A SYSTEMATIC REVIEW

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Does propolis can relief toothache???

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Abstract

Objective: The aim of this literature review is to highlights the role and mechanisms of propolis at the molecular level in relief toothache caused by dental pulp inflammation.

Methods: This review complied data from our study as well as from other researchers, focusing on molecular mechanism of inflammation, dental pain mechanism caused by inflammation and the role of propolis on inflammatory process.

Results: Both in vitro and in vivo or even clinical research revealed that propolis has anti-inflammatory. Propolis could suppresses cyclooxygenase (COX) and lipoxygenase (LOX) enzymes during inflammation. COX-2 is mainly inhibited by flavonoid which suppresses prostaglandin endoperoxide synthase at high concentration depending on the hydrophilicity and structure whereas LOX is mainly inhibited by quercetin component of propolis. The major component of propolis is the caffeic acid (3.4-dihydroxycinnamic acid) phenethyl ester (CAPE). It has anti-inflammatory by inhibits LOX and COX enzymes that are involved in the AA metabolism pathways.

Conclusion: It could be that propolis effective to relief toothache (odontalgia).

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Keywords: Dental pulp, Inflammation, Propolis, Toothache
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Introduction

Dental pulp is a connective tissue uniquely situated within the rigid encasement of mineralized dentin. Although dental pulp shares many properties with other connective tissues of the body, the peculiar location of dental pulp imposes several special characteristics on it.[1] International Association for the Study of Pain (IASP) defined toothache or odontalgia as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Odontalgia pain is the most prevalent form of orofacial pain, occuring in nearly 12% to 14% of the population in United States. Odontogenic pain is usually caused by either noxious physical stimuli or the release of inflammatory mediators that stimulate receptors located on terminal endings of nociceptive (pain detecting) afferent nerve fibers. Physical stimuli, via their effect on dentinal fluid flow, can activate the nociceptors that innervate dentinal tubules, leading to the perception of dentinal pain. Inflammatory mediators, via activation of their respective receptors, can sensitize or depolarize the nociceptors that innervate pulpal tissue. Activation of dental pulp nerves by these physiologic (eg, thermal, mechanical or chemical) stimuli results in a pure sensation of pain.[2]

Following activation, the C and A-delta fibers from orofacial tissue such as dental pulp transmit nociceptive signals, primarily via trigeminal nerves, to the trigeminal nuclear complex located in the medulla. Nociceptors is a stimulus of abundant intensity to stimulate tissue damage that activates specialized nerve. They generate pain stimuli that are located in the dorsal root ganglia adjacent to the spine and dendrite to its periphery. Painful stimuli trigger biological processes that extend or inhibit the pain signal. The fifth (V) cranial nerve or the trigeminal nerve is the principal sensory innervation of the mouth and face. Many trigeminal primary afferent fibres or neurons are characterized by small-diameter axon with slow conduction (A-delta and C-fibre) which terminate in the orofacial tissues as free nerve endings. Noxious stimuli may be mechanical or chemical, that includes bacterial toxins on the exposed dental pulp.[3,4]

The use of natural products and holistic or alternative medicine has popularity among the society, due to the potential side effects and safety concerns of conventional allopathic formulations. Propolis is a natural product derived from plant resins collected by honeybees. Bees used it as glue, a general-purpose sealer and as draught-extruder for beehives. Propolis has been used in folk medicine for centuries.[5] Both in vitro and in vivo or even clinical research revealed that propolis has antimicrobial activity[6] as well as anti-inflammatory,[7] antioxidant,[8] immunomodulatory[9] and regenerative tissue.[10]

In recent years, it has been used in dentistry includes in restorative dentistry as a cariostatic agent, desensitizing and direct pulp capping agent, in endodontics as an intra-canal medicament, intra-canal irrigant.[11] Toothache or odontalgia is unpleasant sensory and emotional experience associated

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with actual or potential tissue damage or described in terms of such damage. Despite having numerous advantages and uses, the role of propolis in relief toothache is probably the least understood. Therefore, this review highlights the role and mechanisms of propolis at the molecular level in relief toothache caused by dental pulp inflammation.

