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(54) Titre : PREPARATIONS ADMINISTRABLES PAR VOIE ORALE  
(54) Title: ORAL COMPOSITIONS

(57) **Abrégé/Abstract:**

The present invention relates to oral compositions containing cranberries or parts of cranberries, such as cranberry extract, or a mixture of such materials and other antibacterial/antimicrobial agents. The invention also relates to methods of treating plaque/gingivitis and other periodontal diseases as well as dental calculus and caries.



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(54) Title: ORAL COMPOSITIONS

## (57) Abstract

The present invention relates to oral compositions containing cranberries or parts of cranberries, such as cranberry extract, or a mixture of such materials and other antibacterial/antimicrobial agents. The invention also relates to methods of treating plaque/gingivitis and other periodontal diseases as well as dental calculus and caries.

## ORAL COMPOSITIONS

TECHNICAL FIELD

5           The present invention relates to oral compositions containing cranberries or parts of cranberries, such as cranberry extract or other members of the Ericaceae family, as antiplaque, anticalculus and anticaries agents.

          Plaque induced diseases, including periodontitis and gingivitis, are believed to involve anaerobic bacterial infections. Periodontal disease affects the periodontium, which  
10       is the investing and supporting tissue surrounding a tooth (i.e., the periodontal ligament, the gingiva, and the alveolar bone). Gingivitis and periodontitis are inflammatory disorders of the gingiva and the periodontal ligament, respectively. Gingivosis and periodontosis are more severe conditions involving degenerative disorders of the tissue. Combinations of inflammatory and degenerative conditions are termed periodontitis complex.

15           Periodontal disease is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at age 35, but even by age 15 it is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis.

          While good oral hygiene, as achieved by brushing the teeth with a cleansing  
20       dentifrice, may help reduce the incidence of periodontal disease, it does not necessarily prevent or eliminate its occurrence. This is because microorganisms contribute to both the initiation and progress of periodontal disease. Thus, in order to prevent or treat periodontal disease, these microorganisms must be suppressed by some means other than simple mechanical scrubbing. Towards this end, there has been a great deal of research aimed at  
25       developing therapeutic dentifrices, mouthwashes, and methods of treating periodontal disease which are effective in suppressing these microorganisms.

          Dental calculus, or tartar as it is sometimes called, is a deposit which forms on the surfaces of the teeth at the gingival margin. Supragingival calculus appears principally in the areas near the orifices of the salivary ducts; e.g., on the lingual surfaces of the lower  
30       anterior teeth and on the buccal surfaces of the upper first and second molars, and on the distal surfaces of the posterior molars.

          Mature calculus consists of an inorganic portion which is largely calcium phosphate arranged in a hydroxyapatite crystal lattice structure similar to bone, enamel and dentine. An organic portion is also present and consists of desquamated epithelial cells, leukocytes,  
35       salivary sediment, food debris and various types of microorganisms.

As the mature calculus develops, it becomes visibly white or yellowish in color unless stained or discolored by some extraneous agent. This is undesirable from an aesthetic standpoint.

5 A wide variety of chemical and biological agents have been suggested in the art to retard calculus formation or to remove calculus after it is formed. Mechanical removal of this material periodically by the dentist is, of course, routine dental office procedure.

The chemical approach to calculus inhibition generally involves chelation of calcium ions and/or crystal growth inhibition which prevents the calculus from forming and/or breaks down mature calculus by removing calcium.

10 An observation that cranberry juice and other beverages could inhibit enzymes from plaque is noted in S. Kasket et al, "*In-vitro* Inhibition of Glucosyltransferase From Plaque Bacterium Streptococcus Mutans by Common Beverage and Food Extracts", Arch Oral Biology, Vol 30, No. 11/12, pp 821-826, 1985.

15 However, the S. Kasket et al disclosure suggests that "the effects of the fruit juices (tested in their system) were attributable mainly to the inhibition of the glucosyltransferase by the endogenous fructose and glucose."

Surprisingly, we have discovered that cranberry extract inhibits glucosyltransferase well beyond what can be attributed to sugars.

This finding is consistent with cranberry providing an anticaries benefit.

