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

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Ingredients: Sorbitol, Water, Biocidin (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*)), Vegetable glycerin, Hydrated silica, Sodium Lauroyl Sarcosinate, Tocopherol, Natural organic flavor, Cellulose Gum, Peppermint oil (*Mentha piperita*), Aloe, Cinnamon oil (*Cinnamomum zeylanicum*), Biosecur® (Tangerine fruit extract (*Citrus reticulata*), Bitter orange fruit extract (*Citrus aurantium*), Sweet orange peel extract (*Citrus sinensis*), Ascorbic acid, Citric acid, Lactic Acid), Clove oil (*Syzygium aromaticum*), Tea Tree oil (*Melaleuca alternifolia*).

Sorbitol

Biological 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 as a standard sweetener in numerous pharmaceutical products as well as in sugar-free chewing gums.[3] *Streptococcus mutans*, the major oral bacteria implicated

[1] Toothpaste formulation. The Journal of the American Dental Association. 2001;132(8):1147.
[2] The Lubrizol Corporation. Formulating Toothpaste Using Carbopol® Polymer. Pharmaceutical Bulletin 24 2010; August 11, 2010: https://www.lubrizol.com/-/media/Lubrizol/Health/Literature/Bulletin-24---Formulating-Toothpaste-Using-Carbopol.pdf Accessed October 2021.
[3] Burt BA. The use of sorbitol- and xylitol-sweetened chewing gum in caries control. J Am Dent Assoc. 2006 Feb;137(2):190-6.

in dental caries, cannot use sorbitol for glucan or fructan synthesis, and thus sorbitol has a limited effect on acid production compared to sucrose, glucose, and fructose. Additionally, in the absence of other sugars, sorbitol interrupts biofilms of both *S. mutans* and *Candida albicans*.[4]

Safety Summary:
Sorbitol is considered safe, and has GRAS (Generally Recognized as Safe) status by the Food and Drug Administration (FDA).[3,5] It is included in the FDA Inactive Ingredients Database.[6] 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.[7]

Zeodent® (Dental Hydrated Silica (113-165)

Biological 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.[8] Zeodent® 165 is a dental thickening silica providing both cleaning and whitening performance.[9]

Safety Summary:
Silicon dioxide has a GRAS status by the FDA.[10] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been established during these times.

Sodium Lauroyl Sarcosinate

Biological Actions:
Not applicable.

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[4] Chan A, Ellepola K, Truong T, et al. Inhibitory effects of xylitol and sorbitol on Streptococcus mutans and Candida albicans biofilms are repressed by the presence of sucrose. Arch Oral Biol. 2020 Nov;119:104886.
[5] U.S. Food and Drug Administration. SCOGS (Select Committee on GRAS Substances). Updated 7/31/2020; https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=SCOGS&sort=Sortsubstance&order=ASC&showAll=true&type=basic&search=. Accessed 10/2021.
[6] U.S. Food and Drug Administration. Inactive Ingredient Database. https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm?event=statusByLetter.page&Alpha=SORBITOL Accessed 10/2021.
[7] Pope E, Koren G, Bozzo P. Sugar substitutes during pregnancy. Can Fam Physician. 2014 Nov;60(11):1003-5.
[8] https://products-re.evonik.com/www2/uploads/productfinder/ZEODENT-113-EN.pdf?xd_co_f=MjAzZTZmODUtMWIyZi00MzMxLTlkMjQtZWJiM2NjZTRjMzEz Accessed 11/2021.
[9] https://products-re.evonik.com/www2/uploads/productfinder/ZEODENT-165-EN.pdf?xd_co_f=MjAzZTZmODUtMWIyZi00MzMxLTlkMjQtZWJiM2NjZTRjMzEz Accessed 11/2021.
[10] U.S. Food and Drug Administration. SCOGS (Select Committee on GRAS Substances). 2018; https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=SCOGS&sort=Sortsubstance&order=ASC&showAll=true&type=basic&search=. Accessed 01/02/2018.

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.[11]

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%.[12] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been established during these times.

Tocopherol

Biological Actions:
Antioxidant, preservative.

Scientific Evidence:
Tocopherols (vitamin E) are fat-soluble antioxidants that neutralize reactive oxygen species, specifically by quenching reactive singlet oxygen, hydroxyl radicals, and reactive nitrogen species.[13] These vitamin E isomers provide protection against peroxidation, particularly when combined with other antioxidants such as ascorbic acid. Ascorbic acid returns tocopherols to a reduced state, effectively renewing their antioxidant potential.[14] For this reason, tocopherols are widely used as antioxidants in many pharmaceuticals, cosmetics, natural supplements, etc., acting to preserve the integrity and prevent deterioration of other substances.[15]

Safety Summary:

Safe and well-tolerated, tocopherols have GRAS status and are a common constituent of many foods.[16]

Peppermint Essential Oil (*Mentha piperita*)

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[11] Vranić E, Lacević A, Mehmedagić A, et al. Formulation ingredients for toothpastes and mouthwashes. Bosn J Basic Med Sci. 2004 Oct;4(4):51-8.
[12] Lanigan RS. Final report on the safety assessment of Cocoyl Sarcosine, Lauroyl Sarcosine, Myristoyl Sarcosine, Oleoyl Sarcosine, Stearoyl Sarcosine, Sodium Cocoyl Sarcosinate, Sodium Lauroyl Sarcosinate, Sodium Myristoyl Sarcosinate, Ammonium Cocoyl Sarcosinate, and Ammonium Lauroyl Sarcosinate. Int J Toxicol. 2001;20 Suppl 1:1-14.
[13] Zingg JM. Vitamin E: an overview of major research directions. Mol Aspects Med. 2007 Oct-Dec;28(5-6):400-22.
[14] Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011 Sep 1;51(5):1000-13.
[15] Suárez-Jiménez GM, López-Saiz CM, Ramírez-Guerra HE, et al. Role of Endogenous and Exogenous Tocopherols in the Lipid Stability of Marine Oil Systems: A Review. Int J Mol Sci. 2016 Nov 24;17(12):1968.
[16] http://wayback.archive-it.org/7993/20171031062544/https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/SCOGS/ucm260987.htm Accessed 5/31/2022.

Biological Actions:
Anticariogenic, antimicrobial, antiseptic, antibiofilm.

Scientific Evidence:
Peppermint oil has been extensively used in food favoring, toothpastes and mouthwashes, soaps, detergents and perfumes.[20] Its main active chemical composition is predominantly composed of menthol, menthone, isomentone, methyl acetate, methofuran, limonene, pulegone, eucalyptol and carvone.[17]

Peppermint essential oil has demonstrated antimicrobial activity against cariogenic oral pathogens by inhibiting the growth of *Streptococcus mutans* and *Lactobacillus casei*, *Aggregatibacter actinomycetemcomitans*, and *Candida 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).[18,21,18]

In vitro experiments also suggest that peppermint essential oil may be considered a safe natural agent in the prevention of dental biofilm formation.[19,19] It has been shown to exert significant antimicrobial effects against Streptococcus mutans and Streptococcus pyogenes.[19,23] Furthermore, when compared with chlorhexidine, peppermint essential oil significantly decreased bacterial adhesion and reduced bacterial viability in biofilms.[19,23] *In vivo* research shows that peppermint essential oil blended toothpaste is significantly more effective at reducing the formation of biofilms when compared to chlorhexidine.[23]

Safety Summary:
Peppermint essential oil is considered safe, nontoxic and non-irritating.[20] It may occasionally be sensitizing and should not be used on the face of infants and small children.[20] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been scientifically established during these times.[20]

Tea Tree Essential Oil (*Melaleuca alternifolia*)

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

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[17] Muntean D, Licker M, Alexa E, et al. Evaluation of essential oil obtained from Mentha×piperita L. against multidrug-resistant strains. Infect Drug Resist. 2019 Sep 13;12:2905-2914.
[18] 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.
[19] Shayegh S, Rasooli I, Taghizadeh M, et al. Phytotherapeutic inhibition of supragingival dental plaque. Nat Prod Res. 2008 Mar 20;22(5):428-39.
[20] Natural Medicines Comprehensive Database. Professional Monograph: Peppermint. 2017; http://naturaldatabase.therapeuticresearch.com. Accessed 21/02/2018.