Methods

Inflammation is a complex biological response of vascular tissue and immune cells to harmful stimuli like for instance irritants, damaged cells and pathogen which can cause severe pain. It can be represented by phagocyte emigration, accumulation of neutrophils, monocytes, macrophages and loss of tissue function. During the process of inflammation, the release of pro-inflammatory cytokine such as Interleukin 6 (IL-6), Interleukin 1 (IL-1), and Tumour Necrosis factor-α (TNF-α) are activated by macrophages.[12] These macrophages stimulate the translocation of Nuclear Factor-KappaB (NF-kB) that has a significant role in the induction of network inflammatory mediators and cytokines. The NF-kB proteins are in a non-stimulated state by an inhibitory protein subunit called IKBα. The activation of NF-kB stimulates the production of enzymes for instance nitric oxide synthase (NOS) which produces nitric oxide (NO). Therefore, agents that could control the activation of NF-kB would likely to be used in therapeutic purpose.[13] Besides that, activation of platelets stimuli leads to release of arachidonic acid (AA) during the inflammatory process. Lipoxygenase (LOX) enzyme converts AA to leukotriene A4 and produces cysteinylleukotrienes and leukotrienes B4. This leads to inflammation and allergy. Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) coverts AA to prostaglandin H2 and produces thromboxanes, prostaglandins and prostacylins which leads to inflammation and pain.[14,15]

Pain is the primary symptom of disease reported by patients to be diagnosed and treated. It is subjective in terms of intensity and symptom behaviour which can be misinterpreted. Pain is associated with physical, biological and psychological influence. Therefore, it is an unpleasant experience with potential or actual tissue damage. A major etiologic factor for pulpal inflammation is the invasion of bacteria or bacteria-derived factors into the dental pulp. Bacteria can invade dental pulp tissue after caries or tooth fracture, via anomalous dentinal tracts, or following dental restorative procedures.[2]

Pulpal C nociceptors are thought to have a predominant role in encoding inflammatory pain arising from dental pulp and periradicular tissue. This hypothesis is support by the distribution of C fibers in dental pulp, their responsiveness to inflammatory mediators, and the strikingly similar perceptual qualities of pain associated with C fiber activation and pulpitis. The response to tissue inflammation or infection is complex and involves the coordinated release of multiple classes of inflammatory mediators. In the inflamed dental pulp, the terminals of nociceptive primary afferents detect the presence of inflammatory mediators with receptors that are synthesized in the afferent fiber's cell body and then transported to the periphery. If the mediator reaches a concentration in the inflamed tissue sufficient to active the receptor, the nociceptive neuron could become activated, ie, the membrane would be depolarized and the signal would beconducted to the central nervous system or sensitized. A sensitized nociceptor displays spontaneous depolarization,

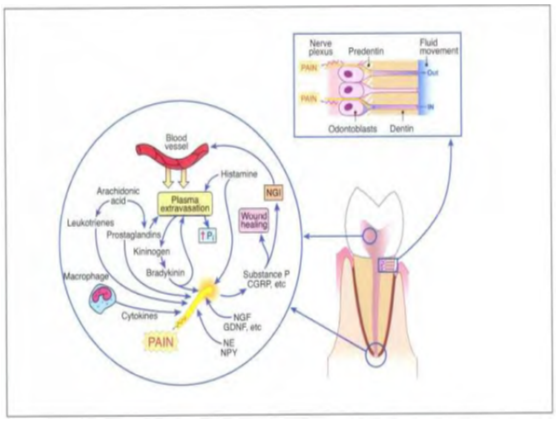

Figure 1 Two mechanisms for the peripheral stimulation of nociceptive neve fibers in tooth pulp. Acute dentinal pain: According to the hydrrodynamic theory, stimuli that cause fluid movement in exposed dentinal tubules result in the stimulation of nociceptive nerve fibers. Pain with inflammation: Inflammation is associated with the synthesis or release of mediators, including prostaglandins, bradykinin, substance P and histamine (as well as other mediators not shown). The interelationships of these inflammtory mediators from a positive feedback loop, allowing inflammation to persist far beyond cessation of the dental procedure. NGI, neurologic inflammation

