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Review

Natural products' potential to maintain/ameliorate oral health: A review

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Abstract

Many diseases such as human dental caries result in the destruction of tooth structure; dental caries is an infectious disease leading to the destruction of tooth structure due to the acids produced on the fermentation of dietary carbohydrates by acidogenic bacteria. Bacteria colonise non-shedding oral surfaces, and produce lactic, acetic, and formic acids. Preserving tooth structure using fluoride in dental products may have its adverse effects on human health. The use of fluoride-containing dental products without supervision in children when the teeth are developing can lead to fluorosis. Therefore, the main aim of the present review was to identify natural oral healthcare products having minimum or no adverse effects in maintaining the integrity of tooth enamel. The active compounds observed in the natural plant products till date are polyphenolic compounds which contain antibacterial effects, and a potential to shift demineralisation to remineralisation. But their mechanism of action remain unclear. Therefore, further studies are needed to determine the effectiveness of these natural products and enhance their effect.

Introduction

Oral diseases are the most common chronic diseases (Frencken *et al.*, 2012) affecting the population. These diseases include dental caries, periodontal diseases, dental erosion, and developmental defects of enamel. Dental caries, also known as tooth decay, is a pathological process caused by the microorganisms in dental plaque resulting in localised destruction of the tissues at the tooth (Banerjee and Watson, 2015). The information regarding dental caries has been reported since 5000 B.C. Investigations are being carried out in order to determine its prevention and treatment. Several *in vivo* and *in vitro* studies have been reported regarding antibiotics that have potential to inhibit dental caries, but their long-term use leads to the alteration in human microflora, thus developing bacterial tolerance, diarrhoea, vomiting, and teeth staining, which further limit their use (Goldin and Gorbach, 1984; Dickinson and Surawicz, 2014; Gopinath *et al.*, 2014; Vennila *et al.*, 2014). In the past few decades, various studies have been reported on fluoride and its anticaries effect by shifting the demineralisation and remineralisation balance. However, using fluoride in dental products may have its adverse effects. The use of fluoride-containing dental products in children without parental supervision, when teeth are developing, can lead to dental fluorosis (Seow, 2015). It may also cause burning mouth syndrome, sore tongue, nausea, vomiting, diarrhoea, increased saliva, stomach pain or cramp, muscle weakness, and seizures if swallowed in high dose (Choi *et al.*, 2012; Dey and Giri, 2015; Waugh *et al.*, 2016).

An oral healthcare product having minimum or no adverse effects is needed to maintain the integrity of tooth. Therefore, there is increasing interest on natural products which may have therapeutic uses in dentistry (Groppo *et al.*, 2008; Newman, 2008). Presently, investigations are being carried out using different foods and beverages such as tea, coffee, grape, propolis, shiitake (*Lentinula edodes*) mushroom, or traditional herbs (Spratt *et al.*, 2012).

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Most researchers have reported that the active compounds observed in natural products are polyphenol compounds, a substance containing a minimum of one aromatic ring with one or more hydroxyl group (Yoo *et al.,* 2011). Some of these compounds which are extracted from different natural products were showed to have bactericidal or bacteriostatic effect on oral biofilms (Ferrazzano *et al.,* 2011); whereas some others were observed to regulate the demineralisation and remineralisation of dental hard tissue (Chu *et al.,* 2007; Cheng *et al.,* 2008). In the present review, we summarised previous studies on the natural products and their active compounds, particularly for the prevention of dental caries.

Galla chinensis

Galla chinensis (GC), hypothetically an interesting agent for the prevention of dental caries, is produced from the leaves of *Rhus chinensis* Mill infested by the Chinese sumac aphids (*Melaphis chinensis* Bell). GC extracts have been reported to effectively inhibit demineralisation and promote remineralisation of dental hard tissue (Chu *et al.,* 2007; Cheng *et al.,* 2008; Zou *et al.,* 2008; Guo *et al.,* 2012). It was reported that the effect of fluoride in shifting demineralisation to remineralisation is enhanced with the presence of GC extracts (Cheng *et al.,* 2008). Huang *et al.* (2010) reported a potent effect of nanohydroxyapatite (HAp) and GC on remineralisation. To date, however, the mechanism of action of GC is unclear, but it has been suggested that the active compound of GC might act as a carrier in supplying calcium ions (Ca^{2+}) from the remineralising solution to the body of the early carious lesion (Chu *et al.,* 2007).

