European Journal of Pharmacology 720 (2013) 77–83

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Use of polyphenols in periodontal inflammation

Iro Palaska [a], Evangelos Papathanasiou [a,b], Theoharis C. Theoharides [a,c,d,*]

[a] Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 150 Harisson Avenue, Boston, MA 0211, USA
[b] Department of Periodontology, Tufts University School of Dental Medicine, 1 Kneeland Street, Boston, MA 02111, USA
[c] Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, 136 Harrison Avenue, Boston, MA 02111, USA
[d] Department of Biochemistry, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

ARTICLE INFO

Article history:
Received 6 July 2013
Received in revised form
23 October 2013
Accepted 24 October 2013
Available online 31 October 2013

Keywords:
Bacteria
Cytokine
Polyphenol
Flavonoid
Inflammation
Mast cell
Periodontitis
Treatment

ABSTRACT

Periodontitis is an oral inflammatory disease of polymicrobial origin that causes the destruction of gingival connective tissue and the alveolar bone supporting the teeth. Host immune and inflammatory responses due to specific periodontopathogens and their metabolic products mediate local tissue destruction. Periodontal disease affects as many as 30% of adults and it is one of the most common chronic human diseases. However, traditional therapeutic modalities for periodontitis, including non-surgical or surgical periodontal therapy and occasional adjunctive antimicrobial therapy, have been only partially successful. Moreover, the widespread development of antibiotic resistance in pathogenic bacteria and unwanted effects on the gut flora necessitates new strategies to better control periodontal inflammation. Recently, natural compounds capable of modulating the host inflammatory response have received considerable attention. Here we review (Pubmed 1997 to 2013) the orally-related anti-bacterial and anti-inflammatory actions of polyphenols, naturally occurring molecules, capable of modulating the host inflammatory response. Of these, certain flavonoids appear to stand out because of their beneficial profile and clinical evidence. Unique formulations of novel flavonoids may be useful for further development as possible therapeutic agents for periodontal inflammation.

Contents

1. Introduction

Periodontitis is among the most common human diseases. It has been estimated that in the US, at least 47% of adults aged 30 years and older have periodontitis (Papapanou, 2012). According to a report by

* Correspondence to: Tufts University School of Medicine, Department of Integrative Physiology and Pathobiology, 136 Harrison Avenue, Suite J304, Boston, MA 02111, United States. Tel.: +1 617 636 6866; fax: +1 617 636 2456.
E-mail address: theoharis.theoharides@tufts.edu (T.C. Theoharides).

0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.10.047

the World Health Organization, periodontitis leading to tooth loss affected 5–15% of most populations worldwide (Armitage, 2004). Periodontitis is a chronic multifactorial inflammatory disease caused by microorganisms and characterized by progressive destruction of the tooth supporting apparatus, leading to tooth loss (Preshaw et al., 2004). Preservation of periodontal health is a key component of oral and overall health and as such is a fundamental human right (Baehni and Tonetti, 2010).

Periodontal breakdown is a result of the complex interplay between the pathogenic bacteria forming the biofilm, and the host's immune responses (Benakanakere and Kinane, 2012b). During the establishment of periodontal disease, Gram-negative microorganisms increase up to 80%, colonizing the gingival sulcus and forming subgingival plaque, leading to the formation of periodontal pockets and gum recession. Periodontitis is mainly clinically characterized by bleeding and swelling of the gums, exposed roots, loose teeth, bad breath and can ultimately lead to tooth loss. Dental bacterial biofilms are the primary etiological factor for periodontal diseases, composed of more than 300 different bacterial species. Among the major pathogens in the periodontal pockets are *P. gingivalis* and *P. intermedia*, while high levels of *A. actinomycetemcomitans* are more commonly detected in patients with aggressive periodontitis (Teles et al., 2013). The cell wall components and various toxic products of periodontal pathogens can trigger the host response and induce destruction of periodontal tissues. This cross-talk between the microbial insult and the immune response is mediated by multiple mediators, including chemokines, cytokines, and metalloproteinases (MMPs) secreted locally by host cells, including neutrophils, mast cells, macrophages and lymphocytes (Benakanakere and Kinane, 2012a). Elevated levels of several inflammatory mediators, such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF-α), interferon gamma (IFN-γ) and prostaglandin E_2 (PGE_2) have been detected in the gingival tissues and the gingival crevicular fluid (GCF) of patients affected by periodontitis (Papathanasiou et al., 2013; Gupta, 2013).

Traditional therapeutic modalities in managing periodontal diseases mainly involve dental cleaning, subgingival scaling/root planing and meticulous oral hygiene, aiming at the reduction of the levels of pathogenic bacteria in periodontal pockets (Heitz-Mayfield, 2002). The most common drugs that have been used as adjuncts to scaling/root planing are antibiotics, administered systemically or topically in periodontal pockets (Heitz-Mayfield, 2009; Leszczynska et al., 2011). Moreover, many clinical trials have explored the use of non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to periodontal therapy to counteract the inflammatory and osteoclastic activity of prostanoids (Salvi and Lang, 2005; Kirkwood et al., 2007; Noguchi and Ishikawa, 2007; Hasturk et al., 2012; Pinho et al., 2008). Due to the heterogeneity of the study designs, it is still difficult to reach a conclusion whether or not there are any additional clinical benefits of such adjunctive medications, but also on the type dose, and the most effective time that the drug should be prescribed. In addition, the majority of these drugs are associated with significant unwanted side effects, including bleeding, gastrointestinal problems as well as renal and hepatic impairment that preclude their widespread use Souza et al., (2012).

