Olivirex – Scientific Validation of Botanical Ingredients

Olive Leaf (*Olea europaea*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant, antiprotozoal, antiviral, hypoglycaemic, hypotensive.[1,2]

Scientific Evidence:
The main active constituents in olive leaf include secoiridoids (oleuropein and its derivatives), hydroxytyrosol, polyphenols (verbascoside, caffeic acid, apigenin-7-glucoside, and luteolin-7-glucoside), triterpenes including oleanolic acid, and flavonoids (rutin and diosmin). Its primary constituents, oleuropein and hydroxytyrosol, are believed to be responsible for the therapeutic properties of olive leaf extract.[2] Oleuropein and hydroxytyrosol have been shown to have antimicrobial activity against a variety of viruses, bacteria, yeasts and fungi.[3]

Oleuropein and caffeic acid have demonstrated antimicrobial activities *in vitro* against the Gram-positive bacteria, *Bacillus cereus* and the Gram-negative bacteria, *Escherichia coli* and *Salmonella enteritidis.*[4] Although individual phenolic compounds in olive leaf extract have demonstrated strong antimicrobial activity, the phenolics when combined demonstrated similar or better effects following *in vitro* assessment with a range of Gram-positive and Gram-negative organisms.[4]

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). Bacteriostatic activity has been demonstrated against *Bacillus subtilis* (20% w/v) and *Salmonella typhi.*[5] Olive leaf extracts 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.[7] 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^{-1}.[7]

Based on *in vitro* studies, olive leaf extract was 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]

The mechanism of action of the antiviral activity of olive biophenols involves interference with viral amino acid production, prevention of virus shedding, inhibition of viral replication, neutralization of reverse transcriptase and protease in retroviruses. Other antiviral mechanisms include prevention of virus entry into cells, disruption of virus structure, and stimulation of phagocytosis.[1] Olive leaf extract has been shown to inhibit human immunodeficiency virus-1 (HIV-1) infection, replication, and cell-to-cell transmission in a dose dependent manner.[9] Antiviral activities of hydroxytyrosol against HIV-1 and influenza virus, and of the polyphenol verbascoside against herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), vesicular stomatitis virus, HIV-1, and hepatitis A virus have also been reported.[1]

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Olive leaf extract has demonstrated virucidal activity against HSV-1 *in vitro*, most likely due to prevention of virus entry into host cells.[10]

Safety Summary:

Contraindicated in persons with known allergies to plants from the Oleaceae family.[3] Olive leaf extract is considered safe and well tolerated at the dose recommended.[11] Exercise caution or avoid during pregnancy and breastfeeding as safety has not been scientifically established during these times.[3]

Garlic (*Allium sativum*)

Medicinal Actions:

Anthelmintic, antiinflammatory, antimicrobial, antioxidant,[12] antiviral.[23,24]

Scientific Evidence:

The main active antimicrobial constituent of garlic is allicin (allyl 2-propene thiosulfinate), which is formed when the herb is crushed and alliinase (an enzyme from the bundle sheath cells) combines with the substrate allin. Crushed garlic contains a number of quorum sensing (QS) compounds such as ajoene and other organosulfides that are produced as degradation products of allicin.[13,14]

Both *in vitro* and *in vivo* studies have identified ajoene as the major QS component of garlic that is able to inhibit the expression of 11 virulence genes controlled by QS – these genes are considered crucial for *Pseudomonas aeruginosa* pathogenicity.[13,15] In addition to *Pseudomonas aeruginosa*, ajoene has demonstrated antimicrobial activity against the following respiratory-associated pathogens; *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Candida albicans*, *Neisseria gonorrhoea*, *Aspergillus niger* and *Paracoccidioides brasiliensis*.[13,16,17] Garlic has also been shown to be effective against a number of multidrug resistant strains of Gram-negative and Gram-positive bacteria including *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus* sp., *Proteus* sp. and *Staphylococcus aureus*.[18,19]