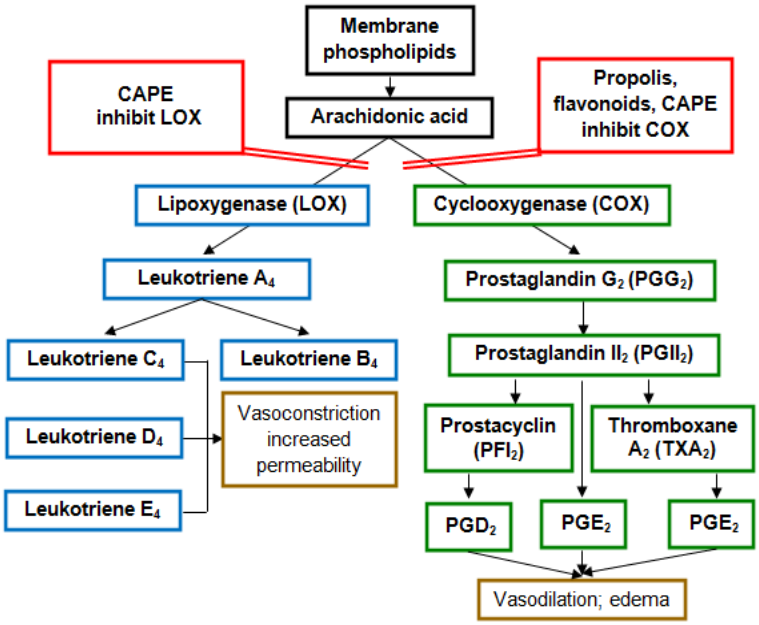

Figure 2 The role of propolis and its components towards phospholipid metabolism and products of arachidonic acid pathway involved in inflammation. Note ═ inhibit

reduced theshold for depolarization and increased after-discharges to supratresholdstimuli. Some inflammatory mediators activate these terminals (eg bradykinin), while others potentiate the effects of inflammatory media-tors (eg, prostaglandins). For example, prostaglandin E_2 substantially increases the stimulatory effect of bradykinin. Therefore, the combination of mediators present is probably more important than the present of any one mediator in determining the physiologic response to inflammation. Figure 1.[1,2]

In a recent years the researchers were searching for natural products with medicinal properties, particularly those from plants and bees to found a natural anti-inflammatory agent. Several plants produce resinous exudates with strong antimicrobial and anti-necrotic properties, in addition to impermeability provided by populus a substance from populus sp.[16] Bees collect resin exudates from certain plants and add their secretion, wood fragments, pollen, and wax; this product from bees and plants is called propolis. The word propolis comes from the Greek pro meaning in defense of and polis city, representing defense of bee cities (or beehives). Propolis has been used in folk medicine since primeval times. Nowadays, propolis is still used in home made remedies and cosmetics. Two characteristics of propolis are its smell and its various colors from dark green to brown.[5]

Propolis chemical composition has been correlated with plant diversity around the beehive.[6] In general, raw propolis contains about: 50%-55% resins and balsams (phenols, phenolic acids, esters, flavanons {quercetin, galangin, pinocembrin}, dihydroflavanons, flavons, flavonols, chalkones, phenolic glycerides, cinnamic acid, coumaric acid, prenylated compounds and artepillin C), 25%-30% waxes, 10% volatile oils, 5% pollen and 5% organic and mineral substances. The components are rich in vitamins such as B1, B2, B6, C, E and mineral elements like Mg, Ca, I, K, Na, Cu, Zn, Mn and Fe. It also contains number of fatty acids and enzymes as succinic dehydrogenase, glucose-6-phosphatase, adenosine triphosphatase and acid phosphatase.[17] Considering that propolis is a complex mixture, synergistic interactions between its compounds must also be considered as an important factor in its anti-inflammatory activity.