Control of the bacterial-induced inflammatory host response, which is mainly responsible for the destruction of the periodontal tissues, is difficult and has not been sufficiently explored. The recent identification of pharmacological properties of polyphenols including flavonoids and proanthocyanidines (PACs) has generated interest in their potential use as adjuncts to managing inflammatory conditions, including periodontitis. As a result, we reviewed the potential use of natural polyphenols that exhibit both anti-bacterial and anti-inflammatory properties (Govindaraj et al., 2011).

2. Polyphenols

Polyphenols are the most abundant antioxidants in the human diet and are widespread constituents of fruits and beverages, such as tea, coffee, and wine (Landete, 2012). They represent a wide variety of compounds divided into several classes, such as phenolic acids, proanthocyanidines and flavonoids (Beecher, 2003). Epidemiological, clinical, and animal studies support a role of polyphenols in the prevention of various chronic diseases, including cardiovascular disease, inflammatory and metabolic diseases, neurodegenerative diseases, and some cancers (Middleton et al., 2000; Mitjavila and Moreno, 2012).

2.1. Proanthocyanidines (PACs)

There has been a growing interest in PACs due to their antioxidant, anti-inflammatory, antibacterial, anti-aging and anticancer properties. PACs is a class of phenolic compounds that take the form of oligomers or polymers of polyhydroxy flavan-3-ol units, such as (+)-catechin and (−)-epicatechin (Yamakoshi et al., 2002). They are widely distributed in the plant kingdom, especially in fruits, berries, nuts, seeds and vegetables (Gu et al., 2004).

A PAC-enriched cranberry fraction inhibited *A. actinomycetemcomitans* lipopolysaccharides (LPS)-induced MMP-3 and MMP-9 production by gingival fibroblasts (Bodet et al., 2007). This fraction inhibited the phosphorylation state and expression of fibroblast's activator protein-1 (AP-1), which is prominently involved in the transcriptional regulation of many pro-inflammatory mediators, such as IL-6, IL-8, PGE_2 and MMPs (La et al., 2009). A PAC-enriched cranberry fraction inhibited IL-6, IL-8, and PGE_2 production by gingival fibroblasts stimulated with LPS from five different periodontopathogens: *A. actinomycetemcomitans*, *F. nucleatum*, *P. gingivalis*, *T. denticola* and *T. forsythia* (Bodet et al., 2007). The A-type cranberry PAC (AC-PAC) inhibited the production of MMPs by human monocyte-derived macrophages stimulated by *A. actinomycetemcomitans* LPS, as well as the catalytic activity of recombinant MMP-1 and MMP-9 associated with reduced phosphorylation of key kinases and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB p65) activity (La et al., 2009). Another in vitro study showed that while AC-PACs did not interfere with growth, they neutralized all the virulence properties of *P. gingivalis* and inhibited the secretion of IL-8 and chemokine (C–C motif) ligand 5 (CCL5) through reduced activation of the NF-κB p65 pathway without affecting the secretion of IL-6 by epithelial cells stimulated with *P. gingivalis* (La et al., 2010). AC-PACs could significantly inhibit osteoclast differentiation, even when cells were treated with the lowest concentration (10 μg/mL) of AC-PACs (Tanabe et al., 2011). PACs extracted from Myrothamnus flabellifolia (MF) showed reduced *P. gingivalis* adhesion and invasion about 50% (Lohr et al., 2011). AC-PACs and licochalcone A inhibited *P. gingivalis* growth and biofilm formation and also reduced LPS-induced secretion of IL-1β, TNF-α, IL-6 and IL-8 (Feldman and Grenier, 2012). In summary, the benefit of PACs in relation to periodontal disease included inhibition of: (a) biofilm formation and adhesion of periodontopathogenic bacteria, (b) proteolytic activities of bacteria, (c) cytokine production by immune and mucosal cells, and (d) inhibition of MMP production (Bonifait and Grenier, 2010).

2.2. Flavonoids

Flavonoids is a subclass of naturally occurring polyphenolic compounds also found in fruits, vegetables, nuts, seeds, herbs, spices and red wine (Middleton et al., 2000). Flavonoids are composed of two aromatic rings linked through three carbon atoms that form an oxygenated heterocyclic ring (Schroeter et al., 2003). Variations on the basic structure of flavonoids yield different classes including flavonols, flavones, flavanols, and flavanones (Huxley et al., 2004).

Flavonoids possess antioxidant, anti-allergic, anti-inflammatory, cyto-protective and antibacterial activity (Middleton et al., 2000; Theoharides et al., 2001; Kempuraj et al., 2005). The inhibitory effects of flavonoids on inflammatory processes involved in periodontitis are depicted in Fig. 1.

