TANG HUMANITAS MEDICINE

Original Article

Merging the old with the new: a cybermedicine marriage for oncology interactions with traditional herbal therapies and complementary medicines

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ABSTRACT

An oncology-specific database called OncoRx (http://bit.ly/cancerRx) was previously set up in cyberspace to aid clinicians in identifying interactions of anticancer drugs (ACDs) and chemotherapy regimens with traditional Chinese medicines (TCMs) and complementary and alternative medicines (CAMs). Since then, users have requested the drug-CAM interactions (DCIs) of 5 specific CAMs (cranberry, melatonin, co-enzyme Q10, huachansu, reishi mushroom) to be updated in the database. Pharmacokinetic properties (metabolism, enzyme induction/inhibition, elimination), TCM properties and DCIs of each CAM were collated with 117 ACDs using 9 hardcopy compendia and online databases as resources. Additionally, individual ACDs and CAMs were used as keywords for PubMed searches in combination with the terms 'anticancer drugs', 'drug interactions', 'herb-drug/drug-herb interactions', 'pharmacokinetic interactions' and 'pharmacodynamic interactions'. DCI parameters consisted of interaction effects, evidence summaries, proposed management plans and alternative non-interacting CAMs, together with relevant citations and update dates of the DCIs. OncoRx is also used as a case to introduce the "Four Pharmaco-cybernetic Maxims" of quality, quantity, relationship and manner to developers of digital healthcare tools. Its role in Hayne's "5S" hierarchy of research evidence is also presented. OncoRx is meant to complement existing DCI resources for clinicians and alternative medicine practitioners as an additional drug information resource that provides evidence-based DCI information for ACD-CAM interactions.

Keywords traditional Chinese medicines, complementary medicines, anticancer drugs, drug-CAM interactions, digital healthcare, pharmaco-cybernetic maxims

INTRODUCTION

The advent of the internet has led to healthcare professionals and patients being more well-informed about medications and diseases through health-related information that can be accessed online. In Europe, it is estimated that the percentage of the population that has used the internet for seeking health information increased from 43% in 2005 to 52% in 2007 (Kummervold et al., 2008) while in the US population, out of the 40% that used the internet for health information, one-third indicated that this information affected their decision making (Baker et al., 2003). Cancer is one of the top few diseases that people seek information online (Shim, 2008). Cancer patients tend to use the internet to seek information regarding treatment therapies, find experiences and/or support from other cancer survivors, help interpret consultations, and even source for second opinions (Ziebland et al., 2004). However, several drug-related problems have arisen in this cybermedicine age (Yap et al., 2009a). For example, some patients may retrieve erroneous information from the internet or misinterpret generalized information about cancer therapies that is not applicable to them. Also, some patients may resort to sourcing for cheaper alternatives to their anticancer drugs (ACDs) online in the attempt to find the best deals for their chemotherapies.

The use of complementary and alternative medicines (CAMs), including traditional Chinese medicinal (TCM) herbs/herbal therapies, is common among cancer patients. Studies have shown that between 9% and 91% of cancer patients in the USA use some form of CAMs after cancer diagnosis (White, 2002), and this usage has increased over the years (DiGianni et al., 2002; Nahleh and Tabbara, 2003; Yates et al., 2005). Besides being used as an adjunct for cancer treatment, many patients also use CAMs for supportive care, such as to boost their immunity and to relieve the adverse effects of fatigue, nausea, vomiting, alopecia and pain (Mansky and Wallerstedt, 2006; Tascilar et al., 2006). In TCM theory, cancer is a result of imbalances between internal conditions of the body and exogenous pathogenic factors such as accumulated toxins, heat and blood stasis (Hsiao and Liu, 2010). One of the basic principles in TCM's approach to cancer therapy is Fu-zheng therapy, which is used to enhance the body's defense mechanism (Macek, 1984). Another principle in TCM involves qi, otherwise known as "vital energy". Qi is fundamental to the maintenance of the body's life activities, with functions in warming, defense, homeostasis and the circulation of blood and bodily fluids (Tan et al., 2008). It is believed that the weakening of qi depresses an individual's immunity and thus increases one's susceptibility to infection

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and cancer progression (Wong et al., 2001). Some herbs, such as the medicinal mushroom *Ganoderma*, strengthen qi, thereby resulting in improved immune functions and anticancer activities (Wong et al., 2001). On the other hand, CAMs with anticancer effects, including TCM herbs and herbal extracts, can also be categorized based on their different mechanisms of action (Hsiao and Liu, 2010). For example, one of the active constituents of huachansu (an extract from toad skin venom secretions), known as bufalin, induces apoptosis and suppresses the proliferation of various cancer cell lines (Jiang et al., 2010; Takai et al., 2008; Yu et al., 2008; Yun et al., 2009).

Many patients consume CAMs without their physician's knowledge and may not be aware that adverse effects from drug-CAM interactions (DCIs) can potentially occur when used concurrently with ACDs (Oldendick et al., 2000). DCIs can lead to increased toxicities, subtherapeutic effects or potentiated adverse effects, resulting in undesirable patient outcomes; some of which can be significant, for example, myelosuppression, liver toxicity or tumor growth stimulation (Sparreboom et al., 2004). As anticancer therapies often involve multiple-drug regimens, the risk of DCIs is compounded. There is abundant information on cancer treatment strategies on the internet (Yap et al., 2009b), but little on DCI information, particularly for TCMs. Conventional drug resources that oncology clinicians use provide detailed information for well-established herbs such as ginseng or St. John's wort, but not for all herbs (British Medical Association and Pharmaceutical Society of Great Britain, 2007; Gerstner Jr., 2008; Jellin and Gregory, 2007; Lacy et al., 2007-2008; Thomson Healthcare, n.d.). On the other hand, TCM resources are limited in the DCI data for clinician use (e-MS Inc., 2004; Rootdown LLC, 2008); thus emphasizing the need for an appropriate resource for oncology clinicians to identify possible DCIs between CAMs and chemotherapies, so that they can make timely interventions to achieve the best therapeutic outcomes for patients.

To aid clinicians with identifying DCIs for ACDs and chemotherapy regimens, an oncology-specific database called OncoRx (http://bit.ly/cancerRx) was previously set up in cyberspace (Yap et al., 2010c). This database provided information on DCIs between 117 ACDs and 166 CAMs. To date, OncoRx has users from a wide variety of disciplines ranging from oncologists and oncology pharmacists, to researchers and naturopaths across different countries. There is a need to keep the database updated with more CAMs and DCIs to cater towards its users. Specifically, several users have requested the DCIs of 5 CAMs to be added to the database – cranberry, melatonin, co-enzyme Q10 (Co-Q10), huachansu and reishi mushroom (lingzhi). The objective of this paper is to use OncoRx and the DCIs detected with these 5 herbs to illustrate how digital healthcare tools can add value to clinical practices in this cybermedicine era. The role of OncoRx as an example of an evidence-based resource is discussed together with several design principles that developers of digital healthcare tools are encouraged to follow.

