BIOTONIC™

Adaptogenic Tonic

Scientific Validation of Botanical Ingredients

Authors: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA. | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

Updated 2022; Joseph Katzinger, ND

Active Ingredients:

Proprietary Herbal Blend: Astragalus Root (Radix Astragalus, *Astragalus membranaceus*), Sweet Wormwood (Herba Artemisia, *Artemisia annua*) aerial parts, Fo-Ti root** (Radix Polygoni Multiflori, *Polygonum multiflorum*), Siberian ginseng root (*Eleutherococcus senticosus*), Ginger rhizome (Radix Zingiberis Officianalis, *Zingiber officinale*), Bai-Zhu Atractylodes (Rhizoma Atractylodis Macrocephalae, *Atractylodes lancea*), Chinese yam rhizome (*Dioscorea villosa*), Poria Sclerotium (*Poria cocos*), Codonopsis root (Radix Codonopsis, *Codonopsis pilosulae*), Chinese Peony root (Radix Peony, *Paeonia lactiflora*), Tumeric root (Tuber Curcumae, *Curcuma longa*), Tangerine Peel (Pericarpium Citri Reticulatae, *Citrus reticulata*), Honey-prepared Chinese licorice root (Glycyrrhizae Uralensis, *Glycyrrhiza uralensis*)

**Fo-Ti is prepared in black soybean. Only premium grade botanicals are used.

Overview

BIOTONIC™ is a proprietary blend of 13 botanicals with a long history of traditional use, particularly in Chinese and other Eastern medicine formulations. Unlike Western medicines which often have one very specific mechanism of action, these botanicals are valued for their broader, adaptogenic, pleiotropic and polyvalent actions. Rather than a single target, these herbs typically have many targets, with the greater effect of normalizing metabolism and promoting resilience in multiple body systems, by activating stress response signaling pathways. As whole herbs rather than isolated components, BIOTONIC™ provides a rich array of phytochemicals which complement and potentiate each other. Many of these botanicals have a variety of multi-system anti-inflammatory and immune-modulatory effects, and generally support gastrointestinal and hepatic function. The positive implications for the cardiovascular and neurological systems, for example, of a more diverse and complex intestinal microbiota along with a well-functioning intestinal mucosa, are now well-understood. The botanicals which comprise this unique adaptogenic formula most likely modulate the expression of thousands of genes which influence health and stress responses. When viewed through the lens of systems biology and/or network pharmacology, we have a much greater appreciation for the wisdom of traditional medicine, and for these potent and trusted herbs.[1]

[1] Panossian A. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann N Y Acad Sci. 2017 Aug;1401(1):49-64.

Radix Astragalus (*Astragalus membranaceus*)

Biological Actions:
Adaptogenic, anti-inflammatory, antioxidant, cardiotonic, immunomodulator, tonic.[2,3]

Traditional Use:
The root of astragalus has been used in traditional Chinese medicine for at least two thousand years.[3] Astragalus has been used to promote health and to strengthen and tonify the Qi (energy), as well as tonify the blood and the spleen.[2,4] In clinical practice, astragalus is used as an adaptogenic agent to restore and balance the body's immune response, and to increase vitality.[4]

Scientific Evidence:
More than 200 compounds have now been isolated from Astragalus root, with most of its biological effects attributed to the isoflavonoids, triterpene saponins, and polysaccharides.[3] This includes over 60 flavonoids, such as formononetin, ononin and calycosin (and its glycoside), 170 saponins, of which 4 major types account for 80% of the total (astragaloside I–VIII, acetyl astragaloside, isoastragaloside I–IV and soyasaponins), and over 30 polysaccharides, primarily classified as dextran and heteropolysaccharides.[3]

Many of the immunomodulating effects of Astragalus root have been attributed to the polysaccharides. Predominantly done *in vitro* or in animal studies, the compounds have been shown to affect both immune signaling and the proliferation of immune cells; for example, increases in the size of immune organs, including the spleen and thymus, as well as increases in the number of B and T lymphocytes, as well as NK cells and macrophages, have all been documented.[5] *Ex vivo* studies in patients with non-small cell carcinoma have demonstrated enhanced T cell-mediated immune responses, maturation of dendritic cells, and modulation of the macrophage M1/M2 polarization toward an M1 phenotype.[6] Human studies have also found a modulation of many inflammatory cytokines associated with patient symptoms, including IL-1β, IL-6, and vascular endothelial growth factor (VEGF).[7] Astragalus root also appears to have immunoregulatory properties as well; participants with allergic

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[2] Bone K, Mills S. Principles and Practice of Phytotherapy: Modern Herbal Medicine. Second ed: Churchill Livingstone, Elsevier; 2013.
[3] Guo Z, Lou Y, Kong M, et al. A Systematic Review of Phytochemistry, Pharmacology and Pharmacokinetics on Astragali Radix: Implications for Astragali Radix as a Personalized Medicine. Int J Mol Sci. 2019 Mar 22;20(6):1463.
[4] Braun L, Cohen M. Herbs and Natural Supplements an Evidenced-Based Guide. 4rt ed. Chatswood, NSW: Elsevier Australia.; 2015.
[5] Zheng Y, Ren W, Zhang L, et al. A Review of the Pharmacological Action of Astragalus Polysaccharide. Front Pharmacol. 2020 Mar 24;11:349.
[6] Bamodu OA, Kuo KT, Wang CH, et al. Astragalus polysaccharides (PG2) Enhances the M1 Polarization of Macrophages, Functional Maturation of Dendritic Cells, and T Cell-Mediated Anticancer Immune Responses in Patients with Lung Cancer. Nutrients. 2019 Sep 20;11(10):2264.
[7] Huang WC, Kuo KT, Bamodu OA, et al. Astragalus polysaccharide (PG2) Ameliorates Cancer Symptom Clusters, as well as Improves Quality of Life in Patients with Metastatic Disease, through Modulation of the Inflammatory Cascade. Cancers (Basel). 2019 Jul 25;11(8):1054.

rhinitis experienced a significant decline in rhinorrhea during a 6 week randomized and controlled double-blinded trial.[8] An extract of astragalus root was also shown to stabilize NK and Treg levels compared to control after an acute bout of exertion among athletes, who are known to have a greater risk for infection following temporary immunosuppression.[9] Though few studies exist, Astragalus root may also have anti-parasitic activity, indicated by the significant inhibition of a highly virulent strain of *Toxoplasma gondii* (by an aqueous extract of Astragalus root) *in vitro*.[10]

A cardiovascular benefit of Astragalus root has long been suspected. *In vitro* studies indicate a benefit for endothelial function, as astragaloside IV was able to increase nitric oxide synthase (NOS) activity and subsequent nitric oxide production, and reduce inflammatory mediator concentrations, including IL-6, TNF-α, VCAM-1, ICAM-1, TLR4, and nuclear factor kappa B (NF-κB) p65.[11] Astragaloside IV has also been shown to increase expression of PPARα, enhance mitochondrial function and increase ATP production, and also upregulate fatty acid β-oxidation in an animal model of heart failure.[12] In a model of vascular injury induced by LPS, astragaloside IV was also shown to activate the Nrf2 signaling pathway, a key mediator of oxidative defense.[13] A systematic review of randomized trials found that when combined with standard therapies, injections of astragalus root have also been shown to improve outcomes of viral myocarditis. However, these trials were limited by sample size and low methodological quality.[14] A more recent systematic review, which included 28 randomized trials, did find several benefits for viral myocarditis, including a reduction in myocardial enzymes and cardiac troponin I levels.[15]

A number of mechanisms have been identified by which Astragalus root may improve metabolic abnormalities. Animal studies have shown improvements in insulin sensitivity, an increase in adiponectin secretion as well as hepatic AMPK production.[5,16] Animal studies also suggest that astragaloside IV may alleviate nerve damage associated with hyperglycemia, in part by limiting mitochondrial damage, and improving mitochondrial electron transport chain complex activity.[17] It has also been shown to prevent endothelial dysfunction associated with hyperglycemia-induced oxidative

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[8] Matkovic Z, Zivkovic V, Korica M, et al. Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. Phytother Res. 2010 Feb;24(2):175-81.
[9] Latour E, Arlet J, Latour EE, et al. Standardized astragalus extract for attenuation of the immunosuppression induced by strenuous physical exercise: randomized controlled trial. J Int Soc Sports Nutr. 2021 Jul 16;18(1):57.
[10] Yang X, Huang B, Chen J, et al. In vitro effects of aqueous extracts of Astragalus membranaceus and Scutellaria baicalensis GEORGI on Toxoplasma gondii. Parasitol Res. 2012 Jun;110(6):2221-7.
[11] Leng B, Tang F, Lu M, et al. Astragaloside IV improves vascular endothelial dysfunction by inhibiting the TLR4/NF-κB signaling pathway. Life Sci. 2018 Sep 15;209:111-121.
[12] Dong Z, Zhao P, Xu M, et al. Astragaloside IV alleviates heart failure via activating PPARα to switch glycolysis to fatty acid β-oxidation. Sci Rep. 2017 Jun 2;7(1):2691.
[13] Li H, Wang P, Huang F, et al. Astragaloside IV protects blood-brain barrier integrity from LPS-induced disruption via activating Nrf2 antioxidant signaling pathway in mice. Toxicol Appl Pharmacol. 2018 Feb 1;340:58-66.
[14] Piao YL, Liang XC. Astragalus membranaceus injection combined with conventional treatment for viral myocarditis: a systematic review of randomized controlled trials. Chin J Integr Med. 2014 Oct;20(10):787-91.
[15] Zheng Q, Zhuang Z, Wang ZH, et al. Clinical and Preclinical Systematic Review of Astragalus Membranaceus for Viral Myocarditis. Oxid Med Cell Longev. 2020 Nov 2;2020:1560353.
[16] Zhang R, Qin X, Zhang T, et al. Astragalus Polysaccharide Improves Insulin Sensitivity via AMPK Activation in 3T3-L1 Adipocytes. Molecules. 2018 Oct 21;23(10):2711.
[17] Ben Y, Hao J, Zhang Z, et al. Astragaloside IV Inhibits Mitochondrial-Dependent Apoptosis of the Dorsal Root Ganglion in Diabetic Peripheral Neuropathy Rats Through Modulation of the SIRT1/p53 Signaling Pathway. Diabetes Metab Syndr Obes. 2021 Apr 14;14:1647-1661.