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.[21] 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.[27]

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.[22] 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.[23] 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*.[24] 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).[30]

TTO is effective against numerous oral pathogens, and has demonstrated a reduction in gingival inflammation comparable to chlorhexidine among patients with chronic gingivitis.[26,25,26] 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.[27] 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.[28,29] Antibacterial 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.[30] TTO has

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[21] 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.
[22] 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.
[23] 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.
[24] 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.
[25] 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.
[26] 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.
[27] 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.
[28] 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.
[29] 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.
[30] Groppo FC, Ramacciato JC, Simões RP, et al. Antimicrobial activity of garlic, tea tree oil, and chlorhexidine

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*.[31] TTO has also demonstrated inhibitory activity against the Gram-positive bacillus *Solobacterium moorei*, an oral microbe associated with halitosis.[32]

TTO has also been shown to decolonize and eradicate biofilms from *Staphylococcus aureus* (both coagulase-negative and coagulase-positive strains).[33] 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*.[34,35,36]

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.[37] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[38]

Cinnamon Essential Oil (*Cinnamomum zeylanicum*)

Biological Actions:
Anticariogenic, antimicrobial, antiplaque.

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 flavoring agent. The main active components of cinnamon essential oil include (E & Z) cinnamaldehyde, linalool, eugenol, camphene, cinnamyl acetate, myrcene, limonene, p-Cymene, α-Terpineol.[39] The essential oil is

against oral microorganisms. Int Dent J. 2002 Dec;52(6):433-7.
[31] 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.
[32] Forrer M, Kulik EM, Filippi A, et al. The antimicrobial activity of alpha-bisabolol and tea tree oil against Solobacterium moorei, a Gram-positive bacterium associated with halitosis. Arch Oral Biol. 2013 Jan;58(1):10-6.
[33] 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.
[34] 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.
[35] 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.
[36] 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.
[37] 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.
[38] Natural Standard. Professional Monograph: Tea tree oil (Melaleuca alternifolia). http://www.naturalstandard.net. Accessed December 24th, 2013.
[39] Narayanankutty A, Kunnath K, Alfarhan A, et al. Chemical Composition of Cinnamomum verum Leaf and Flower Essential Oils and Analysis of Their Antibacterial, Insecticidal, and Larvicidal Properties. Molecules. 2021

thought to exert antibacterial activity via disruption of the cellular membrane, resulting in the leakage of intracellular bacterial compounds, and cinnamaldehyde is an inhibitor of amino acid decarboxylase activity.[40]

In vitro research has shown that cinnamon essential oil has antimicrobial activity against planktonic forms of cariogenic bacteria, including *Streptococcus mutans* and *Lactobacillus casei*.[18] Cinnamon has also demonstrated antiplaque activity by inhibiting *Streptococcus mutans* biofilm development, and a patch containing cinnamon essential oil was shown to reduce *Streptococcus mutans* growth in a placebo-controlled pediatric population.[41,42] Toothpastes formulated with cinnamon essential oil have been shown to completely disrupt *Streptococcus mutans* biofilms, with effects similar to chlorhexidine on microbial growth.[43] Other *in vitro* studies show cinnamon oil exhibits antibacterial activity against oral pathogenic bacteria including *Streptococcus mutans, Fusobacterium nucleatum*, *Actinomyces naeslundii*, *Prevotella nigrescens*, 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.[44,45]

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.[45] In therapeutic doses, *Cinnamomum aromaticum* may be hepatotoxic and may inhibit blood clotting due to the coumarin content, but *Cinnamomum zeylanicum* (*verum*) has not shown any hepatotoxicity or anticoagulant effects in clinical safety trials.[46]

Biosecur® Ingredients

Tangerine Fruit Extract (*Citrus reticulata*)

Biological Actions:

Oct 19;26(20):6303.
[40] Alizadeh Behbahani B, Falah F, Lavi Arab F, et al. Chemical Composition and Antioxidant, Antimicrobial, and Antiproliferative Activities of Cinnamomum zeylanicum Bark Essential Oil. Evid Based Complement Alternat Med. 2020 Apr 29;2020:5190603.
[41] Mala N, Sonal S, Kumar A, et al. Cariostatic Efficacy of Cinnamon Water Extract on Streptococcus mutans: An In vitro Study. J Pharm Bioallied Sci. 2021 Jun;13(Suppl 1):S212-S216.
[42] Gandhi HA, Srilatha KT, Deshmukh S, et al. Comparison of Antimicrobial Efficacy of Cinnamon Bark Oil Incorporated and Probiotic Blend Incorporated Mucoadhesive Patch against Salivary Streptococcus mutans in Caries Active 7-10-year-old Children: An In Vivo Study. Int J Clin Pediatr Dent. 2020 Sep-Oct;13(5):543-550.
[43] de Oliveira Carvalho I, Purgato GA, Píccolo MS, et al. In vitro anticariogenic and antibiofilm activities of toothpastes formulated with essential oils. Arch Oral Biol. 2020 Sep;117:104834.
[44] Bardají DK, Reis EB, Medeiros TC, et al. Antibacterial activity of commercially available plant-derived essential oils against oral pathogenic bacteria. Nat Prod Res. 2016;30(10):1178-81.
[45] Neto JGO, Bento-Bernardes T, Pazos-Moura CC, et al. Maternal cinnamon intake during lactation led to visceral obesity and hepatic metabolic dysfunction in the adult male offspring. Endocrine. 2019 Mar;63(3):520-530.
[46] Ranasinghe P, Jayawardena R, Pigera S, et al. Evaluation of pharmacodynamic properties and safety of Cinnamomum zeylanicum (Ceylon cinnamon) in healthy adults: a phase I clinical trial. BMC Complement Altern Med. 2017 Dec 28;17(1):550.

Antimicrobial, antioxidant, preservative.

Scientific Evidence:
Rich in flavonoids, tangerine fruit contains many secondary metabolites with both antioxidant and antimicrobial compounds, including alkaloids, limonoids, flavonoids, anthocyanins, carotenoids, coumarins, phenol acids, etc.[47,48] Tangerine fruit also provides vitamin C, as well as bioflavonoids which improve its bioavailability.[49]

Many compounds found in tangerines, including limonene, linalool, α-terpineol, terpinen-4-ol, α-pinene, β-myrcene, and carvone are thought to have antimicrobial properties as well.[50] When combined with other citrus extracts (Biosecur®), tangerine fruit extract has been shown to have antibacterial activity against *Vibrio vulnificus* comparable to tetracycline, *in vitro*.[51] This combination has also demonstrated *in vitro* efficacy against *S. mutans* biofilms, reducing CFU by ≥5 $\log_{10}$ below the detection limit, comparable to standard treatments (chlorhexidine digluconate (CHX) and cetylpyridinium chloride (CPC)) and substantially greater than all other antimicrobial treatments evaluated. It also demonstrated efficacy against poly-species biofilms containing *Actinomyces naeslundii*, *Actinomyces odontolyticus*, and *Streptococcus mutans*; targeting of bacterial membranes appears to be the mechanism of action, similar to CHX and CPC.[52]

Safety Summary:

Citrus fruit extracts have GRAS status and are considered safe and well-tolerated at the dose recommended.[53]

Bitter orange fruit extract (*Citrus aurantium*)

Biological Actions:
Antimicrobial, antioxidant, preservative.

Scientific Evidence:
Similar to other citrus fruits, bitter orange contains a diverse range of flavonoids and phenolics, including flavones, flavanones, flavonols, and anthocyanins, many of which have antioxidant and

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[47] Rao MJ, Wu S, Duan M, et al. Antioxidant Metabolites in Primitive, Wild, and Cultivated Citrus and Their Role in Stress Tolerance. Molecules. 2021 Sep 24;26(19):5801.
[48] Kumar D, Ladaniya MS, Gurjar M, et al. Quantification of Flavonoids, Phenols and Antioxidant Potential from Dropped Citrus reticulata Blanco Fruits Influenced by Drying Techniques. Molecules. 2021 Jul 8;26(14):4159.
[49] Vinson JA, Bose P. Comparative bioavailability to humans of ascorbic acid alone or in a citrus extract. Am J Clin Nutr. 1988 Sep;48(3):601-4.
[50] Figueira JA, Porto-Figueira P, Pereira JAM, et al. Tangerines Cultivated on Madeira Island-A High Throughput Natural Source of Bioactive Compounds. Foods. 2020 Oct 15;9(10):1470.
[51] Cormier J, Scott R, Janes M. Antibacterial activity of biosecur(®) citrus extract surface cleaner against Vibrio vulnificus. Open Microbiol J. 2013 Nov 8;7:130-4.
[52] Cieplik F, Kara E, Muehler D, et al. Antimicrobial efficacy of alternative compounds for use in oral care toward biofilms from caries-associated bacteria in vitro. Microbiologyopen. 2019 Apr;8(4):e00695.
[53] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=475&sort=GRN_No&order=DESC&startrow=1&type=basic&search=citrus Accessed 6-1-2022.

