DEVELOPMENT OF AN ONCOLOGY DATABASE FOR DRUG INTERACTIONS OF ANTI-CANCER DRUGS WITH COMPLEMENTARY AND ALTERNATIVE MEDICINE

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Abstract

Cancer is a highly prevalent health problem with increasing incidences worldwide. Many cancer patients are consuming complementary and alternative medicines (CAMs) in addition to their cancer therapy for treatment or prevention, or supportive care therapy. Cancer patients are at risk of suffering from anti-cancer drug (ACD)-CAM interactions due to the narrow therapeutic indices of the ACDs, which can lead to sub-therapeutic effects or increased toxicities which may compromise the efficacy of chemotherapy treatments. Thus, it is important for clinicians to gain quick access to information on ACD-CAM interactions so that they can make a better-informed decision in their clinical practice.

This paper describes the creation of an oncology database that documents interactions between ACDs and CAMs. Drug information regarding CAMs was collated from 9 databases and input into a modified web server with a database engine and a programming interface using various softwares and programming scripts. CAM-related information included their names, cancer indications, mechanisms of actions, and pharmacokinetic properties. Drug interaction parameters included interaction effects, severities, onsets, substantiating evidences, and proposed management plans.

A total of 117 ACDs and 166 CAMs were included in the database. Users are able to search for interactions based on the CAM indications in cancer therapy. This database is intended to complement the currently available databases for clinicians and pharmacists working in the oncology setting, so as to provide better patient care in their practice.

Introduction

Cancer is a highly prevalent health problem with increasing incidence worldwide. In 2007, one in eight deaths was due to cancer (American Cancer Society 2007). It was also estimated that the global burden of cancer is expected to grow to 27 million new cancer cases and 17.5 million cancer deaths by 2050 (American Cancer Society 2007). In the course of cancer therapy, an increasing number of cancer patients are also consuming complementary and alternative medicines (CAMs), including traditional Chinese medicines (TCMs), (Boon *et al.* 2007; (Bressler 2005). CAM usage in the United States has increased over the past 20 years, reaching 36% in 2002 (Bressler 2005). In addition, a study conducted on women with breast cancer showed an increase in CAM usage from 66.7% in 1998 to 81.9% in 2005 (Boon *et al.* 2007). Alternative medicines are usually indicated in cancer for treatment or prevention, or for supportive therapy such as relieving side effects of chemotherapy (e.g. alopecia, nausea and vomiting, immunosuppression). These CAMs are usually taken by cancer patients without the physician's knowledge, thus the patient may not be aware of any adverse effects that may occur. A possible cause could be due to ACD-CAM interactions (Fugh-Berman and Ernst 2001), which leads to a compromise in the efficacy of the chemotherapy treatment.

A drug interaction can be defined as a "pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents." (Tatro 2008) Drug interactions can either be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions usually involve alterations in the absorption, distribution, metabolism, or elimination properties of a drug, which could be due to either enzyme inhibition or enzyme induction (Yap *et al.* 2008). On the other hand, pharmacodynamic interactions can be due to antagonistic, additive, or synergistic effects (Yap *et al.* 2008). While drug interactions typically refer to drug-drug interactions, other interactions such as food-drug or herb-drug interactions also exist, and are important considerations in the therapeutic care of a patient.

ACD-CAM interactions may potentially be detrimental to patients due to the narrow therapeutic indices of ACDs. This can lead to either an increased toxicity or sub-therapeutic effects. It has been reported that the potential for an interaction is ~6% when two drugs are prescribed concurrently, and the probability increases as more drugs are used concurrently (Kuhlmann and Mück 2001). Although little information exists for CAMs, a similar deduction can be drawn from this regarding the likelihood of interactions with CAMs. In addition, some CAM products may contain multiple pharmacologically active constituents, which may further increase the risk of ACD-CAM interactions. These interactions can lead to clinical consequences and increase the consumption of healthcare resources. For example, in a study conducted on hospitalized patients receiving warfarin, the mean length of stay was 3.14 days longer for subjects receiving an interacting drug (Jankel *et al.* 1994). The consequences of such interactions may be significant, potentially resulting in severe morbidity or death.