damage.[18]

Safety Summary:
Considered safe and well tolerated with no adverse reaction expected at the dose recommended.[2] Based on traditional considerations, astragalus is contraindicated in acute infections.[2] Considered safe during pregnancy.[2] Exercise caution during breastfeeding as safety has not been established.[2]

Herba Artemesia/Sweet Wormwood (*Artemisia annua*)

Biological Actions:
Analgesic, antioxidant, antifungal, anthelmintic, anti-inflammatory, antimalarial, antiparasitic, antiprotozoal, antiviral.[19,20]

Traditional Use:
In the Traditional Chinese Medicine system, sweet wormwood has been used for centuries for treating "heat" conditions (yang), such as malaria, and relieving symptoms of febrile diseases, tidal fever, low grade fever and summer heat stroke due to its cooling nature (yin).[21] Other reported historical uses include heat/fever arising from exhaustion, tuberculosis, lice, wounds, dysentery, hemorrhoids, as well as pain and swelling.[22]

Scientific Evidence:
The main phytochemical constituents of sweet wormwood include volatile oils, sesquiterpene lactones (artemisinins), phenolic compounds and flavones.[23] Artemisinins, the endoperoxide sesquiterpene lactones, have been recognized as the major bioactive ingredients responsible for the anti-malarial and anti-parasitic properties of sweet wormwood.[19,24] For example, tea infusions of *Artemisia annua* inhibited parasitemia and gametocytemia of *Plasmodium falciparum in vitro*, an effect largely attributed to the artemisinins content.[25,26] However, it is now believed that other components found in the leaves of *A. annua*, including the flavonoids, other terpenes, coumarins, and phenolic acids, may help to potentiate the artemisinins through several mechanisms, including increasing their bioavailability or

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[18] Zhang Y, Mao XD, Cao AL, et al. Astragaloside IV prevents endothelial dysfunction by improving oxidative stress in streptozotocin-induced diabetic mouse aortas. Exp Ther Med. 2021 Nov;22(5):1197.
[19] Ho WE, Peh HY, Chan TK, et al. Artemisinins: pharmacological actions beyond anti-malarial. Pharmacol Ther. 2014 Apr;142(1):126-39.
[20] Ferreira JF, Luthria DL, Sasaki T, et al. Flavonoids from Artemisia annua L. as antioxidants and their potential synergism with artemisinin against malaria and cancer. Molecules. 2010 Apr 29;15(5):3135-70.
[21] Brown GD. The biosynthesis of artemisinin (Qinghaosu) and the phytochemistry of Artemisia annua L. (Qinghao). Molecules. 2010 Oct 28;15(11):7603-98.
[22] Feng X, Cao S, Qiu F, et al. Traditional application and modern pharmacological research of Artemisia annua L. Pharmacol Ther. 2020 Dec;216:107650.
[23] Bora KS, Sharma A. The genus Artemisia: a comprehensive review. Pharm Biol. 2011 Jan;49(1):101-9.
[24] Carbonara T, Pascale R, Argentieri MP, et al. Phytochemical analysis of a herbal tea from Artemisia annua L. J Pharm Biomed Anal. 2012 Mar 25;62:79-86.
[25] Snider D, Weathers PJ. In vitro reduction of Plasmodium falciparum gametocytes: Artemisia spp. tea infusions vs. artemisinin. J Ethnopharmacol. 2021 Mar 25;268:113638.
[26] Mouton J, Jansen O, Frédérich M, et al. Is artemisinin the only antiplasmodial compound in the Artemisia annua tea infusion? An in vitro study. Planta Med. 2013 Apr;79(6):468-70.

having synergistic activity.[27] A wide variety of flavonoids have been found in *Artemisia annua*, including apigenin, luteolin, cirsilineol, and rhamnetin, thought to have a broad range of biological activities.[20] Although not recommended as a sole treatment for malaria, compounds in *Artemisia annua* may have a role as part of a polytherapy for both malaria and schistosomiasis.[28,29] One water-soluble derivative of artemisinin, dihydroartemisinin (DHA), has been found to exhibit anti-parasitic activity against multiple organisms *in vitro*. For example, it was shown to inhibit the cell cycle of *Giardia lamblia,* and to have cytotoxic effects toward the highly prevalent *Leishmania braziliensis*, in part mediated by disruption of mitochondrial energy production.[30,31] Animal studies suggest DHA also inhibits the schistosomula and adult worms of *Schistosoma japonicum* and *Schistosoma mansoni* in a dose-dependent manner.[32] Artemisinin itself as well as several of its metabolites have also demonstrated anti-parasitic effects toward *Leishmania spp*., with similar findings for *Trypanosoma spp., Toxoplasma gondii, Neospora caninum, Eimeria tenella, Acanthamoeba castellanii, Naegleria fowleri, Cryptosporidium parvum, Giardia lamblia, and Babesia spp,* both *in vitro* and in animal studies, suggesting broad anti-parasitic activity.[33] Extracts from *Artemisia* have also been found to have anti-fungal activity, inhibiting the growth of *Candida albicans* and *Candida dubliniensis*, as well as antimicrobial activity against both Gram positive and Gram negative bacteria.[22]

Artemisia has also been shown to have analgesic properties. In a randomized and placebo-controlled trial, an extract of *Artemisia annua* was found to reduce both pain and stiffness in participants with knee or hip osteoarthritis compared to control.[34] Reductions in pain and tenderness, as well as in inflammatory markers, were also observed in a controlled trial of participants with rheumatoid arthritis.[35] Possible mechanisms may include mitigation of oxidative damage, as well as direct anti-inflammatory effects, including inhibition of NF-κB expression and other inflammatory mediators.[36] Activation of the Nrf2 pathway by DHA is also likely to reduce inflammation by upregulating the transcription of anti-inflammatory and antioxidant defense genes.[37] *Artemisia annua* compounds have also been shown to have immunomodulatory effects, influencing Th17/Treg balance, as well as CD4+

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[27] Gruessner BM, Cornet-Vernet L, Desrosiers MR, et al. It is not just artemisinin: Artemisia sp. for treating diseases including malaria and schistosomiasis. Phytochem Rev. 2019 Dec;18(6):1509-1527.
[28] Gruessner BM, Cornet-Vernet L, Desrosiers MR, et al. It is not just artemisinin: Artemisia sp. for treating diseases including malaria and schistosomiasis. Phytochem Rev. 2019 Dec;18(6):1509-1527.
[29] Cornet-Vernet L, Munyangi J, Chen L, et al. Response to Argemi et al. 2019. Phytomedicine. 2019 Sep;62:152943.
[30] Tian XF, Shen HE, Li J, et al. The effects of dihydroartemisinin on Giardia lamblia morphology and cell cycle in vitro. Parasitol Res. 2010 Jul;107(2):369-75.
[31] Grazzia N, Boaventura S Jr, Garcia VL, et al. Dihydroartemisinin, an active metabolite of artemisinin, interferes with Leishmania braziliensis mitochondrial bioenergetics and survival. Parasitol Res. 2021 Feb;120(2):705-713.
[32] Zhang XG, Li GX, Zhao SS, et al. A review of dihydroartemisinin as another gift from traditional Chinese medicine not only for malaria control but also for schistosomiasis control. Parasitol Res. 2014 May;113(5):1769-73.
[33] Loo CS, Lam NS, Yu D, et al. Artemisinin and its derivatives in treating protozoan infections beyond malaria. Pharmacol Res. 2017 Mar;117:192-217.
[34] Stebbings S, Beattie E, McNamara D, et al. A pilot randomized, placebo-controlled clinical trial to investigate the efficacy and safety of an extract of Artemisia annua administered over 12 weeks, for managing pain, stiffness, and functional limitation associated with osteoarthritis of the hip and knee. Clin Rheumatol. 2016 Jul;35(7):1829-36.
[35] Yang M, Guo MY, Luo Y, et al. Effect of Artemisia annua extract on treating active rheumatoid arthritis: A randomized controlled trial. Chin J Integr Med. 2017 Jul;23(7):496-503.
[36] Wang KS, Li J, Wang Z, et al. Artemisinin inhibits inflammatory response via regulating NF-κB and MAPK signaling pathways. Immunopharmacol Immunotoxicol. 2017 Feb;39(1):28-36.
[37] Li D, Qi J, Wang J, et al. Protective effect of dihydroartemisinin in inhibiting senescence of myeloid-derived suppressor cells from lupus mice via Nrf2/HO-1 pathway. Free Radic Biol Med. 2019 Nov 1;143:260-274.