anti-microbial actions.[54,55] Its broad antioxidant effects have led to widespread use in the medical and food industries.[56] Additionally, a number of anti-inflammatory mechanisms have been identified in bitter orange fruit, at least partly by naringenin and hesperetin.[57]

When combined with other citrus extracts (Biosecur®), bitter orange fruit extract has been shown to have antibacterial activity against *Vibrio vulnificus* comparable to tetracycline, *in vitro*.[59] This combination has also demonstrated *in vitro* efficacy against *S. mutans* biofilms, reducing CFU by ≥5 $\log_{10}$ below the detection limit, comparable to standard treatments (chlorhexidine digluconate (CHX) and cetylpyridinium chloride (CPC)) and substantially greater than all other antimicrobial treatments evaluated. It also demonstrated efficacy against poly-species biofilms containing *Actinomyces naeslundii*, *Actinomyces odontolyticus*, and *Streptococcus mutans*; targeting of bacterial membranes appears to be the mechanism of action, similar to CHX and CPC.[60]

Safety Summary:
Citrus fruit extracts have GRAS status and are considered safe and well-tolerated at the dose recommended.[61]

Sweet orange peel extract (*Citrus sinensis*)

Biological Actions:
Antimicrobial, antioxidant, preservative.

Scientific Evidence:

Sweet orange peels are rich in antioxidants, including carotenoids, vitamin C, and flavonoids, such as flavones, flavanones, chalcones, and dihydrochalcones, catechin, epigallocatechin, vitexin, rutin, luteolin and apigenin.[58] Many phenolics have been identified in orange peels, including gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, caffeic acid and ferulic acid, shown to protect against lipid peroxidation and scavenge activity a range of oxidizing agents.[59]

When combined with other citrus extracts (Biosecur®), sweet orange peel extract has been shown to have antibacterial activity against *Vibrio vulnificus* comparable to tetracycline, *in vitro*.[59] This combination has also demonstrated *in vitro* efficacy against *S. mutans* biofilms, reducing CFU by ≥5 $\log_{10}$ below the detection limit, comparable to standard treatments (chlorhexidine digluconate (CHX) and cetylpyridinium chloride (CPC)) and substantially greater than all other antimicrobial treatments

[54] Zhao HY, Yang L, Wei J, et al. Bioactivity evaluations of ingredients extracted from the flowers of Citrus aurantium L. var. amara Engl. Food Chem. 2012 Dec 15;135(4):2175-81.
[55] Suntar I, Khan H, Patel S, et al. An Overview on Citrus aurantium L.: Its Functions as Food Ingredient and Therapeutic Agent. Oxid Med Cell Longev. 2018 May 2;2018:7864269.
[56] Wang QH, Shu ZP, Xu BQ, et al. Structural characterization and antioxidant activities of polysaccharides from Citrus aurantium L. Int J Biol Macromol. 2014 Jun;67:112-23.
[57] Liu L, Shan S, Zhang K, et al. Naringenin and hesperetin, two flavonoids derived from Citrus aurantium up-regulate transcription of adiponectin. Phytother Res. 2008 Oct;22(10):1400-3.
[58] Montero-Calderon A, Cortes C, Zulueta A, et al. Green solvents and Ultrasound-Assisted Extraction of bioactive orange (Citrus sinensis) peel compounds. Sci Rep. 2019 Nov 6;9(1):16120.
[59] Liew SS, Ho WY, Yeap SK, et al. Phytochemical composition and in vitro antioxidant activities of Citrus sinensis peel extracts. PeerJ. 2018 Aug 3;6:e5331.

evaluated. It also demonstrated efficacy against poly-species biofilms containing *Actinomyces naeslundii*, *Actinomyces odontolyticus*, and *Sterptococcus mutans*; targeting of bacterial membranes appears to be the mechanism of action, similar to CHX and CPC.[60]

Safety Summary:
Orange peel and fruit extracts have GRAS status and are considered safe and well-tolerated at the dose recommended.[60]

Ascorbic acid

Biological Actions:
Antioxidant, preservative (topically).

Scientific Evidence:
Ascorbic acid (vitamin C) is a potent antioxidant, and a prominent ingredient in the food, cosmetic and pharmaceutical fields. It has been shown to prevent lipid peroxidation, reduce unstable species of oxygen, nitrogen and sulfur, as well as regenerate other antioxidants such as tocopherol (Vitamin E).[61] It may also play a role in dental caries prevention and periodontal disease; salivary levels of vitamin C have been inversely correlated with caries activity, and it has been shown to have antimicrobial activity against oral microbial growth, with bactericidal and anti-biofilm activity against *Streptocuccus mutans*.[62,63,64]

Safety Summary:
Safe and well-tolerated, vitamin C has GRAS status and is a common constituent of many foods.[65]

Citric acid

Biological Actions:
Preservative.

Scientific Evidence:
Citric acid is a tricarboxylic acid, ubiquitous in the natural world and an intermediate in the Kreb's (tricarboxylic acid) cycle which generates cellular energy through carbohydrate metabolism. It is widely used in the food and preservative industries, in part for its pH buffering and emulsifying properties. It also is used as a synergist, improving the stability of primary oxidants by acidifying the

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[60] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&sort=GRN_No&order=DESC&startrow=1&type=basic&search=orange Accessed 6-1-2022.
[61] Caritá AC, Fonseca-Santos B, Shultz JD, et al. Vitamin C: One compound, several uses. Advances for delivery, efficiency and stability. Nanomedicine. 2020 Feb;24:102117.
[62] Eydou Z, Jad BN, Elsayed Z, et al. Investigation on the effect of vitamin C on growth & biofilm-forming potential of Streptococcus mutans isolated from patients with dental caries. BMC Microbiol. 2020 Jul 30;20(1):231.
[63] Tada A, Miura H. The Relationship between Vitamin C and Periodontal Diseases: A Systematic Review. Int J Environ Res Public Health. 2019 Jul 11;16(14):2472.
[64] Murererehe J, Uwitonze AM, Nikuze P, et al. Beneficial Effects of Vitamin C in Maintaining Optimal Oral Health. Front Nutr. 2022 Jan 10;8:805809.
[65] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=769&sort=GRN_No&order=DESC&startrow=1&type=basic&search=vitamin%20c Accessed 6-1-2022.

medium.[66]

Safety Summary:
Safe and well-tolerated, citric acid esters are widely used in the food industry and have GRAS status.[67]

Lactic Acid

Biological Actions:
Preservative.

Scientific Evidence:
Lactic acid is widely used in the food industry and is the most widely occurring organic acid in nature. It is primarily used as a pH-adjusting agent and as a preservative, and has humectant properties, which help to limit microbial growth.[75,68,69]

Safety Summary:
Safe and well-tolerated, lactic acid has FDA GRAS status.[70]

Clove Essential Oil (*Syzygium aromaticum*)

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

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.[82]

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 plasmatic 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

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[66] Quitmann H, Fan R, Czermak P. Acidic organic compounds in beverage, food, and feed production. Adv Biochem Eng Biotechnol. 2014;143:91-141.
[67] https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=222&sort=GRN_No&order=DESC&startrow=1&type=basic&search=citric%20acid Accessed 6-1-2022.
[68] Wee YJ, Kim JN, Ryu HW. Biotechnological production of lactic acid and its recent applications. Food Technol Biotechnol. 2006 44:163–172
[69] Ameen, Sara & Caruso, Giorgia. (2017). Lactic Acid in the Food Industry.
[70] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=184.1061 Accessed 6-1-2022.

related to the biofilm of *Porphyromonas gingivalis*.[71] Clove oil has also demonstrated antifungal effects, and the ability to inhibit biofilms formed by multiple species of *Candida* extracted from human saliva.[72] Toothpastes formulated with clove essential oil were also shown to completely disrupt *Streptococcus mutans* biofilms *in vitro*.[50]

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.[80,73] 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.[45]

Safety Summary:
Clove essential oil is considered safe at the dose recommended. In sensitive individuals, the oil may cause dermal irritation.[74] 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.[75]

Aloe Vera (*Aloe barbadensis*)

Biological Actions:
Antifungal, anti-inflammatory, antimicrobial, antioxidant, antiviral, demulcent, emollient, immune enhancing, vulnerary, antibiofilm.

