Chemistry and Biological Activities of Selected Popular Chinese Herbs in the US Market

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I. Introduction

Herbs have been used as medicines and functional foods in the Asian world for thousands of years. Before western medicines were introduced into Asia, herbs had been the main weapon in the treatment of diseases and even today remain a main

source of drugs in the primary health-care. Currently over half of the Chinese population use traditional herbal prescription, particularly when western medicines do not appear to be as effective as in the case of the treatment of chronic ailments such as age-related diseases. The Traditional Chinese Medicine (TCM) in China is undergoing a new renaissance as the current Chinese government has recognized that the TCM is a treasure for the nation and can provide both improved health care for its own citizens as well as serving as an excellent source of phytomedicines for the international export market when it is combined with modern science. As a national strategy, the Chinese government is placing much emphasis toward modernizing TCM. The push toward modernization in this field has led to an increase in the use of modern pharmacological experiments, standardization of the active components, identification and use of marker compounds in herbal prescription, establishing fingerprinting profiles (chemically and genetically) for single and blended herbs, and a wide range of other quality related issues that now face the international acceptance and use of TCM. The long history of TCM, and its associated assumption of safety, if not efficacy, has attracted much interest for the European and North American marketplace to examine and use of Chinese herbs for disease prevention and treatment. Consequently, due to perceived consumer demand for these products, many western companies have been importing, promoting and distributing a wide range of Chinese herbs in the western market and this business appears to be quite fruitful. Popular Chinese herbs including ginseng (*Panex ginseng* C. A. May), ginkgo (*Ginkgo biloba*), Dong quai (*Angelica sinensis* (Oliv.) Diels) and Siberian ginseng (*Eleutherococcus senticosius*) are among the top 20 selling herbs in the US market.

Herbal products are marketed in the United States as dietary supplements and not as medicinal plants or medicines. The US Food and Drug Administration (FDA) defines dietary supplements as: *A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.* The dietary supple-

ments are regulated by Dietary Supplement Health and Education Act (DSHEA). The passage of DSHEA has opened up opportunity for a plethora of new herbs onto the US marketplace, and while providing consumers a wider range of options. In this paper, we present general information on a number of popular Chinese herbs in the US market, discuss their current applications, chemistry and pharmacology. We focus our comments on four popular Asian herbs: *Angelica sinensis* (Oliv.) Diels, *Rhodiola rosea*, *Pueraria lobata* and *Panex ginseng* C. A. May. In addition, a popular dietary supplement, resveratrol will be discussed. Commercially, resveratrol is mainly derived from a common TCM, *Polygonum cuspidatum*.

II. *Angelica sinensis* (Oliv.) Diels (Dong Quai or Dang Gui, or Tang Kuei)

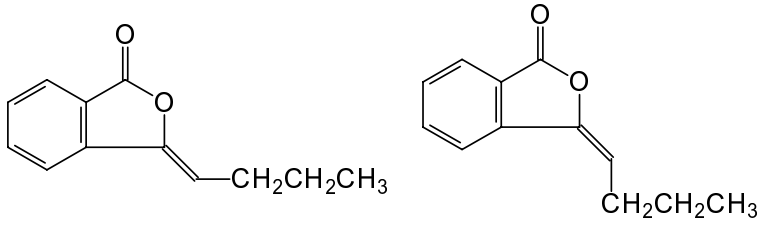
The whole root of this Chinese plant, *Angelica sinensis* (Family: Apiaceae) is used as an herbal medicine in China and is a well recognized tonic herb for women. Traditionally, Dong Quai is used to treat obstetric and gynecological problems and the herb drug acts as a mild laxative, a uterine tonic, antispasmodic, and alterative (blood purifying), increases blood circulation, relaxes the uterus, stabilizes pregnancy, and is used for the regulation of menstrual cycle (A Barefoot Doctors Manual, 1977). Currently, in the US, it is marketed for alleviating female disorders such as premenstrual syndrome, menstrual cramps and to help them with discomfort associated with menopause. Dong Quai is sold as a single herb or herbal extract, or combined with other herbs, such as black cohosh (*Cimicifuga racemosa)*, chase tree berries (*Vitex agnus castus*), blue cohosh (*Caulophyllum thalictroides)* and astragalus (*Astragalus membranaceous)* in complex formulas in the US market.