MATERALS AND METHODS

The list of 5 CAMs (cranberry, melatonin, Co-Q10, huachansu,

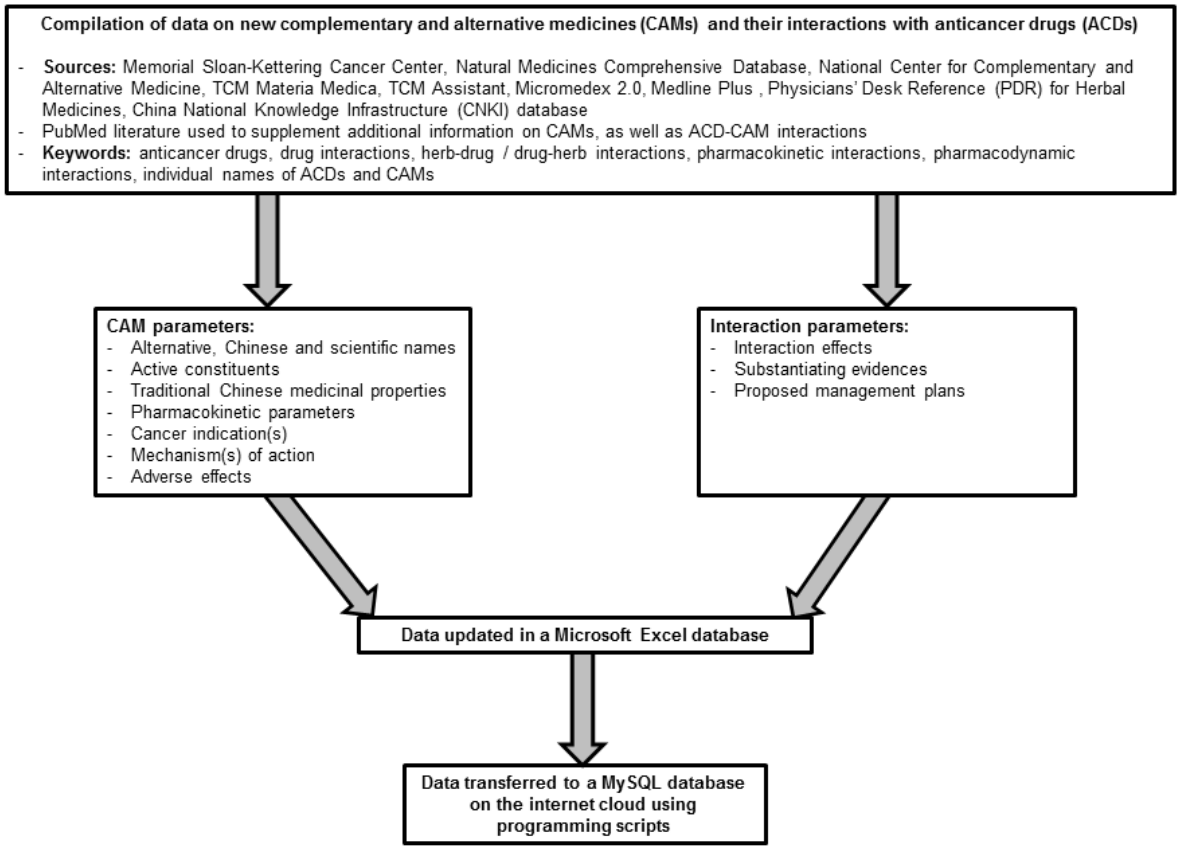
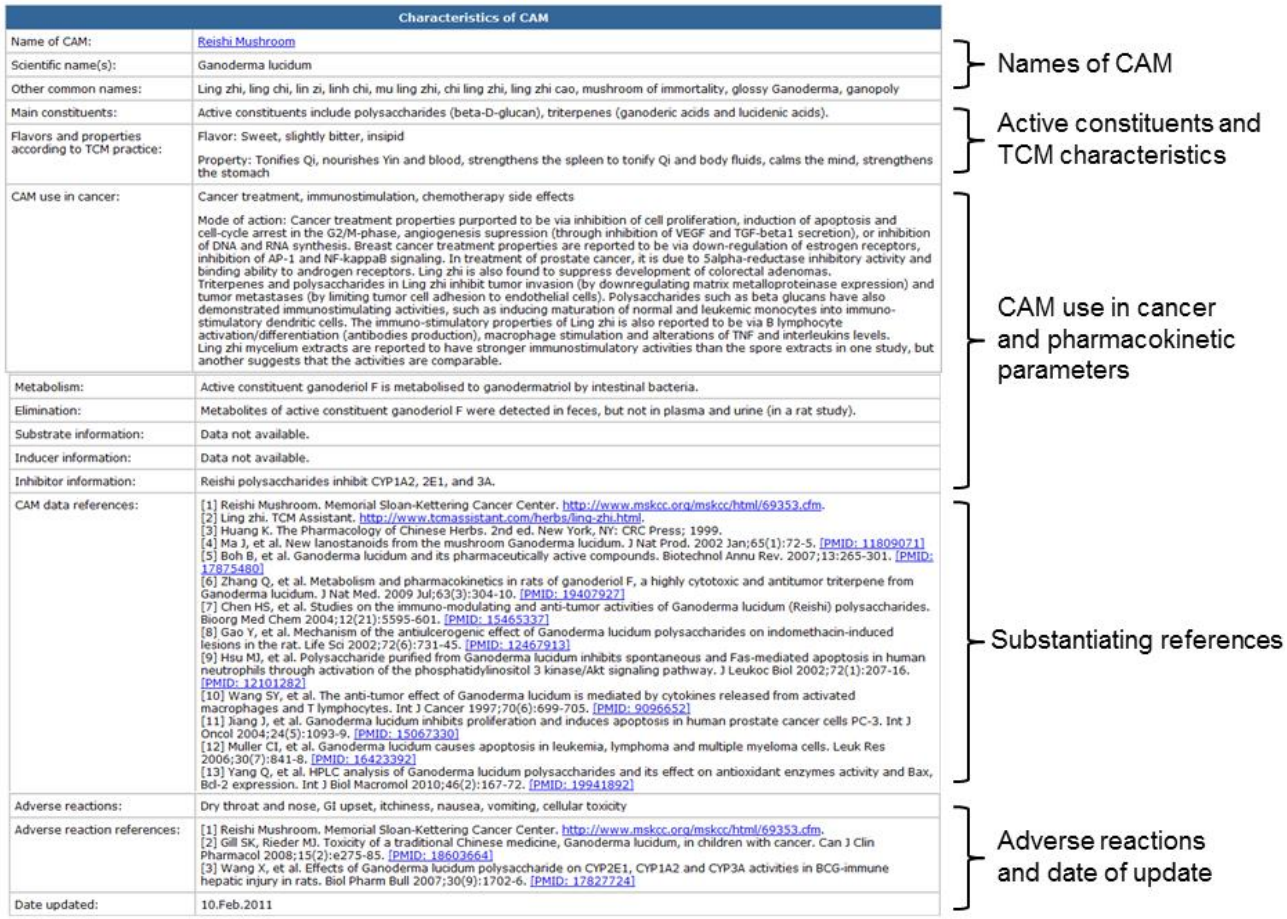


Fig. 1. Flowchart showing methodology of updating the OncoRx database.