Scientific Evidence:
The parenchymatous cells of aloe vera leaves secrete a mucilaginous gel containing 98-99% water and 1-2% active compounds.[76] The key phytochemical compounds of aloe gel include

[71] 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.
[72] 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.
[73] Moon SE, Kim HY, Cha JD. Synergistic effect between clove oil and its major compounds and antibiotics against oral bacteria. Arch Oral Biol. 2011 Sep;56(9):907-16.
[74] de Groot AC, Schmidt E. Essential Oils, Part IV: Contact Allergy. Dermatitis. 2016 Jul-Aug;27(4):170-5.
[75] Natural Medicines Comprehensive Database. Professional Monograph: Clove. 2013; http://naturaldatabase.therapeuticresearch.com. Accessed 02/02/2017.
[76] Nair GR, Naidu GS, Jain S, et al. Clinical Effectiveness of Aloe Vera in the Management of Oral Mucosal Diseases- A Systematic Review. J Clin Diagn Res. 2016 Aug;10(8):ZE01-7.

anthraquinones (aloin and emodin), enzymes (catalase, amylase), fatty acids (lupeol and campesterol), polysaccharides (glucomannans) and glycoproteins.[77] Aloe resin, the solid residue obtained from the latex, consists of mainly hydroxyanthracene derivatives, as well as antioxidants and other polyphenols.[78] The antimicrobial effects of aloe vera contributing to its benefits in dental care have been attributed to the natural anthraquinones found in the plant.[79]

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 aphthous ulcers.[80,81]

In a clinical trial, aloe vera-containing toothpaste demonstrated efficacy in reducing plaque, gingivitis, and overall *Candida* counts when compared to triclosan-containing toothpaste. In addition, individuals treated with aloe vera experienced improved oral health status without any adverse side effects.[82] In another study, the use of toothpaste containing aloe vera demonstrated statistically and clinically significant reductions in plaque and gingivitis compared to baseline values.[83] In a third clinical trial, aloe vera–containing toothpaste showed significant improvements in gingival and plaque index scores and a reduction of microbiologic counts when compared with placebo.[84]

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 fewer side effects when compared to placebo.[85,86,87]

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[77] Sánchez M, González-Burgos E, Iglesias I, et al. Pharmacological Update Properties of Aloe Vera and its Major Active Constituents. Molecules. 2020 Mar 13;25(6):1324.
[78] Añibarro-Ortega M, Pinela J, Barros L, et al. Compositional Features and Bioactive Properties of Aloe vera Leaf (Fillet, Mucilage, and Rind) and Flower. Antioxidants (Basel). 2019 Oct 1;8(10):444.
[79] George D, Bhat SS, Antony B. Comparative evaluation of the antimicrobial efficacy of aloe vera tooth gel and two popular commercial toothpastes: an in vitro study. Gen Dent. 2009 May-Jun;57(3):238-41.
[80] Mangaiyarkarasi SP, Manigandan T, Elumalai M, et al. Benefits of Aloe vera in dentistry. J Pharm Bioallied Sci. 2015 Apr;7(Suppl 1):S255-9.
[81] Neena IE, Ganesh E, Poornima P, et al. An ancient herb aloevera in dentistry: A review. J Oral Res Rev 2015;7:25-30
[82] Khatri SG, Samuel SR, Acharya S, et al. Antiplaque, Antifungal Effectiveness of Aloe vera Among Intellectually Disabled Adolescents: Pilot Study. Pediatr Dent. 2017 Nov 1;39(7):434-438.
[83] Namiranian H, Serino G. The effect of a toothpaste containing aloe vera on established gingivitis. Swed Dent J. 2012;36(4):179-85.
[84] Pradeep AR, Agarwal E, Naik SB. Clinical and microbiologic effects of commercially available dentifrice containing aloe vera: a randomized controlled clinical trial. J Periodontol. 2012 Jun;83(6):797-804.
[85] Gupta RK, Gupta D, Bhaskar DJ, et al. Preliminary antiplaque efficacy of aloe vera mouthwash on 4 day plaque re-growth model: randomized control trial. Ethiopian journal of health sciences. 2014;24(2):139-144.
[86] Chhina S, Singh A, Menon I, et al. A randomized clinical study for comparative evaluation of Aloe Vera and 0.2% chlorhexidine gluconate mouthwash efficacy on de-novo plaque formation. J Int Soc Prev Community Dent. 2016 May-Jun;6(3):251-5.
[87] Vangipuram S, Jha A, Bhashyam M. Comparative efficacy of aloe vera mouthwash and chlorhexidine on periodontal health: A randomized controlled trial. J Clin Exp Dent. 2016 Oct 1;8(4):e442-e447.

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.[88] *In vitro* research also shows that aloe vera gel has significant antibacterial properties against *Actinobacillus actinomycetemcomitans*, *Clostridium bacilli*, *Streptococcus mutans* and *Staphylococcus aureus* at 100% and 50% concentrations.[89] 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*).[90] Additionally, aloe vera extracts have demonstrated an ability to inhibit biofilm formation and growth of multiple methicillin resistant *Staphylococcus aureus* strains, *in vitro*.[91]

Safety Summary:
Contraindicated in persons with a known hypersensitivity to aloe.[92] Considered safe and well tolerated when used topically, with no known interactions.[89] No adverse effects expected during pregnancy and breastfeeding with topical use.[89]

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,

[88] George D, Bhat SS, Antony B. Comparative evaluation of the antimicrobial efficacy of aloe vera tooth gel and two popular commercial toothpastes: an in vitro study. Gen Dent. 2009 May-Jun;57(3):238-41.
[89] Jain S, Rathod N, Nagi R., et al. Antibacterial Effect of Aloe Vera Gel against Oral Pathogens: An In-vitro Study. J Clin Diagn Res. 2016 Nov;10(11):ZC41-ZC44.
[90] Fani M, Kohanteb J. Inhibitory activity of Aloe vera gel on some clinically isolated cariogenic and periodontopathic bacteria. J Oral Sci. 2012 Mar;54(1):15-21.
[91] Saddiq AA, Al-Ghamdi H. Aloe vera extract: A novel antimicrobial and antibiofilm against methicillin resistant Staphylococcus aureus strains. Pak J Pharm Sci. 2018 Sep;31(5(Supplementary)):2123-2130.
[92] Ferreira M, Teixeira M, Silva E, et al. Allergic contact dermatitis to Aloe vera. Contact Dermatitis. 2007 Oct;57(4):278-9.

including catalase and superoxide dismutase.[93,94]

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.*[95,96,97,98,99,100,101] 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.[102] 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*.[103]

Safety Summary:

Considered safe at the recommended dose.[109] No adverse effects expected during pregnancy and breastfeeding.[110]

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

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[93] 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.

[94] Khoo HE, Azlan A, Tang ST, et al. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res. 2017 Aug 13;61(1):1361779.

[95] Huttunen S, Toivanen M, Arkko S, et al. Inhibition activity of wild berry juice fractions against Streptococcus pneumoniae binding to human bronchial cells. Phytother Res. 2011 Jan;25(1):122-7.

[96] Toivanen M, Ryynänen A, Huttunen S, et al. Binding of Neisseria meningitidis pili to berry polyphenolic fractions. J Agric Food Chem. 2009 Apr 22;57(8):3120-7.

[97] Puupponen-Pimiä R, Nohynek L, Alakomi HL, et al. The action of berry phenolics against human intestinal pathogens. Biofactors. 2005;23(4):243-51.

[98] 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.

[99] 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.

[100] Puupponen-Pimiä R, Nohynek L, Alakomi HL, et al. Bioactive berry compounds-novel tools against human pathogens. Appl Microbiol Biotechnol. 2005 Apr;67(1):8-18.

[101] Chatterjee A, Yasmin T, Bagchi D, et al. Inhibition of Helicobacter pylori in vitro by various berry extracts, with enhanced susceptibility to clarithromycin. Mol Cell Biochem. 2004 Oct;265(1-2):19-26.

[102] Hair R, Sakaki JR, Chun OK. Anthocyanins, Microbiome and Health Benefits in Aging. Molecules. 2021 Jan 21;26(3):537.

