



## The Role of Propolis in Inflammation and Orofacial Pain: A Review

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### Authors' contributions

*This work was carried out in collaboration between all authors. Authors AP, A Pau and FDA designed this review, author MR managed the literature search and wrote the first draft of the manuscript. All authors read and approved the final manuscript.*

**Review Article**

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### ABSTRACT

In recent years, the use of natural products and holistic or alternative medicine has gained popularity among the public, due to the potential side effects and safety concerns of conventional allopathic formulations. Natural products have been used since ancient times in folk medicine, involving both eastern and western traditional medicine. Among these natural products, a resinous bee product named propolis has gained popularity. It has been reported to have anti-inflammatory, anti-bacterial, anti-fungal, anti-viral, anti-oxidant and anti-cancer properties. Due to these properties there has been an increasing interest in the use of bee propolis in contemporary dentistry. In dentistry propolis has been tried out almost in every field such as to treat oral cancer, recurrent ulcers, fungal infections, in restorative dentistry as a cariostatic, desensitizing and pulp capping agent, in endodontics as an intra-canal medicament, intra-canal irrigant, in dental trauma as a storage media for an avulsed tooth, in oral surgery to treat dry socket after tooth extraction, in prosthetics to treat denture stomatitis, in periodontics to treat gingivitis, periodontitis and to control bone resorption. Despite having numerous advantages and uses, the role of propolis in orofacial pain is probably the least understood. Hence, this review highlights the anti-inflammatory and pain relieving mechanisms of propolis at the molecular level in orofacial pain.

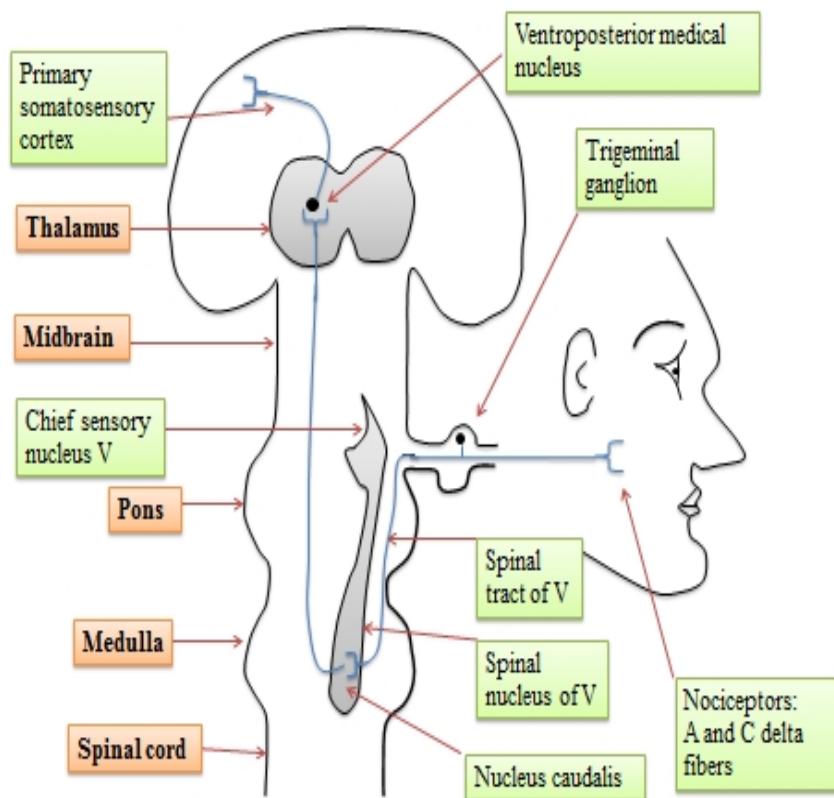
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**Keywords:** Propolis; anti-inflammatory; orofacial pain; analgesic effect.

