicine and conventional medicine carry significant risks of reduced efficacy or adverse effects and the combinations are contraindicated. For instance, in vivo studies have shown that concomitant use of St John's wort with therapeutic agents that are metabolised by the enzyme CYP3A4 has the potential to cause therapeutic failure. In cancer treatments there is also potential for pharmacodynamic interactions between herbal medicine and anti-cancer agents. For example, patients with oestrogen receptor positive breast cancers should be advised to avoid administration of phyto-oestrogen containing herbal preparations. Physicians should be proactive in obtaining a complete medication history, including herbal medicine use, in all their patients receiving cancer chemotherapy, in order to advise them appropriately with a view to making informed decisions about their treatment.

Complementary and alternative medicine (CAM) includes a diverse group of treatments ranging from music therapy, exercise and massage, to systemically administered treatments including nutritional therapies and herbal medicines. The last 15 years have seen a significant increase in the use of CAM. In 1990, a survey in the United States estimated that 34% of the respondents used at least one form of complementary therapy in the previous 12 months.[1] This figure had increased to 42% by 1997.[2] The popularity of CAM use has been mirrored in Australia.[3] In 2004, a South Australian survey reported 52% of respondents had used at least one non-medically prescribed CAM in the previous year. More than 57% of respondents reported using CAM without their health practitioner's knowledge and 50% took conventional medicine on the same day, creating the potential for interactions between conventional medicine and CAM.[3]

In certain diseases such as cancer, there has been an even greater increase in the use of CAM. In 1998, a systematic review of the literature revealed a mean CAM use in 31% among cancer patients.[4] A number of recent studies have suggested this figure may now exceed 80%, although there is variability in use depending on tumour type and ethnic group studied, CAM use being more common in breast cancer patients and individuals from Asian backgrounds.[5, 6] Increased use of CAM in people with cancer is relevant, as even in optimal circumstances there is a low therapeutic index for anti-cancer drugs, which may be further lowered by adverse interactions between CAM and the conventional cancer drugs.

A recent systematic review attempted to identify the principal reasons for CAM use in cancer patients. Although there was a wide range of responses, the most frequent were a perceived beneficial response (38%), wanting 'control' (17%), as a 'last resort' (10%) and 'finding hope' (10%).[7]