A. Chemical Components

The investigation of the phytochemistry of *Angelica sinensis* root has revealed the

presence of several distinct groups of chemical compounds (*1-9*).

1. Amino acids: some 20 amino acids have been reported in *Angelica sinensis* with arginine and glutamic acid as the major ones.
2. Essential oils: forty-nine volatile aromatic compounds have been identified by GC-MS with ligustilides (Figure 1) reported as the major constituents.
3. Sterols: *β*-sitosterol, stigmasterol and *β*-sitosterol-D-glucoside has been identified.
4. Fatty acids and organic acids: palmitic acid, linoleic acid, stearic acid, arachidonic acid, ferulic acid and vanillic acid were present.
5. Coumarins: bergaptene, imperatorin, psoralen, osthole, oxypeucedanin, scopoletin, and umbelliferone were present.
6. Polysaccharides were identified.
7. Other components: E232, angelicide, brefeldin A, tetradecan-1-ol, tetramethylpyarazine were present.



ligustilide *E*-ligustilide

Figure 1. Structures of ligustilide and E-ligustilide

B. Biological activity

The extracts of *Angelica sinensis* showed antiarrhythmic effects on adrenaline induced arrhythmia in cats (*10*). Dong Quai was also found to improve the blood circulation of the injured nerve (*11*), to regulate LPS-induced elevation of Ca^{2+} intracel-

lular level of alveolar macrophages and may inhibit non-specific inflammation of airways in chronic bronchitis (*12*), to protect the human vascular endothelial cell from the effects of oxidized low-density lipoprotein *in vitro* (*13*), to enhance gastric ulcer healing in rats and promote wound repair in RGM-1 cells (*14*) and to stimulate the proliferation, alk. phosphatase (ALP) activity, protein secretion and particularly type I collagen synthesis of human osteoprecursor cells (OPC-1) (*15*).

The *Angelica sinensis* polysaccharides were found to decrease colony formation in spleen hematopoietic tissue of irradiated mice (*16*), to increase the proliferation of several types of precursor cells in healthy and anemic mice and increase hematopoisis (*17*) and showed protective effects on gastrointestinal damage induced by ethanol or indomethacin in rats (*18*), protective effects on hepatic injury induced by acetaminophen in rodents (*19*), anti-anemic and immunofunction regulating activities (*20*), an extensive effect on immunocompetence (*21*), promoting gastric ulcer healing (*22*) and augmenting mice splenocyte proliferation, released IFN-γ and increased IFN-γ bioactivity (*23*).

Recent study also showed that Angelica root and its active components have the ability to inhibit the aggregated amyloid β-peptide (agg Aβ1-40) induced damage of differentiated PC-12 cells (dPC-12), a well-known cell model for Alzheimer disease. Four compounds showing potent activity were identified as *Z*-ligustilide, 11-angeloylsenkyunolide F, coniferyl ferulate and ferulic acid. They were found to significantly inhibit Aβ1-40 toxicity on dPC-12 cells at lower concentrations of 1–10 μg/m (*24*)

III. *Rhodiola rosea* (Golden root, Roseroot, Hong Jing Tian)

The genus of Rhodiola consists of over 200 species, most found in Asia, and many used in traditional Chinese Medicine. In TCM, Rhodiola is used as a general

tonic in the treatment and invigoration of the human body. In the old traditional Chinese medicine pharmacopoeias such as the "Ben Cao", Rhodiola was documented to prolong human life, to enhance the Qi in human body and keep human's body light. In the US market, the best-known Rhodiola species is *Rhodiola rosea* L., also known as golden root or roseroot. *Rhodiola rosea* grows primarily in dry sandy ground at high altitudes in the Arctic areas of Europe and Asia. The plant is perennial with a thick rhizome, which is used as the herbal drug. Rhodiola was first introduced into the US market by Russians as extracts of the *Rhodiola. rosea* root had been long researched and found to contain powerful adaptogens in Russia. In the US, Rhodiola is marketed and sold as a product to improve mental health, and adaptogenic, anti-stress and cardioprotective agents. Rhodiola is sold as single herbal extract though it can be found combined with other well known adaptotenic herbs such as ginseng and Siberian ginseng.