A hypothesis "enamel organic matrix - *Galla chinensis* - Ca" was proposed by Zhang *et al.* (2009a) based on the evidence of atomic force microscopy study. Morphological changes and increased roughness were observed on the carious enamel surface after treatment with the extracts of GC. An abundant number of nano-size elliptical particles were observed to be distributed over the lesion surface (Zhang *et al*., 2009b). Furthermore, in order to analyse the morphological, chemical, and crystal characteristics, scanning of the remineralised early carious lesion using other techniques such as scanning electron microscopy, energy dispersive spectroscopy, and X-ray micro-diffraction was used, respectively (Zhang *et al*., 2009b). GC is a complex compound. Chu *et al.* (2007) extracted GC-B1 and GC-B2 by spectroscopic technique, and they were characterised later as gallic acid and methyl gallate, respectively. In an *in vitro* study, Cheng *et al.* (2008) compared the remineralising effect of GC extract with gallic acid using transverse microradiography (TMR). The results demonstrated that both of these compounds had the potential to reduce integrated mineral loss and lesion depth in comparison to the negative control. Further investigations displayed the potential of GC extract in remineralising the body of lesion, whereas gallic acid showed mineral deposition on the surface layer (Cheng *et al.,* 2008).

In order to observe the potential of GC extracts and gallic acids, researchers carried out investigations to determine the mechanism of remineralisation (Cheng *et al.,* 2009; 2010; Cheng and ten Cate, 2010). Gallic acids were observed to act as calcium carrier, and deposit the mineral on surface of the carious lesion. GC extract contained various polyphenol compounds and had the potential in preventing the mineral deposition on the surface layer of lesion, therefore transmitting calcium ions to the body of the carious lesion. Tang *et al.* (2015) further reported that gallic acids, in addition to up-regulating remineralisation, also have the potential to modulate the morphology and structure of the crystallites.

GC extracts are acidic in pH, which can demineralise enamel. Therefore, Huang *et al.* (2012) in an *in vitro* study determined the effect of pH on stability and demineralisation inhibition properties of GC extract. It was observed that GC extracts were unstable under neutral and alkaline pH levels. Furthermore, they reported that variation in pH levels of GC extract did not have an influence on demineralisation inhibition of dental enamel (Huang *et al.,* 2012).

Moreover, GC extract has also been reported to have potential in inhibiting dental biofilm formation. Cheng *et al.* (2010) in an *in vitro* experiment determined the effect of GC extracts on different stages of inoculated salivary biofilm, and observed a strong potential of the extract to inhibit microbial growth and acid production.

Xie *et al.* (2008) further analysed the potential of GC extract against four early colonisers of oral biofilm (*Streptococcus sanguis, S. mutans, Actinomyces naeslundii,* and *Lactobacillus rhamnosus*). The results showed a strong potential of GC extract in inhibiting multiple species of bacterial colonisation and demineralisation of dental enamel.

Propolis

Propolis has gained a vast research interest due to its antimicrobial effect against various microorganisms. Propolis is a compound comprises of flavonoids, organic acids, phenols, enzymes, vitamins, and minerals (Velikova *et al.*, 2000; Usia *et al.*, 2002). Koo *et al*. (2002b) were the first to report about propolis inhibitory effect against microbial growth and glucosyltransferase activity. Furthermore, Sonmez *et al*. (2005) determined the cytotoxicity of gingival fibroblasts, and reported strong antibacterial and non-cytotoxic activity of propolis.

To determine the mechanism of propolis, Duarte *et al*. (2006b) investigated the effect of different propolis compounds (ethanolic extract and hexane extract) on *S. mutans* biofilms and caries in rats. It was suggested that the anticaries effect of propolis is attributed to the high content of fatty acids which down-regulate acid production and tolerance by cariogenic microorganisms. Furthermore, Kouidhi *et al*. (2010) in an *in vitro* experiment reported a strong anticaries and antibiofilm potentials of Tunisian propolis ethanolic extract.

Magnolia bark

The bark of magnolia plant has been used as medication since the last 2,000 years (Watanabe *et al.*, 1983). Various researchers have reported that magnolol and honokiol, the two compounds of magnolia bark extract (MBE), have the potential to inhibit bacterial growth involved in dental caries (Chang *et al.*, 1998; Ho *et al.*, 2001; Greenberg *et al.*, 2007). On the basis of its anticariogenic properties, a group of researchers added MBE to xylitol chewing gum (Campus *et al.*, 2011). On 30 days randomised controlled intervention trial, a positive effect was observed on the oral health which included the decrease in salivary *S. mutans*, bleeding on probing, and plaque acidogenicity (Campus *et al.*, 2011).