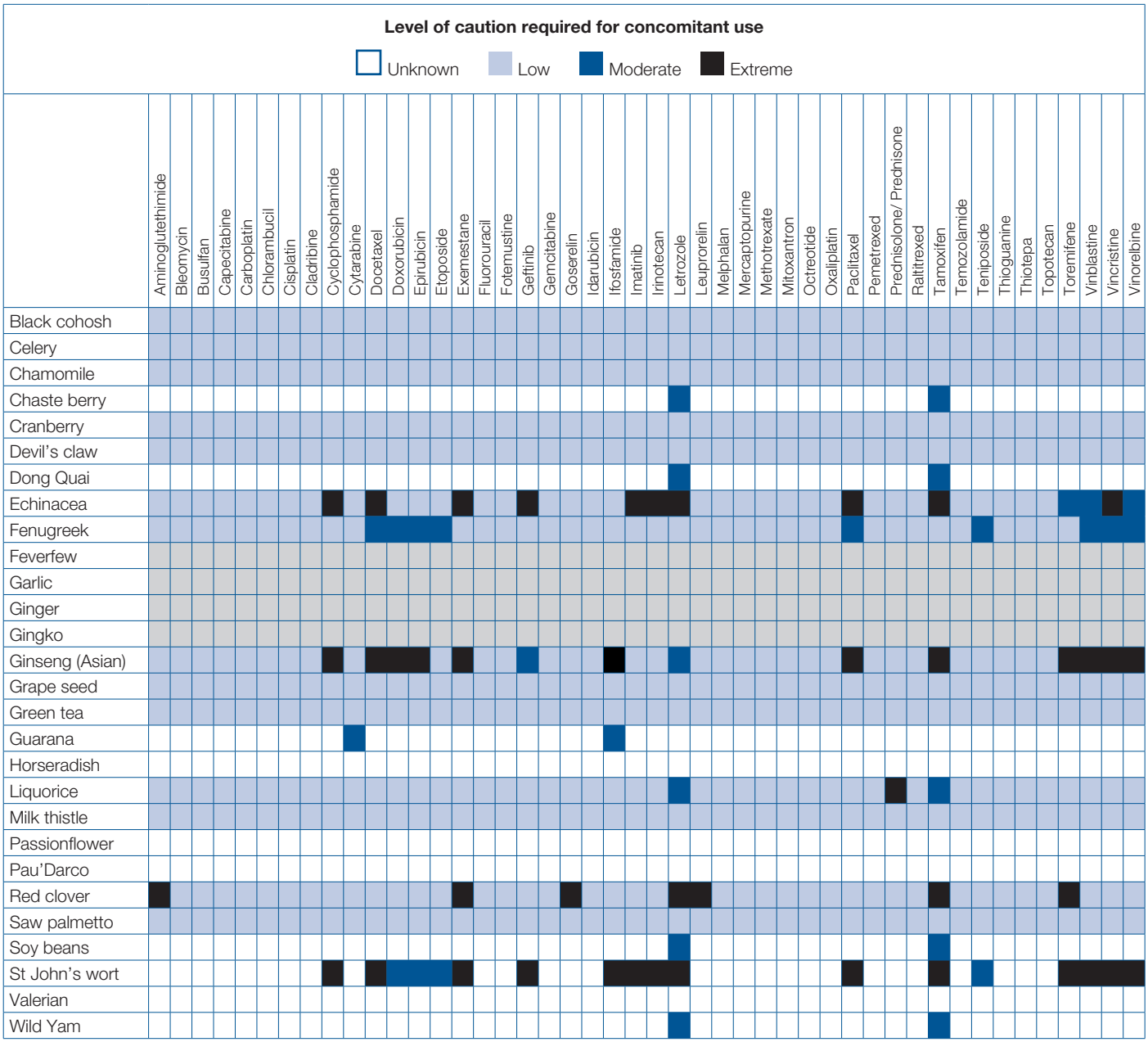
Not surprisingly, CAM is big business. In the US alone, it has been estimated that cancer patients spend over US$30 billion in out-of-pocket expenses on CAM, even though there are relatively few data to indicate the cost-effectiveness of CAM in this treatment setting.[8] This increased use by patients and expense of CAM has highlighted issues in regard to the safety and efficacy of these treatments. This is particularly the case for systemically administered CAMs including herbal medicines, where there is the potential for clinically significant interactions with conventional treatments. In this paper we have provided explanations and examples of proven and potential interactions between CAM and conventional anti-cancer agents, to inform clinicians about these commonly used medicines and highlight the relative dearth of high quality data to guide consumer and healthcare practitioners.

Mechanisms of CAM-drug interactions

The focus of much of the current discussion has been limited to the more commonly used herbal medicine and those mentioned in recent literature, as causing or having the potential to cause herb-drug interactions

with conventional medicine.[9-12] With many conventional agents, herb-drug interactions may not lead to any serious sequelae. However, for some classes of conventional therapeutic agents that have a low therapeutic index (ie. a fine line between a safe/effective dose and a toxic dose), in particular anti-cancer drugs, even minor changes in drug clearance from a patient's body could produce dramatic effects on patient outcomes. Herb-drug interactions occur via several broad mechanisms, including pharmaceutical, pharmacokinetic (PK) and pharmacodynamic (PD) interactions (Table 1).

Table 1: *Level of caution required for the concomitant use of selected anti-cancer agents with herbal medicines. The coloured classification system was derived by the authors based upon their critical, clinical evaluation of available literature. 'Extreme' caution denotes high potential for adverse reactions confirmed from in vivo studies and concomitant use should be avoided. 'Moderate' caution denotes medium potential for adverse reactions (in vitro studies indicate possible interaction) and concomitant use should only be administered under strict, clinical supervision. 'Low' caution denotes little potential for adverse reactions; in vivo and in vitro studies indicate little potential for interactions and concomitant use may be considered. 'Unknown' caution denotes a lack of available clinical evidence to make an appropriate recommendation.*



