Dentalcidin (Broad-Spectrum Toothpaste with Biocidin®) – Scientific Validation of Botanical Ingredients

Sorbitol

Medicinal Actions:
Not applicable.

Scientific Evidence:
Sorbitol is a commonly used polyol in toothpaste formulation.[1] It is primarily used as a humectant to prevent moisture loss and to improve consistency of toothpastes.[2] In addition, sorbitol also acts as a primary or secondary sweetener in toothpastes.[2] Sorbitol has approximately 60 percent of the sweetness of sucrose and is used a standard sweetener in numerous pharmaceutical products as well as in sugar-free chewing gums.[3]

Safety Summary:
Sorbitol is considered safe, and has GRAS (Generally Recognized as Safe) status by the Food and Drug Administration (FDA).[3,4] It is included in the FDA Inactive Ingredients Database.[5] Safety has not been scientifically established during pregnancy and breastfeeding, however due to the presence of polyols in both maternal and fetal samples following normal pregnancy, sorbitol is considered safe in these cohorts when consumed in moderation.[6]

Aloe Vera (*Aloe barbadensis*)

Medicinal Actions:
Antifungal,[7] antiinflammatory,[8] antimicrobial, antiviral, demulcent, emollient, immune enhancing, vulnerary.[9]

Scientific Evidence:
The parenchymatous cells of aloe vera leaves secrete a mucilaginous gel containing 98-99% water and 1-2% active compounds.[10] The key phytochemical compounds of aloe gel include anthraquinones, polysaccharides and glycoproteins.[9] Aloe resin, the solid residue obtained from the latex[9] consists of mainly hydroxyanthracene derivatives.[11] The antimicrobial effects of aloe vera contributing to its benefits in dental care have been attributed to the natural anthraquinones found in the plant.[12]

Aloe vera gel had been used in numerous ways in dentistry including treatment of over extraction socket and in endodontic medicine. Studies have demonstrated that aloe vera has therapeutic benefits in the management of oral lesions such as oral lichen planus, oral submucous fibrosis, radiation-induced mucositis, burning mouth syndrome, xerostomia, and recurrent apthous ulcers.[13,14]

In a clinical trial, aloe vera-containing toothpaste demonstrated efficacy in reducing plaque, gingivitis, and overall candidal counts when compared to triclosan-containing toothpaste. In addition, individuals treated with aloe vera experienced improved oral health status without any adverse side effects.[15] In another study, the use of toothpaste containing aloe vera demonstrated statistically and clinically significant reductions in plaque and gingivitis compared to baseline values.[16] In another clinical trial by Pradeep et al., aloe vera–containing toothpaste showed significant improvements in gingival and plaque index scores and a reduction of microbiologic counts when compared with placebo.[17]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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In several clinical trials, the use of aloe vera mouthwash has been shown to be as effective as chlorhexidine (a common broad-spectrum antibiotic used as an antiplaque agent) at reducing plaque and with less side effects when compared to placebo.[18-20]

A preliminary *in vitro* study demonstrated that aloe vera tooth gel was equally effective as two commonly used toothpastes in controlling organisms of both the normal flora and pathogens of the oral cavity including *Streptococcus mutans, Candida albicans, Lactobacillus acidophilus, Streptococcus mitis, Enterococcus faecalis, Prevotella intermedia* and *Peptostreptococcus anaerobius*. In addition, aloe vera gel has demonstrated superior antibacterial effectiveness against *Streptococcus mitis* despite the absence of additional fluoride.[12]

In vitro research shows that aloe vera gel has significant antibacterial properties against *Actinobacillus actinomycetemcomitans*, *Clostridium bacilli*, *Streptococcus mutans* and *Staphylococcus aureus* at 100% and 50% concentrations.[21] Aloe vera gel has also demonstrated significant inhibitory effects on certain cariogenic organisms (*Streptococcus mutans*), periodontopathic species (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*) and an opportunistic periodontopathogen (*Bacteroides fragilis*).[22]

Safety Summary:
Contraindicated in persons with a known hypersensitivity to aloe.[9] Considered safe and well tolerated at the dose recommend, with no known interactions.[8] No adverse effects expected during pregnancy and breastfeeding.[8]

Vegetable Glycerin

Medicinal Actions:
Not applicable.