T cell and CD8+ memory T cell functions.[38] Lastly, although the mechanism is unclear (and may be related to its anti-inflammatory effects), a water-based extract of *Artemisia annua* was found to significantly reduce elevated liver enzymes among participants with non-alcoholic fatty liver disease, decreasing AST 199% and ALT 216% compared to the control group after 8 weeks.[39]

Safety Summary:
Considered safe and well tolerated at the dose recommended.[19,40] May cause allergic reactions or dermatitis (direct contact).[41] Avoid during the first trimester of pregnancy due to the artemisinin content, which in animals has been associated with miscarriage and fetal abnormalities. Use during the second and third trimester has comparable effects to the use of quinine.[42]

Radix Polygoni Multiflori (*Polygonum multiflorum)*

Biological Actions:
Anti-inflammatory, antioxidant, anti-steatosis, immune modulating, neuroprotective.[43,44]

Traditional Use:
Polygonum multiflorum is a popular Chinese traditional medicine, known as He Shou Wu in China and East Asia, and as Fo-ti in North America. It has been used in traditional Chinese medicine for centuries as a liver and kidney-tonifying remedy and as an antiaging agent.[43] It is thought to be preventative in neurodegenerative and cardiovascular diseases.[44] In clinical practice, polygonum is generally used in combination with other herbs to enhance the therapeutic effects.[43]

Scientific Evidence:
The major phytochemical constituents of *Polygonum multiflorum* include flavones, quinones, stilbenes, phospholipids and phenolic compounds.[43] Immune modulating effects of fo-ti have been attributed to the polysaccharide and anthraquinone content of the herb.[43] An anthraquinone glycoside extract was shown to enhance T and B lymphocyte proliferation, improve macrophage phagocytosis, increase TNF secretion and enhance the activity of NK cells *in vitro*.[45]

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[38] Qiu F, Liu J, Mo X, et al. Immunoregulation by Artemisinin and Its Derivatives: A New Role for Old Antimalarial Drugs. Front Immunol. 2021 Sep 9;12:751772.
[39] Han B, Kim SM, Nam GE, et al. A Randomized, Double-Blind, Placebo-Controlled, Multi-Centered Clinical Study to Evaluate the Efficacy and Safety of Artemisia annua L. Extract for Improvement of Liver Function. Clin Nutr Res. 2020 Oct 28;9(4):258-270.
[40] Bisht D, Kumar D, Kumar D, et al. Phytochemistry and pharmacological activity of the genus artemisia. Arch Pharm Res. 2021 May;44(5):439-474.
[41] Wu P, He Y, Zeng Z, et al. Allergic contact dermatitis by Artemisia: Report of two cases. Contact Dermatitis. 2020 Jul;83(1):31-32.
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[43] Lin L, Ni B, Lin H, et al. Traditional usages, botany, phytochemistry, pharmacology and toxicology of Polygonum multiflorum Thunb.: a review. J Ethnopharmacol. 2015 Jan 15;159:158-83.
[44] Bounda GA, Feng YU. Review of clinical studies of Polygonum multiflorum Thunb. and its isolated bioactive compounds. Pharmacognosy Res. 2015 Jul-Sep;7(3):225-36.
[45] Sun G.B., Guo B.J., Li X.E., et al. The effect of anthraquinone glycoside from Polygonum multiflorum Thunb on cellular immunological function in mice. Pharmacology and Clinics of Chinese Materia Medica. 2006;22:30–32.

Several constituents of polygonum have been found to influence lipid metabolism in vitro using a liver cell line, including 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside (TSG), a stilbene isolated from polygonum, as well as emodin.[46] Raw *Polygonum multiflorum* appeared to reduce expression of key genes involved in lipid synthesis in an animal model, including 3-hydroxy-3-methylglutaryl-CoA reductase and fatty acid synthase.[47] In an animal model of non-alcoholic fatty liver disease, an ethanol extract of *Polygonum multiflorum* prevented the hepatic lipid accumulation and lipid abnormalities which occur in response to a high fat diet, in part mediated via restoration of a healthy gut microbiome and of intestinal barrier function.[48]

Several *in vivo* and *in vitro* studies have demonstrated the anti-inflammatory effects of polygonum and its bioactive constituents. Polygonum works by inhibiting the expression of pro-inflammatory signaling factors, such as NF-κB, TNF-α, inducible nitric oxide synthase (iNOS), cyclooxygenase-2, chemokines and cytokines.[44,49,50]

Polygonum has a history of traditional usage for neuroprotection, with several possible mechanisms; an upregulation of Nrf2 expression has been shown *in vitro* with a specific extract (CRPE56IGIH), which may provide antioxidant and anti-inflammatory effects, preventing neuronal damage.[51] TSG has also been shown to limit β-amyloid toxicity in a *Caenorhabditis elegans* (nematode) model, as well as over-expression of α-synuclein in an animal model.[52,53] A preliminary trial using a *Polygonum multiflorum* extract suggests there may be a cognitive benefit, though more well-controlled trials are needed.[54] Despite polygonum being one of the most popular traditional Chinese medicines, there have been very few clinical studies conducted to assess the traditional indications or to study the therapeutic potential of its bioactive constituents.[44]

Safety Summary:

No adverse effects expected at the dose recommended. In therapeutic doses, polygonum administration

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[46] Wang M, Zhao R, Wang W, et al. Lipid regulation effects of Polygoni Multiflori Radix, its processed products and its major substances on steatosis human liver cell line L02. J Ethnopharmacol. 2012 Jan 6;139(1):287-93.
[47] Xian Z, Liu Y, Xu W. The Anti-hyperlipidemia Effects of Raw Polygonum multiflorum Extract in Vivo. Biol Pharm Bull. 2017;40(11):1839-1845.
[48] Dai X, He L, Hu N, et al. Polygoni Multiflori Radix Praeparata Ethanol Extract Exerts a Protective Effect Against High-Fat Diet Induced Non-Alcoholic Fatty Liver Disease in Mice by Remodeling Intestinal Microbial Structure and Maintaining Metabolic Homeostasis of Bile Acids. Front Pharmacol. 2021 Nov 15;12:734670.
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[50] Pan MH, Chiou YS, Tsai ML, et al. Anti-inflammatory activity of traditional Chinese medicinal herbs. J Tradit Complement Med. 2011 Oct;1(1):8-24.
[51] Park SY, Jin ML, Kang NJ, et al. Anti-inflammatory effects of novel polygonum multiflorum compound via inhibiting NF-κB/MAPK and upregulating the Nrf2 pathways in LPS-stimulated microglia. Neurosci Lett. 2017 Jun 9;651:43-51.
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[53] Zhang L, Yu S, Zhang R, et al. Tetrahydroxystilbene glucoside antagonizes age-related α-synuclein overexpression in the hippocampus of APP transgenic mouse model of Alzheimer's disease. Restor Neurol Neurosci. 2013;31(1):41-52.
[54] Chen L, Huang J, Xue L. [Effect of compound Polygonum multiflorum extract on Alzheimer's disease]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2010 Jun;35(6):612-5. Chinese.

has been linked to cases of liver damage.[44,55] Exercise caution during pregnancy and lactation as safety has not been established during these times.[56]

[55] Wang L, Wang Z, Xing Y, et al. Biomarkers and Mechanism Analysis for Polygoni Multiflori Radix Preparata-Induced Liver Injury by UHPLC-Q-TOF-MS-Based Metabolomics. Evid Based Complement Alternat Med. 2021 Nov 23;2021:7677392.
[56] Natural Medicines. Fo-Ti (Polygonum multiflorum). Professional Monograph. 2012; https://naturalmedicines.therapeuticresearch.com. Accessed 11/10/2015.

Siberian Ginseng (*Acanthopanax senticosus*, previously *Eleutherococcus senticosus*)

Biological Actions:
Adaptogenic, anti-fatigue, anti-inflammatory, antioxidant, antistress, hepatoprotective, immune modulating, neuroprotective, tonic.[2,57,58]

Traditional Use:
Siberian ginseng has been used for over 2000 years in traditional Chinese medicine. Based on traditional use, Siberian ginseng helps to expel wind dampness in the body, to strengthen bones, and to enhance the flow of Qi and blood. It also helps invigorate and tonify the spleen and kidneys and has tranquilizing actions.[2] Siberian ginseng has been used clinically to prevent respiratory illnesses (colds and influenza), to increase vitality and energy, to treat edema, and for joint and back pain.[4] Other traditional uses include insomnia, fatigue, lowered immunity and anorexia.[2]

Scientific Evidence:
The key constituents of Siberian ginseng include phenylpropanoids (e.g., syringin, also known as eleutheroside B, and syringaresinol, also known as eleutheroside E), lignans (e.g., sesamin), saponins (e.g., daucosterol), coumarins, terpenoids, flavonoids, organic acids, and vitamins.[59]

Siberian ginseng is primarily known as an adaptogenic herb.[59] Some of its adaptogenic effects have been attributed to direct modulation of the hypothalamic-pituitary-adrenal axis, though little data exists to support this mechanism in humans. Animal studies suggest it does target regions of the brain associated with the response to stress, the supraoptic nuclei and paraventricular nuclei.[60] However, rather than having one specific molecular or target tissue, growing evidence suggests that Siberian ginseng acts in a polyvalent manner; a systems biology analysis found that adaptogens, including Siberian ginseng, modulated the activity of over 3500 genes, nearly 100 of which were closely associated with adaptive stress response and adaptive stress-response signaling pathways. For example, Siberian ginseng upregulated expression of stress-protective and neuroprotective urocortins while downregulating expression of stress-mimetic and proinflammatory corticotropin-releasing hormone, effectively inhibiting inflammation. The expression of a wide diversity of genes found to prevent stress-induced and aging-related disorders were modulated by Siberian ginseng, including those influencing inflammatory pathways linked to cardiovascular health, neurodegenerative–cognitive impairment and metabolic disorders.[61]

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[57] Monograph. Eleutherococcus senticosus. Altern Med Rev. 2006 Jun;11(2):151-5. PMID: 16813463.
[58] Yan-Lin S, Lin-De L, Soon-Kwan H. Eleutherococcus senticosus as a crude medicine: Review of biological and pharmacological effects. Journal of Medicinal Plants Research. 2011;5(25):5946-5952.
[59] Todorova V, Ivanov K, Delattre C, et al. Plant Adaptogens-History and Future Perspectives. Nutrients. 2021 Aug 20;13(8):2861.
[60] Soya H, Deocaris CC, Yamaguchi K, et al. Extract from Acanthopanax senticosus harms (Siberian ginseng) activates NTS and SON/PVN in the rat brain. Biosci Biotechnol Biochem. 2008 Sep;72(9):2476-80.
[61] Panossian A, Seo EJ, Efferth T. Novel molecular mechanisms for the adaptogenic effects of herbal extracts on isolated brain cells using systems biology. Phytomedicine. 2018 Nov 15;50:257-284.

