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Biocidin Throat Spray – Scientific Validation of Ingredients

Bilberry extract (*Vaccinium myrtillus*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant, urinary antiseptic.[1-3]

Scientific Evidence:
Bilberry is rich in phenolic compounds which possess bacteriostatic and antimicrobial properties.[4] This herb is renowned for its exceptionally high levels of anthocyanins, which are responsible for bilberry's diverse antioxidant effects.[5,6] As a natural antiinflammatory agents, bilberry polyphenols help reduce lipopolysaccharide (LPS)-induced nuclear factor kappa-beta (NF-Kβ) activation.[7]

Based on *in vitro* research, bilberry possesses antiadhesive and antimicrobial properties against the respiratory-associated pathogens *Streptococcus pneumoniae* and *Neisseria meningitidis*.[8] Bilberry extract may also help protect against dental plaque by inhibiting biofilm formation of common oral bacteria including *Streptococcus mutans*, *Fusobacterium nucleatum* and *Actinomyces naeslundii*.[9]

In vitro trials also show that bilberry is able to inhibit the replication of several respiratory viruses including coxsackie virus B1 (CV-B1), human respiratory syncytial virus A2 (HRSV-A2) and influenza virus A/H3N2.[10]

Safety Summary:
Considered safe at the recommended dose.[1] No adverse effects expected during pregnancy and breastfeeding.[2]

Noni (*Morinda citrifolia*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[3,11]

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.[11] *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 deoxyribonucleic acid (DNA).[11] 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.[11] 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 prostaglandins E2 (PGE2) in a dose-dependent manner.[12]

Research supports the use of noni as both a cellular and humoral immunostimulant given its ability to stimulate the proliferation of T and B lymphocytes.[13] 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 interleukin (IL)-4 and increasing the production of interferon (IFN)-γ.[14]

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 tumour

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necrosis factor (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.[15]

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).[16,17]

The active compounds acubin, L-asperuloside and alizarin isolated from noni have demonstrated antibacterial activity against a number of pathogens including *Pseudomonas aeruginosa*, and *Staphylococcus aureus.*[18]

Noni has also demonstrated antifungal activity against *Candida albicans* in a dose-dependent manner.[19] 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*.[20]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[3,21] No adverse effects expected during pregnancy and breastfeeding.[3,22]

Milk thistle (*Silybum marianum*)

Medicinal Actions:
Antimicrobial, antioxidant.[1,2]

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.[1] 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.[23]

Silibinin (an equal extract of silybin A and silybin B) has demonstrated antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus*.[1,24] 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).[24] Silibinin has also demonstrated antioxidant and antiinflammatory properties on LPS-stimulated human monocytes through an inhibitory effect on hydrogen peroxide release and TNF-α production.[25]

Silibin 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.[26] Silibin 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).[26]

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).[27]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae family.[28] No other known warnings, precautions or contraindications.[28] No adverse effects expected during pregnancy and breastfeeding.[28]

Echinacea (*Echinacea purpurea* & *Echinacea angustifolia*)

Medicinal Actions:
Antiinflammatory, antifungal, antiviral, depurative, immune enhancing, immune modulating, lymphatic.[2,3,28]

Scientific Evidence:
Echinacea possesses both antiinflammatory and immunostimulating properties.[29] Alkylamides, one of the active constituents of echinacea are thought to be responsible for the herb's antiiflammatory activity. Emerging research suggests that bacterial lipoproteins and lipopolysaccharides within echinacea (endophytes) represent the major source of immune enhancing properties of this herb.[30,31] Human cells of the innate immune system detect Braun-type lipoproteins and LPS through Toll-like receptor 2 and 4 pathways, macrophage activation and upregulation of NK cell activity in the body.[32,33]

Echinacea has demonstrated antimicrobial activity against a number of respiratory pathogens including *Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Legionella pneumophila* and *Candida albicans*.[34,35] Based on *in vitro* research, echinacea has both antiinflammatory and direct killing activity against *Streptococcus pyogenes, Haemophilus influenzae and Legionella pneumophila.* Echinacea has been shown to inhibit the production of the following cytokines: IL-4, IL-6, IL-8, MCP-1, VEGF, and GROα.[36]

