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(54) Title: METHOD OF REDUCING INFLAMMATION

(57) Abstract: A method of reducing inflammation is provided. The method includes administering a chewing gum to an individual having an inflammatory condition such as heart disease. The chewing gum may further be administered to a subject lacking proper oral care.



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METHOD OF REDUCING INFLAMMATION

BACKGROUND

[0001] The present invention relates to methods of preventing or treating systemic inflammatory conditions.

[0002] Inflammation is a component of the immune response which typically involves the recruitment of immune cells to localized areas in response to tissue injury or to infectious, allergic, or chemical irritation. This recruitment of immune cells is effected by polypeptides known as cytokines released by cells of the immune system to communicate with and to regulate other cells of the immune system. Increased cytokine levels in the general circulation from a localized site of inflammation may increase the risk for developing inflammatory conditions in areas of the body other than the area of the original source of inflammation.

[0003] In the absence of proper oral care, a biofilm known as dental plaque forms on the surface of the teeth, especially along the gingival margin and interdental spaces. When plaque remains on the teeth for more than approximately seventy-two hours, the plaque hardens into tartar or calculus which cannot be completely removed by brushing and flossing. Plaque provides a surface to which the many species of bacteria in the oral cavity can adhere. As dental plaque matures over time, it becomes more pathogenic due to increased levels of anaerobic microorganisms. In response to this infection of gingival tissues, gingival inflammation occurs. Within days of neglect or improper oral care, the dental plaque biofilm may further expand to populate the subgingival space, resulting in a bacterial infection known as periodontitis or periodontal disease.

[0004] The most common and most recognized way of maintaining proper oral hygiene is through regular teeth brushing and flossing. However, brushing and flossing teeth may be inadequate to prevent gingival inflammation and periodontal infection due to a variety of causes such as improper technique and inaccessibility of portions of the dentition and gums to a tooth brush.

[0005] In addition, individuals may not be able or willing to brush and floss teeth regularly and/or properly. For example, certain situations may prevent a subject from

exercising proper oral care such as illness or hospitalization. Other situations may also prevent a subject from exercising proper oral care such as lack of access to proper oral care, inconvenience, non-compliance and the like.

[0006] To promote oral health, attempts have been made to deliver active agents or medicaments to the oral cavity such as zinc salts, anti-microbial agents, oxidants, analogues of vitamin D, halogen ions, folic acid, coenzyme Q10, etc. However, efficacy, absorption, metabolism, release, bioavailability, side effects, regulation and cost associated with pharmaceuticals and medicaments delivered to the oral cavity remain problems.

SUMMARY

[0007] The present invention relates to a method of treating systemic inflammatory conditions by reducing oral inflammation. In particular, the present invention relates to the administration of a chewing gum to an individual having systemic inflammation to reduce inflammation and its causes in the oral cavity of the individual in order to treat systemic inflammation in one or more areas other than the oral cavity. The present invention can also be used to prevent oral inflammation.

[0008] To this end, in an embodiment, a method of treating inflammation is provided. The method includes providing a therapeutically effective amount of a chewing gum without a medicament to a subject having inflammation.

[0009] In an embodiment, the inflammation includes cardiovascular disease.

[0010] In an embodiment, the chewing gum is provided to a subject lacking proper oral care.

[0011] In an embodiment, the chewing gum is provided to a patient in a health care facility.

[0012] In an embodiment, the chewing gum is provided to a subject as a supplement to oral care.

[0013] In an embodiment, the chewing gum includes a flavor selected from the group consisting of an herbal flavor, a lemon flavor, a peppermint flavor and combinations thereof.

[0014] In an embodiment, the flavor is present in an amount of about 0.2% to about 5% by weight of the chewing gum.

[0015] In an embodiment, the herbal flavor includes an herbal extract selected from the group consisting of eucalyptus, clary sage, marjoram, rosemary, thyme, chamomile, lavender, myrrh and combinations thereof.

[0016] In an embodiment, the chewing gum is provided to the subject after a meal.

[0017] In another embodiment, a method of treating an oral inflammatory condition is provided. The method includes providing a therapeutically effective amount of a chewing gum without an inflammation-reducing medicament to a subject having a systemic inflammatory condition in addition to the oral inflammatory condition.

[0018] In an embodiment, the oral inflammatory condition includes gingivitis.

[0019] In an embodiment, the systemic inflammatory condition includes cardiovascular disease.

[0020] In a further embodiment, a method of reducing the risk of acquiring a systemic inflammatory condition is provided. The method includes providing a therapeutically effective amount of a chewing gum without an inflammation-reducing medicament to a subject having an oral inflammatory condition.

[0021] In an embodiment, the oral inflammatory condition includes gingivitis.

[0022] In an embodiment, the systemic inflammatory condition includes cardiovascular disease.

[0023] In an additional embodiment, a method of treating cardiovascular disease is provided. The method includes providing a therapeutically effective amount of a chewing gum without a medicament to a subject having cardiovascular disease.

[0024] It is therefore an advantage of the methods of the present invention to provide a chewing gum that is effective in reducing inflammation in the body by improving oral health.

[0025] Another advantage includes providing a method of preventing or treating inflammation without the side effects associated with the administration of pharmacologic and therapeutic agents.

[0026] A further advantage includes providing a method of stimulating the body's own natural mechanisms to reduce inflammation in a subject.

