

Literature Review

The potency of propolis extract as anti-inflammatory agent for stimulation of reparative dentin formation

Cinitra Anindya¹, Nanik Zubaidah², Ira Widjiastuti²

¹Resident of Conservative Dentistry, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

²Department of Conservative Dentistry, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Background: As an effort to treat a deep caries lesion with a diagnosis of reversible pulpitis, one of the treatment options is pulp capping. For decades, calcium hydroxide has been considered the most acceptable pulp capping material and has been routinely used in dental practice, but it also has some weakness. To overcome that, alternative materials are needed that can provide a better effect. Recently, a lot of research has been done using natural ingredients, including Propolis. Propolis has been known to have strong antimicrobial and anti-inflammatory properties. Therefore, it is necessary to conduct a deeper study regarding the potency of propolis extract as an anti-inflammatory agent for the stimulation of reparative dentin formation so that it can be considered to be used as a pulp capping material. **Purpose:** The aim of this literature review is to highlight the potency of propolis extract as anti-inflammatory agent in the natural stimulation of reparative dentin formation. **Methods:** The search strategy consist of electronic research using databases such as PubMed, Google Scholar, Science Direct, dan Springer Link for studies published from 2003 to 2021 regarding the potency of propolis extract as anti-inflammatory agent for stimulation of reparative dentin formation, including review articles and research articles. **Results:** Propolis and its constituents have been proven to be used as a potent natural anti-inflammatory, it also considered to have the ability to promote reparative dentin formation. However, there are some literatures stated that reparative dentin does not form with the application of propolis, and the causes may vary. **Conclusion:** Propolis extract has a potency as an anti-inflammatory agent in dental pulp inflammation by inhibiting TNF α expression, and increasing TGF- β 1 expression, as well as its potency in stimulating the formation of reparative dentin. Based on this review, further studies are needed.

Keywords: human & medicine; propolis; CAPE; flavonoid; reparative dentin; pulp inflammation; pulp capping

Correspondence: Ira Widjiastuti, Department of Conservative Dentistry, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo No. 47, Surabaya 60132, Indonesia. Email: ira-w@fkg.unair.ac.id

INTRODUCTION

Minimal intervention in dentistry aims to be able to maintain tooth structure in an effort to prevent more complex decay.¹ As an effort to treat deep caries with a diagnosis of reversible pulpitis, one of the treatment options is pulp capping. Pulp capping treatment can be performed on teeth with dentinal caries that are close to the pulp but have not exposed the pulp, or on exposed pulp. Pulp capping treatment is done by placing a biocompatible material on the roof of the dental pulp, to maintain the vitality and normal function of the pulp. Pulp capping is divided into two, namely direct and indirect.²

For decades, calcium hydroxide has been the gold standard as a pulp capping material.³ Calcium hydroxide can stimulate the formation of reparative dentin which is an indication of the success of open pulp treatment.⁴ The use of calcium hydroxide in pulp capping has several weaknesses, namely it can induce pulp inflammation, unpredictable

tissue response, irregularly formed reparative dentin, formation of tunnel defects, has high solubility properties, and does not provide good adaptation to dentin.^{5,6}

To correct the weaknesses of calcium hydroxide, alternative materials are needed that can provide a better effect. Many studies have been carried out using natural materials, including Propolis. Propolis is a resin compound derived from honey bee wax (*Apis mellifera*), consisting of 55% resin, 30% wax and volatile oils, 5% bee pollen, and 10% organic and mineral materials. The diversity of bioactive compounds contained in propolis causes propolis to have several biological activities. Some of the biological activities of propolis are antibacterial, anticancer, anti-inflammatory, antiviral, antifungal and antioxidant activities.⁷⁻⁹

Based on the results of many studies, it was proven that the application of propolis extract could inhibit pulp inflammation, stimulate the formation of hard tooth tissue and stimulate reparative dentin.^{10,11} Some of the literature

that discuss the potency of propolis extract shows the difference of opinion. In a study conducted by Sabir¹² application of propolis extract caused the inflammatory process that occurred in the dental pulp of rats to be inhibited but unable to stimulate the formation of reparative dentin.

Based on the differences of opinion in several studies that have been carried out as described above, a more in-depth discussion is needed through a literature review regarding the potential of propolis extract as an anti-inflammatory to stimulate reparative dentin formation so that it can be considered as an alternative candidate material for pulp capping.