Syringin specifically has also been found to modulate several pathways related to adipocyte metabolism; in vitro it has been shown to reduce the expression of peroxisome proliferator-activated receptor gamma, and enhance phosphorylation of the AMP-activated protein kinase and acetyl-CoA carboxylase, influencing both adipocyte and lipid metabolism.[62] Animal studies also indicate a hypoglycemic effect of syringin, mediated in part by enhanced secretion of beta-endorphin.[63] Extracts of Siberian ginseng also have been shown to have immunomodulatory effects in vitro, including a shift in macrophage polarization, towards the anti-inflammatory M2 subtype, as well as an increase in phagocytic activity.[64] Polysaccharides from Siberian ginseng have been found to interact with toll-like receptors, activating both macrophages and B cells in vitro, and to also stimulate splenocyte proliferation in an animal model.[65,66] Other in vitro effects include a reduction in malondialdehyde, nitric oxide (NO), IL-1β, and TNF-α levels, as well as increases in antioxidant defense enzymes, including glutathione peroxidase and superoxide dismutase.[67]

In a small double-blinded cross-over trial, recreational athletes supplemented with Siberian ginseng had improvements in VO2max, and elevated free fatty acid levels, suggesting improved cardiorespiratory fitness and glycogen sparing over an 8-week period.[68] Clinical trials also suggest a significant improvement in outcomes when given prophylactically for a variety of upper respiratory viral infections.[69]

Safety Summary:
Considered safe and well tolerated with no adverse reactions expected at the dose recommended.[2] Siberian ginseng is not recommended during the acute phase of infections.[2] In therapeutic doses, it may increase plasma drug levels when used in conjunction with digoxin.[2] Exercise caution during pregnancy and lactation as safety has not been established during these times.[70]

Radix Zingiberis Officianalis (*Zingiber officinale*)

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[62] Hossin AY, Inafuku M, Takara K, et al. Syringin: A Phenylpropanoid Glycoside Compound in Cirsium brevicaule A. GRAY Root Modulates Adipogenesis. Molecules. 2021 Mar 11;26(6):1531.
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[69] Panossian A, Brendler T. The Role of Adaptogens in Prophylaxis and Treatment of Viral Respiratory Infections. Pharmaceuticals (Basel). 2020 Sep 8;13(9):236.
[70] Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006–. Eleuthero. 2021 May 17.

Biological Actions:
Antiemetic, anti-inflammatory, antiplatelet, carminative, diaphoretic, digestive stimulant, peripheral circulatory stimulant.[2]

Traditional Use:
Traditionally ginger has been used to enhance digestion, to treat digestive problems including colic, flatulent dyspepsia, cramping, peptic ulcer, loss of appetite, and gastrointestinal infections.[2] It has been used for deficiency and cold syndromes, in large part for digestive and respiratory diseases.[71]

Scientific Evidence:
The key components of ginger include volatile oil, gingerol analogues, diarylheptanoids, phenylalkanoids, and sulfonates. Over 70 compounds have been identified in the volatile oil alone, including sesquiterpenoids and monoterpenes, primarily α-zingiberene and smaller amounts of β-sesquiphellandrene, β-bisabolene, β-phellandrene, and geraniol. The pungent and warm sensation of ginger is largely attributed to the gingerol analogues, including gingerols (predominantly 6-gingerol), shogaols, paradols, and zingerone.[71] Over 40 diarylheptanoids compounds have been discovered in ginger, many with antioxidant, anti-inflammatory, and hepatoprotective properties. Protective effects on the gastrointestinal, nervous, and cardiovascular systems, as well as the liver and kidney, have been shown for various components of ginger.[71]

Many of ginger's constituents have been shown to have anti-inflammatory effects; *in vitro* and animal studies have outlined several mechanisms of action for 6-gingerol, for example, including prevention of reactive oxygen species formation, upregulation of the Nrf2 pathway, inhibition of p38 MAPK activation, down-regulation of the NF-κB pathway, and protection against LPS-induced inflammation, all of which have been associated with protection of the intestinal mucosa and maintenance of an intact barrier.[72,73,74,75] *In vitro* studies also suggest that ginger has favorable effects on the gut microbiome, promoting growth of beneficial bacterial populations, such as *Bifidobacterium* and *Enterococcus*, as well as enhancing production of short-chain fatty acids.[76] Animal models also indicate reductions at the genus level in *Escherichia, Shigella* and *Bacteroides* despite overall increases in bacterial diversity, as well as restoration of the tight junction protein zonula occludens-1 (ZO-1).[77] *In vivo*, ginger was shown to have anti-parasitic effects, demonstrating a significant reduction of the shedding of the cysts of *Blastocystis spp.* in an animal model, with a corresponding

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reduction in nitric oxide and malondialdehyde (comparable to nitazoxanide).[78] Several constituents of ginger, particularly [10]-gingerol, were previously shown to have larvicidal effects against the parasite *Angiostrongylus cantonensis*.[79] Additionally, ethanol extracts of ginger have been shown to inhibit the embryogenesis, infectivity, and viability of *Toxocara canis* eggs in animal studies, the parasitic roundworm spread by both dogs and cats for which 5% of the U.S. population has detectable antibodies against.[80,81]

Several mechanisms of action likely underlie ginger's anti-emetic effects, though 5-HT_3 receptor antagonism is perhaps the strongest candidate.[82] Interestingly, these receptors have recently been linked with inflammatory and metabolic disorders, providing another pathway for ginger's broad effects.[83] The antiemetic and antinausea activities of ginger have been demonstrated in numerous clinical trials, and assessed in several systematic reviews and meta-analyses, demonstrating efficacy during pregnancy, post-operatively, as well as for nausea/vomiting associated with chemotherapy.[2,84,85,86,87] Ginger has also been shown to enhance gastric emptying in healthy patients as well as those with functional dyspepsia.[88,89]

Ginger's anti-inflammatory actions may also underlie its benefit for other body systems. Among people with migraine, a meta-analysis of 3 randomized clinical trials found that in addition to a reduction in nausea and vomiting, ginger was also associated with a significant decrease in pain.[90] A systematic review of 16 randomized and controlled trials found a significant reduction in several biomarkers of inflammation, including CRP, hs-CRP, and TNF-α with ginger supplementation.[91] In addition to a hypotensive effect, an increase in nitric oxide synthesis expression, and an inhibition of platelet aggregation, this anti-inflammatory effect provides a plausible explanation for enhanced

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[78] Abdel-Hafeez EH, Ahmad AK, Kamal AM, et al. In vivo antiprotozoan effects of garlic (Allium sativum) and ginger (Zingiber officinale) extracts on experimentally infected mice with Blastocystis spp. Parasitol Res. 2015 Sep;114(9):3439-44.
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[90] Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: A meta-analysis of randomized controlled studies. Am J Emerg Med. 2021 Aug;46:567-571.
[91] Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020 Nov;135:155224.

cardiovascular health attributed to ginger consumption.[92,93] Ginger has also been associated with hypoglycemic effects, and an improvement in the metabolic profile of people with diabetes. In a systematic review of randomized and controlled trials, ginger supplementation was associated with reductions in fasting blood glucose levels as well as HbA1c, along with both systolic and diastolic blood pressure.[94]

Safety Summary:
Considered safe and well tolerated at the dose recommended.[2] No adverse effects expected during pregnancy and lactation at the dose recommended.[95]

Rhizoma Atractylodis Macrocephalae (*Atractylodes lancea*)

Biological Actions:
Anti-inflammatory, antimicrobial, antioxidant, immunomodulatory.[96,97]

Traditional Use:
The rhizome of Atractylodes has been used in traditional Chinese medicine as a tonic herb, for the treatment of rheumatic diseases, digestive disorders, as well as colds and influenza.[96,97] Atractylodes was used to invigorate the stomach, strengthen the spleen, eliminate dampness, and expel and clear away wind-cold.[96,97] In Thai traditional medicine, it has been used to treat fever and the common cold. The Thai also utilized Atractylodes for the treatment of gastrointestinal disorders including dyspepsia, flatulence, nausea, and non-infectious diarrhea.[97] In Japan, Atractylodes was traditionally used to treat gastrointestinal diseases such as nausea, gastroparesis, and gastric atony.[98]

Scientific Evidence:
Over 200 compounds have been identified in Atractylodes rhizome, most of them in the volatile oil, which provides terpenes, such as atractylenolide (I-IV), and the sesquiterpenenes (primarily hinesol, β-eudesmol, and elemol), as well as alkynes and aromatic glycosides.[97,99,100] Its pharmacological properties have been studied predominantly through *in vitro, ex vivo*, and animal trials.[97]

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[92] Li C, Li J, Jiang F, et al. Vasculoprotective effects of ginger (Zingiber officinale Roscoe) and underlying molecular mechanisms. Food Funct. 2021 Mar 15;12(5):1897-1913.
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[98] Kimura Y, Sumiyoshi M. Effects of an Atractylodes lancea rhizome extract and a volatile component β-eudesmol on gastrointestinal motility in mice. J Ethnopharmacol. 2012 May 7;141(1):530-6.
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[100] Yang L, Yu H, Hou A, et al. A Review of the Ethnopharmacology, Phytochemistry, Pharmacology, Application, Quality Control, Processing, Toxicology, and Pharmacokinetics of the Dried Rhizome of Atractylodes macrocephala. Front Pharmacol. 2021 Nov 3;12:727154.

