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Review Article

A Narrative and Meta-Analytic Study of *in vivo* Efficiency of the Bioactive Compounds of Propolis in Tooth Decay

Yun Jin Kim[1], Yean Kong Yong[2], Muhammad Shahzad Aslam[1]

ABSTRACT

Background: Propolis is one of the major components produced by honeybee. It is well known in different parts of the world such as Iran, Canada, Yemen, Czech Republic, Ethiopia, Bulgaria, Portugal, India, Turkey, Malaysia, the United States of America, Chile, Brazil, and Indonesia. The bioactive constituent of every type of propolis varies depending on the geographical location. Terpenoids, flavonoids, and polyphenol compounds were found to be common in all kinds of propolis. It possess numerous applications such as control of dental infections, plaque cleaning, treating gingivitis, exhibiting antimicrobial effect and treating radiation-induced oral mucositis and cariogenic infections in caries-active patients. **Methodology:** This study thus aimed to undertake a meta-analysis of the efficacy of bioactive compounds of propolis in tooth decay. A total of three *in vivo* studies were systematically reviewed, and two studies with a total of 300 pathogen-free female Wistar rats were included in the final meta-analysis. **Results:** The results were compared among three subcategories of smooth surface caries and sulcal caries (slight, moderate, and severe), supporting a statistically significant ($P = 0.006$) beneficial effect of using fractional propolis. **Conclusion:** Most of the included studies were preliminary, without blind study and lack of information about standard animal housing protocol. More *in vivo* and clinical trials of bioactive compounds of propolis should be encouraged in future.

Key words: Dental hygiene, *in vivo* studies, meta-analysis, propolis, tooth decay, traditional medicine

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INTRODUCTION

Dental caries, commonly known as tooth decay, is an infectious disease caused by dietary sugars, which results in loss of minerals and salts of the tooth and development of cavities.[1] It has been found that sugar has a direct impact on tooth decay, but with the development of fluoride toothpaste, the prevalence of dental caries has significantly decreased despite increase in sugar consumption.[2-4] A recent study also indicated that consumers with a high level of sugar consumption had higher dental caries prevalence.[5] It is interesting to know that females are usually found to display greater prevalence rates as compared to males due to hormonal variations.[6]

Apis are honeybees that give rise to well-known products such as beeswax, nectar, pollen, propolis, bee bread, bee brood, and royal jelly. Propolis is obtained from harvest resins from different botanical species. Honeybees collect them and bring them back to the colony to protect their hives from crack and cover them to defend against pathogens. It is famous due to its traditional medicinal properties such as antioxidant,[7] anticancer especially oral cancer,[8,9] antiviral,[10] antidiabetic,[11] anti-inflammatory,[12] gingivitis,[13] antiplaque,[14] antimicrobial,[15] immunomodulatory,[16] giardiasis[17] and estrogenic.[18]

Propolis is very effective in dental care. A number of publications confirm its effectiveness in treatment against plaque and gingivitis. Therefore, propolis can be used as mouthwash. Propolis mouthwash is found to be effective in Phase-2 clinical trial.[19] Typified propolis (2%) was found more effective against mutans streptococci and lactobacilli than chlorhexidine.

Propolis mouthwash is found patient satisfaction (74%) than chlorhexidine (68%).[20] The anticariogenic action of the commercially available propolis chewing gum with xylitol was observed in 30 healthy children aged 8–11 years with decayed, missing, and filled teeth and was found more effective than xylitol.[21] The application of propolis in different dosage forms is mentioned in Table 1. A list of clinical trials related to oral health and their outcomes is mentioned in Table 2.