20 Although there have been a number of approaches disclosed for combating periodontal disease, caries and calculus, there is still the desire and need to develop improved products possessing such properties. Additionally, although the above described article discloses an *in-vitro* test with cranberry juice, there is no suggestion to form topical compositions such as mouthwashes, toothpastes, chewing gums and lozenges or that such  
25 compositions would be effective. This is due in large part to the short residence time of such compositions in the mouth. Additionally, the many other components in such compositions could affect the release of the active.

It is an object of the present invention to provide compositions which deliver antiplaque, antigingivitis, antiperiodontitis, anticaries and anticalculus benefits employing  
30 cranberries or parts of cranberries, such as extracts or juices. Additionally, other members of the Ericaceae family may be used, such as blueberries.

It is a further object of the present invention to produce an effective product using a mixture of above-mentioned materials and other antibacterial/antimicrobial agents.

It is still a further object of the present invention to provide anticalculus products  
35 which are cosmetically acceptable and do not inhibit remineralization of the teeth.

It is still a further object of the present invention to provide effective methods for combating calculus, plaque, caries, gingivitis and periodontitis.



These and other objects will become more clear from the detailed description which follows.

All percentages and ratios used herein are by weight unless otherwise specified. Also all measurements referred to herein are made at 25°C in the composition or on the  
5 pure material unless otherwise specified.

#### **SUMMARY OF THE INVENTION**

The present invention embraces a toothpaste composition comprising: (a) a safe and effective amount of an active antimicrobial agent selected from the group consisting of an anthocyanin or anthocyanidin selected from the group consisting of cyanidin,  
10 pelargonidin, and delphinidin, derivatives of these materials and mixtures thereof; (b) a silica dental abrasive; and (c) a soluble fluoride ion source.

The present invention also encompasses a method for retarding development of dental calculus, plaque, caries, gingivitis and periodontitis.

#### **DETAILED DESCRIPTION OF THE INVENTION**

15 The compositions of the present invention comprise cranberry extract in a suitable oral care carrier.

By "safe and effective amount" as used herein means sufficient amount of material to provide the desired benefit while being safe to the hard and soft tissues of the oral cavity.

20 By the term "comprising", as used herein, is meant that various additional components can be conjointly employed in the compositions of this invention as long as the listed materials perform their intended functions.

By the term "acceptable carrier", as used herein, is meant a suitable carrier which can be used to apply the present agent(s) to the oral cavity without undue toxicity, irritation,  
25 allergic response and the like, commensurate with a reasonable benefit/risk ratio.

Cranberries. Parts of Cranberries, such as extracts of Cranberries and juices and other members of the Ericaceae family