[0027] Yet another advantage includes providing a method of reducing inflammation in a subject without requiring the physical motions associated with brushing and flossing.

[0028] Additional features and advantages are described herein, and will be apparent from, the following Detailed Description.

DETAILED DESCRIPTION

[0029] The present invention relates to a method of reducing the risk of systemic inflammation or controlling existing systemic inflammation. In particular, the present invention relates to the administration of a chewing gum to an individual having systemic inflammation or a systemic inflammatory condition in order to reduce infection and inflammation in the oral cavity of the individual which contributes to the systemic inflammatory condition.

[0030] Inadequate or improper oral care allows a biofilm to form on the teeth of the individual. As the biofilm develops, numerous bacteria accumulate at vulnerable areas of the gum-tooth interface and bacterial metabolites are released into the gingival epithelium. These bioactive metabolites initiate an immune response leading to the production of cytokines and infiltration of the gingival epithelium with neutrophils. Neutrophils increase the permeability of the gingival blood vessels to plasma proteins which invade the surrounding tissue producing the redness, swelling, sensitivity and bleeding associated with gingivitis. Permeable blood vessels also allow bacteria and their metabolites to reach the bloodstream. The epithelium is also stimulated to produce bioactive mediators involved in further recruitment of other immune cells, such as T-cells and monocytes, and to further produce pro-inflammatory cytokines. This sustained immune response leads to chronic gingivitis. The continued presence of dental plaque allows the bacteria to continue to grow, spread and become more pathogenic resulting in periodontitis or periodontal disease.

[0031] Although gingivitis and periodontal disease are primarily infections of the supporting structures of the teeth, the effects of sustained increased levels of oral bacteria and chronic inflammation of the surrounding gingival tissue associated with gingivitis may directly or indirectly cause systemic effects beyond the oral cavity where the condition originates. In fact, disturbances in the oral cavity, such as tooth

brushing, flossing and chewing, under such conditions may cause or accelerate the entry of the pro-inflammatory mediators associated with the local inflammatory response in the periodontal tissues into systemic circulation. Locally-produced inflammatory mediators may be released into systemic circulation and bacteria associated with gingival inflammation may also stimulate an autoimmune response to cause a pro-inflammatory response.

[0032] Consequently, there appears to be a relationship between oral inflammation and inflammatory reactions throughout the body. This relationship can be extended to specific disease conditions such as cardiovascular disease. For instance, certain bacteria, such as *Chlamydia pneumoniae* and *Porphyromonas gingivalis*, which are typically found in the oral cavity and are associated with periodontitis, have been shown to be present in atherosclerotic plaques.

[0033] Circulating bacteria, bacterial endotoxins and bacterial pro-inflammatory components from an infected oral cavity may adversely affect the vascular endothelium. Damage to the vascular endothelium predisposes the intima of the vessel to focal accumulation of lipids and plasma proteins leading to atheroma formation. The atheroma becomes susceptible to adhesion of monocyte-derived macrophages aided by pro-inflammatory and chemotactic cytokines and adhesion molecules to begin the early formation of an atherosclerotic plaque. Monocyte-derived macrophages then become engorged with low-density lipoproteins to form foam cells followed by the formation of a fibrin cap beneath the endothelium, thereby compromising the integrity of the vessel wall. If the fibrin cap ruptures, a thrombus forms within the vessel to attempt to repair the damaged area and blocks flow through the vessel. Preventing blood from reaching the tissue beyond the thrombus leads to ischemia and, ultimately, to myocardial infarction or stroke.

[0034] Additionally, periodontal bacteria and endotoxins that enter the systemic circulation from the oral cavity in the presence of gingival inflammation may stimulate cytokine production to activate immune responses further increasing levels of cytokines and leukocytes capable of provoking systemic inflammation, arterial blockages and infection. In response to elevated levels of cytokines in systemic circulation from periodontal infection, an acute-phase response occurs. The acute-phase response is characterized by the production of acute-phase proteins by the liver,

such as C-reactive protein and fibrinogen. These proteins are implicated in thrombogenesis through platelet aggregation and increased clotting factors. Acute-phase proteins also contribute to cardiovascular disease, as well as other conditions related to chronic inflammation such as low birth weight, stroke, chronic obstructive pulmonary disease, etc.

[0035] It has been surprisingly found that chewing gum actively decreases plaque, gingivitis and bleeding associated with inflammation in the oral cavity. Therefore, methods of the present invention may include, for example, administering chewing gum to a subject having an inflammatory condition to reduce oral inflammation that can lead to a variety of other systemic inflammatory conditions. In particular, the method can include, for example, administering chewing gum to a subject having cardiovascular disease.

[0036] Without being limited to any particular mechanism, administering a chewing gum to a subject may reduce inflammation by preventing formation of dental plaque and resulting gingivitis. The effect of chewing gum on plaque accumulation and gingivitis may include activation of the salivary defense mechanism which works to limit bacterial growth through the flow of fluid along the surfaces of the teeth and oral cavity. Flavors, such as peppermint, lemon and herbal flavors may further stimulate salivary secretion to enhance the effect of the salivary defense mechanism. Other flavors such as menthol eucalyptol, thymol, methyl salicylate, licorice, and cinnamic aldehyde may have inherent bactericidal properties. Reducing levels of bacteria in the oral cavity may not only reduce the source of local inflammatory mediators, but may also prevent the spread of inflammatory mediators and production of inflammatory mediators in other areas of the body, including the blood. For example, chewing gum may decrease the likelihood that bacteria from gingivitis or other periodontal conditions in the oral cavity induces the production and release of pro-inflammatory mediators leading to inflammatory conditions such as cardiovascular disease. Chewing gum may also decrease the likelihood that bacteria from gingivitis or other periodontal conditions in the oral cavity initiates an immune response that can affect other systems and organs in the body and exacerbate an existing inflammatory condition.