METHODS

The search strategy consists of electronic research using databases such as Pubmed, Google Scholar, Science Direct, dan Springer Link regarding the potency of propolis extract as anti-inflammatory agent for stimulation of reparative

dentin formation. Articles search using keywords such as propolis, CAPE, flavonoids, pulp inflammation, TNF α , TGF- β 1, ERK, odontoblast-like cells, reparative dentin, and pulp capping. The inclusion criteria in searching for literature review sources were in the form of journals written in English and Indonesian, journals of research articles and review articles, and library sources from 2003-2021. Meanwhile, the exclusion criteria in the library sources were sources in the form of blogspot websites, news reports, journals that only included abstracts without the contents of the manuscript, as well as library sources under 2003.

RESULTS

After exclusion of irrelevant articles, 34 articles were included in this review. Information regarding authors, year of publication, the type of study, and main findings are depicted in Table 1 and 2.

Table 1. Summary of research results that show the potency of propolis extract as anti-inflammatory agent for stimulation of reparative dentine formation

Author, year of publication, and type of studies	Title	Main Findings
Ansorge <i>et al.</i> , 2003 <i>In vitro research</i>	Propolis and some of its constituents down-regulate DNA synthesis and inflammatory cytokine production but induce TGF-beta1 production of human immune cells	Application of Propolis extract containing Quercetin 20 μ m, Hesperidin 20 μ m, and CAPE 10 μ m was proven to increase the production of TGF- β 1.
Wang <i>et al.</i> , 2009 <i>In vitro research</i>	The Effect of Caffeic Acid Phenethyl Ester on the Functions of Human Monocyte-derived Dendritic Cells.	Propolis extract containing CAPE can inhibit I κ B phosphorylation and NF- κ B activation in human monocyte-derived dendritic cells (MoDCs).
Handa <i>et al.</i> , 2011 <i>Article review</i>	"Propolis" And Its Potential in Dentistry: A Review	Propolis shows anti-inflammatory effects.
Ahangari <i>et al.</i> , 2012 <i>In vivo research</i>	Effect of Propolis on Dentin Regeneration and the Potential Role of Dental Pulp Stem Cell in Guinea Pigs	Application of Azerbaijani propolis extract showed the formation of odontoblast-like cells and reparative dentin in the observation period of 10, 15 and 30 days.
Sabir, 2014 <i>Article review</i>	Prospect of using propolis in conservative dentistry and endodontic treatment (Basic research vs clinical application)	Propolis has the ability to stimulate the production of TGF- β 1, inhibit pulp inflammation, and stimulate reparative dentin formation.
Widjiastuti <i>et al.</i> , 2014 <i>In vitro research</i>	East Java Propolis Inhibits cytokine Pro-inflammatory in Odontoblast like cells Human Pulp.	Application of 3 μ g/ml East Java propolis extract can inhibit TNF α expression and increase TGF- β 1 expression in odontoblast-like cell cultures of human dental pulp.
Widjiastuti <i>et al.</i> , 2014 <i>In vitro research</i>	The expressions of NF κ B and TGF- β 1 on odontoblast-like cells of human dental pulp injected with propolis extracts	Injection of 1.5 μ g/ml, 3 g/ml, and 6 μ g/ml East Java propolis extract into odontoblast-like cells culture proved that the higher the dose of propolis extract, the ability to inhibit NF- κ B expression and increase TGF- β 1 expression increased.
Jacob <i>et al.</i> , 2015 <i>In vitro research</i>	The effects of Malaysian propolis and Brazilian red propolis on connective tissue fibroblasts in the wound healing process	Application of 500 μ g/ml Malaysian propolis extract on fibroblast cell culture can induce optimal cell proliferation at 48 hours.
Wang <i>et al.</i> , 2015 <i>In vitro research</i>	Polyphenol-rich propolis extracts from China and Brazil exert anti-inflammatory effects by modulating ubiquitination of TRAF6 during the activation of NF- κ B.	Application of 20mg/ml Chinese and Brazilian propolis extract showed the same ability in anti-inflammatory properties through inhibition of NF- κ B.

