Olivirex – Scientific Validation of Botanical Ingredients

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Ingredients:

Olive (*Olea Europaea*) Leaf Extract 375 mg (Standardized to min 18% Oleuropein) (*Olea europaea*). Proprietary Herbal Blend 53 mg: Garlic bulb (*Allium sativum*), Noni fruit extract (*Morinda citrifolia*) , Uva Ursi leaf (*Arctostaphylos uva ursi*), Milk Thistle seed extract (*Silybum marianum*), Cordyceps mycelium (*Cordyceps Sinensis*), St. John's Wort aerial parts *(Hypericum perforatum*), Dandelion root (*Taraxacum officinale)*, Goldenseal root (*Hydrastis canadensis*), White Willow bark (*Salix alba*), Bladderwrack thallus (*Fucus vesiculosus*), American Ginseng plant extract (*Panax quinquefolius*).

Other Ingredients: vegetable cellulose, vegetable capsule

Olive Leaf (*Olea europaea*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant, antiprotozoal, antiviral, cardioprotective, hypoglycemic, hypotensive.[1,2]

Scientific Evidence:

The main active constituents in olive leaf include secoiridoids (oleuropein and its derivatives), hydroxytyrosol, polyphenols (verbascoside, caffeic acid), triterpenes including oleanolic acid, and flavonoids (apigenin, diosmetin, luteolin, quercetin). Its primary constituents, oleuropein and hydroxytyrosol, are believed to be responsible for the majority of the therapeutic properties of olive leaf extract (OLE), though multiple polyphenols within olive leaf have both antioxidant and antimicrobial activity.[2,3]

Oleuropein and hydroxytyrosol have been shown to have antimicrobial activity against a variety of viruses, bacteria, yeasts and fungi.[3,4] Oleuropein and caffeic acid have demonstrated antimicrobial

[1] Obied HK, Prenzler PD, Omar SH, et al. Chapter Six - Pharmacology of Olive Biophenols. In: James CF, ed. Advances in Molecular Toxicology. Vol Volume 6: Elsevier; 2012:195-242.
[2] Olive leaf. Monograph. Altern Med Rev. 2009;14(1):62-66.
[3] Borjan D, Leitgeb M, Knez Ž, et al. Microbiological and Antioxidant Activity of Phenolic Compounds in Olive Leaf Extract. Molecules. 2020 Dec 15;25(24):5946.
[4] Ben-Amor I, Musarra-Pizzo M, Smeriglio A, et al. Phytochemical Characterization of Olea europea Leaf Extracts and Assessment of Their Anti-Microbial and Anti-HSV-1 Activity. Viruses. 2021 Jun 7;13(6):1085.

activities *in vitro* against the Gram positive bacteria, *Bacillus cereus* and the Gram-negative bacteria, *Escherichia coli* and *Salmonella enteritidis*.[5] When combined, the phenolics in OLE demonstrated similar or better effects following *in vitro* assessment with a range of Gram-positive and Gram-negative organisms.[5] Aqueous extracts of olive leaf have demonstrated bactericidal effects *in vitro* against *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli* and *Staphylococcus aureus* (0.6% w/v). OLEs have also shown fungicidal effects against *Trichophyton mentagrophytes, Microsporum canis* and *Trichophyton rubrum* (1.25% w/v), and *Candida albicans* cells (15% w/v).[6] The olive polyphenols, oleuropein and hydroxytyrosol, have been shown to be cytotoxic to both Gram negative and Gram-positive bacteria. In particular, hydroxytyrosol has been shown to inhibit the growth of American Tissue Culture Collection (ATCC) standard bacterial strains, and clinical isolates of *Haemophilus influenzae, Moraxella catarrhalis, Salmonella typhi, Vibrio parahaemolyticus* and *Staphylococcus aureus* with minimum inhibitory concentrations (MICs) ranging from 0.24-31.25 µg/mL.[7] *In vitro*, OLE was also found to be active against *Campylobacter jejuni, Helicobacter pylori* and *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus),* with MICs as low as 0.31-0.78% (v/v).[8]

OLE has also shown antiviral activity *in vitro* against many common viruses, including Epstein Barr virus, HIV-1, HSV-1, and respiratory syncytial virus.[4,9,10] OLE and oleuropein specifically appear to have several antiviral mechanisms, including an ability to prevent viral entry into cells by binding to cellular receptors, as well as a direct virucidal effect.[1] In a small randomized and controlled trial, OLE was given to high school athletes during their competitive season, and while there was no change in illness incidence, supplementation was associated with a 28% reduction in the duration of upper respiratory infections.[11]

In addition to its antimicrobial and antiviral effects, a growing body of evidence also indicates that OLE also has benefit for the cardiovascular system and may improve glucose and lipid metabolism. For example, hydroxytyrosol and tyrosol promote the production and availability of nitric oxide in human aortic endothelial cells, a key modulator of vascular health and blood pressure.[12] OLE has also been shown to improve vascular function and inhibit IL-8 production, a pro-inflammatory cytokine associated with atherosclerosis progression.[13] A systematic review and meta-analysis which included 5 trials and

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[5] Lee OH, Lee BY. Antioxidant and antimicrobial activities of individual and combined phenolics in Olea europaea leaf extract. Bioresour Technol. 2010 May;101(10):3751-4.
[6] Markin D, Duek L, Berdicevsky I. In vitro antimicrobial activity of olive leaves. Mycoses. 2003 Apr;46(3-4):132-6.
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[8] Sudjana AN, D'Orazio C, Ryan V, et al. Antimicrobial activity of commercial Olea europaea (olive) leaf extract. Int J Antimicrob Agents. 2009 May;33(5):461-3.
[9] Ben-Amor I, Gargouri B, Attia H, et al. In Vitro Anti-Epstein Barr Virus Activity of Olea europaea L. Leaf Extracts. Plants (Basel). 2021 Nov 12;10(11):2445.
[10] Omar SH. Oleuropein in olive and its pharmacological effects. Sci Pharm. 2010 Apr-Jun;78(2):133-54.
[11] Somerville V, Moore R, Braakhuis A. The Effect of Olive Leaf Extract on Upper Respiratory Illness in High School Athletes: A Randomised Control Trial. Nutrients. 2019 Feb 9;11(2):358.
[12] Serreli G, Le Sayec M, Diotallevi C, et al. Conjugated Metabolites of Hydroxytyrosol and Tyrosol Contribute to the Maintenance of Nitric Oxide Balance in Human Aortic Endothelial Cells at Physiologically Relevant Concentrations. Molecules. 2021 Dec 10;26(24):7480.
[13] Lockyer S, Corona G, Yaqoob P, et al. Secoiridoids delivered as olive leaf extract induce acute improvements in human vascular function and reduction of an inflammatory cytokine: a randomised, double-blind, placebo-controlled, cross-over trial. Br J Nutr. 2015 Jul 14;114(1):75-83.