[0037] To this end, a chewing gum may be administered to an individual having oral inflammation and/or an inflammatory condition such as cardiovascular disease.

[0038] The chewing gum of the present invention may include a variety of chewing gum formulations and excipients. The chewing gum may include, for example, a water-insoluble gum base and a water-soluble portion. The insoluble gum base may comprise elastomers, resins, fats and oils, softeners, and inorganic fillers. The gum base may or may not include wax. The insoluble gum base may constitute approximately 5 to about 95 percent, by weight, of the chewing gum. In an embodiment, the gum base may comprise about 10 to about 50 percent of the chewing gum, and, alternatively, about 20 to about 35 percent, by weight of the chewing gum.

[0039] In an embodiment, the chewing gum of the present invention may comprise about 20 to about 60 weight percent synthetic elastomer, 0 to about 30 weight percent natural elastomer, about 5 to about 55 weight percent elastomer plasticizer, about 4 to about 35 weight percent filler, about 5 to about 35 weight percent softener, and/or optional minor amounts (about one percent or less) of miscellaneous ingredients such as colorants, antioxidants, etc.

[0040] Synthetic elastomers may include, but are not limited to, polyisobutylene with a weight average molecular weight determined by gel permeation chromatography (GPC) of about 10,000 to about 95,000, or from about 50,000 to about 80,000 GPC weight average molecular weight. Synthetic elastomers may also include isobutylene-isoprene copolymer having styrene-butadiene ratios of about 1:3 to about 3:1 polyvinyl acetate having a GPC weight average molecular weight of about 2,000 to about 90,000, polyisoprene, polyethylene, vinyl acetate-vinyl laurate copolymer having vinyl laurate content of about 5 to about 50 percent by weight of the copolymer, and combinations thereof. Styrene-butadiene, for polyvinyl acetate, may range from about 10,000 to 65,000 GPC weight average molecular weight. In an embodiment, a higher molecular weight polyvinyl acetate is used in the chewing gum base. For vinyl acetate-vinyl laurate, the vinyl laurate content may range from about 10 to about 45 percent.

[0041] Natural elastomers may include natural rubber, such as smoked or liquid latex and guayule, as well as natural gums, such as jelutong, lechi caspi, perillo, sorva, massaranduba balata, massaranduba chocolate, nispero, rosindinha, chicle, gutta hang

kang, and combinations thereof. Synthetic elastomers and/or natural elastomer concentrations may vary depending on whether the chewing gum in which the base is used is adhesive or conventional, or a bubble gum or a conventional gum.

[0042] Elastomer plasticizers may include, but are not limited to, natural rosin esters or estergums, such as glycerol esters of partially hydrogenated rosin, glycerol esters polymerized rosin, glycerol esters of partially dimerized rosin, glycerol esters of rosin, pentaerythritol esters of partially hydrogenated rosin, methyl and partially hydrogenated methyl esters of rosin, and pentaerythritol esters of rosin. Synthetic elastomer plasticizers may include terpene resins derived from alpha-pinene, beta-pinene, and/or d-limonene and any suitable combinations thereof. The elastomer plasticizers may vary depending on the specific application and on the type of elastomer included in the chewing gum.

[0043] The chewing gum may also include fillers/texturizers, such as magnesium and calcium carbonate; ground limestone; silicate types, such as magnesium and aluminum silicate; clay; alumina; talc; titanium oxide; mono-, di- and tri-calcium phosphate; cellulose polymers, such as wood; and combinations thereof.

[0044] The chewing gum may also include softeners or emulsifiers such as tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di- and triglycerides, acetylated monoglycerides, fatty acids (e.g. stearic, palmitic, oleic and linoleic acids), and combinations thereof.

[0045] The chewing gum may also include colorants and whiteners such as FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, and combinations thereof.

[0046] In addition to a water-insoluble gum base portion, the chewing gum composition may include a water-soluble bulk portion and one or more flavoring agents. The water-soluble portion may include bulk sweeteners, high intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

[0047] The softeners, which are also known as plasticizers and plasticizing agents, may constitute between approximately 0.5 to about 15% by weight of the chewing gum. The softeners may include, but are not limited to, carprenin, glycerin, lecithin

and combinations thereof. Aqueous sweetener solutions, such as solutions containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in the chewing gum.

[0048] Bulk sweeteners may include both sugar and sugarless components. Bulk sweeteners may constitute about 5 to about 95% by weight of the chewing gum. In an embodiment, the bulk sweetener may constitute about 20 to about 80% by weight, or about 30 to about 60% by weight of the gum.