The color of propolis varies from region to region. For example, it is dark orange in the northern region, orange in the central coastal, dark brown in the central interior, and brown and dark brown in the southern region of Portugal.[30] The color, aroma and flavor may vary in summer, autumn, and winter seasons.[31] Poplar from Europe and Baccharis from Brazil are well-known propolis in the market, but there are some other kinds of propolis which depend on the geographical region. For example, Okinawan propolis is indigenous to Okinawa, Japan.[32] Varia-

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Table 1: Application of propolis in different dosage form

Dosage form	Methodology/formulation	Application/uses	Problem	Result	References
Mouthwash containing propolis	The alcohol-free mouthwash containing 5% w/v of Brazilian green propolis	Control of plaque and gingivitis	Current commercial brands contain alcohol	Alcohol-free mouthwash contains propolis could fight against plaque and gingivitis	[19]
Mouthwash containing propolis	2% typified propolis, mint flavor, polioxyethelers, sorbitol, blue color and water	Cariogenic infections in the caries-active patient	Dental infection	It is more effective than chlorhexidine	[20]
Propolis sachet	2 mL of AEP (13% solution)	Adjuvant therapy for asthma patient	Asthma	AEP is better than placebo	[22]
Propolis toothpaste	Silicate toothpaste with the extract from propolis	Plaque cleaning	Plaque	The toothpaste shows very good plaque-cleaning, plaque-inhibiting and anti-inflammatory effect	[23]
Chewing gum	The two chewing gums used in this study contained propolis 6.4% and xylitol 15% as the primary ingredient respectively	Natural anticarcinogenic agents	Cariogenic effect of *S. mutans*	It helps to reduce salivary *S. mutans* count when compared to xylitol gum	[21]
Mucoadhesive propolis gel	Brazilian green propolis, purified water, polysorbate 20, propylene glycol and hydroxypropyl methylcellulose	Radiation-induced oral mucositis	Mucositis is a common problem in cancer patient	Mucoadhesive propolis gel could be considered as a potential topical medication for preventing radiation-induced oral mucositis	[24]
Propolis - based chitosan varnish	EPE was ground into fine powder and 2.5 g of propolis was mixed with 25 mL of 80% aqueous ethanol in a test tube and shaken at 70°C for 30 min. After extraction, the mixture was centrifuged at 8000×g to obtain the supernatants. PCV were prepared by the addition of acetic acid to EPE 25%	Antimicrobial activity	Enhancement of propolis	The product is suitable for dental caries	[25]

S. mutans=*Streptococcus mutans*, AEP=Aqueous extract propolis, EPE=Ethanolic propolis extract, PCV=Propolis-based chitosan varnishes

Table 2: List of clinical trials related to oral health and their outcomes

Potential application	Type of clinical trial	Location	Number of patient	Outcome	References
Cavity disinfectants	Randomized clinical trial	Bapuji Dental College and Hospital, Davanagere	10	Propolis extracts can be used as a natural disinfecting agent	[26]
Control of plaque and gingivitis	Clinical trial phase-2	Faculty of Dentistry of Federa University of Minas Gerais, Brazil	25	It could be an alternative alcohol-free subject to further double-blind, randomized clinical trial	[19]
Cariogenic infections in a caries-active patient	Randomized, double-blind, placebo-controlled clinical trial	Dental Clinics at Bandeirante Anhanguera University - UNIBAN, Sao Paulo, Brazil	100	Effective against cariogenic infections when used 2% typified propolis, mint flavor, polioxyethelers, sorbitol, blue color and water	[20]
Dentinal hypersensitivity	A randomized, double-blind study	Department of Conservative Dentistry and Endodontics	156	Propolis was more effective than 5% potassium nitrate	[27]
CP and DMt2 receiving SRP	A masked, randomized clinical trial comparing with placebo	Internal Medicine Hospital, Mansoura University	50	400 mg daily propolis is a potentially viable adjunct to SRP that significantly reduces HbA1c, fasting plasma glucose, serum-(carboxymethyl) lysine levels and improves periodontal therapy outcomes in people with DMt2 and chronic periodontitis	[28]
Gingivitis	Randomized, double-blind, controlled clinical trial	N/A	42	2% typified propolis rinse was equivalent to a positive control rinse during a 21 days	[29]

CP=Chronic periodontitis, DMt2=Type 2 diabetes mellitus, SRP=Scaling and root planing, HbA1c=Hemoglobin A1c, N/A=Not available