2.2.1. Luteolin

Luteolin, is a natural anti-oxidant capable of inhibiting mast cell mediators release, such as histamine, vascular endothelial growth factor (VEGF), IL-6 and TNF-α from human cultured mast cells (Kempuraj et al., 2005) as well as release of leukotrienes (LTs) and prostaglandin D_2 (PGD_2) (Kimata et al., 2000). Luteolin also inhibits mast cell-dependent stimulation of T cells (Kempuraj et al., 2008). Moreover, luteolin inhibited LPS-stimulated TNF-α and IL-6 release through inhibition of protein tyrosine phosphorylation and NF-κB-mediated gene expression from macrophages (Xagorari et al., 2001).

Luteolin proved to be a potent inhibitor of nitric oxide (NO) production in vitro from LPS-stimulated human gingival fibroblasts, important cells in periodontal soft tissue remodeling, through interference with LPS signaling pathways (Gutierrez-Venegas et al., 2006). Another in vitro study showed that luteolin down regulated the production of NO and IL-6 in a concentration-dependent manner with 50 μM luteolin reducing NO production by 86% and 25 μM also blocking completely the secretion of IL-6 by blocking NF-κB signaling through inhibition of nuclear translocation and DNA binding activity of NF-κB p50 subunit (Choi et al., 2011). In a recent in vitro study, luteolin was shown to inhibit the effects of LPS obtained from *P. gingivalis* in human gingival fibroblasts by inhibiting the activation of mitogen-activated protein kinases (MAPK) and serine/threonine-specific protein kinase, as well as the expression of cyclooxygenase-2 (COX-2) (Gutierrez-Venegas and Contreras-Sanchez, 2013). Elevated PGE_2, which is produced by mast cells, was detected in the gingival crevicular fluid of patients with chronic periodontitis compared to periodontally healthy subjects (Preshaw and Heasman, 2002).

2.2.2. Quercetin

Quercetin is one of the most potent scavengers of reactive oxygen species (ROS) including superoxide and reactive nitrogen species (Middleton et al., 2000). The effects of quercetin on a variety of inflammatory processes and immune responses are well established (Min et al., 2007). Several in vitro studies using different cells have shown that quercetin can inhibit LPS-induced TNF-α production in macrophages (Manjeet and Ghosh, 1999) and LPS-induced IL-8 production in human pulmonary epithelial cells (Geraets et al., 2007). In addition, quercetin inhibits immunoglobulin E (IgE)-mediated release of histamine, tryptase and production of inflammatory cytokines such as IL-6, IL-8 and TNFα from human cultured mast cells (Kimata et al., 2000; Kempuraj et al., 2005). Quercetin also inhibits the production and gene expression of TNF via modulation of NF-κB in human peripheral blood mononuclear cells (Nair et al., 2006).

Quercetin inhibited NO production from LPS-induced human gingival fibroblasts in vitro with maximal inhibition of 35%, while inhibition due to luteolin was 90% (Gutierrez-Venegas et al., 2006). Quercetin isolated from the Lotus leaf had in vitro antimicrobial activity against *A. actinomycetemcomitans*, *A. viscosus*, *P. gingivalis*, *F. nucleatum*, and *A. naeslundii* with the minimum inhibitory concentrations of 0.625, 1.25, 1.25, 0.625 and 2.5 mg/mL, respectively (Li and Xu, 2008). Quercetin also reduced LPS-induced osteoclast formation in a rat model (Cheng et al., 2010).

2.2.3. Other types of flavonoids

Licorice-derived licoricidin (LC) and licorisoflavan (LIA) inhibited the secretion of IL-6 and CCL-5, as well as MMP-7,-8, and -9 from LPS-stimulated macrophages by reducing activation of NF-κB p65, but did not affect the secretion of IL-8 (La et al., 2011). The polymethoxy flavonoids nobiletin and tangeretin significantly suppressed the bone-resorbing activity induced by LPS and suppressed NF-κB ligand-induced production of osteoclasts, and restored the alveolar bone mass in a mouse experimental model of periodontitis (Tominari et al., 2012). Epigallocatechin-3-gallate (Chatterjee et al., 2012) inhibited the in vitro growth of *P. gingivalis*, *P. intermedia* and *P. nigrescens*, as well as the adherence of *P. gingivalis* to human buccal epithelial cells (Sakanaka et al., 1996). In another in vitro study, catechin inhibited osteoclast formation of primary osteoclastic cells co-cultured with bone marrow cells and induced apoptotic cell death of osteoclast-like multinucleated cells (Nakagawa and Yokozawa, 2002).

