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International Journal of Pharmacognosy & Chinese Medicine
ISSN: 2576-4772

Astragalus Membranaceus and *Salvia Miltiorrhizae*: An Overview of Ethnopharmacology and Phytochemistry

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Review Article

Volume 7 Issue 2

Received Date: July 31, 2023

Published Date: November 08, 2023

DOI: 10.23880/ipcm-16000252

Abstract

Mostly a common argument is made against use of plant - based alternative and complementary medicine such as Traditional Chinese Medicine (TCM) that their use is based on empiricism, which is considered by adherents of conventional medicine to be unscientific and anti intellectual. It is in this light that the onus now is on natural product scientists to prove the superiority of plant-based medicines as epitomized by TCM through expanding knowledge on the superiority of medicinal plants as the mainstay of human pharmacopoeia. Major scientific databases including but not limited to Scopus, PubMed, PubMed Central, Web of Science, Web of Science Core Collections, Google Scholar, Science Direct etc were critically searched by using a combination of terms. Precisely, *Salvia miltiorrhiza* and *Astragalus membranaceus* were searched from the various databases in combination with chemical composition, isolated compounds, medicinal uses, bioactivity, ethnopharmacology, chemical elucidation using the Boolean operators. It was observed that the two medicinal plants are phytochemically rich with diverse phytocompounds. Most of the phytocompounds isolated from the two medicinal plants were structurally elucidated together with their key biological properties. Most of the compounds from the two medicinal had their anti-cancer properties demonstrated *in vitro* and *in vivo*. Herewith, this review highlighted the centrality of *Astragalus membranaceus* and *Salvia miltiorrhizha* as key sources of bioactive compounds with demonstrable anti-cancer and anti-inflammatory properties.

Keywords: Astragalus Membranaceus; Bioactivity; Chinese Herbal Medicine; Danshen; Huan Qi; Salvia Miltiorrhiza

Abbreviations: TCM: Traditional Chinese Medicine; CHM: Chinese Herbal Medicine; GABA: Gamma Amino Butyric Acid; APS: Astragalus Polysaccharide; ML: Magnesium Lithospermate; MTB: Magnesium Tanshinoate B; DI: Dihydrotanshinone I; CT: Cryptotanshinone; DHTS: Dihydrotanshinone I; STS: Sodium Tanshinone IIA Sulfonate; CASE: Compound Astragalus and Salvia Miltiorrhiza Extract; MAPK: Mitogen Activated Protein Kinase; Hscs: Hepatic Stellate Cells; PAI-1: Plasminogen Activator Inhibitor; Protein; TGF-B: Transforming Growth Factor Beta; DEN: Diethylnitrosamine; HCC: Hepatocellular Carcinoma; HA: Hyaluronic Acid.

Introduction

The ethnobotanical heritage of Asia, specifically China from antiquity has been incorporated into important traditional healing systems such as Traditional Chinese Medicine (TCM). Chinese herbal medicine (CHM) has been practiced more than two millennia with a lot of success in terms of efficacy for many clinical disease conditions. Currently, it is one of the most popular complementary medicines in the world. Traditional Chinese herbal medicine use and practice embodies accumulation of empirical evidence, theoretical assumptions, and philosophical thoughts in relation to man, disease, and herbs. Importantly, the choice and selection of

herbs for the treatment of any particular disease is guided by a system of herbology. Mostly, the main herb for the treatment of the disease, which is figuratively referred to as the 'emperor herb' or 'king herb' is first chosen followed by other herbs, which play various auxiliary functions such as enhancing target site recognition, aiding absorption, reducing toxicity, potentiating the effect of the 'king herb' etc.

Indeed, use of herbs as food and medicine is well entrenched in China. Currently, many studies are not only validating the ethnobotanical claims of Chinese herbs but also exploring the pharmacology, safety, efficacy, and molecular mechanisms of action of some of these herbs. This new trend is welcoming, especially at a time when international demand for Chinese herbal products is soaring. Two of the Chinese herbs, which have enjoyed long uneventful use in traditional Chinese herbal medicine for the treatment of various diseases including cancer, are *Astragalus membranaceus* and *Salvia miltiorrhiza*. This review highlights the biological properties, phytochemical profile and drug discovery prospects of *Astragalus membranaceus* and *Salvia miltiorrhiza*.

Astragalus Membranaceus

Astragalus membranaceus (Bunge) is an age old medicinal herb with immense ethnobotanical usage in China and other Asian countries. In view of its usefulness as a medicinal herb, it has many common names in different Asian countries [1]. For example, 'huang qi' (Chinese), 'hwangqi' (Korea) and commonly referred to as membranous milk-vetch root in English. *A. membranaceus* is referred to as Radix Astragali in most Chinese literatures including the pharmacopoeia of the People's Republic of China, 2005.

Traditional Uses of *Astragalus membranaceus*

The traditional medicinal uses of *A. membranaceus* are well documented in TCM application. For instance, it has been prescribed over thousands of years for general weakness, chronic illness and also to improve general vitality. Also, ancient Chinese writings have recorded the use of Astragalus as having a tonic effect on the spleen, blood and 'qi'. It tonifies the qi of the spleen [2], improves the 'yang qi' of the spleen and stomach, tonifies lung 'qi', cold, sweating, and shortness of breath. Also, it treats night sweat, chronic ulcerations and sores, numbness, limb paralysis and edema [2,3].