Clinicians currently use a variety of resources for information on ACD interactions which include the primary literature, drug information databases (e.g. Micromedex® (Thomson Healthcare 2007), Memorial Sloan Kettering (Louis V. Gerstner 2008)), textbooks on alternative medicines (e.g. Natural Medicines Comprehensive Database (Jellin and Gregory 2007), Chinese Materia Medica (Chang *et al.* 2001)) and conventional drug interaction texts (e.g. Lexi-Comp Drug Information Handbook (Lacy *et al.* 2007-2008), British National Formulary (British Medical Association and Pharmaceutical Society of Great Britain 2007)). However, these databases have limited information on interactions between ACDs and CAMs, particularly for TCM herbs. While monographs of herbs such as ginseng or St. John's wort can be commonly found in databases such as Micromedex® and Memorial Sloan Kettering, monographs of TCMs such as barley are not found in these databases. Although sources such as TCM Assistant (e-MS Inc.) and Rootdown.us (Rootdown LLC 2008) provide information about TCMs, limited data on drug interactions are available from these databases.

It is important for clinicians to gain quick access to resources on ACD-CAM interactions so that it can help them make a more informed decision when confronted with such interactions in clinical practice. Therefore, we aim to fill this gap by creating a comprehensive oncology database that documents ACD-CAM interactions. This database is meant to complement the currently available oncology databases for prediction of drug-drug interactions (Strain *et al.* 1998) and to provide clinicians with a user-friendly interface and easy access to ACD-CAM interaction information.

Materials and Methods

A list of CAMs was compiled from a total of 9 databases based on the common CAMs used by cancer patients at the National Cancer Centre, Singapore. Databases utilized include Chinese material medica (Chang *et al.* 2001), Aetna Intelihealth (Aetna InteliHealth Inc.), TCM Assistant (e-MS Inc.), Memorial Sloan-Kettering (Louis V. Gerstner 2008), Micromedex® (Thomson Healthcare 2007), Natural Medicines Comprehensive Database (Jellin and Gregory 2007), Drugs.com (Drugsite Trust 2000), Caremark (Gold Standard Inc.) and DoubleCheckMD (Enhanced Medical Decisions Inc. 2007). The first 6 databases were used to gather information on CAM characteristics and pharmacokinetics while the latter 6 databases were used to compile data on interactions with ACDs. Interaction checkers were used for gathering of drug interaction information. However, when the checkers were unavailable, monographs of the CAMs would be used instead. Alternative therapies (e.g. Ayurveda), substances with limited documentation on their medicinal properties (e.g. alkaline water), and commercial supplements (e.g. Centrum®) were excluded from our list. A summary of the procedures is shown in Appendix 1.

The CAMs were classified into 8 categories based on their indications in cancer therapy (Louis V. Gerstner 2008): (a) cancer treatment or prevention, (b) immune system-related, (c) alopecia, (d) nausea and vomiting, (e) peripheral neuropathy or analgesics, (f) anti-inflammatory, (g) fatigue syndrome and (h) non-cancer related. CAMs with multiple indications were classified into their respective categories. Information pertaining to the characteristics of the CAMs and their interactions were recorded in a Microsoft Excel 2007 database. These characteristics included their names (common, scientific, Chinese, pinyin), indications in cancer therapy and their mechanisms, and adverse reactions. Pharmacokinetic data (e.g. absorption, distribution, metabolism, elimination and protein binding information) were also recorded if information was available. Other characteristics related to TCM principles such as their hot-cold nature (e.g. hot, warm, cool, cold), nourishing properties (e.g. nourishing yin, yang, qi, or blood) and flavours (e.g. sweet, sour, pungent, salty, or bitter) were also included, where applicable. Drug interaction parameters included interaction effects, severities, onsets, substantiating evidences for detected interactions, and management plans where appropriate.

