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Recent Progress on Anticancer Candidates in Patents of Herbal Medicinal Products

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Abstract: Herbal medicines in treatment of cancer as complementary and alternative therapy are accepted increasingly with growing scientific evidences of biomedical research and clinical trials. Anticancer drugs discovered from herbal medicines have a long history and some of them have been used in clinical setting as the conventional anticancer drugs. Actually, herbal medicines are a source for anticancer drug discovery and drug development. Recently, research continuously focuses on clues from traditional use of herbal medicines to develop new anticancer drugs in single pure compounds. On the other hand, standardized various extracts or fractions with anticancer effects or with adjuvant therapy in cancer treatment coming from single or mixed herbs are also accepted forms as dietary supplements and botanical drug products in the US for current statutory regulations. In the present paper, we analyzed the patented agents in the US from herbal medicines in recent ten years, both as potential anticancer extracts/fractions (containing multi-components) and single pure compound(s) that act as new anticancer substances. This review also highlighted the advances in knowledge about quality control, safety, efficacy and recent progress in anticancer candidates in patents of botanical drug products from herbal medicines.

Keywords: Anticancer drugs, antimetastasis drugs, complementary and alternative medicines, Chinese medicines, herbal medicine, patent.

INTRODUCTION

Anticancer drugs discovered from herbal medicines have a long history and plant-derived compounds have been an important source of several useful anti-cancer agents in clinical practice, such as vinblastine, vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, which are isolated or derived from *Catharanthus roseus* G. Don. (Apocynaceae), *Camptotheca acuminata* Decne (Nys-saceae), *Podophyllum peltatum* Linnaeus (Podophyllaceae) and *Taxus brevifolia* Nutt. (Taxaceae) [1]. In recent years, traditional medicine, such as Chinese medicine, Kampo medicine, Ayurveda and so on, are popular treatment for cancer in Asian countries, and these approaches are also accepted increasingly as complementary and alternative therapies for cancer in the rest of the world. A number of scientific evidences at molecular mechanisms and clinical trial showed they have anticancer potential. Most of the medications in traditional medicine are derived from plants, so we call them herbal medicines.

In Asian countries and regions, such as mainland China, Hong Kong, Taiwan, Japan and Korea, Chinese Medicines are regarded as drugs in their statutory regulations and used in daily cancer clinical practice, for example, herbal medicines are some forms of the drugs listed in Chinese and

Japanese Pharmacopoeias. It is a common model for herbal medicine studies in recent years, the goal of research is to “dig out” major active single herb(s) in a composite formula for some diseases and further explore active compound(s) in the single herb(s), but in daily traditional medicine practice, practitioners rarely use a pure compound to treat diseases, but use a combination of single herbs to mix together (so called Fufang, or composite formula). FDA policy about products derived from herbal medicines regards them to be dietary supplements and botanical drug products, reflecting that FDA recognized the wisdom, experiences and existing problems in herbal medicines for its single and combination use.

In this review, we analyzed anticancer candidates in patents of dietary supplements and botanical drug products from herbal medicines and summarized current progress thereof. We mainly analyzed parts of recent ten years US patents in this study, including those that have been approved and that are under application. The criteria for the selection of the patents included are as follows, first, the patent should describe a compound or an extract that is originally isolated from a herb or medical plant; second, the patented product should be described as an anti-cancer agent, or a complement or supplement to cancer treatment agent; and finally, in <http://www.freepatentsonline.com/>, the relative score of the searched item to the keywords, herbal medicine and cancer, should be in the range from 10 to 1000. And we included some patents from other countries such as China and Europe to give examples of the patent affairs in

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these regions. The data is focused on the US patents (granted or under application) in botanical drugs in the past ten years, and retrieved the data from www.uspto.gov, <http://ep.espacenet.com>, <http://www.freepatentsonline.com>, <http://www.google.com/patents>, <http://patft.uspto.gov/netahtml/PTOsearch-bool.html>, <http://www.wipo.int/pctdb/en/search-simp.jsp> and PubMed by keywords such as anticancer drugs, anti-metastasis drugs, complementary and alternative medicines, Chinese medicines, patents, herbal medicines. We also make a research in the website <http://www.clinicaltrial.gov> to get some information about clinical trial of herbal medicines in the treatment of cancer. Finally, we discussed the advances in knowledge about quality control, safety, efficacy and recent progress in anticancer candidates in patents of dietary supplements and botanical drug products from herbal medicines.

CLAIMING ANTICANCER PROPERTIES OF SINGLE PURE COMPOUND FROM HERBAL MEDICINES

Cancer has become a leading cause of death in the world because changed disease spectrum by social and environmental risk factors [2]. Cancer is a series of malignant diseases with multiple pathological stages (e.g. cancer initiation, promotion and progression) and involved in multiple factors (genetic, environmental, biological, chemical, physical and psychological factors). There are more than a hundred distinct types of malignancies. Cancer is characterized by a rapid and uncontrolled formation of abnormal cells, which may mass together to form a growth of tumor, proliferate throughout the body and initiate abnormal growth at other sites. Therefore, anticancer drugs involve pharmacological effects of cytotoxicity, anti-proliferation, induction of differentiation, anti-inflammation, cell-cycle arrest, induction of apoptosis and/or autophagy, anti-invasion and anti-metastasis.

There is increasing interest in the identification of small molecules or large molecules isolated from natural botanicals with properties to inhibit tumor growth and metastasis. As a candidate, berberine isolated from *Coptis* and other same genus plants has shown this potential [3]. We firstly reported that berberine and *Coptidis Rhizoma* aqueous extract (CRAE) with anticancer properties by its cell death induction and cell migration inhibition in cell models of nasopharyngeal carcinoma and hepatocellular carcinoma [4-6]. One US patent application for berberine in treating lung cancer and breast cancer by its cytotoxicity has been listed in Table 1 [7]. As shown in Table 1 (single pure compound(s) from single medicinal herbs), we can classify the compounds into different categories: anticancer substances with cytotoxicity have saponins [8], stelleramacrin A or purified stelleramacrin B [9], C-2 epimeric xanthenes [10], angeloyl-substituted ingenane and its derivatives [11], methyl-beta-ornicinolcarboxylat [12] and 39-desmethoxyrapamycin [13]; anticancer substances with inhibition of cell growth and induction of apoptosis have the compound isolated from *Saururus chinensis* baill [14], isoindigo, indigo and indirubin [15], Triptolide derivatives [16], 1-propanone-1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl) [17], analogues of boswellic acids [18] and *Scutellaria* flavonoid organic amine derivatives [19]; anticancer substances with

inhibition of the formation of new blood vessels of tumor masses, tumor cell invasion and metastasis have arsenic hexoxide [20], curcumin and curcumin derivatives [21]. At times, some pure compounds from plants seem to have potential in treating cancers, but it failed in clinical trial. For example, swainsonine is an indolizine alkaloid that has been isolated from numerous species of flowering plants and some fungi (e.g. *Locoweed*) and the inventors [22] were able to obtain stable and substantially purified crystalline chloride and bromide salts of swainsonine, and determine their structure by X-ray crystallography. Swainsonine is a golgi mannosidase II inhibitor which can induce hybrid-type glycans of cancer and then suppress various tumor types with direct anti-metastatic and anti-invasion effects on tumor cells, and other anti-cancer activities such as immune stimulatory effects and myeloproliferative as well as hemorestorative activities in *in vitro* and *in vivo* studies [22-25]. A phase II clinical trial of GD0039 (a hydrochloride salt of swainsonine) in 17 patients with renal carcinoma was disappointing [23], while research was still showed that swainsonine is an anti-cancer substance with potential for treating gastric carcinoma [24] and glioma [25]. However, the patents failed in clinical trial can also provide new experiences in developing new anticancer drugs in the future.