Chandrasekhar & Sharma, 2016 <i>Article review</i>	Efficient Agents for Pulp Protection: A Review	Propolis contains iron and zinc which are essential for collagen synthesis. Propolis has antioxidant properties. antibacterial, antifungal, antiviral and anti-inflammatory, and stimulates reparative dentin formation.
Dwiandhono <i>et al.</i> , 2016 <i>In vivo research</i>	The thickness of odontoblast-like cell layer after induced by propolis extract and calcium hydroxide	Application of 0.5 mg propolis extract resulted a significant thicker layer of odontoblast-like cells compared to the application of Ca(OH) ₂ on day 14 and 28 of observation
Sabir <i>et al.</i> , 2016 <i>In vivo research</i>	Impact of the Use of Ethanolic Extract of Propolis, Flavonoid and Non-Flavonoid Propolis for Direct Pulp Capping in Collagen Type I Density	The density of type I collagen in the group that was applied to 0.5 mg of EEP South Sulawesi, and 0.5 mg of propolis flavonoids increased during the observation period (6 hours, 2, 4, and 7 days). However, in the group that was applied to non-flavonoid propolis, it only increased on day 7.
Saleh <i>et al.</i> , 2016 <i>In vivo research</i>	In-Vivo Assessment of Dentin Bridge Formation after Using MTA and Experimental Propolis Paste as Direct Pulp Capping Material	The application of propolis paste which was observed for 7 days did not show the formation of reparative dentin. The formation of reparative dentin was seen after two months of observation.
Widjiastuti <i>et al.</i> , 2017 <i>In vitro research</i>	Stimulation of propolis extract on odontoblast-like cells induced by inactive Lactobacillus Acidophilus on the expression of TLR2 and TNF α .	Application of 3 μ g/ml propolis extract decreased TNF α expression in odontoblast-like cell culture induced by inactive Lactobacillus acidophilus.
Prawitasari <i>et al.</i> , 2018 <i>In vitro research</i>	Differences in thickness of odontoblast-like cells after CAPE and Calcium Hydroxide application.	Application of CAPE showed that the formation of odontoblast-like cells significantly thicker than Ca(OH) ₂ .
Kim <i>et al.</i> , 2019 <i>In vitro research</i>	Combination of mineral trioxide aggregate and propolis promotes odontoblastic differentiation of human dental pulp stem cells through ERK signaling pathway	Application of MTA, propolis or a combination of both can increase the phosphorylation of ERK.
Likitpongpipat <i>et al.</i> , 2019 <i>In vivo research</i>	Promotion of Dental Pulp Wound Healing in New Zealand White Rabbits' Teeth by Thai Propolis Product	Application of 90 mg/ml Thai Propolis extract did not cause inflammation and could stimulate pulp healing.
Sabir, 2019 <i>In vivo research</i>	Indonesian propolis suppressed the expression of COX-2 in inflamed rat dental pulp in direct capping treatment	Application of 0.5 mg South Sulawesi propolis extract showed better anti-inflammatory properties in the inflamed pulp than the application of flavonoid propolis and non-flavonoid propolis.
Shi <i>et al.</i> , 2019 <i>In vitro research</i>	Effects of MTA and Brazilian propolis on the biological properties of dental pulp cells	The application of 10 μ g/ml Brazilian propolis extract showed an increase in ALP expression after 21 days, and causing a decrease in TNF α expression although it was not significant.
Widjiastuti <i>et al.</i> , 2019 <i>In vivo research</i>	Proliferation of odontoblast-like cells following application of a combination of calcium hydroxide and propolis	Application of a combination of Ca(OH) ₂ and propolis showed a significant increase in the proliferation of odontoblast-like cells on day 3 and 7 compared to the application of Ca(OH) ₂ alone.
Widjiastuti <i>et al.</i> , 2020 <i>In vivo research</i>	Propolis extract as pulp capping material enhances odontoblast-like cell thickness and type 1 collagen expression (in vivo)	Application of propolis extract did not show any significant difference in the thickness of odontoblast-like cells compared to CAPE application on days 7 and 14. A significant difference was seen on day 28, where the thickness of odontoblast-like cells after propolis extract application was thicker. There is a significant difference in the expression of type 1 collagen on day 7, 14 and 28 after propolis extract application compared to CAPE.
Rahayu <i>et al.</i> , 2020 <i>In vivo research</i>	Combinations of propolis and Ca(OH) ₂ in dental pulp capping treatment for the stimulation of reparative dentin formation in a rat model	Combinations of propolis and Ca(OH) ₂ showed a higher increase in TGF- β expression on day 7 and 14 compared to the application of Ca(OH) ₂ alone
Pribadi <i>et al.</i> , 2021 <i>In vivo research</i>	The NF- κ B and Collagen Type 1 Expression in Dental Pulp after Treated Calcium Hydroxide Combined with Propolis	Application of combinations of Ca(OH) ₂ and propolis can inhibit pulp inflammation by decreasing the expression of NF- κ B and increasing the expression of type 1 collagen.