Tea

Tea is a beverage consumed widely around the world, particularly in the Asian countries. In the United States, diet tea is considered a major source of flavonols and flavan-3-ols (Song and Chun, 2008). However, tea contains polyphenols whose types and levels depend on the technique from which the tea is being processed (Astill *et al.*, 2001).

The effectiveness of green tea extract (GTE) is attributed to its polyphenolic group (catechins, epigallocatechin-3-gallate, epigallocatechin, epicatechin-3-gallate, and epicatechin) (Taylor *et al.*, 2005). Similarly, oolong tea extract (OTE) is also rich in polyphenolic groups (catechins and oligomerised catechins) (Balentine *et al.*, 1997). In contrast to GTE and OTE, active constituents in black tea are theaflavins (oligomers) and thearubigins (polymers). Various researchers have reported on the biologically active effect of these phenolic groups and theaflavins, particularly in the deterrence of dental caries and oral cancer (Yang, 1997; Yang *et al.*, 1999; 2000; 2002; Hamilton-Miller, 2001).

In various *in vivo* and *in vitro* studies, researchers have reported a potent effect of GTE against dental caries attributed to its polyphenolic group. It has been found to inhibit the bacterial colonisation of the cariogenic bacteria (*S. mutans*). Araghizadeh *et al.* (2013) in an *in vitro* study reported that other than anticariogenic effect, GTE also has the potential to inhibit periodontopathic bacterial colonisation. Furthermore, GTE has also been reported to decrease the incidence of pathological conditions such as oral cancer, stroke, cardiovascular disease, and obesity (Taylor *et al.*, 2005; Chacko *et al.*, 2010).

Another group of researchers (Awadalla *et al.*, 2011) suggested that rinsing with sugar-free solution of green tea can deter the growth of *S. mutans*, which is the cariogenic bacterium in both the saliva and dental plaque. Lee *et al.* (2004) suggested that the use of green tea leaves and brewed black tea could be suitable for the slow release of its active constituents catechins and theaflavins, respectively in order to prevent dental caries. The participants were asked to chew 2 g of green tea leaves or brewed black tea for the duration of 2 - 5 min. Later after rinsing, on performing high-performance liquid chromatography technique of saliva after 1 h, high concentrations of green tea catechins (GTC) (C max = 131.0 - 2.2 μM) and black tea theaflavins (BTT) (C max = 1.8 - 0.6 μM) were observed.

The GTE *Camellia* extract MJ (Taiyo Kagaku), which is also used as a food additive, contains over 1,500 ppm fluoride with approximately 0.06 g catechin/L. Whereas, GTE as a whole has been reported to contain 0.5 - 1 g of catechin/L. An *in situ* experiment was conducted by Suyama *et al.* (2011) using *Camellia* extract MJ in chewing gum, considering it as a rich natural source of fluoride. They observed an increase in acid resistance and remineralisation of dental enamel (Suyama *et al.*, 2011).

Nakahara *et al.* (1993) reported that the antiglucosyltransferase activity of OTE is attributed to its polymeric polyphenolic group. Later, Ooshima *et al*. (1993) in an *in vivo* study on rats evaluated an anticariogenic effect of OTE. The rats were infected with specific cariogenic bacteria, either *S. sobrinus* 6715 or *S. mutans* MT814R. Later, OTE was administered in the diet and drinking water which led to significant reduction in cariogenic bacteria and plaque deposition. In an *in vivo* study, Ooshima *et al.* (1994) reported that OTE had a potent effect in reducing the dental plaque in humans.

Matsumoto *et al*. (1999) reported that other than inhibiting cariogenic bacterial growth, OTE also had the potential to inhibit microbial colonisation on the tooth surface attributed to the polyphenolic group, which led to the reduction in cell surface hydrophobicity of *S. mutans*.

Grapes

Researchers have reported that grape (*Vitis vinifera*) and its seed extracts have an anticariogenic potential (Sarni-Manchado *et al.,* 1999; Daglia *et al.,* 2007a; Thimothe *et al.,* 2007). Duarte *et al.* (2006a) suggested that proanthocyanidins, a type of polyphenols, can inhibit dental caries as it has potential to reduce the activity of the surface-absorbed glucosyltransferase and F-ATPase; furthermore, it can also reduce acid production by cariogenic bacteria. There are a few types of grapes which contain phenolic compounds, and have the potential to reduce glucosyltransferase-B (GtfB) and glucosyltransferase-C (GtfC) activities of the cariogenic bacteria (*S. mutans*) (Yano *et al.,* 2012).