[103] Riihinen K, Ryynänen A, Toivanen M, et al. Antiaggregation potential of berry fractions against pairs of Streptococcus mutans with Fusobacterium nucleatum or Actinomyces naeslundii. Phytother Res. 2011 Jan;25(1):81-7.

antioxidant and anti-inflammatory properties.[104] 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.[105,106,107] *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.[108]

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.[109] 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.[110,111]

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 aureus*, *Escherichia coli*, *Salmonella* and *Shigella*.[112,113] Noni has also been shown to inhibit the activity of enterohemorrhagic *Escherichia coli* (0157) and *Helicobacter pylori*.[114,115]

Noni has demonstrated antifungal activity against *Candida albicans* in a dose dependent

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[104] Inada AC, Figueiredo PS, Santos-Eichler RAD, et al. Morinda citrifolia Linn. (Noni) and Its Potential in Obesity-Related Metabolic Dysfunction. Nutrients. 2017 May 25;9(6):540.
[105] West BJ, Deng S, Uwaya A, et al. Iridoids are natural glycation inhibitors. Glycoconj J. 2016 Aug;33(4):671-81.
[106] Wang MY, Peng L, Weidenbacher-Hoper V, et al. Noni juice improves serum lipid profiles and other risk markers in cigarette smokers. ScientificWorldJournal. 2012;2012:594657.
[107] Wang MY, Peng L, Jensen CJ, et al. Noni juice reduces lipid peroxidation-derived DNA adducts in heavy smokers. Food Sci Nutr. 2013 Mar;1(2):141-9.
[108] Serafini MR, Santos RC, Guimaraes AG, et al. Morinda citrifolia Linn leaf extract possesses antioxidant activities and reduces nociceptive behavior and leukocyte migration. J Med Food. Oct 2011;14(10):1159- 1166.
[109] Dussaussoy E, Brat P, Bony E, et al. Characterization, anti-oxidative and anti-inflammatory effects of Costa Rican noni juice (Morinda citrifolia L.). J Ethnopharmacol. Jan 7 2011;133(1):108-115.
[110] Garcia-Vilas JA, Medina MA, Melo FR, et al. Damnacanthal inhibits IgE receptor-mediated activation of mast cells. Mol Immunol. 2015 May;65(1):86-93.
[111] Kim MH, Jeong HJ. Damnacanthal inhibits the NF-κB/RIP-2/caspase-1 signal pathway by inhibiting p56lck tyrosine kinase. Immunopharmacol Immunotoxicol. 2014 Oct;36(5):355-63.
[112] 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.
[113] Wang MY, West BJ, Jensen CJ, et al. Morinda citrifolia (Noni): a literature review and recent advances in Noni research. Acta Pharmacol Sin. Dec 2002;23(12):1127-1141.
[114] Huang HL, Ko CH, Yan YY, et al. Antiadhesion and anti-inflammation effects of noni (Morinda citrifolia) fruit extracts on AGS cells during Helicobacter pylori infection. J Agric Food Chem. 2014 Mar 19;62(11):2374-83.
[115] Duncan SH, Flint HJ, Stewart CS. Inhibitory activity of gut bacteria against Escherichia coli O157 mediated by dietary plant metabolites. FEMS Microbiol Lett. Jul 15 1998;164(2):283-288.

manner.[116,117] 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*.[118] 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.*[119]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[111,120] No adverse effects expected during pregnancy and breastfeeding.[111,121]

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.[109] 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.[122] In addition to direct anti-bacterial action, silymarin has also been shown to inhibit the adherence and formation of bacterial biofilms. [123] 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.[124]

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[116] Jainkittivong A, Butsarakamruha T, Langlais RP. Antifungal activity of Morinda citrifolia fruit extract against Candida albicans. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Sep;108(3):394-8.
[117] Barani K, Manipal S, Prabu D, et al. Anti-fungal activity of Morinda citrifolia (noni) extracts against Candida albicans: an in vitro study. Indian J Dent Res. 2014 Mar-Apr;25(2):188-90.
[118] Banerjee S, Johnson AD, Csiszar K, et al. An extract of Morinda citrifolia interferes with the serum-induced formation of filamentous structures in Candida albicans and inhibits germination of Aspergillus nidulans. Am J Chin Med. 2006;34(3):503-9.
[119] Kumarasamy B, Manipal S, Duraisamy P, et al. Role of aqueous extract of morinda citrifolia (Indian noni) ripe fruits in inhibiting dental caries-causing streptococcus mutans and streptococcus mitis. J Dent (Tehran). 2014 Nov;11(6):703-10.
[120] West BJ, White LD, Jensen CJ, Palu AK. A double-blind clinical safety study of noni fruit juice. Pac Health Dialog. 2009 Nov;15(2):21-32.
[121] Wang MY, Hurn J, Peng L, et al. A multigeneration reproductive and developmental safety evaluation of authentic Morinda citrifolia (noni) juice. J Toxicol Sci. 2011 Jan;36(1):81-5.
[122] Lee DG, Kim HK, Park Y, Park SC, Woo ER, Jeong HG, Hahm KS. Gram-positive bacteria specific properties of silybin derived from Silybum marianum. Arch Pharm Res. 2003 Aug;26(8):597-600.
[123] 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.
[124] Janeczko M, Kochanowicz E. Silymarin, a Popular Dietary Supplement Shows Anti-Candida Activity. Antibiotics (Basel). 2019 Oct 31;8(4):206.

Silibinin (an equal extract of silybin A and silybin B) has demonstrated antibacterial activity against methicillin-resistant strains of *Staphylococcus aureus*.[109,125] 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).[126] 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.[127,128] Silymarin has also demonstrated antiviral activity against influenza A/PR/8/34 virus when compared with the pharmaceutical agent Oseltamivir (98% vs. 52% respectively).[129] Its ability to suppress cellular inflammation, including inhibition of mTOR, may partly explain its immunomodulating effects.[130,131]

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.[132,133,134]

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

Biological Actions:

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

Scientific Evidence:

Echinacea possesses both anti-inflammatory and immuno-stimulating properties.[135]

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[125] Kang HK, Kim HY, Cha JD. Synergistic effects between silibinin and antibiotics on methicillin-resistant Staphylococcus aureus isolated from clinical specimens. Biotechnol J. 2011 Nov;6(11):1397-408.
[126] Wang X, Zhang Z, Wu SC. Health Benefits of Silybum marianum: Phytochemistry, Pharmacology, and Applications. J Agric Food Chem. 2020 Oct 21;68(42):11644-11664.
[127] Cwikla C, Schmidt K, Matthias A, et al. Investigations into the antibacterial activities of phytotherapeutics against Helicobacter pylori and Campylobacter jejuni. Phytother Res. 2010 May;24(5):649-56.
[128] Olías-Molero AI, Jiménez-Antón MD, Biedermann D, et al. In-Vitro Activity of Silybin and Related Flavonolignans against Leishmania infantum and L. donovani. Molecules. 2018 Jun 27;23(7):1560.
[129] Song JH, Choi HJ. Silymarin efficacy against influenza A virus replication. Phytomedicine. Jul 15 2011;18(10):832-835.
[130] Lovelace ES, Wagoner J, MacDonald J, et al. Silymarin Suppresses Cellular Inflammation By Inducing Reparative Stress Signaling. J Nat Prod. 2015 Aug 28;78(8):1990-2000.
[131] Lovelace ES, Maurice NJ, Miller HW, et al. Silymarin suppresses basal and stimulus-induced activation, exhaustion, differentiation, and inflammatory markers in primary human immune cells. PLoS One. 2017 Feb 3;12(2):e0171139.
[132] Mills S, Bone K. The Essential Guide to Herbal Safety. Philadelphia, U.S.A.: Churchill Livingstone; 2005.
[133] Barbosa CC, Nishimura AN, Santos MLD, et al. Silymarin administration during pregnancy and breastfeeding: evaluation of initial development and adult behavior of mice. Neurotoxicology. 2020 May;78:64-70.
[134] Abenavoli L, Capasso R, Milic N, et al. Milk thistle in liver diseases: past, present, future. Phytother Res. 2010 Oct;24(10):1423-32.
[135] Gan XH, Zhang L, Heber D, et al. Mechanism of activation of human peripheral blood NK cells at the single cell level by Echinacea water soluble extracts: recruitment of lymphocyte-target conjugates and killer cells and activation of programming for lysis. Int Immunopharmacol. Jun 2003;3(6):811-824.

