Dentalcidin™ LS

Liposomal Oral Care Solution with Biocidin®

Scientific Validation of Ingredients

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Active Ingredients: Biocidin® Proprietary Blend Bilberry fruit extract (*Vaccinium myrtillus*), Grape seed extract (*Vitis vinifera*), Shiitake mushroom extract (*Lentinula edodes*), Goldenseal root (*Hydrastis canadensis*), Noni fruit extract (*Morinda citrifolia*), Garlic bulb (*Allium sativum*), White Willow bark (*Salix alba*), Milk Thistle seed (*Silybum marianum*), Raspberry fruit (*Rubus idaeus*), Echinacea Purpurea plant extract (*Echinacea purpurea*), Echinacea Angustifolia root (*Echinacea angustifolia*), Black Walnut hull (*Juglans nigra*), Black Walnut leaf (*Juglans nigra*), Lavender oil (*Lavandula officinalis*), Oregano oil (*Origanum vulgare*), Galbanum oil (*Ferula galbaniflua*), Tea Tree oil (*Melaleuca alternifolia*), Fumitory aerial parts extract (*Fumaria officinalis*), Gentian Lutea root (*Gentiana lutea*), Myrrh resin (*Commiphora myrrh*), Clove bud oil (*Syzygium aromaticum*), Peppermint leaf oil (*Mentha piperita*), Quercetin, CoQ10 (ubiquinone).

Other Ingredients: Vegetable glycerin, purified water, phospholipids (from sunflower seed lecithin), ethanol (sourced from potato and/or sugar cane), tocofersolan, acacia gum, natural mixed tocopherols.

Overview

Biocidin® is a unique blend of 18 botanicals with wide-ranging biological actions, many of which are anti-inflammatory, and modulate both immune function and the balance of the intestinal microbiome. An essential element of Biocidin® is that it provides botanicals with multiple active constituents that have diverse and complementary mechanisms of action, in contrast to isolated components. Plants have evolved a richness in bioactive compounds and secondary metabolites, which provide for their own strategic defense and protection from both microbes and other threats, and which also may be lost with single compounds. For example, an antibacterial constituent such as berberine is substantially less effective without the synergism of Goldenseal's other components which target multi-drug resistance pumps, allowing for its intracellular accumulation.[1]

The botanicals in Biocidin® provide the terpenoids, phenolics, alkaloids and other active components of each plant that individually enhance a variety of functions, including induction of the Nrf2 antioxidant system, inhibition of multiple inflammatory regulators such as NF-κB and the NLRP3 inflammasome, as well as enhancement of both innate and cell-mediated immunity. Many of them have diverse strategies for targeting bacteria, fungi, viruses and other pathogens, resulting in a shift to a more favorable microbiome while also providing enhanced immunity and integrity of the intestinal barrier, but their combined use presents an opportunity for a much broader synergistic effect.

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[1] Abreu AC, Coqueiro A, Sultan AR, et al. Looking to nature for a new concept in antimicrobial treatments: isoflavonoids from Cytisus striatus as antibiotic adjuvants against MRSA. Sci Rep. 2017 Jun 19;7(1):3777.

The use of Biocidin™ LSF for four weeks has been evaluated in a periodontal pilot study by Dr. John Rothchild, DDS in Durango, CO. His research demonstrated a marked reduction of oral pathogens in root canal cavitations from an average of 35 species down to 3 species, with many of the remaining species being considered as normal oral bacteria.[2] Phase contrast microscopy also revealed a significant reduction in plaque and pathogens in before and after testing on patients with periodontal disease.[3] Many of the broad-spectrum botanicals and nutraceuticals in Dentalcidin™ LS can assist in removing biofilms and plaque, as well as promoting healthy teeth and gums.

Liposomal Technology

Liposomes are a type of vesicular carrier designed to improve the delivery of nutraceutical and botanical compounds, as well as medications, and have been extensively used in cosmetic and pharmaceutical industries for decades.[4,5] Liposomes are spherical, microscopic phospholipid carriers, consisting of an aqueous core entrapped by one or more (unilamellar vs. multilamellar) phospholipid membranes.[5] They have several attractive features, including high biocompatibility (e.g. lack of toxicity and/or immune activation), the ability to accommodate both water-soluble (in the aqueous core) and lipid-soluble (in the lamellae, or lipid layer) compounds, and to improve the uptake of poorly absorbed compounds.[5,6]

Many nutraceuticals and botanicals have poor or limited bioavailability, often related to their size, polarity, lack of stability, etc, and liposomes provide a vehicle to increase the absorption and availability of these compounds.[7] For some nutrients, liposomes may also allow for a higher peak plasma level; for example, in a small clinical trial, a liposomal vitamin C was shown to deliver a higher plasma peak compared to non-liposomal oral intake.[8] Plasma levels of quercetin, a flavonoid known to have poor absorption, were approximately 20-fold higher when incorporated into a phytosome (comprised of phospholipids similar to a liposome) compared to a standard form of quercetin.[9]

Liposomes have also been used as a dental agent, offering significant promise to control oral biofilms (preventing caries and gingivitis), and to improve oral lesions and periodontitis.[10] Dentalcidin™ LS utilizes the Quicksilver Delivery System, a natural phospholipid encapsulation technology made using sunflower seed lecithin, designed to improve the bioavailability and stability of these botanicals.[11]

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[2] Rothchild D, J. Preliminary Report of Activity of Dentalcidin LS in Oral Cavitation Pathogens as evidenced by DNA Analysis. Durango, Colorado, 2018.
[3] Rothchild D, J. Preliminary Report of Activity of Dentalcidin LS on dental plaque as evidenced by Phase Contrast Microscopy. Durango, Colorado, 2018.
[4] Akbarzadeh A, Rezaei-Sadabady R, Davaran S, et al. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013 Feb 22;8(1):102.
[5] Subramanian P. Lipid-Based Nanocarrier System for the Effective Delivery of Nutraceuticals. Molecules. 2021 Sep 10;26(18):5510.
[6] Din FU, Aman W, Ullah I, et al. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017 Oct 5;12:7291-7309.
[7] McClements DJ, Li F, et al. The Nutraceutical Bioavailability Classification Scheme: Classifying Nutraceuticals According to Factors Limiting their Oral Bioavailability. Annu Rev Food Sci Technol. 2015;6:299-327.
[8] Davis JL, Paris HL, Beals JW, et al. Liposomal-encapsulated Ascorbic Acid: Influence on Vitamin C Bioavailability and Capacity to Protect Against Ischemia-Reperfusion Injury. Nutr Metab Insights. 2016 Jun 20;9:25-30.
[9] Riva A, Ronchi M, Petrangolini G, et al. Improved Oral Absorption of Quercetin from Quercetin Phytosome®, a New Delivery System Based on Food Grade Lecithin. Eur J Drug Metab Pharmacokinet. 2019 Apr;44(2):169-177.
[10] Şenel S, Özdoğan AI, Akca G. Current status and future of delivery systems for prevention and treatment of infections in the oral cavity. Drug Deliv Transl Res. 2021 Aug;11(4):1703-1734.
[11] https://www.quicksilverscientific.com/quicksilver-delivery-systems Accessed 1/2022.

Biocidin® Ingredients

Bilberry extract (*Vaccinium myrtillus*)

Biological Actions:

Anti-inflammatory, antioxidant, modified microbiome, antibiofilm.

Scientific Evidence:

Bilberries are rich in biologically active compounds, including flavonols (such as quercetin and catechins) as well as phenols, particularly anthocyanins. Bilberries contain between 15-17 different anthocyanidins and anthocyanins (a glycosidic form of anthocyanidins), including delphinidins, cyanidins, petunidins, malvidins, and peonidins, shown to induce cellular protection against antioxidant stress, at least in part by upregulating the expression of antioxidant enzymes, including catalase and superoxide dismutase.[12,13]

Bilberry has demonstrated antimicrobial action towards a number of pathogens *in vitro*, including *Streptococcus pneumoniaea, Neisseria meningitidis, Bacillus cereus*, *Citrobacter freundii*, *Enterococcus faecalis*, *Helicobacter pylori, Salmonella,* and *Staphylococcus aureus.*[14,15,16,17,18,19,20] The diversification of the microbiome and the biotransformation of anthocyanins have been proposed as likely mechanisms for the anti-inflammatory and other beneficial effects of these compounds.[21] Polyphenol constituents in the high molecular size fractions of bilberry have also been shown to exhibit anti-aggregation (inhibit and reverse coaggregation) activity against the pairs of common bacteria causing dental biofilm accumulation including *Streptococcus mutans* with *Fusobacterium nucleatum* or *Actinomyces naeslundii*.[22]

Phenolic compounds found in berries provide bioactive molecules for the prevention and/or treatment of inflammatory diseases, including gingival inflammation.[23] Consumption of bilberry has been shown

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[12] Kuntz S, Kunz C, Herrmann J, et al. Anthocyanins from fruit juices improve the antioxidant status of healthy young female volunteers without affecting anti-inflammatory parameters: results from the randomised, double-blind, placebo-controlled, cross-over ANTHONIA (ANTHOcyanins in Nutrition Investigation Alliance) study. Br J Nutr. 2014 Sep 28;112(6):925-36.