CLAIMING ANTICANCER PROPERTIES OF EXTRACTS OR FRACTIONS FROM HERBAL MEDICINES

In anticancer drug development by single pure compound in particular, governmental funders of research and pharmaceutical companies have spent vast amounts internationally on basic research, but the return on investment is significantly less than anticipated. The major problem underlying is that, as long as the anticancer drugs develop, it becomes more and more difficult to discover novel, innovative compound candidates which may have superior action in clinical practice. Blind synthesis and screening of the chemicals without any direction indicated by any preliminary clinical practice make the screening step become long and money-consuming. More and more investment is put into the screening step of the candidate chemicals, but poor and frustrated output could be found. In recent years, complementary and alternative therapies are highly accepted worldwide, in which medication is mainly botanical drug products from herbal medicines. These kinds of products are extracts/fractions (containing multi-components). With the changes of international food and drug regulations, especially the US regulations, and development of chemical analysis technologies, such as gas chromatography (GC), high performance liquid chromatography (HPLC) and mass spectroscopy (MS) can determine the precise quantity range of the active components in the botanical drug products. The good quality control of natural products from herbal medicines can be applied for the US patents and/or registered as botanical drug products (from 2004). Various extracts or fractions in the US patent (granted or under application) from single or composite medicinal herbs are listed in Table 2. The extracts or fractions used in anticancer or anti-metastasis from single herbs can be found from references 26-52 in Table 2, while those from mixture of herbs can be found from references 53-64 in Table 2. Most of these herbs

Table 1. Single Pure Compound Come From Single Medicinal Herbs.

Patent Number, Date of Publication	Title	Description of Patent	Active Constituents	Cancer type, Mechanism of Anticancer Action	Reference
US20070298132, 12/27/2007	Berberine as a selective lung cancer agent	Berberine or its salts or derivatives are identified as the active compound for selectively inhibiting lung cancer, potentially without toxic side effects.	Berberine	Lung cancer cytotoxicity	[7]
US7514412, 04/07/2009	Anticancer biangeloyl saponins	Novel compounds such as compounds designated herein as Y or Y3, Y1, Y2, Y8, Y9 and Y10 are disclosed. These compounds have anticancer activity. The compounds of the present invention are obtainable from plants or be synthesized chemically.	Saponins isolated from <i>Xanthoceras sorbifolia</i>	Various cancer anticancer	[8]
US5616609, 04/01/1997	Carcinostatic compound and production thereof	Described are stelleramacrin A and stelleramacrin B represented by the following formulas (I) and (II), respectively: a process for the preparation thereof; and anticancer agents containing either of them as an active ingredient. Therapeutics for solid cancer, said therapeutics containing either of gnidimacrin or pimelea factor P.sub.2 as an active ingredient, are also described.	Stelleramacrin A, purified stelleramacrin B, gnidimacrin or pimelea factor P.sub.2	Gastric cancer, pulmonary cancer, liver cancer or leukemia cytotoxicity	[9]
US7592367, 09/22/2009	Compounds from <i>Garcinia Hanburyi</i> , their use in treating cancer and method of separating epimers thereof	Three pairs of C-2 epimeric xanthenes isolated from <i>Garcinia hanburyi</i> and method for efficiently separating the xanthone compounds. The compounds are useful for their anticancer effects	C-2 epimeric xanthenes	Various cancer cytotoxicity	[10]
US6787161, 09/07/2004	Anti-cancer compounds	This invention relates to a compound or group of compounds present in an active principle derived from plants of species <i>Euphorbia peplus</i> , <i>Euphorbia hirta</i> and <i>Euphorbia drummondii</i> . Extracts from these plants have been found to show selective cytotoxicity against several different cancer cell lines	An angeloyl-substituted ingenane and its derivatives	Skin cancer cytotoxicity	[11]
US20070099993, 05/03/2007	Antimicrobial and anticancer properties of methyl-beta-orcinolcarboxylate from lichen (<i>Everniastrum cirrhatum</i>)	The present invention relates to the new use of an already known biomolecule methyl- β -orcinol carboxylate of formula I isolated from a lichen (<i>Everniastrum cirrhatum</i>), for treating pathogenic fungal infections and cancers of humans.	Methyl-beta-orcinolcarboxylate	Various cancer cytotoxicity	[12]
US7183289, 02/27/2007	39-desmethoxyrapamycin, compositions and methods of use thereof	The present invention relates to the medical use of 39-desmethoxyrapamycin, particularly in the treatment of cancer and/or B-cell malignancies, the induction or maintenance of immunosuppression,	39-desmethoxyrapamycin	Various cancer cytotoxicity	[13]

(Table 1) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Active Constituents	Cancer type, Mechanism of Anticancer Action	Reference
US20040024055, 02/05/2004	Pharmaceutical composition containing the extract of saururus chinensis baill useful as an anticancer agent and a process for the preparation thereof	The carcinostatis substances HNP-98701A, HNP-98701B and HNP-98701C of the present invention selectively affect cancer cell line cells and cause apoptosis-type cell death.	Eepi-manassantin A, and manassantin A	Various cancer Apoptosis	[14]
US6933315, 08/23/2005	Derivatives of isoindigo, indigo and indirubin and methods of treating cancer	A compound called NATURA, which is a derivative of Isoindigo is useful in aiding the general health of a patient and specifically is beneficial in preventing or treating cancer.	Isoindigo, indigo and indirubin	Various cancer inhibits cell growth pathway	[15]
Us7662976, 02/16/2010	Triptolide derivatives for modulation of apoptosis and immunosuppression	Variously substituted carbonate and carbamate derivatives of triptolide compounds have good aqueous solubility and convert to biologically active compounds <i>in vivo</i> . The prodrugs are useful as immunosuppressive, anti-inflammatory and anticancer agents.	Triptolide derivatives	Colon cancer, breast cancer, lung cancer, and prostate cancer Modulation of apoptosis and immunosup-pression	[16]
US6498195, 12/24/2002	Use of 1-propanone-1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl) as an anticarcinogenic agent	Compositions and methods are provided for prevention and treatment of cancer. The compositions comprise pure hydroxylated chalcone compounds of licorice root (<i>Glycyrrhiza glabra</i>) including 1-propanone-1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl).	1-propanone-1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl)	Various cancer induces apoptosis, inhibits tumor cell growth,	[17]
US20090298938, 12/03/2009	Use of semi synthetic analogues of boswellic acids for anti-cancer activity	The present invention relates to use of compounds of general formula 1 for anticancerous activity, wherein the said compound being derived semi-synthetically from natural triterpenoic acids known as boswellic acids by the induction of apoptosis thereof cytotoxicity and anti-cancer activity displayed by semi-synthetic Boswellic acids.	Analogues of boswellic acids	Various cancer induces apoptosis	[18]
US20100197619, 08/05/2010,	Cyclin-dependent protein kinases inhibitor of Scutellaria flavonoid organic amine derivatives, synthesis and use thereof	The present invention provides a series of cyclin-dependent protein kinases (Cdks) inhibitors, <i>Scutellaria</i> flavonoid organic amine derivatives, synthesis and use thereof. The product is expected to become high efficient and low toxicity anti-cancer drugs.	<i>Scutellaria</i> flavonoid organic amine derivatives	Various cancer Apoptosis, cyclin-dependent protein kinases (Cdks) inhibitors	[19]
US6589567, 07/08/2003	Anti-cancer therapy agent of arsenic hexoxide (As ₄ O ₆) of a natural chemical substance and its pharmaceutical composition	This invention is about the identification of the HD-2, a natural chemical substance that was separated and purified from a natural Arsenic hexoxide (As ₄ O ₆), a natural chemical substance obtained from Sinsuk after eliminating the toxic property, has a potent anti-cancer efficacy by its direct cytotoxicity on tumor cells and suppresses the formation of new blood vessels of tumor masses.	Arsenic hexoxide	Various cancer cytotoxicity on tumor cells and suppresses the formation of new blood vessels of tumor masses	[20]