A modified web server with a database engine and a programming interface to the database was constructed using Adobe Dreamweaver CS4 software (*Adobe Systems Incorporated, San Jose, California*) and various programming scripts. Web documents were designed using a combination of hypertext markup language (HTML), extensible hypertext markup language (XHTML), javascripts, hypertext preprocessor (PHP) and structured query language (MySQL) scripts. The graphical user interfaces were created using various web elements such as forms, drop down menus and lists. XAMPP (*version 2.5, Apache Friends*) and Filezilla (*version 3.2.0, SourceForge.net*) software programmes were used to upload the web documents onto the web server. The collated data on CAMs and their interactions were transferred from the Microsoft Excel tables into a (MySQL) database using SQL Manager 2007 for MySQL (*version 4.4, EMS Database Management Solutions*).

Results and Discussion

Database statistics

A total of 117 ACDs and 166 CAMs were collated in the database. A detailed list of ACDs and CAMs are shown in Appendix 2 and Appendix 3 respectively. The ACDs are classified based on their pharmacological categories, while the CAMs are sorted by their indications. CAMs with more than one indication would be placed into their respective categories as previously described in the methods.

Interactions were detected for 37 CAMs (22.3%), from which 943 ACD-CAM drug pairs were documented. Table 1 shows a summary of the interactions between the various classes of CAMs and ACDs. Among the CAMs that were indicated for cancer, those for treatment and prevention had the highest percentage of documented interactions (35.9%) while those for treatment of fatigue had the lowest percentage (6.8%). No interactions were found for CAMs indicated for prevention of alopecia, and nausea and vomiting.

Substantiating evidences for the interactions were varied, and included case reports, clinical studies, animal and in vitro studies, as well as theoretical postulations based on similarities in pharmacokinetic parameters of the ACDs and CAMs (e.g. substrate, inducer and inhibitor information). Majority of the ACD-CAM interactions were pharmacokinetic in nature, in which the CAM affected the metabolism of the ACD through inducing or inhibiting cytochrome P450 (CYP450) isozymes. Of these, 20 CAMs interacted with the CYP3A4 variety, making it the most commonly affected isozyme.

Table 1. Summary of interactions between complementary and alternative medicines (CAMs) and anti-cancer drugs (ACDs).

Classes of CAMs	No. of CAMs in each class	No. of interacting CAMs	No. of interactions
Cancer treatment and prevention	65	17	339
Immune system-related	17	7	145
Alopecia	3	0	0
Nausea and vomiting	1	0	0
Peripheral neuropathy and analgesic	14	4	103
Anti-inflammatory	39	9	247
Fatigue syndrome	5	4	64
Non-cancer related	67	11	354

The ratio of interactions-to-CAMs was also calculated for each category to determine the probability of a detected drug interaction of a CAM with similar indications. The ratio for the entire dataset was approximately 5.7, which implied that each CAM could potentially interact with approximately 6 ACDs. However, this value is relatively skewed as majority (78.7%) of herbs have no documented interactions. Certain CAMs had a much higher number of interactions with the ACDs. For example, black cohosh and St. John's wort had exceedingly large numbers of interactions at 48 and 45 respectively.

ACD-CAM interactions within each category of cancer indication

Many of the CAMs do not share similar chemical properties and mechanisms of action for their indication in cancer. As such, no obvious trends in the interactions could be observed within classes of CAMs used for the same purpose. For example, although both aloe vera and ginseng (genus *panax*) have analgesic properties, the mechanism of action for aloe vera involves the inhibition of bradykinin by a contained carboxypeptidase (Foster and et al. 1999), while ginseng contains ginsenosides that have stimulatory and inhibitory effects on the CNS (Attele *et al.* 1999).