Table 2. Summary of research results that does not show the potency of propolis extract as anti-inflammatory agent for stimulation of reparative dentine formation

Author, year of publication, and type of studies	Title	Main Findings
Sabir, 2005 <i>In vivo research</i>	Inflammatory response in rat dental pulp after application of propolis ethanol extract	Application of 0.5 mg South Sulawesi propolis extract showed a mild inflammatory response on week 1, and moderate inflammation on week 2 and 4.
Sabir <i>et al.</i> , 2005 <i>In vivo research</i>	Histological analysis of rat dental pulp tissue capped with propolis	Application of 0.5 mg flavonoid of South Sulawesi propolis showed that in week 1, pulp inflammation was not visible, but on week 2, and 4 there was mild and moderate inflammation. Application of 0.5 mg non-flavonoid of South Sulawesi propolis showed pulp inflammation since the first week.
Sabir, 2006 <i>In vivo research</i>	Rat Dental Pulp Response to Propolis as a Direct Pulp Capping Material	Application of 0.5 mg South Sulawesi propolis extract caused inflammation during week 1, 2, and 4, the inflammation was inhibited but unable to stimulate the formation of reparative dentin.
Djurica <i>et al.</i> , 2008 <i>In vivo research</i>	The Effect of Caffeic Acid Phenethyl Ester on Healing Capacity and Repair of the Dentin-Pulp Complex: In Vivo Study	Application of 20µmol/ml CAPE did not inhibit inflammation of the dental pulp in the week 4 and 14 and reparative dentin formation was absent.
Wang <i>et al.</i> , 2009 <i>In vitro research</i>	The Effect of Caffeic Acid Phenethyl Ester on the Functions of Human Monocyte-derived Dendritic Cells.	CAPE did not affect MAPK phosphorylation in human monocyte-derived dendritic cells (MoDCs).
Parolia <i>et al.</i> , 2010 <i>In vivo research</i>	A comparative histological analysis of human pulp following direct pulp capping with Propolis, mineral trioxide aggregate and Dycal	Application of propolis extract showed mild inflammatory response on day 15 and 45 of observation period.
Ahangari <i>et al.</i> , 2012 <i>In vivo research</i>	Effect of Propolis on Dentin Regeneration and the Potential Role of Dental Pulp Stem Cell in Guinea Pigs	Application of Azerbaijani propolis extract showed a mild inflammatory response on day 10, 15 and 30 of observation period.
Bufalo <i>et al.</i> , 2013 <i>In vitro research</i>	Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF-kB and MAPK activation in macrophages.	Application of 10µg/ml propolis extract for 1 hour on macrophage cell culture showed that ERK 1/2 was not affected.
Więckiewicz <i>et al.</i> , 2013 <i>Article review</i>	Does Propolis Help to Maintain Oral Health?	The effectiveness of propolis extract compared with Ca(OH) ₂ in the stimulation of reparative dentin formation is still debated because the stimulative effect on dental pulp depends on the flavonoid contained in propolis extract.
Jacob <i>et al.</i> , 2015 <i>In vitro research</i>	The effects of Malaysian propolis and Brazilian red propolis on connective tissue fibroblasts in the wound healing process	Application of 1,10,100,250,500 and 1000µg/ml Brazilian red propolis extract showed no significant cell proliferation.
Gamal <i>et al.</i> , 2017 <i>In vivo research</i>	Histological evaluation of response to direct pulp capping with propolis: Experimental study in rabbit.	Application of propolis showed minimal inflammatory response on week 1, 2, and 4 of observation period

DISCUSSION

Inflammation is a beneficial body response that indicates that the body is being exposed to injury, but inflammation should not occur excessively because it will hinder the healing process, so inflammation must be regulated or inhibited. If immune cells are unable to repair through homeostatic mechanisms, the damage will be widespread, and can continue to be irreversible and can even cause cell death. Likewise, the response of the dental pulp, injury to the pulp can result in an inflammatory response in the pulp or called pulpitis).^{12,13}