Table 3: List of major type of propolis in a different part of the world

Origin	Pharmacological activity	*In vitro/in vivo* model	Bioactive compounds	Method identification of bioactive compounds	Result	References
Iranian propolis	Chemoprotection against gastric cancer	*In vivo*	Suberosin, tschimgin (bornyl p-hydroxybenzoate), tschimganin (bornyl vanillate), ferutinin (ferutinol p-hydroxybenzoate) and tefernin (ferutinol vanillate)	NMR	A	[38,39]
Canadian propolis fractions	Anti-oxidant	*In vitro*	Chrysin, pinocembrin, palmitic acid, naringenin/ pinobanksin, isopentyl caffeate, acacetin/caffeic acid	ESI-MS fingerprint	B	[40]
Yemen propolis	N/A	N/A	Triterpenoids, a-, p-amyryl, dammaradienyl acetates), n-alkenes, nalkanes, n-alkanoic acids, long chain wax esters, nalkanols and methyl n-alkanoates	GC-MS	C	[41]
Czech republic propolis	Antiviral	*In vitro*	Flavonoids, quercetin dihydrate, chrysin, pinocembrin Galangin, phenyl carboxylic acids, benzoic acid Cinnamic acid, caffeic acid, p-coumaric acid	HPLC	D	[10]
Ethiopian propolis	N/A	N/A	Triterpenoids such as a- and p-amyrins, a- and P-amyryl acetates, lupeol, a- and p-lupeyl acetates, n-alkanes, n-alkenes, long chain wax esters, methyl n-alkanoates	GC-MS	E	[42]
Bulgarian propolis	N/A	N/A	Pinocembrin, galangin, chrysin, tectochrysin, quercetin, isorhamnetin, kaempferol, 3,7-dihydroxy-5-methoxy flavanones and 2,5-dihydroxy-7-methoxy flavanones	HPLC, MS	F	[43]
Portugal propolis	Anti-inflammatory and antimicrobial	*In vitro*	N/A	N/A	G	[44]
Bulgarian propolis	N/A	N/A	Dihydrocaffeic acid, dihydroferulic acid, dihydroxyacetophenone, hydroxymethoxyacetophenone, p-phenethyl alcohol, benzyl alcohol pinobanksin, pinostrobin, dimethyl kaempferol	Capillary GC-MS	H	[45]
Southern portugal	Antioxidant activity	*In vitro*	Polyphenol and flavonoids	UV	I	[46]
Indian propolis	Antioxidant activity	*In vitro*	Pinocembrin and galangin	NMR	J	[47]
Portuguese propolis	Antioxidant and chemopreventive	*In vitro*	Ellagic acid, luteolin, a dimethoxylated Flavonol, dihydroxy-dimethoxyflavone, chrysoeriol-methyl ether, quercetin and kaempferol derivatives, dihydroflavones such as dihydroflavonols such as pinobanksin-3-O-pentenoate and pinobanksin-3-O-hexanoate	LC-DAD-ESI-MSn	K	[48,49]
Turkish propolis	Antioxidant and anti-cancer	*In vitro*	Polyphenols	UV	L	[50]
MP	Anti-oxidant and cardioprotective	*In vivo*	Flavonoids and polyphenols	UV	M	[51]
Indonesian propolis	Antioxidant	*In vitro*	Propolin d, Propolin c, Propolin f Propolin g, 5-pentadecylresorcinol, 5-heptadecylresorcional, 5-(8z, 11z heptadecadienyl)-resorcional, 5-(11z heptadecenyl)-resorcional	NMR	N	[52]