Quorum sensing inhibitors such as garlic 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).[13] Synergistic effects have been observed between garlic and gentamicin for infectious diseases caused by *Escherichia coli* strains.[20]

Garlic is an effective virulence blocking agent in *Streptococcus pyogenes* (group A streptococci) infection. *In vitro* research revealed allicin was able to neutralize the haemolytic activity of streptolysin O, a potent cytolytic toxin produced by nearly all strains of *Streptococcus pyogenes*.[21]

The thiosulfinates in garlic have demonstrated virucidal activity against a number of viruses including HSV-1, HSV-2, influenza B virus, parainfluenza virus type 3, coxsackie virus, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2.[22,23]

Garlic has also demonstrated antibacterial activity against oral microbes associated with dental plaque and caries including *Streptococcus mutans, Streptococcus sanguis, Streptococcus salivarius, Pseudomonas aeruginosa*, and *Lactobacillus* spp.[24,25] Other periodontal pathogens for which garlic has demonstrated antimicrobial activity include *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. Garlic appears to inhibit the growth of these organisms through antiproteolytic activity and by inhibiting total protease activity.[26,27]

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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.[28]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[29] No adverse effects expected during pregnancy and breastfeeding.[29]

Golden Seal (*Hydrastis canadensis*)

Medicinal Actions:
Antibacterial, antihistamine, antiinflammatory, antimicrobial, antiviral,[30] mucous membrane trophorestorative[3,12,29,31,32]

Scientific Evidence:
Golden seal root contains a number of alkaloids, the most abundant of which is berberine. Both *in vitro* and *in vivo* studies have revealed that berberine possesses antimicrobial activity against bacteria, yeast, fungi, parasites and viruses.[30,33,34]

Golden seal leaves are rich in flavonoids (specifically sideroxylin, 8 desmethyl-sideroxylin and 6 desmethyl-sideroxylin).[35] While the flavonoids from golden seal have no inherent bactericidal properties, they enhance the antimicrobial activity of berberine by acting as efflux pump inhibitors.[35] It should be noted that one of the major mechanisms by which bacteria become resistant to antibiotics is by over expression of efflux pumps.[36]

The combined effects of the active constituents in golden seal make this herb a potent antimicrobial agent for a number of microbial pathogens including methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus sanguis*, *Bacillus subtilis*, *Mycoplasma mycoides capri*, *Escherichia coli, Neisseria gonorrhoeae* isolates (including antibiotic-resistant strains), *Campylobacter jejuni, Vibrio cholera* and *Helicobacter pylori*.[34,35,37-41]

Berberine has demonstrated antifungal activity against 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*.[42]

One of the key mechanisms by which golden seal inhibits microbial growth is through quenching of the agr quorum sensing system.[35,41] QS is a bacterial cell-to-cell communication that controls genes and influences a number of processes including bioluminesence, sporulation, competence, antibiotic production, biofilm formation and virulence factor secretion.[43]

Berberine has also demonstrated antimicrobial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum.*[44] When compared with sterile saline irrigation, berberine was found to be more effective at eradicating the endodontic pathogens *Fusobacterium nucleatum, Enterococcus faecalis* and *Prevotella intermedia*.[45]

In vitro studies have shown that berberine possesses significant antimicrobial activity against a number of protozoans including *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Leishmania donovani*. The mechanism by which golden seal inhibits parasitic growth appears to be through lysis of the trophozoite forms.[46]

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Berberine has also been shown to inhibit the growth of several viruses including cytomegalovirus,[47] HSV-1[48] and human H1N1 stains of influenza A viruses. As an antiinflammatory agent, berberine works by inhibiting influenza A-induced production of tumour necrosis factor-α (TNF-α) and prostaglandins E2 (PGE2) from infected macrophages.[30]

Safety Summary:

Exercise caution in patients with kidney disease.[3] No other known warnings, precautions or contraindications at the dose recommended.[33] Contraindicated during pregnancy in therapeutic doses.[3] Discouraged during breastfeeding in therapeutic doses.[12]