[0049] Sugar sweeteners may include saccharide-containing components commonly known in the chewing gum art, such as sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, galactose, corn syrup solids, and the like, either alone or in combination. Additionally or alternatively, sugarless sweeteners may be used in the chewing gum, such as bulk polyol sweeteners or any other suitable sugarless sweetener or combinations thereof. Sugarless sweeteners may include, but are not limited to, sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates, maltitol, lactitol, and the like, alone or in combination.

[0050] High intensity artificial sweeteners may also be used in combination with the above including, but not limited to, sucralose, aspartame, aspartame derivatives and conjugates, such as neotame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones, thaumatin, monellin, or any other suitable high-intensity sweetener, alone or in combination thereof. In order to provide longer lasting sweetness and flavor perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the artificial sweetener. Such techniques as wet granulation, wax granulation, spray drying, spray chilling, fluid bed coating, coacervation, and fiber extension or other methods known in the art may be used to achieve the desired release characteristics.

[0051] The amount of the artificial sweetener may vary greatly and may depend on such factors as potency of the sweetener, rate of release, desired sweetness of the product, level and type of flavor used and cost considerations. Thus, the level of artificial sweetener may vary from about 0.02 to about 8% by weight of the chewing gum. When carriers used for encapsulation are included, the amount of the encapsulated sweetener may be proportionately higher.

[0052] Combinations of sugar and/or sugarless sweeteners may be used in chewing gum. Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

[0053] If a low calorie gum is desired, a low caloric bulking agent may be used. Examples of low caloric bulking agents may include polydextrose, raftilose, raftilin, fructooligosaccharides (NutraFlora), palatinose oligosaccharide, guar gum hydrolysate (Sun Fiber), or indigestible dextrin (Fibersol). However, any other suitable low-calorie bulking agent may be used.

[0054] The chewing gum may also include at least one flavorant or flavoring agent. The flavor may be used in amounts of approximately 0.1 to about 15 weight percent of the gum, and in an embodiment, about 0.2 to about 5%. The flavorant or flavor may include any natural or synthetic oil and/or flavor as is commonly known in the art. Suitable flavorants include, but are not limited to, oils derived from plants and fruits such as citrus oils; fruit essences, fruit juices, fruit concentrates, and fruit purees of, for example, berry, lemon, lime, strawberry, orange, apple and the like; peppermint oil; spearmint oil; other mint oils; clove oil; oil of wintergreen; anise and the like; flavors derived from spices and the like; flavor oils such as menthol eucalyptol, thymol, methyl salicylate, licorice, cinnamic aldehyde and the like; and combinations thereof. The chewing gum may also include herbal flavors such as herbal extracts. Herbal extracts may include eucalyptus, clary sage, marjoram, rosemary, thyme, chamomile, lavender, myrrh or any other suitable polyol sweetener or combinations thereof. Artificial flavoring agents and components may also be used as the flavorant or flavor. Natural and artificial flavoring agents may be combined in any sensorally acceptable fashion as is commonly known in the art. The flavorant or flavor may be encapsulated or non-encapsulated. Encapsulated flavorant may be used to increase or decrease the flavor release rate as is commonly known in the art. In an embodiment, a flavor, such as a peppermint flavor, an herbal flavor, a lemon flavor or combinations thereof, is included in the chewing gum to contribute to reducing inflammation.

[0055] The chewing gum may or may not include an active ingredient or medicament. As used herein, "medicament" may include a pharmacologic or therapeutic agent or component or metabolite thereof that demonstrates pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a condition,

or disease. The medicament may include an ingredient that is typically not a component of a chewing gum as described above. For example, a medicament may exclude components such as flavors.

[0056] The chewing gum may or may not include an inflammation-reducing agent or medicament. As used herein, an inflammation-reducing medicament refers to a medicament that at least contributes to reducing inflammation. In an embodiment, in the absence of an inflammation-reducing medicament, at least one flavor, such as a peppermint flavor, an herbal flavor, a lemon flavor or combination thereof, is included in the chewing gum to enhance the effect of the chewing gum to reduce inflammation. However, it is believed that the chewing gum can be effective in the present invention even in the absence of such active ingredients. In an embodiment, the chewing gum may include active ingredients or medicaments other than an inflammation-reducing medicament. Such as an anti-bacterial agent and the like.

[0057] The chewing gum center may be manufactured by any suitable method known in the art. Once the chewing gum center is produced, the chewing gum center may or may not be coated or surface-treated by any suitable method known in the art. In an embodiment, the chewing gum may include a coated chewing gum comprising a gum center and a sugar or sugar alcohol coating. The coating may initially be in a liquid state, such as a syrup, which contains the coating ingredients previously described herein in an amount from about 30% to about 85% by weight of the coating, and a solvent, such as water, in an amount from about 15% to about 70% by weight of the coating. In an embodiment, the coating material or syrup is applied or distributed over the gum center one or more times providing additional coating material or syrup to produce one or more coatings or layers of coating as desired. In an embodiment, the coated chewing gum product may contain about 10% to about 65% coating.

[0058] In an embodiment, a soft coating may be formed by adding a powder coating after a liquid coating. The powder coating may include natural carbohydrate gum hydrolysates, maltodextrin, gelatin, cellulose derivatives, starches, modified starches, sugars, sugar alcohols, natural carbohydrate gums and fillers, such as talc, calcium carbonate and the like, and combinations thereof.