Atractylodes extract has been shown to delay gastric emptying and stimulate small intestinal motility in mice.[98] It has also demonstrated antiulcer properties in animal models, with some evidence that it may promote the healing of intestinal injuries.[101,102,103] An Atractylodes isolate, β-eudesmol, demonstrated anti-inflammatory effects by down-regulation of IL-6 production and expression, via the modulation of NF-κB.[104] Antimicrobial activity of Atractylodes has been demonstrated *in vitro* against *Staphylococcus aureus, Escherichia coli, Saccharomyces cerevisiae, Candida albicans*, *Rhodotorula glutinis* and *Saprolegnia*.[104,105,106] In an animal model, it was also shown to promote the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, and to prevent the dysbiosis that normally follows antibiotic use.[107,108,109] Animal models have also shown an increase in the expression of the tight junction proteins zonula occludens-1 (ZO-1) and occludin, further suggesting a role in restoring intestinal barrier integrity.[110] *In vitro* data suggests an immunomodulatory effect on intestinal cells, including an activation of T cells in Peyer's patches.[111] While human clinical trials are lacking, a small phase 1 trial suggests Atracylodes extracts have an immunomodulatory effect, generally inhibiting inflammatory signals while promoting B and T cell activity.[112]

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[101] Plengsuriyakarn T, Viyanant V, Eursitthichai V, et al. Anticancer activities against cholangiocarcinoma, toxicity and pharmacological activities of Thai medicinal plants in animal models. BMC Complement Altern Med. 2012 Mar 27;12:23.
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[104] Seo MJ, Kim SJ, Kang TH, et al. The regulatory mechanism of β-eudesmol is through the suppression of caspase-1 activation in mast cell-mediated inflammatory response. Immunopharmacol Immunotoxicol. 2011 Mar;33(1):178-85.
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[110] Shi K, Qu L, Lin X, et al. Deep-Fried Atractylodis Rhizoma Protects against Spleen Deficiency-Induced Diarrhea through Regulating Intestinal Inflammatory Response and Gut Microbiota. Int J Mol Sci. 2019 Dec 23;21(1):124.
[111] Qin J, Wang HY, Zhuang D, et al. Structural characterization and immunoregulatory activity of two polysaccharides from the rhizomes of Atractylodes lancea (Thunb.) DC. Int J Biol Macromol. 2019 Sep 1;136:341-351.
[112] Kulma I, Panrit L, Plengsuriyakarn T, et al. A randomized placebo-controlled phase I clinical trial to evaluate the immunomodulatory activities of Atractylodes lancea (Thunb) DC. in healthy Thai subjects. BMC Complement Med Ther. 2021 Feb 12;21(1):61.

Safety Summary:
Considered safe and well tolerated with no adverse reactions expected at the dose recommended.[99] Atractylodes may cause an allergic reaction in individuals with a known sensitivity to plants from the Asteraceae/Compositae family.[99] Exercise caution during pregnancy and lactation as safety has not been established during these times.[99]

Wild Yam (*Dioscorea villosa*)

Biological Actions:
Anti-inflammatory, antioxidant, hepatoprotective.[4,113,114]

Traditional Use:
In traditional Western medicine, wild yam has been used for gastrointestinal disorders including colic, gastrointestinal irritation, spasm, diverticulitis and for neuralgic affection and asthma due to its antispasmodic, anti-inflammatory and autonomic nervous system-relaxant properties.[4] It has also been used for rheumatoid arthritis and hormonal imbalance associated with menopause.

Scientific Evidence:
The active constituents of wild yam include phenols, phytosterols, steroidal saponins (diosgenin, dioscin, dioscorin), alkaloids and flavonoids. Animal studies also suggest that wild yam or its extracts have a hypoglycemic effect, reducing fasting glucose and increasing insulin levels, though no human data exists to verify these effects.[115] Preclinical studies suggest steroidal saponins have anti-inflammatory and antioxidant effects, modulating inflammatory pathways primarily through the Nf-κB, TLR4 and MAPKs pathways.[116] Dioscin specifically has been shown in animal studies to support intestinal barrier function, by increasing the expression of zonula occludens-1, occludin and mucin-2.[117]

Although diosgenin is used as a precursor for estrogen and progesterone by the pharmaceutical industry, this conversion is a synthetic one, and a small clinical trial demonstrated no benefit of a wild yam extract on menopausal symptoms.[118] However, diosgenin has demonstrated hepatoprotective, neuroprotective, antioxidative and hypolipidemic effects *in vitro* and in animal models, with multiple

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[113] Bone K. A Clinical Guide to Blending Liquid Herbs: Herbal Formulations for the Individual Patient. Edinburgh, Scotland: Churchill Livingstone; 2003.
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[116] Passos FRS, Araújo-Filho HG, Monteiro BS, et al. Anti-inflammatory and modulatory effects of steroidal saponins and sapogenins on cytokines: A review of pre-clinical research. Phytomedicine. 2022 Feb;96:153842.
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[118] Komesaroff PA, Black CV, Cable V, et al. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. Climacteric. 2001 Jun;4(2):144-50.

mechanisms for its effects.[119,120,121] *In vitro* trials with diosgenin have reported anti-inflammatory activity through the down-regulation of cyclooxygenase expression.[122] And several steroidal glycosides in Dioscorea have also exhibited hepatoprotective effects, specifically against oxidative damage.[123] Dioscorea saponins have also demonstrated cytotoxic and antifungal activity in vitro.[124] To date, wild yam has not been studied under clinical trial conditions, rather evidence is derived mainly from traditional use and *in vitro* and animal studies.

Safety Summary:
Considered safe and well tolerated with no known interactions and contraindications.[113] Due to its saponin content, wild yam may cause irritation of the gastric mucosa and reflux when taken in therapeutic doses.[113] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[113]

Sclerotium Poriae Cocos (*Poria cocos*)

Biological Actions:
Antihyperglycemic, anti-inflammatory, antioxidant, diuretic, immune modulating, sedative.[125,126,127]

Traditional Use:
Sclerotium Poriae Cocos, also known as poria mushroom or Fu-ling, is a saprophytic fungus used in traditional Chinese and Japanese medicine due to its diuretic, sedative, and tonic effects.[126] It has been used in traditional medicine to treat chronic gastritis, edema, nephrosis, gastric atony, acute gastroenteric catarrh, dizziness, nausea and emesis.[125]

Scientific Evidence:
The major constituents of poria mushroom include triterpenoids (Lanostane-, Eburicane-, *seco* Lanostane and seco-Eburicane-type triterpenes) and polysaccharides.[126] *In vivo* administration of polysaccharides isolated from poria mushroom have demonstrated broad spectrum anti-inflammatory activity.[128] Poria polysaccharides have been shown to activate macrophages to induce nitric oxide

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[119] Son IS, Kim JH, Sohn HY, et al. Antioxidative and hypolipidemic effects of diosgenin, a steroidal saponin of yam (Dioscorea spp.), on high-cholesterol fed rats. Biosci Biotechnol Biochem. 2007 Dec;71(12):3063-71.
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[122] Moalic S, Liagre B, Corbière C, et al. A plant steroid, diosgenin, induces apoptosis, cell cycle arrest and COX activity in osteosarcoma cells. FEBS Lett. 2001 Oct 12;506(3):225-30.
[123] Siddiqui MA, Ali Z, Chittiboyina AG, et al. Hepatoprotective Effect of Steroidal Glycosides From Dioscorea villosa on Hydrogen Peroxide-Induced Hepatotoxicity in HepG2 Cells. Front Pharmacol. 2018 Jul 23;9:797.
[124] Sautour M, Mitaine-Offer A-C, Lacaille-Dubois M-A. The Dioscorea genus: a review of bioactive steroid saponins. J Nat Med. 2007;61(2):91-101.
[125] Sun Y. Biological activities and potential health benefits of polysaccharides from Poria cocos and their derivatives. Int J Biol Macromol. 2014 Jul;68:131-4.
[126] Ríos JL. Chemical constituents and pharmacological properties of Poria cocos. Planta Med. 2011 May;77(7):681-91.
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production and iNOS transcription through the activation of NF-κB/Rel.[128] Treatment of murine macrophages has resulted in NF-κB/Rel activation and iNOS expression through the p38 kinase pathway and membrane receptors (CD14, Toll-like receptor 4, and CR3), which are critically involved in the signal transduction leading to NF-κB/Rel activation.[128]

Pachymic acid, a lanolin triterpene extracted from poria, has demonstrated anti-inflammatory effects in multiple disease models, and also appears to directly inhibit the NF-κB and MAPK pathways, as well as to activate the Nrf2 antioxidant defense pathway.[129,130] Pachymic acid has been found to induce apoptosis in neoplastic cells *in vitro*.[131,132,133] Pachymic acid also modulates the GABA receptor, thereby contributing to a sedative effect in animals.[134] It has also demonstrated an inhibitory effect on the 5-HT_{3A} receptor, along with 2 other triterpenoids found in poria, likely contributing to the anti-nausea effect reported with traditional usage.[135,136] Similarly, a potassium-sparing increase in urinary output has been observed in animals following administration of the triterpenoids in poria, lending support to the reported traditional use as a diuretic.[137] Crude extracts of poria have also been shown to have a hypoglycemic effect in animals, likely through an increase in insulin sensitivity.[138]

Poria mushroom is known as an immunomodulatory agent that alters the activity of immune function through modulation of cytokine expression.[126] Ethanol extracts of poria mushroom have demonstrated immunomodulatory activities *in vitro*.[127] In human peripheral blood monocytes,poria has enhanced the secretion of immune stimulators IL-1β, IL-6 and TNF-α, and suppressed the secretion of an immune suppressor, transforming growth factor-β (TGF-β).[127] Poria extracts have also been shown to regulate the balance between the Th1/Th2 axis and the Th17/Treg axis, promote repair of the gut mucosa, and regulate brain-gut peptides in animals.[139] Additionally, several compounds present in poria have demonstrated broad nematicidal activity, killing over 90% of *Panagrellus redivivue*, *Meloidogyne arenaria*, *Bursaphelenchus xylophilus* within 12 hours *in vitro*.[140] Human clinical trials are needed to verify many of

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[129] Gui Y, Sun L, Liu R, et al. Pachymic acid inhibits inflammation and cell apoptosis in lipopolysaccharide (LPS)-induced rat model with pneumonia by regulating NF-κB and MAPK pathways. Allergol Immunopathol (Madr). 2021 Sep 1;49(5):87-93.
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[140] Li GH, Shen YM, Zhang KQ. Nematicidal activity and chemical component of Poria cocos. J Microbiol. 2005 Feb;43(1):17-20.

the effects observed *in vitro* and in animal studies.