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[17] Burdulis D, Sarkinas A, Jakutiene I, et al. Comparative study of anthocyanin composition, antimicrobial and antioxidant activity in bilberry (Vaccinium myrtillus L.) and blueberry (Vaccinium corymbosum L.) fruits. Acta Pol Pharm. Jul-Aug 2009;66(4):399-408.

[18] Nohynek LJ, Alakomi HL, Kähkönen MP, et al. Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. Nutr Cancer. 2006;54(1):18-32.

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[23] Widén C, Coleman M, Critén S, et al. Consumption of bilberries controls gingival inflammation. Int J Mol Sci. 2015

to demonstrate ameliorating effect on markers of gingival inflammation by reducing interleukin (IL)-1β, IL-6 and vascular endothelial growth factor (VEGF) and therefore reducing gingivitis to a similar extent compared to standard of care.[26]

Safety Summary:

Considered safe at the recommended dose.[12] No adverse effects expected during pregnancy and breastfeeding.[13]

Noni (*Morinda citrifolia*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant.

Scientific Evidence:

To date, over 200 different compounds have been identified in the noni plant, including phenolics, flavonoids, anthraquinones, iridoids, lignans, and triterpenoids, which give rise to noni's potent antioxidant and anti-inflammatory properties.[24] The majority of these compounds have biological activity; iridoids have been shown to prevent the formation of advanced glycation end products (AGEs), with clinical trials among heavy smokers, who are known to have excessive oxidant exposure, demonstrating the iridoids in noni to be associated with a mitigation in both oxidative damage to DNA as well as cigarette-smoke induced dyslipidemia.[25,26,27] *In vitro* research has also shown that noni is highly effective at inhibiting hydroxyl radicals, known to cause oxidative damage to proteins, lipids, as well as DNA.[28]

As a natural anti-inflammatory agent, noni inhibits LPS-induced activation of a number of chemical mediators, including cyclooxygenase (COX)-1 and COX-2, nitric oxide and prostaglandins E_2 (PGE_2) in a dose dependent manner.[29] Damnacanthal, an anthraquinone found in noni, has been found to have immunomodulating and anti-inflammatory activity; it has been shown to suppress mast cell activation and allergic reactions by inhibiting the activation of several inflammatory mediators, including NF-κB and $p56^{lck}$ tyrosine kinase.[30,31]

A number of active compounds in noni, including aucubin, L-asperuloside and alizarin as well as the phenolics 5,15-dimethylmorindol, ferulic acid, p-hydroxycinamic acid, methyl 4-hydroxybenzoate, methyl ferulate, and methyl 4-hydroxycinnamate have demonstrated antibacterial activity against a number of pathogens including *Pseudomonas aeruginosa*, *Proteus morganii*, *Staphylococcus*

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aureus, *Escherichia coli*, *Salmonella* and *Shigella*.[32,33] Noni has also been shown to inhibit the activity of enterohemorrhagic *Escherichia coli* (0157) and *Helicobacter pylori*.[34,35]

Noni has demonstrated antifungal activity against *Candida albicans* in a dose dependent manner.[36,37] 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*.[38] Based on *in vitro* research, aqueous extracts of noni fruits are capable of inhibiting the growth of dental caries causing oral pathogens including *Streptococcus mutans* and *Streptococcus mitis.*[39]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[14,40] No adverse effects expected during pregnancy and breastfeeding.[14,41]

Milk Thistle (*Silybum marianum*)

Biological Actions:

Antimicrobial, antioxidant, anti-inflammatory, antibiofilm.

Scientific Evidence:

Milk thistle is rich in flavonolignans which are composed of silybin A and silybin B (diastereoisomers), silydianin, silychristin and diastereoisomers isosilybin A and isosilybin B. These polyphenolic molecules are collectively referred to as silymarin.[12] Research has shown that the flavonolignans from milk thistle possess potent antibacterial activity against Gram-positive bacteria, but no antimicrobial activity against Gram-negative bacteria.[42] In addition to direct anti-bacterial action, silymarin has also been shown to inhibit the adherence and formation of bacterial biofilms.[43]

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[32] Zhang WM, Wang W, Zhang JJ, et al. Antibacterial Constituents of Hainan Morinda citrifolia (Noni) Leaves. J Food Sci. 2016 May;81(5):M1192-6.
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[43] Evren E, Yurtcu E. In vitro effects on biofilm viability and antibacterial and antiadherent activities of silymarin. Folia Microbiol (Praha). 2015 Jul;60(4):351-6.

Silymarin also inhibits the growth of multiple species of *Candida*, destabilizing mature biofilms and inhibiting the secretion of phospholipases and proteinases, an important determinant of fungal virulence.[44]

Silibinin (an equal extract of silybin A and silybin B) has demonstrated antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus*.[12,45] When silibinin was combined with the antibiotics oxicillin or ampicillin there was a more than four-fold reduction in the minimum inhibitory bactericidal concentrations. Based on *in vitro* research, silibinin's antimicrobial properties are due to its ability to inhibit ribonucleic acid (RNA) and protein synthesis of Gram-positive organisms (as opposed to attacking the bacterial membrane).[46] Ethanol extracts of silibin have also demonstrated *in vitro* antibacterial activity against *Campylobacter jejuni*, and the purified flavonolignan dehydroisosilybin has inhibited the *in vitro* growth of two species of *Leishmania* parasites.[47,48] Silymarin has also demonstrated antiviral activity against influenza A/PR/8/34 virus when compared with the pharmaceutical agent Oseltamivir (98% vs. 52% respectively).[49] Its ability to suppress cellular inflammation, including inhibition of mTOR, may partly explain its immunomodulating effects.[50,51]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae (aka Asteraceae) family. No other known warnings, precautions or contraindications. No adverse effects expected during pregnancy and breastfeeding.[52,53,54]

Echinacea (*Echinacea purpurea & Echinacea angustifolia*)

Biological Actions:

Anti-inflammatory, antifungal, antiviral, immune-modulator.

Scientific Evidence:

Echinacea possesses both anti-inflammatory and immuno-stimulating properties.[55] Alkylamides, one

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of the active constituents of echinacea, are thought to be responsible for the herb's anti-inflammatory activity. The alkylamides have been found to modulate production of the inflammatory mediators TNFα and PGE_2, and to inhibit mast cell degranulation.[56]

Echinacea has demonstrated *in vitro* antimicrobial activity against many common pathogens including *Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Propionibacterium acnes*, *Legionella pneumophila*, *Clostridium difficile* and *Candida albicans*.[57,58] 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.[59]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae aka (Asteraceae family).[13] Exercise caution with patients taking immunosuppressant medications (short term use only).[13] No other known warnings, precautions or contraindications.[60] No adverse effects expected during pregnancy and breastfeeding.[13,65,61]

Goldenseal (*Hydrastis canadensis*)

Biological Actions:

Antibacterial, antihistamine, anti-inflammatory, antiviral, antifungal, antiprotozoal, antibiofilm.

Scientific Evidence:

Goldenseal root contains multiple alkaloids, the most abundant of which is berberine, as well as canadine, canadaline, and hydrastine. Both *in vivo* and *in vitro* studies have revealed that berberine possesses antimicrobial activity against bacteria, fungi and parasites.[13,67] Goldenseal leaves are also rich in flavonoids; two of which (6,8-di-C-methylluteolin 7-methyl ether and 6-C-methylluteolin 7-methyl ether) have demonstrated antibacterial activity against the oral pathogens *Streptococus mutans* and *Fusobacterium nucleatum*, while others (specifically sideroxylon, 8-desmethyl-sideroxylon and 6-desmethyl-sideroxylin) don't appear directly antibacterial, but instead enhance the action of berberine by acting as efflux pump inhibitors.[62] It should be noted that one of the major mechanisms by which bacteria become resistant to antibiotics is by overexpression of efflux pumps, which are also known as multidrug resistance pumps.[63] In one *in vitro* study, inhibition

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of programming for lysis. Int Immunopharmacol. Jun 2003;3(6):811-824.