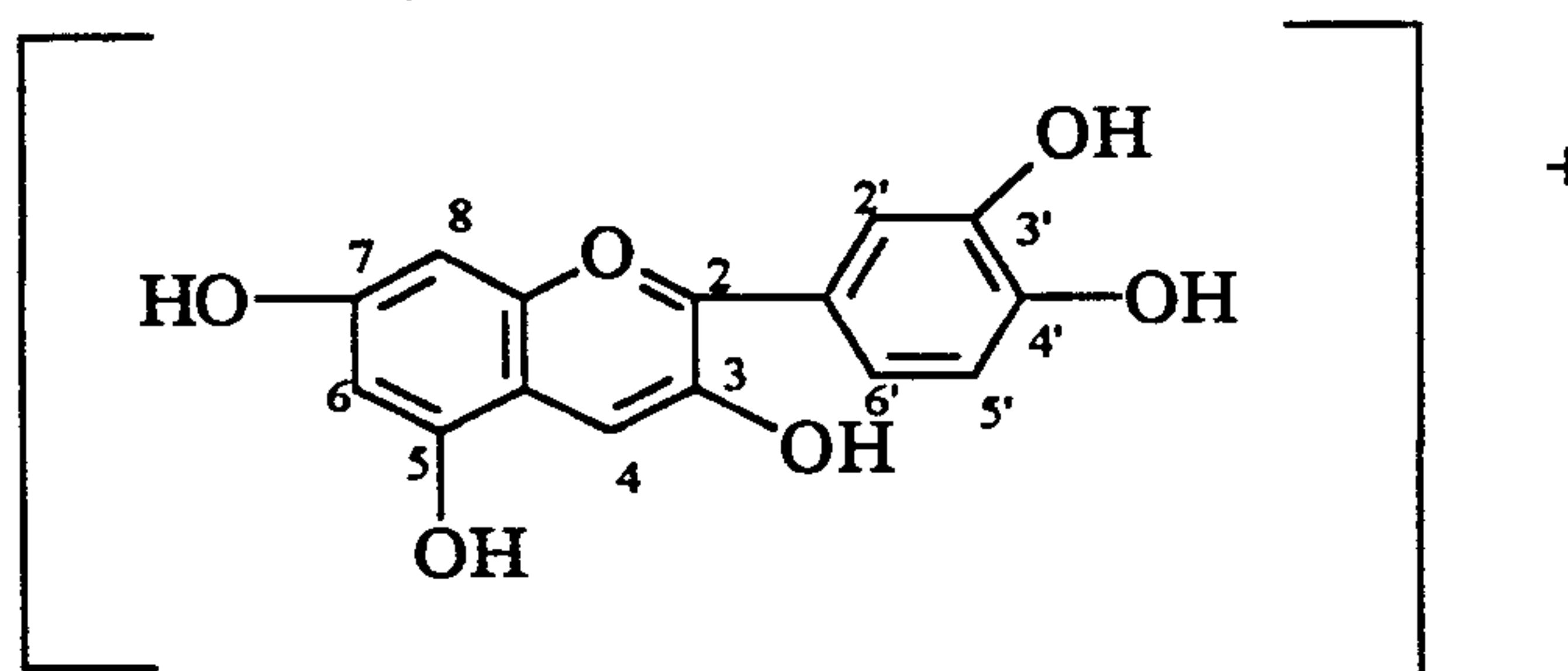
The materials useful in the present invention are those listed in the heading, as well as the specific chemicals which are present in those materials. Cranberry extracts are the  
30 preferred materials for use in the present invention and extraction can be done in a number of different ways, such as is shown in the examples.

Agents which may provide activity from cranberries are the pigments found in the skins of the berries.

35 Cranberry pigments fall into two main groups. The plastid pigments are associated with protoplasmic structure and include water-insoluble chlorophylls, carotene, and xanthophyll. The sap soluble pigments include the anthocyanins and anthoxanthins. The

anthoxanthins, or yellow flavonoids of cranberries, comprise quercetin-3-galactoside as the major pigment, followed by quercetin-3-rhamnoside, quercetin-3-arabinoside, quercetin, myricetin-3-arabinoside, and myricetin-3-digalactoside. The flavonoid pigments are of much greater importance than the water-insoluble pigments not only because they are present in much greater quantities, but because the flavonoids, particularly anthocyanins, are more stable than the chlorophylls or carotenoids.