(Table 1) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Active Constituents	Cancer type, Mechanism of Anticancer Action	Reference
US20100197584, 08/05/2010	Use of curcumin to block brain tumor formation in mice	The present invention provides compositions and methods of using curcumin or curcumin derivatives or analogs to activate the pro-apoptotic enzymes caspase-3/7 in cancer cells.	Curcumin and curcumin derivatives	Brain tumor prevent tumor formation, or tumor cell invasion or metastasis	[21]
US6395745, 05/28/2002	Alkaloid halide salts of swainsonine and methods of use	The present invention relates to stable and substantially purified synthetic halide salts of swainsonine. Golgi mannosidase II inhibitors such as swainsonine have cancer suppressing properties in a wide variety of tumor types including direct anti-metastatic and anti-invasion effects on tumor cells, and other anti-cancer activities such as immune stimulatory effects and myeloproliferative and hemorestorative activities as described herein.	Swainsonine	Various cancer Golgi mannosidase II inhibitors	[22]

Table 2. Various Extracts or Fractions Come From Single or Composite Medicinal Herbs.

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US20100009017, 01/14/2010	Anticancer Methods Using Extracts of <i>Anemarrhena asphodeloides</i> Bunge	Selective apoptotic extracts of <i>Anemarrhena asphodeloides</i> Bunge are provided. Also provided are methods of using said extracts to induce apoptosis in specific cells, especially in a human.	Extracts of <i>Anemarrhena asphodeloides</i> Bunge	Breast cancer Apoptosis	[26]
US6599540, 07/29/2003	Use of a <i>Serenoa repens</i> extract for the production of a medicament to treat prostate cancer	The invention relates to the use of a lipid-sterolic <i>Serenoa repens</i> extract for the production of a medicament which is administered in an isolated manner or in an associated manner, in a simultaneous, separated or staggered manner, with prostatectomy, radiotherapy and/or hormonotherapy in order to prevent and/or treat prostate cancer.	Lipid-sterol extract	Prostate cancer prevent and/or treat prostate cancer.	[27]
US20080199550, 08/21/2008	Novel Anticancer Agent, Methods for Obtaining the Same and Pharmaceutical Compositions hereof	This invention relates to novel herbal anticancer agents.	Sphaeranthus	Various cancer Anticancer effect	[28]
US20090258096, 10/15/2009	Anticancer Methods Employing Extracts of <i>Gleditsia sinensis</i> Lam	Selective apoptotic extracts of <i>Gleditsia sinensis</i> Lam are provided. Also provided are methods of using said extracts to induce apoptosis in specific cells, especially in a human.	Oleanolic acid and saponin	Breast cancer Estrogen receptor (ER) negative breast cancer. Apoptosis	[29]

(Table 2) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US6790464, 09/14/2004	Herbal compositions for prostate conditions	The invention provides a composition having beneficial effects in preventing and treating prostate disorders including prostatitis, benign prostate hyperplasia and prostatic carcinoma.	<i>Radix Asparagi</i>	Prostate cancer preventing and treating prostate disorders including prostatic carcinoma	[30]
US7618661, 11/17/2009	Process for preparation of <i>Rhus verniciflua</i> extracts having excellent anti-cancer activity and anti-cancer pharmaceutical composition containing the same	Provided is a process for preparation of a <i>Rhus verniciflua</i> extract, thereby obtaining extract powder and irradiating far-infrared to the extract powder, thereby improving anti-cancer activity.	Allergens removed <i>Rhus verniciflua</i> extracts	Various cancer cytotoxicity	[31]
US6660309, 12/09/2003	Antitumor agent	A composition is obtained from Banyan tree bark that has insulin antisecretory and cytotoxic properties.	Banyan tree bark fraction	Various cancer cytotoxicity	[32]
US7250180, 07/31/2007	Anti-prostate cancer composition and therapeutic uses therefor	The invention is based on BIRM, an extract of the plant <i>Solanaceae-Dulcamara</i> and its previously unrecognized anti-prostate cancer activity. Also disclosed are methods for preparing compositions for administration to humans for treating prostate cancer.	Extract of <i>Solanaceae-Dulcamara</i>	Prostate cancer Anti-prostate cancer, cytotoxicity	[33]
US20040043083, 03/04/2004	Anticancer composition comprising sesquiterpenes isolated from <i>resina ferulae</i>	A pharmaceutical composition exhibits a potent anticancer activity.	Sesquiterpenes	Lung cancer, ovary cancer and so on Inhibition of proliferation.	[34]
US20030165579, 09/04/2003	<i>Euphorbia antiquorum</i> extract, a pharmaceutical composition containing the same and methods for treatment of cancers	An herbal extract of <i>Euphorbia antiquorum</i> is provided. The herbal extract of the invention demonstrates <i>in vitro</i> inhibition of growth of hepatoma cells, colorectal adenocarcinoma cells, monocyte-like lymphoma and leukemia cells.	<i>Euphorbia antiquorum</i> extract	Liver cancer and colon cancer cytotoxicity	[35]
US7285571, 10/23/2007	Herbal chemical composition for the treatment of cancer	The present invention relate to a novel synergistic composition of lignans exhibiting anticancer activities for breast, cervix, neuroblastoma, colon, liver, lung, mouth, ovary and prostate cancer.	(-)- Matairesinol, (-)- Wikstromol, Dibenzylbutyrol actol	Various cancer cytotoxicity	[36]
US7078063, 07/18/2006	Water soluble extract from plant of <i>Solanum</i> genus and the preparation process thereof, and pharmaceutical composition containing the water soluble extract	A water soluble extract from a plant of <i>Solanum</i> genus consists essentially of at least 60%–90% of solamargine and solasonine. The water soluble extract can be used as an active component in a pharmaceutical composition for inhibiting the growth of tumor/cancer cells, in particular liver cancer cells, lung cancer cells and breast cancer cells.	solamargine and solasonine	Liver cancer, lung cancer and breast cancer cytotoxicity	[37]