Sixty-five CAMs were indicated for cancer treatment and prevention. This could be due to a direct antineoplastic effect of the CAM. An example of a CAM in this category is cat's claw (Louis V. Gerstner 2008). Cat's claw inhibits the CYP3A4 isozyme, leading to a decreased rate of drug metabolism. Thus it can interact with ACDs that are substrates of this isozyme (Budzinski *et al.* 2000). It also theoretically interacts with immunosuppressants due to its inherent immunostimulating activity, such as stimulating phagocytosis, increasing respiratory cellular activity and mobility of leucocytes (Sandoval *et al.* 2000).

Apart from cancer treatment, CAMs are also used concurrently with chemotherapy in the form of supportive care. One such group includes the immunostimulants, which are used to boost the immunity of the patient undergoing chemotherapy. Asian ginseng, an immunostimulant (Louis V. Gerstner 2008), has a total of 16 interactions. Apart from interacting with immunosuppressant drugs, it also has several pharmacodynamic interactions, such as potentiating the effects of monoamine oxidase inhibitors like procarbazine, leading to headaches, tremors, insomnia or manic episodes (Miller 1998; (Jones and Runikis 1987; (Shader and Greenblatt 1988).

Fenugreek (Louis V. Gerstner 2008), psoralea fruit (Chang *et al.* 2001) and swertiae herba (Chang *et al.* 2001) are indicated for alopecia. On the other hand, ginger is indicated for nausea and vomiting (Louis V. Gerstner 2008). From our review, no interactions could be found for these CAMs. Of the 14 CAMs indicated for relieving pain in patients undergoing chemotherapy, 4 had potential interactions documented: namely devil's claw (Unger and Frank 2004), Asian ginseng (Jones and Runikis 1987; (Gurley *et al.* 2000; (Gurley *et al.* 2002; (Shader and Greenblatt 1985; (Shin *et al.* 2000), mate (Pollock *et al.* 1999; (American Society of Health-System Pharmacists 1998) and St. John's wort (Gurley *et al.* 2002; (Henderson *et al.* 2002; (Foster *et al.* 2003; (Komoroski *et al.* 2004; (Markowitz *et al.* 2003; (Frye *et al.* 2004; (Müller *et al.* 1998; (Mathijssen *et al.*) via

pharmacokinetic or pharmacodynamic means. CAMs with anti-inflammatory properties formed a significant proportion of CAMs used for supportive treatment, with a total of 39 CAMs, among which comfrey interacted with CYP3A4 substrates and hepatotoxic drugs, such as dactinomycin and mitomycin.

Approximately 80% of CAMs indicated for treatment of fatigue had recorded interactions with an ACD. One drug in this category was St. John's wort, which interacted with CYP1A2, 2C9 and 3A4 substrates (Roby *et al.* 2000). From our results, there were a total of 45 ACDs which interacted with St. John's wort.

Advantages and limitations of our database

As part of our analysis, the number of CAMs and ACDs that were documented in each of the databases was also compiled, and the results shown in Table 2. The most comprehensive database for CAMs was the Natural Medicines Comprehensive Database, which recorded a total of 106 monographs. Micromedex® and the Memorial Sloan-Kettering databases also tended to provide a more comprehensive list of CAMs as compared to Drugs.com, DoubleCheckMD and Caremark websites.

Table 2. Number of CAMs listed in each individual database.

Database (No. of CAMs listed in the database)	
Caremark (29)	Micromedex®(95)
DoubleCheckMD (41)	Memorial Sloan-Kettering (91)
Drugs.com (41)	Natural Medicines Comprehensive Database (106)

The main advantage of our database is its ability to provide CAM-ACD interaction information in the form of a centralized database. Many drug interactions involving CAMs have not been well-documented in literature. Furthermore, as information may not be consistent among the available sources, healthcare providers searching for CAM-drug interactions typically utilize more than one resource. For example, certain TCMs (e.g. earthworm, cattle gallstone) were not found across the 6 databases. Our database included information about TCMs compiled from additional sources specific to CAMs such as Natural Medicines Comprehensive Database (Jellin and Gregory 2007) and Chinese Materia Medica (Chang *et al.* 2001), thus it would reduce the time required for clinicians to search for drug interactions from our database.