Scientific Evidence:
Glycerin is used in toothpaste formulations as a humectant to prevent drying out and subsequent hardening of the paste.[2,23] In addition, glycerin is also used as a sweetener in toothpastes to improve flavor.[2,23]

Safety Summary:
Glycerin has GRAS status by the FDA.[4] It is considered safe and is included in the FDA Inactive Ingredients Database.[5] Safety has not been scientifically established during pregnancy and breastfeeding, however it is considered “probably compatible” due to its characteristics which suggest that it does not represent a significant risk to the embryo, fetus or a nursing infant.[24]

Zeodent® (Dental Hydrated Silica 113-165)

Medicinal Actions:
Not applicable.

Scientific Evidence:
Zeodent® 113 is a dental cleaning silica solution regularly used in standard toothpaste formulations to achieve high quality cleaning performance. Zeodent® 165 is a dental thickening silica providing extreme cleaning and whitening performance.[25]
Safety Summary:

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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PHONE: NZ: 09 425 4250 / 021 941 556. AUST: 001169 425 4250 /00116 21 941 556.

Silicon dioxide has a GRAS status by the FDA.[4] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.

Sodium Lauroyl Sarcosinate

Medicinal Actions:
Not applicable.

Scientific Evidence:
Sodium lauroyl sarcosinate is a surfactant and is used in toothpaste formulations as a foaming agent to enhance the cleaning effect. Surfactants act by lowering surface tension to solubilize substances, thereby allowing penetration and loosening of surface deposits and plaque dissolution, which makes it easier to clean teeth. In addition, surfactants also aid in dispersing the flavor in toothpaste.[23]

Safety Summary:
Based on a comprehensive safety assessment, the Cosmetic Ingredient Review Expert Panel has concluded that sodium lauroyl sarcosinate is safe to use in rinse-off products and in leave-on products at concentrations up to 5%.[26] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.

Cellulose Gum

Medicinal Actions:
Not applicable.

Scientific Evidence:
Cellulose gum, also known as sodium carboxymethyl cellulose, is used in toothpaste formulations as a binder. Binding agents are hydrophilic colloids that prevent the separation of the dry and liquid toothpaste components. They also provide viscoelasticity and form to the paste. By binding water, cellulose gum also helps prevent the paste from drying out.[1,23]

Safety Summary:
Sodium carboxymethyl cellulose has a GRAS status by the FDA.[4] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.

Spearmint (*Mentha spicata*) Essential Oil

Medicinal Actions:
Anticariogenic, antimicrobial, antiplaque, antiseptic.[27-29]

Scientific Evidence:
Spearmint is frequently utilized as a natural flavoring in toothpastes and mouthwashes.[29] In Western and Eastern cultures it has a long-standing use as an aromatic, stomachic, stimulant, antiseptic, local anesthetic and antispasmodic agent.[29] Spearmint is composed of a mixture of compounds, including α-pinene, ß-pinene, carvone, 1.8-cineole, linalool, limonene, myrcene, caryophyllene and menthol.
Based on *in vitro* research, spearmint essential oil has demonstrated antimicrobial activity against oral pathogens by inhibiting the growth of *Streptococcus mutans* and *Lactobacillus casei*. *Streptococcus*

mutans is associated with initial caries, whereas *Lactobacillus casei* is associated with advanced caries.[27]

Both *in vitro* and *in vivo* studies show that spearmint essential oil can significantly decrease bacterial adhesion and reduce bacterial viability in biofilms. Spearmint oil has also demonstrated antibacterial activity against both *Streptococcus mutans* and *Streptococcus pyogenes*.[28]

Safety Summary:
Spearmint essential oil is considered safe, nontoxic, nonirritating and nonsensitizing.[29] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times, avoid using in amounts greater than those typically found in food.[30]

Peppermint (*Mentha x piperita*) Essential Oil

Medicinal Actions:
Anticariogenic,[27] antimicrobial,[31] antiseptic.[29]

Scientific Evidence:
Peppermint oil has been extensively used in food favoring, toothpastes and mouthwashes, soaps, detergents and perfumes.[29] Its main active chemical composition is predominantly composed of menthol, menthone, 1.8-cineole, methyl acetate, methofuran, isomethone, limonene, α-pinene and ß-pinene.[29]

Peppermint essential oil has demonstrated antimicrobial activity against cariogenic oral pathogens by inhibiting the growth of *Streptococcus mutans* and *Lactobacillus casei* (*in vitro* research).[27]