(Table 2) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US6902748, 06/07/2005	Medicines manufactured from old platycodon extracts	The present invention relates to anticancer agents, of which medical treatment materials are extracted from 20-year (or older) perennial old <i>platycodon</i> (i.e., old <i>platycodon</i>).	Old <i>Platycodon extract</i>	Various cancer cytotoxicity	[38]
US6613754, 09/02/2003	Polysaccharide-based extract from ganoderma, pharmaceutical use thereof, and process for preparing the same	The polysaccharide-based extract of ganoderma genus can be used in an orally active medicinal product which has immunopotentiating and antitumoral effects.	Polysaccharide-based extract	Various cancer cytotoxicity	[39]
US7201928, 04/10/2007	Extracts of orange peel for prevention and treatment of cancer	Compositions and methods of inhibiting tumor cell growth and treating and preventing cancer are provided based on administration of an orange peel extract either alone or in combination with other phytochemicals.	Flavone components	Various cancer inhibitory effects of cell proliferation	[40]
US20080207578, 08/28/2008	Method of inducing apoptosis in cancer treatment by using Cucubritacins	This invention relates to the preparation and use of anti-cancer compounds/formulation containing cucurbitacins.	Cucurbitacins	Various cancer induces apoptosis	[41]
US7033617, 04/25/2006	Use of Anoectochilus formosanus plant extracts and their derived fractions as herbal medicines or nutraceutical supplements for chemoprevention or treatment of human malignancies	The present invention provides medicinally active extracts and fractions, and a method for preparing the same by extracting and fractioning constituents from the tissue of plant components of the <i>Anoectochilus</i> family. These active extracts and fractions are useful for preventing or inhibiting tumor growth.	Crude or fraction of <i>Anoectochilus formosanus Hayata</i>	Various cancer apoptosis, <i>in vivo</i> tumor growth inhibition	[42]
US20060280817, 12/14/2006	Pharmaceutical composition useful for the treatment of hepatocellular carcinoma	The present invention relates to anticancer activity against hepatocellular carcinoma of an extract and fraction isolated from flowers of <i>Butea monosperma</i> .	Flavonoid glycosides such as butrin and isobutrin	Anti-hepatocellular carcinoma <i>via</i> inhibition of oxidative stress and polyamine biosynthetic pathway	[43]
US6808724, 10/26/2004	Artemisolide compound isolated from the aerial parts of <i>Artemisia sylvatica</i> , isolation method, and use thereof	The present invention relates to a novel compound isolated from <i>Artemisia Sylvatica</i> , expressed by the formula 1, a method of isolation, and its use thereof, and more particularly to a novel compound isolated from <i>Artemisia Sylvatica</i> , a method of isolation, and its use in inhibiting farnesyl transferase activity.	Artemisolide	Various cancer inhibiting farnesyl transferase activity	[44]
US7306817, 12/11/2007	Herbal composition for treating CD33+ acute and chronic myeloid leukemia and a method thereof	A method of treating CD33+ acute and chronic myeloid leukemia in animals including humans, using fraction nos. 1 and 9 obtained from water.	3-O-p-coumaryl quinic acid	Leukemia, destruction of CD33 ⁺ myeloid leukemic cells	[45]

(Table 2) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US20050175623, 08/11/2005	Saponins as anticancer agent	The invention described herein encompasses novel discovery of anticancer agents and its compositions comprising saponins, a group of triterpenoid and steroidal saponins found in plants including <i>Quillaja saponaria</i> Molina (soap tree).	A group of triterpenoid and steroidal saponins	Various cancer directly kill cancer cells through deconstruction of the cell membrane	[46]
US6451353, 09/17/2002	<i>Fagopyrum cymosum</i> (Trev.) Meisn composition, method to prepare and analyze the same and uses thereof	This invention provides different compositions extracted from <i>Fagopyrum cymosum</i> (Trev.) Meisn. Said compositions comprise active components for therapeutic applications in treating lung cancer, gastric cancer, cervical cancer, sarcoma and other neoplasms.	Tannins and procyanidins	Various cancer Anticancer and reduce adverse effects associated with chemotherapy and radiotherapy	[47]
US20100028472, 02/04/2010	Herbal composition and process for its preparation	A herbal composition comprising a therapeutically effective amount of the extract of <i>Piper betle</i> leaves as an active ingredient either alone, or with a pharmaceutically acceptable excipient. A significant invention in the art of cancer particularly leukemia.	Extract of <i>Piper betle</i> leaves	Leukemia. Against the Bcr-Abl mutated imatinib-resistant cell lines.	[48]
US20040116394, 06/17/2004	Method for treating cancer using betulinic acid rich herbal extract	This invention relates to an orally effective herbal extract-based composition having broad-spectrum anticancer activity. Inhibits Protein Kinase C activity of cancer cells and induces apoptosis.	Zizyphus	Various cancer Apoptosis	[49]
US20060034951, 02/16/2006	Active fraction having anti-cancer and anti-metastasis isolated from leaves and stems of ginseng	Provided is a composition that contains, as an active ingredient, an extract or polysaccharides separated from the leaves and/or stems of plants belonging to <i>Panax</i> genus, for an anticancer drug or its adjuvant,	Polysaccharides	Various cancer Hemotopoiesis enhancement, cancer metastasis inhibition, bone marrow defense	[50]
US20040009244, 01/15/2004	Composition comprising <i>Melissa</i> leaf extract for anti-angiogenic and matrix metalloproteinase inhibitory activity	The present invention relates to a composition comprising <i>Melissa</i> leaf extract that inhibits angiogenesis and matrix metalloproteinase activity.	Rosmarinic acid	Various cancer Hhhibits angiogenesis and matrix metalloproteinase activity	[51]
US7709031, 05/04/2010	Angiogenic agents from plant extracts, gallic acid, and derivatives	An extract of Chinese blackberry (<i>Rubus suavissimus</i>) has been found to inhibit angiogenesis, and two active fractions isolated.	Various derivatives of gallic acid	Various cancer antiangiogenesis	[52]
US6649185, 11/18/2003	Herbal formulation	This invention relates to a new herbal formulation which has been found to be effective for the treatment of cancer. More particularly, the formulation can be used to treat haematological malignancies.	<i>Tinospora cordifolia</i> and <i>Aloa vera</i> (<i>Aloa barbedensis</i>)	Various cancer Haematological malignancies	[53]

(Table 2) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US5876728, 03/02/1999	Natural composition extracted from plants used in the treatment of cancer	The invention is a method of treating cancer comprising administering an effective amount of either a composition of three herbal extracts consisting essentially of Goldenseal, Myrtle, and Centaurea.	Extract of three herbs or seven herbs in a mixture of water and ethyl ether	Various cancer Cytotoxicity	[54]
US5437866, 08/01/1995	Herbal treatment of malignancy	A protocol using natural extracts which permit amelioration of malignancies in humans is disclosed. The protocol mandatorily includes an extract of <i>Lentinus edodes</i> and mung beans, and optionally further includes the combined extract of <i>Hedyotis diffusa</i> and <i>Scutellaria barbata</i> .	Extracts of <i>Lentinus edodes</i> , mung bean, <i>Hedyotis diffusa</i> and <i>Scutellaria barbata</i>	Various cancer <i>in vivo</i> tumor growth inhibition	[55]
US6936284, 08/30/2005	Composition having anticancer activity	To conduct a search for natural drugs and their formulae derived from natural substances that hardly cause side effects and drug tolerance, based on quite a new idea having departed from conventional drugs.	A dry product of <i>Angelica keiskei</i> and/or a dry product of <i>Theaceae</i> <i>Camellia</i>	Various cancer An anticancer activity and is selectively cytotoxic to cancer cells	[56]
US20080280839, 11/13/2008	Anti-Cancer Activity of <i>Androsace Umbellata</i> Merr. Extract and Contained Triterpene Saponin	The present invention relates to an <i>Androsace umbellata</i> Merr. extract having anticancer activity and a triterpene saponin compound isolated therefrom.	<i>Androsace umbellata</i> (Lour.) Merr. extract, saxifragifolin B and saxifragifolin D	Various cancer Inhibits cancer cell growth and induces apoptosis	[57]
US20050058722, 03/17/2005	Herbo-mineral formulation for refractory leukemias and lymphomas	A pharmaceutical or medicinal preparation comprising a mixture of arsenic trioxide (As_2O_3) and the herbs <i>Aloe Vera</i> (<i>Aloe Barbedensis</i>), <i>Withania Somnifera</i> , <i>Glycine Max</i> , <i>Rubia Cordifolia</i> and <i>Acacia Catechu</i> , or a mixture of the active ingredients that have been extracted from those herbs. The herbo-mineral formulation of the invention is effective for the treatment of cancer, in particular refractory leukemias	Arsenic trioxide and other five herbs,	Leukemia and kymphoma Refractory leukemias Apoptosis	[58]
US20070082072, 04/12/2007	Herbal Composition for Treating Cancer	The present invention relates to an herbal composition that provides anti-cancer effects, especially for breast cancer. <i>Wubeizi</i> , <i>Lonicera japonica</i> , <i>Astragalus membranaceus</i> , <i>Rehmanniae Radix</i> , <i>Glycyrrhizae Radix</i> and <i>Panax schinseng</i> .	6 Herbal Composition	Various cancer Apoptosis	[59]
US20050208070, 09/22/2005	Compositions of botanical extracts for cancer therapy	Methods and compositions for prevention and therapy of cancer are provided. Compositions comprising therapeutically effective amounts of two or more of an extract of <i>Ganoderma lucidum</i> , an extract of <i>Salvia miltiorrhiza</i> and an extract of <i>Scutellaria barbata</i> and optionally a therapeutically effective amount of an extract of <i>Hippophae rhamnoides</i> are provided.	Extracts of said 3 herbs, and optionally, <i>Hippophae rhamnoides</i> (sea buckthorn)	Various cancer Cytotoxicity, Cox-2 inhibition	[60]