The genus Astragalus comprises over 2,000 species distributed worldwide [3]. Most studies on *A. membranaceus* have concentrated on its immuno - modulatory polysaccharides. Also, other studies have demonstrated effects of non-polysaccharide phyto-components on immune deficiency disorders. It is therefore not surprising that various formulations of *A. membranaceus* are currently being used in China and other countries as adjunctive therapy in the management of cancers. Also, it is used to improve functional capacity of many organs such as the heart, liver and kidneys in view of its adaptogenic properties [4].

Parts of a Membranaceus Used in TCM

Dry roots, powdered or in decoction is used for most of its traditional medicinal applications. It is also used in combination with other Chinese medicinal herbs in various combinations to achieve a specific therapeutic objectives [4].

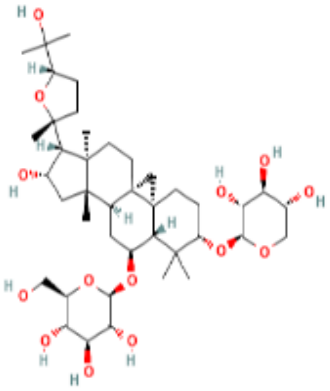
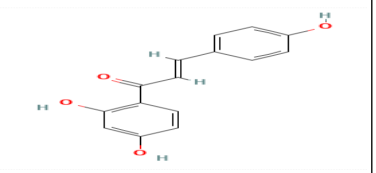
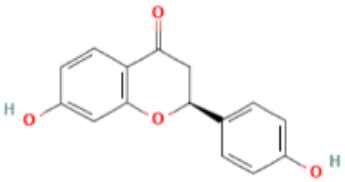
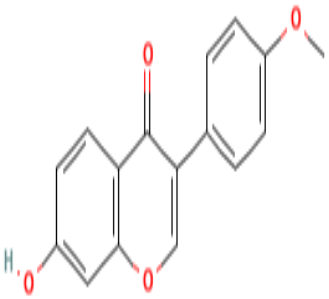
Phytochemical Composition of a Membranaceus

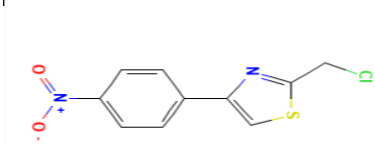
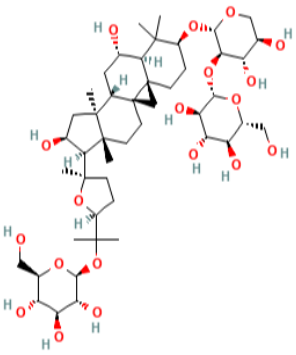
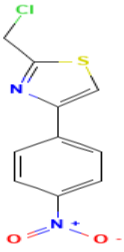
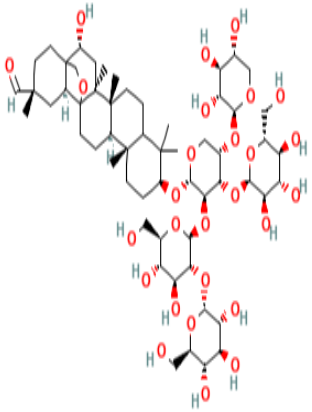
The major phytocompounds well characterized in *A. membranaceus* include, polysaccharides, saponins, flavonoids, amino acids and some trace elements [5]. The polysaccharides of *A. membranaceus* that have received much investigative attention includes polysaccharide fraction F3, polysaccharides A, B and C (Identified as glucans), and polysaccharides D (A heteropolysaccharides) [5]. Also, the roots of *A. membranaceus* were shown to contain a series of cycloartene triterpene glycosides, also identified as astragalosides I – VII (Saponins). Their structures are based on the aglycone cycloastragenol and were shown to contain 1-3 sugars located on 3-, 6-, and 25- positions [6].

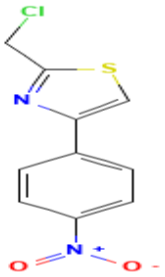
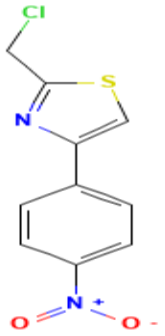
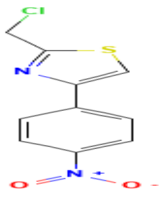
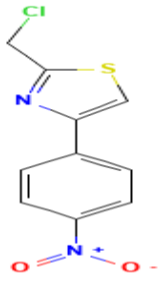
Additionally, several other saponins have been reported with their structures based on the oleanene skeleton [6]. The flavonoids identified in the roots of *A. membranaceus* by using high performance liquid chromatography - electrospray ionization mass spectrometry include calycosin-7-0-beta-D-glucoside, calycosin-7-0-beta-D-glucoside-6'-0-malonate (2), ononin, (6aR, 11a R)-3-hydroxy-9, 10-dimethoxypterocarpan-3-0-beta-D-glucoside, Calycosin, (3R)-7, 2'-dihydroxy-3', 4'-dimethoxy-isoglyvan-7-0-beta-D-glucoside, formononetin-7-O-beta-D-glucoside-6'-O-malonate, and formononetin [7]. Other phytochemicals identified in *A. membranaceus* are phytosterols (A volatile oil), amino acids (e.g. Gamma amino butyric acid (GABA)), L-canavanine, zinc, iron, copper, magnesium, manganese, calcium, potassium, sodium, colbalt, rubidium, molybdenum, chromium, vanadium, tin, silver, tantalum, hafnium, europium, thorium [7]. Organic compounds from the roots of *A. membranaceus* include choline, betaine, gluconic acid, β - sitosterols, aromatic compounds (Essential oil linoleic acid, bitter compounds, and asparagine).