Characteristics of CAM	
Name of CAM:	Reishi Mushroom
Scientific name(s):	Ganoderma lucidum
Other common names:	Ling zhi, ling chi, lin zi, linh chi, mu ling zhi, chi ling zhi, ling zhi cao, mushroom of immortality, glossy Ganoderma, ganopoly
Main constituents:	Active constituents include polysaccharides (beta-D-glucan), triterpenes (ganoderic acids and lucidenic acids).
Flavors and properties according to TCM practice:	Flavor: Sweet, slightly bitter, insipid Property: Tonifies Qi, nourishes Yin and blood, strengthens the spleen to tonify Qi and body fluids, calms the mind, strengthens the stomach
CAM use in cancer:	Cancer treatment, immunostimulation, chemotherapy side effects Mode of action: Cancer treatment properties purported to be via inhibition of cell proliferation, induction of apoptosis and cell-cycle arrest in the G2/M-phase, angiogenesis supression (through inhibition of VEGF and TGF-beta1 secretion), or inhibition of DNA and RNA synthesis. Breast cancer treatment properties are reported to be via down-regulation of estrogen receptors, inhibition of AP-1 and NF-kappaB signaling. In treatment of prostate cancer, it is due to 5alpha-reductase inhibitory activity and binding ability to androgen receptors. Ling zhi is also found to suppress development of colorectal adenomas. Triterpenes and polysaccharides in Ling zhi inhibit tumor invasion (by downregulating matrix metalloproteinase expression) and tumor metastases (by limiting tumor cell adhesion to endothelial cells). Polysaccharides such as beta glucans have also demonstrated immunostimulating activities, such as inducing maturation of normal and leukemic monocytes into immuno-stimulatory dendritic cells. The immuno-stimulatory properties of Ling zhi is also reported to be via B lymphocyte activation/differentiation (antibodies production), macrophage stimulation and alterations of TNF and interleukins levels. Ling zhi mycelium extracts are reported to have stronger immunostimulatory activities than the spore extracts in one study, but another suggests that the activities are comparable.
Metabolism:	Active constituent ganoderiol F is metabolised to ganodermatriol by intestinal bacteria.
Elimination:	Metabolites of active constituent ganoderiol F were detected in feces, but not in plasma and urine (in a rat study).
Substrate information:	Data not available.
Inducer information:	Data not available.
Inhibitor information:	Reishi polysaccharides inhibit CYP1A2, 2E1, and 3A.
CAM data references:	[1] Reishi Mushroom. Memorial Sloan-Kettering Cancer Center. http://www.mskcc.org/mskcc/html/69353.cfm. [2] Ling zhi. TCM Assistant. http://www.tcmassistant.com/herbs/ling-zhi.html. [3] Huang K. The Pharmacology of Chinese Herbs. 2nd ed. New York, NY: CRC Press; 1999. [4] Ma J, et al. New lanostanoids from the mushroom Ganoderma lucidum. J Nat Prod. 2002 Jan;65(1):72-5. [PMID: 11809071] [5] Boh B, et al. Ganoderma lucidum and its pharmaceutically active compounds. Biotechnol Annu Rev. 2007;13:265-301. [PMID: 17875480] [6] Zhang Q, et al. Metabolism and pharmacokinetics in rats of ganoderiol F, a highly cytotoxic and antitumor triterpene from Ganoderma lucidum. J Nat Med. 2009 Jul;63(3):304-10. [PMID: 19407927] [7] Chen HS, et al. Studies on the immuno-modulating and anti-tumor activities of Ganoderma lucidum (Reishi) polysaccharides. Bioorg Med Chem 2004;12(21):5595-601. [PMID: 15465337] [8] Gao Y, et al. Mechanism of the antiulcerogenic effect of Ganoderma lucidum polysaccharides on indomethacin-induced lesions in the rat. Life Sci 2002;72(6):731-45. [PMID: 1246791] [9] Hsu MJ, et al. Polysaccharide purified from Ganoderma lucidum inhibits spontaneous and Fas-mediated apoptosis in human neutrophils through activation of the phosphatidylinositol 3 kinase/Akt signaling pathway. J Leukoc Biol 2002;72(1):207-16. [PMID: 12101282] [10] Wang SY, et al. The anti-tumor effect of Ganoderma lucidum is mediated by cytokines released from activated macrophages and T lymphocytes. Int J Cancer 1997;70(6):699-705. [PMID: 9096652] [11] Jiang J, et al. Ganoderma lucidum inhibits proliferation and induces apoptosis in human prostate cancer cells PC-3. Int J Oncol 2004;24(5):1093-9. [PMID: 15067330] [12] Muller CI, et al. Ganoderma lucidum causes apoptosis in leukemia, lymphoma and multiple myeloma cells. Leuk Res 2006;30(7):841-8. [PMID: 16423392] [13] Yang Q, et al. HPLC analysis of Ganoderma lucidum polysaccharides and its effect on antioxidant enzymes activity and Bax, Bcl-2 expression. Int J Biol Macromol 2010;46(2):167-72. [PMID: 19941892]
Adverse reactions:	Dry throat and nose, GI upset, itchiness, nausea, vomiting, cellular toxicity
Adverse reaction references:	[1] Reishi Mushroom. Memorial Sloan-Kettering Cancer Center. http://www.mskcc.org/mskcc/html/69353.cfm. [2] Gill SK, Rieder MJ. Toxicity of a traditional Chinese medicine, Ganoderma lucidum, in children with cancer. Can J Clin Pharmacol 2008;15(2):e275-85. [PMID: 18603664] [3] Wang X, et al. Effects of Ganoderma lucidum polysaccharide on CYP2E1, CYP1A2 and CYP3A activities in BCG-immune hepatic injury in rats. Biol Pharm Bull 2007;30(9):1702-6. [PMID: 17827724]
Date updated:	10.Feb.2011

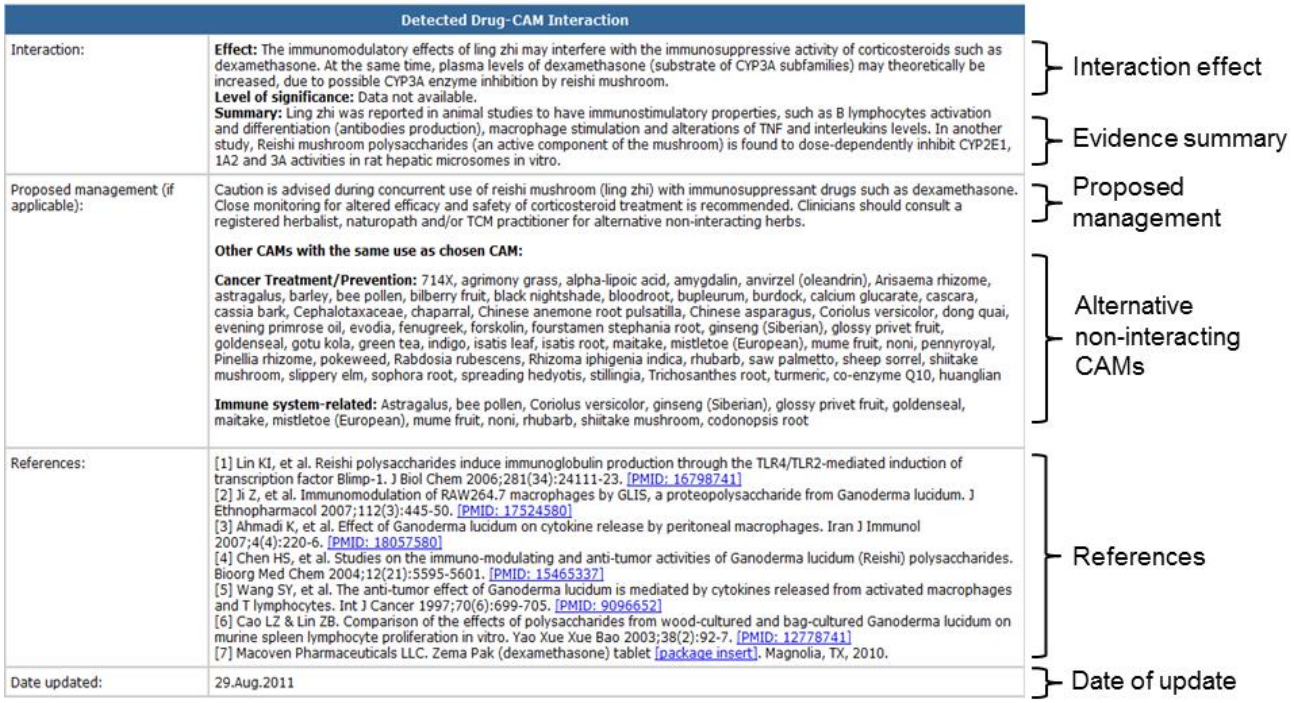
Fig. 2. Screenshot of OncoRx search between reishi mushroom and dexamethasone, showing the section on CAM characteristics.

reishi mushroom) was determined before data on their pharmacokinetic properties and characteristics were compiled. Additionally, the DCIs of each CAM were collated with the 117 ACDs in the database. Nine hardcopy compendia and online databases were used as resources. These included the databases from Memorial Sloan-Kettering Cancer Center (Gerstner Jr., 2008), Natural Medicines Comprehensive Database (Jellin and Gregory, 2007), National Center for Complementary and Alternative Medicine (National Institutes of Health and National Center for Complementary and Alternative Medicine), TCM Materia Medica (Raymond, 2000), TCM Assistant (e-MS Inc., 2004), Micromedex 2.0 (Thomson Healthcare, n.d.), Medline Plus (National Institutes of Health, 1995) and Physicians' Desk Reference for Herbal Medicines (Gruenwald et al., 2007). An additional database, the China National Knowledge Infrastructure (CNKI) database (Tsinghua Tongfang Knowledge Network Technology Co. Ltd., 2006) was also used for compiling information on the herbal therapies huachansu and reishi mushroom. Data compiled included the Chinese, scientific and alternative names of the CAMs, their active constituents, TCM properties (if applicable), pharmacokinetic parameters, cancer indications and mechanisms of action, as well as adverse effects. Published literature from PubMed was used to supplement additional information regarding the CAMs, as well as to search for DCIs with the ACDs. The common and scientific names of the CAMs (i.e. cranberry [*Vaccinium macrocarpon*], melatonin, co-enzyme Q10 [ubiquinone], huachansu [*Bufo gargarizans*] and reishi mushroom [*Ganoderma lucidum*, lingzhi]) were used as keywords for the searches in combination with the terms 'anticancer drugs', 'drug interactions', 'herb-drug/drug-herb interactions', 'pharmacokinetic interactions' and 'pharmacodynamic interactions', as well as the individual ACD names and their pharmacological categories (Table 1). DCI parameters consisted of interaction effects, substantiating evidences and proposed management plans. All the data were first updated in Microsoft Excel, and then transferred to a MySQL (structured query language) database in the internet cloud. Fig. 1 shows a summary flowchart of the methodology for updating the database.