PK interactions can result when common or competing pathways of absorption, metabolism, distribution or elimination exist between the constituents of herbal medicine and conventional therapeutic agents. These interactions most commonly involve intestinal and hepatic drug metabolising enzymes (such as cytochrome P450, or "CYP" enzymes) and drug transporters such as the ABC transporters including P-glycoprotein (P-gp), breast cancer resistance protein and multi-drug resistance proteins which are found in numerous healthy tissues including the gut epithelium, liver and central nervous system, as well as, chemotherapy resistant tumour cells.[13] Two of the most important CYP enzymes for metabolism of xenobiotics in humans are CYP3A4 and CYP2D6 (Table 1). CYP3A4 is responsible for the metabolism of numerous therapeutic drugs. For instance, in cancer, CYP3A4 plays at least some role in the metabolism of agents such as the taxanes (docetaxel and paclitaxel), vinca alkaloids (vincristine, vinblastine, vindesine and vinorelbine), camptothecins (irinotecan), the hormones exemestane, tamoxifen and letrozole, and the epidermal growth factor receptor inhibitors (gefitinib and erlotinib).[12] Substrates for the drug transporter, P-gp, among cancer drugs include many of the naturally derived anti-cancer drugs including the taxanes, vinca alkaloids, epipodophyllotoxins and anthracyclines.[14]

Drug interactions can result if herbal constituents induce or inhibit these drug metabolising and transporter pathways, thereby altering the bioavailability or elimination of the conventional therapeutic agent. If bioavailability is increased (ie. increased concentrations of a drug in the body after a given dose) this may lead to increased drug toxicity, while a reduction in bioavailability may lead to compromised therapeutic efficacy. It has been recently proposed by a number of authors that some of the effects on these drug metabolising pathways might be mediated through activation of the pregnane X receptor (PXR), a ligand activated nuclear receptor that is part of the superfamily of nuclear receptors. PXR regulates the induction of CYP3A gene expression by xenobiotics, but may also regulate the induction of other genes involved in drug metabolising pathways, including CYP2B, CYP2C, CYP24, glutathione S-transferases, sulfotransferases, glucuronosyltransferases, and drug transporters, organic anion-transporting polypeptide 1A4, P-gp and multidrug resistance-associated proteins 2 and 3.[15,16] It has been recently shown that PXR is activated by a number of herbal remedies including ginkgo biloba (higher doses), St John's wort, and traditional Chinese remedies including Tian Xian, Wu Wei Zi and Gan Cao, demonstrating that herbal remedies have the potential to have a major impact on drug metabolism.[17-19]

PD interactions may occur when the bioavailable constituents of a herbal compound act in an additive, synergistic or antagonistic manner with a therapeutic agent. It is worth noting that disease states themselves can change the PK or PD of a drug and extrapolating data from healthy volunteers to patients is not always possible.[20] For example, CYP 3A-mediated drug metabolism may be impaired in patients with an acute phase response, as occurs in numerous illnesses including rheumatological conditions, acute infections and patients with advanced cancer, and probably contributes to the marked variability in drug pharmacokinetics and toxicity that has been noted in these circumstances.[21]

Although the potential for herb-drug interactions remains theoretical, for many therapeutic agents the consequences are potentially significant in terms of disease outcome and morbidity; any theoretical interaction should be regarded as clinically relevant.

Examples of herb-drug interactions

It is not possible to discuss all possible interactions between various types of CAM and conventional anti-cancer treatments. We have chosen to provide representative examples of the types of interactions that are described above to demonstrate that drug-CAM interactions do occur and may lead to adverse outcomes. However, often the potential for interaction with anti-cancer drugs has to be extrapolated from pre-clinical studies or interactions with drugs from other therapeutic classes. These examples emphasise the need to perform well designed PK/PD studies with other CAM and anti-cancer treatments to improve our knowledge of CAM-drug interactions (including an understanding of the possible mechanism) and the safety of cancer treatments.