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of the efflux pump allowed a much greater intracellular concentration of berberine, potentiating its antibiotic activity 500-fold against some organisms, indicating the importance of the synergistic interactions among Goldenseal's constituents.[64]

The combined effects of the active constituents in goldenseal make this herb a potent antimicrobial agent for a number of Gram-positive and Gram-negative organisms including methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus sanguis*, *Pseudomonas aeruginosa*, *Mycoplasma mycoides capri*, *Escherichia coli*, *Neisseria gonorrhoeae* isolates (including antibiotic-resistant strains), *Campylobacter jejuni, Vibrio cholera* and *Helicobacter pylori*.[65,66,67,68,69] Berberine, as part of quadruple therapy, has been found to be non-inferior to bismuth for the eradication of H. pylori in a phase 4 trial.[70] One of the key mechanisms by which goldenseal inhibits microbial growth is through quenching of the *agr* quorum sensing (QS) system.[71] The QS system is bacterial cell-to-cell communication that controls gene expression and influences many physiological processes including bioluminescence, sporulation, competence, antibiotic production, biofilm formation and virulence factor secretion.[72] Berberine specifically has been shown to disrupt biofilms in *Salmonella typhimurium*, at least in part by reducing the number of type I fimbriae, an important virulence factor among members of the *Enterobacteriaceae* family.[73]

Berberine has demonstrated antifungal activity against the non-albicans *Candida* species (specifically *Candida krusei*, *Candida Kefyr*, *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis).* When combined with the antimycotic drugs miconazole or fluconazole, berberine was able to reduce biofilm formation of pathogenic *C. albicans*.[74] *In vitro* data shows anti-fungal activity against not just *Candida*, but also *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Trichophyton rubrum*, *Epidermophyton floccosum*, and *Microsporum gypseum*.[67] One analysis revealed a probable mechanism of action to be the disruption of both plasma and mitochondrial fungal membranes, as well as disruption of fungal biofilms.[75] *In vitro* studies have shown that berberine possesses significant antimicrobial activity against a number of protozoans including *Blastocystis hominis*, *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis* and *Leishmania donovani*.[67] Multiple mechanisms of action have been documented for

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berberine's anti-protozoal activity, including a direct effect, via oxidative bursts in parasites, as well as an indirect effect, via modulation of the mitogen activated protein kinase (MAPK) cascade.[76]

Based on *in vitro* experiments, berberine possesses antimicrobial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum.* Berberine in combination with C-methyl flavonoids exhibited an additive antimicrobial effect when tested against *Streptococcus mutans*.[77] 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*.[78]

Safety Summary:

No known warnings, precautions or contraindications when used topically at the recommended dose.[13] Contraindicated during pregnancy in therapeutic doses.[14] Discouraged during breastfeeding in therapeutic doses.[12]

Shiitake mushroom (*Lentinula edodes*)

Biological Actions:

Antibacterial, antifungal, antioxidant, immune modulating, antibiofilm.

Scientific Evidence:

Shiitake mushroom contains many compounds of interest for their immunomodulating properties. Among these are the beta-glucan lentinan, the activated hexose correlated compound (AHCC), and the polysaccharide arabinoxylan. In addition to immunomodulatory effects when taken orally, *in vitro* research has demonstrated direct antibacterial activity against a number of organisms including *Bacillus* sp, *Escherichia coli*, *Enterobacter sp., Klebsiella* sp., *Serratia* sp., *Pseudomonas aeruginosa*, *Listeria monocytogenes, Salmonella poona, Cupriavidus* sp., *Staphylococcus* sp. (including methicillin-resistant *Staphylococcus aureus* (MRSA)), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Enterococcus faecalis*.[79,80,81,82] One mechanism of action for this antibacterial activity is protein leakage following destruction of the bacterial cell membrane.[83]

Shiitake mushroom extracts have also demonstrated anti-biofilm activity against oral pathogens associated with dental caries and plaque accumulation, including *Streptococcus mutans* and

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[81] Hatvani N. Antibacterial effect of the culture fluid of Lentinus edodes mycelium grown in submerged liquid culture. Int J Antimicrob Agents. Jan 2001;17(1):71-74.
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[83] Erdoğan Eliuz EA. Antibacterial activity and antibacterial mechanism of ethanol extracts of Lentinula edodes (Shiitake) and Agaricus bisporus (button mushroom). Int J Environ Health Res. 2021 Apr 24:1-14.

Actinomyces naeslundii.[84,85,86] Other compounds in Shiitake extract have also demonstrated the ability to disrupt bacterial biofilms, including erythritol, adenosine, carvacrol, and may help to support oral health, in part, by an anti-cariogenic effect.[87,88]

In vitro studies have demonstrated anti-gingivitis 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*.[92,89,90] 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.[92,96] 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.[91,92] Unlike antibiotics, the probiotic strains *Bifidobacterium* and *Lactobacillus spp* were not affected by the antimicrobial activities of shiitake mushroom.[89]

Shiitake has also displayed antifungal activity against the following microbes; *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Scedosporium apiospermum*.[86]

Safety Summary:
Considered safe and well tolerated at doses of up to 2.5mg Lentinex per day for 6 weeks.[93] Doses of 9 grams per day of liquid AHCC have also been trialed for two weeks in healthy adults with no changes in blood chemistry markers or significant adverse events.[94] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[95]

White willow bark (*Salix alba*)

Biological Actions: Analgesic, anti-inflammatory.

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[84] Papetti A , Signoretto C , Spratt DA , et al. Components in Lentinus edodes mushroom with anti-biofilm activity directed against bacteria involved in caries and gingivitis. Food Funct. 2018 Jun 20;9(6):3489-3499.
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[90] Ciric L, Tymon A, Zaura E, et al. In vitro assessment of shiitake mushroom (Lentinula edodes) extract for its antigingivitis activity. J Biomed Biotechnol. 2011;2011:507908.
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[93] Gaullier JM, Sleboda J, Øfjord ES, et al. Supplementation with a soluble β-glucan exported from Shiitake medicinal mushroom, Lentinus edodes (Berk.) singer mycelium: a crossover, placebo-controlled study in healthy elderly. Int J Med Mushrooms. 2011;13(4):319-26.
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Scientific Evidence:

The key active constituents of white willow bark are comprised of phenolic glycosides including the salicylates salicortin and salicin.[12] However, an analysis of white willow bark revealed at least 16 other important compounds, including the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol), condensed tannins, catechin, amelopsin, taxifolin, 7-O-methyltaxifolin-3'-O-glucoside, and 7-O-methyltaxifolin.[96,97,98,99] Initially it was thought that salicin (converted to salicylic acid *in vivo*) was responsible for the anti-inflammatory effects of this herb.[104] More recent evidence suggests that the potent anti-inflammatory effect is derived from the sum total of the biologically active components, given white willow bark's effects are much broader acting than non-steroidal anti-inflammatory drugs (NSAIDs) which contain acetylsalicylic acid.[100] Unlike NSAIDs, white willow bark is not associated with unwanted side effects of gastric erosion.[105]

The synergistic effect of the salicylates, flavonoids and tannins found in white willow bark have been shown to inhibit COX-2 and subsequent generation of free radicals by converting arachidonic acid to prostaglandins.[101] *In vitro* studies assessing LPS activated monocytes show that *Salix alba* is able to block nitric oxide release and reduce IL-6 and TNFα production.[104,102] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block NF-κB activation.[104,105] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[104] An antioxidant effect was also recently documented for salicin specifically, mediated in part by activation of the PI3K/Akt/GSK3β pathway, which plays a role in cellular protection, particularly against ischemic injury.[103]

Safety Summary:

Contraindicated in people with salicylate sensitivity.[107] Children under age 16 should not consume white willow bark to avoid Reye syndrome.[107] No other known warnings, precautions or contraindications at the dose recommended.[14] Should be avoided during pregnancy.[104] Discouraged during breastfeeding in therapeutic doses.

Garlic (*Allium sativum*)

Biological Actions:

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[100] Shara M, Stohs SJ. Efficacy and Safety of White Willow Bark (Salix alba) Extracts. Phytother Res. 2015 Aug;29(8):1112-6.
[101] Fiebich BL, Chrubasik S. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. Phytomedicine. 2004 Feb;11(2-3):135-8.
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[103] Park JH, Lee TK, Kim DW, et al. Neuroprotective Effects of Salicin in a Gerbil Model of Transient Forebrain Ischemia by Attenuating Oxidative Stress and Activating PI3K/Akt/GSK3β Pathway. Antioxidants (Basel). 2021 Apr 20;10(4):629.
[104] Oketch-Rabah HA, Marles RJ, Jordan SA, et al. United States Pharmacopeia Safety Review of Willow Bark. Planta Med. 2019 Nov;85(16):1192-1202.

Anti-inflammatory, antimicrobial, antioxidant, antibiofilm.

Scientific Evidence:

The most biologically active constituent of garlic is allicin (S-(2-propenyl)-2-propene-1-sulfinothioate), which is formed when the herb is crushed and alliinase (an enzyme from the bundle sheath cells) combines with the substrate alliin (S-allyl-L-cysteine sulfoxide).[105] Bulbs of garlic contain hundreds of other phytochemicals, including many sulfur containing compounds, ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithiins (2-vinyl-(4H) -1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide (DADS), diallyl sulfide (DAS), diallyl trisulfide (DATS)), N-acetylcysteine (NAC), S-allyl-cysteine (SAC), and others.[112]

Much of the antimicrobial activity of garlic has been attributed to allicin activity, and includes both Gram-positive and Gram-negative microorganisms, as well as antibiotic-resistant bacteria, including *Shigella*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus mutans*, *Streptococcus pyogenes*, *Salmonella enterica*, *Klebsiella aerogenes*, *Vibrio*, *Mycobacteria*, *Proteus vulgaris*, and *Enterococcus faecalis.*[112,106] The antimicrobial activity of allicin has been partly attributed to the S-allylmercapto modification of thiol-containing proteins in bacteria, such as glutathione, leading to either necrosis or apoptosis.[107] However, allicin is a very unstable compound, and thus unlikely to be the only antimicrobial component of garlic *in vivo*.