## 1. INTRODUCTION

Orofacial pain (OFP) is defined as a common pain condition associated with the hard and soft tissues of the face and mouth [1]. Orofacial pain comprises a heterogeneous group of disorders that cause ongoing pain in the head and face region. Although there are many proposed classifications, one system divides these pains into musculoskeletal, neuropathic, and neurovascular pains [2]. Orofacial pain is generally associated with temporomandibular disorders (TMD) but could also arise from other sources, such as dental origins or trigeminal neuralgia [1]. OFP like pain elsewhere in the human body is usually the result of tissue damage and inflammation as well as the activation of nociceptors which transmit a noxious stimulus to the brain [2]. OFP as a symptom can be due to masticatory musculoskeletal pain, neurovascular pain, rheumatic disease or psychological abnormality and many more [3]. These pain disorders include inflammation of orofacial tissues and are classified from acute pulpitis (toothache) to chronic arthritic conditions affecting the temporomandibular joint (TMJ) [4]. OFP affects the motor and sensory functions of trigeminal nerve system and structures it innervates [3] and not all OFP may respond to treatment and medication [5]. Therefore, the mechanism of OFP and nociceptive pathways should be well understood for the management of OFP and inflammatory pain.

Nociceptors can be defined as the 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 [6]. 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 [5]. Noxious stimuli may be mechanical or chemical, that includes surgical incision of the oral mucosa, inflammation in jaw muscles, and bacterial toxins on the exposed dental pulp. Figure 1 shows the pathway of transmission of nociceptive signals from the orofacial region. Activated nociceptive endings can stimulate the primary afferent fibres from the trigeminal ganglion. These afferents fibres conduct nerve impulses into the central nervous system stimulating the brain with sensory information about the location, duration and intensity of the stimulus [4].



**Fig. 1. Nociceptive transmission connected with trigeminal nerve (V).**

## 2. PAIN AND ITS MECHANISM (Fig. 1.)

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 [7]. Pain is associated with physical, biological and psychological influence. Therefore, it is an unpleasant experience with potential or actual tissue damage. There are five main classifications of pain mechanism which are explained in Table 1.

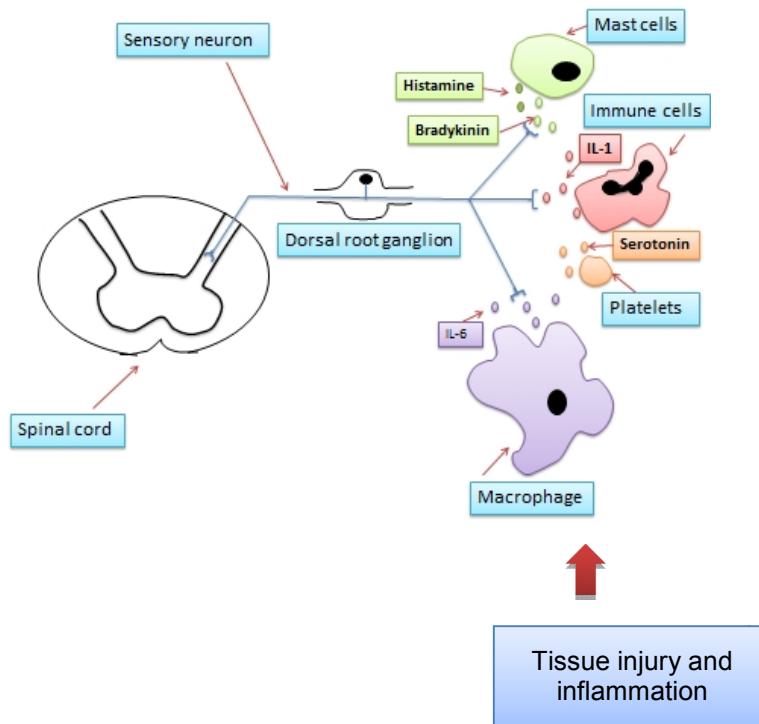
Subsequent to tissue damage, peripheral nociceptors become sensitized to noxious stimuli due to increasing level of inflammatory mediators. Numerous chemical mediators such as bradykinins, histamines, and prostaglandins are associated in the stimulation of the nociceptive endings. Their release causes inflammation and damage of the tissue innervated by the nociceptive endings [4]. Hence, complex interaction between immune and neural takes place in the afferent's peripheral endings in the orofacial tissues and cell body in trigeminal ganglion and this can be initiated or continued by inflammation [4,5].