A. Chemical components

The investigation of the phytochemistry of *Rhodiola rosea* root has revealed the presence of several distinct groups of chemical compounds (*25-28*).

1. Phenylpropanoids: rosavin, rosin, rosarin were present (Figure 2).
2. Phenylethanol derivatives: salidroside (Figure 2), tyrosol were present.
3. Flavanoids: acetylrodalgin, kaempferol, kaempferol 7-rhamnoside, rodiolin, rodionin, rodiosin, tricin; tricin 5-glucoside, tricin 7-glucoside have been identified.
4. Monoterpenes: such as rosiridol, rosaridin were present.
5. Sterols: daucosterol, β-sitosterol were present.
6. Phenolic acids: chlorogenic acid, hydroxycinnamic acis, gallic acid have been identified.
7. Polysaccharides.
8. Tannins.

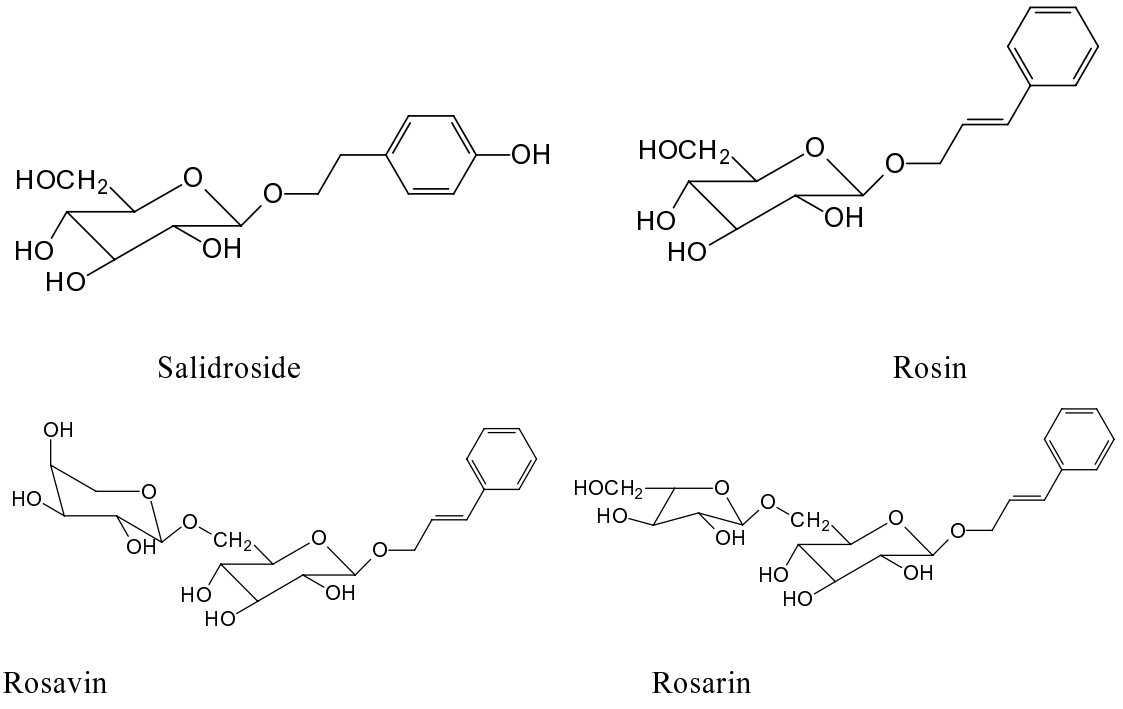


Figure 2. Structures of marker compounds in Rhodiola rosea

B. Biological activities

Extracts of *Rhodiola rosea* exhibited adaptogenic effects in mice and rabbits (*29*), cardio-protective and antiaderenergic activity during stress (*30*). One standardized extract SHR-5 was reported to significantly relieve stress-induced fatigue in a double blind cross-over study (*31*). An alcohol-aqueous extract (1:1) was found to improve learning and long-time memory in mice (*32*). Rhodiola extracts were also reported to prevent ischemic brain damage development (*33*), to scavenge free radicals (*34*), to show anti-tumor effect in experiments on inbred and noninbred mice and rats with transplantable NK/Ly tumor, Ehrlich's adenocarcinoma, melanoma B16 and Lewis lung carcinoma (*35*). In a small clinical trial with 12 superficial bladder patients, the

oral administration of Rhodiola extract was found to improve the characteristics of the erothelial tissue integration, parameters of leukocyte integrins and T-cell immunity and average frequency of relapses for these patients has been found to fall twice (*36*).