Because echinacea supports low-running immune systems, it is and effective herb during times of stress which can be associated with increased susceptibility to common colds and respiratory infections. This herb is also safe to use in persons with well-performing immune systems without any risk of over stimulation.[37] Based on clinical trials by Goel et al., therapeutic doses of echinacea can improve the systemic immune response in subjects suffering from the common cold. Supplementation with echinacea reduced daily cold and flu symptoms and resulted in a significant and sustained increase in the total number of circulating white blood cells, monocytes, neutrophils and NK cells.[38,39]

As a natural antiviral agent, echinacea has demonstrated efficacy against a number of respiratory viruses including influenza viruses (A and B strains), respiratory syncytial virus, and rhinovirus.[34,40-43] Echinacea has also demonstrated potent antiviral activity against strains of highly pathogenic avian influenza viruses including human Victoria (H3N2) and PR8 (H1N1), avian strains KAN-1 (H5N1) and FPV (H7N7), and the pandemic S-OIV (H1N1).[44] Based on *in vitro* research, possible antiviral mechanisms of action for echinacea include proinflammatory cytokine inhibition (specifically IL-6 and IL-8) and upregulation of inducible nitric oxide synthase.[41,45-47]

Safety Summary:
Contraindicated in persons allergic to plants from the Compositae family.[2] Exercise caution with patients taking immunosuppressant medications (short term use only).[2] No other known warnings, precautions or contraindications.[48] No adverse effects expected during pregnancy and breastfeeding.[2,28]

Golden seal (*Hydrastis canadensis*)

Medicinal Actions:
Antibacterial, antihistamine, antiinflammatory, antimicrobial, mucous membrane trophorestorative.[1,3,28,49,50]

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 and fungi.[2,51]

Golden seal leaves are rich in flavonoids (specifically sideroxylin, 8 desmethyl-sideroxylin and 6 desmethyl-sideroxylin).[52] While the flavonoids from golden seal have no inherent bactericidal properties, they enhance the antimicrobial activity of berberine by acting as efflux pump inhibitors.[52] It should be noted that one of the major mechanisms by which bacteria become resistant to antibiotics is by over expression of efflux pumps.[53]

The combined effects of the active constituents in golden seal make this herb a potent antimicrobial agent for a number of respiratory-associated pathogens including methicillin-resistant *Staphylococcus aureus*, and *Neisseria gonorrhoeae* isolates (including antibiotic-resistant strains).[51,52,54] Berberine has also 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*.[55]

One of the key mechanisms by which golden seal inhibits microbial growth is through quenching of the agr quorum sensing (QS) system.[52,56] 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.[57]

Berberine has been shown to inhibit the growth of several viruses including cytomegalovirus and human H1N1 stains of influenza A viruses. As an antiinflammatory agent, berberine works by inhibiting influenza A-induced production of TNF-α and PGE2 from infected macrophages.[58]

Berberine has also demonstrated antimicrobial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum.*[59] 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*.[60]

Safety Summary:
Exercise caution in patients with kidney disease.[3] No other known warnings, precautions or contraindications at the dose recommended.[2] Contraindicated during pregnancy in therapeutic doses.[3] Discouraged during breastfeeding in therapeutic doses.[1]

Shiitake mushroom (*Lentinula edodes*)

Medicinal Actions:
Antibacterial, antifungal, antioxidant, immune modulating.[3,61]

Scientific Evidence:
Shiitake mushroom contains activated hexose correlated compound (AHCC), which possesses immune-modulating properties.[62] Another mechanism by which Shiitake enhances immune function is

by increasing the Th-1 cytokine IL-2.[63] In human trials, Shiitake mushroom has also been shown to increase the number of circulating B cells in healthy elderly adults.[64]

Shiitake mushroom also contains the polysaccharides lentinan, LEM, KS-2 and eritadenine, which have demonstrated antimicrobial and antiviral activity.[65] As an antimicrobial agent, lentinan works by activating macrophages and the cytokines TNF-α and IFN-γ with resultant stimulation of T lymphocytes and enhanced immunity.[65]