Milk Thistle (*Silybum marianum*)

Medicinal Actions:

Antimicrobial, antioxidant[12,33] antiviral.[49,50]

Scientific Evidence:

Milk thistle is rich in flavanolignans which comprise 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.[12] Research has shown that the flavanolignans from milk thistle possess potent antibacterial activity against Gram-positive bacteria, but no antimicrobial activity against Gram-negative bacteria or fungi.[51]

Silibinin (an equal extract of silybin A and silybin B) has demonstrated antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus*.[12,52] When silibinin was combined with the antibiotics oxacilin 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).[52] Ethanol extracts of silybin have also demonstrated antibacterial activity against *Campylobacter jejuni*.[38] In addition, silibinin has demonstrated antioxidant and antiinflammatory properties on LPS-stimulated human monocytes through an inhibitory effect on hydrogen peroxide release and TNF-α production.[53]

Silybin derivatives of milk thistle have demonstrated significant antiviral activity. In animal studies, silybin derivatives significantly reduced influenza virus A/PR8 replication and its associated mortality in infected mice.[54] In the trial by Song and Choi, silymarin demonstrated greater antiviral activity against influenza A/PR/8/34 virus than the pharmaceutical agent Tamiflu® (oseltamivir) (98% vs. 52% respectively).[50]

Silybin appears to work by inhibiting several components induced by influenza A virus infection including oxidative stress, the activation of extracellular signal-regulated kinase (ERK)/p38 mitogen-activated protein kinase (MAPK) and IκB kinase (IKK) pathways, as well as the expression of autophagic genes (Atg7 and Atg3).[54]

Silibinin has also demonstrated antiviral activity against HSV-2 via an extracellular, virucidal mechanism (*in vitro* research).[55] Furthermore, silymarin also plays a beneficial role in viral hepatitis via inhibition of inflammatory and cytotoxic processes induced by viral infection.[49]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae family.[29] No other known warnings, precautions or contraindications.[29] No adverse effects expected during pregnancy and breastfeeding.[29]

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

Medicinal Actions:
Antibacterial, antifungal, antiinflammatory,[56] antiseptic, antiviral, vulnerary.[57]

Scientific Evidence:
Biologically active compounds of St. John's wort include naphthodianthrones (hypericin, pseudohypericin), phloroglucinols (hpyerforin), flavonoids (quercetin, hyperin, rutin), biflavones, phenylpropanes, proanthocyanidins and volatile oils.[58]

Ethanolic extracts of St. John's wort have demonstrated antibacterial activity *in vitro* against the Gram-positive bacteria *Enterococcus faecalis* and *Staphylococcus aureus*.[59]

Hyperforin has been shown to be the main antibacterial constituent of St. John's wort.[58] Based on *in vitro* research, hyperforin is able to inhibit the growth of a number of Gram-positive organisms including *Corynebacterium diphtheriae*[60] and multiresistant *Staphylococcus aureus* (MRSA) strains.[58,61,62]

The antifungal activity of flavonoids and volatile oils from St. John's wort has been demonstrated in several studies.[57,58] Ethanolic extracts of St. John's wort have demonstrated fungistatic activity against *Fusarium oxysporum* and *Penicillium canescens*.[58] The flavonoids derived from St. John's wort have been shown to inhibit the growth of the phytopathogenic fungus *Helminthosporium sativum*, and *Fusarium graminearu*.[57,58] 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*. [57,58]

Based on *in vitro* research, hypericin is able to inactivate a wide variety of lipid containing (enveloped) viruses. Hypericin has demonstrated virucidal activity against the following enveloped viruses HIV-1,[63] HSV-1 and HSV-2,[64] bovine viral diarrhoea virus, influenza A, parainfluenza virus type 3,[64] radiation leukemia virus, Moloney leukemia virus,[65] vaccina virus,[64] vesicular stomatitis virus,[64] murine cytomegalovirus,[63] Sendai virus, Sindbis virus,[63] equine infectious anaemia virus, bovine immunodeficiency virus, and human cytomegalovirus.[57,66] 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).[57,66]