**Table 1. Five main classifications of pain mechanism**

<b>Classification of pain mechanism</b>	<b>Definition and characteristic</b>
<b>Central nociceptive</b>	An enhancement in the function of neurons and circuits in nociceptive pathways caused by increase in membrane excitability and synaptic efficacy. This indicates that the somatosensory nervous system is in response to neural injury and inflammation [8].
<b>Peripheral sensitization</b>	Pain arising from dysfunction of peripheral nervous system. The damaged somatic tissues near to the nerve structures release inflammatory mediators that can chemically stimulate neural tissues [7, 8].
<b>Peripheral nociceptive</b>	All innervated tissues other than the peripheral nerves activate this mechanism. The pain arising from somatic and visceral tissues are carried by small-diameter afferent fibers [7].
<b>Sympathetically dependent pain</b>	Constant pain and allodynia usually because of chronic maladaptive sensitization neurons in the dorsal horn of the spinal cord, which leads to release of catecholamines and not because of amplified sympathetic tone [7, 8].
<b>Cognitive-affective(psychosocial)</b>	Plays vital role during the shift from acute to chronic pain especially in causative, cognitive and behavioural aspects of chronic pain [7].

### 3. INFLAMMATION AND ITS MOLECULAR MECHANISM (FIG. 2.)

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 [9]. 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- $\alpha$  (TNF- $\alpha$ ) are activated by macrophages. These macrophages stimulate the translocation of Nuclear Factor-KappaB (NF- $\kappa$ B) [10,11] that has a significant role in the induction of network inflammatory mediators and cytokines [12]. The NF- $\kappa$ B proteins are in a non-stimulated state by an inhibitory protein subunit called IKB $\alpha$ . The activation of NF- $\kappa$ B stimulates the production of enzymes for instance nitric oxide synthase (NOS) which produces nitric oxide (NO) [13]. Therefore, agents that could control the activation of NF- $\kappa$ B would likely to be used in therapeutic purpose [14]. Besides that, activation of platelets stimuli leads to release of arachidonic acid (AA) during the inflammatory process [15]. 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 [9,10,15].



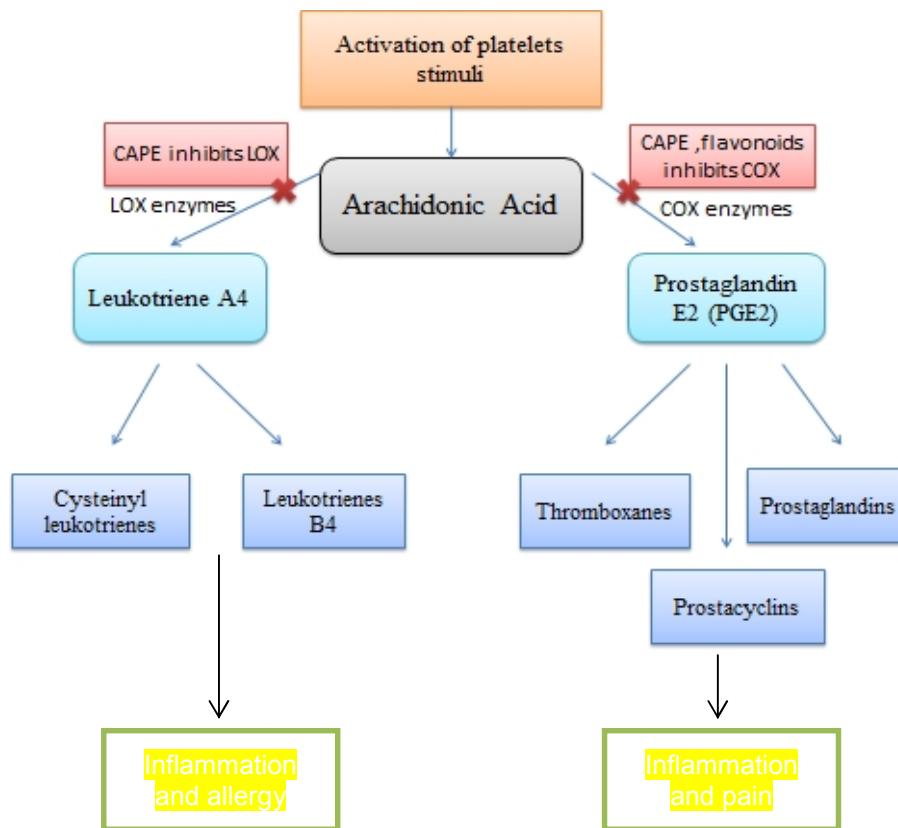
**Fig. 2. Inflammatory mediators involved in altering the sensitivity of peripheral nociceptors in sensory neurons.**