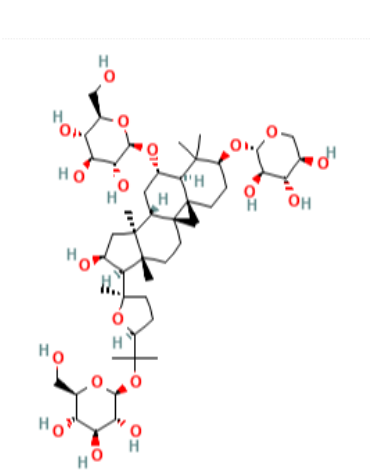
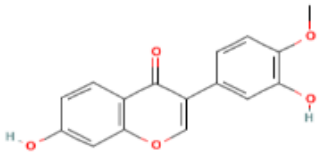
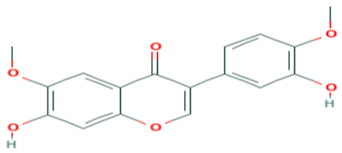
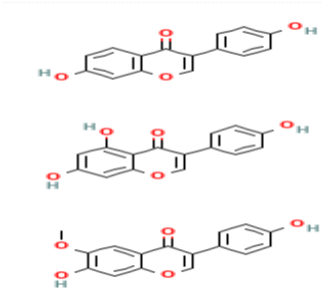
Biological Activities of a Membranaceus

Due to the usefulness of *A. membranaceus*, a number of studies have investigated its biological and pharmacological properties in a view to explain some of its ethno-medicinal claims and uses as elaborated (Table 1).

Name of Isolated Compound	IUPAC Name of Isolated Compound	Chemical Formula of Isolated Compound	Chemical Structure of Isolated Compound	Bioactivity of Isolated Compound	Reference
Astragaloside I	(2*R*,3*R*,4*S*,5*S*,6*R*)-2-[[(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-14-hydroxy-15-[(2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-7,7,12,16-tetramethyl-6-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxy-9-pentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}]octadecanyl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	**C41 H68 O14**		**Immuno modulation** Increase proliferation and antibody production from T- and B-lymphocytes	[8]
Isoliquiritigenin	(*E*)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one	**C15 H12 O4**		**Anti-inflammatory** Inhibits IL-6, IL-12 p40, and TNF-a	[9]
Liquiritigenin	(E)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one	**C15 H12 O4**		**Anti-inflammatory** Inhibits IL-6, IL-12 p40, and TNF-a	[9]
Formononetin	7-hydroxy-3-(4-methoxyphenyl) chromen-4-one	**C16 H12 O4**		**Anti-cancer** initiates growth-inhibitory and pro-apoptotic activities in human colon cancer cells **Anti-angiogenic property** downregulated the expression of the key pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and matrix metalloproteinases	[10]

Astragalus Polysaccharide (APS)	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		**Macrophage activation** stimulates macrophages to express iNOS (inducible NO synthase) gene through the activation of NF-κB/Rel (nuclear factor-κB/Rel).	[11]
Astragaloside V	(2*S*,3*R*,4*S*,5*S*,6*R*)-2-[(2*S*,3*R*,4*S*,5*R*)-2-[[(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-9,14-dihydroxy-7,7,12,16-tetramethyl-15-[(2*R*,5*S*)-2-methyl-5-[2-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxypropan-2-yl] oxolan-2-yl]-6-pentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}]octadecanyl] oxy]-4,5-dihydroxyoxan-3-yl] oxy-6-(hydroxymethyl)oxane-3,4,5-triol	**C47 H78 O19**		**Inhibition of advanced glycation end product (AGE)** inhibits the formation of N^E - (carboxymethyl) lysine (CML) and pentosidine	[12]
Astragalus Polysaccharide (APS)	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		**Renal protective effect (glomerulonephritis therapeutic potential)** significantly decreased the proteinuria and morphological changes on glomerulonephritis rats	[13]
Astragalus Saponin I	(2*R*,4*S*,5*R*,10*S*,13*R*,14*R*,18*S*,20*R*)-10-[(2*S*,3*R*,4*S*,5*S*)-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-4,5-dihydroxy-6-(hydroxymethyl)-3-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxyoxan-2-yl] oxy-4-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxy-5-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl] oxyoxan-2-yl]oxy-2-hydroxy-4,5,9,9,13,20-hexamethyl-24-oxahexacyclo[15.5.2.0^{1,18}.0^{4,17}.0^{5,14}.0^{8,13}] tetracosane-20-carbaldehyde	**C58 H94 O24**		**Anti-Diabetic Nephropathy** reduced oxidative stress intensity, and the blood glucose level of Diabetic Nephropathy rats. Reduced microalbuminuria level, advanced glycated end-products either in serum or in kidney cortex, and the aldose reductase activity. The expression of transforming growth factor Beta-1 mRNA in kidney cortex by RT-PCR analysis was markedly declined. Both the relative grade of mesangium hyperplasia by microscopical observation and the thickness of glomerular base membrane by electron microscope measurement were decreased significantly	[14]

Water-soluble polysaccharide (RAP)	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		**immunomodulating effects** stimulates the proliferation of human peripheral blood mononuclear cells and enhances its interleukin production.	[15]
Astragalus polysaccharide (APS)	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		**Growth-promoting effect.** enhances ileal digestabilities and serum concentrations of amino acids in early weaned piglets regulates amino acid metabolism to beneficially increase the entry of dietary amino acid into the systemic circulation	[16]
Astragalus polysaccharide (APS)	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		Activates Mouse B cells and macrophages	[17]
(Acidic Polysaccharide (AMon-S))	2-(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole	**C10 H7 CIN2 O2 S**		significant reticuloendothelial system-potentiating activity	[18]