325 participants found a mean reduction of 5.78 mmHg in systolic blood pressure at a dose of 500mg OLE per day, a reduction in the range consistent with healthy dietary patterns such as the Mediterranean diet, while a dose of 1000mg per day had nearly the same effect as an ACE inhibitor in the control group.[14] Animal studies suggest that oleuropein-induced upregulation of the Nrf2-mediated signalling pathway and a subsequent improvement in mitochondrial function may also provide a mechanism for the anti-hypertensive effect of OLE.[15] Both oleuropein and oleanolic acid have been shown to be an agonist for the G-protein coupled receptor TGR5, which in animal studies reduces both insulin and glucose levels.[16] In a randomized and double-blinded placebo-controlled cross-over trial, 46 middle aged men at risk for the metabolic syndrome had a 15% improvement in insulin sensitivity and a 28% improvement pancreatic β-cell responsiveness when supplemented with olive leaf phenolics (primarily oleuropein and hydroxytyrosol) over a 6-week period (compared to a 6-week placebo).[17] Similarly, a controlled trial of OLE supplementation among women with obesity found significant decreases in BMI, fat mass, and body weight, as well as significant decreases in serum levels of fasting blood sugar, insulin, LDL cholesterol, total cholesterol, leptin, fatty free acid, and homeostasis model assessment–insulin resistance compared to placebo (when combined with a hypocaloric diet).[18]

Safety Summary:

Contraindicated in persons with known allergies to plants from the Oleaceae family. OLE is considered safe and well tolerated at the dose recommended.[19] Exercise caution or avoid during pregnancy and breastfeeding as safety has not been established during these times.

Garlic (*Allium sativum*)

Biological Actions:

Anthelmintic, anti-inflammatory, antimicrobial, antioxidant.[20]

Scientific Evidence:

The most biologically active constituent of garlic is allicin (S-(2-propenyl)-2-propene-1-sulfinothioate), which is formed when the herb is crushed and alliinase (an enzyme from the bundle sheath cells) combines with the substrate alliin (S-allyl-L-cysteine sulfoxide).[21] Bulbs of garlic contain hundreds of other

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[14] Ismail MA, Norhayati MN, Mohamad N. Olive leaf extract effect on cardiometabolic profile among adults with prehypertension and hypertension: a systematic review and meta-analysis. PeerJ. 2021 Apr 7;9:e11173.
[15] Sun W, Wang X, Hou C, et al. Oleuropein improves mitochondrial function to attenuate oxidative stress by activating the Nrf2 pathway in the hypothalamic paraventricular nucleus of spontaneously hypertensive rats. Neuropharmacology. 2017 Feb;113(Pt A):556-566.
[16] Sato H, Genet C, Strehle A, et al. Anti-hyperglycemic activity of a TGR5 agonist isolated from Olea europaea. Biochem Biophys Res Commun. 2007 Nov 3;362(4):793-8.
[17] de Bock M, Derraik JG, Brennan CM, et al. Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial. PLoS One. 2013;8(3):e57622.
[18] Haidari F, Shayesteh F, Mohammad-Shahi M, et al. Olive Leaf Extract Supplementation Combined with Calorie-Restricted Diet on Reducing Body Weight and Fat Mass in Obese Women: Result of a Randomized Control Trial. Clin Nutr Res. 2021 Oct 31;10(4):314-329.
[19] Susalit E, Agus N, Effendi I, et al. Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril. Phytomedicine. 2011 Feb 15;18(4):251-8.
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[21] El-Saber Batiha G, Magdy Beshbishy A, G Wasef L, et al. Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review. Nutrients. 2020 Mar 24;12(3):872.

phytochemicals, including many sulfur containing compounds, ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithiins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide (DADS), diallyl sulfide (DAS), diallyl trisulfide (DATS)), N-acetylcysteine (NAC), S-allyl-cysteine (SAC), and others.[21]

Much of the antimicrobial activity of garlic has been attributed to allicin activity, and includes both Gram-positive and Gram-negative microorganisms, as well as antibiotic-resistant bacteria, including *Shigella*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Salmonella enterica*, *Klebsiella aerogenes*, *Vibrio*, *Mycobacteria*, *Proteus vulgaris*, and *Enterococcus faecalis*.[21,22] The antimicrobial activity of allicin has been partly attributed to the S-allylmercapto modification of thiol-containing proteins in bacteria, such as glutathione, leading to either necrosis or apoptosis.[23] However, allicin is a very unstable compound, and thus unlikely to be the only antimicrobial component of garlic *in vivo*.

Both *in vitro* and *in vivo* studies have identified the two ajoenes (Z and E) as components of garlic that are able to inhibit virulence genes controlled by quorum sensing (QS) systems, virulence factors that are also of critical importance to the formation of biofilms and antibiotic resistance.[24,25] Ajoenes have shown antimicrobial activity against a variety of both Gram-negative and Gram-positive bacteria and may play a role in the effectiveness of garlic against a number of pathogens with multiple drug-resistances.[26,27] DAS has also been found to inhibit the transcription of virulence genes in *Pseudomonas aeruginosa* which are regulated by the QS system, as well as most of the key genes in the QS system, indicating that multiple components within garlic may target this mechanism.[28] Furthermore, QS inhibitors have demonstrated a synergistic effect when combined with antibiotics. Based on *in vitro* research, the addition of ajoene to a *Pseudomonas* biofilm plus tobramycin killed more than 90% of the bacteria (compared with no effect when tobramycin was tested in isolation).[24] Allicin also has an extensive number of bacterial and fungal pathogens for which it acts synergistically against when coupled with other antibiotics.[29] Research shows that garlic has a temporal effect on commensal flora – when initially exposed to the herb, probiotic strains such as *Lactobacillus* are transiently inhibited, followed by a resurgence of growth with bacterial counts comparable to levels preceding garlic intervention.[30]

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[22] Wallock-Richards D, Doherty CJ, et al. Garlic revisited: antimicrobial activity of allicin-containing garlic extracts against Burkholderia cepacia complex. PLoS One. 2014 Dec 1;9(12):e112726.
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[27] Karuppiah P, Rajaram S. Antibacterial effect of Allium sativum cloves and Zingiber officinale rhizomes against multiple-drug resistant clinical pathogens. Asian Pac J Trop Biomed. 2012 Aug;2(8):597-601.
[28] Li WR, Zeng TH, Yao JW, et al. Diallyl sulfide from garlic suppresses quorum-sensing systems of Pseudomonas aeruginosa and enhances biosynthesis of three B vitamins through its thioether group. Microb Biotechnol. 2021 Mar;14(2):677-691.
[29] Choo S, Chin VK, Wong EH, et al. Review: antimicrobial properties of allicin used alone or in combination with other medications. Folia Microbiol (Praha). 2020 Jun;65(3):451-465.
[30] Filocamo A, Nueno-Palop C, Bisignano C, et al. Effect of garlic powder on the growth of commensal bacteria from the gastrointestinal tract. Phytomedicine. 2012 Jun 15;19(8-9):707-11.