Both *in vitro* and *in vivo* studies have identified the two ajoenes (Z and E) as components of garlic that are able to inhibit virulence genes controlled by quorum sensing (QS) systems, virulence factors that are also of critical importance to the formation of biofilms and antibiotic resistance.[108,109] Ajoenes have shown antimicrobial activity against a variety of both Gram-negative and Gram-positive bacteria, and may play a role in the effectiveness of garlic against a number of pathogens with multiple drug-resistances.[110,111] DAS has also been found to inhibit the transcription of virulence genes in *Pseudomonas aeruginosa* which are regulated by the QS system, as well as most of the key genes in the QS system, indicating that multiple components within garlic may target this mechanism.[112] Furthermore, QS inhibitors have demonstrated a synergistic effect when combined with antibiotics. Based on *in vitro* research, the addition of ajoene to a *Pseudomonas* biofilm plus tobramycin killed more than 90% of the bacteria (compared with no effect when tobramycin was tested in isolation).[115] Allicin also has an extensive number of bacterial and fungal pathogens for which it acts synergistically against when coupled with other antibiotics.[113]

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[111] Karuppiah P, Rajaram S. Antibacterial effect of Allium sativum cloves and Zingiber officinale rhizomes against multiple-drug resistant clinical pathogens. Asian Pac J Trop Biomed. 2012 Aug;2(8):597-601.
[112] Li WR, Zeng TH, Yao JW, et al. Diallyl sulfide from garlic suppresses quorum-sensing systems of Pseudomonas aeruginosa and enhances biosynthesis of three B vitamins through its thioether group. Microb Biotechnol. 2021 Mar;14(2):677-691.
[113] Choo S, Chin VK, Wong EH, et al. Review: antimicrobial properties of allicin used alone or in combination with other medications. Folia Microbiol (Praha). 2020 Jun;65(3):451-465.

Garlic is also known to have anti-fungal activity against a variety of organisms, including *Candida*, *Torulopsis*, *Trichophyton*, *Cryptococcus*, *Aspergillus*, *Trichosporon*, and *Rhodotorula* species. Garlic has been shown to target fungal cell walls, and cause irreversible structural changes in the fungal cells, leading to cell death.[112] Anthelmintic activity against *Haemonchus contortus*, *Trichuris muris* and *Angiostrongylus cantonensis* has also been demonstrated with various garlic extracts, and allicin, ajoenes, and diallyl trisulfide have all shown activity against a variety of parasites.[112]

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.[114] 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.[115,116] 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 anti-proteolytic activity and by inhibiting total protease activity.[117,118]

Other *in vitro* experiments using crude garlic extract show that it possesses greater antibacterial activity against *Streptococcus mutans* than chlorhexidine.[119] 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.[120] Garlic has also demonstrated activity against pathological strains isolated from periodontal and dental caries including *Staphylococcus aureus*.[121] In addition to its antimicrobial effects, it has also shown efficacy in the treatment of recurrent aphthous ulcers.[122]

Safety Summary: No known warnings, precautions or contraindications when used topically at the dose recommended.[57] No adverse effects expected during pregnancy and breastfeeding.[57,123]

Grape Seed (*Vitis vinifera*)

Biological Actions:

Antimicrobial, anti-inflammatory, antioxidant, antibiofilm.

Scientific Evidence:

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[114] Groppo FC, Ramacciato JC, Motta RH, et al. Antimicrobial activity of garlic against oral streptococci. Int J Dent Hyg. 2007 May;5(2):109-15.
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[118] Bakri IM, Douglas CW. Inhibitory effect of garlic extract on oral bacteria. Arch Oral Biol. 2005 Jul;50(7):645-51.
[119] Jain I, Jain P, Bisht D, et al. Use of traditional Indian plants in the inhibition of caries-causing bacteria--Streptococcus mutans. Braz Dent J. 2015 Mar-Apr;26(2):110-5.
[120] Fani MM, Kohanteb J, Dayaghi M. Inhibitory activity of garlic (Allium sativum) extract on multidrug-resistant Streptococcus mutans. J Indian Soc Pedod Prev Dent. 2007 Oct-Dec;25(4):164-8.
[121] Bin C, Al-Dhabi NA, Esmail GA, et al. Potential effect of Allium sativum bulb for the treatment of biofilm forming clinical pathogens recovered from periodontal and dental caries. Saudi J Biol Sci. 2020 Jun;27(6):1428-1434.
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[123] Dante G, Bellei G, Neri I, et al. Herbal therapies in pregnancy: what works? Curr Opin Obstet Gynecol. 2014 Apr;26(2):83-91.

Grape seeds are a rich source of bioactive polyphenols, including proanthocyanidins, anthocyanins, flavonoids (flavonols and flavan-3-ols), stilbenes (resveratrol) and phenolic acids. Many of these polyphenols are known to have antioxidant effects, both upregulating antioxidant enzymes and directly neutralizing reactive oxygen species (ROS).[131]

Grape seed extracts (GSEs) have demonstrated antimicrobial activity against several respiratory pathogens including *Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterococcus faecalis, Streptococcus* sp. Group F*, Streptococcus pneumoniae and Pseudomonas aeruginosa*.[124] GSE 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.[125] An *in vitro* study found that at a low concentration, GSE disrupted the membranes of *Borrelia burgdorferi sensu lato,* while at a higher concentration, bacteria and cysts completely disappeared, leaving only fragments.[126] Other *in vitro* studies suggest that GSE also has the potential to protect against dental caries, demonstrating an ability to inhibit the growth of *Streptococcus mutans* as well as its formation of biofilms, and to reduce periodontal inflammation.[127,128,129] Other *in vitro* studies indicate grape seed extract supports healthy remineralization of teeth and may be more effective than oral fluoride or calcium glycerophosphate/phosphate.[130,131] It appears to restore dentin remineralization by potentiating collagen cross linking.[132]

Safety Summary: No known warnings, precautions or contraindications at the dose recommended.[14] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[14]

Black Walnut (*Juglans nigra*)

Biological Actions:

Antimicrobial, antioxidant, antibiofilm.

Scientific Evidence:

The main active constituents of black walnut include naphthoquinones (juglone and plumbagin), tannins (ellagic acid and tannic acid) and flavanoids.[12,57,133] Black walnut hull and kernels have

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[124] Cueva C, Mingo S, Muñoz-González I, et al. Antibacterial activity of wine phenolic compounds and oenological extracts against potential respiratory pathogens. Lett Appl Microbiol. 2012 Jun;54(6):557-63.
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[127] Zhao W, Xie Q, Bedran-Russo AK, et al. The preventive effect of grape seed extract on artificial enamel caries progression in a microbial biofilm-induced caries model. J Dent. 2014 Aug;42(8):1010-8.
[128] Bogdan C, Pop A, Iurian SM, et al. Research Advances in the Use of Bioactive Compounds from Vitis vinifera By-Products in Oral Care. Antioxidants (Basel). 2020 Jun 8;9(6):502.
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[130] Benjamin S, Sharma R, Thomas SS, et al. Grape seed extract as a potential remineralizing agent: a comparative in vitro study. J Contemp Dent Pract. 2012 Jul 1;13(4):425-30.
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[132] Delimont NM, Carlson BN. Prevention of dental caries by grape seed extract supplementation: A systematic review. Nutr Health. 2020 Mar;26(1):43-52.
[133] Amarowicz R, Dykes GA, Pegg RB. Antibacterial activity of tannin constituents from Phaseolus vulgaris, Fagoypyrum esculentum, Corylus avellana and Juglans nigra. Fitoterapia. 2008 Apr;79(3):217-9.

recently been shown to contain phenolics, including the antioxidants penta-O-galloyl-β-d-glucose, epicatechin gallate, quercetin, (-)-epicatechin, rutin, quercetin 3-β-d-glucoside, gallic acid, (+)-catechin, ferulic acid, and syringic acid, many of which have established physiological effects.[134,135,136]

Several compounds in black walnut have been found to have antimicrobial activity, including quercetin-3-O-glucoside (aka isoquercitin, eriodictyol-7-O-glucoside, quercetin, azelaic acid, and glansreginin A, demonstrating antibacterial activity against the Gram-positive bacterium (*S. aureus*).[137] Individually many of these compounds have shown broad antimicrobial activity, e.g. quercetin-3-O-glucoside has demonstrated anti-fungal activity, disrupting the membrane of Candida albicans; eriodictyol-7-O-glucoside has an antibacterial effect on the Gram-positive bacteria *Micrococcus luteus*, and *Staphyloccous aureus*.[138,139] Juglone has demonstrated anti-bacterial and anti-parasitic activity against a variety of organisms *in vitro*, and inhibited both the formation of new biofilms as well as biofilm formation in *Candida albicans*.[140,141,142,143]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[57] Contraindicated during pregnancy and breastfeeding in therapeutic doses.[144]

Raspberry (*Rubus idaeus*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant, antibiofilm.