Astragaloside VII	(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(hydroxymethyl)-6-[[(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-14-hydroxy-7,7,12,16-tetramethyl-15-[(2*R*,5*S*)-2-methyl-5-[2-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl]oxypropan-2-yl] oxolan-2-yl]-6-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxy-9-pentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}] octadecanyl]oxy]oxane-3,4,5-triol	**C47 H78 O19**		**Immunomodulatory and anticancer effects.** prominent IL-2 inducing activity; IL-2 has shown powerful immuno stimulatory and antineoplastic properties	[19]
Afrormosin	7-hydroxy-6-methoxy-3-(4-methoxyphenyl) chromen-4-one	**C17 H14 O5**		**Anti-oxidant**	[20]
Calycosin	7-hydroxy-3-(3-hydroxy-4-methoxyphenyl) chromen-4-one	**C16 H12 O5**		**Anti-oxidant**	[20]
Odoratin	7-hydroxy-3-(3-hydroxy-4-methoxyphenyl)-6-methoxychromen-4-one	**C17 H14 O6**		**Anti-oxidant**	[20]
Isoflavones	 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one;7-hydroxy-3-(4-hydroxyphenyl) chromen-4-one;7-hydroxy-3-(4-hydroxyphenyl)-6-methoxychromen-4-one	**C17 H14 O6**		**Anti-oxidant**	[20]

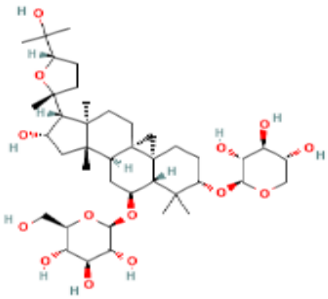
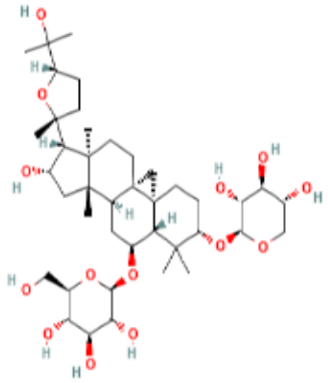
Astragaloside IV	(2*R*,3*R*,4*S*,5*S*,6*R*)-2-[[(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-14-hydroxy-15-[(2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-7,7,12,16-tetramethyl-6-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxy-9-pentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}]octadecanyl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	C41 H68 014		**Anti-inflammatory action** Inhibit NF-κB and expression of adhesion molecules in LPS-stimulated endothelial cells.	[21]
Astragaloside IV	(2*R*,3*R*,4*S*,5*S*,6*R*)-2-[[(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-14-hydroxy-15-[(2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-7,7,12,16-tetramethyl-6-[(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxyoxan-2-yl]oxy-9-pentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}]octadecanyl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol	**C41 H68 014**		**Anti-inflammation action** Suppress airway inflammation and hyper-responsiveness in chronic asthma animal model	[22]

Table 1: Isolated Compounds from *Astragalus membranaceus.*

Herb Drug Interactions Involving a Membranaceus

Not much scientific reports are currently available regarding herb-drug interactions involving *A. membranaceus*. However, there are some few reports that seem to indicate possible herb-drug interactions involving *A. membranaceus*. For example, it was demonstrated that effect of recombinant IL - 2 was potentiated 10 fold by Astragalus extracts [23]. Similarly, the effect of recombinant IL - 1 was shown to be improved by Astragalus extracts in chronic viral cervicitis [24]. Speculatively, Astragalus extracts were said to have the potential to reduce immunosuppressive effects of corticosteroids and cyclosporine and this view was based on the T cell stimulatory effect of Astragalus extracts.

Toxicity related effects of A. membranaceus So far, there has not been any toxicity reports associated with the use of *Astragalus membranaceus* preparations in both pre - clinical and clinical studies, largely confirming its long uneventful ethnobotanical usage. Indeed, Astragalus is safe, in view of the fact that doses as high as 100 mg/kg administered to rats produced no observable adverse effects. In a study involving use of mice, the LD_{50} for Astragalus was determined to be almost 40 g/kg when administered through the intra peritoneal route yet presented no observable adverse effects or organ related toxicities.

Salvia Miltiorrhiza

S. miltiorrhiza is an important Asian medicinal herb, common in China. In China, *S. miltiorrhiza* is integral in traditional Chinese herbal medicine. It is perhaps for this reason that it is prominently captured in the Chinese herbal pharmacopoeia as 'Danshen'. Indeed, *S. miltiorrhiza* has many folk uses as well as demonstrated therapeutic application in China and other countries.

Traditional Uses of *S. Miltiorrhiza*

Locally, in China various formulations of *S. miltiorrhiza* have been used primarily to treat coronary heart diseases, myocardial infarction, and hypertension [25-27]. 'Huoxue Huayu' (TCM - promote blood circulation and removes blood stasis), used over 1000 years [28].