Garlic is also known to have anti-fungal activity against a variety of organisms, including *Candida*, *Torulopsis*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Trichosporon*, and *Rhodotorula* species. Garlic has been shown to target fungal cell walls, and cause irreversible structural changes in the fungal cells, leading to cell death.[21] Anthelmintic activity against *Haemonchus contortus*, *Trichuris muris* and *Angiostrongylus cantonensis* has also been demonstrated with various garlic extracts, and allicin, ajoenes, and diallyl trisulfide have all shown activity against a variety of parasites.[21]

In addition to its broad anti-microbial effects, garlic has also been found to have anti-inflammatory, antioxidant, and cardiometabolic effects. Allicin specifically has been shown to active the Nrf2 pathway, attenuate an LPS-induced inflammatory response, and limit reactive oxygen species, mitochondrial dysfunction, and lipid peroxidation among cultured human umbilical vein endothelial cells (HUVECs).[31] It has also been found to prevent endothelial injury resulting from oxidized LDL (ox-LDL) in a HUVEC model.[32] Allicin was responsible for a "browning" of white adipocytes in an *in vitro* model by enhancing the expression of brown adipocyte-specific genes, a finding with implications for metabolic disease, supported by a human clinical trial in which garlic improved multiple components of the metabolic syndrome.[33,34] A review of randomized and double-blinded studies show a consistent hypotensive effect, with the potential for cardiovascular risk reduction.[35]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[36] Caution advised if risk of bleeding disorder present.[37] No adverse effects expected during pregnancy and breastfeeding.[36,38]

Noni (*Morinda citrifolia*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant.[39,40]

Scientific Evidence:

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[31] Zhang M, Pan H, Xu Y, et al. Allicin Decreases Lipopolysaccharide-Induced Oxidative Stress and Inflammation in Human Umbilical Vein Endothelial Cells through Suppression of Mitochondrial Dysfunction and Activation of Nrf2. Cell Physiol Biochem. 2017;41(6):2255-2267.
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[40] Singh B, Sharma RA. Indian Morinda species: A review. Phytother Res. 2020 May;34(5):924-1007.

To date, over 200 different compounds have been identified in the noni plant, including phenolics, flavonoids, anthraquinones, iridoids, lignans, and triterpenoids, which give rise to noni's potent antioxidant and anti-inflammatory properties.[41] The majority of these compounds have biological activity; iridoids have been shown to prevent the formation of advanced glycation end products (AGEs), with clinical trials among heavy smokers, who are known to have excessive oxidant exposure, demonstrating the iridoids in noni to be associated with a mitigation in both oxidative damage to DNA as well as cigarette-smoke induced dyslipidemia.[42,43,44] *In vitro* research has also shown that noni is highly effective at inhibiting hydroxyl radicals, known to cause oxidative damage to proteins, lipids, as well as DNA.[45]

As a natural anti-inflammatory agent, noni inhibits LPS-induced activation of a number of chemical mediators, including cyclooxygenase (COX)-1 and COX-2, nitric oxide and prostaglandins E_2 (PGE_2) in a dose dependent manner.[46] Damnacanthal, an anthraquinone found in noni, has been found to have immunomodulating and anti-inflammatory activity; it has been shown to suppress mast cell activation and allergic reactions by inhibiting the activation of several inflammatory mediators, including NF-κB and $p56^{lck}$ tyrosine kinase.[47,48] Noni also possesses immune stimulating properties, and based on *in vivo* and *in vitro* studies, enhances both cellular and humoral-mediated immunity.[49,50]

Noni has recently been found to influence glucose metabolism; animal studies suggest that this may occur via several mechanisms, including an increased sensitivity to insulin via an inhibition of protein tyrosine phosphatase 1B (PTP1B), a known inducer of insulin resistance, as well as through inhibition of forkhead box O (FoxO1) transcription, a key regulator of gluconeogenesis.[51,52] Human clinical trials are sparse but have demonstrated a hypoglycemic and anti-inflammatory effect of noni among participants with type 2 diabetes.[53]

A number of active compounds in noni, including aucubin, L-asperuloside and alizarin as well as the

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[41] Inada AC, Figueiredo PS, Santos-Eichler RAD, et al. Morinda citrifolia Linn. (Noni) and Its Potential in Obesity-Related Metabolic Dysfunction. Nutrients. 2017 May 25;9(6):540.
[42] West BJ, Deng S, Uwaya A, et al. Iridoids are natural glycation inhibitors. Glycoconj J. 2016 Aug;33(4):671-81.
[43] Wang MY, Peng L, Weidenbacher-Hoper V, et al. Noni juice improves serum lipid profiles and other risk markers in cigarette smokers. ScientificWorldJournal. 2012;2012:594657.
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[53] Algenstaedt P, Stumpenhagen A, Westendorf J. The Effect of Morinda citrifolia L. Fruit Juice on the Blood Sugar Level and Other Serum Parameters in Patients with Diabetes Type 2. Evid Based Complement Alternat Med. 2018 Aug 6;2018:3565427.

phenolics 5,15-dimethylmorindol, ferulic acid, p-hydroxycinnamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate have demonstrated antibacterial activity against a number of pathogens including *Pseudomonas aeruginosa*, *Proteus morganii*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* and *Shigella*.[54,55] Noni has also been shown to inhibit the activity of enterohemorrhagic *E. coli* (0157) and *Helicobacter pylori*.[56,57]

Traditionally noni was used for tuberculosis infections, which has now been substantiated by *in vitro* studies indicating noni is nearly as effective as Rifampin (with inhibition rates of 89% and 97% respectively).[58,59] Noni has demonstrated antifungal activity against *Candida albicans* in a dose dependent manner.[60,61] Aqueous extracts of noni may also help protect against the conversion of cellular *Candida albicans* into the hyphenated or filamentous form of the yeast. Germ tube formation or hyphenation from blastoconidia by *Candida* species is thought to be a virulence factor in their pathogenesis. Similarly, noni has been shown to inhibit the germination of spores from the filamentous fungi *Aspergillus nidulans*.[62]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[63] No adverse effects expected during pregnancy and breastfeeding.[64]

Uva ursi (*Arctostaphylos uva ursi*)

Biological Actions:

Anti-inflammatory, antimicrobial, urinary antiseptic.[65]

Scientific Evidence:

Biologically active compounds of uva ursi include hydroquinone glycosides (arbutin, methylarbutin), polyphenols, phenolic acids, tannins, flavonoids, and volatile oils. Much of uva ursi's antimicrobial effects

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[54] Zhang WM, Wang W, Zhang JJ, et al. Antibacterial Constituents of Hainan Morinda citrifolia (Noni) Leaves. J Food Sci. 2016 May;81(5):M1192-6.
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have been attributed to arbutin (hydroquinone β-D-glucoside), which is metabolized in the intestinal tract to its aglycone, hydroquinone.[66] Hydroquinone has demonstrated anti-bacterial activity against *Staphylococcus aureus*, MRSA, and extended spectrum β-lactamase *S. aureus*, in part by destroying the bacterial cell wall and membrane, followed by leakage of intracellular content.[67]

Ethanolic extracts have exhibited antimicrobial activity against a variety of organisms including *Staphylococcus aureus, Escherichia coli, Mycobacterium smegmatis, Shigella sonnei*, and *Shigella flexeneri*.[68] In vitro research also shows ethanolic extracts of uva ursi and its ethyl acetate fractions are able to inhibit the growth of *Proteus vulgaris, Enterococcus faecalis*, *Enterobacter aerogenes*, *Staphylococcus aureus* and *Escherichia coli*.[69] Tannins present in uva ursi also appear to affect cell surface hydrophobicity of some bacteria, such as *Helicobacter pylori*, potentially preventing adhesion to the gastric mucosa.[70] Consistent with its historical use for urinary tract health, women with recurrent cystitis receiving an extract of uva ursi and dandelion had no subsequent infections over a one-year trial period, compared to 23% of the placebo group.[71]

Safety Summary:

Contraindicated in therapeutic doses in people with renal disorders and in children under 12 years of age.[72] Contraindicated during pregnancy.[72] Discouraged during breastfeeding in therapeutic doses.