RESULTS

Database structure

When users search for a DCI in the OncoRx database, for example, reishi mushroom and dexamethasone (a steroid commonly used for the control of chemotherapy-induced nausea and vomiting) (Chan et al., 2011), they will be shown a display of their selections of ACD and CAM, followed by 3 separate sections: (i) the pharmacokinetic parameters of the ACD, (ii) the characteristics of the CAM, and (iii) the detected DCI. In terms of the CAM characteristics (Fig. 2), information shown to the users includes the scientific and other common names of the CAM, in this case, *Ganoderma lucidum* and lingzhi respectively. The main active constituents (beta-D-glucan, ganoderic and lucidenic acids) are also displayed together with its TCM characteristics (sweet, slightly bitter; tonifies Qi, nourishes the Yin and blood). Additionally, its intended use in cancer (cancer treatment and immunostimulation), metabolism and enzyme induction and/or inhibition effects, as well as elimination information is provided together with a reference list and hyperlinks. A list of adverse reactions is also provided.



Detected Drug-CAM Interaction	
Interaction:	**Effect:** The immunomodulatory effects of ling zhi may interfere with the immunosuppressive activity of corticosteroids such as dexamethasone. At the same time, plasma levels of dexamethasone (substrate of CYP3A subfamilies) may theoretically be increased, due to possible CYP3A enzyme inhibition by reishi mushroom. **Level of significance:** Data not available. **Summary:** Ling zhi was reported in animal studies to have immunostimulatory properties, such as B lymphocytes activation and differentiation (antibodies production), macrophage stimulation and alterations of TNF and interleukins levels. In another study, Reishi mushroom polysaccharides (an active component of the mushroom) is found to dose-dependently inhibit CYP2E1, 1A2 and 3A activities in rat hepatic microsomes in vitro.
Proposed management (if applicable):	Caution is advised during concurrent use of reishi mushroom (ling zhi) with immunosuppressant drugs such as dexamethasone. Close monitoring for altered efficacy and safety of corticosteroid treatment is recommended. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs. **Other CAMs with the same use as chosen CAM:** **Cancer Treatment/Prevention:** 714X, agrimony grass, alpha-lipoic acid, amygdalin, anvirzel (oleandrin), Arisaema rhizome, astragalus, barley, bee pollen, bilberry fruit, black nightshade, bloodroot, bupleurum, burdock, calcium glucarate, cascara, cassia bark, Cephalotaxaceae, chaparral, Chinese anemone root pulsatilla, Chinese asparagus, Coriolus versicolor, dong quai, evening primrose oil, evodia, fenugreek, forskolin, fourstamen stephania root, ginseng (Siberian), glossy privet fruit, goldenseal, gotu kola, green tea, indigo, isatis leaf, isatis root, maitake, mistletoe (European), mume fruit, noni, pennyroyal, Pinellia rhizome, pokeweed, Rabdosia rubescens, Rhizoma iphigenia indica, rhubarb, saw palmetto, sheep sorrel, shiitake mushroom, slippery elm, sophora root, spreading hedyotis, stillingia, Trichosanthes root, turmeric, co-enzyme Q10, huanglian **Immune system-related:** Astragalus, bee pollen, Coriolus versicolor, ginseng (Siberian), glossy privet fruit, goldenseal, maitake, mistletoe (European), mume fruit, noni, rhubarb, shiitake mushroom, codonopsis root
References:	[1] Lin KI, et al. Reishi polysaccharides induce immunoglobulin production through the TLR4/TLR2-mediated induction of transcription factor Blimp-1. J Biol Chem 2006;281(34):24111-23. [PMID: 16798741] [2] Ji Z, et al. Immunomodulation of RAW264.7 macrophages by GLIS, a proteopolysaccharide from Ganoderma lucidum. J Ethnopharmacol 2007;112(3):445-50. [PMID: 17524580] [3] Ahmadi K, et al. Effect of Ganoderma lucidum on cytokine release by peritoneal macrophages. Iran J Immunol 2007;4(4):220-6. [PMID: 18057580] [4] Chen HS, et al. Studies on the immuno-modulating and anti-tumor activities of Ganoderma lucidum (Reishi) polysaccharides. Bioorg Med Chem 2004;12(21):5595-5601. [PMID: 15465337] [5] Wang SY, et al. The anti-tumor effect of Ganoderma lucidum is mediated by cytokines released from activated macrophages and T lymphocytes. Int J Cancer 1997;70(6):699-705. [PMID: 9096652] [6] Cao LZ & Lin ZB. Comparison of the effects of polysaccharides from wood-cultured and bag-cultured Ganoderma lucidum on murine spleen lymphocyte proliferation in vitro. Yao Xue Xue Bao 2003;38(2):92-7. [PMID: 12778741] [7] Macoven Pharmaceuticals LLC. Zema Pak (dexamethasone) tablet [package insert]. Magnolia, TX, 2010.
Date updated:	29.Aug.2011

Fig. 3. Screenshot of OncoRx search between reishi mushroom and dexamethasone, showing the section on drug-CAM interactions.

The DCI parameters of the database (Fig. 3) include the identified DCI effect, an evidence summary of the DCI with relevant references, as well as a proposed management plan. In this example, a pharmacokinetic and pharmacodynamic interaction is detected – plasma dexamethasone levels may be increased due to cytochrome P450 (CYP) 3A isozyme inhibition, and the immunostimulatory properties of reishi mushroom may interfere with the immunosuppressive effects of dexamethasone. Close monitoring of altered efficacy and safety of corticosteroidal treatment is advised and clinicians should consult a herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs. A list of CAMs within the cancer treatment/prevention and immune-system-related categories that the database does not detect any interactions with is also provided. An additional feature that has been added to OncoRx is the update date of the DCI, which is intended to show how current the information is to its users.

CAM interactions with anticancer drugs

Co-enzyme Q10 (Co-Q10)

Co-Q10, also known as ubiquinone, is generally used for cancer prevention or treatment due to its free radical scavenging and membrane stabilizing properties (Memorial Sloan-Kettering Cancer Center, 2011). Other non-cancer-related indications include improvements of heart function in heart failure (Belardinelli et al., 2006), and the treatment of hypertension (Rosenfeldt et al., 2007) and cyclic vomiting syndrome (Boles et al., 2010). Co-Q10 was found to decrease the cardiotoxicity caused by anthracyclines (Table 1), such as daunorubicin and doxorubicin (Conklin, 2005), in small-scale human studies which showed smaller reductions in cardiac functions, the absence of QRS depression and QT prolongation, and an increased cumulative tolerable dose of doxorubicin (Conklin, 2005; Tsubaki et al., 1984). However, the long-term effects of combination therapy on cardiac functions were not measured. The mechanism of cardio-protection was suggested to be due to its ability to prevent the anthracyclines from being reduced to their semiquinone forms, which cause high oxidative stress in cardiac cells (Conklin, 2005). Evidence of its protective effect on anthracycline-induced cardiotoxicity was also demonstrated in animals (Combs et al., 1977; Shinozawa et al., 1996). However, in another study on mice pretreated with co-Q10, the concentration of the major metabolite of doxorubicin (aglycone I) was higher in the co-Q10 group compared to saline controls (Shinozawa et al., 1991). The authors advised caution over concurrent administration with co-Q10. As such, caution is advised in patients concurrently on co-Q10 and anthracyclines since the long-term effects of cardio-protection are still not well established. Patients should still be monitored for signs and symptoms of cardiotoxicity, and an alternative non-interacting CAM should be considered with the help of a registered herbalist, naturopath or an alternative medicine practitioner.

Cranberry

Cranberry (*Vaccinium macrocarpon*) is commonly used for the prevention of urinary tract infections in women (Stothers, 2002). It is also known to be effective in suppressing Helicobacter pylori infections (Zhang et al., 2005). The anthocyanins, proanthocyanidins, and flavonol glycoside fractions within cranberry juice have been suggested to have anticancer properties (Ferguson et al., 2004; Ferguson et al., 2006; Neto et al., 2008; Seeram et al., 2004), with its extracts showing antiproliferative effects in vitro (Sun and Hai Liu, 2006).