(Table 2) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Cancer types, Mechanism of Anticancer Action; Cancer Types	Reference
US20080233218, 09/25/2008	Methods for treating oral cancers with herbal compositions	The inventive subject matter relates to methods for treating oral cancers, comprising administration of a composition comprising therapeutically effective amounts of supercritical extracts of rosemary, turmeric, oregano and ginger.	Hydroalcoholic extracts of said 9 herbs	Various cancer Anti-oral cancers <i>via</i> modulating gene expression	[61]
US20070160691, 07/12/2007	Pharmaceutical composition for treating and preventing cancer comprising cinnamoni cortex extract and zizyphi fructus extract	Disclosed is a pharmaceutical composition for treating and preventing cancer, comprising a Cinnamoni Cortex extract and a Zizyphi Fructus extract..	<i>Cinnamoni Cortex</i> extract and a <i>Zizyphi Fructus</i> extract	Various cancer Induces apoptosis and inhibits metastasis	[62]
US6780441, 08/24/2004	Composition of eleven herbs for treating cancer	The herbal formulation of the invention is effective for the treatment of cancer, in particular squamous cell carcinomas, tumours and other metastatic states, including lung cancer.	A mixture of 11 herbal extract	Squamous cell carcinomas Anti-metastasis	[63]
US20060216366, 09/28/2006	Herbal compositions useful in cancer treatment	The composition can be processed into a form for administering to human patients with a cancerous disease for improving their health.	4 Herbal compositions	Various cancer Anti-metastasis	[64]

have similar anticancer action with single pure compounds by their cytotoxicity, inhibition of cancer growth and proliferation, as well as suppression of cancer invasion and metastasis in forms of extract or fraction from single or combination herbs [26-64]. Most of the studies were conducted in *in vitro* system, leaving the problem that if these extract and fractions could be effective *in vivo* and in clinical practice. Also, the quality assurance of the herbal extract and fraction is the major problem needed to be carefully concerned. First of all, since the products are always extracted from the herbs, the difference from batch to batch of the herb should be carefully checked during manufacturing. The secondary metabolites that herbs contain may be affected by the growth conditions of the plants, such as light, water and nutrients. Therefore, a Good Agriculture Practice (GAP) standard should be required for each kind of medical plant and the GAP base for each herb should be addressed. The herbs used in botanical drug production should come from the GAP base. Second, the manufacturing process of the herbal drug should be under restricted and real-time control. It is highly recommended that drug investigator should well document the manufacturing process in their pre-clinical study of the drug, which may include good and reasonable optimization of the extraction process, careful validation and some minor adjustments on the process from bench-top to manufacturing. And the production of herbal should follow the guideline of Good Manufacturing Practice (GMP). These will ensure the stability and reproducibility of the herbal drugs. And at last but not the least, the quality control document should be well

prepared by the drug investigators during the pre-clinical studies. This may include isolation and identification of major compounds, establishment and optimization of chemical analysis system for the raw herbs, the manufacturing process and the final products. In China, the State Food and Drug Administration (SFDA) requires that the identified compounds should comprise at least more than 50% of the herbal extract, and it will be highly recommended that chemical analysis and quality assurance may be carried out in more than one approach. Combined approaches for the qualitative and quantitative analysis of the product will increase the success rate of drug application. The scheme of basic production process of herbal drugs, including pure compounds and fractions/extracts, is shown in Fig. (1).

COMBINATION OF HERBAL PRODUCT AND CHEMO- AND RADIO-THERAPY AND THE HERB-DRUG INTERACTION IN CANCER THERAPY

Conventional cancer therapies have surgical resection, chemotherapy and radiotherapy. Chemotherapeutants and radiotherapy may cause severe toxicity. Common adverse effects associated with cancer chemotherapy include gastrointestinal complications (e.g., diarrhea, nausea, vomiting, anorexia and mucositis), appetite loss, bone marrow/hematological complications (e.g., leukopenia, neutropenia, anemia, hemorrhage, and thrombocytopenia), fatigue, weight loss, insomnia, pain and even life threat etc. These symptoms not only affect the quality of life, but also reduce the tolerance and response to anti-cancer drugs, thereby affecting the prognosis and survival to disease. How to improve the