In addition, our database is able to detect conflicting evidence from numerous sources, if any. Links to the PubMed abstracts of references are also provided where possible so as to provide the user with easy access to the relevant drug interaction literature. For example, if CYP3A4 is known to be inhibited in vitro but induced in animal models, both results will be listed for the user with the appropriate references. This enables the clinician to be better informed in his clinical management of patients in his practice.

Nevertheless, our project is not without its own limitations. The list of CAMs in our database is currently not exhaustive, and can be expanded to include more categories such as vitamins and minerals, and commercially available products. Our database is also limited to interaction searches between single ACD-CAM pairs. Users who want to search for interactions between multiple ACDs and CAMs have to carry out multiple searches. In addition, some CAMs are known by various names (e.g. Asian ginseng is also known as Chinese, Korean and Oriental ginsengs, all of which fall under the *Panax* genus), and it is difficult for users to search for the CAM if they are not familiar with the name that is currently indexed in our database. Future work on the database would cater for multiple searches of ACD interactions with CAMs, as well as include a search box which allows users to search for interactions using alternative indexed CAM names.

Conclusion

A computerized database on CAM-ACD interactions has been created. This database compiles drug interaction information from 9 databases: Chinese material medica (Chang *et al.* 2001), Aetna Intelihealth (Aetna InteliHealth Inc.), TCM Assistant (e-MS Inc.), Memorial Sloan-Kettering (Louis V. Gerstner 2008), Micromedex® (Thomson Healthcare 2007), Natural Medicines Comprehensive Database (Jellin and Gregory 2007), Drugs.com (Drugsite Trust 2000), Caremark (Gold Standard Inc.) and DoubleCheckMD (Enhanced Medical Decisions Inc. 2007). A total of 943 interactions are included in this database, of which most interactions are predominantly pharmacokinetic in nature, involving the induction of cytochrome P450 isoenzymes. Users are able to search for drug interactions for ACDs with all CAMs in the database, as well as narrowing their searches based on the CAM indications in cancer therapy. This drug interaction database created will be beneficial for clinicians and pharmacists working in the oncology setting for providing better patient care in their daily practice.