Safety Summary:
Contraindicated in persons with known sensitivity to St. John's wort or any of its constituents.[57] Avoid using in cases of known photosensitivity, or in patients taking photosensitising agents.[57] In therapeutic 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.[57] Adverse effects associated with St. John's wort are rare and tend to be mild.[57] No adverse effects expected during pregnancy and breastfeeding.[33]

Uva Ursi (*Arctostaphylos uva ursi*)

Medicinal Actions:
Antiinflammatory,[57] antimicrobial, astringent, urinary antiseptic.[67]

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Scientific Evidence:
Biologically active compounds of uva ursi include hydroquinone glycosides (arbutin, methylarbutin), and polyphenols, phenolic acids, tannins, flavonoids and volatile oils.[67] The key active constituent responsible for uva ursi's antimicrobial activity is thought to be arbutin.[67]

Ethanolic extracts of uva ursi have exhibited antimicrobial activity against a variety of organisms including *Staphylococcus aureus*, *Bacillus subtilis*, *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, Streptococcus faecalis*, *Enterobacter aerogenes*, *Staphylococcus aureus, Salmonella typhi* and *Candida albicans*.[69]

The hydroquinone glycoside arbutin has also been reported to be active against *Candida albicans*, *Staphylococcus aureus* and *Escherichia coli.*[67]

The antibacterial effect of uva ursi may also be beneficial in the gastrointestinal tract. Based on *in vitro* research, aqueous extracts of uva ursi are able to modulate cell surface hydrophobicity and have demonstrated antibacterial effects against a number of *Helicobacter pylori* strains.[70]

Safety Summary:
Contraindicated in therapeutic doses in people with kidney disorders and in children under 12 years of age.[57] Contraindicated during pregnancy and breastfeeding.[57]

American Ginseng (*Panax quinquefolium* L.)

Medicinal Actions:
Adaptogen, antioxidant,[71] hepatoprotective, immunostimulant, tonic.[72]

Scientific Evidence:
Ginsenosides and polysaccharides have been recognized as the two major active components of American ginseng.[71] Ginseng polysaccharides have demonstrated significant free radical scavenging effects, as well as increased nitric oxide, TNF-α and interleukin-6 (IL-6) release from macrophages.[71]

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*.[73]

Based on a systematic review, American ginseng has been shown to be effective in the prevention and treatment of acute respiratory infections and the common cold.[74] When taken preventatively, it helps reduce the incidence and severity of common colds, and shortens the duration of colds or acute respiratory infections.[74]

Safety Summary:
Contraindicated in therapeutic doses with conditions manifested by acute inflammation, high fever, or irritability.[72] Exercise caution or avoid during pregnancy and breastfeeding as safety has not been scientifically established during these times.[75]

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Bladderwrack (*Fucus vesiculosus*)

Medicinal Actions:
Antibacterial,[76] anticomplementary, antifungal, antiinflammatory, antioxidant, antiviral, demulcent,[29] gastric protective, immunomodulatory, thyroid stimulant.[77]

Scientific Evidence:
The active constituents of bladderwrack include iodine (free and protein bound), polysaccharides (alginic acid, fucans, fucoidan), polyphenols, lipids and sterols.[29]

Research shows that 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.[78] This effect was not identified with other species of Candida tested (including *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, *Candida brumpli*, and *Candida tropicalis*). Bladderwrack mucopolysaccharides have also demonstrated antibacterial action via growth inhibition of multiple strains of *Neisseria meningitidis* and *Escherichia coli*.[76]

The polysaccharide fucoidan has been shown to possess anti RNA and deoxyribonucleic acid (DNA) virus functions.[77] Based on *in vivo* and *in vitro* studies, fucoidan is effective against a number of viruses including HSV-1, HSV-2, poliovirus III, adenovirus III, coxsackie B3 virus and coxsackie A16.[77]