Ecological Distribution of *S. Miltiorrhiza*

S. miltiorrhiza is widely distributed in Asia, particularly in China.

Parts of S Miltiorrhiza Used in TCM

In most historical documentations on the medicinal uses of *S. miltiorrhiza* as well as pre -clinical and clinical

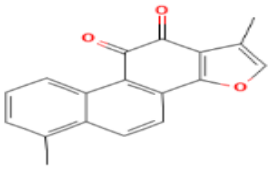
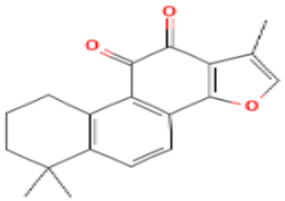
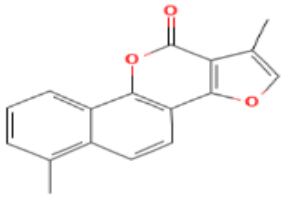
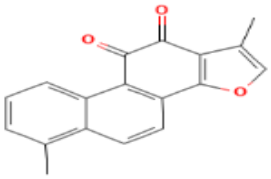
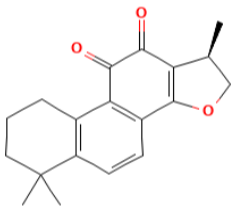
studies, the dry roots are normally used [29,30].

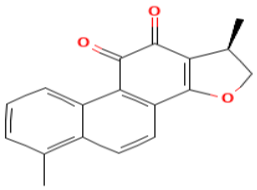
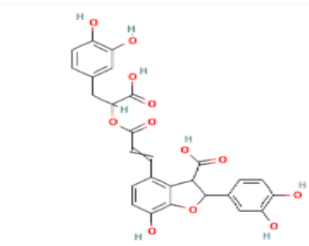
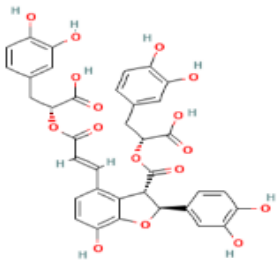
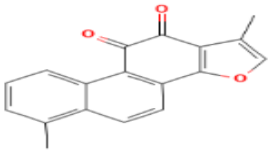
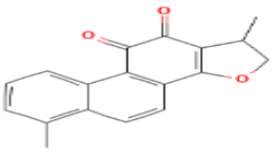
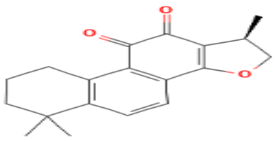
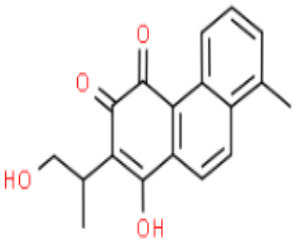
Phytochemical Composition of *S. Miltiorrhiza*

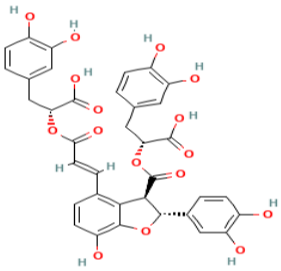
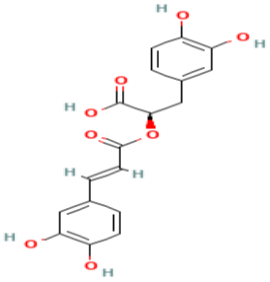
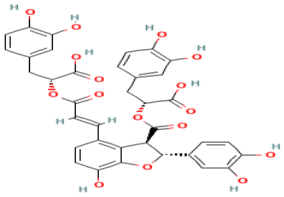
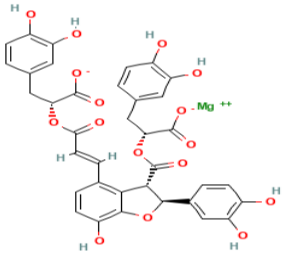
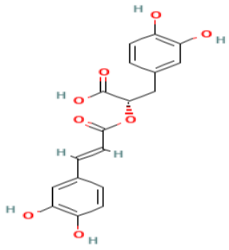
Well over 80 different phyto-compounds are reportedly identified from *S. miltiorrhiza* [30]. Of these 80 phytochemicals 50 were identified as water soluble while the remaining were said to be fat – soluble [31]. The water - soluble compounds comprises mainly polyphenolic acids, of which the main ones are salvianolic acids, protocatechuic aldehyde, salvianolic acid A and B [31]. On the other hand, the fat - soluble phytochemicals are mainly diterpenes of the tanshinone subclass, which includes tanshinone IIA and cryptotanshinone. Other phytochemicals of *S. miltiorrhiza* includes beta - sitosterol, ursolic baicalin, tannins and vitamin E [28].

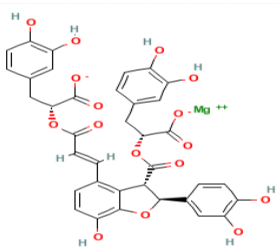
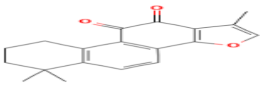
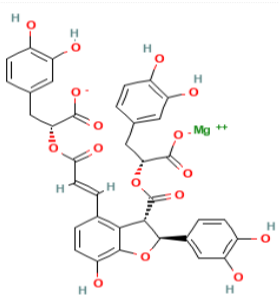
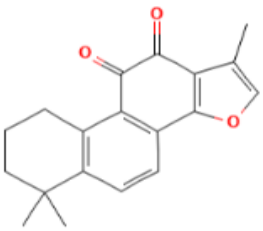
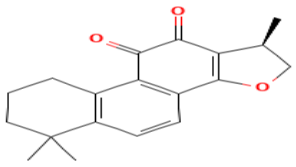
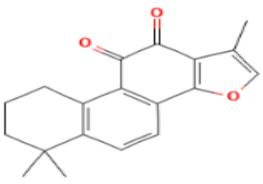
Biological and Pharmacological Properties of *S. Miltiorrhiza*