Neuroprotective effects of the major component of Rhodiola, salidroside have been studied. The salidroside was found to protect the PC12 cells against hypoglycemia and serum limitation-induced cytotoxicity possibly by the way of the modulation of apoptosis-related gene expression, the restoration of the mitochondrial membrane potential, and the inhibition of the intracellular ROS production (*37*). Similarly, the treatment of PC12 cells with salidroside can block H_2O_2-induced apoptosis by regulating Bcl-2 family members and by suppressing cytochrome c release and caspase cascade activation (*38*). Recent research also suggested that the extract of Rhodiola significantly extend the lifespan of the fruit fly, *Drosophia melanogaster* (*39*).

IV. *Pueraria lobata* (Kudzu, Ge Geng)

Kudzu is one of the earliest medicinal plants that has been used in TCM thousands of years ago. The roots of kudzu have been used as anti-diarrhetic, antipyretic, diaphoretic, and anti-emetic agents and to treat alcohol-related problems (intoxication and alcohol-abuse). Currently, kudzu is marketed as a rich source of isoflavones, as an herb for women's health and as an anti-alcohol abuse plant material. As a plant for women's health, this herbal drug is formulated together with soy isoflavone extract, red clove isoflavone extract and chase tree berries.

A. Chemistry

The chemistry of kudzu has been studied extensively. The major components were isoflavones and saponins (*40-48*) including:

1. Isoflavones: Puerarin (Figure 3), daidzin, daidazein-4, 7-diglucoside, 6,7- dimethoxy-3',4'-methylenedioxyisoflavone, formononetin, mirificin, 3'-methoxy puerarin, genistein 8-C-glucoside, genistin, genistein, 6"-O-malonyldaidzin, 3'-hydroxy-4'-*O*-β-D-glucosylpuerarin and 3'-methoxydaidzin have been identified.
2. Chalcones: isoliquiritigenin was present.
3. Aromatic glycoside: pueroside-A and –B**,** but-2-enolides, sophoroside A.
4. Sterols: β-sitosterol, daucosterol have been identified.
5. Saponins: kudzusaponins A1, A2, A3, A4, A5, SA1, SA2, SA3, SA4, SB1 and C1, soyasaponins SA3, and I have been identified.
6. Tryptophan derivatives: PF-P was present.
7. Volatile compounds: such as methyl palmitate, dimethyl suberate and furfuryl alcohol were present.

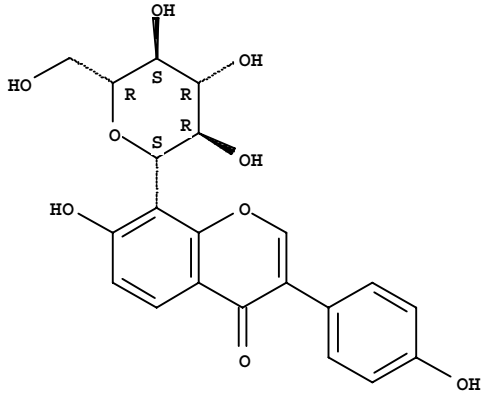


Figure 3. Structure of Puerarin

B. Biological activities

Kudzu extracts have shown antimutagenic activity (*49*), antidipsotropic activity (*50*) and suppressed alcohol preference in a pharmacogenetic rat model of alcoholism (*51*). The flavone extracts of kudzu affect coronary circulation, cardiac hemodynamics

and myocardial metabolism in dogs and show hypotensive effect on anesthetized dogs and unanesthetized, hypertensive dogs, decreased vascular resistance in anesthetized dogs, and increased peripheral and cerebral circulation (*52,53*). Puerarin showed stimulatory effect on α_{1A}-adrenoceptor to increase glucose uptake into cultured C_2C_{12} cells of mice (*54*). Puerarin, daidzin and daidzein showed antiinebriation and the anti-dipsotropic effects (*55*). Biochanin A isolated from Kudzu root displayed the most active inhibition on arachidonic acid release in HT-29 human colon cancer cells, and exhibited its most potent suppression in RAW 264.7 cell without showing cytotoxicity (*56*).