Based on *in vitro* research, Shiitake mushroom has demonstrated antibacterial activity against a number of respiratory-associated pathogens including: *Streptococcus pyogenes, Klebsiella* sp., *Pseudomonas aeruginosa* and *Staphylococcus* sp. (including methicillin-resistant *Staphylococcus aureus* (MRSA)).[66-70] Shiitake has also demonstrated antifungal activity against the following organisms: *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Scedosporium apiospermum*.[68-70]

Shiitake may be effective against oral pathogens associated with dental caries and dental plaque accumulation.[71,72] *In vitro* studies have demonstrated antigingivitis and anticaries activities of Shiitake against the following oral pathogens: *Streptococcus sanguinis, Streptococcus mutans, Fusobacterium nucleatum*, *Prevotella intermedia, Veillonella dispar, Neisseria subflava, Actinomyces naeslundii* and *Lactobacillus casei*.[71,73-75] Shiitake protects against gingivitis and caries through a number of mechanisms including inhibition of cell division, prevention of coaggregation and biofilm formation as well as disruption of preexisting biofilms.[71,73] These effects are explained in part by Shiitake's alpha-glucan content. Shiitake mushroom is rich in alpha-gluconase, an enzyme that has been shown to inhibit sucrose-induced formation of oral biofilms from *Streptococcus mutans* and *Streptococcus sobrinus* species.[76,77]

Safety Summary:
Considered safe and well tolerated at doses of up to 2.5mg per day for 6 weeks.[64] Doses of 9 grams per day of liquid AHCC have also been trailed for two weeks in healthy adults with no changes in blood chemistry markers or significant adverse events.[78] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[79]

White willow bark (*Salix alba*)

Medicinal Actions:
Analgesic, antiinflammatory.[1]

Scientific Evidence:
The key active constituents of white willow bark comprise of phenolic glyosides including the salicylates salicortin and salicin.[1] Other important actives include the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol) and condensed tannins.[80-82]

Initially it was thought that salicin (converted to salicylic acid *in vivo*) was responsible for the antiinflammatory effects of this herb.[82] 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.[1,81] Unlike NSAIDs, white willow bark is not associated with the unwanted side effects of gastric erosion.[82]

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.[83] Other downstream products of COX activity include nitric oxide release and upregulation of proinflammatory cytokines.[81]

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.[81,84] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block transcription factor NF-Kβ activation.[81,82] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[81]

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]

Garlic (*Allium sativum*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[1]

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 QS compounds such as ajoene and other organosulfides that are produced as degradation products of allicin.[85,86]

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*.[87]

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.[85,88] 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*.[85,89,90] Garlic has also been shown to be effective against a number of multi-drug-resistant strains of *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[91,92]

QS 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).[85]

The thiosulfinates in garlic have demonstrated virucidal activity against a number of respiratory viruses including; influenza B virus, parainfluenza virus type 3, coxsackie virus, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2.[93,94]

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..[95,96] 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.[97,98]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[28] No adverse effects expected during pregnancy and breastfeeding.[28]

Grape seed (*Vitis vinifera*)

Medicinal Actions:
Antibacterial, antiinflammatory, antioxidant.[3]

Scientific Evidence:
Grape seed contains over 95% flavonols, which are predominately comprised of oligomeric proanthocyanins (~82%) and active monomeric proanthocyanins (~12%).[99]

Grape seed extracts have demonstrated antimicrobial activity against a number of respiratory pathogens including *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus* sp. Group F*, Streptococcus pneumoniae and Pseudomonas aeruginosa*.[100] Grape seed extract has also demonstrated antibacterial activity against MRSA strains when assayed through *in vitro* experiments. While the underlying mechanism has not been fully elucidated, grape seed appears to reduce microbial growth by disrupting or breaking down cell wall surfaces.[99]

Another subclass of flavonols found in grape seed identified as procyanidins have demonstrated strong antiviral properties when compared with other botanical agents. These compounds were able to inhibit the replication of influenza A virus at several stages of the life cycle.[101] The mechanism by which grape seed exerts antiviral effects relates to the herb's immunostimulatory properties. Grape seed helps upregulate Th-1 immune responses by inducing IFN-γ in mononuclear cells.[102]