Sulphated polysaccharides have also been shown to inhibit the growth of a number of enveloped viruses, namely HSV, human cytomegalovirus, vesicular stomatitis virus, Sindbis virus, vaccinia virus and HIV.[79]

Safety Summary:
Contraindicated in therapeutic doses in persons with hyperthyroidism, and cardiac problems associated with hyperthyroidism.[29] Bladderwrack may interact with antithyroid and hypothyroid medications, having an additive effect.[80] Avoid using during pregnancy and breastfeeding.[33]

Cordyceps (*Cordyceps Sinensis*)

Medicinal Actions:
Adaptogen, antiinflammatory, antioxidant,[81] antimicrobial,[82] antitussive, expectorant,[83] immune modulating, neuro-, liver- and renoprotective.[84,85] .

Scientific Evidence:
The phytochemical constituents of cordyceps include nitrogenous compounds (cordycepin and adenosine), sterols (ergosterol) polysaccharides, proteins, phenolics, isoflavones and organic acids.[84] Polysaccharides account for the antiinflammatory, antioxidant and immunomodulatory effects of the herb. Cordycepin contributes to the antibacterial activity, and ergosterol is believed to exhibit immunomodulatory activity.[82]

In clinical trials, the use of polysaccharides derived from cordyceps have improved physical performance and quality of life.[86] Elderly patients affected by chronic obstructive pulmonary disease have demonstrated an increase in red blood cell super oxide dismutase activity, which was associated with significant clinical improvements in cough, phlegm, appetite, pulmonary symptoms and vitality.[86]

The antibacterial activity of cordyceps has been confirmed through *in vitro* research. Cordycepin (from *Cordyceps* species) 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*.[82,87]
The peptide cordymin (from *Cordyceps militaris*) has been shown to exhibit antifungal activity. Based on *in vitro* experiments, cordymin is able to inhibit mycelial growth of a number of fungal organisms including *Bipolaris maydis, Mycosphaerella arachidicola, Rhizoctonia solani* and *Candida albicans.*[88]

Safety Summary:
Cordyceps is considered safe and well tolerated at the dose recommended.[89] 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.[89] Exercise caution or avoid during pregnancy and breastfeeding as safety has not been scientifically established during these times.[89]

Dandelion (*Taraxacum officinale*)

Medicinal Actions:
Antiinflammatory, antimicrobial[90] antioxidant,[56] antiviral, bitter tonic,[33] choleretic.[91]

Scientific Evidence:
The main phytochemical compounds of dandelion include terpenes, phenolic compounds and storage carbohydrates. The root contains antiinflammatory and antimicrobial sesquiterpene lactones, immune stimulating phenolic acids and the prebiotic-acting oligosaccharide soluble fibre inulin.[56]

Based on *in vitro* experiments, dandelion-derived polysaccharides and oligosaccharides have demonstrated antibacterial activity against *Escherichia coli, Bacillus subtilis* and *Staphylococcus aureus.*[92] Dandelion polysaccharide compounds have also been shown to inhibit the growth of *Staphylococcus epidermidis*, *Salmonella typhimurium*, and *Streptococcus*.[93]

An ethanol extract of dandelion has demonstrated antimicrobial activity against Gram-positive bacterial strains including *Staphylococcus aureus*, MRSA and *Bacillus cereus*.[90,94]

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 on virus replication.[91]

The triterpenoids taraxasterol and taraxerol have exhibited significant inhibitory effects on Epstein-Barr virus early antigen induction.[95]

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.[33]

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Noni (*Morinda citrifolia*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant,[3,96] antiviral, immune enhancing.[97]
Scientific Evidence:
To date, over 160 different phytochemical compounds have been identified in the noni plant. The major secondary metabolites include phenolic compounds, organic acids and alkaloids which give rise to noni's potent antioxidant and antiinflammatory properties.[96]