V. Ginseng (*Panax ginseng* C. A. May)

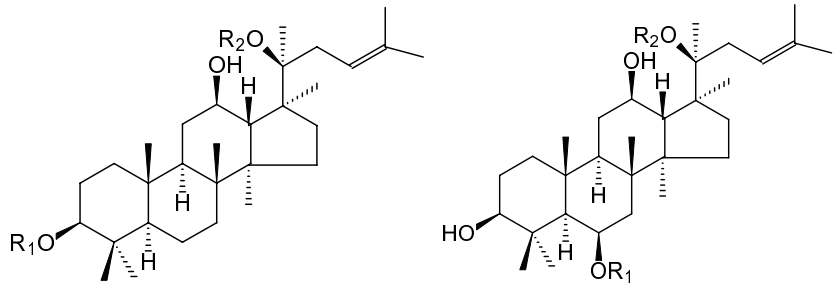
Ginseng (*Panex ginseng* C. A. May) is the most valuable TCM herb. It is not only widely used by Asian countries, such as China, Korea and Japan, but also widely used in many western countries. For thousands of years, ginseng has been used as a tonic to increase nonspecific resistance against a wide array of various stress agents, to prevent and cure many health conditions, and has been used as an emergency medicine to save dying patients. In the US, it is marketed to improve mental performance in times of stress, to enhance overall health and vitality, to improve resistance to the damaging effects of stress, and to increases endurance. Ginseng is used and marketed as a major tonic, stimulant, and immune booster. Ginseng is available in the US market in a myriad of products as a powder, extract (7% ginsenosides and 15% ginsenosides extract), or combined with other herbs such as American ginseng, Rhodiola, Siberian ginseng and various vitamins. The dosage varies based upon each of its formulations.

A. Chemical components

The chemistry of ginseng has been extensively studied, and the main components

include saponins and polysaccharides (*57-59*).

1. Saponins: about 30 saponins have been purified from the root of ginseng with Ginsenoside, Rg_1, Re, Rb_1, Rc, Rd and Rf as the major saponins (structures are shown in Figure 4) have been identified in root extracts.
2. Sterols: β-sitosterol, stigmasterol, campesterol were present.
3. Polyalkynes: heptadeca-1-en-4,6-diyne-3,9,10-triol, panaxynol, panaxynol, panaxydol, and panaxytriol, ginsenoynes A, B, C, D and E have been identified.
4. Fatty acids: linoleic acid, palmitic acid, oleic acid, and linolenic acid were present.
5. Amino acids.
6. Peptides.
7. Polysaccharides.



Rb1	Glc(2-1)Glc	Glc(6-1)Glc	Re	Glc(2-1)Rha	Glc
Rb2	Glc(2-1)Glc	Glc(6-1)Ara(p)	Rf	Glc(2-1)Glc	H
Rc	Glc(2-1)Glc	Glc6Ara(f)	Rg1	Glc	Glc
Rd	Glc(2-1)Glc	Glc			

Figure 4. Structures of the major ginsenoside in Asian ginseng root.

B. Biological activities

Extensive pharmacological studies have been reported on ginseng powder, ginseng extracts and ginseng components (*58,59*). Ginseng was found to improve different aspects of cognitive performance of healthy young adult (*60*), and to result in a reduction of bile flow and bile secretion of total lipids and cholesterol, while increase the secretion of proteins in a dose-dependent manner (*61*). The butanol fraction of ginseng was found to inhibit gastric damage (*62*). Ginseng saponins were discovered to contain components potentiating the apoptosis of MMS-exposed NIH3T3 cells via p53 and p21 activation, accompanied with by down-regulation of cell cycle-related protein expression (*63*), protecting hippocampal CA1 and CA3 cells against KA-induced neurotoxicity (*64*) and inhibiting EGF-induced cell proliferation via decrease of c-fos and c-jun gene expression in primary cultured rabbit renal proximal tubular cells (*65*). Ginsenoside Rb1, Rg3, and Panax ginseng butanol fraction showed strong inhibitory effects on inflammatory mediators from LPS-stimulated RAW 264.7 cells (*66*). Topical application of ginsenosides significantly attenuated ear edema induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and ginsenosides also suppressed expression of cyclooxygenase-2 (COX-2) and activation of NF-κB in the TPA-treated dorsal skin of mice (*67*). The total ginseng saponins and ginsenoside Rb1 and Rg1 showed neuro-protective effects on spinal cord neurons, with Rb1 and Rg1 protecting spinal neurons from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by H_2O_2 (*68*). Rb1 showed nootropic properties (*69*), ginsenoside Rb2 showed epidermis proliferative effect (*70*) and ginsenoside Rg(2) blocked the nicotinic acetylcholine receptors in bovine chromaffin cells (*71*). Ginsenoside Rg3 was found to modulate Ca^{2+} channel currents in rat sensory neurons (*72*) and to inhibit N-methyl-D-aspartate (NMDA) receptors (*73*).