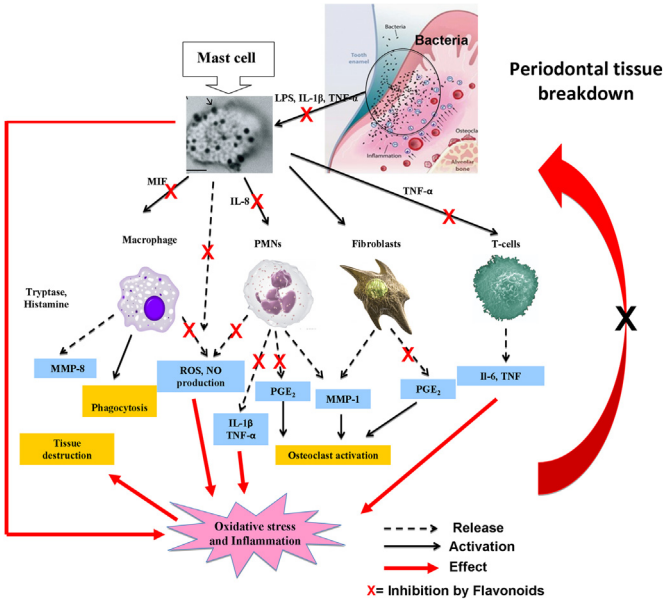

Fig. 1. Diagrammatic representation of the proposed pathways involved in periodontal inflammation and sites of the inhibitory action of flavonoids.

3. Clinical use

The use of therapeutic agents in oral hygiene products, or through local delivery vehicles, is a well established approach for improving periodontal health (Ciancio, 2011). A number of human and rodent studies using polyphenols are summarized in Table 1.

3.1. Toothpaste

Adding active agents to dentifrices is a common method to enhance mechanical plaque removal and to prevent the establishment of periodontal inflammation. One clinical study showed that two pharmaceutical preparations containing 0.1% quercetin and naringenin in the form of toothpaste significantly inhibited plaque formation by reducing the accumulation of microorganisms and by preventing the bacterial adhesion on the tooth surface (Ammar et al., 1990). Another prospective clinical study using a dentifrice containing an extract (0.5%) of *Scutellaria baicalensis* (which contains baicalein, baicalin, wogonin and acteoside), demonstrated significant reduction of plaque, gingivitis and biofilm vitality after 21 days, compared to placebo (Arweiler et al., 2011). Topical application of a green tea catechin (1.0%)-containing dentifrice in the periodontal lesions of a rat model, reduced inflammatory cell infiltration to a greater degree at 8 weeks

Table 1
The use of flavonoids as therapeutic agents in periodontal inflammation.

Study design	No of subjects	Observation period	Flavonoids	Model	Target	Effect	References
Prospective clinical study	10	3 weeks	Naringerin (0.1%) Quercetin (0.1%)	Toothpaste – Placebo – Formula I: quercetrin – Formula II: naringerin	Dental plaque formation	– Formula I: 32% decrease in accumulation of dental plaque – Formula II:34% decrease in accumulation of dental plaque	Ammar et al. (1990)
Prospective clinical study	40			Toothpaste	Loe &Silness gingival index (**GI**)	**GI:** 1.585±0.218 (PLA); 0.934±0.239 (SB)	Arweiler et al. (2011)
	20: control group	21 days	Sculletaria baicalensis extract (0.5%): baicalein, baicalin, wogonin acteoside	– Placebo **(PLA)** – Experimental toothpaste **(SB)**	Loe &Silness plaque index (**PI**)	**PI:** 2.250±0.383 (PLA); 1.700±0.229 (SB)	
	20: experimental group			Topical application for 1 min per day.	Biofilm vitality (**VF%**)	**VF:** 83.06±6.55 (PLA); 73.14±9.39 (SB)	
Prospective clinical pilot study	6	8 weeks	Green tea catechin:	Slow-release local delivery system in periodontal pockets≥5mm	Probing depths (PD)	**PD**	Hirasawa, et al. (2002)
	3: scaled group (I) 3: non-scaled group (II)		MIC 1.0 mg/ml	Test strips (I + II) Placebo strips (I + II) Replacement of the strips every week		Scaled group+test strips: **BL:** 4.7± 0.8 mm **Week 8:** 3.3± 0.5 mm Scaled group+placebo strips: **BL:** 5.0± 0.8 mm **Week 8:** 4.9± 0.8 mm	
Experimental study:rat model	24: 4 groups	8 weeks	Green tea catechin (1.0%)	Toothpaste	Distances:		
	1: no treatment			Control	CEJ-ABC*	CEJ–ABC Group 1: 466±40 Group 2: 691±87 Group 3: 697±67 Group 4: 603±131	Maruyama et al. (2011)
	2: periodontal inflammation			Experimental toothpaste	CEJ–JE*	CEJ–JE Group 1: 0±0 Group 2: 133±102 Group 3: 143±56 Group 4: 29±30	
	3: periodontal. inflammation +control toothpaste			Daily topical application for 4 weeks	PMNs per unit area	PMNs per unit area Group 1: 1.7±0.2 Group 2: 2.8±0.4 Group 3: 2.5±0.6 Group 4: 1.3±0.3	
	4: periodontal inflammation +experimental toothpaste				*CEJ: cemento-enamel junction *JE: junctional epithelium *ABC: alveolar bone crest		
Epidemiological cross-sectional study questionnaire	3956 Japanese women	-	Isoflavones genistein, daidzein	Dietary daily intake (per os)	Prevalence of periodontal disease	Inverserelationship between isoflavone intake and prevalence of periodontal disease	Tanaka et al. (2008)