Scientific Evidence:

Raspberry is rich in anthocyanins (mainly cyanidin-3-sophoroside) and phenolic compounds (primarily ellagitannins and ellagic acid). Raspberry also contains quercetin and kaempferol-based flavanols.[145,146,147] Research shows that antioxidant properties of raspberry are attributed to its

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[134] Wenzel J, Storer Samaniego C, Wang L, et al. Antioxidant potential of Juglans nigra, black walnut, husks extracted using supercritical carbon dioxide with an ethanol modifier. Food Sci Nutr. 2016 May 20;5(2):223-232.
[135] Ho KV, Roy A, Foote S, et al. Profiling Anticancer and Antioxidant Activities of Phenolic Compounds Present in Black Walnuts (Juglans nigra) Using a High-Throughput Screening Approach. Molecules. 2020 Oct 2;25(19):4516.
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[139] Chu LL, Pandey RP, Jung N, et al. Hydroxylation of diverse flavonoids by CYP450 BM3 variants: biosynthesis of eriodictyol from naringenin in whole cells and its biological activities. Microb Cell Fact. 2016 Aug 5;15(1):135.
[140] Jha BK, Jung HJ, Seo I, et al. Juglone induces cell death of Acanthamoeba through increased production of reactive oxygen species. Exp Parasitol. 2015 Dec;159:100-6.
[141] Emelyanova EV, Solyanikova IP. Understanding the Mechanism of Formation of a Response to Juglone for Intact and Immobilized Bacterial Cells as Recognition Elements of Microbial Sensors: Processes Causing the Biosensor Response. Biosensors (Basel). 2021 Feb 21;11(2):56.
[142] Wianowska D, Garbaczewska S, Cieniecka-Roslonkiewicz A, et al. Comparison of antifungal activity of extracts from different Juglans regia cultivars and juglone. Microb Pathog. 2016 Nov;100:263-267.
[143] Gumus B, Acar T, Atabey T, et al. The battle against biofilm infections: juglone loaded nanoparticles as an anticandidal agent. J Biotechnol. 2020 Jun 10;316:17-26.
[144] Natural Medicines Comprehensive Database. Black Walnut Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed July 17th, 2012
[145] Godevac D, Tesević V, Vajs V, et al. Antioxidant properties of raspberry seed extracts on micronucleus distribution in peripheral blood lymphocytes. Food Chem Toxicol. 2009 Nov;47(11):2853-9.
[146] Mullen W, McGinn J, Lean ME, et al. Ellagitannins, flavonoids, and other phenolics in red raspberries and their contribution to antioxidant capacity and vasorelaxation properties. J Agric Food Chem. 2002 Aug 28;50(18):5191-6.
[147] Kähkönen M, Kylli P, Ollilainen V, et al. Antioxidant activity of isolated ellagitannins from red raspberries and cloudberries. J Agric Food Chem. 2012 Feb 8;60(5):1167-74.

polyphenolic compounds, specifically ellagitannins, which are highly effective free radical scavengers. Results of an *in vitro* study indicate that raspberry's phenolics are able to protect DNA and decrease lipid peroxidation of lymphocytes in a concentration dependent manner.[153]

The active ellagitannin constituents (sanguiin H-6 and lambertianin C) have also demonstrated anti-inflammatory properties. Based on *in vitro* research, they inhibit the increase of NF-κB driven nuclear transcription and resultant TNFα production in a dose dependent manner.[148] Phenolic compounds also possess antimicrobial properties and have been shown to inhibit the growth of both Gram-positive and Gram-negative pathogenic bacterial strains including *Staphylococcus aureus* and *Salmonella enterica* sp., as well as *Staphylococcus epidermidis, Helicobacter pylori, Bacillus cereus, Campylobacter jejuni* and *Candida albicans*.[19,21,149,150]
Additionally, raspberry has demonstrated antigingivitis and anticaries activities against *Streptococcus sanguinis, Streptococcus mutans, Fusobacterium nucleatum*, *Prevotella intermedia, Veillonella dispar, Neisseria subflava, Actinomyces naeslundii* and *Lactobacillus casei*.[96,151]

Mechanisms by which raspberry protects against oral pathogens include: preventing bacterial coaggregation and biofilm formation, destabilization of the cytoplasmic membrane, permeabilization of plasma membrane and inhibition of extracellular microbial enzymes, as well as direct actions on microbial metabolism by depriving the cells of the substrates necessary for growth disruption of preexisting biofilms and reducing the expression of genes involved in gingival cellular proliferation and differentiation.[159],[22] 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 anti-adherence activity.[19] Growth of the probiotic strain *Lactobacillus rhamnosus* does not appear to be inhibited by the phenolic properties of raspberry.[21,157]

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

Fumitory (*Fumaria officinalis*)

Biological Actions:
Antimicrobial, antioxidant.

Scientific Evidence:
The active constituents of fumitory include alkaloids, flavonoids, and organic acids.[12] The biological activities of this herb are mainly associated with the isoquinoline alkaloids, in particular protopine.[152,153] The antioxidant capacity of fumitory, however, is thought to be due to the synergistic

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[148] Sangiovanni E, Vrhovsek U, Rossoni G, et al. Ellagitannins from Rubus berries for the control of gastric inflammation: in vitro and in vivo studies. PLoS One. 2013 Aug 5;8(8):e71762.
[149] Puupponen-Pimiä R, Nohynek L, Hartmann-Schmidlin S, et al. Berry phenolics selectively inhibit the growth of intestinal pathogens. J Appl Microbiol. 2005;98(4):991-1000.
[150] Nile SH, Park SW. Edible berries: bioactive components and their effect on human health. Nutrition. 2014 Feb;30(2):134-44.
[151] Canesi L, Borghi C, Stauder M, et al. Effects of fruit and vegetable low molecular mass fractions on gene expression in gingival cells challenged with Prevotella intermedia and Actinomyces naeslundii. J Biomed Biotechnol. 2011;2011:230630.
[152] Hentschel C, Dressler S, Hahn EG. Fumaria officinalis (Echter Erdrauch)--klinische Anwendung [Fumaria officinalis (fumitory)--clinical applications]. Fortschr Med. 1995 Jul 10;113(19):291-2. German.
[153] Rakotondramasy-Rabesiaka L, Havet JL, C. Porte, et al. Solid–liquid extraction of protopine from Fumaria

effect of its constituents.[154]

While the scientific evaluation of this herb is somewhat limited, an *in vitro* study assessing a methanol extract of fumitory demonstrated significant antimicrobial activity against the following microorganisms; *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Cladosporium herbarum*.[162] Reviews of the alkaloids found in Fumaria species suggests possible anti-viral, anti-biofilm, hepatoprotective, anti-fungal, and gastroprotective effects, but more research is needed to substantiate these findings.[155,156]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[157] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[158,159]

Gentian (*Gentiana lutea*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant, antibiofilm.

Scientific Evidence:

Gentian contains several secoiridoid bitter compounds including gentisin, gentiopicrin, amarogentin, gentianine, gentianadine, sweroside and swertiamarin. The medicinal constituents also include a group of xanthones (isovitexin and isogentisin) as well as phenolic acids and phytosterol flavonoids.[12,168,160] These active constituents give rise to the herb's potent antioxidant, anti-inflammatory and antibacterial properties.[168]

An *in vitro* analysis of gentian's antimicrobial properties found inhibition of the growth of both Gram-positive and Gram-negative organisms bacteria including *Listeria monocytogenes, Staphylococcus aureus*, *Salmonella typhimurium, Escherichia coli, Pseudomonas aeruginosa* and *Micrococcus luteus,* as well as *Candida albicans.* Although the widest spectrum of activity was attributed to gentiopicrin, a dominant role for any individual component was not observed, but rather a synergistic antimicrobial effect among gentian's constituents.[161]

Safety Summary:

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officinalis L.—Kinetic modelling of influential parameters. Industrial Crops and Products. 2009;29(2-3):516-523.
[154] Sengul M, Yildiz H, Gungor N, et al. Total phenolic content, antioxidant and antimicrobial activities of some medicinal plants. Pak J Pharm Sci. 2009 Jan;22(1):102-6.
[155] Zhang R, Guo Q, Kennelly EJ, et al. Diverse alkaloids and biological activities of Fumaria (Papaveraceae): An ethnomedicinal group. Fitoterapia. 2020 Oct;146:104697.
[156] Sonigra P, Meena M. Metabolic Profile, Bioactivities, and Variations in the Chemical Constituents of Essential Oils of the Ferula Genus (Apiaceae). Front Pharmacol. 2021 Mar 12;11:608649.
[157] Brinkhaus B, Hentschel C, Von Keudell C, et al. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. Scand J Gastroenterol. 2005 Aug;40(8):936-43.
[158] Newall CA, Anderson LA, Philpson JD. Herbal Medicine: A Guide for Healthcare Professionals. London, UK: The Pharmaceutical Press; 1996.
[159] Assessment report on Fumaria officinalis L., herba (PDF) (Report). European Medicines Agency, Committee on Herbal Medicinal Products (HMPC). EMA/HMPC/576232/2010. Accessed 6-28-2021.
[160] Calliste CA, Trouillas P, Allais DP, et al. Free radical scavenging activities measured by electron spin resonance spectroscopy and B16 cell antiproliferative behaviors of seven plants. J Agric Food Chem. 2001 Jul;49(7):3321-7.
[161] Savikin K, Menković N, Zdunić G, et al. Antimicrobial activity of Gentiana lutea L. extracts. Z Naturforsch C J Biosci. 2009 May-Jun;64(5-6):339-42.