#### **4. PROPOLIS AND ITS CHARACTERISTICS**

Propolis is a resinous, balsamic substance that has been used worldwide for many years to cure wounds. The priests in Ancient Egypt frequently used it as a medicine and as an embalming cream. Later it was used by the Greeks, to whom we owe the name “propolis”. Pro means “before” and Polis means “city” or defender of the city. Propolis is a green-brown, brown or black colour substance with sharp bitter flavour and a sweet, agreeable aroma. It is hard and brittle when cold, but becomes soft and very sticky when warm. The colour of propolis depends on its botanical origin and age [16,17]. Propolis is classified into 12 types according to physicochemical properties and geographic locations; however, only three types are identified related to the botanical origin [18]. Propolis is a bee product, composed mainly of plant resins and beeswax, therefore its chemical composition varies due to the geographic and plant origins of these resins, as well as the species of bee [19]. Many researchers have studied the composition of propolis and found it to be very complex [20-25]. Propolis is usually consumed as an extract, so the type of solvent and extractive procedures employed further affect its composition. Propolis contains about: 50-55 % resins and balsams (phenols, phenolic acids, esters, flavanons {quercetin, galangin, pinocembrin}, dihydroflavanons, flavans, 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 [26].

#### **5. ROLE OF PROPOLIS IN INFLAMMATION (TABLE 2)**

Studies have shown that propolis suppresses LOX and COX enzymes during inflammation [10]. 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[10, 27]. It has also been shown that flavonoid inhibits the accumulation of mast cells [28]. 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[27].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 (Fig. 3). Therefore, the AA metabolism is arrested and there is no release of prostaglandins and leukotriene, responsible for inflammation and pain [10]. 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[29]. In the same research it has shown that, CAPE decreases the infiltration of inflammatory cells such as neutrophils and monocytes.



**Fig. 3. Enzymes and products of Arachidonic acid pathways involved in inflammation.**

Based on the literature, CAPE is well known as a specific inhibitor for the activation of NF- $\kappa$ B [12,13,30]. It blocks the release of IL-1 $\beta$  which is stimulated by NF- $\kappa$ B promoter and simultaneously inhibits the NF- $\kappa$ B activity[12, 30]. Studies on rats reported that CAPE protects against lipopolysaccharides (LPS) and has free radical scavenging property that decreases the pro-inflammatory cytokines[20].CAPE has preventive effect on the inflammatory cellular infiltration which leads to decreases in PGE2, ROS and NO[13,30-33]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 [11].

## 6. ROLE OF PROPOLIS IN PAIN AND HEALING (TABLE 2)

Wound healing involves numerous cell population, the cytokines, growth factors and chemical mediators and the extracellular matrix (ECM). Healing mechanism is a dynamic and continuous process and occurs when the haemostasis and inflammation process is switched off [34]. Proliferative phase and angiogenesis takes place, subsequently regeneration of connective tissue by collagen and fibroblast happens and lastly the remodelling of skin process with scar formation takes place[35].Wound healing can be affected by infection and metabolic disorders. These factors result in obstructing healing and repair processes. The process of inflammation cell invasion, fibroblast migration to collagen and ECM deposition are delayed in this condition [34,35]. Therefore, the acute wound could

turn into chronic wound which is categorised association of abundant neutrophils infiltration, destructive enzymes and ROS [34].

