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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.

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

Keywords: Dental pulp, Inflammation, Propolis, Toothache


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. 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, occurring 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.

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.

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. Both in vitro and in vivo or even clinical research revealed that propolis has antimicrobial activity as well as anti-inflammatory, antioxidant, immunomodulatory and regenerative tissue.

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. 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 pathogens 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. 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. 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) converts AA to prostaglandin H2 and produces thromboxanes, prostaglandins and prostacyclins which leads to inflammation and pain.

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 be conducted to the central nervous system or sensitized. A sensitized nociceptor displays spontaneous depolarization,

![Figure 1](image.png) Two mechanisms for the peripheral stimulation of nociceptive nerve fibers in tooth pulp. Acute dentinal pain: According to the hydrodynamic 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 interrelationships of these inflammatory mediators from a positive feedback loop, allowing inflammation to persist far beyond cessation of the dental procedure. NGI, neurologic inflammation.
Propolis chemical composition has been correlated with plant diversity around the beehive. In general, raw propolis contains about 50%-55% resins and balsams (phenols, phenolic acids, esters, flavonons {quercetin, galangin, pinocembrin}, dihydroflavanons, flavons, flavonols, chalcones, 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, 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. 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 ethyl 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.

Propolis compounds have recently become the subject of investigation in order to determine its therapeutic application in dentistry. Flavonoids are consider as the most biologically active substance in propolis. 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. 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. It has also been shown that flavonoid inhibits the accumulation of mast cells. 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 anti-oxidant properties. 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 reduced threshold for depolarization and increased after-discharges to suprathreshold stimuli. Some inflammatory mediators activate these terminals (e.g. bradykinin), while others potentiate the effects of inflammatory media-tors (e.g. prostaglandins). For example, prostaglandin E2 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 2  The role of propolis and its components towards phospholipid metabolism and products of arachidonic acid pathway involved in inflammation. Note inhibit
inflammation and pain. 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.

Based on the literature, CAPE is well known as a specific inhibitor for the activation of NF-κB. It blocks the release of IL-1β which is stimulated by NF-κB promoter and simultaneously inhibits the NF-κB activity. 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.

Conclusion
Propolis is a natural products by honeybee that have been used in apitherapy for long time due to its various properties. Many study has been proved that propolis and/or its components has very good antibacterial and anti-inflammatory 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