Alkylamides, one 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.[136]

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*.[137,138] 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.[139]

Safety Summary:

Contraindicated in persons allergic to plants from the Compositae aka (Asteraceae family).[110] Exercise caution with patients taking immunosuppressant medications (short term use only).[110] No other known warnings, precautions or contraindications.[140] No adverse effects expected during pregnancy and breastfeeding.[110,161,141]

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.[110,163] Goldenseal leaves are also rich in flavonoids; two of which (6,8-di-C-methylluteolin 7-methyl ether and 6-C-methylluteolin 7-methyl ether) have demonstrated antibacterial activity against the oral pathogens *Streptococcus mutans* and *Fusobacterium nucleatum*, while others (specifically sideroxylon, 8-desmethyl-sideroxylon and 6-desmethyl-sideroxylin) don't appear directly

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[136] Gulledge TV, Collette NM, Mackey E, et al. Mast cell degranulation and calcium influx are inhibited by an Echinacea purpurea extract and the alkylamide dodeca-2E,4E-dienoic acid isobutylamide. J Ethnopharmacol. 2018 Feb 15;212:166-174.
[137] Hudson JB. Applications of the phytomedicine Echinacea purpurea (Purple Coneflower) in infectious diseases. J Biomed Biotechnol. 2012;2012:769896.
[138] Sharifi-Rad M, Mnayer D, Morais-Braga MFB, et al. Echinacea plants as antioxidant and antibacterial agents: From traditional medicine to biotechnological applications. Phytother Res. 2018 Sep;32(9):1653-1663.
[139] Sterer N, Rubinstein Y. Effect of various natural medicinals on salivary protein putrefaction and malodor production. Quintessence Int. 2006 Sep;37(8):653-8.
[140] Ardjomand-Woelkart K, Bauer R. Review and Assessment of Medicinal Safety Data of Orally Used Echinacea Preparations. Planta Med. 2016 Jan;82(1-2):17-31.
[141] Perri D, Dugoua JJ, Mills E, et al. Safety and efficacy of echinacea (Echinacea angustafolia, e. purpurea and e. pallida) during pregnancy and lactation. Can J Clin Pharmacol. 2006 Fall;13(3):e262-7.

antibacterial, but instead enhance the action of berberine by acting as efflux pump inhibitors.[142] 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.[143] In one *in vitro* study, inhibition of the efflux pump allowed a much greater intracellular concentration of berberine, potentiating its antibiotic activity 500-fold against some organisms, indicating the importance of the synergistic interactions among Goldenseal's constituents.[144]

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*, *Mycoplasma mycoides capri*, *Escherichia coli*, *Neisseria gonorrhoeae* isolates (including antibiotic-resistant strains), *Campylobacter jejuni, Vibrio cholera* and *Helicobacter pylori*.[145,146,147,148,149] Berberine, as part of quadruple therapy, has been found to be non-inferior to bismuth for the eradication of *Helicobacter pylori* in a phase 4 trial.[150] One of the key mechanisms by which goldenseal inhibits microbial growth is through quenching of the *agr* quorum sensing (QS) system.[151] 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.[152] 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.[153]

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

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[142] Hwang BY, Roberts SK, Chadwick LR, et al. Antimicrobial constituents from goldenseal (the Rhizomes of Hydrastis canadensis) against selected oral pathogens. Planta Med. 2003 Jul;69(7):623-7.
[143] Junio HA, Sy-Cordero AA, Ettefagh KA, et al. Synergy-directed fractionation of botanical medicines: a case study with goldenseal (Hydrastis canadensis). J Nat Prod. 2011 Jul 22;74(7):1621-9.
[144] Tegos G, Stermitz FR, Lomovskaya O, et al. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. Antimicrob Agents Chemother. 2002 Oct;46(10):3133-41.
[145] Cwikla C, Schmidt K, Matthias A, et al. Investigations into the antibacterial activities of phytotherapeutics against Helicobacter pylori and Campylobacter jejuni. Phytother Res. 2010 May;24(5):649-56.
[146] Scazzocchio F, Cometa MF, Tomassini L, et al. Antibacterial activity of Hydrastis canadensis extract and its major isolated alkaloids. Planta Med. 2001 Aug;67(6):561-4.
[147] Arjoon AV, Saylor CV, May M. In Vitro efficacy of antimicrobial extracts against the atypical ruminant pathogen Mycoplasma mycoides subsp. capri. BMC Complement Altern Med. 2012 Oct 2;12:169.
[148] Cybulska P, Thakur SD, Foster BC, et al. Extracts of Canadian first nations medicinal plants, used as natural products, inhibit neisseria gonorrhoeae isolates with different antibiotic resistance profiles. Sex Transm Dis. 2011 Jul;38(7):667-71.
[149] Wang X, Yao X, Zhu Z, et al. Effect of berberine on Staphylococcus epidermidis biofilm formation. Int J Antimicrob Agents. 2009 Jul;34(1):60-6.
[150] Zhang D, Ke L, Ni Z, et al. Berberine containing quadruple therapy for initial Helicobacter pylori eradication: An open-label randomized phase IV trial. Medicine (Baltimore). 2017 Aug;96(32):e7697.
[151] Cech NB, Junio HA, Ackermann LW, et al. Quorum quenching and antimicrobial activity of goldenseal (Hydrastis canadensis) against methicillin-resistant Staphylococcus aureus (MRSA). Planta Med. 2012 Sep;78(14):1556-61.
[152] Rutherford ST, Bassler BL. Bacterial quorum sensing: its role in virulence and possibilities for its control. Cold Spring Harb Perspect Med. 2012 Nov 1;2(11):a012427.
[153] Xu C, Wang F, Huang F, et al. Targeting effect of berberine on type I fimbriae of Salmonella Typhimurium and its effective inhibition of biofilm. Appl Microbiol Biotechnol. 2021 Feb;105(4):1563-1573.

was able to reduce biofilm formation of pathogenic *Candida albicans*.[154] *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*.[163] 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.[155] *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*.[163] Multiple mechanisms of action have been documented for 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.[156]

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*.[157] 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*.[158]

Safety Summary:

No known warnings, precautions or contraindications when used topically at the recommended dose.[110] Contraindicated during pregnancy in therapeutic doses.[111] Discouraged during breastfeeding in therapeutic doses.[109]

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,

[154] Wei GX, Xu X, Wu CD. In vitro synergism between berberine and miconazole against planktonic and biofilm Candida cultures. Arch Oral Biol. 2011 Jun;56(6):565-72.
[155] da Silva AR, de Andrade Neto JB, da Silva CR, et al. Berberine Antifungal Activity in Fluconazole-Resistant Pathogenic Yeasts: Action Mechanism Evaluated by Flow Cytometry and Biofilm Growth Inhibition in Candida spp. Antimicrob Agents Chemother. 2016 May 23;60(6):3551-7.
[156] Saha P, Bhattacharjee S, Sarkar A, et al. Berberine chloride mediates its anti-leishmanial activity via differential regulation of the mitogen activated protein kinase pathway in macrophages. PLoS One. 2011 Apr 5;6(4):e18467.
[157] Hwang BY, Roberts SK, Chadwick LR, et al. Antimicrobial constituents from goldenseal (the Rhizomes of Hydrastis canadensis) against selected oral pathogens. Planta Med. 2003 Jul;69(7):623-7.
[158] Xie Q, Johnson BR, Wenckus CS, et al. Efficacy of berberine, an antimicrobial plant alkaloid, as an endodontic irrigant against a mixed-culture biofilm in an in vitro tooth model. J Endod. 2012 Aug;38(8):1114-7.

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*.[159,160,161,162] One mechanism of action for this antibacterial activity is protein leakage following destruction of the bacterial cell membrane.[163]

Shiitake mushroom extracts have also demonstrated anti-biofilm activity against oral pathogens, including *Streptococcus mutans* and *Actinomyces naeslundii.*[164] 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.[165,166]

Shiitake has also displayed antifungal activity against the following microbes; *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Scedosporium apiospermum*.[182] Unlike antibiotics, the probiotic strains *Bifidobacterium* and *Lactobacillus spp* were not affected by the antimicrobial activities of shiitake mushroom.[185]

Safety Summary:

Considered safe and well tolerated at doses of up to 2.5mg Lentinex per day for 6 weeks.[167] 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.[168] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[169]

White willow bark (*Salix alba*)

[159] Hearst R, Nelson D, McCollum G, et al. An examination of antibacterial and antifungal properties of constituents of Shiitake (Lentinula edodes) and oyster (Pleurotus ostreatus) mushrooms. Complement Ther Clin Pract. 2009 Feb;15(1):5-7.
[160] Rao JR, Smyth TJ, Millar BC, et al. Antimicrobial properties of shiitake mushrooms (Lentinula edodes). Int J Antimicrob Agents. 2009 Jun;33(6):591-2.
[161] 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.
[162] Kuznetsov OIu, Mil'kova EV, Sosnina AE, et al. [Antimicrobial action of Lentinus edodes juice on human microflora]. Zh Mikrobiol Epidemiol Immunobiol. 2005 Jan-Feb;(1):80-2.
[163] 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.
[164] 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.
[165] Avinash J, Vinay S, Jha Ket al. The Unexplored Anticaries Potential of Shiitake Mushroom. Pharmacogn Rev. 2016 Jul-Dec;10(20):100-104.
[166] Lingström P, Zaura E, Hassan H, et al. The anticaries effect of a food extract (shiitake) in a short-term clinical study. J Biomed Biotechnol. 2012;2012:217164.
[167] 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.
[168] Spierings EL, Fujii H, Sun B, et al. A Phase I study of the safety of the nutritional supplement, active hexose correlated compound, AHCC, in healthy volunteers. J Nutr Sci Vitaminol (Tokyo). 2007 Dec;53(6):536-9.
[169] Natural Medicines Comprehensive Database. Shitake Mushroom Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed December 22nd, 2013.