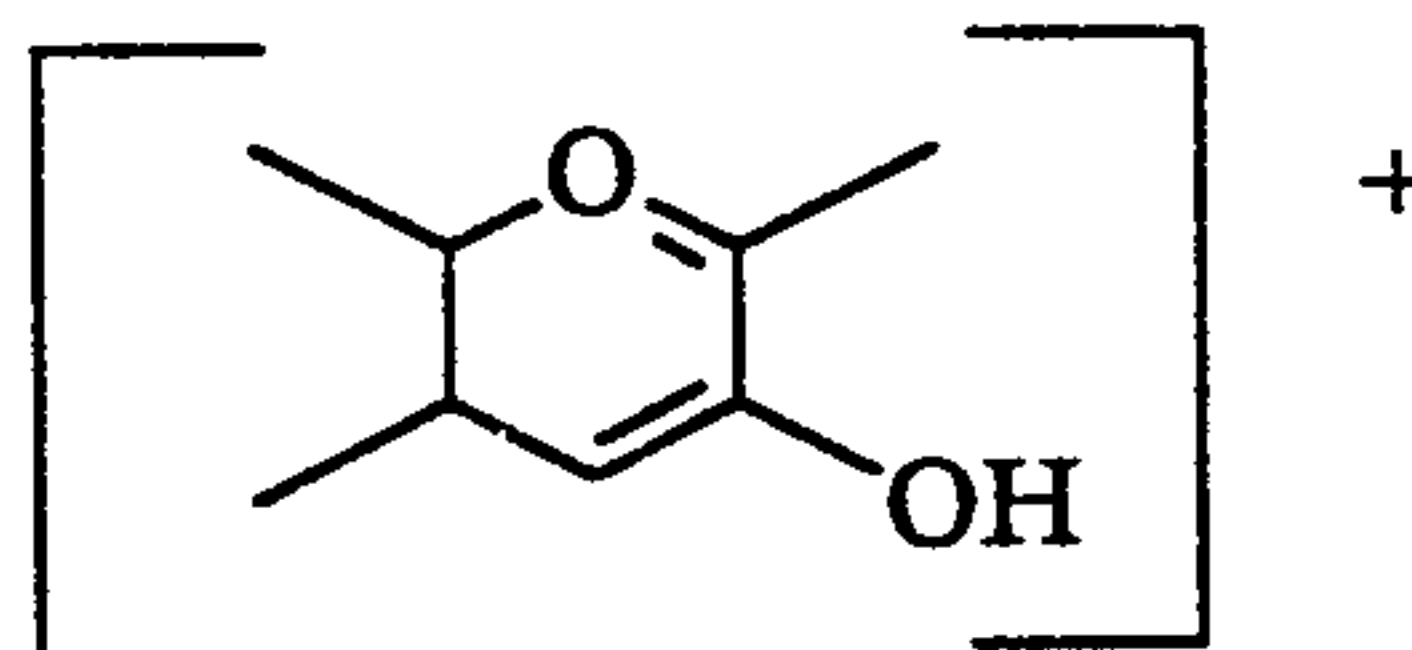
Anthocyanins are by far the most important pigment of cranberries. Anthocyanin as is derived from the Greek words for flower and blue, and introduced in 1835 by the French botanist L. C. Marquart to describe the blue pigment of comflowers. It has since been used in wider sense to include a large group of water soluble pigments of similar structure comprising the red, violet, and blue pigments of plant materials, since it was recognized that these pigments were merely different forms of the same substance. Anthocyanins are all based chemically on a single aromatic structure a 3, 5, 7, 3', 4' - pentahydroxy flavylium cation, cyanidin.



15

It consists of two benzene rings A and B joined by a 3 carbon link formed into a pyrone ring, which is considered associated with the B ring. The different classes of flavonoid compounds differ from one another only by the state of oxidation of this 3 carbon link. In the anthocyanins the state of oxidation may be represented as:

20

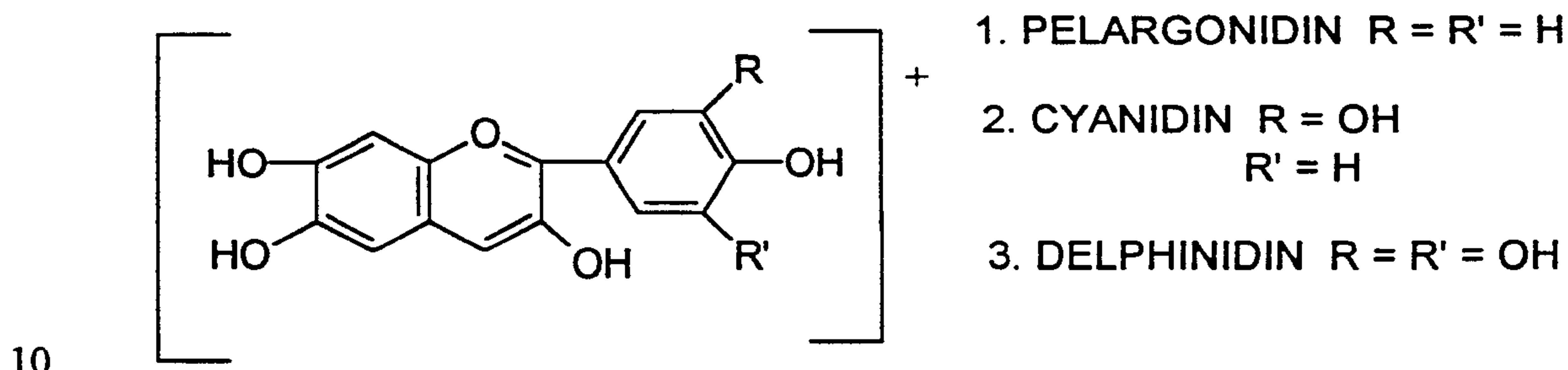


Anthocyanins are glycosidic, or sugar containing, in their natural state. According to Harborne (1967) the attached sugar may be glucose, galactose, arabinose, rhamnose, xylose, and many combinations of these sugars. The sugars are usually found in the 3, 5 and rarely in the 7 position of the molecule as defined above. The sugars impart stability and water solubility to the anthocyanin.

The aglycones, or sugar-free compounds are commonly known as anthocyanidins. The aglycones are insoluble in water, and tend to fade rapidly. Anthocyanins may be split up into anthocyanidins and sugar components by boiling in 20% hydrochloric acid for 3

minutes. The enzyme glucosidase has the same effect, splitting off the sugar and rendering the pigment less stable.

With few exceptions all anthocyanidins are hydroxylated in the 3, 5, and 7 positions, and fall into 3 major divisions; pelargonidin, cyanidin, and delphinidin, with 4, 5, and 6 hydroxyl groups respectively. The cyanidin group is most common in nature, followed by delphinidin and pelargonidin. In general the pelargonidins comprise the pink, scarlet, and orange red pigments, the cyanidins are crimson and magenta, while the delphinidins are mauve and blue. The basic structures may be represented as follows:



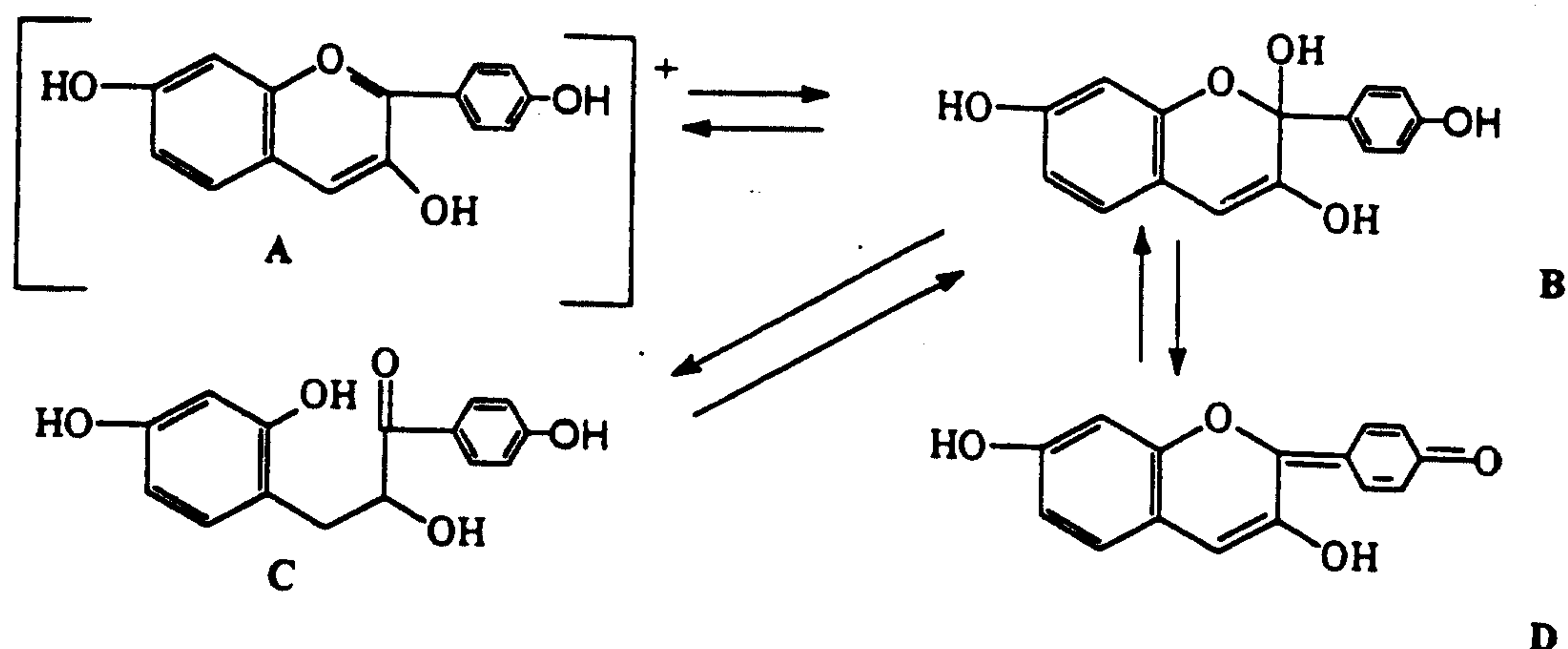
The visible color of the anthocyanidins depends on the number and orientation of hydroxyl and methoxyl groups on molecules. Increasing numbers of hydroxyl groups are associated with deepening of color. Color is dependent on the solvent used; a given anthocyanin pigment is bluer in alcoholic solutions than in aqueous solutions. pH has a marked effect on the color of anthocyanins. As the pH of the pigment solution is raised to near neutrality the pigment is transformed into the colorless pseudo-base form ( $A \rightarrow B$ ), which may convert to the yellow chalcone form by the opening of the 3 carbon ring ( $B \rightarrow C$ ). As the pH is raised above 7 deep violet or purple anhydrous bases are formed ( $B \rightarrow D$ ). This form is unstable and degrades rapidly. Although these reactions are reversible, substantial pigment losses due to degradation occur while the pigment is held at higher pH's.