Safety Summary:
Considered safe with no known adverse effects and interactions.[141] Exercise caution during pregnancy and lactation as safety has not been established during these times.[141]

Radix Codonopsis (*Codonopsis pilosulae*)

Biological Actions:
Anti-fatigue, antioxidant, antiulcer, immunomodulatory, prebiotic.[142,143,144]

Traditional Use:
Codonopsis has been used in traditional Chinese medicine to treat digestive dysfunction and associated symptoms such as poor appetite, dyspepsia, indigestion, loose stools and fatigue.[144,] It was also used for pulmonary insufficiencies such as shortness of breath, coughing, wheezing, and symptoms of COPD.[145] Codonopsis exhibits similar therapeutic effects to *Panax ginseng*, and is often used as a substitute for this herb.[143] In traditional Chinese medicine, codonopsis is often used in combination with other herbs to improve qi deficiency, replenish vital energy, nourish the blood, spleen, and lungs, improve gastrointestinal function, enhance immunity, and delay senescence.[145,146,147]

Scientific Evidence:
The main constituents of codonopsis include sterols, triterpenes, glycosides, alkaloids and polysaccharides.[143] More recently, other bioactive compounds were discovered in codonopsis, including tryptophan, syringin, tangshenoside I, codonopyrrolidium A, and lobetyolin, which suggest possible hypoglycemic as well as neuro- and gastroprotective properties.[148,147] Pharmacological studies on codonopsis indicate it does provide protection against peptic ulceration, and also has beneficial effects on bowel regulation, as well as a favorable effect on the growth of *Bifidobacterium* and *Lactobacillus* (animal studies), possibly as a prebiotic.[149,150,151] Inulin-type fructans in codonopsis

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[141] Natural Medicines. Poria Mushroom. Professional Monograph. 2013; https://naturalmedicines.therapeuticresearch.com. Accessed 23/09/2015.
[142] Ng TB, Liu F, Wang HX. The antioxidant effects of aqueous and organic extracts of Panax quinquefolium, Panax notoginseng, Codonopsis pilosula, Pseudostellaria heterophylla and Glehnia littoralis. J Ethnopharmacol. 2004 Aug;93(2-3):285-8.
[143] Yongxu S, Jicheng L. Structural characterization of a water-soluble polysaccharide from the roots of Codonopsis pilosula and its immunity activity. Int J Biol Macromol. 2008 Oct 1;43(3):279-82.
[144] Wang ZT, Ng TB, Yeung HW, et al. Immunomodulatory effect of a polysaccharide-enriched preparation of Codonopsis pilosula roots. Gen Pharmacol. 1996 Dec;27(8):1347-50.
[145] Shergis JL, Liu S, Chen X, et al. Dang shen [Codonopsis pilosula (Franch.) Nannf] herbal formulae for chronic obstructive pulmonary disease: a systematic review and meta-analysis. Phytother Res. 2015 Feb;29(2):167-86.
[146] Liu M, Tan H, Zhang X, et al. Hematopoietic effects and mechanisms of Fufang e'jiao jiang on radiotherapy and chemotherapy-induced myelosuppressed mice. J Ethnopharmacol. 2014 Mar 28;152(3):575-84.
[147] Liang Y, Wei G, Ning K, et al. Contents of lobetyolin, syringin, and atractylolide III in Codonopsis pilosula are related to dynamic changes of endophytes under drought stress. Chin Med. 2021 Nov 22;16(1):122.
[148] Gao S, Liu J, Wang M, et al. Exploring on the bioactive markers of Codonopsis Radix by correlation analysis between chemical constituents and pharmacological effects. J Ethnopharmacol. 2019 May 23;236:31-41.
[149] Wang ZT, Du Q, Xu GJ, et al. Investigations on the protective action of Condonopsis pilosula (Dangshen) extract on experimentally-induced gastric ulcer in rats. Gen Pharmacol. 1997 Mar;28(3):469-73.
[150] Fu YP, Feng B, Zhu ZK, et al. The Polysaccharides from Codonopsis pilosula Modulates the Immunity and Intestinal Microbiota of Cyclophosphamide-Treated Immunosuppressed Mice. Molecules. 2018 Jul 20;23(7):1801.
[151] Fu YP, Li LX, Zhang BZ, et al. Characterization and prebiotic activity in vitro of inulin-type fructan from Codonopsis pilosula roots. Carbohydr Polym. 2018 Aug 1;193:212-220.

are likely responsible for both the prebiotic effects as well as the protection of the gastric mucosa, in part by upregulating the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase.[152] Polysaccharides from codonopsis have been associated with anti-fatigue effects in animal studies, at least in part by increasing both hepatic and muscle glycogen stores.[153] Codonopsis oligosaccharides have also been associated with a variety of immunomodulatory effects in animals, including an upregulation of intestinal mucosal immunity. [150,154]

A systematic review of randomized trials evaluating codonopsis use for patients with COPD found improvements in quality of life, lung function, exercise capacity, and exacerbations of COPD, with few adverse effects. However, significant heterogeneity between trials and low quality study designs prevented a strong recommendation for its use.[145] In a small double-blinded and randomized placebo-controlled trial, the combination of Gingko biloba and codonopsis was shown to improve cognitive to a greater degree than either placebo or Ginkgo alone; notable about this study was the young population, with a mean age of 28.[155] Its effect on cognitive function in older adults has not been established in clinical trials.

Safety Summary:
Codonopsis is considered safe and well tolerated.[145] In therapeutic doses, concomitant use may interact with antiplatelet or anticoagulant medications.[156] Exercise caution during pregnancy and lactation as safety has not been established during these times.[156]

Radix Peony (*Paeonia lactiflora*)

Biological Actions:
Anticonvulsant, anti-inflammatory, antioxidant, hepatoprotective, immunomodulatory, muscle relaxant, neuroprotective, spasmolytic.[113,157]

Traditional Use:
Peony has been used in traditional Chinese medicine to invigorate and cool the blood and clear the liver.[113] Clinically, it is utilized for the treatment of wounds and fungal infections, as well as pain and spasmodic conditions.[158] Peony has also been used in combination with other herbs as a uterine

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[152] Li J, Wang T, Zhu Z, et al. Structure Features and Anti-Gastric Ulcer Effects of Inulin-Type Fructan CP-A from the Roots of Codonopsis pilosula (Franch.) Nannf. Molecules. 2017 Dec 18;22(12):2258.
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[154] Bai RB, Zhang YJ, Fan JM, et al. Immune-enhancement effects of oligosaccharides from Codonopsis pilosula on cyclophosphamide induced immunosuppression in mice. Food Funct. 2020 Apr 30;11(4):3306-3315.
[155] Singh B, Song H, Liu XD, et al. Dangshen (Codonopsis pilosula) and Bai guo (Gingko biloba) enhance learning and memory. Altern Ther Health Med. 2004 Jul-Aug;10(4):52-6.
[156] Natural Medicines. Codonopsis. Professional Monograph. 2013; https://naturalmedicines.therapeuticresearch.com. Accessed 2015/09/25.
[157] Lee SJ, Lee IS, Mar W. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 activity by 1,2,3,4,6-penta-O-galloyl-beta-D-glucose in murine macrophage cells. Arch Pharm Res. 2003 Oct;26(10):832-9.
[158] Peony (Paeonia Spp). Monograph. Altern Med Rev. 2001;6(5):495-499.

tonic.[159,160]

Scientific Evidence:

The active constituents of peony include glycosides (paeoniflorin is typically 40% of total glycosides), flavonoids, proanthocyanidins, tannins, terpenoids, triterpenoids, and complex polysaccharides.[158] An extract of peony, termed total glucosides of paeony (TGP), contains at least fifteen monoterpene glycosides, such as paeoniflorin, albiflorin, oxypaeoniflorin, and has been shown to have hepatoprotective and immunomodulatory actions, as well as a general anti-inflammatory effect.[161,162] Animal studies suggest it may also modulate the gut microbiome as well as intestinal mucosal immunity.[163] TGP has been used adjunctively to reduce the toxicity of standard treatments for rheumatoid arthritis; a systematic review of 39 trials found a reduction in hepatic adverse effects and leukopenia when TGP was used with other therapies for rheumatoid arthritis, i.e. methotrexate and leflunomide.[164] TGP has also shown benefit in clinical trials for other autoimmune conditions, including Sjögren's syndrome and psoriasis, for which it demonstrated non only improvement in symptoms, but also a reduction in adverse effects associated with standard therapies.[165,166] Extracts of peony have also been found to have an anti-fungal effect, inhibiting cell wall synthesis and biofilm formation in *C. albicans*.[167,168] Paeoniflorin, while lacking any direct parasitic activity, was shown to inhibit hepatic fibrosis and granuloma in an animal model of *S. japonicum*, most likely through inhibition of IL-13.[169]

When combined with *Glycyrrhizae* radix (known as Shakuyaku-kanzo-to), peony root has been shown in clinical trials to provide relief for severe muscle cramping, though more data is needed.[170] Paeoniflorin alone has been found to have similar anti-inflammatory properties to TGP, and in animals has demonstrated an anti-convulsant effect, not by influencing GABA levels, but by modulating the metabotropic glutamate receptor 5 (mGluR5).[171] In an animal model of myocardial infarction,