[0059] By way of example, and not limitation, examples of the chewing gum formulations suitable for use in the present invention are set forth in Table 1 below.

TABLE 1

	Example 1— Herbal Flavor	Example 2— Herbal Flavor	Example 3— Peppermint Flavor	Example 4— No Flavor
Center				
Gum Base	48.00	42.50	47.60	42.50
Sorbitol	46.00	48.50	43.14	48.92
Glycerin	3.20	6.00	7.44	6.00
Triacetin	0.50	0.30	-	1.25
Lecithin	-	-	-	0.45
Herbal Lemon Mint Flavor	1.50	1.80	-	-
Balm Mint Powder Extract	-	0.02	-	-
Peppermint Flavor	-	-	1.22	-
Menthol	0.30	-	0.47	-
Acesulfam K	0.01	0.02	-	0.02
Encapsulated Acesulfam K	0.25	-	-	-
Encapsulated Aspartame	0.25	0.86	0.13	0.86
Total Center	100.00	100.00	100.00	100.00
Coating				
Xylitol	88.99	89.05	88.27	89.65
Gum Acacia	9.0	9.20	9.22	9.20
Color	0.81	0.82	0.83	0.82
Peppermint Flavor	-	-	1.00	-
Herbal Lemon Mint Flavor	0.87	0.60	-	-
Menthol	-	-	0.35	-
Talc	0.18	0.18	0.18	0.18
Carnauba Wax	0.15	0.15	0.15	0.15
Total Coating	100.00	100.00	100.00	100.00
The finished product is approximately 67.5% center and 32.5% coating.				

[0060] The chewing gum may be administered to subjects who are at risk for, or who have, systemic inflammation. Inflammation may cause or may be manifested in an inflammatory condition. Inflammatory conditions may include cardiovascular disease, stroke, arthritis, Alzheimer's disease, kidney disease, cancer, lupus, asthma, psoriasis, pancreatitis, autoimmune disease, fibrosis, surgical complications, anemia, fibromyalgia or any other disease or condition related to inflammation.

[0061] The methods of the present invention are especially suited for subjects lacking proper oral care. A subject may lack proper oral care if the subject is unable to practice proper procedures for caring for his teeth and gums such as brushing and flossing his teeth. For example, a subject may be unable to physically perform the required motions to properly clean his teeth, such as a patient in a health care facility or one who has restricted mobility. A further example of a subject lacking proper oral

care may include one who improperly or ineffectively brushes and flosses his teeth due to inadequate technique or instrumentation, or inaccessible dentition. While the methods of the present invention may be applied to individuals lacking proper oral care, it should also be appreciated that the methods of the present invention may be used to supplement proper oral care.

[0062] A therapeutically effective amount or the amount of chewing gum provided or administered to a subject at a particular time may include any amount able to be chewed at one time by the subject. For example, the amount of chewing gum administered to a subject may include about 1 to about 5 grams of chewing gum. In an embodiment, about 2 to about 4 grams is administered. In an embodiment, about 3 grams of chewing gum is administered to a subject. The amount of chewing gum administered to a subject may include any number of pieces of chewing gum necessary to achieve the desired amount.

[0063] Chewing gum may be administered to a subject at any suitable frequency and duration. In an embodiment, the chewing gum is administered to a subject about three times per day. In an embodiment, the chewing gum is administered to a subject after ingestion of food or fluids such as after a meal. Administering a chewing gum following a meal may also have the benefit of promoting the removal of remnants of the meal from the oral cavity which would otherwise contribute to the formation of the biofilm precursor to plaque. The gum may be chewed for any suitable period of time such as at least about ten minutes. In an embodiment, the gum is chewed for at least about twenty minutes.

[0064] To assess the effect of chewing gum on reducing inflammation and, in particular, reducing dental plaque accumulation and gingivitis, two double-blinded studies were performed on parallel groups of suitable subjects. The studies used a 21-day, partial mouth gingivitis model, described below, to accelerate plaque formation and gingivitis development. In one study, a group administered chewing gum was compared to a group not administered chewing gum. In the second study, four parallel groups were evaluated and compared. Each of the four groups was provided either a sugar-free chewing gum with herbal flavoring, a sugar-free chewing gum with no herbal flavoring, a commercial sugar-free chewing gum, or no chewing gum as a control. The general formula for the gums used in the study included about 20% to

about 27% gum base; about 50% to about 68% bulk polyol sweeteners such as sorbitol, xylitol, or mannitol; about 0.1% to about 0.4% high-intensity sweeteners such as aspartame, acesulfame K; about 10% to about 23% filler ingredients such as calcium carbonate; and about 0.5% to about 2.9% flavors, including herbal extracts. The herbal-flavored chewing gum is made with food-approved ingredients currently used in sugar-free chewing gums. The herbal mint flavoring was based on common chewing gum flavors with the addition of herbal flavors such as eucalyptus, clary sage, marjoram, rosemary, thyme, chamomile, lavender, and myrrh. The placebo gum was similar in composition to the test gums, but did not contain any herbs or herbal flavor.

[0065] The subjects were distributed into equivalent groups of about forty individuals according to three variables: gender, baseline gingival bleeding and inflammation scores of a designated test portion of the mouth. The subjects were also distributed to produce groups with the same potential for forming plaque and developing experimental gingivitis in order to minimize the sample variance within groups.