Based on *in vitro* research, grape seed has demonstrated antiplaque and antibiofilm activity against oral microbes associated with periodontitis and other acute periodontal diseases. The antimicrobial activity of grape seed has been documented for the following organisms: *Porphyromonas gingivalis, Fusobacterium nucleatum, Streptococcus mutans, Streptococcus sobrinus, Lactobacillus rhamnosus* and *Actinomyces viscosus*.[103] The proathocyanidins found in grape seed have also demonstrated a protective effect against endotoxin-induced experimental periodontitis (animal research).[104] Other *in vitro* studies indicate grape seed extract supports healthy remineralization of teeth and may be more effective than oral fluoride or calcium glycerophosphate.[105,106]

Safety Summary: No known warnings, precautions or contraindications at the dose recommended.[3] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[3]

Black walnut (*Juglans nigra*)

Medicinal Actions:
Antimicrobial, depurative.[1]

Scientific Evidence:
The main active constituents of black walnut include naphthoquinones (juglone and plumbagin), tannins (ellagic acid) and flavanoids.[1,28,107] Tannins comprise ~45% of the medicinal actives and exert an astringent effect on mucosal tissue by dehydrating mucosal secretions and protecting the outer layer of mucosal cells.[108]

Antimicrobial, antifungal and antiviral actions have also been attributed to the plumbagin and juglone content of black walnut. *In vitro* studies suggest these quinones exert their cytotoxic effects on microorganisms through redox cycling and the oxidation of glutathione.[109]

Based on *in vitro* research, black walnut has demonstrated broad spectrum antimicrobial activity against the following respiratory and oral pathogens: *Staphylococcus aureus*, *Micrococcus luteus* and

Streptococcus mutans.[107,110] Black walnut has also been shown to inhibit biofilm formation and adherence of methicillin-resistant *Staphylococcus aureus*.[111]

Respiratory-associated yeast and fungal organisms susceptible to black walnut comprise of *Candida albicans, Trichophyton rubrum, Aspergillus niger* and *Rhyzopus nigricans.*[110]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[28] Contraindicated during pregnancy and breastfeeding in therapeutic doses.[112]

Raspberry (*Rubus idaeus*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[1,3]

Scientific Evidence:
Raspberry is rich in anthocyanins (mainly cyanidin-3-sophoroside) and phenolic compounds (primarily ellagitannins and ellagic acid). Raspberry also contains quercetin and kaempherol-based flavanols.[113-115] Research shows that antioxidant properties of raspberry are attributed to the polyphenolic compounds (specifically ellagitannins) which are highly effective free radical scavengers.[113,115] Results of an *in vitro* study indicate that raspberry's phenolic compounds are able to protect DNA and decrease lipid peroxidation of lymphocytes in a concentration-dependent manner.[113]

The active ellagitannin constituents (sanguiin H-6 and lambertianin C) have also demonstrated antiinflammatory properties. Based on *in vitro* research, they inhibit the increase of NF-Kβ driven nuclear transcription and resultant TNF-α production in a dose-dependent manner.[116] Raspberry actives also been shown to reduce inflammation by inhibiting the release of the enzyme elastase secreted by neutrophils, which is considered a major component of the inflammatory cascade.[117]

Phenolic compounds also possess antimicrobial properties and have been shown to inhibit the growth of the following respiratory-associated pathogens: *Pseudomonas aeruginosa, Staphylococcus aureus* (including methicillin-resistant strains) and *Candida albicans*.[4,118-121] The mechanism by which phenolic compounds affect the growth of different bacterial species include destabilization of the cytoplasmic membrane, permeabilization of plasma membranes and inhibition of extracellular microbial enzymes. Phenolic compounds also have direct actions on microbial metabolism by depriving bacterial cells of the substrates necessary for growth.[122] Adherence of bacteria to epithelial surfaces is a prerequisite for colonization of many pathogens, therefore the antimicrobial activity of raspberry may be related in part to the antiadherence activity suggested by Puupponen et al.[4]