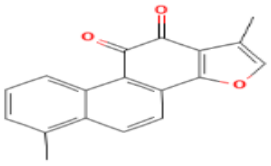
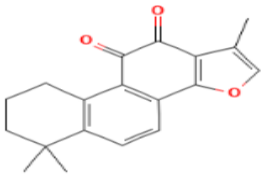
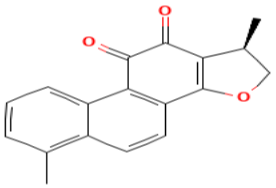
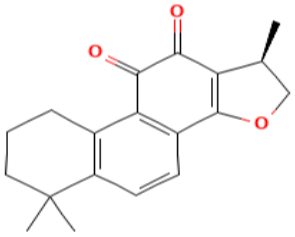
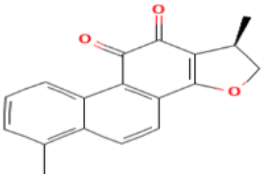
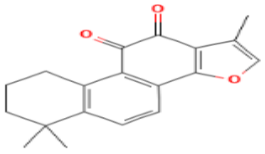
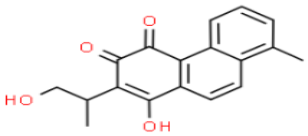
Various preparations of *S. miltiorrhiza* have been reported in cell, animal as well as clinical studies. Importantly, the various biological activities of *S. miltiorrhiza* have been attributed to its phyto-constituents Table 2.

Name of Isolated Compound	IUPAC Name of Isolated Compound	Chemical Formula of Isolated Compound	Chemical Structure of Isolated Compound	Bioactivity of Isolated Compound	References
Tanshinone I	1,6-dimethylnaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H12 03**		**Anti-cancer** Induce apoptosis in colon cancer cells	[32]
Tanshinone IIA	1,6,6-trimethyl-8,9-dihydro-7H-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Anti-cancer** cytotoxic compounds in human leukemia cells	[33]
Neo-tanshinlactone	6,14-dimethyl-12,17-dioxatetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadeca-1(10),2,4,6,8,11(15),13-heptaen-16-one	**C17 H12 O3**		**Anti-breast cancer** Inhibits estrogen receptor over-expressing breast cancer cell	[34]
Tanshinone I	1,6-dimethylnaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H12 03**		**Anti-cancer** Inhibits the migration and invasion of human lung adenocarcinoma cell line, CL1-5	[35]
Cryptotanshinone	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g][1]benzofuran-10,11-dione	**C19 H20 O3**		**Anti-bacterial activity**	[36]

Dihydrotanshinone I	(1*R*)-1,6-dimethyl-1,2-dihydronaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H14 O3**		**Anti-bacterial activity**	[36]
Lithospermic acid	4-[3-[1-carboxy-2-(3,4-dihydroxyphenyl) ethoxy]-3-oxoprop-1-enyl]-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-3-carboxylic acid	**C27 H22 O12**		**Anti-viral activity** exhibited potent effect against HIV-1 integrase activity in vitro and viral replication in vivo	[37]
Lithospermic acid B	(2*R*)-2-[(*E*)-3-[(2*S*,3*S*)-3-[(1*R*)-1-carboxy-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoic acid	**C36 H30 016**		**Anti-viral activity** exhibited potent effect against HIV-1 integrase activity in vitro and viral replication in vivo	[37]
Tanshinone I	1,6-dimethylnaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H12 03**		**Anti-inflammatory** Inhibits IL-12 production in mouse macrophages and on IFN-γ production	[38]
Dihydrotanshinone	1,6-dimethyl-1,2-dihydronaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H14 O3**		**Anti-inflammatory** Inhibits IL-12 production in mouse macrophages and on IFN-γ production	[38]
Cryptotanshinone	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g] [1]benzofuran-10,11-dione	**C19 H20 O3**		**Anti-inflammatory** Inhibits IL-12 production in mouse macrophages and on IFN-γ production	[38]
Tanshinone VI	***Retrieved from Chemspider. com*** 1-Hydroxy-2-(1-hydroxy-2-propanyl)-8-methyl-3,4-phenanthrenedione	C18 H16 O14		**Anti-inflammatory**. protects the myocardium against hypoxia/reoxygenation injury and attenuates progression of in vitro myocardial remodeling (heart disease).	[39]

Salvianolic acid B (Sal-B)	(2*R*)-2-[(*E*)-3-[(2*R*,3*R*)-3-[(1*R*)-1-carboxy-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoic acid	**C36 H30 O16**		**Anti-Cancer activity** Inhibits head and neck squamous cell carcinoma (HNSCC). Effectively suppress COX-2 expression and induce apoptosis in a variety of cancer cell lines	[40]
Rosmarinic acid	(2*R*)-3-(3,4-dihydroxyphenyl)-2-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxypropanoic acid	**C18 H16 O8**		**Anti-oxidant activity** Potential natural phenolic antioxidants for food, pharmaceutical, cosmetics or nutraceutical industries	[41]
Salvianolic acid B	(2*R*)-2-[(*E*)-3-[(2*R*,3*R*)-3-[(1*R*)-1-carboxy-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoic acid	**C36 H30 O16**		**Anti-oxidant activity** Potential natural phenolic antioxidants for food, pharmaceutical, cosmetics or nutraceutical industries	[41]
Magnesium lithospermate B (MLB)	Magnesium;(2*R*)-2-[(*E*)-3-[(2*S*,3*S*)-3-[(1*R*)-1-carboxylato-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoate	**C36 H28Mg O16**		**Vasodilation.** regulate Ca^{2+} homeostasis in cultured rat thoracic aorta vascular smooth muscle cells (VSMCs)	[42]
Sodium rosmarinate (SR)	(2*S*)-3-(3,4-dihydroxyphenyl)-2-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxypropanoic acid	**C18 H16 O8**		**Vasodilation.** regulate Ca^{2+} homeostasis in cultured rat thoracic aorta vascular smooth muscle cells (VSMCs)	[42]