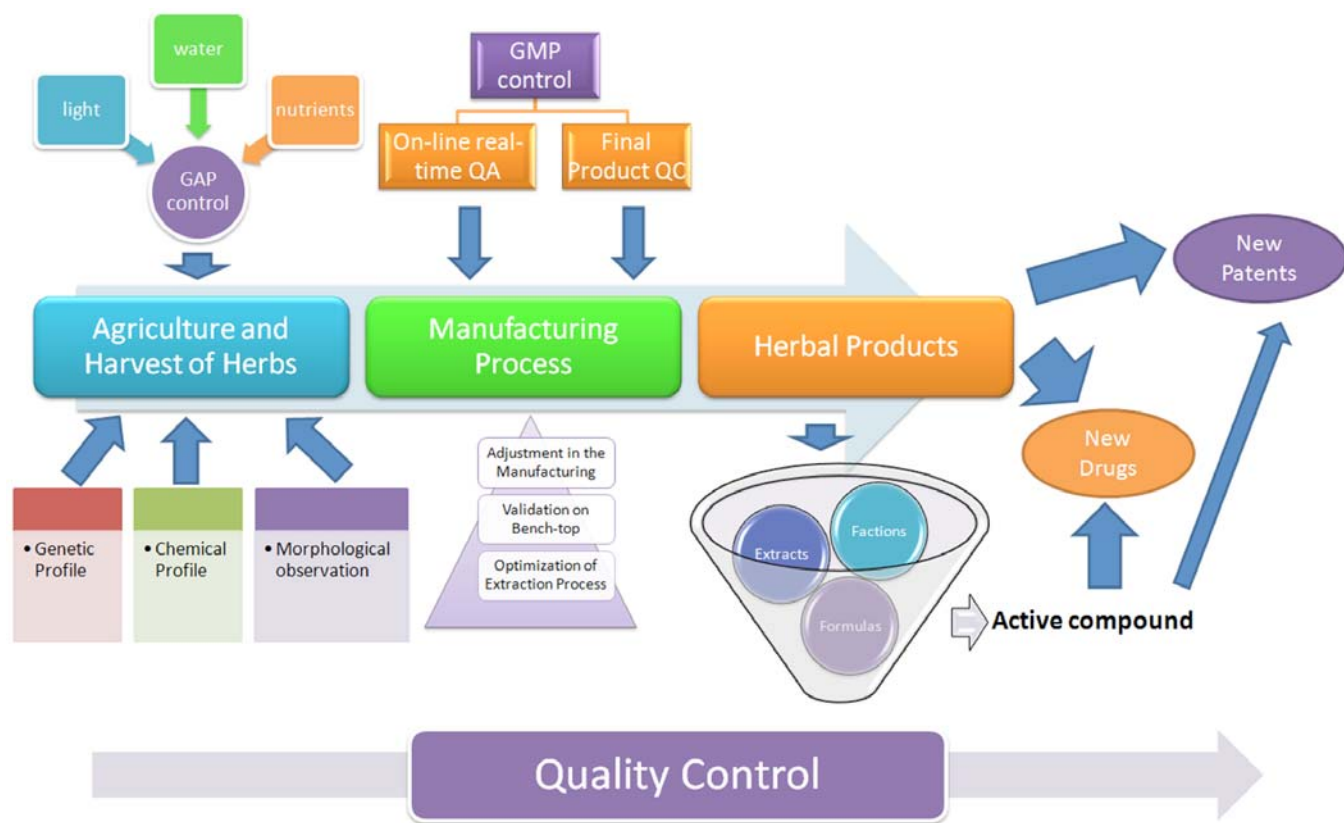


Fig. (1). The overall scheme of the development of a patented herbal drug by quality control.

situations of cancer patient ongoing or after conventional cancer therapies is a great challenge. For these purposes, various extracts or fractions in the US patent (granted or under application) from single or composite medicinal herbs are listed in Table 3. These various extracts or fractions used in combination therapy claimed that herbal medicines can enhance therapeutic index or reduce side effects of the chemotherapeutic drugs [65-73]. However, there's a lack of clinical studies for confirming the claims at clinical level.

Herb-drug interactions are complicated issues. The interaction of herb and drug may increase the drug action or decrease it. This may depend on the complication system of drug metabolism enzymes in human body. Herbal products may activate or suppress the CYPs activities which will result in changes in the pharmacokinetics of the drug, including the changes in bio-availability, the metabolite of the drug and the excretion rate. In particular, if the drugs are designed in a pro-drug form, which should be preliminary metabolized before it could take action, this kind of interaction may directly affect the drug effect. In Table 4, we summarized herb-herb or drug interactions in forms of extract or fractions from single herbs which are claimed to increase bioavailability and/or bioefficacy of anticancer drugs. These patents disclosed beneficial effects for anticancer drugs when combining anticancer drugs with indicating extract or fractions though most of the studies conducted in *in vitro* and *in vivo* studies [74-79].

Herbal medicine is a multi-component system with complication and unclear composition, among which partial

compounds are responsible for the anticancer effect. In the past years, many novel separation techniques with significant advantages over conventional methods have been introduced and applied to separation and analysis of the chemical constituents of anticancer in herbal medicines. It is still a challenge for preparing a pharmaceutical formulation containing two or more active anticancer ingredients or isolating specific anticancer active constituents from herbal medicines. In Table 5, we choose three patents which disclosed the process for preparing pharmaceutical formulations using supercritical fluids and fermenting panax genus plant or panax notoginseng solution with anticancer effects [80-82].

CLINICAL TRIAL

Not as many as the patents approved, there are only a few of clinical studies focusing on the anti-tumor effect of herbal medicines [83-100]. To sort them by their locations, it is noticed that the major part of these clinical trials is conducted in United States (13 in 18). For the other parts, 2 are carried out in Canada, 1 in Taipei, 1 in India, and 1 in South Africa. It is interesting to find that though China is the origin of the use of herbal medicines in clinical practice, it is United States where most of the clinical trials choose to be carried out. It is somehow a good point to see some of these clinical trials are under restricted regulation and double-blind, randomized, placebo-controlled conditions, which may put out more reliable results to draw conclusion of the herbal medicine's action. To sort by their progress, it could

Table 3. Various Extracts or Fractions Used in Combination Therapy of Herbal Medicines and Drugs.

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Reference
US20090130101, 05/21/2009	anti-cancer therapy with an extract of <i>Scutellaria Barbata</i>	Methods of treating cancer with a combination of an extract of <i>Scutellaria barbata</i> D. Don and at least one additional anticancer chemotherapeutic agent are provided.	Extract of <i>Scutellaria barbata</i> D. Don	[65]
US20080311230, 12/18/2008	Preparation of <i>Artemisia</i> to treat human cancer, autoimmune disease, IgA-Nephropathy, and to counteract weight loss in cancer patients	Anti-cancer drugs that were effective in the beginning start losing their efficacy, and are less tolerated. Also in autoimmune diseases, the immune system is overreacting. This herbal invention, based on <i>Artemisia</i> species, ginger root and large cardamom, each targeting at different factors involved in weight loss and autoimmune diseases, is effective	<i>Artemisia</i> oils and other 2 herbs	[66]
US7407675, 08/05/2008	Anti-neoplastic compositions comprising extracts of black cohosh	The present invention further provides a combination of anti-neoplastic agents, comprising an effective anti-neoplastic amount of an ethyl acetate extract of black cohosh and an effective anti-neoplastic amount of at least one additional chemopreventive or chemotherapeutic agent. Methods for treating and preventing neoplasia are also provided.	Ethyl acetate extract of black cohosh	[67]
US6432454, 08/13/2002	Processes of making north american ginseng fractions, products containing them, and use as immunomodulators	The invention is directed to chemical processes of preparing fractions from North American ginseng (<i>Panax quinquefolium</i>) and pharmaceutical compositions containing these fractions. The products of the present invention may be used to stimulate the production of cytokines and/or antibodies, or as therapeutics targeted at conditions characterized by low immunity, such as the common cold, influenza, chronic fatigue syndrome, AIDS and cancer.	Polysaccharide	[68]
US7192612, 03/20/2007	Compositions and methods based on synergies between capsicum extracts and tea catechins for prevention and treatment of cancer	The invention described herein encompasses methods and compositions of preventing or treating cancer comprising the administration of a combination of therapeutically effective amount of catechins, a group of polyphenols found in green tea, and <i>Capsicum</i> extracts. The invention also encompasses the varying modes of administration of the therapeutic compounds, including a formulation which may be used as a therapeutic compound for the treatment of cancer or as a dietary supplement for the prevention of cancer.	Epigallocatechin gallate (EGCg), epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC)	[69]
US6713093, 03/30/2004	Antialopecia agent	The present invention provides an antialopecia agent which is a drug for protecting, reducing or preventing alopecia frequently occurring as the side effect of anticancer agents.	Oolong tea extract	[70]
US20040197427, 10/07/2004	Herbal composition for improving anticancer activity, immune response and hematopoiesis of the body, and protecting the body from oxidative damage, and the method of preparing the same	Disclosed is a herbal composition comprising a first hot-water extract from a mixture of the plants.	Polysaccharide fraction	[71]
US20080213386, 09/04/2008	Nutraceutical for the prevention and Treatment of Cancers and Diseases affecting the liver	The composition can be taken as a daily dietary supplement to enhance normal physiological functions of the body. The compositions are also useful for administration to patients with pre-existing hepatitis and/or liver cirrhosis. The compositions or extracts thereof may be useful for treating other cancers and other disorders, diseases, or conditions.	Vitamins and nutrients that provide a novel nontoxic treatment for liver cancers, hepatitis, and liver cirrhosis.	[72]

(Table 3) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Reference
US7025993, 04/11/2006	Herbal composition PHY906 and its use in chemotherapy	The present invention relates to herbal compositions and herbal extracts useful for increasing the therapeutic index of drugs, including those used in the treatment of disease, especially viral infections and neoplasms of cancer. Furthermore, this invention improves the treatment of disease by increasing the therapeutic index of chemotherapy drugs by administering the herbal composition PHY906 to a person undergoing such chemotherapy.	Four herbal composition	[73]

Table 4. Herb-herb or Drug Interactions in Forms of Extract or Fractions from Single Herbs Increase Bioavailability and/or Bio-efficacy.