Studies have shown that propolis quickens the wound healing in orofacial pain. It controls neutrophil infiltration and the action of propolis via anti-inflammatory pathways [28,35-43] Besides that, research has proven that mouth rinse that contains propolis in alcohol aqueous solution heals the intra-buccal surgical wounds. Therefore, use of propolis enhances epithelial repair after tooth extraction and exerts pain killing with anti-inflammatory effect on OFP [29,35]. Generally, the normal process of wound healing depends on balance between oxidative and anti-oxidative agents. Higher level of ROS and oxidative stress lead to impaired wound healing. CAPE in propolis as antioxidant controls this process and therefore accelerates wound healing [26-28]. Studies have also shown the use EEP (ethanol extract propolis) as an intracanal medicament and pulp capping agent in endodontic therapy, promotes wound healing, bone regeneration and dentine bridge formation [44- 46].

## **7. ALLERGIC REACTIONS TO PROPOLIS**

Allergic reactions to propolis or products containing propolis are widely reported in the worldwide health literature [47,48]. The reactions include contact dermatitis, stomatitis, lip swelling, perioral eczema, and dyspnoea [49]. The major allergens in propolis are caffeate esters, which are responsible for allergies to this product. Most allergic reactions are mediated by immunoglobulin E (IgE) and involve the skin, gastrointestinal tract and respiratory system. The prevalence of systemic reactions in bee keepers is low (6.5%): just 2% experience anaphylactic reactions. However, the risk of developing such reactions increases when an individual has an atopic disease that originates from an inherited predisposition of the immune system to favour IgE-mediated hypersensitivity reactions[50]. Even though, based on the data collected to date, propolis is considered a safe substance when properly administered. Scientific research has shown that this resin maintains its main pharmacological properties regardless of its botanical origin, despite the difficulty in standardising its formulations. Propolis is a sensitizer capable of triggering allergic reactions in heavy users and therefore should not be administered to patients with any allergic predisposition or previous history of allergies. When appropriate precautions are taken, propolis is a promising substance from a pharmacological point of view. It is versatile and does not cause undesirable side effects in most people. It is important to highlight the need to disseminate the pharmaceutical indications of natural products and their therapeutic limits and adverse reactions to both health professionals and the general population so that such products can be safely and effectively used.

**Table 2. Propolis and its role in inflammation (molecular level), pain and healing**

<b>Author and year</b>	<b>Aim of the study</b>	<b>Type of the study</b>	<b>Sample type</b>	<b>Type of propolis</b>	<b>Result/outcome</b>
Borrelli et al. [27]	Phytochemical compounds in anti-inflammatory effect	Animal models	Male Wistar rats	Italian ethanol extract propolis (EEP)	<ul style="list-style-type: none"> <li>• CAPE produces a significant inhibition of leukocytes migration.</li> <li>• CAPE reduces arthritis which delays T-lymphocyte-mediated hypersensitivity reaction.</li> </ul>
Paulino et al. [13]	Analgesic, anti-inflammatory effects and in vitro contraction of airway smooth muscle	Animal models	Guinea pigs and male Swiss mice	Bulgarian propolis	<ul style="list-style-type: none"> <li>• Propolis inhibits abdominal constriction.</li> <li>• Propolis shows potent analgesic effect during neurogenic phase.</li> </ul>
Blonska et al. [33]	Inducible gene expression in J774A.1 macrophages	Cell cultures	Mouse's macrophage cell line J774A.1	Ethanol extract of propolis from Poland	<ul style="list-style-type: none"> <li>• EEP influences the IL-1<math>\beta</math> and iNOS mRNA synthesis.</li> <li>• High dose of flavone inhibits nitrite production.</li> </ul>
Marquez et al. [12]	Inhibition of T-Cell activation by NF- $\kappa$ B and NFAT-cells	Cell cultures	Jurkat cells	Propolis from Germany	<ul style="list-style-type: none"> <li>• CAPE inhibits antigen-specific T-cell proliferation and cell cycle progression.</li> <li>• CAPE inhibits NF-<math>\kappa</math>B transcriptional activity.</li> <li>• CAPE inhibits nuclear factor of activated T-cells (NFAT)dephosphorylation.</li> </ul>
Han et al. [38]	Burn wound healing in rats	Animal models	60 male Wistar albino rats	Turkish propolis	<ul style="list-style-type: none"> <li>• Propolis shows better healing, regenerative and reparative properties compared to silver sulfadiazine.</li> <li>• Better treatment for burns</li> </ul>