Epidemiological study questionnaire	940 Japanese men	-	Green tea catechines	Daily intake number of cups per day	Probing depth (PD) Attachment loss (AL) Bleeding on probing (BOP)	**PD**: 0.023 mm decrease **AL**: 0.028 mm decrease **BOP**: 0.63 decrease	Kushiyama et al. (2009)
Experimental study: rat model	24: 3 groups 1: control group 2: periodontitis group 3: periodontitis+cocoa group	4 weeks	Cocoa flavonoids: catechin, epicathechin (42 mg/g)	Daily intake of a 10% cocoa-enriched diet (per os)	Gingival oxidative stress	**Group 3:** Cocoa-enriched diet diminished periodontitis-induced oxidative stress	Tomofuji, et al., (2009)

compared to the application of the control dentifrice, and lowered levels of expression of lipid peroxidation, oxidative protein damage, and TNF-α (Maruyama et al., 2011). A propolis containing toothpaste was recently shown to improve oral health and gingivitis in eight patients who underwent implant-supported prosthodontic rehabilitation as compared to a negative control (Morawiec et al., 2013).

3.2. Topical application

Hydroxypropylcellulose strips containing green tea catechin (1.0 g/ml) applied in pockets of periodontal patients once a week for 8 weeks showed an anti-bactericidal effect against *P. gingivalis* and *P. intermedia* species; the combined use of mechanical treatment and the application of green tea catechin using this slow-release local delivery system was effective in improving the periodontal status (Hirasawa et al., 2002).

3.3. Oral intake

Isoflavones, such as genistein and daidzein, have numerous biological effects (Messina, 1999). There was a significant inverse dose–response relationship between the intake of isoflavones and the prevalence of periodontal disease in young Japanese women (Tanaka et al., 2008). The intake of green tea was also inversely related with the mean probing depth clinical attachment loss and bleeding on probing among 940 Japanese men (Kushiyama et al., 2009). Rats with experimental periodontitis that were fed with a cocoa-enriched diet had decreased levels of serum reactive oxygen metabolites in contrast with the rats that were fed a regular diet (Tomofuji et al., 2009).

4. Conclusions

The development of periodontitis is a multifactorial process, through which bacterial-induced inflammation, modified by environmental and genetic factors, leads to an excessive host response and associated tissue destruction. It is therefore reasonable to try to control the inflammation using both conventional mechanical therapy and pharmacological adjuncts (Bartold and Van Dyke, 2013). Administration of unique flavonoids, either by adding them to several oral hygiene products or through local delivery vehicles, could play an important role in periodontal therapy. Quercetin and luteolin are generally safe. In fact, quercetin was effective in a clinical trial for the inflammatory bladder disease interstitial cystitis (Katske, Shoskes et al., 2001;Theoharides et al., 2008) as well as to reduce contact dermatitis in humans (Weng et al., 2012). Further preclinical animal and human clinical studies are required to show in what combinations and formulations flavonoids may best reduce periodontal inflammation.

Disclosures

TCT in the inventor of US Patents Nos. 6,624,148; 6,689,784; 6,984,667, and EPO 1365777, which cover methods and compositions using flavonoids in inflammatory conditions, including oral inflammation and periodontitis.

Author's contributions

IP and EP did most of the literature search and wrote the original draft. IP drew the figure, and TCT formulated the idea, wrote and corrected the paper.

Acknowledgments

Aspects of the work discussed were funded in part by Theta Biomedical Consulting and Development Co. Inc. (Brookline, MA).