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Indication in Cancer Therapy	Reference
US20040052873, 03/18/2004	Bioavailability / bioefficacy enhancing activity of cuminum cyminum and extracts and fractions thereof	The present invention is directed to preparation of active extracts/fraction from the plant <i>Cuminum cyminum</i> and methods of using such products to enhance bioavailability and/or bioefficacy of anti-cancer drugs, natural products and essential nutraceuticals.	Extract and fractions of <i>cuminum cyminum</i>	Enhancing the bioavailability of anti-cancer drug	[74]
US20100112101, 05/06/2010	Bio-availability/bio-efficacy enhancing activity of Stevia Rebaudiana and extracts and fractions and compounds thereof	The present invention discloses novel bioenhancing agents comprising raw powder or extract or active fraction(s) or compound(s) derived from genus <i>Stevia</i> preferably <i>Stevia rebaudiana</i> leaf, to potentially enhance the bio-availability and bio-efficacy of a number of anticancer drugs.	Extract or active fraction(s) or compound(s) derived from genus <i>Stevia</i> preferably <i>Stevia rebaudiana</i> leaf	Enhancing the bioavailability and bio-efficacy of anti-cancer drugs	[75]
US20060057234, 03/16/2006	Composition comprising pharmaceutical/nutraceutical agent and a bio-enhancer obtained from <i>Glycyrrhiza glabra</i>	The invention relates to a new use of a non-alkaloid compound that is plant derived glycoside 'glycyrrhizin' as a highly potent bio-enhancer of activity and availability of antibiotics and other drugs including anti-infective and anticancer agents.	Non-alkaloid compound that is plant derived glycoside 'glycyrrhizin'	bio-enhancer and bioavailability facilitator for anti-cancer drugs	[76]
US5653981, 08/05/1997	Use of <i>nigella sativa</i> to increase immune function	A pharmaceutical composition for treatment of cancer and other conditions and the prevention of side effects of anticancer chemotherapy and increasing the immune function contains an extract of the plant <i>Nigella sativa</i> .	Plant seed extract of <i>Nigella sativa</i> Linn (N. sativa)	Prevention of side effects of anticancer chemotherapy and increasing the immune function	[77]
US20050214390, 09/29/2005	Bioavailability enhancing activity of <i>Carum carvi</i> extracts and fractions thereof	The present invention relates to the use of extracts of <i>Carum carvi</i> as bioenhancers, either alone or in combination with piperine or <i>Zinzeber officinale</i> extract to improve the bioavailability of a wide variety of drugs.	<i>Carum carvi</i> extract or fraction	Bioavailability enhancer	[78]

(Table 4) Contd....

Patent Number, Date of Publication	Title	Description of Patent	Extracts, Fractions and Active Constituents	Indication in Cancer Therapy	Reference
US6617335, 09/09/2003	Preparation and drug composition of bis-benzyl-isoquinoline class alkaloids	This invention relates to the preparation of bis-isoquinoline derivatives of general formula (I) and salts thereof, which possesses multi-drug resistance (MDR) reversal activities. Drug compositions and formulations comprising bis-isoquinoline derivatives of general formula (I) and salts thereof are provided for use as sensitivity enhancers in cancer chemotherapy. Methods for inhibiting MDR by treatment with bis-isoquinoline derivatives are also provided.	Bis-isoquinoline derivatives	Multi-drug resistance (MDR) reversal activities	[79]

Table 5. New Patented Techniques in Chemical Isolation and Analysis.

Patent Number, Date of Publication	Title	Description of Patent	Reference
US20040202681, 10/14/2004	Process for preparing pharmaceutical formulations using supercritical fluids	The invention is directed to a process for preparing a pharmaceutical formulation containing two or more active pharmaceutical ingredients comprising: (a) contacting two or more active pharmaceutical ingredients with a supercritical fluid to form a supercritical fluid solution; and (b) separating the active ingredients from the supercritical solution to yield a powder precipitate.	[80]
US20030190378, 10/09/2003	Extract of processed Panax genus plant, the preparation method thereof, and compositions containing the same	The present invention relates to an extract of processed Panax genus plant, the preparation thereof and compositions containing the same having anticancer or anti-allergic activity. Panax genus plants and subsequent bio-converting treatment such as lactic fermenting and intestinal-bacterial fermenting process so as to make a ratio of ginsenoside (Rk ₂ +Rh ₃ +protopanaxadiol+20-dehydroprotopanaxadiol) to (Rg ₃ +Rg ₅ +Rk ₁) of above 0.1. The extract of processed Panax genus plant in the present invention has inhibitory effect for cancer or allergic diseases and it is useful in the prevention or treatment of cancer or allergic diseases.	[81]
US20080220100, 09/11/2008	Fermented Panax notoginseng solution with anti-cancer effects and manufacture method thereof	This invention relates to a fermented <i>Panax notoginseng</i> solution and manufactured method thereof. The manufacture method comprises activating a <i>Lactobacillus</i> spp, fermenting a <i>Panax notoginseng</i> medium with the <i>Lactobacillus</i> spp. to form a fermented solution, and centrifuging the fermented solution to obtain a supernatant. The supernatant has anti-cancer effects.	[82]

be observed that most of the studies are carried out in phase II clinical trial, which assess how well the drug works in patients. One drug is undertaken in phase III clinical trial and one is in post-marketing stage. 7 of the studies also carry out Phase I clinical trial to assess the safety of the herbal materials, which may be under critical concerns for the use of herbal medicines. Interestingly, there's no clinical study focusing on the direct anti-tumor activity of the herbal medicine, which is contradictory with the patent affairs, where many patents reported anti-tumor effect of the herbal drugs. The major purpose of herbal medicine intervention in these clinical trials is to reduce the adverse effect of chemo-radio-therapy, to give a support care to cancer patients, and to increase the quality of life of the patients. Prevention of tumorigenesis by herbal medicines is also under investigation. This contradiction leads us to think about the

future use of patents reporting anti-tumor activity of herbal medicines, and it may criticize the accreditation process of patent application in the world. Should we need more restricted criteria in the assessment to the patent application materials? And should the operability of the patent in clinical trials be in prior considered in the assessment to the patent application? These questions need to be taken into consideration by both investigators and administrative departments. The detail information about clinical trials conducted for herbal medicine in the treatment of cancer is listed in Table 6.

CURRENT & FUTURE DEVELOPMENTS

Herbal medicines can be used in some countries based on both scientific and culture aspects. It may be a world-wide phenomenon that the use of herbal medicines depends on

Table 6. Herbal Medicine Under Clinical Trials.