In vitro research has shown that noni is highly effective at inhibiting hydroxyl radicals which are known to cause oxidative damage to proteins, lipids and DNA.[96] Noni has also been shown to decrease nitric oxide production. Nitric oxide is a compound produced by macrophages that plays a key role in inflammation and has also been shown to interfere with DNA repair processes. Based on animal trials, the antinociceptive and antiinflammatory effects of noni appear to work in a dose-dependent manner.[96]

As a natural antiinflammatory agent, noni inhibits LPS-induced activation of a number of chemical mediators including cycoloxygenase (COX)-1 and COX-2, nitric oxide and PGE2 in a dose dependent manner.[98] Noni possess natural immune stimulating properties and has been shown to enhance both cellular and humoral-mediated immunity.[99]

Research supports the use of noni as a broad acting immunostimulant given its ability to enhance the proliferation of both T and B lymphocytes.[99] Based on *in vitro* and *in vivo* animal studies, noni may help reduce the adverse effects of allergy-mediated respiratory conditions by down regulating the T-helper (Th)-2 cytokine IL-4, and by increasing the production of interferon (IFN)-γ.[100]

Other *in vitro* trials have also confirmed noni's immunomodulatory properties. In murine effector cells (thymocytes and splenocytes), noni stimulated the release of a number of mediators including TNF-α, IL-1β, IL-10, IL-12 p70, IFN-γ and nitric oxide and suppressed IL-4. The opposing effects of noni on IL-12 and IL-4 cytokines suggests the herb may enhance the cytotoxicity of natural killer (NK) cells and T lymphocytes.[101]

The active compounds acubin, L-asperuloside and alizarin isolated from noni have demonstrated antibacterial activity against a number of pathogens including *Pseudomonas aeruginosa*, *Proteus morganii*, *Stapylococcus aureus*, *Bacillis subtilis*, *Escherichia coli*, *Salmonella* and *Shigella*.[97] Noni has also been shown to inhibit the activity of enterohemorrhagic *E. coli* (0157) and *Helicobacter pylori*.[102]

Noni has also demonstrated antifungal activity against *Candida albicans* in a dose-dependent manner.[103] 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*.[104]

Traditionally noni was used for tuberculosis infections, which has now been substantiated by *in vitro* studies, indicating noni is nearly as effective as Rifampicin (with inhibition rates of 89% and 97% respectively).[105,106]

The iridoid and hemiterpene glycosides, anthraquinones, and saccharide fatty acid esters isolated from noni fruit extract have also demonstrated antiviral activity. Based on *in vitro* studies, these bioactive compounds were able to inhibit Epstein-Barr virus early antigen induction more effectively than beta carotene and quercetin.[107]

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Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[3,108] No adverse effects expected during pregnancy and breastfeeding.[3,109]

White Willow Bark (*Salix alba*)

Medicinal Actions:
Analgesic, antiinflammatory.[12]

Scientific Evidence:
The key active constituents of white willow bark comprise of phenolic glycosides including the salicylates salicortin and salicin.[12] Other important actives include the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol) and condensed tannins.[110-112]

Initially it was thought that salicin (converted to salicylic acid *in vivo*) was responsible for the antiinflammatory effects of this herb.[112] More recent evidence suggests that the potent antiinflammatory effect of white willow bark is derived the sum total of the medicinal actives given the analgesic effects are much broader acting than non-steroidal antiinflammatory drugs (NSAIDs) which contain acetyl salicylic acid.[12,111] Unlike NSAIDs, white willow bark is not associated with the unwanted side effects of gastric erosion.[112]

The synergistic effect of the salicylates, flavonoids and tannis found in white willow bark have been shown to inhibit COX-2 and subsequent generation of free radicals by converting arachidonic acid to prostaglandins.[113] Other downstream products of COX activity include nitric oxide release and upregulation of proinflammatory cytokines.[111]

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.[111,114] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block transcription factor NF-Kβ activation.[111,112] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[111]

Safety Summary:
Contraindicated in people with salicylate sensitivity.[3] No other known warnings, precautions or contraindications at the dose recommended.[3] No adverse effects expected during pregnancy and breastfeeding.[3]

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