No other known warnings, precautions or contraindications at the dose recommended.[13] No adverse effects expected during pregnancy and breastfeeding.[57]

Tea Tree oil (*Melaleuca alternifolia*)

Biological Actions:
Anti-inflammatory, antimicrobial, antiseptic, antibiofilm.

Scientific Evidence:

Tea tree oil (TTO) is composed of a complex mixture of compounds, mainly monoterpene and sesquiterpene hydrocarbons and their associated alcohols, such as α-pinene, sabinene, α-terpinene, limonene, p-cymene, 1,8-cineole, γ-terpinene, terpinolene, terpinen-4-ol (T4O), α-terpineol, aromadendrene, ledene, δ-cadinene, globulol and viridiforol.[162] The diverse active constituents give rise to tea tree's antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria as well as yeast and fungi.[173]

The main antibacterial constituents of TTO are terpinen-4-ol and γ-terpinene. It has been indicated that terpene compounds found in TTO act on the phospholipid layer of the microbial cell membrane, destroying its normal structure and function.[163] Transmission electron microscopy images reveal that TTO penetrates through the cell wall and cytoplasmic membrane of bacteria and fungi, causing damage to these structures, organelle damage, and ultimately death.[164] TTO has demonstrated consistent effective antimicrobial activity against MRSA, vancomycin-resistant *Enterococcus*, multi-resistant *Pseudomonas aeruginosa*, extended spectrum-beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*.[165] The antimicrobial effect of TTO against *Pseudomonas aeruginosa* was found to be superior to commercially used antibacterial agents (specifically 0.1% chlorhexidine and 70% ethanol solutions).[176]

TTO is effective against numerous oral pathogens, and has demonstrated a reduction in gingival inflammation comparable to chlorhexidine among patients with chronic gingivitis.[172,166,167] Topical application of TTO in a gel format has also demonstrated efficacy in controlling microbial biofilms and bacterial counts associated with salivary *Streptococcus mutans* in orthodontic patients.[168] Terpinen-4-ol specifically has been shown to modulate the expression of genes associated with biofilm formation and adherence, suggesting at least one mechanism of action for its antimicrobial effects.[169,170] Antibacterial

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[162] Lam NS, Long X, Su XZ, et al. Melaleuca alternifolia (tea tree) oil and its monoterpene constituents in treating protozoan and helminthic infections. Biomed Pharmacother. 2020 Oct;130:110624.
[163] Takarada K, Kimizuka R, Takahashi N, et al. A comparison of the antibacterial efficacies of essential oils against oral pathogens. Oral Microbiol Immunol. 2004 Feb;19(1):61-4.
[164] Li WR, Li HL, Shi QS, et al. The dynamics and mechanism of the antimicrobial activity of tea tree oil against bacteria and fungi. Appl Microbiol Biotechnol. 2016 Oct;100(20):8865-75.
[165] Warnke PH, Lott AJ, Sherry E, et al. The ongoing battle against multi-resistant strains: in-vitro inhibition of hospital-acquired MRSA, VRE, Pseudomonas, ESBL E. coli and Klebsiella species in the presence of plant-derived antiseptic oils. J Craniomaxillofac Surg. 2013 Jun;41(4):321-6.
[166] Casarin M, Pazinatto J, Santos RCV, et al. Melaleuca alternifolia and its application against dental plaque and periodontal diseases: A systematic review. Phytother Res. 2018 Feb;32(2):230-242.
[167] Hammer KA, Dry L, Johnson M, et al. Susceptibility of oral bacteria to Melaleuca alternifolia (tea tree) oil in vitro. Oral Microbiol Immunol. 2003 Dec;18(6):389-92.
[168] Santamaria M Jr, Petermann KD, Vedovello SA, et al. Antimicrobial effect of Melaleuca alternifolia dental gel in orthodontic patients. Am J Orthod Dentofacial Orthop. 2014 Feb;145(2):198-202.
[169] Bordini EAF, Tonon CC, Francisconi RS, et al. Antimicrobial effects of terpinen-4-ol against oral pathogens and its capacity for the modulation of gene expression. Biofouling. 2018 Aug;34(7):815-825.
[170] Cordeiro L, Figueiredo P, Souza H, et al. Terpinen-4-ol as an Antibacterial and Antibiofilm Agent against Staphylococcus aureus. Int J Mol Sci. 2020 Jun 25;21(12):4531.

effects of mouthwash-containing TTO have demonstrated significant antibacterial activity against *Streptococcus mutans* and other oral microorganisms, with reduced levels of microorganisms maintained throughout the five week duration of the study.[171] TTO has demonstrated *in vitro* 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*.[172] TTO has also demonstrated inhibitory activity against the Gram-positive bacillus *Solobacterium moorei*, an oral microbe associated with halitosis.[173]

TTO has also been shown to decolonize and eradicate biofilms from *Staphylococcus aureus* (both coagulase-negative and coagulase-positive strains).[174] Numerous *in vitro* studies have demonstrated the potent antifungal activity of TTO against *Candida albicans* in both planktonic and biofilm culture. TTO has also demonstrated antifungal activity against *Saccharomyces uvarum* and *Trichophyton rubrum*.[175,176,177]

Safety Summary:

Considered safe and well tolerated at the dose recommended. TTO is generally regarded as non-toxic, and non-irritating, though a small number of individuals have an allergy to TTO oxidation products.[178] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[179]

Galbanum oil (*Ferula galbaniflua*)

Biological Actions:

Anti-inflammatory, antimicrobial, antiseptic.

Scientific Evidence:

Galbanum is composed of mainly monoterpene and sesquiterpene hydrocarbons and their associated alcohols. It is the high concentrations of monoterpenes and sesquiterpenes that give rise to galbanum's anti-inflammatory, antimicrobial and antiseptic properties, with monoterpene hydrocarbons comprising over 95% of Galbanum oil.[191,180,181] Often considered synonymous with

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[171] Groppo FC, Ramacciato JC, Simões RP, et al. Antimicrobial activity of garlic, tea tree oil, and chlorhexidine against oral microorganisms. Int Dent J. 2002 Dec;52(6):433-7.
[172] Takarada K, Kimizuka R, Takahashi N, et al. A comparison of the antibacterial efficacies of essential oils against oral pathogens. Oral Microbiol Immunol. 2004 Feb;19(1):61-4.
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[174] Brady A, Loughlin R, Gilpin D, et al. In vitro activity of tea-tree oil against clinical skin isolates of meticillin-resistant and -sensitive Staphylococcus aureus and coagulase-negative staphylococci growing planktonically and as biofilms. J Med Microbiol. 2006 Oct;55(Pt 10):1375-1380.
[175] Ramage G, Milligan S, Lappin DF, et al. Antifungal, cytotoxic, and immunomodulatory properties of tea tree oil and its derivative components: potential role in management of oral candidosis in cancer patients. Front Microbiol. 2012 Jun 18;3:220.
[176] Irkin R, Korukluoglu M. Growth inhibition of pathogenic bacteria and some yeasts by selected essential oils and survival of L. monocytogenes and C. albicans in apple-carrot juice. Foodborne Pathog Dis. 2009 Apr;6(3):387-94.
[177] Flores FC, de Lima JA, Ribeiro RF, et al. Antifungal activity of nanocapsule suspensions containing tea tree oil on the growth of Trichophyton rubrum. Mycopathologia. 2013 Apr;175(3-4):281-6.
[178] Hammer KA, Carson CF, et al. A review of the toxicity of Melaleuca alternifolia (tea tree) oil. Food Chem Toxicol. 2006 May;44(5):616-25.
[179] Natural Standard. Professional Monograph: Tea tree oil (Melaleuca alternifolia). http://www.naturalstandard.net. Accessed December 24th, 2013.
[180] Nazari ZE, Iranshahi M. Biologically active sesquiterpene coumarins from Ferula species. Phytother Res. 2011 Mar;25(3):315-23.
[181] Kanani MR, Rahiminejad MR, Sonboli A, et al. Chemotaxonomic significance of the essential oils of 18 Ferula species (Apiaceae) from Iran. Chem Biodivers. 2011 Mar;8(3):503-17.

Ferula gummosa, these species are distinct, with greater amounts of feselol and sterol compounds found in *Ferula galbaniflua*. Feselol has been shown to inhibit *Pseudomonas aeruginosa*, *Staphyloccocus epidermidis*, and *Staphylococcus aureus* in vitro.[182]

Terpenes have been shown to be active against bacteria, fungi, viruses, and protozoa. The mechanism by which terpenes exert their antimicrobial properties involves disruption of the lipophilic compounds of cellular membranes of pathogens.[183] Galbanum oil has demonstrated a cytotoxic effect *in vitro* against the protozoa *Leishmania amazonensis*, with a higher selectivity index than 15 other essential oils tested. This may at least in part be due to the presence of the monoterpene β-pinene.[184]

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.[194]

Safety Summary:
Galbanum oil is generally regarded as non-toxic, non-irritating and non-sensitizing.[191] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[185]

Lavender oil (*Lavandula officinalis*)

Biological Actions:
Antifungal, anti-inflammatory, antimicrobial, antibiofilm.