[0066] In an effort to optimize oral health prior to beginning a three-week period of testing, each of the subjects underwent a screening exam and was provided oral hygiene instructions instructing them to perform daily brushing with a regular commercial dentifrice and flossing. Immediately prior to the trial period, each subject underwent prophylaxis including scaling and polishing of the entire dentition. Plaque and gingivitis scores from this pre-trial period were then used as a baseline for longitudinal comparisons and for assignment of subjects to treatment groups for the trial period.

[0067] During the three-week trial period, all subjects were asked to abstain from all oral hygiene procedures other than those performed as part of the study and not to use any other unassigned dental products or chewing gum. In addition, the subjects were not permitted to brush the dentition in a portion of the mouth to be tested, but were allowed to brush the remainder of the dentition twice daily using the assigned dentifrice. The test quadrant was selected based on the lack of interfering restorations, missing teeth, or other abnormalities. In most cases, the test teeth comprised five teeth from canine to the second molar inclusive.

[0068] A removable tooth shield was placed over the test portion to prevent the mechanical action of a toothbrush from reaching the teeth and gums of the test area during tooth brushing. Tooth shields were constructed from vacuum-formed mouth-guard plastic and shaped according to a dental impression taken of the mandibular teeth of each subject. The tooth shield was trimmed to include only the teeth and gingival margin and to eliminate contact with the cervical margin of each tooth, thereby reducing the risk of plaque being disturbed during insertion or removal of the shield. The material was trimmed vertically on the buccal side to a length just short of the vestibule and frenum attachments, and on the lingual side to a length short of the floor of the mouth. The material was further trimmed mesially to the middle of the lateral incisor, and distally behind the second molar.

[0069] After brushing with the shield in position, subjects carefully removed the tooth shield to avoid scraping off any deposits, and rinsed the mouth once with tap water. Those subjects assigned a chewing gum were advised to chew two pieces (approximately 3 grams) of the assigned gum three times per day (after breakfast, lunch, and dinner) for twenty minutes so that the effect of subsequent chewing of the gum could be assessed.

[0070] At the end of the three-week trial period, clinical assessments were repeated for soft tissue, plaque, and gingivitis as performed during the baseline examination.

[0071] The primary results of the study are presented in terms of scores describing plaque accumulation and level of gingivitis using Plaque, Modified Gingival and Gingival Bleeding Indices. The scores for these indices were summed and averaged to provide mean per site scores for each subject at each clinical examination. Data from the gingivitis and plaque indices were grouped and analyzed separately according to the shield-protected teeth and the corresponding brushed teeth. Data for each scoring index was analyzed by analysis of covariance using the baseline (pre-trial) data as the covariate. The covariate (baseline data) was included in the statistics model for increased precision in determining the effect of the test products on the scores. Any variations between treatment groups that existed in the baseline data were compensated for by adjusted means generated by this procedure. Statistical significance of mean data for age and compliance was determined parametrically by

analysis of variance for testing of differences between the product groups. Longitudinal (within-treatment) comparisons were also performed for scoring index means using a one-sample t-test on the changes from baseline to the final examination. All comparisons were tested at an overall 0.05 level of significance using two-sided tests.

[0072] Plaque and gingivitis was scored on the buccal and lingual surfaces of the five posterior mandibular teeth (i.e. the canine through second molar inclusive) that were protected by the tooth shield, as well as the five contralateral teeth in the opposite mandibular quadrant that are treated by tooth brushing. Adjacent teeth or other suitable teeth were substituted for any unavailable or non-scorable teeth.

[0073] Supragingival dental plaque accumulation on the teeth was measured by means of a modification of the Turesky et al. refinement of the Quigley-Hein index (MQHI). MQHI is a numerical index based on plaque area that focuses on the gingival third of the tooth. This weighting of score to differentiate relatively subtle amounts of plaque enables it to reflect the realities of the plaque-gingival inflammation relationship rather than just aesthetic considerations. To conduct the assessment, plaque was first stained with a disclosant and scored according to a five-point interval scale in which the higher value denotes a quantitative increase in plaque. Each tooth was visually divided into six areas for scoring: 1) mesio-facial, 2) mid-facial, 3) disto-facial, 4) mesiolingual, 5) mid-lingual, and 6) disto-lingual. Thus, the maximum score per tooth is 30. If there was no visible plaque, the MQHI score = 0. If there were separate flecks of plaque at the cervical margin of the tooth, the MQHI score = 1. If there was a thin, continuous band of plaque up to 1 mm wide at the cervical margin, the MQHI score = 2. If there was a band of plaque wider than 1 mm but covering less than one-third of the crown, the MQHI score = 3. If there was plaque covering at least one-third but less than two-thirds of the crown, the MQHI score = 4, and if plaque covered two-thirds or more of the crown, the MQHI score = 5. The scores from the six areas of the tooth were summed and divided by 6 to give the mean score for the tooth. Finally, by adding the indices for the teeth and dividing by the number of teeth examined, the mean score for the individual was obtained.