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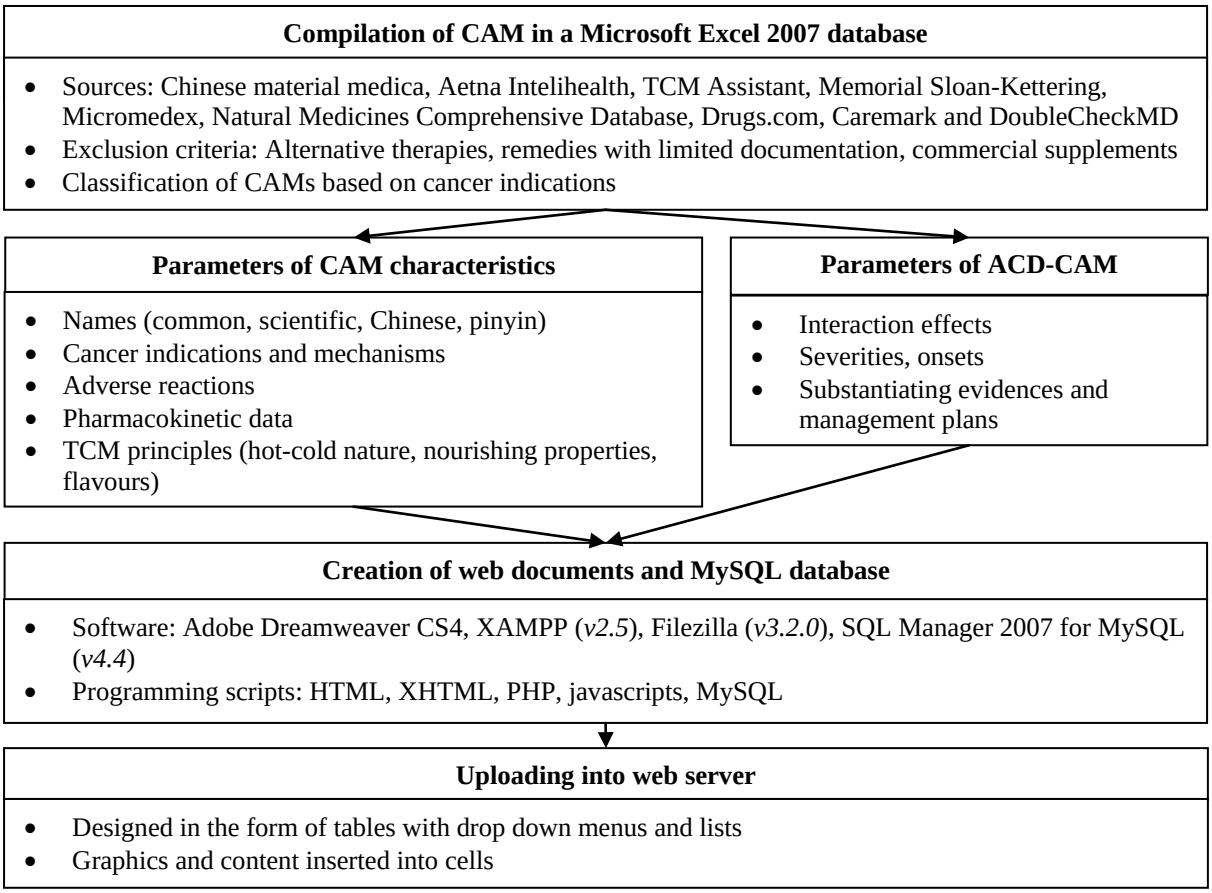
Appendix 1. Summary of procedures used in creating the anti-cancer drug (ACD)-complementary and alternative medicine (CAM) interaction database.



Appendix 2. List of anti-cancer drugs (ACDs) included in the database, categorized by pharmacological class.

List of ACDs
Alkylating agents Carmustine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, lomustine, mechlorethamine, mephalan, procarbazine, temozolomide
Antimetabolites Capecitabine, cytarabine, fluorouracil, gemcitabine, methotrexate, pemetrexed
Antimicrotubules Docetaxel, paclitaxel, vinblastine, vincristine, virorelbine
Biological modifiers Aldesleukin, filgrastim, interferon alfa-2a and -2b, pegfilgrastim
Corticosteroids Dexamethasone, metyleprednisolone, prenisolone, prednisone
Hormone antagonists Anastrozole, exemestane, fulvestrant, goserelin, letrozole, leuprolide, nilutamide, tamoxifen, toremifene
Platinum compounds Cisplatin, carboplatin, oxaliplatin
Topoisomerase inhibitors Doxorubicin, epirubicin, etoposide, irinotecan, mitoxantrone, topotecan
Tyrosine kinase inhibitors and monoclonal antibodies Bortezomib, cetuximab, erlotinib, gefitinib, imatinib, rituximab, sorafenib, sunitinib, trastuzumab
Other cancer drugs *Angiogenesis inhibitor*: Thalidomide *Antidotes*: Leucovorin, mesna *Cytotoxic antibiotic*: Bleomycin *Retinoid*: Alitretinoin

Appendix 3. List of complementary and alternative medicines (CAMs) included in the database, categorized by therapeutic indication*.