Ethanol, the most commonly used solvent for propolis preparations, and other solvents such as ethylic ether, water, methanol, petroleum ether, and chloroform are used for extracting and identifying many propolis compounds. Moreover, glycerin, propylene glycol and some solutions have been used in propolis preparations by the pharmaceutical and cosmetic industry.[18]

Propolis compounds have recently become the subject of investigation in order to determine its therapeutic application in dentistry.[19] Flavonoids are consider as the most biologically active substance in propolis.[20] In the last 20 years, there has been increased commercial interest in propolis use due to its therapeutic properties to treat many diseases. Nowadays, we can found propolis is commercially in sprays, ointments, capsules, capillary lotions and toothpastes because of its bacteriostatic activity and pharmacological properties.

Many studies have shown that propolis could suppresses LOX and COX enzymes during inflammation.[12] COX-2 is mainly inhibited by flavonoid which suppresses prostaglandin endoperoxide synthase at high concentration depending on the hydrophilicity and structure whereas LOX is mainly inhibited by quercetin component of propolis.[21] It has also been shown that flavonoid inhibits the accumulation of mast cells.[22] The major component of propolis is the caffeic acid (3,4-dihydroxycinnamic acid) phenethyl ester (CAPE) which is a biologically active compound. It has anti-inflammatory and antioxidant properties.[21] Due to its lipophilic nature; it is easy for CAPE to enter the cells. CAPE inhibits LOX and COX enzymes that are involved in the AA metabolism pathways figure 2. Therefore, the AA metabolism is arrested and there is no release of prostaglandins and leukotriene, responsible for

inflammation and pain.[12] In addition, research shows that CAPE inhibits the release of the inflammatory cytokines and simultaneously increases the production of anti-inflammatory cytokines such as IL-10 and IL-4. In the same research it has shown that, CAPE decreases the infiltration of inflammatory cells such as neutrophils and monocytes.[23]

Based on the literature, CAPE is well known as a specific inhibitor for the activation of NF-kB. It blocks the release of IL-1β which is stimulated by NF-kB promoter and simultaneously inhibits the NF-kB activity.[24] CAPE has preventive effect on the inflammatory cellular infiltration which leads to decreases in PGE2, ROS and NO. Flavonoids and CAPE, the most potent natural components of propolis have been compared with COX inhibitor indomethacin (IM) and the LOX inhibitor nordihydroguaiaretic acid (NDGA) and found to have the same effect as the IM and NDGA.[24-26]

Conclusion

Propolis is a natural products by honeybee that have been used in apiteraphy for long time due to its various properties. Many study has been proved that propolis and/or its components has very good antibacterial and antiinflammatory property therefore it could be concluded that propolis effective to relief toothache (odontalgia).

Acknowledgment

None.

Conflict of Interest

The authors report no conflict of interest.