[0074] Inflammation of the gingival tissue was measured visually using the Modified Gingival Index (MGI). The gingival margin was defined as the portion

located on the enamel or at various levels apical to the cemento-enamel junction. Although the margin should be thin, the buccal and lingual gingiva may present a rounded termination against the tooth, thereby forming the entrance or orifice of the gingival crevice. The MGI included the visible symptoms of gingival inflammation as defined by Lobene. In particular, the marginal and papillary gingival segments of each tooth were defined as clinically healthy having no inflammation if gingiva color was pale pink to pink, the surface after drying is matt with varied degree of stippling, and the gingiva was firm upon palpation with a pocket probe. Accordingly, no inflammation was observed, the MGI score = 0. If there was mild inflammation having a slight change in color, little change in texture of any portion of the marginal or papillary gingival unit, but not the entire gingival unit, the MGI score = 1. If the mild inflammation involved the entire marginal or papillary gingival unit the MGI score = 2. If there was glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit, the MGI score = 3 for moderate inflammation. In the presence of marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration of the gingival, the MGI score = 4 for severe inflammation.

[0075] Gingival bleeding was assessed according to the Gingival Bleeding Index (GBI) which indicates the tendency of bleeding of the gingiva upon gentle stroking with a probe along the inner wall of the gingival crevice using a refinement of the GBI by Ainamo and Bay. The principle of the GBI as defined by Saxton and van der Ouderaa is that bleeding is the most significant parameter of gingival inflammation and that the number of elicited bleeding points represents the gingival condition. Severity of bleeding was assessed based upon the ease with which bleeding was elicited by a blunt, periodontal probe. Severity was proportional to the time required to observe bleeding after probing. The periodontal probe was inserted into the gingival crevice and moved around the crevice, gently stretching the sulcular epithelium. Each of the three gingival areas (i.e. mesial, buccal, and lingual) of the test teeth in one quadrant were probed in this manner before recording the number of gingival units which bleed. If no bleeding of the gingival units is observed after 30 seconds, the GBI score = 0. If bleeding is observed after 30 seconds, the GBI score = 1. If bleeding occurs instantaneously, the GBI score = 2. The number of elicited

bleeding points are totaled and divided by the units probed (maximum = 28) to provide a mean score.

[0076] The use of the tooth shield to protect the test teeth from mechanical oral hygiene resulted in significant increases in plaque and gingivitis for each of the treatment groups. Specifically, the baseline MQH scores for each of the groups in the two studies ranged between 2.39 and 2.89 with no significant difference between the groups. After the three-week test period, a significant increase in MQH scores occurred for each group to a range of between 3.27 and 3.59. The baseline MGI scores for each of the groups in the first study ranged between 0.83 and 0.88 with no significant difference between the groups. After the three-week test period, a significant increase in MGI scores occurred for each group to a range of between 1.18 and 1.48. Similarly, in the second study, the baseline MGI scores significantly increased from a range of between 1.21 and 1.28 to a range of between 1.44 and 1.80 after the three-week test period. The baseline GBI scores for each of the groups in the two studies ranged between 0.09 and 0.19 with no significant difference between the groups. After the three week test period, a significant increase in MGI scores occurred for each group to a range of between 0.19 and 0.71. Thus, this clinical model is a valid and effective method for determining the efficacy of therapeutic dental products in preventing the formation of plaque and gingivitis.

[0077] The results of the two studies demonstrate that plaque accumulation and gingivitis are reduced in subjects administered chewing gum. More specifically, as illustrated in Table 2, a statistically significant reduction in plaque occurred in the shielded teeth of subjects administered peppermint and herbal flavored gums in comparison to no gum control. Additionally, there was a statistically significant decrease of 7.3% in the Plaque Index scores for the peppermint gum and an 8.9% decrease in the Plaque Index scores for the herbal lemon flavor gum compared to the group not administered chewing gum. Gum with no flavor was not statistically significant in comparison to no gum.

[0078] The results of the study also showed that a decrease in gingivitis occurred in subjects administered chewing gum as indicated by a statistically significant decrease in the Gingival Index scores and in the Bleeding Index scores of the subjects in the first study administered the herbal lemon flavor gum (-18% and -26%,

respectively) compared to the group not administered chewing gum. A statistically significant decrease also occurred in the Gingival Index scores of the subjects in the second study administered the peppermint gum (-13%), herbal lemon flavor gum (-20%) and unflavored gum (-15%) compared to the group not administered chewing gum. In addition, a decrease in the Bleeding Index scores occurred in subjects administered the peppermint gum (-25%), herbal lemon flavor gum (-32%) and unflavored gum (-4%) compared to the group not administered chewing gum. Although the decrease in the Bleeding Index scores was not statistically significant, the combined decrease in gingival index scores and bleeding index scores indicates a significant reduction of gingivitis in subjects administered chewing gum. The decrease in the Plaque Index scores as well as the Gingival and Bleeding Index scores for unflavored gum further indicates that just chewing non-flavored gum can reduce gingivitis and that the flavor in the gums may have an added effect of decreasing gingivitis and the plaque that causes gingivitis.