Title	Location	Phase	Allocation	Control	Masking	Drug	Reference
Compound Herbal Formula (TPE-1) for Leukopenia and Cancer-related Fatigue in Breast Cancer Patients With Radiotherapy	Taipei	phase II, phase III	Randomized	Dose comparison	Double Blind	Compound Herbal Formula (TPE-1)	[83]
Iscar for Supplemental Care in Stage IV Lung Cancer	US	Phase II	Non-Randomized	Dose comparison	Open Label	Iscar is an herbal medicine made from the total plant extract of mistletoe.	[84]
Boswellia Serrata and Standard Treatment or Standard Treatment Alone in Treating Patients Who Have Undergone Surgery and Radiation Therapy for Newly Diagnosed or Recurrent High-Grade Glioma	US	Phase II	Randomized	Active Control	not clear	Boswellia serrata	[85]
A Clinical Study of PHY906 as a Modulator of CPT-11 in Patients With Metastatic Colorectal Cancer	US	Phase I, Phase II	not clear	Single Group Assignment	Open Label	PHY906	[86]
Sho-Saiko-To Following Removal of Liver Cancer By Embolization in Treating Patients With Liver Cancer That Cannot Be Surgically Removed	US	Phase II	N/A	N/A	N/A	Sho-saiko-to	[87]
Safety and Pharmacokinetics of Jin Fu Kang in Comb w/Docetaxel for Patients w/Non-Small Cell Lung Cancer	US	Phase II	Non-Randomized	uncontrolled	Open Label	Jin Fu Kang	[88]
Ginger Control of Chemotherapy Induced Nausea and Vomiting	US	Phase II	Randomized	Placebo	Double Blind	Ginger	[89]
Combination Chemotherapy After Surgery With or Without Chinese Herbal Therapy to Treat Symptoms in Women With Breast Cancer	US	Phase I, Phase II	Randomized	Placebo	Double Blind	Chinese herbal therapy (CHT)	[90]
Survey of the Use of Alternative Medical Therapies in Adult Cancer Patients Enrolled in Phase I Clinical Trials	US	Phase I	N/A	N/A	N/A	Alternative Medical Therapies	[91]
Treatment of Anal High-grade Squamous Intraepithelial Lesions (HSIL) Through Use of a Chinese Herbal Topical Cream (AIJP)	US	Phase II	Randomized	Placebo	Double Blind	AIJP (Arnebia Indigo Jade Pearl)	[92]
Study of Botanical PHY906 Plus Capecitabine for Advanced Unresectable Hepatocellular Carcinoma	US	Phase I, Phase II	Non-Randomized	Historical control	Open Label	PHY906	[93]
ACAPHA in Preventing Lung Cancer in Former Smokers With Bronchial Intraepithelial Neoplasia	Canada	Phase II	Randomized	Placebo	Double Blind	multi-herbal agent ACAPHA	[94]
Pycnogenol for the Treatment of Lymphedema of the Arm in Breast Cancer Survivors	US	Phase II	Randomized	Placebo	Double Blind	Pycnogenol	[95]
Siliphos in Advanced Hepatocellular Carcinoma	US	Phase I	Non-Randomized	N/A	Open Label	siliphos	[96]

(Table 6) Contd....

Title	Location	Phase	Allocation	Control	Masking	Drug	Reference
Trial of Blue Citrus Compared to Placebo in Patients Receiving Aromatase Inhibitor Therapy for Estrogen Receptor Positive Post-Menopausal Breast Cancer	US	Phase II	Randomized	Placebo	Double Blind	Blue Citrus	[97]
Angelica Sinensis for the Treatment of Hot Flashes in Men Undergoing LHRH Therapy for Prostate Cancer	Canada	Phase IV	Randomized	Placebo	Double Blind	<i>Angelica Sinensis</i>	[98]
A Safety Study of <i>Lessertia Frutescens</i> in Adults	South Africa	Phase I	Randomized	Placebo	Double Blind	<i>Lessertia frutescens</i> (L.) Goldblatt & J.C. Manning (syn. <i>Sutherlandia frutescens</i> (L.) R. Br.)	[99]
Pilot Study of Curcumin Formulation and Ashwagandha Extract in Advanced Osteosarcoma (OSCAT)	India	Phase I, Phase II	Non-Randomized	uncontrolled	Open Label	Curcumin Formulation, and Ashwagandha Root Powder Extract	[100]

traditional culture and lessons from the forerunners however, more and more scientific evidences have been obtained from *in vitro* studies and in animal models. The US patents have been issued for herbal compositions which were used in the treatment of cancer and cancer-related health problems in the past years. We believe such application for the US patent will be increased. In fact, as the world economic structure changes, the accumulated research results of herbal medicines and market demand on the botanical drugs require more innovative knowledge for patent application [101]. In this review, a total of 15 single pure compounds and 57 herbal compositions from single herbs or herbal mixture in the US patent (granted or under application) were reported for cancer types, anticancer mechanism, cancer-related health problems and the herbal preparation method etc. Although the patents listed in these tables do not cover all patent application situations, they represent some hot research materials and topics in herbal medicines and cancer research, for example, regarding anticancer effect of berberine [7], saponins [8], curcumin [21] in Table 1, we can find over 43, 100 and 204 references respectively from PubMed (date of retrieving with key word as “berberine and anticancer”, “saponins and anticancer” and “curcumin and anticancer” was November 3, 2010).

69% of anticancer drugs approved were either natural products or developed based on knowledge gained from natural products between the 1980s and 2002 [102], which may indicate that drug development based on the components with lead structures of potent bioactivity isolated from medical plants has been a major strategy for developing new anticancer drugs from herbal medicines. However, cancer is a genomic disease associated with multiple risky factors. There are six hallmarks for every type of cancer [103]: self-sufficiency in growth signals, resistance to growth inhibitory signals and anti-cancer therapy, evasion of programmed cell death, unlimited replication capability, sustained ability of angiogenesis, and invasion and metastasis.

The complicated pathology may require multi-targeted treatment in cancer therapy. In the Tables 2, 3 and 4. We summarized the extracts and fractions from herbal medicines, whose therapeutic efficacy is based on the combined action of a mixture of constituents. These extracts and fractions offer new treatment opportunities for cancer in multi-components and multi-targets system. Theoretically, therapeutic principles for multi-components in the extracts and fractions involve bioavailability, interference with cellular transport processes, activation of pro-drugs or deactivation of active compounds to inactive metabolites, inhibition of binding to target proteins, action of synergistic partners at different points of the same signaling cascade or different signaling pathways. It is a pity that many of these extracts and fractions are not yet deeply studied.

Overviewing the listed patents in the tables, many patented single pure compounds and various extracts/fractions from single or composite medicinal herbs are not yet used as drugs for anticancer. There is a long way to go before it becomes a new drug, even though it is just used as botanical drug products. However, these patented materials should not remain unused and more studies should be conducted to get portfolio patents to validate the anticancer application in clinical settings. To push deep studies for these products of the patents, we should focus on preclinical (quality, safety and efficacy) and clinical studies because the lack of pharmacological and clinical data on the majority of herbal medicinal products is a major impediment to the integration of herbal medicines into conventional medical practices [104]. Various "-Omics" technologies and systems biology may facilitate unravelling complicated and/or synergistic effects of herbal mixtures.

Invention and development of PHY906 [73] is a good example for new botanic drug from herbal medicines for increasing the therapeutic index of chemotherapy drugs by administering PHY906 to cancer patients undergoing chemotherapy. PHY906 is a composite formula consisting of

four Chinese medicinal herbs (*Scutellaria baicalensis*, *Glycyrrhiza uralensis*, *Ziziphus jujuba*, and *Paeonia lactiflora*). The first thing is how to guarantee the products in consistency from batch to batch. The inventors have spent as long as ten years to establish and continually improve the platform for quality control of PHY906 [105,106]. At the same time, the inventors did much work for mechanism of action and drug metabolism of PHY906 in *in vitro* and *in vivo* studies for gastrointestinal malignancies [107,108]. The inventors have also finished several phase I/ II clinical trials and demonstrated the potential benefit for advanced hepatocellular carcinoma, advanced pancreatic and other gastrointestinal malignancies in clinical settings [109,110]. This is the first composite formula from Chinese medicinal herbs to be used in carrying out the phase I/II clinical trials in the US and has been recognized with high international reputation [111]. We think these series research for PHY906 will serve as a model for dietary supplements and botanical drug products from herbal medicines in terms of multi-components, quality control, mechanism of action and drug metabolism and translational research.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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