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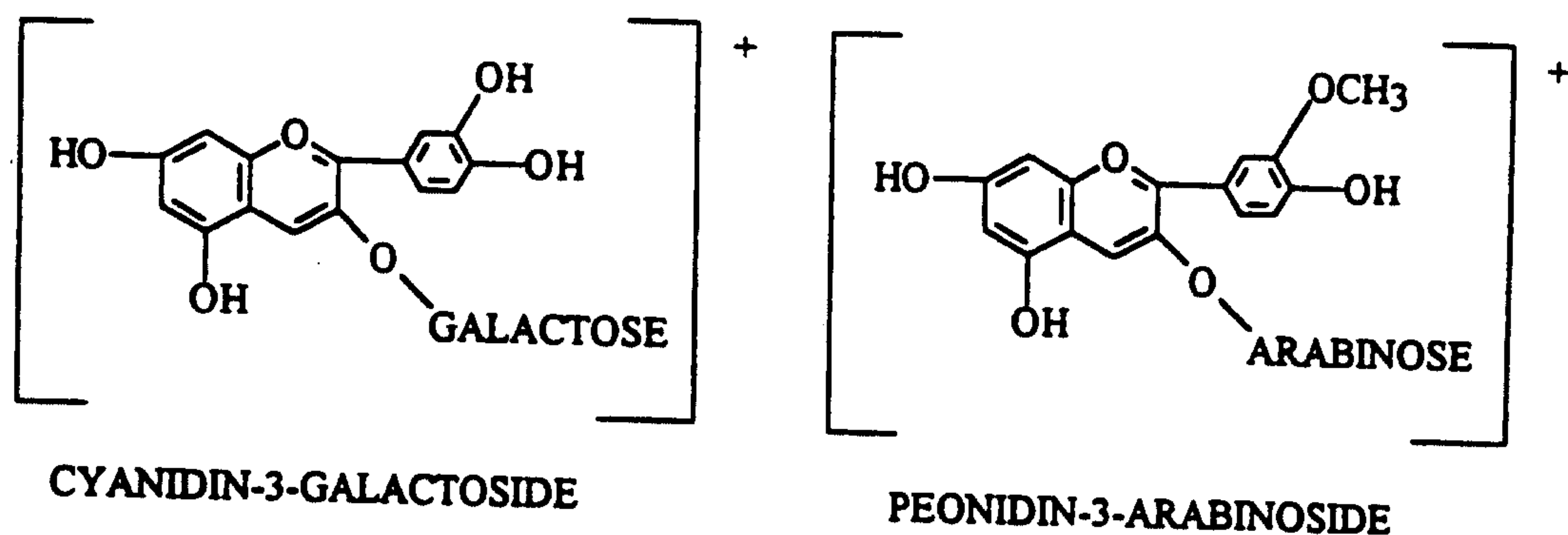
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The anthocyanins of the cranberry, four in number, are cyanidin-3-galactoside, cyanidin-3-arabinoside, peonidin-3-galactoside, and peonidin-3-arabinoside.