<b>Hu et al. [39]</b>	Acute inflammation	Animal models	60 ICR and Wistar rats	North China's Ethanol extract propolis(EEP) and water extracts propolis (WEP)	<ul style="list-style-type: none"> <li>• and promotes fast reepithelialisation.</li> <li>• Shows significant anti-inflammatory properties by inhibiting the release of prostaglandins and leukotriene.</li> <li>• WEP and EEP inhibits the swelling, leakage and increase of WBC.</li> <li>• Inhibits the increase of PGE<sub>2</sub> and NO in carrageenan-induces pleurisy exudation.</li> <li>• WEP and EEP decrease the inducing effects of cytokines.</li> </ul>
<b>Samet et al. [40]</b>	Recurrent aphthous stomatitis(RAS)	Human	19 patients suffering from RAS minor	Propolis from United States of America	<ul style="list-style-type: none"> <li>• Achieves reductions in number of aphthous ulcers</li> </ul>
<b>Pagliarone et al. [41]</b>	Pro-inflammatory cytokine production and Toll-like receptor 2 (TLR-2) and Toll-like receptor 4 (TLR-4) expression	Animal models	Stressed, Male BALB/c mice	Brazilian propolis	<ul style="list-style-type: none"> <li>• Suppresses IL-1<math>\beta</math> and IL-6.</li> <li>• Propolis shows significant increase in corticosterone production.</li> <li>• Inhibits TLR-2 mRNA and TLR-4 gene expression</li> </ul>
<b>deMoura et al. [42]</b>	Inflammatory angiogenesis	Animal models	Female Swiss mice	Brazilian green propolis	<ul style="list-style-type: none"> <li>• Decreases leukocyte accumulation and cytokine production.</li> <li>• Decreases the production of TNF-<math>\alpha</math> and TGF-<math>\beta</math>1.</li> </ul>
<b>Korish et al. [31]</b>	Systemic inflammatory response and protect hepatic and	Animal models	50 adult male Wistar rats	Saudi Arabia propolis	<ul style="list-style-type: none"> <li>• Significant increase of anti-inflammatory cytokines.</li> </ul>

<b>Kamburoglu et al. [43]</b>	neuronal cells in acute septic shock Analgesic effect.	Animal models	Adult male albino Swiss-Webster mice	WEP (water extract propolis), EEP and acetone extract propolis(AEP) of Anatolian propolis Not specified	<ul style="list-style-type: none"> <li>• WEP shows significant analgesic effect.</li> </ul>
<b>Ozório et al. [45]</b>	Standardized Propolis Extract as Pulpotomy Agents in Primary Pig Teeth	Animal models	Nine 4 months old male pigs		<ul style="list-style-type: none"> <li>• The formation of a partial mineralized tissue barrier after 21 days.</li> <li>• A complete calcified bridge after 42 days.</li> <li>• Stimulates cell immunity, increases the reparative capacity, and causes less tissue irritation.</li> </ul>
<b>Parolia et al. [46]</b>	Inflammatory Response and dentin bridge formation	Human	Thirty-six intact human premolars	Not specified	<ul style="list-style-type: none"> <li>• Propolis reduces inflammation and stimulated dentin bridge formation.</li> </ul>

## **8. CONCLUSION**

Propolis is one of the few natural products that have maintained its popularity over a long period of time due to its wide spectrum properties. With the evidence of research done on propolis and its component it can be concluded that propolis has very good anti-inflammatory property thereby could be effective to treat orofacial pain and promote healing. Further research on the exploration of analgesic effect of propolis will be very interesting.

## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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