V. Resveratrol and *Polygonum cuspodatum*

Resveratrol (3,5,4′-trihydroxystilbene) (Figure 5) is a compound found mainly in the skin of grapes, peanuts, mulberries, disease resistance to plants (*74*). The epidemiologic finding of an inverse relationship between consumption of red wine andmortality rates from cardiovascular disease and certain cancers has been called the "French paradox". The growth-inhibitory effects of resveratrol are mediated through induction of apoptosis and cell cycle arrest in both rat and human cancer cells. Resveratrol-induced apoptosis has been repeatedly reported to be accompanied by increased caspase activity, up-regulation of p53, Bax, down-regulation of Bcl-2, Bcl-X_L, survivin, and cIAPs in a variety of human cancers. Resveratrol caused cell cycle arrest via up-regulation of p21, p27, p16, and down-regulation of cyclin D1, cyclin E, Cdk2, Cdk4, Cdk7 in human colon carcinoma cells (*75*). Resveratrol has also been shown to induce GSH synthesis through activation of Nrf2 (*76*). Furthermore, resveratrol induced S phase arrest through ATM/ATR-Chk1/2-Cdc25C pathway (*77*). Resveratrol treatment induced apoptosis in DMBA/TPA induced mouse skin tumorigenesis through mitochondrial pathway (*78*). On the other hand, in vitro and animal experiments have shown that it exhibits many biological effects such as protection against atherosclerosis, antioxidant activity, inhibition of platelet aggregation, and antimutagenic and anticarcinogenic properties (*74,79*).

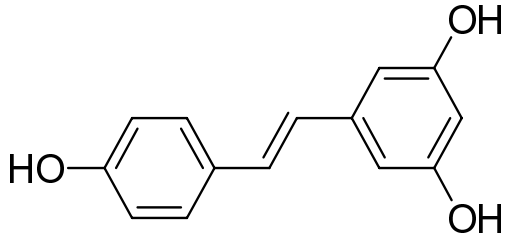


Figure 5. Structure of resveratrol

However, the main reason that reveratrol gains much popularity in the US market in the past two years is due to its reported anti-ageing activities. Wood et al. (*80*) reported that resveratrol activated sirtuins (Sir2) in the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila*, and extend their lifespan. The capacity of resveratrol to increase lifespan was later verified in further studies (*81-83*).

Since the contents of resveratrol in grapes and peanuts are relatively small, the commercial source of resveratrol is obtained from a TCM plant, the dried roots of *Polygonum cuspidatum* Sieb. Et Zucc. Roots of *Polygonum cuspidatum* contain cis- and trans-resveratrols and their corresponding glucosides (*84*).

VI. Concluding remarks on TCM quality

As Chinese herbal medicines move into the US markets, and into the dietary supplement mainstream, the value of these products to the health care industry and to consumers will be predicated largely on their proper use, additional scientific studies using both animal and human studies to evaluate efficacy, and ensuring that a quality product reaches the consumer. Issues and problems that now surround these medicinal plants include lack of botanical authentication; lack of natural product standardization whether for a single, blended or complex herbal mix; and the spiking or adulteration of final products. Other product problems on Asian herbs such as the presence of undesired heavy metals, pesticides and nontarget plant debris in the final products are also part and parcel of such a QC imperative, though not addressed in this brief overview. All of these issues can be minimized or eliminated with a strong scientific-driven quality control program that if implemented can further promote Chinese Traditional Medicines to the mantle it richly deserves within an integrated western health care system.

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