Cranberry can inhibit CYP2C9 and 3A4, therefore it can theoretically interact with ACDs that are substrates of these isozymes (Table 1). In vitro studies have shown cranberry juice to inhibit CYP2C9-mediated metabolism of phenytoin (Ushijima et al., 2009a). Furthermore, the international normalized ratios of warfarin, another CYP2C9 substrate, were shown to be elevated in numerous case reports (Grant, 2004; Griffiths et al., 2008; Hamann et al., 2011; Paeng et al., 2007; Suvarna et al., 2003; Welch and Forster, 2007). The CYP3A inhibition activity of cranberry juice was demonstrated in human and animal studies using midazolam and nifedipine probes (Ngo et al., 2009). However, there is conflicting evidence on the enzyme inhibiting potential of this CAM. Pharmacokinetic studies showed that cranberry did not inhibit CYP1A2, 2C9, or 3A4 in vitro and in vivo (Lilja et al., 2007;

Ushijima et al., 2009b). In another clinical study involving 14 healthy volunteers, cranberry juice did not significantly reduce CYP2C9-mediated metabolism of flurbiprofen (Greenblatt et al., 2006). Nonetheless, caution is advised in patients who are concurrently on cranberry juice and ACDs that are CYP1A2, 2C9 or 3A4 substrates. Such patients should be monitored for increased plasma ACD levels and signs and symptoms of ACD-associated toxicities. Dosage adjustments should be carried out where appropriate and clinicians should refer to the ACD package inserts for more detailed dosing information.

Huachansu

Huachansu is an extract derived from skin venom secretions of toads (*Bufo gargarizans*). Its active constituents consist of indole alkaloids and cardiac glycosides (bufalin, resibufogenin, cinobufagin), which are thought to be responsible for its anticancer properties (Meng et al., 2009; Yang et al., 2006). The mechanisms of action for its anticancer activity include the induction of apoptosis, inhibition of cell proliferation and cancer angiogenesis, disruption of the cell cycle and immunoregulatory effects (Qi et al., 2011). In addition, huachansu has hepatoprotective effects as well (Qin et al., 2008).

Numerous studies have shown huachansu's anticancer activities through its synergistic actions with ACDs. In vitro and in vivo studies showed that huachansu and its bufalin and cinobufacin constituents act by either inhibiting cell and tumor proliferation, angiogenesis, or inducing apoptosis. These synergistic effects occurred in combination with cisplatin (Hashimoto et al., 1997), etoposide (Zhang et al., 2007), fluorouracil (Han et al., 2006), gemcitabine (Yang et al., 2008), paclitaxel (Xu, 2009) and vinorelbine (Wu et al., 2004).

Bufalin, an active constituent in huachansu, inhibited CYP3A4 activity both in vitro and in vivo (Li et al., 2009). Significant increases in areas under the concentration-time curves and half-lives, as well as decreases in clearance and formation of metabolites, were observed after administration of midazolam in Wistar rats. Therefore, this CAM could interact with ACDs that are CYP3A4 substrates, leading to increased plasma levels of these drugs (Table 1). These include the alkylating agents, antimetabolites, antimicrotubules, corticosteroids, hormone agonists/antagonists, topoisomerase inhibitors and the tyrosine kinase inhibitors, among others. Patients concurrently on huachansu and these agents should be monitored for increased plasma ACD levels, and dosage adjustments carried out when necessary. In particular, clinicians should refer to the package inserts of ACDs such as erlotinib, ixabepilone and trabectedin for specific dosing instructions.

Melatonin

Melatonin is commonly used as a supplement to treat jet lag and insomnia (Brzezinski, 1997). However, it also has anticancer activities against mammary tumors (González et al., 2010), hepatic (Martín-Renedo et al., 2008) and pancreatic carcinomas (Leja-Szpak et al., 2010) based on several in vitro and animal studies. The mechanisms of action for its anticancer effects are suggested to be due to its pro-apoptotic (Leja-Szpak et al., 2010; Trubiani et al., 2005), oncostatic (Ortíz-López et al., 2009) and antiangiogenic activities (Park et al., 2009). In addition, it has anti-cachectic, anti-asthenic and thrombopoietic activities, as well as improving cardiotoxicity and neurotoxicity profiles (Lissoni, 2002; Lissoni et al., 1999; Lissoni et al., 1997), thus making it potentially useful for the supportive care of cancer patients.

The immunostimulatory properties of melatonin can be a double-edged sword in cancer treatment. While it can exhibit some benefits with certain ACD therapies, such as cyclophosphamide, as a result of increased interleukin-2 production and enhanced T-helper cell activity (Caroleo et al., 1992; Zupancic et al., 2009); these same properties can also interfere with the immunosuppressive activities of the corticosteroids (Haldar et al., 2004), which in turn may render chemotherapy less effective (Table 1). These DCIs are of high severity (Jellin and Gregory, 2007) and the effects may be more pronounced when this CAM is used together with interleukin-2 (Lissoni et al., 1993). As such, melatonin should not be used concurrently with corticosteroids. However, if avoidance is not possible, monitoring for altered efficacy and safety of corticosteroid therapy should be carried out

Table 1. Interactions between complementary and alternative medicines (CAMs) and anticancer drugs (ACDs)

CAM	Interaction with ACDs	Interaction effect and mechanism	Evidence	Proposed management
Co-enzyme Q10	Daunorubicin, doxorubicin (Combs et al., 1977; Conklin, 2005; Greenberg and Frishman, 1990; Shinozawa et al., 1991; Shinozawa et al., 1996)	Co-enzyme Q10 may decrease anthracycline-induced cardiotoxicity due to its free radical scavenging properties, and its ability to prevent the ACDs from being reduced to their semiquinone forms, which cause oxidative damage to mitochondrial DNA of cardiomyocytes.	Cardio-protective effects of co-enzyme Q10 were found in both animal and human studies. However, one animal study also showed conflicting results. Small-scale human studies showed smaller reductions in cardiac function, absence of QRS depression and QT prolongation, and an increased cumulative tolerable dose of doxorubicin. However, long-term cardio-protective effects are not well-established. In contrast, a study of mice pretreated with co-enzyme Q10 showed that the concentrations of aglycone I (major metabolite of doxorubicin) in the kidney and heart were significantly higher in the co-enzyme Q10 group compared to the saline controls.	Caution is advised. Patients concurrently on co-enzyme Q10 and anthracyclines should be closely monitored for anthracycline-induced cardiotoxicities. A suitable non-interacting alternative should be considered with the help of a registered herbalist, naturopath and/or TCM practitioner.
Cranberry	Capecitabine, tegafur (Clarke	Increased plasma ACD	Contradictory evidence exists.	Caution is advised. Patients

	et al., 2010; Grant, 2004; Greenblatt et al., 2006; Griffiths et al., 2008; Lilja et al., 2007; Paeng et al., 2007; Suvarna et al., 2003; Ushijima et al., 2009a; Welch and Forster, 2007; Zikria et al., 2010)	levels due to inhibition of CYP2C9 by cranberry.	An in vitro study suggested that cranberry juice might inhibit CYP2C9-mediated metabolism of phenytoin. Furthermore, cranberry juice was reported to elevate the international normalized ratios of patients on warfarin (CYP2C9 substrate) in various case reports. Additionally, a man concurrently on warfarin, phenytoin and digoxin died from gastrointestinal and pericardial hemorrhaging due to an interaction with cranberry juice. In contrast, an in vivo study involving warfarin, tizanidine and midazolam probes showed that cranberry juice did not inhibit CYP2C9, 1A2 or 3A4. In another study of 14 healthy volunteers, cranberry juice did not significantly reduce CYP2C9-mediated metabolism of flurbiprofen.	taking these agents concurrently should be carefully monitored for increased plasma ACD levels. Dosage adjustments should be carried out when necessary. In addition, patients concurrently on capecitabine and cranberry juice should be monitored for capecitabine toxicity and doses adjusted accordingly based on patient's tolerance level. Clinicians are referred to the product information for further information on dosage adjustments for capecitabine.
Cranberry	**Alkylating agents** Cyclophosphamide, ifosfamide **Antimicrotubules** Paclitaxel **Hormone agonists/ antagonists** Tamoxifen, norethisterone **Tyrosine kinase inhibitors** Bortezomib, imatinib **Retinoids:** Tretinoin (Clarke et al., 2010; Grant, 2004; Greenblatt et al., 2006; Griffiths et al., 2008; Lilja et al., 2007; Ngo et al., 2009; Paeng et al., 2007; Roxane Laboratories Inc., 2007; Suvarna et al., 2003; Uesawa and Mohri, 2006; Ushijima et al., 2009a; Welch and Forster, 2007; Zikria et al., 2010)	Increased plasma ACD levels due to inhibition of CYP2C9 and 3A4 by cranberry.	Contradictory evidence exists. Cranberry juice inhibited enteric, but not hepatic, CYP3A-mediated metabolism in studies using midazolam (humans) and nifedipine (animals) as probes. In addition, an in vitro study suggested that cranberry juice might inhibit CYP2C9-mediated metabolism of phenytoin. Furthermore, cranberry juice was reported to elevate the international normalized ratios of patients on warfarin (CYP2C9 substrate) in various case reports. Additionally, a man concurrently on warfarin, phenytoin and digoxin died from gastrointestinal and pericardial hemorrhaging due to an interaction with cranberry. In contrast, an in vivo study involving warfarin, tizanidine and midazolam probes showed that cranberry juice did not inhibit CYP2C9, 1A2 or 3A4. In another study of 14 healthy volunteers, cranberry juice did not significantly reduce CYP2C9-mediated metabolism of flurbiprofen.	Caution is advised. Patients should be carefully monitored for increased plasma ACD levels and any adverse effects or toxicities. Dosage adjustments should be carried out where appropriate. The product information of cyclophosphamide also recommends regular monitoring of the patient's hematological profile (particularly neutrophil and platelet counts) to determine the degree of hematopoietic suppression.
Cranberry	**Alkylating agents** Busulfan, carmustine, procarbazine, thiotepa **Antimetabolites** Methotrexate **Antimicrotubules** Docetaxel, ixabepilone, vinblastine, vincristine, vindesine, vinorelbine	Increased plasma ACD levels due to inhibition of CYP3A4 by cranberry.	Contradictory evidence exists. Cranberry juice inhibited enteric, but not hepatic, CYP3A-mediated metabolism in studies using midazolam (humans) and nifedipine (animals) as probes. In contrast, an in vivo study involving warfarin, tizanidine and midazolam probes showed that cranberry juice did not inhibit CYP2C9, 1A2 or 3A4.	Caution is advised. Patients should be carefully monitored for increased plasma ACD levels and any adverse effects or toxicities. Dosage adjustments should be carried out where appropriate. In addition, the following should be taken into account with these ACDs: (a) Erlotinib: Doses should be