Reference

Ammar, N., Diwanny, A.E., Osman, N., Gaafar, S., Amin, N., 1990. Flavonoids as possible preventive for dental plaque. Arch. Pharm. Res. 13, 211–213.
Armitage, G.C., 2004. Periodontal diagnoses and classification of periodontal diseases. Periodontology 2000 34, 9–21.
Arweiler, N.B., Pergola, G., Kuenz, J., Hellwig, E., Sculean, A., Auschill, T.M., 2011. Clinical and antibacterial effect of an anti-inflammatory toothpaste formulation with Scutellaria baicalensis extract on experimental gingivitis. Clin. Oral Invest. 15, 909–913.
Baehni, P., Tonetti, M.S., 2010. Conclusions and consensus statements on periodontal health, policy and education in Europe: a call for action–consensus view 1. Consensus report of the 1st European Workshop on Periodontal Education. Eur. J. Dent. Educ. 14 (Suppl. 1), 2–3.
Bartold, P.M., Van Dyke, T.E., 2013. Periodontitis: a host-mediated disruption of microbial homeostasis. Unlearning learned concepts. Periodontology 2000 62, 203–217.
Beecher, G.R., 2003. Overview of dietary flavonoids: nomenclature, occurrence and intake. J. Nutr. 133, 3248S–3254S.
Benakanakere, M., Kinane, D.F., 2012a. Innate cellular responses to the periodontal biofilm. Front. Oral Biol. 15, 41–55.
Benakanakere, M., Kinane, D.F., 2012b. Innate cellular responses to the periodontal biofilm. Front. Oral Biol. 15, 41–55.
Bodet, C., Chandad, F., Grenier, D., 2007. Cranberry components inhibit interleukin-6, interleukin-8, and prostaglandin E production by lipopolysaccharide-activated gingival fibroblasts. Eur. J. Oral Sci. 115, 64–70.
Bonifait, L., Grenier, D., 2010. Cranberry polyphenols: potential benefits for dental caries and periodontal disease. J. Can. Dent. Assoc. 76, a130.
Chatterjee, A., Saluja, M., Agarwal, G., Alam, M., 2012. Green tea: A boon for periodontal and general health. J. Indian Soc. Periodontol. 16, 161–167.
Cheng, W.C., Huang, R.Y., Chiang, C.Y., Chen, J.K., Liu, C.H., Chu, C.L., Fu, E., 2010. Ameliorative effect of quercetin on the destruction caused by experimental periodontitis in rats. J. Periodontal. Res. 45, 788–795.
Choi, E.Y., Jin, J.Y., Choi, J.I., Choi, I.S., Kim, S.J., 2011. Effects of luteolin on the release of nitric oxide and interleukin-6 by macrophages stimulated with lipopolysaccharide from Prevotella intermedia. J. Periodontol. 82, 1509–1517.
Ciancio, S.G., 2011. Controlling biofilm with evidence-based dentifrices. Compend. Contin. Educ. Dent. 32, 70–76.
Feldman, M., Grenier, D., 2012. Cranberry proanthocyanidins act in synergy with licochalcone A to reduce Porphyromonas gingivalis growth and virulence properties, and to suppress cytokine secretion by macrophages. J. Appl. Microbiol. 113, 438–447.
Geraets, L., Moonen, H.J., Brauers, K., Wouters, E.F., Bast, A., Hageman, G.J., 2007. Dietary flavones and flavonoles are inhibitors of poly (ADP-ribose)polymerase-1 in pulmonary epithelial cells. J. Nutr. 137, 2190–2195.
Govindaraj, J., Emmadi, P., Puvanakrishnan, R., 2011. Therapeutic effects of proanthocyanidins on the pathogenesis of periodontitis – an overview. Indian J. Exp. Biol. 49, 83–93.
Gu, L., Kelm, M.A., Hammerstone, J.F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S., Prior, R.L., 2004. Concentrations of proanthocyanidins in common foods and estimations of normal consumption. J. Nutr. 134, 613–617.
Gupta, G., 2013. Gingival crevicular fluid as a periodontal diagnostic indicator-II: inflammatory mediators, host-response modifiers and chair side diagnostic aids. J. Med. Life, 6; , pp. 7–13.
Gutierrez-Venegas, G., Contreras-Sanchez, A., 2013. Luteolin and fisetin inhibit the effects of lipopolysaccharide obtained from Porphyromonas gingivalis in human gingival fibroblasts. Mol. Biol. Rep. 40, 477–485.
Gutierrez-Venegas, G., Kawasaki-Cardenas, P., rroyo-Cruz, S.R., Maldonado-Frias, S., 2006. Luteolin inhibits lipopolysaccharide actions on human gingival fibroblasts. Eur. J. Pharmacol. 541, 95–105.
Hasturk, H., Kantarci, A., Van Dyke, T.E., 2012. Paradigm shift in the pharmacological management of periodontal diseases. Front. Oral Biol. 15, 160–176.
Heitz-Mayfield, L.J., 2009. Systemic antibiotics in periodontal therapy. Aust. Dent. J. 54 (Suppl. 1), S96–101.
Heitz-Mayfield, L.J., Trombelli, L., Heitz, F., Needleman, I., Moles, D., 2002. A systematic review of the effect of surgical debridement vs non-surgical debridement for the treatment of chronic periodontitis. J. Clin. Periodontol. 29 (Suppl. 3), 92–102.
Hirasawa, M., Takada, K., Makimura, M., Otake, S., 2002. Improvement of periodontal status by green tea catechin using a local delivery system: a clinical pilot study. J. Periodontal Res. 37, 433–438.
Huxley, R.R., Lean, M., Crozier, A., John, J.H., Neil, H.A., 2004. Oxford Fruit and Vegetable Study Group, 2004. Effect of dietary advice to increase fruit and vegetable consumption on plasma flavonol concentrations: results from a randomised controlled intervention trial. J. Epidemiol. Community Health 58, 288–289.
Katske, F., Shoskes, D.A., Sender, M., Poliakin, R., Gagliano, K., Rajfer, J., 2001. Treatment of interstitial cystitis with a quercetin supplement. Tech. Urol. 7, 44–46.
Kempuraj, D., Madhappan, B., Christodoulou, S., Boucher, W., Cao, J., Papadopoulou, N., Cetrulo, C.L., Theoharides, T.C., 2005. Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. Br. J. Pharmacol. 145, 934–944.