In addition to its antimicrobial effects, raspberry has also demonstrated antiviral activity against a number of respiratory pathogens. Based on *in vitro* research, methanol extracts of raspberry have been shown to inhibit the replication of coxsackie virus B1, influenza A virus and influenza virus A/H3N2.[10]

Research also shows that raspberry is effective against oral pathogens associated with dental caries and gingivitis. Raspberry has demonstrated antigingivitis and anticaries activities against the following organisms: *Streptococcus sanguinis, Streptococcus mutans, Fusobacterium nucleatum*, *Prevotella intermedia, Veillonella dispar, Neisseria subflava, Actinomyces naeslundii* and *Lactobacillus casei*.[73,75] Mechanisms by which raspberry protects against oral pathogens include: preventing bacterial coaggregation and biofilm formation, disruption of preexisting biofilms and decreasing the expression of genes involved in gingival cellular proliferation and differentiation.[75]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended. Take away from alkaloid-containing medications, metal ion supplements and vitamin B1 (thiamine).[28] No adverse effects expected during pregnancy and breastfeeding.[28]

Fumitory (*Fumaria officinalis*)

Medicinal Actions:
Antimicrobial, antioxidant.[123]

Scientific Evidence:
The active constituents of fumitory include alkaloids, flavonoids and organic acids.[1] The biological activities of this herb are mainly associated with the isoquinoline alkaloids, in particular protopine.[124,125] Protopine, has also demonstrated antihistamine effects.[126] The antioxidant capacity of fumitory is thought to be due to the synergistic effect of the active constituents.[123]

To date the scientific evaluation of fumitory as an antimicrobial agent is somewhat limited. Results of an *in vitro* study assessing a methanol extract of fumitory have demonstrated significant antimicrobial activity against the following respiratory-associated microorganisms: *Pseudomonas aeruginosa, Staphylococcus aureus* and *Cladosporium herbarum*.[123] The isoquinoline alkaloids from fumitory have also demonstrated significant antifungal activity against *Candida albicans*.[127]

In vitro research also suggests fumitory possesses antiviral properties. Fumitory isoquinolones and their derivatives have demonstrated selective inhibition against parainfluenza type 3 virus.

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[128] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[126]

Gentian (*Gentiana lutea*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[1,3,129]

Scientific Evidence:
Gentian contains a number of secoiridoid bitter compounds including; gentiopicrin, amarogentin, gentianine, gentianadine, swerosid and swertiamarin. The medicinal constituents also include a group of xanthones (isovitexin and isogentisin) as well as phenolic acids and phytosterol flavanoids.[1,129-131] These active constituents give rise to the herb's potent antioxidant, antiinflammatory and antibacterial properties.[129,131]

The antioxidant and cytoprotective action of gentian is due to the herb's ability to scavenging reactive oxygen species such as hydroxyl radicals, thereby reducing free radical injury to cells.[130-132]

Based on *in vitro* trials, the antiinflammatory activity arises from gentian's ability to inhibit myeloperoxidase enzymes which are released during degranulation of neutrophils and monocytes. Myeloperoxidase upregulation is known to contribute to the development of inflammatory and immune-mediated conditions.[129]

The bitter compounds in gentian include gentiopicrin and xanthone isogentisin. These substances possess antimicrobial properties and have been shown to inhibit the growth of a number of respiratory-

associated pathogens including *Streptococcus pyogenes, Staphylococcus aureus*, *Pseudomonas aeruginosa, Sarcina lutea, Micrococcus flavus, Micrococcus luteus* and *Candida albicans.*[133,134]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[2] No adverse effects expected during pregnancy and breastfeeding.[28]

Tea tree oil (*Melaleuca alternifolia*)

Medicinal Actions:
Antifungal, antimicrobial.[135-141]

Scientific Evidence:
Tea tree oil is composed of a complex mixture of compounds, mainly monoterpene and sesquiterpene hydrocarbons and their associated alcohols such as pinene, sabinene, α-terpinene, limonene; p-cymene, 1,8-cineole, γ-terpinene, terpinolene, terpinen-4-ol, α-terpineol, aromadendrene, ledene, δ-cadinene, globulol and viridiforol.[138,139,141,142] The diverse active constituents give rise to tea tree's antimicrobial activity against a broad range of Gram-positive and Gram-negative bacteria and fungi.[139,143]