	Corticosteroids Dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone **Hormone agonists/ antagonists** Anastrozole, bicalutamide, cyproterone, flutamide, letrozole, medroxyprogesterone, toremifene **Topoisomerase inhibitors** Doxorubicin, etoposide, irinotecan, topotecan **Tyrosine kinase inhibitors** Dasatinib, erlotinib, gefitinib, lapatinib, sunitinib **Other anticancer drugs** Bexarotene, temsirolimus, trabectedin (Bristol-Myers Squibb Co, 2010; Clarke et al., 2010; Janssen Inc., 2011; Lilja et al., 2007; Ngo et al., 2009; OSI Pharmaceuticals Inc., 2008; Uesawa and Mohri, 2006)			reduced in 50 mg decrements if a dose reduction is necessary. (b) Ixabepilone: A 20% dose reduction is generally recommended in the event of hematological (e.g. reduced neutrophil and platelet counts, febrile neutropenia) and non-hematological toxicities (e.g. Grade 2 or 3 neuropathy, any other non-neuropathic Grade 3 toxicities). If toxicities occur, treatment should be delayed to allow recovery. If toxicities recur, an additional 20% dose reduction should be made. For severe Grade 3 neuropathy lasting $\geq$ 7 days or any Grade 4 toxicities, treatment should be discontinued. (c) Trabectedin: A dose reduction to 1.2 mg/m^2 must be carried out for subsequent cycles, if any of the following occur: - Neutropenia lasting for more than 5 days or associated with fever or infection - Thrombocytopenia - Increase of bilirubin to above upper limit of normal (ULN) and/or alkaline phosphatase more than 2.5 × ULN - Increase of liver aminotransferases to more than 2.5 × ULN that has not recovered by day 21 - Any other grade 3 or 4 adverse reactions (e.g. nausea, vomiting, fatigue) Once a dose has been reduced, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced to 1 mg/m^2. If further dose reductions are necessary, treatment discontinuation should be considered.
Huachansu	**Alkylating agents** Busulfan, carmustine, cyclophosphamide, ifosfamide, procarbazine, thiotepa **Antimetabolites** Methotrexate **Antimicrotubules** Docetaxel, ixabepilone, paclitaxel, vinblastine, vincristine, vindesine, vinorelbine **Corticosteroids** Dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone **Hormone agonists/ antagonists**	Increased plasma ACD levels due to inhibition of CYP3A4 by huachansu.	Bufalin (a constituent of huachansu) modestly inhibited CYP3A4 both in vitro and in vivo. Additionally, significant increases in areas under the concentration-time curves and half-lives, as well as decreases in clearance and formation of metabolites, were observed after administration of midazolam in Wistar rats.	Caution is advised. Plasma ACD levels should be monitored in patients concurrently taking huachansu and dosage adjustments carried out where appropriate. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs. In addition, the following should be taken into account with these ACDs: (a) Erlotinib: Doses should be reduced in 50 mg decrements if a dose reduction is necessary. (b) Ixabepilone: A 20% dose reduction is generally recommended in the event of hematological (e.g. reduced neutrophil and platelet counts, febrile neutropenia) and

	Anastrozole, bicalutamide, cyproterone, exemestane, flutamide, fulvestrant, letrozole, medroxyprogesterone, norethisterone, tamoxifen, toremifene **Topoisomerase inhibitors** Doxorubicin, etoposide, irinotecan, topotecan **Tyrosine kinase inhibitors** Bortezomib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, sunitinib **Other anticancer drugs** Bexarotene, temsirolimus, trabectedin (Bristol-Myers Squibb Co, 2010; Janssen Inc., 2011; Li et al., 2009; OSI Pharmaceuticals Inc., 2008)			non-hematological toxicities (e.g. Grade 2 or 3 neuropathy, any other non-neuropathic Grade 3 toxicities). If toxicities occur, treatment should be delayed to allow recovery. If toxicities recur, an additional 20% dose reduction should be made. For severe Grade 3 neuropathy lasting $\geq$ 7 days or any Grade 4 toxicities, treatment should be discontinued. (c) Trabectedin: A dose reduction to 1.2 mg/m^2 must be carried out for subsequent cycles, if any of the following occur: - Neutropenia lasting for more than 5 days or associated with fever or infection - Thrombocytopenia - Increase of bilirubin to above upper limit of normal (ULN) and/or alkaline phosphatase more than 2.5 × ULN - Increase of liver aminotransferases to more than 2.5 × ULN that has not recovered by day 21 - Any other grade 3 or 4 adverse reactions (e.g. nausea, vomiting, fatigue) Once a dose has been reduced, dose escalation in the subsequent cycles is not recommended. If any of these toxicities reappear in subsequent cycles in a patient exhibiting clinical benefit, the dose may be further reduced to 1 mg/m^2. If further dose reductions are necessary, treatment discontinuation should be considered.
Melatonin	Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone) (Haldar et al., 2004; Jellin and Gregory, 2007; Lissoni et al., 1999; Lissoni et al., 1993; Lissoni et al., 1997)	The immunostimulatory effects of melatonin may interfere with the immunosuppressive activity of corticosteroids.	Animal studies have shown that melatonin reverses the immunosuppressive activity of dexamethasone. Small clinical studies have also shown that myelosuppression occurred less frequently in patients concurrently on melatonin and chemotherapy. However, the immunostimulatory effects of melatonin occurred only in the presence of interleukin-2, which led to increases in the numbers of lymphocytes, natural killer cells, CD25-positive cells and eosinophils.	Concurrent use of corticosteroids and melatonin should be avoided. However, if avoidance is not possible, monitoring for altered efficacy and safety of corticosteroid therapy is recommended. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs.
Reishi mushroom	**Alkylating agents** Busulfan, cyclophosphamide, dacarbazine, ifosfamide, procarbazine, thiotepa **Antimetabolites** Methotrexate **Antimicrotubules** Docetaxel, ixabepilone, paclitaxel, vinblastine,	Plasma levels of ACDs may be increased due to inhibition of CYP1A2, 2E1 and/or 3A by reishi mushroom.	*Ganoderma lucidum* polysaccharide (GLPS), a major active constituent of reishi mushroom, dose-dependently inhibited CYP1A2, 2E1 and 3A in vitro.	Caution is advised. Patients taking these agents together should be monitored for increased plasma levels and altered pharmacological effects of the ACDs. Dosage adjustments should be carried out where appropriate. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs.