Biological Actions: Analgesic, anti-inflammatory.

Scientific Evidence:

The key active constituents of white willow bark are comprised of phenolic glycosides including the salicylates salicortin and salicin.[109] However, an analysis of white willow bark revealed at least 16 other important compounds, including the flavonoids naringenin and isosalipurpuroside (also known as eriodictyol), condensed tannins, catechin, amelopsin, taxifolin, 7-O-methyltaxifolin-3'-O-glucoside, and 7-O-methyltaxifolin.[170,171,172,173] Initially it was thought that salicin (converted to salicylic acid *in vivo*) was responsible for the anti-inflammatory effects of this herb.[194] 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.[174] Unlike NSAIDs, white willow bark is not associated with unwanted side effects of gastric erosion.[195]

The synergistic effect of the salicylates, flavonoids and tannins found in white willow bark have been shown to inhibit COX-2 and subsequent generation of free radicals by converting arachidonic acid to prostaglandins.[175] *In vitro* studies assessing LPS activated monocytes show that *Salix alba* is able to block nitric oxide release and reduce IL-6 and TNF α production.[194,176] While the underlying mechanisms have not been fully elucidated, white willow bark appears to induce monocyte apoptosis and block NF-κB activation.[194,195] This multifactorial effect is thought to be an innate protective mechanism to control local and systemic inflammatory responses in the body.[194] An antioxidant effect was also recently documented for salicin specifically, mediated in part by activation of the PI3K/Akt/GSK3β pathway, which plays a role in cellular protection, particularly against ischemic injury.[177]

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[170] Pobłocka-Olech L, van Nederkassel AM, Vander Heyden Y, et al. Chromatographic analysis of salicylic compounds in different species of the genus Salix. J Sep Sci. 2007 Nov;30(17):2958-66.
[171] Bonaterra GA, Heinrich EU, Kelber O, et al. Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv(®)) in LPS-activated human monocytes and differentiated macrophages. Phytomedicine. 2010 Dec 1;17(14):1106-13.
[172] Bonaterra GA, Kelber O, Weiser D, et al. In vitro anti-proliferative effects of the willow bark extract STW 33-I. Arzneimittelforschung. 2010;60(6):330-5.
[173] Agnolet S, Wiese S, Verpoorte R, et al. Comprehensive analysis of commercial willow bark extracts by new technology platform: combined use of metabolomics, high-performance liquid chromatography-solid-phase extraction-nuclear magnetic resonance spectroscopy and high-resolution radical scavenging assay. J Chromatogr A. 2012 Nov 2;1262:130-7.
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[176] Drummond EM, Harbourne N, Marete E, et al. Inhibition of proinflammatory biomarkers in THP1 macrophages by polyphenols derived from chamomile, meadowsweet and willow bark. Phytother Res. 2013 Apr;27(4):588-94.
[177] Park JH, Lee TK, Kim DW, et al. Neuroprotective Effects of Salicin in a Gerbil Model of Transient Forebrain Ischemia by Attenuating Oxidative Stress and Activating PI3K/Akt/GSK3β Pathway. Antioxidants (Basel). 2021 Apr 20;10(4):629.

Safety Summary:

Contraindicated in people with salicylate sensitivity.[197] Children under age 16 should not consume white willow bark to avoid Reye syndrome.[197] No other known warnings, precautions or contraindications at the dose recommended.[111] Should be avoided during pregnancy/lactation.[178]

Garlic (*Allium sativum*)

Biological Actions:

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).[179] 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.[202]

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*.[202,180] 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.[181] 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

[178] Oketch-Rabah HA, Marles RJ, Jordan SA, et al. United States Pharmacopeia Safety Review of Willow Bark. Planta Med. 2019 Nov;85(16):1192-1202.
[179] El-Saber Batiha G, Magdy Beshbishy A, G Wasef L, et al. Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review. Nutrients. 2020 Mar 24;12(3):872.
[180] Wallock-Richards D, Doherty CJ, et al. Garlic revisited: antimicrobial activity of allicin-containing garlic extracts against Burkholderia cepacia complex. PLoS One. 2014 Dec 1;9(12):e112726.
[181] Müller A, Eller J, Albrecht F, et al. Allicin Induces Thiol Stress in Bacteria through S-Allylmercapto Modification of Protein Cysteines. J Biol Chem. 2016 May 27;291(22):11477-90.

resistance.[182,183] 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.[184,185] 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.[186] 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).[205] Allicin also has an extensive number of bacterial and fungal pathogens for which it acts synergistically against when coupled with other antibiotics.[187]

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.[202] 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.[202]

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.[188] 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.[189,190] 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

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[182] Jakobsen TH, van Gennip M, Phipps RK, et al. Ajoene, a sulfur-rich molecule from garlic, inhibits genes controlled by quorum sensing. Antimicrob Agents Chemother. 2012 May;56(5):2314-25.
[183] Nadell CD, Xavier JB, Levin SA, et al. The evolution of quorum sensing in bacterial biofilms. PLoS Biol. 2008 Jan;6(1):e14.
[184] Naganawa R, Iwata N, Ishikawa K, et al. Inhibition of microbial growth by ajoene, a sulfur-containing compound derived from garlic. Appl Environ Microbiol. 1996 Nov;62(11):4238-42.
[185] 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.
[186] 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.
[187] 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.
[188] 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.
[189] Chavan SD, Shetty NL, Kanuri M. Comparative evaluation of garlic extract mouthwash and chlorhexidine mouthwash on salivary Streptococcus mutans count - an in vitro study. Oral Health Prev Dent. 2010;8(4):369-74.
[190] Houshmand B, Mahjour F, Dianat O. Antibacterial effect of different concentrations of garlic (Allium sativum) extract on dental plaque bacteria. Indian J Dent Res. 2013 Jan-Feb;24(1):71-5.

anti-proteolytic activity and by inhibiting total protease activity.[191,192]

Other *in vitro* experiments using crude garlic extract show that it possesses greater antibacterial activity against *Streptococcus mutans* than chlorhexidine.[193] 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.[194] Garlic has also demonstrated activity against pathological strains isolated from periodontal and dental caries including *Staphylococcus aureus*.[195] In addition to its antimicrobial effects, it has also shown efficacy in the treatment of recurrent aphthous ulcers.[196]

Safety Summary: No known warnings, precautions or contraindications when used topically at the dose recommended.[153] No adverse effects expected during pregnancy and breastfeeding.[153,197]

[191] Shetty S, Thomas B, Shetty V, et al. An in-vitro evaluation of the efficacy of garlic extract as an antimicrobial agent on periodontal pathogens: A microbiological study. Ayu. 2013 Oct;34(4):445-51.
[192] Bakri IM, Douglas CW. Inhibitory effect of garlic extract on oral bacteria. Arch Oral Biol. 2005 Jul;50(7):645-51.
[193] 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.
[194] 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.
[195] 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.
[196] Hoglund KB, Barnett BK, Watson SA, et al. Activity of bioactive garlic compounds on the oral microbiome: a literature review. Gen Dent. 2020 May-Jun;68(3):27-33.
[197] 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 Seed (*Vitis vinifera*)

Biological Actions:

Antimicrobial, anti-inflammatory, antioxidant, antibiofilm.

Scientific Evidence:

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).[221]

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*.[198] 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.[199] 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.[200] 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.[201,202,203] 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.[204,205] It appears to restore dentin remineralization by potentiating collagen cross linking.[206]

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[198] 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.
[199] Su X, Howell AB, D'Souza DH. Antibacterial effects of plant-derived extracts on methicillin-resistant Staphylococcus aureus. Foodborne Pathog Dis. 2012 Jun;9(6):573-8.
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[203] Delimont NM, Carlson BN. Prevention of dental caries by grape seed extract supplementation: A systematic review. Nutr Health. 2020 Mar;26(1):43-52.
[204] 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.
[205] Jawale KD, Kamat SB, Patil JA, et al. Grape seed extract: An innovation in remineralization. J Conserv Dent. 2017 Nov-Dec;20(6):415-418.
[206] Delimont NM, Carlson BN. Prevention of dental caries by grape seed extract supplementation: A systematic review. Nutr Health. 2020 Mar;26(1):43-52.