Milk Thistle (*Silybum marianum*)

Biological Actions:

Antimicrobial, antioxidant, anti-inflammatory, antiviral, choleretic, hepatoprotective.[20,73,74]

Scientific Evidence:

Milk thistle is rich in flavonolignans which are composed of silybin A and silybin B (diastereoisomers), silydianin, silychristin and diastereoisomers isosilybin A and isosilybin B. These polyphenolic molecules are collectively referred to as silymarin.[20] Research has shown that the flavonolignans from milk thistle

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[66] Asensio E, Vitales D, Pérez I, et al. Phenolic Compounds Content and Genetic Diversity at Population Level across the Natural Distribution Range of Bearberry (Arctostaphylos uva-ursi, Ericaceae) in the Iberian Peninsula. Plants (Basel). 2020 Sep 22;9(9):1250.
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possess potent antibacterial activity against Gram-positive bacteria, but no antimicrobial activity against Gram-negative bacteria.[75] In addition to direct antibacterial action, silymarin has also been shown to inhibit the adherence and formation of bacterial biofilms.[76] Silymarin also inhibits the growth of multiple species of *Candida*, destabilizing mature biofilms and inhibiting the secretion of phospholipases and proteinases, an important determinant of fungal virulence.[77]

Silibinin (an equal extract of silybin A and silybin B) has demonstrated antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus*.[20,78] When silibinin was combined with the antibiotics oxicillin or ampicillin there was a more than four-fold reduction in the minimum inhibitory bactericidal concentrations. Based on *in vitro* research, silibinin's antimicrobial properties are due to its ability to inhibit ribonucleic acid (RNA) and protein synthesis of Gram-positive organisms (as opposed to attacking the bacterial membrane).[79] Ethanol extracts of silibin have also demonstrated *in vitro* antibacterial activity against *Campylobacter jejuni*, and the purified flavonolignan dehydroisosilybin has inhibited the *in vitro* growth of two species of *Leishmania* parasites.[80,81] Silymarin has also demonstrated antiviral activity against influenza A/PR/8/34 virus when compared with the pharmaceutical agent Oseltamivir (98% vs. 52% respectively).[82] Its ability to suppress cellular inflammation, including inhibition of mTOR, may partly explain its immunomodulating effects.[83,84] Several preclinical and *in vitro* studies suggest antiviral activity against multiple viruses, including HBV, HCV, mediated in part by inhibition of multiple steps of the viral life cycle.[85]

Silibinin has also demonstrated antioxidant and anti-inflammatory properties in LPS-stimulated human monocytes through an inhibitory effect on hydrogen peroxide release and tumor necrosis factor-alpha (TNFα) production.[86] Silibin's anti-inflammatory targets may also include the NLRP3 inflammasome, with

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several models citing an inhibition NF-κB and NLRP3 signalling pathways.[87,88,89] The involvement of the NLRP3 inflammasome in multiple inflammatory conditions, including NAFLD and diabetes, suggests a mechanism of potential benefit for milk thistle, with growing clinical support. A review of 8 randomized trials of participants with NAFLD found a significant reduction in transaminase levels with silymarin use, and a recent meta-analysis points to a general improvement in the glycemic profile of participants with glucose or lipid abnormalities.[90,91] Silymarin supplementation was also associated with an improvement in antioxidant levels and total antioxidant capacity, as well as reduced inflammation in a triple-blind trial of participants with diabetes.[92]

Milk thistle has several hepatoprotective effects, including the upregulation of thioredoxin and sirtuins, as well as the bile salt export pump, in addition to having an anti-fibrotic effect on stellate cells in myofibroblasts.[93,94] Silymarin provides protection against multiple exogenous toxins, mediated in part by an activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of cellular antioxidant enzymes.[95,96] The upregulation of Nrf2 increases expression of multiple antioxidant and detoxification enzymes, which have been associated with improved intestinal immune function, barrier integrity, and reduced mucosal injury and inflammation.[97,98]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae (aka Asteraceae) family. No other known warnings, precautions or contraindications. No adverse effects expected during pregnancy and breastfeeding.[99,100,101]

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Cordyceps (*Cordyceps Sinensis*)

Biological Actions:

Anti-inflammatory, antioxidant, antimicrobial, antitussive, expectorant, immune modulating, neuroprotective.[102,103]

Scientific Evidence:

The phytochemical constituents of cordyceps include nitrogenous compounds (cordycepin and adenosine), sterols (ergosterol), polysaccharides, proteins, phenolics, nucleosides, isoflavones and organic acids.[102] The anti-inflammatory, antioxidant and immunomodulatory effects of the herb have been attributed primarily to the structurally diverse polysaccharides, which comprise 3-8% of the fruiting body, and modulate numerous immune signals, including MAPK and NF-κB signalling pathways, phagocytosis, NK-cell activity, etc.[104] Cordycepin also contributes to the antibacterial activity, and ergosterol is believed to exhibit immunomodulatory activity.[105] Additionally, cordycepin inhibits multiple inflammatory pathways in microglia, including iNOS, Akt, MAPKs, NF-κB, COX-2, and attenuates LPS-induced inflammation, suggesting a potential for potent neuroprotection.[106]

In clinical trials, the use of polysaccharides derived from cordyceps have improved physical performance and quality of life.[107] In a randomized and double-blinded clinical trial, a cultured isolate of *Cordyceps sinensis* was shown to increase NK cell activity nearly 40% in healthy participants, compared to a decline in NK cell activity among those receiving placebo.[108] Elderly patients affected by chronic obstructive pulmonary disease have demonstrated an increase in red blood cell superoxide dismutase activity, which was associated with significant clinical improvements in cough, phlegm, appetite, pulmonary symptoms and vitality.[107]

The antibacterial activity of cordyceps has been confirmed through *in vitro* research. Cordycepin (from *Cordyceps* sp.) has been shown to inhibit the growth of *Clostridium paraputrificum* and *Clostridium perfringens.* Growth inhibition of *Clostridium* species did not show any adverse effect on the growth of beneficial bacteria including *Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium adolescentis, Lactobacillus acidophilus* and *Lactobacillus casei.*[105,109]

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Safety Summary:

Cordyceps is considered safe and well tolerated at the dose recommended.[110] In therapeutic doses, cordyceps may potentially increase the risk of bleeding when combined with antiplatelet or anticoagulant drugs. Cordyceps may also interfere with immunosuppressive therapy when administered in therapeutic doses.[cx] Exercise caution or avoid during pregnancy and breastfeeding as safety has not been established during these times.[110]

St. John's Wort *(Hypericum perforatum*)

Biological Actions:

Antibacterial, antifungal, anti-inflammatory, antiviral, vulnerary.[72,111]

Scientific Evidence:

Biologically active compounds of St. John's wort include naphthodianthrones (hypericin, pseudohypericin), phloroglucinols (hyperforin), flavonoids (quercetin, hyperin, rutin), biflavones, phenylpropanes, proanthocyanidins and volatile oils.[112]

Ethanolic extracts of St. John's wort have demonstrated antibacterial activity *in vitro* against the Gram positive bacteria *Enterococcus faecalis* and *Staphylococcus aureus.*[113] Methanolic extracts have also shown efficacy against multiple strains of *S. aureus* and coagulase-negative *staphylococci.*[114] Hyperforin has been shown to be the main antibacterial constituent of St. John's wort.[112] Based on *in vitro* research, hyperforin can inhibit the growth of a number of Gram-positive organisms including *Corynebacterium diphtheriae* and MRSA.[115,116]