Black cohosh (Cimicifuga racemosa)

Black cohosh is promoted for use in the treatment of menopausal symptoms and menstrual conditions, although its efficacy has yet to be conclusively substantiated in clinical trials. It may be misconceived as having oestrogenic properties due to its effect in menopausal herbal medicine products such as Remifemin®. However, black cohosh's effect may be due to more of a dopaminergic, rather than an oestrogenic profile,[22] or the result of constituents that have selective oestrogen receptor modulator activity.[23] Therefore, the theoretical caution in regard to administration of black cohosh in patients with oestrogen dependent tumours may be unfounded.

While there have been no direct in vivo studies, an in vitro study suggests that black cohosh may also influence the efficacy of selected chemotherapeutic agents used in the treatment of breast cancer.[24] Results showed that black cohosh enhanced the sensitivity of mouse mammary cancer cells to doxorubicin and docetaxel, but reduced sensitivity to cisplatin. Whilst the mechanisms of interaction and clinical relevance of this study are not yet clear, caution may be warranted in cancer patients receiving black cohosh in conjunction with chemotherapy. An in vivo study in rats also investigated the use of black cohosh and tamoxifen on implanted endometrial adenocarcinoma cells. It showed that black cohosh did not enhance or reduce the inductive effect of tamoxifen on tumour growth, but may have reduced the metastasising potential of the tumour potentiated by tamoxifen.[25]

A number of randomised studies have failed to show benefit for black cohosh compared to placebo in the treatment of hot flushes or vasomotor symptoms of menopause, which are common problems for women undergoing chemotherapy.[26,27]

A clinical trial has shown that black cohosh may have an inhibitory effect on CYP2D6 activity, but no significant effect on the activities of CYP3A4, CYP1A2 and CYP2E1 in healthy volunteers.[28] Caution may be warranted therefore in patients receiving therapeutic agents metabolised by CYP2D6. A further study, again in healthy volunteers, has shown that black cohosh has no effect on the drug disposition of digoxin, which may be indicative of a lack of effect of the herb on the activity of P-gp.[29] There have also been reports of black cohosh inducing acute hepatotoxicity, leading in some instances to hepatic failure necessitating liver transplantation.[30]

In summary, evidence regarding the potential interaction between black cohosh and therapeutic agents is suggestive, but limited, and further clinical and pharmacokinetic studies are required.

Fenugreek (Trigonella foenum graecum)

The German Commission E has approved the internal use of fenugreek as an appetite stimulant and topically as a poultice to treat local inflammation. Although no herb-drug interactions have been reported for fenugreek, it has several constituents that could theoretically cause interactions with some medicines. It has been suggested that the coumarin content could theoretically potentiate the anticoagulant effect of warfarin. However, a clinical study in patients with coronary artery disease receiving 5g of fenugreek powder for three months, found no significant effect on blood coagulation parameters, although in vitro investigations showed inhibition of platelet aggregation.[31]

Fenugreek also contains several flavonoids, including quercetin, which has been implicated in CYP3A4 inhibition. One study demonstrated that quercetin increased the bioavailability of verapamil in rabbits in vivo, suggesting CYP3A4 inhibition as a possible mechanism.[32] Another trial showed that the area under the curve (AUC) of cyclosporine (a CYP3A4 substrate) was increased when it was co-administered with quercetin to healthy volunteers (n=8), the highest increase occurring when participants received quercetin for three days prior to commencement of cyclosporine.[33] An animal study also demonstrated that quercetin can increase the bioavailability of orally administered paclitaxel.[34] Increases in area under the AUC and Cmax were observed when paclitaxel was administered with quercetin, possibly as a result of intestinal P-gp and CYP3A4 inhibition. Previous in vitro studies also demonstrated an inhibitory effect of quercetin on P-gp.[35] However, information regarding plasma concentrations and bioavailability of quercetin following oral administration of recommended doses of fenugreek is largely unknown. Thus, there is the potential for interaction between fenugreek and conventional therapeutic agents as a result of the quercetin content. Caution is warranted in co-administering fenugreek together with agents that are CYP3A4 substrates and/or substrates for P-gp.

St John's wort (Hypericum perforatum)

St John's wort is commonly used for the treatment of mild to moderate depression, as well as other psychiatric disorders such as seasonal affective disorder and mild anxiety.[36] Although its overall mechanism of action is unclear, hyperforin is believed to be one of the constituents responsible for its antidepressant effect. Several in vitro studies have indicated hyperforin acts by inhibiting the re-uptake of neurotransmitters such as serotonin, noradrenaline and possibly dopamine.[37] Despite these findings, St John's wort herbal medicine products with minimal amounts of hyperforin present, have been demonstrated to have some efficacy as an antidepressant suggesting other constituents may also have a role.