Magnesium lithospermate (ML)	Magnesium;(2*R*)-2-[(*E*)-3-[(2*S*,3*S*)-3-[(1*R*)-1-carboxylato-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoate	**C36 H28 MgO16**		**Vasodilation.** regulate Ca^{2+} homeostasis in cultured rat thoracic aorta vascular smooth muscle cells (VSMCs)	[42]
Tanshinone II-A	1,6,6-trimethyl-8,9-dihydro-7*H*-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Modulates collagen metabolism** prevented cardiac fibrosis and improved cardiac function	[43]
Magnesium tanshinoate B (MTB)	Magnesium;(2*R*)-2-[(*E*)-3-[(2*S*,3*S*)-3-[(1*R*)-1-carboxylato-2-(3,4-dihydroxyphenyl) ethoxy]carbonyl-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-4-yl]prop-2-enoyl] oxy-3-(3,4-dihydroxyphenyl) propanoate	**C36 H28 MgO16**		**Anti-hypertensive**	[44]
Tanshinone IIA	1,6,6-trimethyl-8,9-dihydro-7*H*-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Anti-oxidant activity** inhibits NADPH oxidase	[45]
Cryptotanshinone	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g] [1]benzofuran-10,11-dione	**C19 H20 O3**		**Anti-Cancer** suppress prostate cancer growth and androgen signaling.	[46]
Tanshinone IIA	1,6,6-trimethyl-8,9-dihydro-7*H*-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Anti-Cancer** suppress prostate cancer growth and androgen signaling.	[46]

Tanshinone I	1,6-dimethylnaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H12 O3**		**Anti-Cancer** suppress prostate cancer growth and androgen signaling.	[46]
Tanshinone IIA	1,6,6-trimethyl-8,9-dihydro-7*H*-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Anti-Cancer** Inhibits Osteosarcoma by inducing cell apoptosis and inhibiting proliferation, migration, and invasion *in vitro*	[46]
Dihydrotanshinone I (DI)	(1*R*)-1,6-dimethyl-1,2-dihydronaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H14 O3**		**Anti-Cancer** inhibits the growth of human cervical cancer cells	[47]
Cryptotanshinone (CT)	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g][1]benzofuran-10,11-dione	**C19 H20 O3**		Inhibitor of both human acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) Potential drug for treatment of Alzheimer's disease	[48]
15, 16-Dihydrotanshinone I (DHTS)	(1*R*)-1,6-dimethyl-1,2-dihydronaphtho[1,2-g][1] benzofuran-10,11-dione	**C18 H14 O3**		**Anti- Cancer** Induces apoptosis in human colorectal cancer cells	[49]
Tanshinone II-A	1,6,6-trimethyl-8,9-dihydro-7*H*-naphtho[1,2-g][1] benzofuran-10,11-dione	**C19 H18 O3**		**Anti- Cancer** inhibited migration and invasion of human colon carcinoma (CRC) cells	[50]
Retrieved from Chemspider.com **Tanshinone VI**	1-Hydroxy-2-(1-hydroxy-2-propanyl)-8-methyl-3,4-phenanthrenedione	**C18 H16 O14**		**Anti-Cancer** inhibits the expression of intercellular adhesion molecule-l and vascular cell adhesion molecule-l	[51]

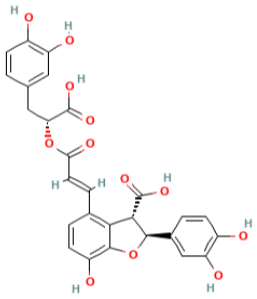
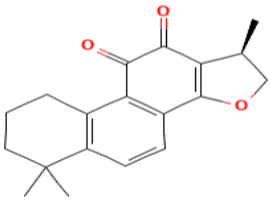
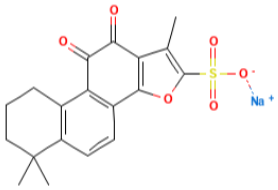
lithospermic acid in Salvianolate	(2*S*,3*S*)-4-[(*E*)-3-[(1*R*)-1-carboxy-2-(3,4-dihydroxyphenyl) ethoxy]-3-oxoprop-1-enyl]-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-1-benzofuran-3-carboxylic acid	**C27 H22 O12**		**Anti-Oxidant Activity** inhibits Reactive Oxygen Species (ROS) and iNOS production and increases total antioxidant capacity (TAOC) and NO levels in H_2O_2-treated cardiomyocytes *in vitro* via downregulation of Smad2/3 and TGFβ1 expression.	[52]
Cryptotanshinone	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g][1]benzofuran-10,11-dione	**C19 H20 O3**		**Antibacterial activity** Inhibits clinic isolated methicillin and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA)	[53]
Sodium tanshinone IIA sulfonate (STS)	sodium;1,6,6-trimethyl-10,11-dioxo-8,9-dihydro-7*H*-naphtho[1,2-g][1]benzofuran-2-sulfonate	**C19 H17 NaO6 S**		**Cardioprotective activity.** reduce myocardial infarct size	[54]