The antifungal activity of flavonoids and volatile oils from St. John's wort has been demonstrated in several studies.[112] Ethanolic extracts of St. John's wort have demonstrated fungistatic activity against *Fusarium oxysporum* and *Penicillium canescens.*[112] The flavonoids derived from St. John's wort have been shown to inhibit the growth of the phytopathogenic fungus *Helminthosporium sativum,* and *Fusarium graminearu*.[112] Volatile oil and water-soluble fractions of an alcohol extract of St. John's wort have also exhibited antifungal activity against *Microsporum gypseum, Trichophyton rubrum, Aspergillus flavus, Curvularia lunata* and *Fusarium vasiinfectum.*[112]

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In addition to its antimicrobial and anti-fungal effects, St. John's wort has also demonstrated prebiotic effects. While demonstrating antimicrobial effects *in vitro* against several pathogens, including *S. aureus* and *Enterococcus faecalis*, *L. monocytogenes*, a high polyphenol extract (MAE) of St. John's wort stimulated the growth of two probiotic species, Saccharomyces *boulardii* and *Lactiplantibacillus plantarum*.[117] Animal studies have shown shifts in the microbiome associated with positive metabolic changes following St. John's wort administration.[118]

In vitro research shows that hypericin inactivates a wide variety of lipid containing (enveloped) viruses. Hypericin has demonstrated virucidal activity against the following enveloped viruses HIV-1, HSV-1 and HSV-2, bovine viral diarrhoea virus, influenza A, parainfluenza virus type 3, radiation leukemia virus, Moloney leukemia virus, vaccina virus, vesicular stomatitis virus, murine cytomegalovirus, Sendai virus, Sindbis virus, equine infectious anaemia virus, bovine immunodeficiency virus, and human cytomegalovirus.[119,120,121] The mechanisms by which hypericin inactivates these viruses is either through virucidal activity (by inhibiting viral infectivity), and/or antiviral activity (by inhibiting viral replication). However, it is not clear that the *in vitro* antiviral effects translate into *in vivo* effects; there is a distinct possibility that, for the most part, antiviral effects require the presence of light.[122,123]

St. John's wort and both hypericin and hyperforin specifically have been shown to have anti-inflammatory effects, with preliminary studies suggesting potential to mitigate the low-grade inflammation associated with metabolic diseases.[124] *In vitro* and *in vivo* animal studies indicate protection of pancreatic beta cells against inflammation, lipotoxicity and glucotoxicity, as well as an attenuation of abnormal lipid metabolism.[125,126,127]

Safety Summary:

Contraindicated in persons with known sensitivity to St. John's wort or any of its constituents.[72] Avoid using in cases of known photosensitivity, or in patients taking photosensitising agents.[72] In therapeutic

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doses, St. John's wort has the potential to reduce the effects of a range of medications, and is contraindicated with antiplatelet and anticoagulant, calcium channel antagonists, cancer chemotherapeutic, immunosuppressant and HIV medications, as well as digoxin, finasteride and methadone.[lxxii] Adverse effects associated with St. John's wort are rare and tend to be mild.[lxxii] No adverse effects expected during pregnancy and breastfeeding.[73]

Dandelion (*Taraxacum officinale)*

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant, antiviral, choleretic.[128]

Scientific Evidence:

Over 100 distinct phytochemical compounds have been identified in dandelion root, including polyphenols, hydroxycinnamic acids, flavonoids, triterpenes, minerals (primarily potassium), as well as anti-inflammatory and antimicrobial sesquiterpene lactones, and the prebiotic-acting oligosaccharide soluble fiber inulin.[129] Many of the compounds found in dandelion root have antioxidant and anti-inflammatory actions; ethanolic extracts, for example, have demonstrated protection to both hepatic and neurologic damage in animal and *in vitro* models, in part mediated via upregulation of antioxidant enzymes, including superoxide dismutase and catalase, as well as the Nrf2 antioxidant pathway.[130,131,132] Methanolic extracts have also displayed anti-inflammatory effects *in vitro*, including inhibition of the NF-κB pathway.[133]

Based on *in vitro* experiments, dandelion-derived polysaccharides and oligosaccharides have demonstrated antibacterial activity against *Escherichia coli,* and *Staphylococcus aureus*.[134] Dandelion polysaccharide compounds have also been shown to inhibit the growth of *Staphylococcus epidermidis, Salmonella typhimurium,* and *Streptococcus.*[135] An ethanol extract of dandelion has demonstrated antimicrobial activity against Gram-positive bacterial strains including *Staphylococcus aureus,* MRSA and *Bacillus cereus*, while a methanol extract demonstrated anti-biofilm effects against *S. aureus*.[136,137]

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Both *in vitro* and *in vivo* trials show that dandelion extracts are able to inhibit human influenza virus A/Puerto Rico/8/34 (H1N1) (PR8) and A/WSN33 (WSN) viruses. Dandelion has also demonstrated inhibition of polymerase activity and reduced virus nucleoprotein (NP) RNA levels. The mechanisms by which dandelion reduces viral growth involves inhibition of virus replication.[138] Taraxasterol and taraxerol have shown inhibitory effects on early antigen induction of the Epstein-Barr virus, and taraxasterol has molecular targets which appear to inhibit HBV replication *in vitro*.[139,140]

Safety Summary:

Contraindicated in known allergy, closure of bile duct, cholecystitis and intestinal obstruction. Considered safe and well tolerated at the dose recommended with no known interactions. No adverse effects expected during pregnancy and breastfeeding.[141]

Goldenseal (*Hydrastis canadensis*)

Biological Actions:

Antibacterial, antihistamine, anti-inflammatory, antiviral, antifungal, anti-protozoal, cardio-metabolic aid.[20,39,99,142]

Scientific Evidence:

Goldenseal root contains multiple alkaloids, the most abundant of which is berberine, as well as canadine, canadaline, and hydrastine. Both *in vivo* and *in vitro* studies have revealed that berberine possesses antimicrobial activity against bacteria, fungi and parasites.[73,142] Goldenseal leaves are also rich in flavonoids; two of which (6,8-di-C-methylluteolin 7-methyl ether and 6-C-methylluteolin 7-methyl ether) have demonstrated antibacterial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum*, while others (specifically sideroxylon, 8-desmethyl-sideroxylon and 6-desmethyl-sideroxylin) don't appear directly antibacterial, but instead enhance the action of berberine by acting as efflux pump inhibitors.[143] It should be noted that one of the major mechanisms by which bacteria become resistant to antibiotics is by overexpression of efflux pumps, which are also known as multidrug resistance pumps.[144] In one *in vitro* study, inhibition of the efflux pump allowed a much greater intracellular concentration of berberine, potentiating its antibiotic activity 500-fold against some organisms, indicating the importance of the synergistic interactions among Goldenseal's constituents.[145]

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[145] Tegos G, Stermitz FR, Lomovskaya O, et al. Multidrug pump inhibitors uncover remarkable activity of plant

The combined effects of the active constituents in goldenseal make this herb a potent antimicrobial agent for a number of Gram-positive and Gram-negative organisms including methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus sanguis*, *Pseudomonas aeruginosa*, *Mycoplasma mycoides capri*, *Escherichia coli*, *Neisseria gonorrhoeae* isolates (including antibiotic-resistant strains), *Campylobacter jejuni, Vibrio cholera* and *Helicobacter pylori*.[146,147,148,149,150] Berberine, as part of quadruple therapy, has been found to be non-inferior to bismuth for the eradication of H. pylori in a phase 4 trial.[151] One of the key mechanisms by which goldenseal inhibits microbial growth is through quenching of the *agr* quorum sensing (QS) system.[152] The QS system is bacterial cell-to-cell communication that controls gene expression and influences many physiological processes including bioluminescence, sporulation, competence, antibiotic production, biofilm formation and virulence factor secretion.[153] Berberine specifically has been shown to disrupt biofilms in *Salmonella typhimurium*, at least in part by reducing the number of type I fimbriae, an important virulence factor among members of the *Enterobacteriaceae* family.[154]