Scientific Evidence:
Lavender oil contains a complex mixture of aromatic compounds, specifically terpenes and sesquiterpenes which include linalyl acetate, linalool, caryophyllene, terpinen-4-ol, 2-myrcene, trans-ocimene, borneol, 1,8-cineole, camphor and limonene.[201,186,187]

This essential oil has been found to be active against many species of bacteria and fungi. 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.[188] Lavender oil also has antibacterial activity against both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus in vitro*.[201,202,189]

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[182] Amin A, Hanif M, Abbas K, et al. Studies on effects of umbelliferon derivatives against periodontal bacteria; antibiofilm, inhibition of quorum sensing and molecular docking analysis. Microb Pathog. 2020 Jul;144:104184.
[183] Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev. 1999 Oct;12(4):564-82.
[184] Andrade MA, Azevedo CD, Motta FN, et al. Essential oils: in vitro activity against Leishmania amazonensis, cytotoxicity and chemical composition. BMC Complement Altern Med. 2016 Nov 8;16(1):444.
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[187] de Groot A, Schmidt E. Essential Oils, Part V: Peppermint Oil, Lavender Oil, and Lemongrass Oil. Dermatitis. 2016 Nov/Dec;27(6):325-332.
[188] Takarada K, Kimizuka R, Takahashi N, et al. A comparison of the antibacterial efficacies of essential oils against oral pathogens. Oral Microbiol Immunol. 2004 Feb;19(1):61-4.
[189] Nelson RR. In-vitro activities of five plant essential oils against methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium. J Antimicrob Chemother. 1997 Aug;40(2):305-6.

Lavender oil has demonstrated both fungistatic and fungicidal activity against *Candida albicans.* Research also shows lavender is effective against both vaginal and oropharyngeal strains of *Candida albicans. In vitro*, lavender oil inhibited both germ tube formation and hyphal elongation of *Candida albicans.*[200]

Based on *in vitro* experiments, lavender also 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-KB activation and IL-1β production.[199]

Safety Summary:

Lavender oil is generally regarded as non-toxic, non-irritant and non-sensitizing.[191] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[190]

[190] Brendler T, Gruenwald J, Jaenicke C. Comm. E Monograph: Lavandulae flos In: Heilpflanzen - Herbal Remedies. In: Publishers MS, ed; 2003. Accessed December 25th, 2013.

Oregano oil (*Origanum vulgare*)

Biological Actions:

Antibacterial, antifungal, anti-inflammatory, antioxidant, antibiofilm.

Scientific Evidence:

Active constituents of oregano oil include monoterpenes and sesquiterpene hydrocarbons, as well as phenolic compounds; the main terpenes are thymol, carvacrol, p-cymene, γ-terpinene, and linalool.[191]

Based on *in vitro* research, oregano oil showed high a inhibitory effect against multiple organisms, against both Gram-positive and Gram-negative bacteria, including *Listeria monocytogenes, Escherichia coli, Salmonella enteritidis, Pseudomonas aeruginosa, Staphylococcus aureus* and erythromycin-resistant Group A *Streptococcus pyogenes*.[210] Both carvacrol and oregano oil were also found to inhibit the growth of *Borrelia burgdorferi in vitro,* and dissolve its biofilms to a greater degree than 33 other essential oils tested.[192] In an animal model, oregano oil was found to have significant antibacterial activity against 11 multi-drug resistant strains, and effectively eradicated the biofilms for each pathogen tested.[193] *In vitro* testing found oregano oil to inhibit all 59 strains of bacteria isolated from subjects with cystic fibrosis, many of which were also multi-drug resistant.[194] This broad antibacterial activity suggests the possibility that oregano oil has multiple cellular targets, though it is clear that both thymol and carvacrol target bacterial membrane proteins, increasing the permeability of the cell membrane.[209,210]

Oregano oil has also demonstrated antifungal activities against *Candida* species.[195] In the study by Pozzatti et al, oregano inhibited the growth and hyphenation of both *Candida albicans* and *Candida dubliniensis*.[196] One mechanism of its 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.[215] Additionally, thymol and carvacrol overwhelm *Candida* antioxidant defense systems with an oxidative radical cascade, inhibit ergosterol synthesis, and also target efflux pump activity.[197,198]

Safety Summary:

Generally considered safe and well tolerated at the dose recommended. Active phenolic compounds such as thymol and carvacrol in oregano oil may, in some sensitive individuals, cause skin and mucus membrane irritation.[191] Exercise caution during pregnancy and breastfeeding as safety has not

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[191] Lombrea A, Antal D, Ardelean F, et al. A Recent Insight Regarding the Phytochemistry and Bioactivity of Origanum vulgare L. Essential Oil. Int J Mol Sci. 2020 Dec 17;21(24):9653.
[192] Feng J, Zhang S, Shi W, et al. Selective Essential Oils from Spice or Culinary Herbs Have High Activity against Stationary Phase and Biofilm Borrelia burgdorferi. Front Med (Lausanne). 2017 Oct 11;4:169.
[193] Lu M, Dai T, Murray CK, et al. Bactericidal Property of Oregano Oil Against Multidrug-Resistant Clinical Isolates. Front Microbiol. 2018 Oct 5;9:2329.
[194] Pesavento G, Maggini V, Maida I, et al. Essential Oil from Origanum vulgare Completely Inhibits the Growth of Multidrug-Resistant Cystic Fibrosis Pathogens. Nat Prod Commun. 2016 Jun;11(6):861-4.
[195] Vahedi G., Khosravi A.R., Shokri H., et al. A. Fungicidal Effect of Origanum vulgare Essential Oil against Candida Glabrata and Its Cytotoxicity against Macrophages. J. HerbMed Pharmacol. 2016;5:78–84.
[196] Pozzatti P, Loreto ES, Nunes Mario DA, et al. Activities of essential oils in the inhibition of Candida albicans and Candida dubliniensis germ tube formation. Journal de Mycologie Médical 2010;20(3):185-189.
[197] Bae YS, Rhee MS. Short-Term Antifungal Treatments of Caprylic Acid with Carvacrol or Thymol Induce Synergistic 6-Log Reduction of Pathogenic Candida albicans by Cell Membrane Disruption and Efflux Pump Inhibition. Cell Physiol Biochem. 2019;53(2):285-300.
[198] Khan A, Ahmad A, Ahmad Khan L, Pet al. Effect of two monoterpene phenols on antioxidant defense system in Candida albicans. Microb Pathog. 2015 Mar;80:50-6.

been established during these times.[199]

Quercetin

Biological Actions:
Antioxidant, antihistamine, anti-inflammatory, antimicrobial, immune modulating.

Scientific Evidence:
Quercetin is a flavanol which belongs to a group of polyphenolic substances known as flavonoids or bioflavonoids. It can be found in a wide variety of fruits and vegetables such as apples, berries, grapes, citrus fruit, onions, broccoli, and other green leafy vegetables. Quercetin is also naturally present in black and green tea and red wine as well as many seeds and nuts, flowers, barks, and leaves.[219]

Quercetin acts through multiple mechanisms to exert anti-microbial effects, including destruction of the bacterial cell envelope, preventing bacterial adhesion, inhibiting bacterial nucleic acid synthesis and inhibiting biofilm formation.[200] A systematic review established that quercetin exhibits beneficial effects in oral health via its broad pharmacological properties as a preventive and therapeutic agent in dental caries with anti-inflammatory effects against oral pathogens.[201] In clinical research, topical application of quercetin has demonstrated accelerated healing properties to minor aphthous ulcers when compared to topical benzydamine hydrochloride mouthwash.[202] Quercetin has been found effective *in vitro* against many organisms associated with dental plaque, including *Actinomyces naeslundii*, *Actinomyces viscosus*, *Aggregatibacter actinomycecomitans*, *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus aureus*, *Lactobacillus casei,* as well as *Candida albicans.*[203] Other *in vitro* experiments show that quercetin possesses antimicrobial activity against *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* bacteria which are associated with early onset, progressive and refractory periodontal disease, as well as *Actinomyces viscosus, Fusobacterium nucleatum* and *Actinomyces naeslundii*, also known to cause periodontitis.[204,205] Quercetin has been shown to reduce the biofilm formation of *Streptococcus mutans* by inhibiting the expression of the related genes, while exhibiting no cytotoxicity for human dental pulp cells.[206] Quercetin also demonstrated antibacterial properties against *Streptococcus mitis*, by inhibiting adhesion, biofilm formation and maturation.[207]

The anti-inflammatory properties of quercetin have also been evaluated through *in vitro* research using human gingival fibroblasts and human mesenchymal stem cells. Quercetin decreased the release of the

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[199] Natural Medicines Comprehensive Database. Oregano Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed December 25th, 2013.
[200] Wang Y, Tao B, Wan Y, et al. Drug delivery based pharmacological enhancement and current insights of quercetin with therapeutic potential against oral diseases. Biomed Pharmacother. 2020 Aug;128:110372.
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[203] Gutiérrez-Venegas G, Gómez-Mora JA, Meraz-Rodríguez MA, et al. Effect of flavonoids on antimicrobial activity of microorganisms present in dental plaque. Heliyon. 2019 Dec 13;5(12):e03013.
[204] Geoghegan F, Wong RW, Rabie AB. Inhibitory effect of quercetin on periodontal pathogens in vitro. Phytother Res. 2010 Jun;24(6):817-20.
[205] Li M, Xu Z. Quercetin in a lotus leaves extract may be responsible for antibacterial activity. Arch Pharm Res. 2008 May;31(5):640-4.
[206] Yue JX, Yang HY, Han L, et al. [Inhibitory effect of quercetin on the biofilm formation of Streptococcus mutans]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2016 Jun;51(6):368-73.
[207] Shahzad M, Millhouse E, Culshaw S, et al. Selected dietary (poly)phenols inhibit periodontal pathogen growth and biofilm formation. Food Funct. 2015 Mar;6(3):719-29.