Table 2: Isolated Compounds from *Salvia miltiorrhiza.*

Herb-Drug Interactions Involving *S. Miltiorrhiza*

Concomitant use of 'Danshen' and warfarin (An anti - coagulant / anti - thrombotic drug) has been linked to bleeding and prolonged prothrombin time [55]. Warfarin prevents atrial fibrillation, valvular heart disorders, deep vein thrombosis [55]. Similarly, 'Danshen' inhibits platelet adhesion and aggregation to suppress the formation of thromboxane A2 [55]. As a result, co - administration of 'Danshen' and warfarin at enhances anti-coagulation and possible bleeding. Indeed, the herb - drug interaction between 'Danshen' and warfarin was linked to active components of 'Danshen'. For example, tanshinones inhibit CYP1A1, CYP2C6 and CYP2C11 - dependent hepatic metabolism of warfarin, leading to increased plasma concentration of warfarin [56]. Again, interaction between 'Danshen' and aspirin has been reported [57,58].

Similarly, 'Danshen' was shown to augment the effects of aspirin, through reduction of aspirin protein binding, which leads to increased plasma concentration of aspirin and its effects thereof. Also, 'Danshen' has been reported to exert digoxin - like immune reactivity, and this observation was reported to have led to a false interference of digoxin plasma concentration [57]. 'Danshen' has been shown to alter the pharmacokinetic profile of theophylline, a drug mostly metabolized by CYP1A2 and CYP2E1 [59,60]. Similarly, 'Danshen' was shown to have influenced the metabolism and excretion of losartan and EXP3174 *in vivo* [61].

Adverse Effects of *S. Miltiorrhiza*

Reported adverse effects of *S. miltiorrhiza* include thirst, and gastrointestinal discomfort, especially when one uses the dripping pill formulation.

Toxicity of *S. Miltiorrhiza*

In a study using mice, the LD_{50} for 'Danshen' was reported to be 25.807 g/kg which is many folds higher than the therapeutic dose (6.56 mg/kg body weight), indicating that 'Danshen' is safe at least in mice [31].

Studies on Combined Effects of a Membranaceus and *S. Miltiorrhiza*

Undoubtedly, the ethno-botanical use of both *A. membranaceus* and *S. miltiorrhiza* in China coupled with their recent therapeutic application in China has stimulated vigorous scientific investigations on these two herbs. In most studies either the extracts of the two herbs or their phyto-compounds are combined in various combinations not only to reflect their ethno-botanical uses but also to achieve specific therapeutic objective. From Table 3, some of the studies that investigated combined effects of phytocomponents *A. membranaceus* and *S. miltiorrhiza* are exemplified.

Herbal Components / Extracts	Investigated Disease Condition	Putative Mechanism of Action	References
A. membranaceus and S. miltiorrhiza extracts	Liver fibrosis indices	Lowered serum fibrosis indices including HA, LN, IV-C, PCIII in fibrotic patients	[62,63]
Astragalus, Astragalus polysaccharide and Salvianolic acid	Liver fibrosis in an CCl_4-induced rat model	CASE inhibited Smad2 C/L phosphorylation and also reduced the expression of α-SMA in myofibroblast	[64]
CASE	Cancer cell proliferation and invasion	CASE ameliorated HepG2 cell proliferation and invasion by modulating TGF-β/Smad pathway	[65]
CASE	Keloid fibroblast cell proliferation and invasion	CASE inhibited Keloid cell proliferation and invasion via modulation of TGF-β/Smad and MAPK pathway	[66]
CASE	HCC in rats	CASE ameliorates DEN-induced HCC in rats by modulating TGF-β/Smad signaling to decrease PAI-I mRNA transcripts	[67]
CASE	HCC in rats and HepG2 cells	CASE inhibited HepG2 cell proliferation and invasion by modulating Smad3L phosphorylation	[68]
CASE	Keloid fibroblast cells in rabbits	CASE reduced keloid formation by modulating the TGF-β/Smad signaling pathway	[69]
CASE	HSCs, HepG2 cells	Modulation of MAPK - regulated TGF-β/Smad signaling	[68]

Table 3: Studies on combined extracts of *Astragalus membranaceus* and *Salvia miltiorrhiza.*

Compound astragalus and *Salvia miltiorrhiza* extract (CASE), mitogen activated protein kinase (MAPK), hepatic stellate cells (HSCs), plasminogen activator inhibitor protein 1 (PAI-1), transforming growth factor beta (TGF-β), diethylnitrosamine (DEN), hepatocellular carcinoma (HCC), hyaluronic acid (HA)

Conclusion

On the basis of these impressive highlights on *Astragalus membranaceus* and *Salvia miltiorrhiza* with regards to their potential as sources of small molecules for pharmacotherapy and also as natural templates for pharmaceutical semi-synthesis of analog drugs, their bio-sustainability should engage the attention of natural product scientists. Further, research efforts should focus on translational studies particularly on some of the promising small molecule compounds isolated from *Astragalus membranaceus* and *Salvia miltiorrhiza* for clinical trials.

Funding

Authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgement

My appreciation goes to Prof. S. Tayman (Department of Chemistry, University of Cape Coast, Cape Coast, Ghana) for inspiration.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interests

The author (s) declares no potential conflicts of interest with regards to the research, authorship, and/or publication of this article.

Sample Availability

Not applicable.

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