Berberine has demonstrated antifungal activity against the non-albicans *Candida* species (specifically *Candida krusei*, *Candida Kefyr*, *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis).* When combined with the antimycotic drugs miconazole or fluconazole, berberine was able to reduce biofilm formation of pathogenic *Candida albicans*.[155] *In vitro* data shows anti-fungal activity against not just *Candida*, but also *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *Microsporum gypseum*.[142] One analysis revealed a probable mechanism of action to be the disruption of both plasma and mitochondrial fungal membranes, as well as disruption of fungal biofilms.[156] *In vitro* studies have shown that berberine possesses significant antimicrobial activity against a number of protozoans including *Blastocystis hominis*, *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Leishmania donovani*.[142] Multiple mechanisms of action have been documented for berberine's anti-protozoal

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antimicrobials. Antimicrob Agents Chemother. 2002 Oct;46(10):3133-41.

[146] Cwikla C, Schmidt K, Matthias A, et al. Investigations into the antibacterial activities of phytotherapeutics against Helicobacter pylori and Campylobacter jejuni. Phytother Res. 2010 May;24(5):649-56.

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[148] Arjoon AV, Saylor CV, May M. In Vitro efficacy of antimicrobial extracts against the atypical ruminant pathogen Mycoplasma mycoides subsp. capri. BMC Complement Altern Med. 2012 Oct 2;12:169.

[149] Cybulska P, Thakur SD, Foster BC, et al. Extracts of Canadian first nations medicinal plants, used as natural products, inhibit neisseria gonorrhoeae isolates with different antibiotic resistance profiles. Sex Transm Dis. 2011 Jul;38(7):667-71.

[150] Wang X, Yao X, Zhu Z, et al. Effect of berberine on Staphylococcus epidermidis biofilm formation. Int J Antimicrob Agents. 2009 Jul;34(1):60-6.

[151] Zhang D, Ke L, Ni Z, et al. Berberine containing quadruple therapy for initial Helicobacter pylori eradication: An open-label randomized phase IV trial. Medicine (Baltimore). 2017 Aug;96(32):e7697.

[152]Cech NB, Junio HA, Ackermann LW, et al. Quorum quenching and antimicrobial activity of goldenseal (Hydrastis canadensis) against methicillin-resistant Staphylococcus aureus (MRSA). Planta Med. 2012 Sep;78(14):1556-61.

[153] Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med. 2012 Nov 1;2(11):a012427.

[154] Xu C, Wang F, Huang F, et al. Targeting effect of berberine on type I fimbriae of Salmonella Typhimurium and its effective inhibition of biofilm. Appl Microbiol Biotechnol. 2021 Feb;105(4):1563-1573.

[155] Wei GX, Xu X, Wu CD. In vitro synergism between berberine and miconazole against planktonic and biofilm Candida cultures. Arch Oral Biol. 2011 Jun;56(6):565-72.

[156] da Silva AR, de Andrade Neto JB, da Silva CR, et al. Berberine Antifungal Activity in Fluconazole-Resistant Pathogenic Yeasts: Action Mechanism Evaluated by Flow Cytometry and Biofilm Growth Inhibition in Candida spp. Antimicrob Agents Chemother. 2016 May 23;60(6):3551-7.

activity, including a direct effect, via oxidative bursts in parasites, as well as an indirect effect, via modulation of the mitogen activated protein kinase (MAPK) cascade.[157]

Berberine has also been shown to inhibit the growth of several viruses including cytomegalovirus, human papillomavirus (HPV), CHIKV, HSV-I and human H1N1 strains of influenza A.[158] One mechanism for its antiviral activity is the inhibition of the MAPK pathway, a common viral target to manipulate cellular functions. Berberine has also demonstrated an ability to reduce inflammation triggered by viral infections, mediated in part by activation of AMP-activated protein kinase (AMPK), and inhibition of NF-κB. [159] Additionally, both *in vitro* and *in vivo* models suggest an antihistamine effect of berberine, in part mediated via mast cell stabilization as well as enhanced function and quantity of T_{reg} cells.[160,161] Berberine also has the ability to upregulate the Nrf2 signaling pathway, a gatekeeper for cellular antioxidant defense.[162]

In addition to its many antimicrobial actions, berberine has been shown to broadly alter microbiome composition and functionality. In one animal model this was associated with a decrease in the gut microbiota metabolite trimethylamine (TMA, a marker for atherosclerosis) following a decrease in the population of pathogenic bacteria and an increase in beneficial bacteria.[163] The shift in the microbiome population frequencies is comparable to a probiotic-like effect that may help to explain favorable cardiometabolic effects, (often attributed to an increased production of short chain fatty acids as well as reduced levels of LPS) including improved lipid metabolism and insulin sensitivity.[164] For example, in one animal model berberine was shown to reduce the activity of *Clostridium* cluster XIVa and IV. This subsequently reduced the production of bile salt hydrolase, an inhibitor of taurocholic acid (TCA) synthesis. An increase in TCA activates intestinal farnesoid X receptor (FXR), involved in the metabolism of bile acids, lipids, and glucose. A parallel effect is observed with an increase in the population of butyrate-producing bacteria, which can also reduce serum lipids and glucose.[165,166] Another mechanism was recently revealed in a clinical trial of participants with NAFLD; berberine was shown to influence sphingolipid metabolism, including a decrease in serum ceramides. This was

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[157] Saha P, Bhattacharjee S, Sarkar A, et al. Berberine chloride mediates its anti-leishmanial activity via differential regulation of the mitogen activated protein kinase pathway in macrophages. PLoS One. 2011 Apr 5;6(4):e18467.
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[162] Ashrafizadeh M, Fekri HS, Ahmadi Z, et al. Therapeutic and biological activities of berberine: The involvement of Nrf2 signaling pathway. J Cell Biochem. 2020 Feb;121(2):1575-1585.
[163] Li X, Su C, Jiang Z, Yang Y, et al. Berberine attenuates choline-induced atherosclerosis by inhibiting trimethylamine and trimethylamine-N-oxide production via manipulating the gut microbiome. NPJ Biofilms Microbiomes. 2021 Apr 16;7(1):36.
[164] Habtemariam S. Berberine pharmacology and the gut microbiota: A hidden therapeutic link. Pharmacol Res. 2020 May;155:104722.
[165] Zhang L, Wu X, Yang R, et al. Effects of Berberine on the Gastrointestinal Microbiota. Front Cell Infect Microbiol. 2021 Feb 19;10:588517.
[166] Tian Y, Cai J, Gui W, et al. Berberine Directly Affects the Gut Microbiota to Promote Intestinal Farnesoid X Receptor Activation. Drug Metab Dispos. 2019 Feb;47(2):86-93.

correlated with improvements in glucose and lipid profiles compared to a lifestyle intervention, as well as a reduction in hepatic fat content among participants receiving berberine.[167]