	vincristine, vindesine, vinorelbine **Hormone agonists/ antagonists** Anastrozole, bicalutamide, cyproterone, exemestane, flutamide, fulvestrant, letrozole, medroxyprogesterone, norethisterone, tamoxifen, toremifene **Topoisomerase inhibitors** Doxorubicin, etoposide, irinotecan, topotecan **Tyrosine kinase inhibitors** Bortezomib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, sunitinib **Other anticancer drugs** Bexarotene, temsirolimus, trabectedin (Wang et al., 2007)			
Reishi mushroom	**Corticosteroids** Dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone (Ahmadi and Riazipour, 2007; Cao and Lin, 2003; Chen et al., 2004; Gao et al., 2003a; Gao et al., 2002; Gao et al., 2003b; Gao et al., 2002; Hsu et al., 2002; Ji et al., 2007; Lin et al., 2006; Mao et al., 1999; Ulbricht et al., 2010; Wang et al., 1997)	Plasma levels of the corticosteroids may be increased due to inhibition of CYP3A isozymes by this herb. Furthermore, the immunomodulatory effects of this herb may interfere with the immunosuppressive activity of the corticosteroids.	*Ganoderma lucidum* polysaccharide (GLPS), a major active constituent of reishi mushroom, dose-dependently inhibited CYP1A2, 2E1 and 3A in vitro. The immunostimulatory properties of reishi mushroom have also been shown to be via lymphocyte activation, macrophage and cytokine stimulation based on animal and in vitro studies. In addition, 3 clinical studies involving treatment with extracts of this herb for 12 weeks showed enhanced immune responses in advanced-stage cancer patients.	Caution is advised during concurrent use of reishi mushroom with these agents. Monitoring for altered efficacy and safety of corticosteroid treatment is recommended. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs.

Reishi mushroom

Reishi mushroom (*Ganoderma lucidum*), more commonly known as lingzhi, is a herb that is often used by cancer patients for the prevention and/or treatment of disease (Weng and Yen, 2010), or relieving the side-effects of chemotherapy. Its active constituents include the polysaccharide beta-D-glucan and the triterpenes ganoderic and lucidenic acids (Huang, 1999). The triterpenes and polysaccharides inhibit tumor invasion by down-regulating matrix metalloproteinase expression and inhibit tumor metastases by limiting tumor cell adhesion to endothelial cells (Chen et al., 2008; Li et al., 2008), while the latter also has immunostimulation properties via lymphocyte activation, and macrophage and cytokine stimulations (Chen et al., 2004; Gao et al., 2003a; Gao et al., 2002; Gao et al., 2003b; Hsu et al., 2002; Mao et al., 1999; Ulbricht et al., 2010; Wang et al., 1997). Lingzhi can increase the sensitivity of cancer cells to some ACDs, such as cisplatin in ovarian cancer (Zhao et al., 2011). In addition, this herb has antioxidant effects (Wachtel-Galor et al., 2004a; Wachtel-Galor et al., 2004b), relieves chemotherapy-induced nausea and vomiting (Wang et al., 2005), as well as increases the efficacy of radiotherapy in vitro and in animals (Kim et al., 2008).

Ganoderma lucidum polysaccharide (GLPS), a major active constituent, was found to dose-dependently inhibit CYP1A2, 2E1 and 3A in vitro (Wang et al., 2007). ACDs that are substrates of these isozymes may potentially interact with lingzhi, leading to increased plasma levels of the ACDs (Table 1). Patients concurrently on these agents should be carefully monitored for increased plasma ACD levels, as well as altered pharmacological effects of the ACDs. Dose adjustments should be carried out where necessary according to product information by the manufacturers. Lingzhi can also manifest pharmacokinetic interactions with the corticosteroids through the same DCI mechanism. Furthermore, the immunostimulatory properties of lingzhi can also interfere with the immunosuppressive activities of the corticosteroids. Thus, regular monitoring for altered efficacy and safety of corticosteroid treatment is recommended. Clinicians should consult a registered herbalist, naturopath and/or TCM practitioner for alternative non-interacting herbs.

DISCUSSION

In TCM practice, herbal combinations are often used to promote desirable interactions (Poon et al., 2010). One of the key principles for TCM prescriptions is the coordination of the seven effects in compatibility (i.e. using alone, mutually

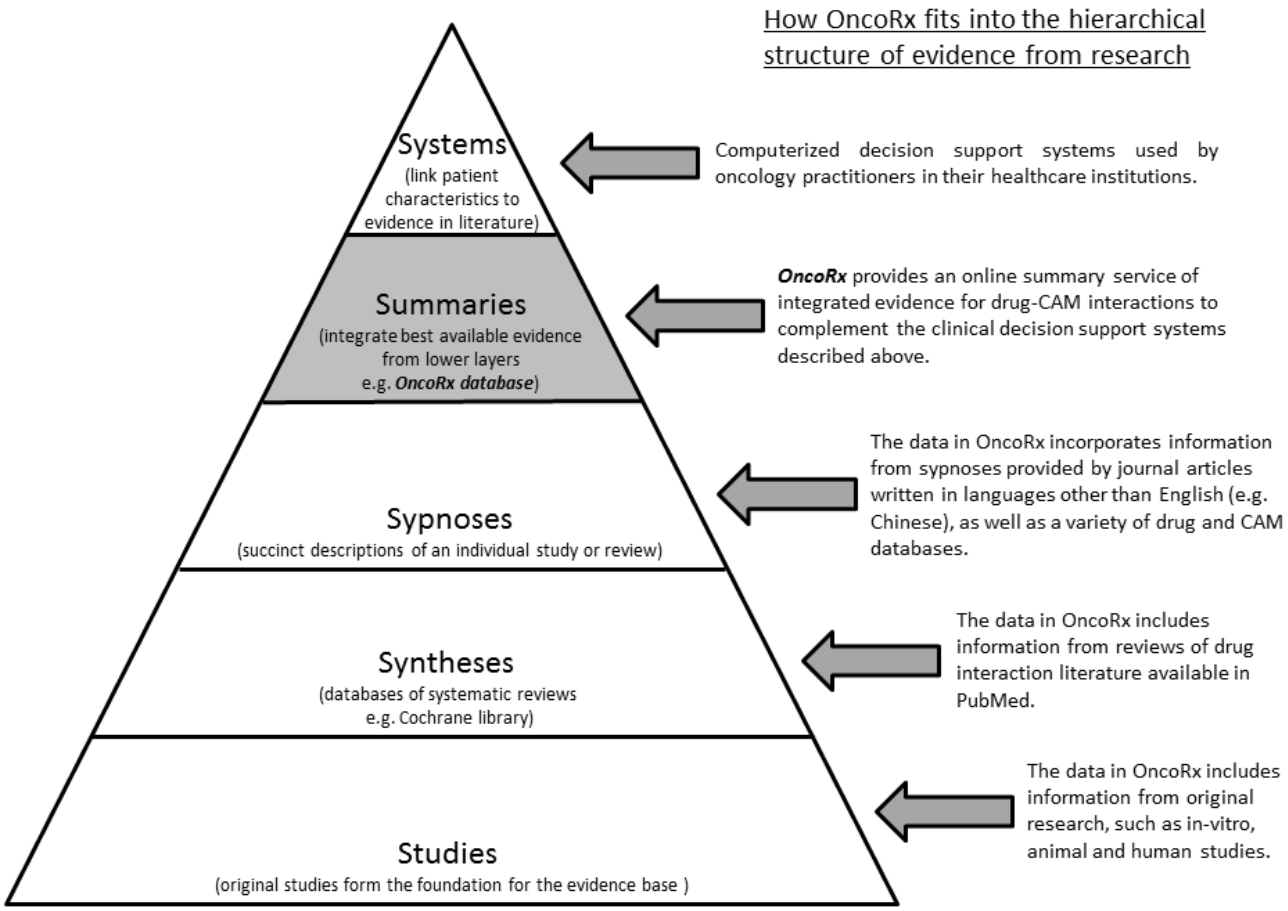


Fig. 4. Haynes "5S" pyramid model showing how OncoRx fits in the research evidence.

reinforcing, assisting, incompatibility, inhibition, detoxifying and antagonism) (Zhou, 2009), whereby the TCM herbs are used in combinations within a prescription to enhance their therapeutic effects, minimize toxicity and side-effects, or produce an effect not seen in the use of single herbal entities (Poon et al., 2010; Sagar and Wong, 2008). Not surprisingly, such combinations are also used in Western medicine to enhance the clinical effects of treatment. In fact, this forms the basis of the multiple-agent chemotherapy cocktails used for cancer therapy (Gao and Wu, 2008; Yap et al., 2008). However, some combinations, more popularly referred to as DCIs, may lead to negative clinical outcomes (e.g. decreasing the effectiveness of therapy and/or manifesting toxicities/ side-effects). These outcomes are the ones that are of major concern in the oncology practice.