References

1. Okiji, T. Pulp as a connective tissue. In: Hargreaves KM, Goodis HE. eds. Seltzer and bender's dental pulp. Chicago: Quintessence Publishing Co Inc; 2002. p. 95-122.
2. Hargreaves KM. Pain mechanisms of the pulpodentin complex. In: Hargreaves KM, Goodis HE. eds. Seltzer and bender's dental pulp. Chicago: Quintessence Publishing Co Inc.; 2002. p. 181-204.
3. Trowbridge HO. Histology of pulpal inflammation. In: Hargreaves KM, Goodis HE. eds. Seltzer and bender's dental pulp. Chicago: Quintessence Publishing Co Inc.; 2002. p. 227-246.
4. Rajoo M, Parolia A, Pau A, et al. The role of propolis in inflammation and orofacial pain: a review. Ann Res & Rev Biol 2014;4: 651-664.
5. Marcucci MC, Rodriguez J, Ferrerez F, et al. Chemical composition of Brazilian propolis from Sao Paulo State. Z Naturforsch [C] 1998;53: 117-119.
6. Sforcin JM, Fernandes AJr, Lopes CA, et al. Seasonal effect on Brazilian propolis antibacterial activity. J Ethnopharmacol 2000;73: 243-249.
7. Wang K, Zhang J, Ping S, et al. Anti-inflammatory effects of ethanol extracts of Chinese propolis and buds frompoplar (Populus x canadensis). J Ethnopharmacol. 2014; 155: 300-311trolled trial. J Periodontol 2017;1: 1-14.
8. Wiwekowati, Astawa P, Jawi IM, et al. Antioxidant activity of Apis Mellifera sp. propolis extract from Java (Indonesia). IRJEIS 2017;3: 18-23.
9. Sforcin JM. Propolis and the immune system : a review. J Ethnopharmacol 2007;113: 1-14.
10. Sabir A, Mooduto L, Kaelan C, et al. Impact of the use of ethanolic extract of propolis, flavonoid and non-flavonoid propolis for direct pulp capping in collagen type I density. Braz J Oral Sci 2016;15: 264-268.
11. Jain S, Rai R, Sharma V, et al. Propolis in oral health: a natural remedy. World J Pharm Sci 2014;2: 90-94.
12. Mirzoeva OK, Calder PC. The effect of propolis and its components on eicosanoid production during the inflammatory response. Prostaglandins Leukot Essent Fatty Acids 1996;55: 441-449.
13. Márquez N, Sancho R, Macho A, et al. Caffeic acid phenethyl ester inhibits T-cell activation by targeting both nuclear factor of activated Tcells and NF-κB transcription factors. J Pharmacol Exp Ther 2004;308: 993-1001.
14. Fouad AF. Molecular mediators of pulpal inflammation. In: Hargreaves KM, Goodis HE. eds. Seltzer and bender's dental pulp. Chicago: Quintessence Publishing Co Inc.; 2002. p. 247-279.
15. Martel-Pelletier J, Lajeunesse D, Reboul P, et al. Therapeutic role of dual inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs. Ann Rheum Dis 2003;62: 501-509.
16. Greenaway W, Scaysbrook T, Whatley FR. The composition and plant origins of propolis: a report of work at Oxford. Bee World 1990;71: 107-118.
17. Parolia A, Thomas MS, Kundabala M, et al. Propolis and its potential uses in oral health. Int J Med and Med Science 2010;2: 210-215.
18. Castaldo S, Capasso F. Propolis, an old remedy used in modern medicine. Fitoterapia 2002;73: S1-S6.
19. Sabir A. Using propolis as a therapeutic agent in dentistry. Cakradonya Dent J 2012;4: 480-486.
20. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacol Ther 2002;96: 67202.
21. Borrelli F, Maffia P, Pinto L, et al. Phytochemical compounds involved in the anti-inflammatory effect of propolis extract. Fitoterapia 2002;73: S53-S63.
22. Ferreira FM, de-Lima AAS, Gregio AMT, et al. Mast cell population on oral ulcers of rats treated by Brazilian propolis. Pharmacologyonline 2006;2: 178-189.
23. de-Moura SA, Ferreira MA, Andrade SP, et al. Brazilian green propolis inhibits inflammatory angiogenesis in a murine sponge model. Evid Based Complement Alternat Med 2011;2011: 182703.
24. Ramos AFN, Miranda JL. Propolis: a review of its anti-inflammatory and healing actions. J Venom Anim Toxins incl Trop Dis 2007;13: 697-710.
25. Blonska M, Bronikowska J, Pietsz G, et al. Effects of ethanol extract of propolis (EEP) and its flavones on inducible gene expression in J774A.1 macrophages. J Ethnopharmacol 2004;91: 25-30.
26. Korish AA, Arafa MM. Propolis derivatives inhibit the systemic inflammatory response and protect hepatic and neuronal cells in acute septic shock. Braz J Infect Dis 2011;15: 332-338.