Based on *in vitro* experiments, peppermint essential oil may be considered a safe natural agent in the prevention of dental biofilm formation.[31,32] It has been shown to exert significant antimicrobial effects against *Streptococcus mutans* and *Streptococcus pyogenes.*[31,32] Furthermore, when compared with chlorhexidine, peppermint essential oil significantly decreased bacterial adhesion and reduced bacterial viability in biofilms.[31,32] *In vivo* research shows that peppermint essential oil blended toothpaste is significantly more effective at reducing the formation of biofilms when compared to chlorhexidine.[32]

Safety Summary:
Peppermint essential oil is considered safe, nontoxic and nonirritating.[29] It may occasionally be sensitizing and should not be used on the face of infants and small children.[29] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.[33]

Tea Tree (*Melaleuca alternifolia*) Essential Oil

Medicinal Actions:
Antiinflammatory, antimicrobial, antiseptic.[34,35]

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.[29,36-38] 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.[37,39]

Mechanisms of antimicrobial and antiinflammatory action of tea tree oil can also be attributed to its hydrocarbon structure and lipophilicity.[34]

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.[35] 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.[40] Antibacterial effects of mouthwash-containing tea tree oil have demonstrated significant antibacterial activity against *Streptococcus mutans* and other oral microorganisms. Reduced levels of microorganisms were maintained throughout the five week duration of the study.[41]

Based on *in vitro* research, tea tree oil has demonstrated growth-inhibiting and bactericidal effects as well as adhesion-inhibiting effects against a number of oral organisms including *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Fusobacterium nucleatum, Streptococcus mutans*, and *Streptococcus sobrinus*.[42] Tea tree oil has also demonstrated inhibitory activity against the Gram-positive bacillus *Solobacterium moorei,* an oral microbe associated with halitosis.[39] *In vitro* susceptibility experiments have shown that a wide range of oral bacteria are susceptible to, and rapidly killed by tea tree oil.[43]

Safety Summary:
Considered safe and well tolerated at the dose recommended. Tea tree oil is generally regarded as non-toxic, and non-irritating.[29] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[44]

Cinnamon (*Cinnamomum zeylanicum*) Essential Oil

Medicinal Actions:
Anticariogenic, Antimicrobial,[45,43,44] antiplaque.[27]

Scientific Evidence:
Cinnamon essential oil can be extracted from both the bark and the leaf. The bark oil is used in the food and pharmaceutical industries, while the leaf oil is mainly used as a flavouring agent. The main active components of cinnamon essential oil include cinnamaldehyde, camphor, cinnamyl acetate, caryophyllene, *trans* α-bergamotene, caryophillene oxide, linalool, geraniol, bornyl acetate, α-cubebene, γ-elemene, α-copaene, guaiol, and eugenol.[46] The antimicrobial activity of cinnamon essential oil has been attributed to cinnmaldehyde.[46]

Based on *in vitro* research, cinnamon essential oil has demonstrated antimicrobial activity against planktonic forms of cariogenic bacteria by inhibiting *Streptococcus mutans* and *Lactobacillus casei*.[27] Cinnamon has also demonstrated antiplaque activity by inhibiting *Streptococcus mutans* biofilm development.[27] Other *in vitro* studies show cinnamon oil exhibits antibacterial activity against oral pathogenic bacteria including *Streptococcus mutans,*[45,47,48] *Fusobacterium nucleatum*, *Actinomyces naeslundii*, *Prevotella nigrescens*,[48] and bacteria involved in dental caries such as Gram-positive *Streptococcus salivarius*, *Lactobacillus* sp., *Bacillus* sp., *Micrococcus* sp., *Staphylococcus aureus* and Gram-negative *Halobacterium* sp*., Veilonella* sp., *Pseudomonas aeruginosa* and *Pseudomonas* sp.[45]
Safety Summary:
Cinnamon oil is considered safe at the dose recommended. Cinnamon bark oil and leaf oil may cause dermal irritation, most likely due to the cinnamic aldehyde content. When used externally, dilution should not exceed 0.1%. Internal use is contraindicated during pregnancy. In therapeutic doses, cinnamon may be hepatotoxic and may inhibit blood clotting due to the eugenol content.[8,29]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

NUTRITIONALMEDICINENZ.COM / BIOCIDIN.NZ.

PHONE: NZ: 09 425 4250 / 021 941 556. AUST: 001169 425 4250 /00116 21 941 556.