In a related clinical trial, this metabolic effect was marked by changes in hemoglobin A1c (HbA1c) among over 400 subjects with diabetes participating in a randomized and controlled parallel 4-arm trial, supplemented with either berberine, probiotics, berberine and probiotics, or placebo. Both groups receiving berberine had significantly greater reductions in HbA1c; metagenomic and metabolomic analysis revealed significant shifts in the microbiome, and a correlation between the HbA1c decrease and a decrease in the population of *Ruminococcus bromii*, a species known to increase the biotransformation of the bile acid deoxycholic acid species (DCAs).[168] Cardiometabolic changes, including more favorable glucose and lipid profiles, were recently supported by a systematic review and meta-analysis of randomized controlled trials.[169]

Safety Summary:

Exercise caution in patients with kidney disease.[39] No other known warnings, precautions or contraindications at the dose recommended.[73] Contraindicated during pregnancy in therapeutic doses.[39] Discouraged during breastfeeding in therapeutic doses.[20]

White willow bark (*Salix alba*)

Biological Actions: Analgesic, anti-inflammatory.[20]

Scientific Evidence:

The key active constituents of white willow bark are comprised of phenolic glycosides including the salicylates salicortin and salicin.[20] However, an analysis of white willow bark revealed at least 16 other important compounds, including the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol), condensed tannins, catechin, amelopsin, taxifolin, 7-O-methyltaxifolin-3'-O-glucoside, and 7-O-methyltaxifolin.[170,171,172,173] Initially it was thought that salicin (converted to salicylic acid *in vivo*) was responsible for the anti-inflammatory effects of this herb.[171] More recent evidence suggests that the potent anti-inflammatory effect is derived from the sum total of the biologically active components,

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[167] Chang X, Wang Z, Zhang J, et al. Lipid profiling of the therapeutic effects of berberine in patients with nonalcoholic fatty liver disease. J Transl Med. 2016 Sep 15;14:266.
[168] Zhang Y, Gu Y, Ren H, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTE study). Nat Commun. 2020 Oct 6;11(1):5015.
[169] Ye Y, Liu X, Wu N, et al. Efficacy and Safety of Berberine Alone for Several Metabolic Disorders: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Front Pharmacol. 2021 Apr 26;12:653887.
[170] Pobłocka-Olech L, van Nederkassel AM, Vander Heyden Y, et al. Chromatographic analysis of salicylic compounds in different species of the genus Salix. J Sep Sci. 2007 Nov;30(17):2958-66.
[171] Bonaterra GA, Heinrich EU, Kelber O, et al. Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv(®)) in LPS-activated human monocytes and differentiated macrophages. Phytomedicine. 2010 Dec 1;17(14):1106-13.
[172] Bonaterra GA, Kelber O, Weiser D, et al. In vitro anti-proliferative effects of the willow bark extract STW 33-I. Arzneimittelforschung. 2010;60(6):330-5.
[173] Agnolet S, Wiese S, Verpoorte R, et al. Comprehensive analysis of commercial willow bark extracts by new technology platform: combined use of metabolomics, high-performance liquid chromatography-solid-phase extraction-nuclear magnetic resonance spectroscopy and high-resolution radical scavenging assay. J Chromatogr A. 2012 Nov 2;1262:130-7.

given white willow bark's effects are much broader acting than non-steroidal anti-inflammatory drugs (NSAIDs) which contain acetylsalicylic acid.[174] Unlike NSAIDs, white willow bark is not associated with unwanted side effects of gastric erosion.[172]

The synergistic effect of the salicylates, flavonoids and tannins found in white willow bark have been shown to inhibit COX-2 and subsequent generation of free radicals by converting arachidonic acid to prostaglandins.[175] *In vitro* studies assessing LPS activated monocytes show that *Salix alba* is able to block nitric oxide release and reduce IL-6 and TNF-α production.[171,176] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block NF-κB activation.[171,172] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[171] An antioxidant effect was also recently documented for salicin specifically, mediated in part by activation of the PI3K/Akt/GSK3β pathway, which plays a role in cellular protection, particularly against ischemic injury.[177]

Safety Summary:

Contraindicated in people with salicylate sensitivity.[174] White willow bark contains salicylic acid, the active constituent in aspirin. Although dosing with aspirin during viral infection is contraindicated in children under 16, the levels in Biocidin are very small. There have been no reported cases of Reye's Syndrome with the use of Biocidin. If known metabolic defects are present, it may be prudent to avoid all salicylic acid containing products - as determined by practitioner discretion. No other known warnings, precautions or contraindications at the dose recommended.[39] Should be avoided during pregnancy/lactation.[178]

Bladderwrack (*Fucus vesiculosus*)

Biological Actions:

Antibacterial, antifungal, anti-inflammatory, antioxidant, antiviral, immunomodulatory, prebiotic.[xcix,179,180]

Scientific Evidence:

The active constituents of bladderwrack include polysaccharides (alginic acid, laminarans, fucoidans), carotenoids (Fucoxanthin), polyphenols, lipids, sterols, and minerals (potassium, sodium, magnesium,

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[174] Shara M, Stohs SJ. Efficacy and Safety of White Willow Bark (Salix alba) Extracts. Phytother Res. 2015 Aug;29(8):1112-6.
[175] Fiebich BL, Chrubasik S. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. Phytomedicine. 2004 Feb;11(2-3):135-8.
[176] Drummond EM, Harbourne N, Marete E, et al. Inhibition of proinflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. Phytother Res. 2013 Apr;27(4):588-94.
[177] Park JH, Lee TK, Kim DW, et al. Neuroprotective Effects of Salicin in a Gerbil Model of Transient Forebrain Ischemia by Attenuating Oxidative Stress and Activating PI3K/Akt/GSK3β Pathway. Antioxidants (Basel). 2021 Apr 20;10(4):629.
[178] Oketch-Rabah HA, Marles RJ, Jordan SA, et al. United States Pharmacopeia Safety Review of Willow Bark. Planta Med. 2019 Nov;85(16):1192-1202.
[179] Criado MT, Ferreirós CM. Toxicity of an algal mucopolysaccharide for Escherichia coli and Neisseria meningitidis strains. Rev Esp Fisiol. 1984 Jun;40(2):227-30.
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iodine (free and protein bound)).[181] Fucoidans, sulfated heteropolysaccharides found in brown algae, have been recognized to have antioxidant, immunomodulatory, and anti-inflammatory activity.[182] Fucoidan from *Fucus vesiculosus* has been shown to inhibit NF-κB, both COX-1 and COX-2 enzymes, α-glucosidase, α-amylase, as well as dipeptidyl peptidase-IV (DPP-IV), suggesting several potential mechanisms for the anti-inflammatory and anti-hyperglycemic effects observed in animal studies.[183,184,185]

The mucopolysaccharides from bladderwrack possess antimicrobial properties. Based on *in vitro* studies, bladderwrack exhibits antifungal activity by selectively binding to *Candida guilliermondii* cells, thereby inhibiting their growth. This effect was not observed with other species of Candida tested (including *Candida albicans, Candida krusei, Candida parapsilosis, Candida brumpli,* and *Candida tropicalis).*[186] Bladderwrack mucopolysaccharides have also demonstrated antibacterial action via growth inhibition of multiple strains of *Neisseria meningitidis* and *Escherichia coli.*[179] In addition to antimicrobial effects, polysaccharides from brown algae, including *Fucus vesiculosus*, have been found to have a prebiotic effect, increasing multiple beneficial strains of *Lactobacillus* and *Bifidobacterium* as well as short chain fatty acid (SCFA) availability in several *in vitro* and animal models.[187] Clinical trials suggest a possible anti-inflammatory and antimicrobial effect in the GI tract; an uncontrolled trial of an extract of *Fucus vesiculosus/Undaria pinnatifida* given to professional athletes revealed a 45% significant increase in fecal lysozyme concentrations, and a trend toward reduced calprotectin levels in healthy adults.[188]