#### Acceptable Carrier

The carrier for the active component(s) can be any vehicle suitable for use in the oral cavity. Such carriers include the usual components of mouthwashes, toothpastes, tooth powders, prophylaxis pastes, lozenges, gums and the like and are more fully described hereinafter. Dentifrices and mouthwashes are the preferred systems.

In addition to the active agent(s), the present compositions may contain another antiplaque/gingivitis agent such as quaternary ammonium compounds, water insoluble agents such as triclosan, teas, as defined herein later, stannous salts and zinc salts. These types of agents are described in U.S. patent 4,894,220; January 16, 1990 to Nabi et al, U.S. Patent 4,656,031, April 7, 1987 to Lane et al; and U.S. Patent 5,004,597, April 2, 1991 to Majeti et al.

The abrasive polishing material contemplated for use in the present invention can be any material which does not excessively abrade dentin. These include, for example, silicas including gels and precipitates, calcium carbonate, dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and other such as disclosed



by Cooley et al. in U.S. Patent 3,070,510, December 25, 1962. Mixtures of abrasives may also be used.

5 Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with sources of soluble fluoride and polyphosphonates. For these reasons they are preferred for use herein.

10 The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 to 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Patent No. 3,538,230, issued March 2, 1970 and DiGiulio, U.S. Patent No. 3,862,307, June 21, 1975. Preferred are the silica xerogels marketed under the trademark "Syloid" by the W. R. Grace & Company, Davison Chemical Division. Preferred precipitated silica materials  
15 include those marketed by the J. M. Huber Corporation under the trademark, "Zeodent", particularly the silica carrying the designation "Zeodent 119". These silica abrasives are described in U.S. Patent No. 4,340,583, July 29, 1982.

20 The abrasive in the compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a toothpowder.

25 Flavoring agents can also be added to dentifrice compositions. Suitable flavoring agents include oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Sweetening agents which can be used include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Flavoring and sweetening agents are generally used in dentifrices at levels of from about 0.005% to about 2% by weight.

30 Dentifrice compositions can also contain emulsifying agents. Suitable emulsifying agents are those which are reasonably stable and foam throughout a wide pH range, including nonsoap anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Many of these suitable surfactants are disclosed by Gieske et al. in U.S. Patent No. 4,051,234, September 27, 1977.

35 Water is also present in the toothpastes of this invention. Water employed in the preparation of commercially suitable toothpastes should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 50%, preferably from about 20% to 40%, by weight of the toothpaste compositions herein. These amounts of

water include the free water which is added plus that which is introduced with other materials such as with sorbitol.

In preparing toothpastes, it is necessary to add some thickening material to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers of the type mentioned previously herein, xanthan gum, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition can be used.

It is also desirable to include some humectant material in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, and other edible polyhydric alcohols at a level of from about 15% to about 70%.

Another preferred embodiment of the present invention is a mouthwash composition. Conventional mouthwash composition components can comprise the carrier for the active agents of the present invention. Mouthwashes generally comprise from about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavor, sweeteners, humectants and sudsing agents such as those mentioned above for dentifrices. The humectants, such as glycerin and sorbitol give a moist feel to the mouth. Generally, on a weight basis the mouthwashes of the invention comprise 0% to 60% (preferably 10% to 25%) ethyl alcohol, 0% to 20% (preferably 5% to 20%) of a humectant, 0% to 2% (preferably 0.01% to 0.15%) emulsifying agent, 0% to 0.5% (preferably 0.005% to 0.06%) sweetening agent such as saccharin, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, and the balance water.