Clove (*Syzygium aromaticum*) Essential Oil

Medicinal Actions:
Analgesic, antiinflammatory, antimicrobial,[45,47,49] antioxidant,[50] antiseptic.[29]

Scientific Evidence:
Clove essential oil has been used traditionally as an anaesthetic for toothache, skin infections, digestive upsets, parasite eradication, as well as a natural flavouring agent. Due to its eugenol and other polyphenolic components clove oil exerts potent antimicrobial, antiinflammatory and antioxidant properties.[50]

Based on *in vitro* research, clove essential oil may be a potential natural antibacterial agent against cariogenic bacteria and for the prevention of periodontitis. Eugenol extracted from clove has been shown to exhibit antibacterial activity against *Porphyromonas gingivalis* (*in vitro* research). Other therapeutic effects of eugenol include its ability to damage to the cell membrane and destroyed the integrity of plasmatic membranes of bacteria. In addition, eugenol has been shown to supress biofilm formation, reduce preformed biofilm and down-regulate the expression of virulence factor genes related to the biofilm of *Porphyromonas gingivalis*.[49] Clove essential oil and its main compounds have demonstrated antibacterial activity *in vitro* against the following oral pathogens; *Streptococcus mutans*, *Streptococcus sanguinis*, *Streptococcus sobrinus*, *Streptococcus ratti*, *Streptococcus criceti*, *Streptococcus anginosus*, *Streptococcus gordonii*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Porphylomonas gingivalis* either alone or in combination with the antibiotic ampicillin.[47,51]

Based on further *in vitro* experiments, clove essential oil may also exhibit antimicrobial properties against bacteria involved in dental caries such as Gram-positive *Streptococcus salivarius*, *Lactobacillus* sp., *Bacillus* sp., *Micrococcus* sp., *Staphylococcus aureus* and Gram-negative *Halobacterium* sp., *Veilonella* sp., *Pseudomonas aeruginosa* and *Pseudomonas* sp.[45]

Safety Summary:
Clove essential oil is considered safe at the dose recommended. In sensitive individuals, the oil may cause dermal irritation.[5] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times, avoid using in amounts greater than those typically found in food.[52]

Royal Jelly

Medicinal Actions:
Antimicrobial.[53]

Scientific Evidence:
Royal jelly is secreted by the hypopharyngeal and mandibular glands of *Apis mellifera* bees to provide food for the Queen bee.[53] Highly nutritious, royal jelly provides essential amino acids, lipids, vitamins and acetylcholine.[53]

The antimicrobial properties of royal jelly are derived from the bioactive compound hydroxyl-decenoic acid which comprises approximately 10% of the total weight. Hydroxyl-decenoic acid has been shown to down regulate the expression of a number of genes involved in the colonization and pathogenesis of *Streptococcus mutans*. It has also capable of decreasing the adherence of *Streptococcus mutans* to

cell surfaces, indicating a relevance to the pathogenicity of carogenic biofilm, also known as dental plaque and dental caries formation.[53]

Safety Summary:
Considered safe with no adverse reaction expected when used orally and topically at the dose recommended. Avoid in individuals with history of allergy or asthma. Avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.[54]

Simethicone

Medicinal Actions:
Not applicable.

Scientific Evidence:
Simethicone is the mixture of dimethicone and silicon dioxide, which is added to toothpaste formulations as an antifoaming agent. It is also used in cosmetics, foods, as well as oral and topical pharmaceutical formulations.[5]

Safety Summary:
Simethicone is regarded as a relatively nontoxic and nonirritant material when used as an excipient. Simethicone has GRAS status by the FDA. It is included in the FDA Inactive Ingredients Database.[5] Considered safe to use during pregnancy and breastfeeding.[24]

Sodium Benzoate

Medicinal Actions:
Not applicable.

Scientific Evidence:
Sodium benzoate is a preservative agent added to toothpaste formulations to prevent the unwanted growth of microorganisms.[1,23]

Safety Summary:
Sodium benzoate has GRAS status by the FDA.[4] It is included in the FDA Inactive Ingredients Database.[5] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.

Biocidin® Ingredients
Bilberry (*Vaccinium myrtillus*)

Medicinal Actions:
Antibiofilm,[55] antiinflammatory, antimicrobial,[56] antioxidant.[8,11,57]

Scientific Evidence:
Bilberry is rich in phenolic compounds which possess bacteriostatic and antimicrobial properties.[56] This herb is renowned for its exceptionally high levels of anthocyanins, which are responsible for bilberry's diverse antioxidant effects.[58,59] As natural antiinflammatory agents, bilberry polyphenols help reduce lipopolysaccharide (LPS)-induced nuclear factor kappa-beta (NF-Kβ) activation.[60]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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PHONE: NZ: 09 425 4250 / 021 941 556. AUST: 001169 425 4250 /00116 21 941 556.