The main antibacterial constituents of tea tree oil are terpinen-4-ol and γ-terpinene. It has been indicated, that terpene compounds found in tea tree oil act on the phospholipid layer of the microbial cell membrane destroying its normal structure and function.[140] Tea tree oil has demonstrated consistent effective antimicrobial activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, multi-resistant *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.[144] The antimicrobial effect of tea tree oil against *Pseudomonas aeruginosa* was found to be superior to commercially used antibacterial agents (0.1 % chlorhexidine and 70% ethanol solutions).[144] Tea tree oil has also been shown to decolonize and eradicate biofilms from *Staphylococcus aureus* (both coagulase-negative and coagulase-positive strains).[136] Numerous *in vitro* studies have also documented the potent antifungal activity of tea tree oil against *Candida albicans* in both planktonic and biofilm culture.[135,137]

The antiviral activity of tea tree oil has been primarily attributed to terpinen-4-ol and its ability to prevent the viruses from entering host cells and by inhibiting the 'uncoating' phase of replication.[145,146] Based on *in vitro* research, tea tree oil has demonstrated an inhibitory effect on influenza A virus and influenza A/PR/8 virus subtype H1N1.[145-147] Tree oil has also demonstrated strong antiviral activity against influenza virus A strain NWS/G70C (H11N9) by inactivating the virus and inducing viral decay both in aerosol form as well as in the vaporized phase.[148]

Research shows tea tree oil is capable of killing oral pathogens. In a clinical setting, tea tree oil has demonstrated anti-inflammatory properties when applied topically to inflamed gingival tissue in subjects with severe chronic gingivitis.[149] Topical application of tea tree oil in a gel format has also demonstrated efficacy in controlling microbial biofilms associated with salivary *Streptococcus mutans* in orthodontic patients.[150] Based on *in vitro* research, tea tree oil has demonstrated growth-inhibiting and bactericidal effects as well as adhesion-inhibiting effects on a number of oral organisms including *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Streptococcus mutans*, and *Streptococcus sobrinus*.[140] Tea tree oil has also demonstrated inhibitory activity against the Gram-positive bacillus *Solobacterium moore,* an oral microbe associated with halitosis.[143]

Safety Summary:

Considered safe and well tolerated at the dose recommended. Tea tree oil is generally regarded as non-toxic, and non-irritating.[141] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[151]

Galbanum oil (*Ferula galbaniflua*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antiseptic.[141,152]

Scientific Evidence:
Galbanum is composed of mainly monoterpene and sesquiterpene hydrocarons and their associated alcohols including tricyclene, α-pinene, camphene, β-pinene, myrcene, δ-3-carene, limonene, cis-ocimene, trans-ocimene and terpinolene.[141,153] It is the high concentrations of monoterpenes and sesquiterpenes that give rise to galbanum's antiinflammatory, antimicrobial and antiseptic properties.[141,154]

Terpenes have been shown to be active against bacteria, fungi and viruses. The mechanism by which terpenes exert their antimicrobial properties involves disruption of the lipophilic compounds of the cellular membranes of pathogens.[155]

To date, few scientific studies have been conducted with galbanum oil. Traditionally the herb has been used in the treatment of inflammatory and skin disorders, in wound healing and for ailments of the respiratory, digestive and nervous systems.[141,154]

Safety Summary:
Galbanum oil is generally regarded non-toxic, non-irritating and non-sensitizing.[141] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[156]

Lavender oil (*Lavandula officinalis*)

Medicinal Actions:
Antifungal, antiinflammatory, antimicrobial.[141,157-160]

Scientific Evidence:
Lavender oil contains a complex mixture of aromatic compounds including terpenes and sesquiterpenes (which include linalyl acetate), linalool, caryophyllene, terpinen-4-ol, 2-myrcene, trans-ocimenel, borneol, 1,8-cineole, camphor and limonene.[141,159,161]