It is known that many cancer patients consume CAMs for cancer treatment and supportive care. This is especially true for Asian countries. For example, 45% of Japanese and 61% of Taiwanese patients with cancer use CAMs concurrently with their cancer therapies (Chang and Li, 2004; Hyodo et al., 2005). In the Taiwanese population, it was found that TCMs were the most common form of CAM, followed by Western-style health products (Chang and Li, 2004). In the Singaporean population, ~ 55 - 76% of cancer patients consume CAMs on top of their cancer therapies (Chow et al., 2010; Lim et al., 2005), with the oncologists being unaware of this behavior in 86% of the cases (Chow et al., 2010). Furthermore, many patients do not want to discuss their CAM use with their healthcare providers for fear of clinician indifference or opposition to their use of CAMs, or a negative response from them (Tasaki et al., 2002). However, clinicians need to know when their patients consume CAMs concurrently with anticancer therapies, so that the potential for DCIs can be minimized. As such, they need to have adequate information and the appropriate knowledge to discuss various options that are available for their patients, so that the patients are better informed to participate in the management of their own conditions. This paper has demonstrated the potential of CAMs to interact with cancer therapy through the DCIs of 5 common CAMs identified by users of the OncoRx database. Even though majority of the DCIs are theoretical in nature, it is still relevant for practitioners to know that such interactions may exist, so that they can make well-informed decisions with regards to the therapeutic management of their patients.

In this day and age where cyber-technologies are prevalent, many healthcare applications tapping on WiFi or 3G networks have sprung up in response to the popularity of mobile devices (e.g. Blackberry, Android phones, iPhone) and tablets (e.g. iPad, Samsung Galaxy Tab). It is imperative that drug information databases provide accurate data about CAMs that is evidence-based to clinicians on-the-go, since undesirable consequences may result from cancer patients obtaining erroneous information on the internet or misinterpreting generalized information that is not tailored to their needs (Yap et al., 2009a). OncoRx was designed with the clinician end-users in mind. Responding to feedback from users of this database, priority was given to the 5 CAMs described here as a first update to the CAM module of the database (Yap et al., 2010c). The design principles of this database followed the "Four Pharmaco-cybernetic Maxims" for developing pharmaceutical tools, in relation to quality, quantity, relationship and manner (Yap et al., 2009c); and developers of digital healthcare tools are encouraged to follow these principles as well. The "relationship" principle describes the pertinent issue regarding the kinds of DCI data that are relevant

for clinicians to know. We had previously sought the opinions of pharmacy practitioners regarding the drug interaction parameters that were essential for a drug information resource to be relevant in their daily practices (Yap et al., 2010a). Our results showed that the top 3 parameters were the mechanism and severity of the interaction, and the presence of a management plan. Since the main target audiences of OncoRx are clinicians and healthcare practitioners, we ensured that these 3 parameters would be shown to users for any searched interactions.

Even though most of the interactions in OncoRx are either theoretical or extrapolated from in vitro and animal studies, the DCI information provided follows the "quality" principle by ensuring that it is evidence-based (i.e. from published literature, other established databases known by clinicians, and package information from drug manufacturers). Although one may argue that these DCIs may not be clinically-relevant since they are not from clinical studies, but the ethical issue of carrying out DCI studies in humans, which defies the Hippocratic Oath to do no harm, has to be taken into consideration. It is important for users of digital healthcare tools, such as OncoRx, to realize that the information provided by these tools is generally meant to complement, and not replace, the expertise and clinical judgment of healthcare practitioners. These tools are potential avenues whereby clinicians can tap on to learn about the possibility of such DCIs occurring and their postulated interaction mechanisms, so that they can clarify their doubts regarding the DCIs and better manage their patients' chemotherapies.

The "quantity" maxim states that the information provided to users of a drug database must be adequate so that they know enough to minimize the likelihood of drug-related problems, in this case–drug-CAM interactions. As such, the data provided by OncoRx is categorized under relevant headings with short, concise summaries to inform clinician users at the point of patient care (Table 1). In addition, the data in OncoRx follows the "manner" principle because effort is made to present the drug-, CAM- and DCI-related information in an appropriate manner that avoids ambiguity and misinterpretation by its users. Bearing in mind that OncoRx is targeted towards clinicians, even though a fair amount of medical and scientific jargon is presented to its users (Figs. 2 and 3), the information provided can be easily understood by the majority of healthcare practitioners in general practices. Besides the top 3 parameters identified by the pharmacy practitioners described previously, a summary of the evidence with appropriate citations and hyperlinks are also incorporated in the database, so that clinicians can gain an overall picture regarding the DCIs, yet gives them an option to go further into the literature if more details are required.

Following the "5S" pyramid model of evidence from research proposed by Haynes (Haynes, 2006), OncoRx fits into the "summaries" level of the hierarchical structure, whereby clinicians can complement the DCI information provided by this database with that of decision support systems to better manage the pharmacotherapies of their patients (Fig. 4). Its data comprises of information from a variety of sypnoses, syntheses and original studies, thus making it a comprehensive database for oncology drug interactions. As an online passive decision support service that aims to provide good quality DCI data to oncology practitioners, details of the methodology for collating and compiling the relevant data have also been explicitly published (Yap et al., 2010c). Furthermore, an ongoing effort is being made by its developers to ensure that its drug interaction content and key references are peer-reviewed to ensure that its quality is of an acceptable standard (Yap et al., 2010b). A new feature that reflects the date of the DCI update has also been recently incorporated. It is intended that the database be updated annually once it is able to detect a substantial amount of DCIs.

Haynes identified from his model several limitations that are especially pertinent as one goes higher up the pyramid (Haynes, 2006). Resources higher up the hierarchy tend to be less readily available. This trend is a result of the high costs of maintaining large and comprehensive systems and/or applications, which generally leads to the costs being passed along to consumers. OncoRx is one of the few drug databases catered specifically towards chemotherapy drug interactions. It was originally created as a free online resource, available at http://bit.ly/cancerRx, as a proof-of-concept to detect clinically-relevant oncology interactions with single-agent and multiple-agent chemotherapies. Since its conception, it has been recognized as a first-of-its-kind to aid in improving the pharmaceutical care of cancer patients (Fua et al., 2011; Poon, 2011). Next, sypnoses and syntheses that are generated on the same topic may provide conflicting results. These conflicts can be resolved by considering the original studies. OncoRx attempts to resolve this issue by including a summary of the conflicting data together with the relevant citations for clinicians so that they are aware of these disagreements during the pharmacotherapeutic management of their patients, and they can search deeper into the literature if needed.

As with most electronic services providing evidence-based information, the compilation and processing of published literature for the OncoRx database takes time and is manpower intensive. The database is currently maintained by its creator who is dual-trained in pharmacy and cybermedicine. The motivation for maintaining OncoRx (on a voluntary basis) is to provide unbiased DCI information for practical use by clinicians dealing with cancer patients. Therefore, content updates and troubleshooting of usability issues are not as fast and efficient as commercial databases managed by large companies. Furthermore, as a database that caters towards an international audience, OncoRx is not able to provide specific management recommendations unless they are recommended by authors of the original studies and/or the pharmaceutical manufacturers, since clinical practices in different countries and institutions may differ. There is also no guarantee that patients may not have unique characteristics that may warrant tailoring of the management plans. Despite these limitations, it is the hope of its creator that the database will expand with time to include DCIs with more CAMs, so that it will become a more comprehensive and clinically useful resource for oncology clinicians and CAM practitioners.

CONCLUSION

This is the first major update on the CAM module of the OncoRx database since its conception. The potential for CAMs to interact with ACDs has been demonstrated though the DCIs described in this update. In addition, this paper uses this database as a case study for developers to design digital healthcare tools and/or applications according to the "Four Pharmaco-cybernetic Maxims" of quality, quantity, relationship and manner. As a drug information resource that provides evidence-based DCI information for healthcare professionals, this paper also positions OncoRx in the "5S" hierarchy of research evidence, so that they can make the best out of the information from this database as a complement to their existing resources for ACD-CAM interactions.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest directly relevant to the study.

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