Based on *in vitro* experiments, bilberry may affect the coaggregation capabilities of oral pathogens, which is an interspecies adhesion process essential for the development of dental plaque. Polyphenol constituents in the high molecular size fractions of bilberry have been shown to exhibit antiaggregation (inhibit and reverse coaggregation) activity against the pairs of common bacteria causing dental biofilm accumulation including *Streptococcus mutans* with *Fusobacterium nucleatum* or *Actinomyces naeslundii*.[55]

Safety Summary:
Considered safe at the recommended dose.[11] No adverse effects expected during pregnancy and breastfeeding.[8]

Noni (*Morinda citrifolia*)

Medicinal Actions:
Antibacterial,[61] antiinflammatory, antimicrobial, antioxidant.[57,62]

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.[62]

Based on *in vitro* research, aqueous extract of noni fruits are capable of inhibiting the growth of dental caries-causing oral pathogens including *Streptococcus mutans* and *Streptococcus mitis*.[61]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[57,63] No adverse effects expected during pregnancy and breastfeeding.[57,64]

Milk Thistle (*Silybum marianum*)

Medicinal Actions:
Antimicrobial, antioxidant.[8,11]

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.[11]

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. Silybin affects the growth of Gram-positive organisms by inhibiting ribonucleic acid (RNA) and protein synthesis .[65]

Safety Summary:
Contraindicated in persons allergic to plants from the Compositae family.[9] No other known warnings, precautions or contraindications.[9] No adverse effects expected during pregnancy and breastfeeding.[9]

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

Medicinal Actions:
Antiinflammatory, antimicrobial, depurative, immune enhancing, immune modulating, lymphatic.[8,9,57]

Scientific Evidence:
Echinacea possesses both antiinflammatory and immunostimulating properties.[66] 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.[67,68] 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 natural killer cell activity in the body.[69,70]

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*.[71,72] 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: interleukin (IL)-4, IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, vascular endothelial growth factor (VEGF), and growth-regulated protein alpha (GROα).[73]

Based on salivary incubation bioassays, echinacea may inhibit oral malodor production, also known as halitosis. Using an *in vitro* model for oral malodor production, echinacea has demonstrated antibacterial activity against Gram-positive streptococci and significant antimalodorous activity.[74]

Safety Summary:
Contraindicated in persons allergic to plants from the Compositae family.[8] No other known warnings, precautions or contraindications.[75] No adverse effects expected during pregnancy or breastfeeding.[8,9]

Golden Seal (*Hydrastis canadensis*)

Medicinal Actions:
Antihistamine, antiinflammatory, antimicrobial,[76] mucous membrane trophorestorative.[9,11,57,77,78]

Scientific Evidence:
Golden seal root contains a number of alkaloids, of which the most abundant is berberine. Both *in vitro* and *in vivo* studies have revealed that berberine possesses antimicrobial activity against bacteria and fungi.[8,79] Golden seal leaves are rich in flavonoids (specifically sideroxylin, 8 desmethyl-sideroxylin and 6 desmethyl-sideroxylin).[80] While the flavonoids from golden seal have no inherent bactericidal properties, they enhance the antimicrobial activity of berberine by acting as efflux pump inhibitors.[80] It should be noted that one of the major mechanisms by which bacteria become resistant to antibiotics is by over expression of efflux pumps.[81] One of the key mechanisms by which golden seal inhibits microbial growth is through quenching of the agr quorum sensing (QS) system.[80,82] 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.[83]

Based on *in vitro* experiments, berberine possesses antimicrobial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum.*[76] Berberine in combination with C-methyl flavonoids exhibited an additive antimicrobial effect when tested against *Streptococcus mutans*.[76] When compared with sterile saline irrigation, berberine was found to be more effective at eradicating the endodontic pathogens in a biofilm tooth model using *Fusobacterium nucleatum, Enterococcus faecalis* and *Prevotella intermedia*. [84]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

NUTRITIONALMEDICINENZ.COM / BIOCIDIN.NZ.

PHONE: NZ: 09 425 4250 / 021 941 556. AUST: 001169 425 4250 /00116 21 941 556.