Xie *et al*. (2008) later assessed and reported that the additional potential of grape other than demineralisation inhibition is to promote remineralisation of an artificial carious lesion developed on the root of the tooth. It is proposed by various researchers that the seed extract has a potential for remineralisation by promoting deposition of mineral content on the superficial layer of the lesion (Kosasi *et al.,* 1989; Xie *et al.,* 2008). Later, on comparing the effect of grapes seed extracts and fluoride (Fluorinol®), separately, and in combination (2,000 μg/mL of seed extract and 10.2 mg/mL fluoride), the antiplaque and antioxidant potency of grape seed extracts was observed to increase when used in combination with fluoride (Furiga *et al.,* 2014).

The phenolic content in the wines produced by grape extract have been suggested to inhibit bacterial growth. The phenolic compounds in wine, also in grape and pomace extracts, have been reported to have bactericidal effect on the cariogenic bacteria (*Streptococcus* spp.) (Thimothe *et al.,* 2007). Munoz-Gonzalez *et al*. (2014) determined the effect of red wine and alcohol-free red wine on biofilm model of the supra-gingival plaque, and reported that both of them possessed strong antimicrobial effect, particularly against *F. nucleatum* and *S. oralis*.

Coffee

Other than tea, other most commonly consumed drink globally is coffee which has been reported to be effective against various diseases including dental caries (Daglia *et al.,* 2007b; Antonio *et al.,* 2011; 2012). The effectiveness of coffee against bacteria is due to the presence of polyphenols (Koo *et al.,* 2002a; Yatsuda *et al.,* 2005; Farah *et al.,* 2006). Antonio *et al.* (2011; 2012) observed bactericidal effect of coffee against *S. mutans* in addition to demineralisation inhibition potential of biofilm-coated dental enamel. The bactericidal effect of coffee is attributed to the bacterial lysis followed by calcium release. Meckelburg *et al*. (2014) also reported that the consumption of coffee could be effective in inhibiting bacterial growth.

Cacao bean

The major compound of chocolate from cacao beans is polyphenols which have antiglucosyltransferase potential. Ooshima *et al.* (2000b) in an *in vitro* study reported anticariogenic potential, but not strong enough to reduce the cariogenic activity of sucrose. They further suggested that cocoa has the potential to become a novel anticariogenic prophylactic agent (Ooshima *et al.,* 2000a).

Hesperidin

Hesperidin is a natural product rich in citrus flavonoids, and has the potential to preserve collagen matrix of the bovine dentinal matrix against the proteolytic degradation. Liu *et al*. (2004) reported the mechanism of action and interaction of hesperidin with the collagenous and non-collagenous proteins, which resulted in stabilising the collagen matrix and promoting remineralisation of the human dental hard tissue.

Hiraishi *et al.* (2011) determined that hesperidin had the capability to reduce demineralisation from acids, and increase remineralisation process. Later, a group of scientists studied the effect of hesperidin on mineral loss and depth of lesion which displayed the potential of the product to inhibit demineralisation and promote remineralisation under fluoride-free conditions (Islam *et al.*, 2012).

Poly-γ-glutamic acid

Poly-γ-glutamic acid (PGGA) is a naturally occurring homopolyamide containing D- and L-forms of glutamic acid units, and connected via amide linkages (Qamar *et al.*, 2016). These linkages are moulded between the α-amino and γ-carboxyl group. Qamar *et al.* (2016) suggested that PGGA, being a highly viscous material, had the potential for coating the enamel surface of the tooth by forming a protective layer. The α-COOH group in PGGA molecule is free, and may promote binding of protective coating layer to the enamel surface, thus inhibiting the dissolution of the enamel HAp.

Furthermore, as a mechanism of action, the anionic α-COOH group has been proposed as capable to bind cationic entity of other molecule or biopolymer, or can behave or remain as a free carboxylic acid. Therefore, PGGA can dissolve particularly Ca and Mg compounds to form a stable ionic complexes (Qamar *et al*., 2016; 2019).

Conclusion

It can be concluded from the present review that natural products do have potent effect in inhibiting dental caries, but not without some drawbacks. Firstly, they have a weaker effect than traditional antimicrobials or fluoride-containing chemotherapeutic agents. Secondly, the active compounds in various natural products are still unclear; therefore, further studies are required to determine the active compounds in natural products with cariogenic potential, and modify them for stronger potential.

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