Safety Summary: No known warnings, precautions or contraindications at the dose recommended.[111] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[111]

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.[109,153,207] Black walnut hull and kernels have 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.[208,209,210]

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 (*Staphylococcus aureus*).[211] 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 *Staphylococcus aureus*.[212,213] 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*

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[207] 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.
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[209] 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.
[210] Vu DC, Vo PH, Coggeshall MV, et al. Identification and Characterization of Phenolic Compounds in Black Walnut Kernels. J Agric Food Chem. 2018 May 2;66(17):4503-4511.
[211] Ho KV, Lei Z, Sumner LW, et al. Identifying Antibacterial Compounds in Black Walnuts (Juglans nigra) Using a Metabolomics Approach. Metabolites. 2018 Sep 29;8(4):58.
[212] Yun J, Lee H, Ko HJ, et al. Fungicidal effect of isoquercitrin via inducing membrane disturbance. Biochim Biophys Acta. 2015 Feb;1848(2):695-701.
[213] 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.

albicans.[214,215,216,217]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[153]

Contraindicated during pregnancy and breastfeeding in therapeutic doses.[218]

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.[219,220,221] Research shows that antioxidant properties of raspberry are attributed to its 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.[243]

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.[222] 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,*

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[214] 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.
[215] 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.
[216] 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.
[217] 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.
[218] Natural Medicines Comprehensive Database. Black Walnut Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed July 17th, 2012
[219] 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.
[220] 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.
[221] 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.
[222] 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.

Helicobacter pylori, Bacillus cereus, Campylobacter jejuni and *Candida albicans*.[116,118,223,224] The mechanism by which phenolic compounds affect the growth of different bacterial species include destabilization of cytoplasmic membrane, permeabilization of plasma membrane and inhibition of extracellular microbial enzymes. They also have direct actions on microbial metabolism by depriving the cells of the substrates necessary for growth.[119] 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.[116] Growth of the probiotic strain *Lactobacillus rhamnosus* does not appear to be inhibited by the phenolic properties of raspberry.[118,247]

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended. No adverse effects expected during pregnancy and breastfeeding.[153]

Fumitory (*Fumaria officinalis*)

Biological Actions:

Antimicrobial, antioxidant.

Scientific Evidence:

The active constituents of fumitory include alkaloids, flavonoids, and organic acids.[109] The biological activities of this herb are mainly associated with the isoquinoline alkaloids, in particular protopine.[225,226] The antioxidant capacity of fumitory, however, is thought to be due to the synergistic effect of its constituents.[227]

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*.[251] 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.[228,229]

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[223] 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.
[224] Nile SH, Park SW. Edible berries: bioactive components and their effect on human health. Nutrition. 2014 Feb;30(2):134-44.
[225] 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.
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[227] 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.
[228] Zhang R, Guo Q, Kennelly EJ, et al. Diverse alkaloids and biological activities of Fumaria (Papaveraceae): An ethnomedicinal group. Fitoterapia. 2020 Oct;146:104697.
[229] 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.

Safety Summary:

No known warnings, precautions or contraindications at the dose recommended.[230] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[231,232]

Gentian (*Gentiana lutea*)

Biological Actions:

Anti-inflammatory, antimicrobial, antioxidant, antibiofilm.

Scientific Evidence:

Gentian contains a number of 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.[109,257,233] These active constituents give rise to the herb's potent antioxidant, anti-inflammatory and antibacterial properties.[257]

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.[234]

Safety Summary:

No other known warnings, precautions or contraindications at the dose recommended.[110] No adverse effects expected during pregnancy and breastfeeding.[153]

Galbanum oil (*Ferula galbaniflua*)

Biological Actions:

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[230] 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.

[231] Newall CA, Anderson LA, Philpson JD. Herbal Medicine: A Guide for Healthcare Professionals. London, UK: The Pharmaceutical Press; 1996.

[232] 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.

[233] 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.

[234] 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.

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.[260,235,236] Often considered synonymous with *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*, *Staphylococcus epidermidis*, and *Stapylococcus aureus* in vitro.[237]

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.[238] 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.[239]

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.[263]

Safety Summary:

Galbanum oil is generally regarded as non-toxic, non-irritating and non-sensitizing.[260] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[240]

Lavender oil (*Lavandula officinalis*)

Biological Actions:

Antifungal, anti-inflammatory, antimicrobial, antibiofilm.

Scientific Evidence:

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[235] Nazari ZE, Iranshahi M. Biologically active sesquiterpene coumarins from Ferula species. Phytother Res. 2011 Mar;25(3):315-23.
[236] 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.
[237] 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.
[238] Cowan MM. Plant products as antimicrobial agents. Clin Microbiol Rev. 1999 Oct;12(4):564-82.
[239] 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.
[240] Natural Medicines Comprehensive Database. Galbanum Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed December 25th, 2013.

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.[270,241,242]

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.[243] Lavender oil also has antibacterial activity against both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus in vitro*.[270,271,244] 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.*[269]

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.[268]

Safety Summary:

Lavender oil is generally regarded as non-toxic, non-irritant and non-sensitizing.[260] No adverse effects expected during pregnancy and breastfeeding at the dose recommended.[245]

Oregano oil (Origanum vulgare)

Biological Actions:

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

Scientific Evidence:

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[241] Evandri MG, Battinelli L, Daniele C, et al. The antimutagenic activity of Lavandula angustifolia (lavender) essential oil in the bacterial reverse mutation assay. Food Chem Toxicol. 2005 Sep;43(9):1381-7.
[242] de Groot A, Schmidt E. Essential Oils, Part V: Peppermint Oil, Lavender Oil, and Lemongrass Oil. Dermatitis. 2016 Nov/Dec;27(6):325-332.
[243] 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.
[244] 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.
[245] Brendler T, Gruenwald J, Jaenicke C. Comm. E Monograph: Lavandulae flos In: Heilpflanzen - Herbal Remedies. In: Publishers MS, ed; 2003. Accessed December 25th, 2013.

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.[246]

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*.[279] 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.[247] 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.[248] *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.[249] 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.[278,279]

Oregano oil has also demonstrated antifungal activities against *Candida* species.[250] In the study by Pozzatti et al, oregano inhibited the growth and hyphenation of both *Candida albicans* and *Candida dubliniensis*.[251] 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.[284] Additionally, thymol and carvacrol overwhelm *Candida* antioxidant defense systems with an oxidative radical cascade, inhibit ergosterol synthesis, and targets efflux pump activity.[252,253]

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,

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[246] 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.
[247] 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.
[248] 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.
[249] 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.
[250] 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.
[251] 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.
[252] 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.
[253] 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.

cause skin and mucus membrane irritation.[260] Exercise caution during pregnancy and breastfeeding as safety has not been established during these times.[254]

Vegetable Glycerin

Biological Actions:
Not applicable.

Scientific Evidence:
Glycerin is used in toothpaste formulations as a humectant to prevent drying out and subsequent hardening of the paste.[2,255] In addition, glycerin is also used as a sweetener in toothpastes to improve flavor.[2,288]

Safety Summary:

Glycerin has GRAS status by the FDA.[256] It is considered safe and is included in the FDA Inactive Ingredients Database.[257] Safety has not been 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.[258]

Cellulose Gum

Biological 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.[1,11]

Safety Summary:

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[254] Natural Medicines Comprehensive Database. Oregano Monograph. http://naturaldatabase.therapeuticresearch.com. Accessed December 25th, 2013.
[255] Vranić E, Lacević A, Mehmedagić A, et al. Formulation ingredients for toothpastes and mouthwashes. Bosn J Basic Med Sci. 2004 Oct;4(4):51-8.
[256] U.S. Food and Drug Administration. SCOGS (Select Committee on GRAS Substances). 2018; https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=SCOGS&sort=Sortsubstance&order=ASC&showAll=true&type=basic&search=. Accessed 11/2021.
[257] Rowe RC, Sheskey PJ, Quinn ME, Association AP. Handbook of Pharmaceutical Excipients. Pharmaceutical Press; 2009.
[258] Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.

Sodium carboxymethyl cellulose has a GRAS status by the FDA.[259] Exercise caution or avoid using during pregnancy and breastfeeding as safety has not been established during these times.

[259] U.S. Food and Drug Administration. SCOGS (Select Committee on GRAS Substances). 2018; https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=SCOGS&sort=Sortsubstance&order=ASC&showAll=true&type=basic&search=. Accessed 01/02/2018.