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[8] Contraindicated during pregnancy in therapeutic doses.[57] Discouraged during breastfeeding in therapeutic doses.[11]

Shiitake Mushroom (*Lentinula edodes*)

Medicinal Actions:
Antibacterial, antifungal, antioxidant, immune modulating.[57,85]

Scientific Evidence:
Active constituents of shiitake mushroom include the polysaccharide lentinan, shiitake mushroom mycelium, culture media extracts (LEM, LAP and KS-2) and eritadenine, all of which have demonstrated antimicrobial, antiviral and antitumour activity.[86,87] As an antimicrobial agent, lentinan works by activating macrophages and the cytokines tumor necrosis factor (TNF)-α and interferon (IFN)-γ with resultant stimulation of T lymphocytes and enhanced immunity.[86]

Shiitake may be effective against oral pathogens associated with dental caries and dental plaque accumulation.[88,89] *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*.[88,90-92] 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.[88,90] 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.[93,94]

Safety Summary:
Considered safe and well tolerated at doses of up to 2.5 mg per day for 6 weeks.[95] 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.[96] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[97]

White Willow Bark (*Salix alba*)

Medicinal Actions:
Analgesic, antiinflammatory.[11]

Scientific Evidence:
The key active constituents of white willow bark comprise of phenolic glyosides including the salicylates salicortin and salicin.[11] Other important actives include the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol) and condensed tannins.[98-100]

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.[99,101] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block transcription factor NF-Kβ activation.[99,100] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[99]

Safety Summary:

Contraindicated in people with salicylate sensitivity.[57] No other known warnings, precautions or contraindications at the dose recommended.[57] No adverse effects expected during pregnancy and breastfeeding.[57]

Garlic (*Allium sativum*)

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

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.[102,103]

Based on *in vivo* experiments, a garlic mouthwash solution has demonstrated significant antibacterial activity against *Streptococcus mutans*, with a maintenance of reduced salivary levels of microorganisms during the study period.[41,104]

Garlic has demonstrated antibacterial activity against several oral microbes associated with dental plaque and caries including *Streptococcus mutans, Streptococcus sanguis, Streptococcus salivarius, Pseudomonas aeruginosa*, and *Lactobacillus* spp.[105,106] 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.[107,108]

Other *in vitro* experiments using crude garlic extract show that it possesses greater antibacterial activity against *Streptococcus mutans*, than chlorhexidine.[109] Garlic extract has also demonstrated inhibitory activity on multidrug-resistant strains of *Streptococcus mutans* isolated from human carious teeth, suggesting that toothpastes or mouthwashes containing garlic extract may be used for prevention of dental caries.[110]

Garlic allicin has been shown to inhibit Gram-positive oral bacteria including *Streptococcus mutans*, *Streptococcus sobrinus*, and *Actinomyces oris*. Allicin was also bactericidal to *Streptococcus mutans* grown in mature biofilms (*in vitro* research).[111]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[9] No adverse effects expected during pregnancy and breastfeeding.[9]

Grape Seed (*Vitis vinifera*)

Medicinal Actions:
Antibacterial,[112,113] antibiofilm, antiinflammatory, antioxidant.[57]

Scientific Evidence:
Grape seed contains over 95% flavonols, which are predominately comprised of oligomeric proanthocyanins (~82%) and active monomeric proanthocyanins (~12%).[114]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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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*.[113] The proathocyanidins found in grape seed have also demonstrated a protective effect against endotoxin-induced experimental periodontitis (animal research).[115] Other *in vitro* studies indicate grape seed extract supports healthy remineralization of teeth and may be more effective than oral fluoride or calcium glycerophosphate.[116,117]

In an oral bacteria biofilm model, gape seed extract rich in flavan-3-ols demonstrated strong antimicrobial activity against *Actinomyces oris*, *Fusobacterium nucleatum* and *Streptococcus oralis*, and resulted in a decrease in cell viability of the whole biofilm.[112]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[57] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[57]

Black Walnut (*Juglans nigra*)

Medicinal Actions:
Antimicrobial.[11]

Scientific Evidence:
The main active constituents of black walnut include naphthoquinones (juglone and plumbagin), tannins (ellagic acid) and flavanoids.[9,11,118] Tannins comprise approximately 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.[119]

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.[120]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[9] Contraindicated during pregnancy and breastfeeding in therapeutic doses.[121]