inflammatory mediator prostaglandin E2, downregulated IL-6 messenger RNA levels, reduced the expression of profibrotic markers during wound healing and decreased reactive oxygen species levels.[208,209]

Safety Summary:
Quercetin is considered safe and well tolerated with no interactions expected at the recommended dose. Although animal studies suggest impaired kidney function may be a contraindication, no human data has confirmed this finding.[210] Contraindicated in persons with a known hypersensitivity to quercetin. Adverse effects are rare and may include nausea, dyspnea, headache, and mild tingling of the extremities.[231] Not recommended during pregnancy and breastfeeding as safety has not been established during these times.[211]

[208] Gómez-Florit M, Monjo M, Ramis JM. Quercitrin for periodontal regeneration: effects on human gingival fibroblasts and mesenchymal stem cells. Sci Rep. 2015 Nov 12;5:16593.
[209] Gómez-Florit M, Monjo M, Ramis JM. Identification of quercitrin as a potential therapeutic agent for periodontal applications. J Periodontol. 2014 Jul;85(7):966-74.
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Coenzyme Q10 (Ubiquinone)

Biological Actions:
Anti-inflammatory, antioxidant, mitochondrial cofactor, tissue protection.

Scientific Evidence:
CoQ10 is the only fat-soluble antioxidant synthesized endogenously and is ubiquitous throughout the body. It is necessary for membrane integrity and intracellular energy production and serves as an essential co-factor in mitochondrial bioenergetics, as a key component for adenosine triphosphate (ATP) production and cellular respiration. It also acts as a powerful antioxidant in the inner mitochondrial membrane and modulates the activity of genes associated with inflammation. At the mitochondrial level, CoQ10 is essential for the optimal function of multiple body systems, including the cardiovascular and immune systems.[212,234]

Metabolically active cells such as heart, immune system, gingiva and gastric mucosa are susceptible to CoQ10 deficiency due to their greater requirements for normal cellular function.[213] A deficiency of CoQ10 has been found in the gingiva of individuals with periodontal disease, and in several randomized clinical trials topical application of CoQ10 has shown improvement in multiple parameters, including gingival bleeding, plaque scores, gingival crevicular fluid flow, probing depth and attachment loss, the gingival index, bleeding on probing, and peptidase activity of periodontopathic microorganisms when given both with and without mechanical debridement.[214,215,216,217] Topical CoQ10 has also been shown to improve periodontal disease in combination with mechanical debridement among smokers, a group known to have a poorer response to standard therapy.[218]

Safety Summary:
Supplementation with CoQ10 is considered safe and well tolerated.[234] Adverse effects are generally no greater than placebo even at high doses, with mild gastrointestinal upset reported only very occasionally.[219] Doses of 200 mg per day of CoQ10 have been safely used for five months during pregnancy (starting week 20) in women at risk of developing preeclampsia.[220] Avoid using during breastfeeding due to a lack of safety data.[221]

Myrrh Resin (*Commiphora myrrh*)

Biological Actions:

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[216] Hanioka T, Tanaka M, Ojima M, et al. Effect of topical application of coenzyme Q10 on adult periodontitis. Mol Aspects Med. 1994;15 Suppl:s241-8.
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[221] Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006–. Coenzyme Q10. 2021 May 17.

Anti-inflammatory, antimicrobial, antioxidant, astringent, vulnerary.

Scientific Evidence:
Myrrh resin is a sticky, water-insoluble substance extracted from the bark of the *Commiphora* plant. Traditionally it has been considered an important herbal medicine throughout the Middle East, China, and India for at least 3,000 years. The use of myrrh in traditional Western herbal medicine includes mouth ulcers, inflammation of the gums and oral mucosa (including gingivitis and stomatitis), as well as pharyngitis, laryngitis and respiratory infections. The three main active compounds of myrrh include the resin, the gum, and the volatile oil. Myrrh resin has strong antimicrobial, anti- inflammatory, vulnerary and astringent properties and has a soothing effect on inflamed tissues in the mouth and throat. Myrrh is often used as a component of gargles, mouthwashes, toothpastes or paints for prevention and treatment of dental ailments.[245,246] In a randomized and controlled trial, a mouthwash containing Myrrh extract was shown to improve healing following tooth extraction compared to standard saline, including favorable gains in edema, tenderness, and socket size.[222]

In vitro research shows that the sesquiterpene fractions extracted from myrrh resin possess antibacterial and antifungal activity by inhibiting the growth of standard pathogenic strains of *Escherichia coli*, S*taphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*.[223] The resin has also shown antimicrobial activity against *Enterococcus faecalis* and *Fusobacterium nucleatum,* two species predominant in persistent infections following root canal treatment, and found in dentinal tubules or the roots of non-treated teeth with apical lesions.[224] The diterpenoids and triterpenoids also found in the resin may help to explain broad antimicrobial and anti-parasitic activity.[245]

Safety Summary:
Considered safe at the recommended dosage.[225] Contraindicated in persons with known hypersensitivity to myrrh. Side effects may include a burning sensation on the skin or mucous membranes. Contraindicated during pregnancy and breastfeeding. [245]

Clove Essential Oil (*Syzygium aromaticum*)

Biological Actions:
Analgesic, anti-inflammatory, antimicrobial, antioxidant, antiseptic.

Scientific Evidence:
Clove essential oil has been used traditionally as an anesthetic for toothache, skin infections, digestive upsets, parasite eradication, as well as a natural flavoring agent. Due to its eugenol and other polyphenolic components, clove oil exerts potent antimicrobial, anti-inflammatory and antioxidant properties.[254]

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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*. Other therapeutic effects of eugenol include its ability to damage the cell membrane and destroy the integrity of plasma membranes of bacteria. In addition, eugenol has been shown to suppress biofilm formation, reduce preformed biofilm and down-regulate the expression of virulence factor genes related to the biofilm of *Porphyromonas gingivalis*.[226] Clove oil has also demonstrated anti-fungal effects, and the ability to inhibit biofilms formed by multiple species of *Candida* extracted from human saliva.[227] Toothpastes formulated with clove essential oil were also shown to completely disrupt *Streptococcus mutans* biofilms *in vitro*.[228]

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.[252,229] Clove oil also exhibits 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.[251]

Safety Summary:
Clove essential oil is considered safe at the dose recommended. In sensitive individuals, the oil may cause dermal irritation.[230] 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.[231]

Peppermint Leaf (*Mentha piperita*)

Biological Actions:
Anticariogenic, antimicrobial, antiseptic.

Scientific Evidence:
Peppermint oil has been extensively used in food favoring, toothpastes and mouthwashes, soaps, detergents, and perfumes.[263] Its main active chemical composition is predominantly composed of menthol, menthone, isomentone, methyl acetate, methofuran, limonene, pulegone, eucalyptol and carvone.[232]

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[226] Zhang Y, Wang Y, Zhu X, et al. Antibacterial and antibiofilm activities of eugenol from essential oil of Syzygium aromaticum (L.) Merr. & L. M. Perry (clove) leaf against periodontal pathogen Porphyromonas gingivalis. Microb Pathog. 2017 Dec;113:396-402.
[227] Guimarães Silva Vasconcelos P, Medeiros de Almeida Maia C, Mendes de Vasconcelos V, et al. In vitro inhibition of a multispecies oral cavity biofilm by Syzygium aromaticum essential oil. Gerodontology. 2021 Oct 11.
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Peppermint essential oil has demonstrated antimicrobial activity against cariogenic oral pathogens by inhibiting the growth of *Streptococcus mutans* and *Lactobacillus casei*, *Aggregatibacter actinomycetemcomitans*, and *C. albicans*, and has shown efficacy against multi-drug resistant strains of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (*in vitro* research).[261,264,233]

In vitro experiments also suggest that peppermint essential oil may be considered a safe natural agent in the prevention of dental biofilm formation.[262,234] It has been shown to exert significant antimicrobial effects against *Streptococcus mutans* and *Streptococcus pyogenes*.[262,266] Furthermore, when compared with chlorhexidine, peppermint essential oil significantly decreased bacterial adhesion and reduced bacterial viability in biofilms.[262,266] *In vivo* research shows that peppermint essential oil blended toothpaste is significantly more effective at reducing the formation of biofilms when compared to chlorhexidine.[266]

Safety Summary:
Peppermint essential oil is considered safe, nontoxic and non-irritating.[263] It may occasionally be sensitizing and should not be used on the face of infants and small children.[263] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.[235]

[233] Raghavan R, Devi MPS, Varghese M, et al. Effectiveness of Mentha piperita Leaf Extracts against Oral Pathogens: An in vitro Study. J Contemp Dent Pract. 2018 Sep 1;19(9):1042-1046.
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