Based on *in vivo* and *in vitro* studies, fucoidans have demonstrated antiviral activity against several viruses, including HSV-1, HSV-2, poliovirus III, adenovirus III, coxsackie B3 virus and coxsackie A16.[180]

Safety Summary:

Contraindicated in therapeutic doses in persons with hyperthyroidism, and cardiac problems associated with hyperthyroidism.[99] Bladderwrack may interact with antithyroid and hypothyroid medications, having an additive effect, though in clinical trials with brown seaweeds no effect on thyroid function has been observed.[189] While in vitro studies suggest a possible anticoagulant effect of

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[181] Catarino MD, Silva AMS, Cardoso SM. Phycochemical Constituents and Biological Activities of Fucus spp. Mar Drugs. 2018 Jul 27;16(8):249.
[182] Sanjeewa KKA, Herath KHINM, Yang HW, Choi CS, Jeon YJ. Anti-Inflammatory Mechanisms of Fucoidans to Treat Inflammatory Diseases: A Review. Mar Drugs. 2021 Nov 28;19(12):678.
[183] Pozharitskaya ON, Obluchinskaya ED, Shikov AN. Mechanisms of Bioactivities of Fucoidan from the Brown Seaweed Fucus vesiculosus L. of the Barents Sea. Mar Drugs. 2020 May 22;18(5):275.
[184] Shan X, Liu X, Hao J, et al. In vitro and in vivo hypoglycemic effects of brown algal fucoidans. Int J Biol Macromol. 2016 Jan;82:249-55.
[185] Lean QY, Eri RD, Fitton JH, et al. Fucoidan Extracts Ameliorate Acute Colitis. PLoS One. 2015 Jun 17;10(6):e0128453.
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[189] Keleszade E, Patterson M, Trangmar S, et al. Clinical Efficacy of Brown Seaweeds Ascophyllum nodosum and Fucus vesiculosus in the Prevention or Delay Progression of the Metabolic Syndrome: A Review of Clinical Trials. Molecules. 2021 Jan 30;26(3):714.

fucoidan, this has not been observed after oral ingestion.[190] Avoid using during pregnancy.[73] Discouraged during breastfeeding in therapeutic doses.

American ginseng (*Panax quinquefolius*)

Biological Actions:

Adaptogen, antioxidant, antiviral, hepatoprotective, immunostimulant, tonic.[191,192]

Scientific Evidence:

The primary bioactive types of compounds in North American Ginseng (NAG) are polysaccharides and triterpenoid saponins known as ginsenosides. NAG polysaccharides have demonstrated significant free radical scavenging effects, as well as increased nitric oxide, TNF-α and interleukin-6 release from macrophages, acting as an immunostimulant.[193,191] A general induction of a T(h)1 transcriptional profile (observed in human peripheral blood mononuclear cells) by NAG polysaccharides is likely responsible for the immunomodulation.[194] Interestingly, ginsenosides have also been associated with a reduction in inflammasome activity, suggesting a role in limiting more chronic inflammatory processes.[195] Components in NAG berries have also shown, in animal trials, to provide protection against acetaminophen induced liver damage, while extracts from NAG roots improved liver function and related metabolic abnormalities in a model of fatty liver syndrome.[196,197]

Quinqueginsin, a novel protein isolated from American ginseng root has been shown to possess ribonucleolytic activity toward yeast tRNA. Quinqueginsin has also been found to inhibit cell free translation and has demonstrated antifungal activity against *Fusarium oxysporum*, *Rhizoctonia solani*, and *Coprinus comatus*.[198]

Several antiviral mechanisms have been elucidated for ginsenosides, including interaction with a viral

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[190] Irhimeh MR, Fitton JH, Lowenthal RM. Pilot clinical study to evaluate the anticoagulant activity of fucoidan. Blood Coagul Fibrinolysis. 2009 Oct;20(7):607-10.
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[192] Ghosh R, Bryant DL, Farone AL. Panax quinquefolius (North American Ginseng) Polysaccharides as Immunomodulators: Current Research Status and Future Directions. Molecules. 2020 Dec 11;25(24):5854.
[193] Ghosh R, Smith SA, Nwangwa EE, et al. Panax quinquefolius (North American ginseng) cell suspension culture as a source of bioactive polysaccharides: Immunostimulatory activity and characterization of a neutral polysaccharide AGC1. Int J Biol Macromol. 2019 Oct 15;139:221-232.
[194] Lemmon HR, Sham J, Chau LA, et al. High molecular weight polysaccharides are key immunomodulators in North American ginseng extracts: characterization of the ginseng genetic signature in primary human immune cells. J Ethnopharmacol. 2012 Jun 26;142(1):1-13.
[195] Yi YS. Roles of ginsenosides in inflammasome activation. J Ginseng Res. 2019 Apr;43(2):172-178.
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[197] Singh RK, Lui E, Wright D, et al. Alcohol extract of North American ginseng (Panax quinquefolius) reduces fatty liver, dyslipidemia, and other complications of metabolic syndrome in a mouse model. Can J Physiol Pharmacol. 2017 Sep;95(9):1046-1057.
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hemagglutinin protein which prevents viral attachment to cell receptors, as observed with influenza A.[199] A systematic review of 5 clinical trials concluded that American ginseng was effective in reducing the duration of colds or acute respiratory infections when taken preventatively, with a tendency to reduce the incidence as well, though more trials were needed for the latter.[200] A more recent systematic review and meta-analysis found evidence for both a reduction in incidence and duration of seasonal upper respiratory infections, and possibly benefit as an adjunct to influenza vaccination.[201] A systematic review of both Panax ginseng and NAG found the majority of included studies (randomized trials) also found a modest benefit for fatigue with low risk of adverse effects.[202] Lastly, a small but randomized and controlled cross-over trial found a significant reduction in both HbA1c and fasting glucose among participants with type 2 diabetes, as well as improvements in LDL-C and blood pressure following supplementation with NAG extract, suggesting a possible benefit for metabolic diseases.[203]

Safety Summary:

Considered safe and well-tolerated at the dose recommended.[204] Exercise caution or avoid during pregnancy as safety has not been established during these times.[205] Discouraged during breastfeeding in therapeutic doses.

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[200] Seida JK, Durec T, Kuhle S. North American (Panax quinquefolius) and Asian Ginseng (Panax ginseng) Preparations for Prevention of the Common Cold in Healthy Adults: A Systematic Review. Evid Based Complement Alternat Med. 2011;2011:282151.

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[202] Arring NM, Millstine D, Marks LA, et al. Ginseng as a Treatment for Fatigue: A Systematic Review. J Altern Complement Med. 2018 Jul;24(7):624-633.

[203] Vuksan V, Xu ZZ, Jovanovski E, et al. Efficacy and safety of American ginseng (Panax quinquefolius L.) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: a double-blind, randomized, cross-over clinical trial. Eur J Nutr. 2019 Apr;58(3):1237-1245.

[204] Mucalo I, Jovanovski E, Vuksan V, et al. American Ginseng Extract (Panax quinquefolius L.) Is Safe in Long-Term Use in Type 2 Diabetic Patients. Evid Based Complement Alternat Med. 2014;2014:969168.

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