Suitable lozenge and chewing gum components are disclosed in U.S. Patent No. 4,083,955, April 11, 1978 to Grabenstetter et al.

Other optional components useful in the present invention are pyrophosphate salts such as those described in U.S. 4,515,772, May 7, 1985 to Parran et al. Also useful are nonionic antimicrobials such as triclosan described in U.S. 4,894,220, January 16, 1990 to Nabi et al.

Another agent which can be used in the present compositions is an alkali metal bicarbonate, such as sodium bicarbonate. These are stable items of commerce and can be used together with a peroxide compound in separate compartments such as disclosed in U.S. 4,849,213 and U.S. 4,528,180, both to Schaeffer.



The pH of the present compositions and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Such pH's are generally from about 3 to about 10, preferably from about 4 to about 8.5.

#### METHOD OF MANUFACTURE

5 The carrier compositions of the present invention can be made using methods which are common in the oral products area.

For example, toothpaste compositions may be prepared by mixing part of the humectant and water together and heating to 66°-71°C. The fluoride source, if present, is then added along with the sweetener, the opacifier and the flavor. The cranberry extract  
10 may be combined with the glycerine prior to adding to the other components.

#### COMPOSITIONS USE

The present invention in its method aspect involves applying to the oral cavity safe and effective amounts of the compositions. Generally an amount of at least about 5 grams  
15 of a mouthwash and at least about 0.5 of a toothpaste or liquid dentifrice.

The following examples further describe and demonstrate preferred embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the spirit and scope thereof.

20

#### EXAMPLE I

Given below is a mouthrinse composition representative of the present invention:

	<u>Component</u>	<u>Wt. %</u>
	Cranberry Extract	1.25
	Glycerine	12.00
25	SD Alcohol	14.00
	Distilled Water	71.50
	Sodium saccharin	0.15
	Monosodium Phosphate	0.50
	Flavor (Herbal Alpine)	0.10
30	Pluronic F (68) <sup>TM</sup>	0.50

#### EXAMPLE II

Given below is a dentifrice composition representative of the present invention:

	<u>Component</u>	<u>Wt. %</u>
	Cranberry Extract	5.00
35	Glycerine	19.00
	Sorbitol (70%)	18.00
	Water	6.91



	Sodium Fluoride	0.24
	Sodium Saccharin	0.15
	Monosodium Phosphate	1.00
	Titanium Dioxide	0.50
5	Silica	20.00
	Flavor	0.90
	SAS (27.9% sol'n)	4.00
	Fumed Silica	2.00
	Sodium CMC	0.30
10	PEG 400	3.00
	Sorbital Solution	19.00
	NaOH (50%)	(pH 6.5)

15 In the above compositions, the cranberry extract level may be varied from about 0.005 grams to about 10 grams. Additionally, the compositions may contain secondary antiplaque/antigingivitis or anticaries components, such as black tea, oolong tea, green tea, quaternary ammonium compounds, water insoluble non-cationic compounds such as triclosan, and metal salts such as stannous salts and zinc salts. Furthermore, other members of the Ericaceae family may be used. Green, oolong, and black teas are members of the general tea family (Camillia Sinensis).

**CLAIMS:**

1.       **A toothpaste composition comprising:**  
5       **(a) a safe and effective amount of an active antimicrobial agent selected from the group consisting of an anthocyanin or anthocyanidin selected from the group consisting of cyanidin, pelargonidin, and delphinidin, derivatives of these materials and mixtures thereof;**  
      **(b) a silica dental abrasive; and**  
      **(c) a soluble fluoride ion source.**
- 10       **2.       A composition according to claim 1 wherein said composition contains a soluble pyrophosphate ion source as an anticalculus agent.**
- 3.       A composition according to claim 1 which contains another antiplaque agent selected from the group consisting of tea (Camillia Sinensis), metal salts, triclosan and mixtures thereof.**
- 15       **4.       Use of a safe and effective amount of a toothpaste composition according to claim 1, 2 or 3 to reduce plaque on the enamel surfaces of a human or lower animal susceptible to plaque or calculus formation.**