List of CAMs
Cancer treatment and prevention 714X, agrimony grass, alpha-lipoic acid, amygdalin, anvirzel (oleandrin), arisaema rhizome, astragalus, barley, bee pollen, bilberry fruit, bitter melon, black nightshade, bloodroot, blue-green algae, bupleurum, burdock, calcium glucarate, cascara, cassia bark, cat's claw, cephalotaxaceae, chaparral, Chinese anemone root pulsatilla, Chinese asparagus, comfrey, coriolus versicolor, evening primrose oil, evodia, fenugreek, forskolin, fourstamen stephania root, garlic, ginseng (American, Siberian), glossy privet fruit, goldenseal, gotu kola, green tea, indigo, isatis leaf, isatis root, licorice, maitake, milk thistle, mistletoe (European), mume fruit, noni, pau d'arco, pennyroyal, pinellia rhizome, pokeweed, rabdosia rubescens, rhizoma iphigenia indica, rhubarb, saw palmetto, scullcap/skullcap, sheep sorrel, shiitake mushroom, slippery elm, sophora root , soy, spreading hedyotis, stillingia, trichosanthes root, turmeric
Immune system-related Astragalus, bee pollen, blue-green algae, cordyceps, coriolus versicolor, Echinacea, ginseng (American, Asian, Siberian), glossy privet fruit, maitake, mistletoe (European), mume fruit, noni, reishi mushroom, rhubarb, shiitake mushroom
Alopecia Fenugreek, psoralea fruit, swertiae herba
Nausea and vomiting Ginger
Peripheral neuropathy and analgesic Achyranthes Root, aloe vera, corydalis, devil's claw, divaricate saposhnikovia root, eucommia bark, fourstamen stephania root, ginseng (Asian), maté, noni, rhizoma sinomenii acuti, schefflera, St. John's wort, willow bark
Anti-inflammatory Achyranthes root, aloe vera, arnica, berberidaceae, black nightshade, bupleurum, butcher's broom, cat's claw, chamomile (German), chaparral, cinnamon, comfrey, devil's claw, divaricate saposhnikovia root, eucommia bark, fenugreek, forsythia fruit, fourstamen stephania root, gotu kola, licorice, lobelia, nettle, pennyroyal, pseudoginseng, pygeum, rehmannia root, reishi mushroom, rhizoma sinomenii acuti, rhubarb, sassafras, saw palmetto, scullcap/skullcap, sheep sorrel, slippery elm, Solomon’s seal, tea tree oil, tree peony bark, turmeric, willow bark
Fatigue syndrome Blue-green algae, cordyceps, guarana, maté, St. John's wort
Non-cancer related Acorus, alangiaceae, atractylodes rhizome, biond magnolia flower, birthwort fruit, black cohosh, borage, buffalo horns, capsaicin, cattle gallstone, chasteberry, Chinese gentian root, Chinese lobelia, Chinese magnoliavine fruit (schisandra), Chinese plantain and plantain seed, chocolate vine stem, chrysanthemum, climbing groundsel, cocklebur fruit, common aucklandia root (costus root), corn silk, croton seed, danshen, dong quai, dwarf lilyturf tuber, earthworm, endothelium corneum glgeriae galli, ephedra, feverfew, figwort, finger citron fruit, fleeceflower root, folium ilicis chinensis, gelatine, ginkgo, glehnia, green tangerine orange peel, gypsum mineral, hawthorn, herba euphorbiae humifusae, horse chestnut, ilex, kava, largehead atractylodes rhizome, lightyellow sophora root, nux vomica seed, passionflower, peppermint, qing hao, red clover, rhizoma menispermi, safflower flower, senega root, shrubalthea flower, snakegourd fruit, song luo, spicebush root, stemona root, Szechwan lovage rhizome, tall gastrodia tuber and armillaria, tangerine peel, tendrilleaf fritillary bulb, valerian, wild indigo, wolfberry tree bark, wolly grass root, wormwood

*CAMs that have multiple indications are included in their respective categories.