There have been many studies aimed at treating vital pulps that have perforated, among others, using propolis. The composition of propolis varies greatly depending on the origin of propolis based on its geographical location. The main components of propolis are flavonoids and phenolic acids, including CAPE which contains up to 50% of the entire composition.¹⁴⁻¹⁶ The content of propolis consists mostly of resins, bees wax and fatty acids, aromatic oils, pollen, and other components such as minerals and vitamins. These components are rich in mineral elements such as Mg, Ca, I, K, Na, Cu, Zn, Mn, and Fe. The composition of propolis also contains lots of vitamins A, C, B1, B2, B6, C, D, and E. These various ingredients will work together synergistically to become antibacterial, antibiofilm, anti-fungal, anti-viral, and anti-inflammatory agents.^{17,18} Propolis has several important pharmacological effects, including immunomodulatory activity that promotes the healing process, and induces collagen formation. Propolis is thought to have a fairly good adaptability to the dentin surface due to the presence of bees wax as one of the chemical elements contained in propolis. In addition, propolis also contains flavonoids which are thought to produce crystals if they react with dentin so that they will bind and close the open dentinal tubules.¹⁹

In the inflammatory process caused by mechanical injury and microorganisms, it will cause phosphorylation of I κ B so that NF- κ B bonds from I κ B are released and translocation occurs into the cell nucleus and secretes pro-inflammatory cytokines, including TNF α which plays the most role in acute inflammation. Propolis inhibit inflammation because CAPE, which is the active ingredient of propolis extract, works by inhibiting the I κ B signaling pathway, so there is no addition of phosphate groups, as a result, phosphorylation of I κ B is inhibited and causes NF- κ B activity, as well, become obstructed. As a result, there is no translocation of NF- κ B into the cell nucleus which results in inhibition of the release of pro-inflammatory cytokines such as TNF α , so that inflammation can be reduced.²⁰⁻²⁴

Some references state that reparative dentin can be formed after administration of propolis extract. Due to the ability of propolis to reduce inflammation in the pulp chamber and induce the formation of reparative dentin through the release of various cytokines, TGF- β 1 as an anti-inflammatory cytokine will stimulate cell proliferation and differentiation so that reparative dentin can be formed.²⁵⁻²⁹

In conclusion, propolis extract has a potency as an anti-inflammatory agent in dental pulp inflammation by inhibiting TNF α expression, and increasing TGF- β 1 expression, as well as its potency in stimulating the formation of reparative dentin. Based on this review, further studies are needed.

REFERENCES

1. da Rosa WLO, Cocco AR, Silva TM, Mesquita LC, Galarc AD, Silva AF, Piva E. Current trends and future perspectives of dental pulp capping materials: A systematic review. *J Biomed Mater Res Part B*. 2017;1-11.
2. Garg N, Garg A. *Textbook of Endodontics*. 3rd ed. Jaypee Brothers Medical Publishers (P) Ltd; 2014.
3. Dean JA. Treatment of deep caries, vital pulp exposure, and pulpless teeth. In: McDonald and Avery's *Dentistry for the Child and Adolescent*. 10th ed. Saunders Elsevier Inc; 2015. p: 221–242.
4. Sahar H, Dalia E. The Adverse Effects of Nano bond Adhesive Systems Used as Direct Pulp Capping Materials. *Eur J Dent Med*. 2012;4:14-25.
5. Janebodin K, Horst OV, Osathanon T. Dental pulp response to pulp capping materials and bioactive molecules. *CU Dent J*. 2010;33:229-48.
6. Bogen G, Kim JS, Backland LK. Direct pulp capping with mineral trioxide aggregate. *J Am Dent Assoc*. 2008;139: 305-15.
7. Siregar HC, Fuah AM, Octaviany Y. *Propolis; Madu Multikhasiat*. Penebar Swadaya Grup; 2011.
8. Banskota AH, Teruka Y, Adnyana IK, Midosikawa M, Matsushige K, Kadota S. Anti-inflammatory effect of propolis through inhibition of nitric oxide production on carrageen-induced mouse paw edema. *Phytomedicine*. 2001;8:16–23.
9. Nagaoka T, Banskota AH, Tezuka Y, Midorikawa K, Matsushige K, Kadota S. Caffeic acid phenethyl ester (CAPE) analogues: Potent nitric oxide inhibitors from the Netherlands propolis. *Biol Pharm Bull*. 2003;26:487–91.
10. Jain S, Rair R, Sharma V, Batra M. Propolis in oral health: A natural remedy. *World J Pharm Sci*. 2014;2(1):90-4.
11. Agrawal N, Gupta ND, Tewari RK, Garg AK, Singh R. Oral health from hive: Potential uses of propolis in dentistry. *Biolife*. 2014;2:1110-6.
12. Sabir A. Respons pulpa gigi tikus terhadap propolis sebagai bahan kaping pulpa langsung. *IJD Edisi Khusus KPPIKG*. 2006;14:57-61.
13. Torabinejad M, Walton RE. *Endodontics Principles and Practice*. 5th ed. St. Louis: Saunders Elsevier Inc; 2012.
14. Banerjee R, Becker D, Dickman M, Gladyshev V, Ragsdale S. *Redox Biochemistry*. Wiley Interscience. A John Wiley & Sons, Inc; 2008.
15. Parolia A, Kundabala M, Rao NN, Acharya SR, Agrawal P, Mohan M, Thomas M. A comparative histological analysis of human pulp following direct pulp capping with Propolis, mineral trioxide aggregate and Dycal. *Aust Dent J*. 2010;55:59-64.
16. Sabir A. Indonesian propolis suppressed the expression of COX-2 in inflamed rat dental pulp in direct capping treatment. *J Dentomaxillofac Sci*. 2019;4(2):109.
17. Yuanita T. *Propolis pada imunopatobiologi penyembuhan periodontitis apikalis kronis*. Surabaya: Airlangga University Press; 2017.