Kempuraj, D., Tagen, M., Iliopoulou, B.P., Clemons, A., Vasiadi, M., Boucher, W., House, M., Wolferg, A., Theoharides, T.C., 2008. Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells. Br. J. Pharmacol. 155, 1076–1084.
Kimata, M., Shichijo, M., Miura, T., Serizawa, I., Inagaki, N., Nagai, H., 2000. Effects of luteolin, quercetin and baicalein on immunoglobulin E-mediated mediator release from human cultured mast cells. Clin. Exp. Allergy 30, 501–508.
Kirkwood, K.L., Cirelli, J.A., Rogers, J.E., Giannobile, W.V., 2007. Novel host response therapeutic approaches to treat periodontal diseases. Periodontology 2000 43, 294–315.
Kushiyama, M., Shimazaki, Y., Murakami, M., Yamashita, Y., 2009. Relationship between intake of green tea and periodontal disease. J. Periodontol. 80, 372–377.
La, V.D., Howell, A.B., Grenier, D., 2009. Cranberry proanthocyanidins inhibit MMP production and activity. J. Dent. Res. 88, 627–632.
La, V.D., Howell, A.B., Grenier, D., 2010. Anti-porphyromonas gingivalis and anti-inflammatory activities of A-type cranberry proanthocyanidins. Antimicrob. Agents Chemother. 54, 1778–1784.
La, V.D., Labrecque, J., Grenier, D., 2009. Cytoprotective effect of proanthocyanidin-rich cranberry fraction against bacterial cell wall-mediated toxicity in macrophages and epithelial cells. Phytother. Res. 23, 1449–1452.
La, V.D., Tanabe, S., Bergeron, C., Gafner, S., Grenier, D., 2011. Modulation of matrix metalloproteinase and cytokine production by licorice isolates licoricidin and licorisoflavan A: potential therapeutic approach for periodontitis. J. Periodontol. 82, 122–128.
Landete, J.M., 2012. Updated knowledge about polyphenols: functions, bioavailability, metabolism, and health. Crit. Rev. Food Sci. Nutr. 52, 936–948.
Leszczynska, A., Buczko, P., Buczko, W., Pietruska, M., 2011. Periodontal pharmacotherapy – an updated review. Adv. Med. Sci. 56, 123–131.
Li, M., Xu, Z., 2008. Quercetin in a lotus leaves extract may be responsible for antibacterial activity. Arch. Pharm. Res. 31, 640–644.
Lohr, G., Beikler, T., Podbielski, A., Standar, K., Redanz, S., Hensel, A., 2011. Polyphenols from Myrothamnus flabellifolia Welw. inhibit in vitro adhesion of Porphyromonas gingivalis and exert anti-inflammatory cytoprotective effects in KB cells. J. Clin. Periodontol. 38, 457–469.
Manjeet, K.R., Ghosh, B., 1999. Quercetin inhibits LPS-induced nitric oxide and tumor necrosis factor-alpha production in murine macrophages. Int. J. Immunopharmacol. 21, 435–443.
Maruyama, T., Tomofuji, T., Endo, Y., Irie, K., Azuma, T., Ekuni, D., Tamaki, N., Yamamoto, T., Morita, M., 2011. Supplementation of green tea catechins in dentifrices suppresses gingival oxidative stress and periodontal inflammation. Arch. Oral Biol. 56, 48–53.
Messina, M.J., 1999. Legumes and soybeans: overview of their nutritional profiles and health effects. Am. J. Clin. Nutr. 70, 439S–450S.
Middleton, E.J., Kandaswami, C., Theoharides, T.C., 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. Pharmacol. Rev. 52, 673–751.
Min, Y.D., Choi, C.H., Bark, H., Son, H.Y., Park, H.H., Lee, S., Park, J.W., Park, E.K., Shin, H.I., Kim, S.H., 2007. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line. Inflamm. Res. 56, 210–215.
Mitjavila, M.T., Moreno, J.J., 2012. The effects of polyphenols on oxidative stress and the arachidonic acid cascade. Implications for the prevention/treatment of high prevalence diseases. Biochem. Pharmacol. 84, 1113–1122.
Morawiec, T., Dziedzic, A., Niedzielska, I., Mertas, A., Tanasiewicz, M., Skaba, D., Kasperski, J., horowska-Pieniazek, A., Kucharzewski, M., Szaniawska, K., Wieckiewicz, W., Wieckiewicz, M., 2013. The biological activity of propolis-containing toothpaste on oral health environment in patients who underwent implant-supported prosthodontic rehabilitation. Evid. Based Complement Alternat. Med. 2013, 704947, http://dx.doi.org/10.1155/2013/704947. (Epub 2013 May 14).
Nair, M.P., Mahajan, S., Reynolds, J.L., Aalinkeel, R., Nair, H., Schwartz, S.A., Kandaswami, C., 2006. The flavonoid quercetin inhibits proinflammatory cytokine (tumor necrosis factor alpha) gene expression in normal peripheral blood mononuclear cells via modulation of the NF-kappa beta system. Clin. Vaccine Immunol. 13, 319–328.
Nakagawa, T., Yokozawa, T., 2002. Direct scavenging of nitric oxide and superoxide by green tea. Food Chem. Toxicol. 40, 1745–1750.
Noguchi, K., Ishikawa, I., 2007. The roles of cyclooxygenase-2 and prostaglandin E2 in periodontal disease. Periodontology 2000 43, 85–101.
Papapanou, P.N., 2012. The prevalence of periodontitis in the US: forget what you were told. J. Dent. Res. 91, 907–908.
Papathanasiou, E., Teles, F., Griffin, T., Arguello, E., Finkelman, M., Hanley, J., Theoharides, T.C., 2013. Gingival crevicular fluid levels of interferon-gamma, but not interleukin-4 or -33 or thymic stromal lymphopoietin, are increased in inflamed sites in patients with periodontal disease. J. Periodontal Res.. 10.1111/jre.12078. Epub ahead of print.
Pinho, M.N., Pereira, L.B., de Souza, S.L., Palioto, D.B., Grisi, M.F., Novaes Jr., A.B., Taba Jr., M., 2008. Short-term effect of COX-2 selective inhibitor as an adjunct for the