This essential oil of lavender has been found to be active against many species of bacteria and fungi. Based on *in vitro* studies, lavender oil has demonstrated antibacterial activity against both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus*.[159,160,162]

Lavender oil has demonstrated both fungistatic and fungicidal activity against *Candida albicans.* Research also shows lavender is effective against oropharyngeal strains of *Candida albicans.* In the study by D'Auria et al., lavender oil inhibited both germ tube formation and hyphal elongation of *Candida albicans.*[158]

Based on *in vitro* experiments, lavender helps protect against LPS-induced inflammation from Gram-negative bacteria. Exposure to LPS in tissues induces an inflammatory reaction which triggers the

release of proinflammatory cytokines and subsequent free radical pathology. Research by Huang et al. verified lavender oil was able to inhibit LPS-dependent superoxide anion generation, NF-Kβ activation and IL-1β production.[157]

Inhalations of lavender oil have been shown to be effective against allergy-mediated bronchial asthma. Animal studies show inhaled lavender helps reduce allergic inflammation and mucosal hyperplasia. Lavender oil also reduced the Th-2 cytokines IL-4 and IL-5 in bronchoalveolar lavage fluids and lung tissue.[163]

Safety Summary:
Lavender oil is generally regarded as non-toxic, non-irritant and non-sensitizing.[141] No adverse effects are expected during pregnancy and breastfeeding at the dose recommended.[164]

Oregano oil (*Origanum vulgare*)

Medicinal Actions:
Antibacterial, antifungal, antiinflammatory.[137,165]

Scientific Evidence:
Active constituents of oregano oil include phenolic monoterpenes and sesqueterpenes such as carvacol, thymol, p-cymene, cis-ocimene, caryophyllene and linalool.[141] Research shows that antimicrobial activity of oregano oil is predominantly attributed to carvacrol and thymol.[166,167]

Oregano oil has demonstrated antibacterial activity against the following respiratory pathogens: *Staphylococcus aureus* (including methicillin-resistant strains)*, Klebsiella pneumonia, Pseudomonas aeruginosa*, *Mycoplasma mycoides* subsp. *carpi*, *Micrococcus flavus* and *Mycobacterium terrae*.[165,167-171] The bacteriostatic and bactericidal properties of oregano oil are thought to be due to its effects on cell membrane and membrane components of microorganisms. Based on *in vitro* trials, oregano oil and its constituents impair cell membrane integrity and damage intracellular nucleic acids by stimulating potassium and phosphate ion leakage and changes to the internal pH of the cell.[165] In a comparative *in vitro* study by Sokovic et al., oregano oil demonstrated greater antibacterial activity than streptomycin against the following pathogens: *Micrococcus flavus, Pseudomonas aeruginosa, and Staphylococcus aureus*.[167]

Oregano oil has also demonstrated antifungal activities against Candida species.[137,172] In the study by Pozzatti et al., oregano inhibited the growth and hyphenation of both *Candida albicans* and *Candida dubliniensis*.[173] The main mechanism of the antifungal activity is associated with the lipophilicity of oregano oil and consequent interaction with the microbial cell membrane. The lipophilic nature of the oil results in changes and losses of enzymatic and structural components of fungal cells such as adenosine triphosphatase, 1,3-β-D-glucan synthases, chitin and mannans, which are also components involved in germ tube formation.[173] Oregano oil may also exert its antifungal effects through the inhibition of chain respiration through interactions with mitochondrial membranes with resultant decreased energy production and inhibition of germ tube formation and/or cell growth.[172-174] The antifungal activity of oregano has also been documented for the following species: *Candida tropicalis, Candida krusei, Candida guillermondii*, *Candida parapsilosis, Cryptococcus neoformans, Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum canis, Epidermophyton floccosum, Aspergillus niger, Aspergillus fumigatus* and *Aspergillus flavus*.[175]

Safety Summary:
Generally considered safe and well tolerated at the dose recommended. Active phenolic compounds such as thymol and cavacrol in oregano oil may in some sensitive individuals cause skin and mucus

membrane irritation.[141] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[176]

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