St John's wort has been shown to be a potent modulator of several cytochrome P450 enzymes. Its constituents have both inductive and inhibitory effects. In vitro studies have shown that extracts of St John's wort significantly inhibit the activity of CYP 1A2, 2D6, 2C9, 2C19 and 3A4. In vivo studies have shown ST JOHN'S WORT derivatives produce significant induction of hepatic and intestinal CYP3A4 if administered for longer than a two week period, while having no inductive effect on cytochromes P450 2C9 or 2D638 and a possible inductive effect on CYP1A2.[39] In the clinical setting, the predominant effect of co-administration of St John's wort is indication of metabolism with the associated risk of lack of efficacy due to sub-therapeutic concentrations.

Hyperforin, a major constituent of St John's wort, is believed to be responsible for inducing intestinal expression of P-gp, enhancing its drug efflux function.[40,41] Two studies have directly investigated clinically significant interactions between St John's wort and anti-cancer agents. The first of these examined the effect of St John's wort on the metabolism of irinotecan, a pro-drug of SN-38 and a known CYP3A4 substrate.[42] A 42% decrease in the AUC was observed for the combination of irinotecan and St John's wort compared to irinotecan alone. The second study investigated the effect of St John's wort on imatinib and found that the clearance of imatinib increased by 43% when co-administered with St John's wort.[43] CYP3A4 is the major enzyme responsible for the metabolism of imatinib with CYPs 1A2, 2D6, 2C9 and 2C19 contributing to a lesser extent. These studies clearly indicate the potential for clinically significant interactions between St John's wort and anti-cancer agents.

Other trials have demonstrated clinically significant interactions between St John's wort and conventional medicines.[44] Several case reports suggest St John's wort is responsible for interactions with cyclosporine with one case resulting in acute heart transplant rejection.[45] Two possible mechanisms of interaction between St John's wort and cyclosporine include induction of intestinal and hepatic CYP3A4, as well as induced expression of intestinal P-gp drug transporters.

St John's wort has also been shown to interact with fexofenadine, which is not metabolised by CYP enzymes, but is a measure of P-gp function providing further evidence as to the involvement of St John's wort in multiple induction mechanisms.[46] Thus, concomitant treatment with St John's wort and other agents that are CYP3A4 substrates or substrates for the P-gp drug transport system may affect clinical outcomes.

Phyto-oestrogen containing herbal medicines

Many women self-medicate with complementary medicines to alleviate menopausal symptoms.[47] In vitro studies have been performed investigating the proliferative effects of herbal substances and purified extracts that are marketed for menopausal symptom relief using MCF-7 cultured breast cancer cells. Products containing soy, red clover, dong quai and ginseng have all been shown to produce increases in MCF-7 cell proliferation in the absence of oestrogen.[48] A similar in vitro assay recently published investigating purified genistein, daidzein and resveratrol, all phyto-oestrogens, also showed increases in the proliferation of MCF-7 cells.[49] Research conducted in athymic mice with implanted MCF-7 cells showed that dietary genistein was able to negate the anti-oestrogenic effects of concurrent tamoxifen[50]. These proliferative effects have not been shown in vivo, however since it is unlikely that any such study would be attempted, it would be prudent to advise women with oestrogen receptor positive breast cancers and who are undergoing treatment with anti-oestrogens, to avoid self-medication with any herbs containing phyto-oestrogens.[51, 52]

Conclusion

The increasing use of herbal medicine and complementary therapies has led to concerns about the appropriate concomitant use of pharmaceutical and herbal medicine. The data we have examined highlight the validity of concerns about potential adverse interactions between CAM and conventional treatments. However, there are enormous gaps in our knowledge because of the lack of well-conducted clinical and pharmacokinetic studies of CAM and conventional treatments in many therapeutic settings. It is imperative that these gaps are filled to ensure that patients receive the safest and most effective therapies.

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