treatment of periodontal disease: a clinical double-blind study in humans. Braz. Dent. J. 19, 323–328.
Preshaw, P.M., Heasman, P.A., 2002. Prostaglandin E2 concentrations in gingival crevicular fluid: observations in untreated chronic periodontitis. J. Clin. Periodontol. 29, 15–20.
Preshaw, P.M., Seymour, R.A., Heasman, P.A., 2004. Current concepts in periodontal pathogenesis. Dent. Update 31, 570–578.
Sakanaka, S., Aizawa, M., Kim, M., Yamamoto, T., 1996. Inhibitory effects of green tea polyphenols on growth and cellular adherence of an oral bacterium, Porphyromonas gingivalis. Biosci. Biotechnol. Biochem. 60, 745–749.
Salvi, G.E., Lang, N.P., 2005. Host response modulation in the management of periodontal diseases. J. Clin. Periodontol. 32 (Suppl. 6), 108–129.
Schroeter, H., Holt, R.R., Orozco, T.J., Schmitz, H.H., Keen, C.L., 2003. Nutrition: milk and absorption of dietary flavanols. Nature 426, 787–788.
Souza, J.A., Rossa Jr., C., Garlet, G.P., Nogueira, A.V., Cirelli, J.A., 2012. Modulation of host cell signaling pathways as a therapeutic approach in periodontal disease. J. Appl. Oral Sci. 20, 128–138.
Tanabe, S., Santos, J., La, V.D., Howell, A.B., Grenier, D., 2011. A-type cranberry proanthocyanidins inhibit the RANKL-dependent differentiation and function of human osteoclasts. Molecules 16, 2365–2374.
Tanaka, K., Sasaki, S., Murakami, K., Okubo, H., Takahashi, Y., Miyake, Y., 2008. Relationship between soy and isoflavone intake and periodontal disease: the freshmen in Dietetic Courses Study II. BMC Public Health 8, 39.
Teles, R., Teles, F., Frias-Lopez, J., Paster, B., Haffajee, A., 2013. Lessons learned and unlearned in periodontal microbiology. Periodontology 2000 62, 95–162.
Theoharides, T.C., Alexandrakis, M., Kempuraj, D., Lytinas, M., 2001. Anti-inflammatory actions of flavonoids and structural requirements for new design. Int. J. Immunopathol. Pharmacol. 14, 119–127.
Theoharides, T.C., Kempuraj, D., Vakali, S., Sant, G.R., 2008. Treatment of refractory interstitial cystitis/painful bladder syndrome with CystoProtek – an oral multi-agent natural supplement. Can. J. Urol. 15, 4410–4414.
Tominari, T., Hirata, M., Matsumoto, C., Inada, M., Miyaura, C., 2012. Polymethoxy flavonoids, nobiletin and tangeretin, prevent lipopolysaccharide-induced inflammatory bone loss in an experimental model for periodontitis. J. Pharmacol. Sci. 119, 390–394.
Tomofuji, T., Ekuni, D., Irie, K., Azuma, T., Endo, Y., Tamaki, N., Sanbe, T., Murakami, J., Yamamoto, T., Morita, M., 2009. Preventive effects of a cocoa-enriched diet on gingival oxidative stress in experimental periodontitis. J. Periodontol. 80, 1799–1808.
Weng, Z., Zhang, B., Asadi, S., Sismanopoulos, N., Butcher, A., Fu, X., Katsarou-Katsari, A., Antoniou, C., Theoharides, T.C., 2012. Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. PloS One 7 (3), e33805.
Xagorari, A., Papapetropoulos, A., Mauromatis, A., Economou, M., Fotsis, T., Roussos, C., 2001. Luteolin inhibits an endotoxin-stimulated phosphorylation cascade and proinflammatory cytokine production in macrophages. J. Pharmacol. Exp. Ther. 296, 181–187.
Yamakoshi, J., Saito, M., Kataoka, S., Kikuchi, M., 2002. Safety evaluation of proanthocyanidin-rich extract from grape seeds. Food Chem.Toxicol. 40, 599–607.