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[159] Harada M, Suzuki M, Ozaki Y. Effect of Japanese Angelica root and peony root on uterine contraction in the rabbit in situ. J Pharmacobiodyn. 1984 May;7(5):304-11.
[160] Pizzorno JE, Murray MT. Textbook of Natural Medicine. 5th ed. Chapter 53. Churchill Livingstone; 2020.
[161] Zhang W, Dai SM. Mechanisms involved in the therapeutic effects of Paeonia lactiflora Pallas in rheumatoid arthritis. Int Immunopharmacol. 2012 Sep;14(1):27-31.
[162] Li H, Cao W, Lu M, et al. Urinary and Serum Metabolomics Analyses Uncover That Total Glucosides of Paeony Protect Liver against Acute Injury Potentially via Reprogramming of Multiple Metabolic Pathways. Evid Based Complement Alternat Med. 2017;2017:9038260.
[163] Peng J, Lu X, Xie K, et al. Dynamic Alterations in the Gut Microbiota of Collagen-Induced Arthritis Rats Following the Prolonged Administration of Total Glucosides of Paeony. Front Cell Infect Microbiol. 2019 Jun 12;9:204.
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[165] Liu X, Li X, Li X, et al. The efficacy and safety of total glucosides of peony in the treatment of primary Sjögren's syndrome: a multi-center, randomized, double-blinded, placebo-controlled clinical trial. Clin Rheumatol. 2019 Mar;38(3):657-664.
[166] Yu C, Fan X, Li Z, et al. Efficacy and safety of total glucosides of paeony combined with acitretin in the treatment of moderate-to-severe plaque psoriasis: a double-blind, randomised, placebo-controlled trial. Eur J Dermatol. 2017 Apr 1;27(2):150-154.
[167] Lee HS, Kim Y. Development of Candida albicans Biofilms Is Diminished by Paeonia lactiflora via Obstruction of Cell Adhesion and Cell Lysis. J Microbiol Biotechnol. 2018 Mar 28;28(3):482-490.
[168] Lee HS, Kim Y. Paeonia lactiflora Inhibits Cell Wall Synthesis and Triggers Membrane Depolarization in Candida albicans. J Microbiol Biotechnol. 2017 Feb 28;27(2):395-404.
[169] Li X, Shen J, Zhong Z, et al. Paeoniflorin ameliorates schistosomiasis liver fibrosis through regulating IL-13 and its signalling molecules in mice. Parasitology. 2010 Jul;137(8):1213-25.
[170] Ota K, Fukui K, Nakamura E, et al. Effect of Shakuyaku-kanzo-to in patients with muscle cramps: A systematic literature review. J Gen Fam Med. 2020 Feb 16;21(3):56-62.
[171] Hino H, Takahashi H, Suzuki Y, et al. Anticonvulsive effect of paeoniflorin on experimental febrile seizures in immature rats: possible application for febrile seizures in children. PLoS One. 2012;7(8):e42920.

paeoniflorin has been shown to improve the left ventricular ejection fraction and limit adverse ventricular remodeling after myocardial infarction.[172] Animal studies also indicate a mitigation of vascular damage induced by hyperglycemia, as well as mitigation of neurological and cognitive deficits induced via several mechanisms, including Aβ-mediated neuroinflammation.[173,174,175] Mechanistic data suggests paeoniflorin's anti-inflammatory effects may have broadly protective benefits, ranging from atherosclerosis and cardiovascular protection to neurological benefits, including an analgesic effect.[176,177]

Safety Summary:
Considered safe with no adverse effects or interactions expected.[113] No adverse effects expected during pregnancy and lactation at the dose recommended.[113]

Tuber Curcumae (*Curcuma longa*)

Biological Actions:
Anti-inflammatory, antimicrobial, antioxidant, cardioprotective, carminative, cholagogue, choleretic, hepatoprotective, hypolipidemic, neuroprotective, vasoprotective.[2,178]

Traditional Use:
Turmeric has a long history of use in Ayurvedic medicine for the treatment of inflammatory conditions, as a tonic, and blood purifying agent. It has also been used for poor appetite and for liver disorders.[2] In traditional Chinese medicine turmeric has been used to invigorate the blood and as a qi or vital energy stimulant.[2] Other traditional applications include use as a tonic, anti-inflammatory, circulatory stimulant, analgesic, and for digestive disorders, with widespread use around the world, including Peru, the Philippines, Indonesia, Australia, and Thailand.[179]

Scientific Evidence:
The main constituents of turmeric include volatile oils (natlantone, tumerone and zingiberone) and curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin), as well as proteins, sugars

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[172] Chen H, Dong Y, He X, et al. Paeoniflorin improves cardiac function and decreases adverse postinfarction left ventricular remodeling in a rat model of acute myocardial infarction. Drug Des Devel Ther. 2018 Apr 12;12:823-836.
[173] Wang JS, Huang Y, Zhang S, et al. A Protective Role of Paeoniflorin in Fluctuant Hyperglycemia-Induced Vascular Endothelial Injuries through Antioxidative and Anti-Inflammatory Effects and Reduction of PKCβ1. Oxid Med Cell Longev. 2019 Apr 10;2019:5647219.
[174] Cho EJ, Kim HY, Lee AY. Paeoniflorin ameliorates Aβ-stimulated neuroinflammation via regulation of NF-κB signaling pathway and Aβ degradation in C6 glial cells. Nutr Res Pract. 2020 Dec;14(6):593-605.
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[176] Jiao F, Varghese K, Wang S, et al. Recent Insights Into the Protective Mechanisms of Paeoniflorin in Neurological, Cardiovascular, and Renal Diseases. J Cardiovasc Pharmacol. 2021 Jun 1;77(6):728-734.
[177] Andoh T, Kobayashi N, Uta D, et al. Prophylactic topical paeoniflorin prevents mechanical allodynia caused by paclitaxel in mice through adenosine A1 receptors. Phytomedicine. 2017 Feb 15;25:1-7.
[178] Jabczyk M, Nowak J, Hudzik B, et al. Curcumin in Metabolic Health and Disease. Nutrients. 2021 Dec 11;13(12):4440.
[179] Ayati Z, Ramezani M, Amiri MS, et al. Ethnobotany, Phytochemistry and Traditional Uses of Curcuma spp. and Pharmacological Profile of Two Important Species (C. longa and C. zedoaria): A Review. Curr Pharm Des. 2019;25(8):871-935.

and resins.[180] While the bulk of the research focus has been focused on curcumin, there is some evidence that the other components found in turmeric root also have important biological actions; bisdemethoxycurcumin has been shown to reduce the virulence and interfere with the biofilm formation of methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro*, and help to protect gastrointestinal integrity in animal studies.[181,182] Demethoxycurcumin has been found to help preserve endothelial function, inhibit COX-2 expression and NF-κB activation, and increase expression of antioxidant enzymes in animal models and *in vitro*.[183]

Curcumin, sometimes referred to as the golden nutrient, has clearly been shown to target many signaling pathways, with many biological actions, including antioxidant, anti-inflammatory, antiarthritic, anti-atherosclerotic, antimicrobial, wound healing activities.[184] Curcumin targets transcription factors, inflammatory mediators, protein kinases and enzymes, with targets including Nrf2, NF-κB, p38 MAPK, COX-2, 5-lipoxygenase, PGE2, FOXO3, inducible NOS, and TNF-α.[184] Curcumin has multiple anti-inflammatory actions, including decreasing the expression of NF-κB by acting on peroxisome proliferator-activated receptor gamma (PPARγ), and inhibiting assembly of the NLRP3 inflammasome.[185,186] The pro-inflammatory pathway associated with activation of the NLRP3 inflammasome has been associated with multiple inflammatory disease states, including stroke, pre-eclampsia, autoimmune and cardiometabolic diseases, and may be one mechanism by which curcumin mitigates tissue damage.[187,188,189] For example, in animal studies curcumin has mitigated white matter damage following ischemic stroke, and demonstrated hepatoprotective properties against aflatoxin in part by preventing NLRP3 activation, as well as by activating Nrf2 and glutathione defenses.[190,191] Curcumin also appears to interact with the farnesoid X receptor (FXR), promoting bile acid homeostasis in an animal model of cholestasis.[192]

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[180] He Y, Yue Y, Zheng X, et al. Curcumin, inflammation, and chronic diseases: how are they linked? Molecules. 2015 May 20;20(5):9183-213.
[181] Wang S, Kang OH, Kwon DY. Bisdemethoxycurcumin Reduces Methicillin-Resistant Staphylococcus aureus Expression of Virulence-Related Exoproteins and Inhibits the Biofilm Formation. Toxins (Basel). 2021 Nov 15;13(11):804.
[182] Zhang J, Yang Y, Han H, et al. Bisdemethoxycurcumin attenuates lipopolysaccharide-induced intestinal damage through improving barrier integrity, suppressing inflammation, and modulating gut microbiota in broilers. J Anim Sci. 2021 Nov 1;99(11):skab296.
[183] Hatamipour M, Ramezani M, Tabassi SAS, et al. Demethoxycurcumin: A naturally occurring curcumin analogue for treating non-cancerous diseases. J Cell Physiol. 2019 Nov;234(11):19320-19330.
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[186] Hasanzadeh S, Read MI, Bland AR, et al. Curcumin: an inflammasome silencer. Pharmacol Res. 2020 Sep;159:104921.
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[188] Zhang Y, Yang W, Li W, et al. NLRP3 Inflammasome: Checkpoint Connecting Innate and Adaptive Immunity in Autoimmune Diseases. Front Immunol. 2021 Oct 11;12:732933.
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[190] Ran Y, Su W, Gao F, et al. Curcumin Ameliorates White Matter Injury after Ischemic Stroke by Inhibiting Microglia/Macrophage Pyroptosis through NF-κB Suppression and NLRP3 Inflammasome Inhibition. Oxid Med Cell Longev. 2021 Sep 30;2021:1552127.
[191] Wang Y, Liu F, Liu M, et al. Curcumin mitigates aflatoxin B1-induced liver injury via regulating the NLRP3 inflammasome and Nrf2 signaling pathway. Food Chem Toxicol. 2022 Jan 19;161:112823.
[192] Yang F, Tang X, Ding L, et al. Curcumin protects ANIT-induced cholestasis through signaling pathway of

A broad range of clinical studies in humans has supported the use of supplemental curcumin or turmeric. Two systematic reviews of randomized controlled trials found curcumin supplementation improved several parameters in study participants with diabetes, including fasting blood glucose, HbA1c, systolic and diastolic blood pressure, and serum creatinine levels, likely through antioxidant and anti-inflammatory mechanisms.[193,194] A second systematic review of gastrointestinal disease and turmeric/curcumin supplementation found generally favorable effects on inflammatory bowel disease, irritable bowel syndrome, as well as peptic ulcer disease.[195] Although more data is needed, a meta-analysis of 10 randomized trials found a *Curcuma longa* extract provided significantly more pain-relief and functional improvement than placebo for osteoarthritis of the knee.[196] In participants with the metabolic syndrome, a range of inflammatory markers, including serum levels of TNF-α, IL-6, TGF-β and MCP-1 were reduced with curcumin supplementation compared to placebo, in a randomized and controlled trial.[197] Although isolated curcumin has been more heavily researched, with a recent focus on more highly absorbable forms, evidence also suggests that it is the interaction of curcumin and the gut microbiota (rather than direct curcumin absorption) which at least partly underlies is biological effects.[198]

Safety Summary:
Considered safe and well tolerated with no adverse reaction expected at the recommended dose.[2] Avoid in persons with biliary tract obstruction.[2] Considered to likely be safe and well tolerated during pregnancy and breastfeeding, though additional human studies are needed.[199]

Pericarpium Citri Reticulatae (*Citrus reticulata*)

Biological Actions:
Anti-inflammatory, antimicrobial, antioxidant, vasoprotective.[200,201]

FXR-regulated bile acid and inflammation. Sci Rep. 2016 Sep 14;6:33052.
[193] Jie Z, Chao M, Jun A, et al. Effect of Curcumin on Diabetic Kidney Disease: A Systematic Review and Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Clinical Trials. Evid Based Complement Alternat Med. 2021 Dec 2;2021:6109406.
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[201] Yu X, Sun S, Guo Y, et al. Citri Reticulatae Pericarpium (Chenpi): Botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. J Ethnopharmacol. 2018 Jun 28;220:265-282.