TABLE 2
SUMMARY OF
FINAL PLAQUE (MQH), GINGIVITIS (MGI), AND GINGIVAL BLEEDING (GBI) SCORES
FOR SHIELDED TEETH

Test Group		Plaque		Gingivitis			
		Final MQH [§]	Reduction (Significance)	Final MGI [§]	Reduction (Significance)	Final GBI [§]	Reduction (Significance)
First Study	Example 1—Herbal Gum	3.43	5% (p=0.03)	1.46	18% (p=0.001)	0.53	26% (p=0.04)
	No-Gum	3.60	-----	1.78	-----	0.72	-----
Second Study	Example 2—Herbal Lemon	3.27	9% (p=0.007)	1.18	20% (p=0.003)	0.19	32% (p=0.06)
	Example 3—Peppermint	3.32	8% (p=0.01)	1.29	13% (p=0.03)	0.21	25% (none)
	Example 4—Unflavored	3.37	6% (none)	1.26	15% (p=0.02)	0.27	4% (none)
	No-Gum	3.59	-----	1.48	-----	0.28	-----

[§] Adjusted mean score after 3 weeks of treatment, n~35 per group

[0079] As indicated in Table 3 below, the further positive effect of the chewing gums on unshielded teeth maintained with regular brushing and flossing after only three weeks indicates that the chewing gums may provide some additional oral hygiene benefits beyond regular oral care.

TABLE 3

SUMMARY OF FINAL PLAQUE (MQH), GINGIVITIS (MGI), AND GINGIVAL BLEEDING (GBI) SCORES FOR NON-SHIELDED TEETH

Test Group		Plaque		Gingivitis			
		Final MQH [§]	Reduction (Significance)	Final MGI [§]	Reduction (Significance)	Final GBI [§]	Reduction (Significance)
First Study	Example 1—Herbal Gum	2.71	0% (p=0.78)	1.31	10% (p=0.06)	0.24	8% (p=0.66)
	No-Gum	2.69	-----	1.45	-----	0.26	-----
Second Study	Example 2—Herbal Lemon	2.52	10% (p=0.006)	0.97	17% (p=0.01)	0.07	42% (p=0.07)
	Example 3—Peppermint	2.68	4% (none)	1.06	9% (p=0.03)	0.09	25% (none)
	Example 4—Unflavored	2.60	7% (none)	1.12	4% (none)	0.11	8% (none)
	No-Gum	2.79	-----	1.17	-----	0.12	-----

[§] Adjusted mean score after 3 weeks of treatment, n~35 per group

[0080] The overall safety data collected during this three-week clinical trial also demonstrated that there is little or no risk or significant side effects associated with regular use of the chewing gums described herein.

[0081] Therefore, the results of this human clinical investigation demonstrate that use of a chewing gum as the sole method or as a supplemental method of addressing

oral hygiene for three weeks provides a safe and effective way to significantly reduce plaque and gingivitis compared to a no-gum control.

[0082] It should be understood that various changes and modifications to the embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

The invention is claimed as follows:

1. A method of treating or preventing systemic inflammation comprising:
providing a therapeutically effective amount of a chewing gum without a medicament to a subject having inflammation or at risk for inflammation.
2. The method of Claim 1, wherein the inflammation includes cardiovascular disease.
3. The method of Claim 1, wherein the chewing gum is provided to a subject lacking proper oral care.
4. The method of Claim 1, wherein the chewing gum is provided to a patient in a health care facility.
5. The method of Claim 1, wherein the chewing gum is provided to a subject as a supplement to oral care.
6. The method of Claim 1, wherein the chewing gum includes a flavor selected from the group consisting of an herbal flavor, a lemon flavor, a peppermint flavor, a citrus flavor, a fruit flavor, a spearmint flavor, a mint flavor, a clove flavor, a wintergreen flavor, an anise flavor, a fruit flavor, a spice flavor and combinations thereof.
7. The method of Claim 6, wherein the flavor is present in an amount of about 0.2% to about 5% by weight of the chewing gum.
8. The method of Claim 6, wherein the herbal flavor includes an herbal extract selected from the group consisting of eucalyptus, clary sage, marjoram, rosemary, thyme, chamomile, lavender, myrrh and combinations thereof.

9. The method of Claim 1, wherein the chewing gum is provided to the subject after a meal.

10. A method of treating an oral inflammatory condition comprising:
providing a therapeutically effective amount of a chewing gum without an inflammation-reducing medicament to a subject having a systemic inflammatory condition in addition to the oral inflammatory condition.

11. The method of Claim 10, wherein the oral inflammatory condition includes gingivitis.

12. The method of Claim 10, wherein the systemic inflammatory condition includes cardiovascular disease.

13. The method of Claim 10, wherein the chewing gum is provided to a subject lacking proper oral care.

14. The method of Claim 10, wherein the chewing gum is provided to a patient in a health care facility.

15. The method of Claim 10, wherein the chewing gum is provided to a subject as a supplement to oral care.

16. The method of Claim 10, wherein the chewing gum includes a flavor selected from the group consisting of an herbal flavor, a lemon flavor, a peppermint flavor, a citrus flavor, a fruit flavor, a spearmint flavor, a mint flavor, a clove flavor, a wintergreen flavor, an anise flavor, a fruit flavor, a spice flavor and combinations thereof.

17. A method of reducing the risk of acquiring a systemic inflammatory condition comprising:

providing a therapeutically effective amount of a chewing gum without an inflammation-reducing medicament to a subject having an oral inflammatory condition.

18. The method of Claim 17, wherein the oral inflammatory condition includes gingivitis.

19. The method of Claim 17, wherein the systemic inflammatory condition includes cardiovascular disease.

20. A method of treating cardiovascular disease comprising:

providing a therapeutically effective amount of a chewing gum without a medicament to a subject having cardiovascular disease.