18. Merlini R, Parolia A, Pau A, Amalraj FD. The role of propolis in inflammation and orofacial pain: A review. *Ethnopharmacology*. 2013;149:651-64.
19. Sabir A. Respons inflamasi pada pulpa gigi tikus setelah aplikasi ekstrak etanol propolis (EEP). *Dent J (Majalah Kedokteran Gigi)*. 2005;38(2):77-83.
20. Sankar G. *Handbook of Transcription Factor NF-kappaB*. CRC Press. Taylor & Francis Group; 2020.
21. Wang LC, Chu KH, Liang YC, Lin YL, Chiang BL. Caffeic acid phenethyl ester inhibits nuclear factor-kappaB and protein kinase B signalling pathways and induces caspase-3 expression in primary human CD4+ T cells. *Clin Exp Immunol*. 2010;160(2):223-32.
22. Wang L, Lin Y, Liang Y, Yang Y, Lee J, Yu H, Wu W, Chiang B. The effect of caffeic acid phenethyl ester on the functions of human monocyte-derived dendritic cells. *BMC Immunol*. 2009;10:39.
23. Búfalo MC, Ferreira I, Costa G, Francisco V, Liberal J, Cruz MT, Lopes MC, Batista MT, Sforcin JM. Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF-κB and MAPK activation in macrophages. *J Ethnopharmacology*. 2013;149(1):84-92.
24. Rohman MS, Rastini EK, Sarbini D, Titi AW, Widodo, Sargowo D. Inhibition of NFκB activation by CAPE (Caffeic Acid Phenethyl Ester), An Active Component of Honeybee Hives, in OXLDL- Treated HUVEC'S (Human Umbilical Vein Endothelial Cells). *Jurnal Kedokteran Brawijaya*. 2006;21(1):1-5.
25. Rahayu RP, Pribadi N, Widjiastuti I, Nugrahani NA. Combinations of propolis and Ca(OH)₂ in dental pulp capping treatment for the stimulation of reparative dentin formation in a rat model. *F1000Research*. 2020;9:308.
26. Chandrasekhar H, Sharma S. Efficient Agents for Pulp Protection: A Review. *J Pharm Sci & Res*. 2016;8(11): 1308-11.
27. Ahangari Z, Nasari M, Jalili M, Mansouri Y, Mashhadiabbas F, Torkaman A. Effect of Propolis on Dentin Regeneration and the Potential Role of Dental Pulp Stem Cell in Guinea Pigs. *Cell J*. 2012;13(4):223-8.
28. Sabir A. Prospect of using propolis in conservative dentistry and endodontic treatment (Basic research vs clinical application). *Dentika Dent J*. 2014;18(2):185-9.
29. Saleh R, Nagi S, Ezzat M, Abd El-Alim S, Zaazou M, Abu-seida A, Ibrahim M. In-Vivo Assessment of Dentin bridge Formation after Using MTA and Experimental Propolis Paste as Direct Pulp Capping Material. *Res J Pharm Biol Chem Sci*. 2016;7:1244-50.