Raspberry (*Rubus idaeus*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[11,57]

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.[122-124] Research shows that the antioxidant properties of raspberry speak to the polyphenolic compounds (specifically ellagitannins) which are highly effective free radical scavengers.[122,124] Results of an *in vitro* study indicate that raspberry's phenolic compounds are able to protect deoxyribonucleic acid (DNA) and decrease lipid peroxidation of lymphocytes in a concentration-dependent manner.[122] Phenolic compounds also possess antimicrobial properties. 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.[125] 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.[56]

Assay studies reveal that raspberry is effective against oral pathogens associated with dental caries and gingivitis. Raspberry demonstrated antigingivitis and anticaries activities against *Streptococcus sanguinis, Streptococcus mutans, Fusobacterium nucleatum*, *Prevotella intermedia, Veillonella dispar, Neisseria subflava, Actinomyces naeslundii* and *Lactobacillus casei*.[90,92] Mechanisms by which raspberry protects against oral pathogens include: preventing bacterial coaggregation and biofilm formation, disruption of preexisting biofilms and by decreasing the expression of genes involved in gingival cellular proliferation and differentiation.[92]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended. No adverse effects expected during pregnancy and breastfeeding.[9]

Fumitory (*Fumaria officinalis*)

Medicinal Actions:
Antimicrobial, antioxidant.[126]

Scientific Evidence:
The active constituents of fumitory include alkaloids, flavonoids and organic acids.[11] The biological activities of this herb are mainly associated with the isoquinoline alkaloids, in particular protopine.[127,128] 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*.[126] The isoquinoline alkaloids from fumitory have also demonstrated significant antifungal activity against *Candida albicans*.[129]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[130] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[131]

Gentian (*Gentiana lutea*)

Medicinal Actions:
Antiinflammatory, antimicrobial, antioxidant.[11,57,132]

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.[11,132-134] These active constituents give rise to the herb's potent antioxidant, antiinflammatory and antibacterial properties.[132,134]

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.*[135,136]

Safety Summary:
No known warnings, precautions or contraindications at the dose recommended.[8] No adverse effects expected during pregnancy and breastfeeding.[9]

Galbanum (*Ferula galbaniflua*) Essential Oil

Medicinal Actions:
Antiinflammatory, antimicrobial, antiseptic.[29,137]

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.[29,138] It is the high concentrations of monoterpenes and sesquiterpenes that give rise to galbanum's antiinflammatory, antimicrobial and antiseptic properties.[29,137]

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.[139]

Safety Summary:
Galbanum oil is generally regarded non-toxic, non-irritating and non-sensitizing.[29] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[140]

Lavender (*Lavandula officinalis*) Essential Oil

Medicinal Actions:
Antibacterial,[42] antifungal, antiinflammatory, antimicrobial.[29,141-144]

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.[29,143,145]

Based on *in vitro* research, lavender essential oil can inhibit the growth of Gram-negative oral bacteria associated with periodontal disease including; *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, and *Fusobacterium nucleatum*. Although lavender oil did not demonstrate bactericidal activity, minimum inhibitory concentration values showed that lavender oil works as a natural bacteriostatic agent.[42]

In other *in vitro* experiments, lavender demonstrated protection 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.[141]

Safety Summary:
Lavender oil is generally regarded as non-toxic, non-irritant and non-sensitizing.[29] No adverse effects are expected during pregnancy and breastfeeding at the dose recommended.[146]

Oregano (*Origanum vulgare*) Essential Oil

Medicinal Actions:
Antibacterial, antifungal, antiinflammatory.[147-149]

Scientific Evidence:
Active constituents of oregano oil include phenolic monoterpenes and sesqueterpenes such as carvacol, thymol, p-cymene, cis-ocimene, caryophyllene and linalool.[29] Research shows that antimicrobial activity of oregano oil is predominantly attributed to carvacrol and thymol.[150,151] 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.[147]

In vitro experiments show that oregano oil is highly active against *Streptococcus mutans* and *Candida albicans* and also demonstrated moderate activity against *Lactobacillus acidophilus*.[149]

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.[29] Exercise caution during pregnancy and breastfeeding as safety has not been scientifically established during these times.[152]

AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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AUTHORS: Corene Humphreys, ND, BHSc, Dip Med Herb, Dip Hom, QTA (Microbiology). | Anita Kasa, BNat, Dip Herb Med, Dip Nutr, Dip Yoga.

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