Traditional Use:

Pericarpium citri reticulatae (PCR) is the dried, ripe fruit peel of *Citrus reticulata*, often referred to as Chenpi.[202] It has been widely used as a herbal medicine in Korea, China, and Japan, to treat indigestion and inflammatory disorders of the respiratory tract including bronchitis and asthma, to promote the circulation of qi, soothing emotions such as anger, irritability, and frustration, for a variety of "stagnation" characteristics of qi, including food stagnation, with pain and distention symptoms, indigestion, abdominal fullness and distention, as well as for drying dampness and resolving phlegm.[201,202]

Scientific Evidence:

The main bioactive constituents of PCR consist of essential oils (D-limonene, β-myrcene, α-pinene, β-pinene α-terpineol, terpinen-4-ol, γ-terpinen, and linalool) and flavonoids (primarily hesperidin, as well as nobiletin and tangeretin). [201,203] The volatile constituents of the fruit peel have demonstrated antibacterial activity against *Escherichia coli, Staphylococcus aureus,* and antifungal activity against *Aspergillus flavus, Aspergillus niger, Aspergillus fumigatus* and *Candida albicans*.[200]

Unique bioflavonoids found in PCR termed poly-methoxy flavones (PMFs) have been shown to possess anti-inflammatory effects, and to modulate lipid metabolism within adipocytes, preventing lipid accumulation.[204] Animal studies suggest that modification of the gut microbiota by PMFs may underlie this effect, and that it also may provide protection against obesity and diabetes resulting from a high fat diet.[205,206] Interestingly, a systems pharmacology-based strategy identified 39 bioactive components within PCR, and 121 potential protein targets, related to diseases of the cardiovascular system, respiratory system, and gastrointestinal system.[207] One target appears to be PPARγ, which is upregulated by PCR, an effect which has the potential to improve myocardial function, as well as to prevent atherosclerosis subsequent to diabetic cardiopathy.[208] Hesperidin also appears to prevent cardiomyocyte apoptosis and mitigate oxidative damage via up-regulation of PPARγ expression.[209,210] Hesperidin and naringenin were also predicted to have hepatoprotective effects, by influencing

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[202] Qin K, Zheng L, Cai H, et al. Characterization of Chemical Composition of Pericarpium Citri Reticulatae Volatile Oil by Comprehensive Two-Dimensional Gas Chromatography with High-Resolution Time-of-Flight Mass Spectrometry. Evid Based Complement Alternat Med. 2013;2013:237541.

[203] Wang Y, Yi L, Liang Y, et al. Comparative analysis of essential oil components in Pericarpium Citri Reticulatae Viride and Pericarpium Citri Reticulatae by GC-MS combined with chemometric resolution method. J Pharm Biomed Anal. 2008 Jan 7;46(1):66-74.

[204] Vajdi M, Farhangi MA. Citrus peel derived' Poly-Methoxylated Flavones (PMF). Int J Vitam Nutr Res. 2021 May 27:1-16.

[205] Tung YC , Chang WT , Li S , et al. Citrus peel extracts attenuated obesity and modulated gut microbiota in mice with high-fat diet-induced obesity. Food Funct. 2018 Jun 20;9(6):3363-3373.

[206] Guo J, Tao H, Cao Y, et al. Prevention of Obesity and Type 2 Diabetes with Aged Citrus Peel (Chenpi) Extract. J Agric Food Chem. 2016 Mar 16;64(10):2053-61.

[207] Zhou W, Chen Z, Lu A, et al. Systems Pharmacology-Based Strategy to Explore the Pharmacological Mechanisms of Citrus Peel (Chenpi) for Treating Complicated Diseases. Am J Chin Med. 2021;49(2):391-411.

[208] Cheng H, Wu X, Ni G, et al. Citri Reticulatae Pericarpium protects against isoproterenol-induced chronic heart failure via activation of PPARγ. Ann Transl Med. 2020 Nov;8(21):1396.

[209] Selvaraj P, Pugalendi KV. Hesperidin, a flavanone glycoside, on lipid peroxidation and antioxidant status in experimental myocardial ischemic rats. Redox Rep. 2010;15(5):217-23.

[210] Agrawal YO, Sharma PK, Shrivastava B, et al. Hesperidin blunts streptozotocin-isoproternol induced myocardial toxicity in rats by altering of PPAR-γ receptor. Chem Biol Interact. 2014 Aug 5;219:211-20.

apoptotic, inflammatory, and energy metabolism.[211] Tangeretin has also been shown to improve adipose thermogenesis as well as the diversity of the gut microbiota in an animal model.[212] Alkaloids in PCR have also shown benefit in an animal model of histamine-induced asthma.[213] Randomized clinical trials are needed to verify many of the benefits observed *in vitro* and animal models.

Safety Summary:
Considered safe at the recommended dose with no known adverse effects.[214] In therapeutic doses, PCR may cause hyperkalemia when used in conjunction with potassium sparing diuretics.[214] Exercise caution during pregnancy and lactation as safety has not been established during these times.

Glycyrrhizae Uralensis (*Glycyrrhiza uralensis*)

Biological Actions:
Anti-inflammatory, antimicrobial, demulcent, hepatoprotective, mild laxative, mucoprotective, antiulcer.[2,215]

Traditional Use:
Glycyrrhiza uralensis also known as Chinese or Ural licorice is one of the most frequently used herbs in traditional Chinese medicine.[215] It has been used for improving overall health, to lengthen life-span, as a cure for injury and swelling, and also for detoxification.[216] In Japan, extract and flavonoid-rich fractions of Chinese licorice are used for the treatment of gastritis as well as gastric and duodenal ulcers.[216]

Scientific Evidence:
The key constituents of Chinese licorice include phenolic compounds, pterocarpans, essential oils, triterpenoids, alkaloids, polyamines and polysaccharides.[215] Ethanolic extracts and several compounds (pterocarpans and isoflavonoids) isolated from Chinese licorice have exhibited strong antibacterial activity against *Streptococcus mutans in vitro*.[215] Indeed, *Glycyrrhiza uralensis* extracts have shown antimicrobial activity against several oral pathogens, including *Candida albicans*, with a mouthwash shown to inhibit bacterial growth in a double-blinded clinical trial.[217,218] Other *in vitro* trials have shown that the flavonoids isolated from Chinese licorice possess antimicrobial activities against methicillin sensitive *Staphylococcus aureus (MSSA),* methicillin resistant *Staphylococcus aureus* (MRSA), *Micrococcus luteus, Bacillus subtilis, Klebsiella pneumoniae* and *Pseudomonas*

[211] Wu J, Ye X, Yang S, et al. Systems Pharmacology Study of the Anti-Liver Injury Mechanism of Citri Reticulatae Pericarpium. Front Pharmacol. 2021 Apr 12;12:618846.
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aeruginosa.[216]

Several compounds isolated from *Glycyrrhiza uralensis* have also been shown to have anti-inflammatory effects in an *in vitro* model of osteoarthritis.[219] A prenylated isoflavone extracted from *G. uralensis,* gancaonin N, has also demonstrated anti-inflammatory properties *in vitro*, including an inactivation of the MAPK and NF-κB signaling pathways.[220] Flavonoids extracted from Chinese licorice have been found to prevent the activation of the NLRP3 inflammasome, restore diversity of the gut microbiota, increase glutathione levels, and provide hepatoprotection in animal models.[221,222] Similarly, the chalcone isoliquiritigenin (extracted from Chinese licorice) inhibits the NLRP3 inflammasome, providing protection against diet-induced adipocyte inflammation in an *ex vivo* culture.[223] Consistent with its traditional usage, *Glycyrrhiza uralensis* was shown to upregulate expression of *muc1* and *muc3*, intestinal mucosa protective proteins associated with inflammatory bowel disease.[224,225] Similarly, licoflavone, extracted from *Glycyrrhiza sp.,* has demonstrated anti-ulcer effects in an animal model.[226] Finally, *Glycyrrhiza uralensis* has traditionally been used to enhance absorption of poorly absorbed medicines and botanicals, and is thus widely used in oriental medicine prescriptions to increase the absorption/potency of other herbal therapies.[227,228]

Safety Summary:

Considered safe at the recommended dose.[2] In therapeutic doses, *Glycyrrhiza uralensis* may cause hypertension, sodium and water retention and hypokalemia by inhibiting renal 11β-HSD2.[2,229] Avoid in therapeutic doses with diuretics and laxative medications.[2] Contraindicated in therapeutic doses in cholestatic liver disorders, liver cirrhosis, hypertension, hyperkalemia, severe renal disease, edema, congestive heart failure and pregnancy.[2] Avoid during pregnancy, though considered safe during lactation.[2]

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