A=Iranian propolis is beneficial in N-methyl-N-nitro-N-nitrosoguanidine induced gastric cancer at 100 ug/mL through inhibition of cell proliferation and apoptosis induction, B=Ethanolic extract of Canadian propolis fractions showed higher polyphenol and flavonoid concentrations and higher antioxidant capacity as compared to commercial propolis and water extracts, C=Bioactive compounds indicates its pharmacological potential, D=Propolis extracts might be suitable for topical application against herpes infection, E=The difference among chemical composition of propolis in all parts of the world is due to diverse environmental source vegetation, F=The chemical composition of Bulgarian propolis is different from USSR due to geographical difference as bees collect propolis from resinous tree buds, G=Hydroalcoholic extract showed promising anti-microbial and anti-inflammatory activities, H=North and South Bulgaria have identified fifteen phenolic acids, I=There could be the possibility of difference in quality of propolis due to different zones in the same area, J=Galangin possess the highest anti-oxidant activity as compared to pinocembrin, K=Propolis exhibit anti-cancer activity on primary cultured cancerous renal cells, L=Ethanolic extract of Turkish propolis possess good antioxidant and anticancer properties, M=MP exhibits cardioprotective activity against ISO-induced oxidative stress through its direct cytotoxic radical-scavenging activities, N=All prenylflavanones demonstrated significant radical scavenging activity against diphenylpicrylhydrazyl radicals, MP=Malaysian propolis, N/A=Not available

tion of bioactive compounds is huge from region to region and among different countries. Even within one country, there exists biochemical variation. For example, Brazil propolis has classified into 13 groups.[33] A number of bioactive compounds have been isolated from Brazil propolis such as 3-prenyl-4-dihydrocinnamoloxycinnamic acid, 2,2-dimethyl-6-carboxyethenyl-2-Hlbenzopyran, 3-prenyl-4-hydroxycinnamic acid, 2,2-dimethyl-6-carboxyethenyl-2-H1benzopyrane, 3,5-diprenyl-4-hydroxycinnamic acid, 2,2-dimethyl-6-carboxyethenyl-8-prenyl-2-H-1-benzopyran, labdanetype diterpenes, and prenylated chromane derivative.[34-37] Table 3 enlists propolis of different regions with their chemical constituents and pharmacological activities.

There is an increase in the prevalence of tooth decay among preschool and schoolchildren in different countries such as India[53] and Saudi Arabia[54] and tropical countries such as Vietnam, Cambodia, Indonesia and

Myanmar.[55] It is essential to explore the role of bioactive compounds in biomedicine. The selection of propolis is based on available literature as potential treatment options. In 2014, a meta-analysis has reported statistically insignificant evidence of an effect on reducing dental plaque using propolis. The results have shown an improvement in reducing dental plaque, but the overall results were not significant.[56] Till now, no investigation has made an effort to understand the relationship of potential bioactive compounds of propolis and their preclinical or clinical effect on oral health. Most of the meta-analyses were based on the outcome of propolis in a different clinical trial. There is a huge variation among bioactive compounds of propolis even within same countries which no one accounts in the previous meta-analysis. The role of bioactive compounds and their *in vivo* efficacy are unclear. Hence, this meta-analysis aimed to investigate the efficacy of bioactive compounds of propolis for preventing tooth decay in animals.

METHODOLOGY

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using keywords propolis and/or bioactive compounds and/or clinical trial and/or *in vivo* studies and/or animal studies. A preliminary search on the PubMed, PubMed Central, CNKI, Scopus, Web of Science, Google Scholar, and PsycINFO databases yielded 15,537 papers published in English between January 1, 2000, and December 31, 2018. Inclusion and exclusion criteria were based on the study design, participants, intervention, outcome criteria as mentioned in Table 4. Studies included in the systematic review focused on identified bioactive compounds mentioned in Table 5. Characteristics of the studies included are mentioned in Table 6.

Methodological quality (MQ) was studied using a wide-ranging 12-item assessment as mentioned in Figure 1. MQ scores were based on yes (1) or no (1). Usage of systematic reviews (SRs) of experimental animal studies is not yet a common practice, but awareness of the merits of conducting such SRs is steadily increasing. Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) riskofbias (RoB) tool for animal studies is used in this study as mentioned in Table 7. The SYRCLE's RoB tool is an adapted version of the Cochrane RoB tool.[57]

Statistical analysis

Meta-analysis was conducted using the Review Manager 5.3 software. The summary measures were reported as odds ratios or as a standard mean difference with 95% confidence intervals. The presence of heterogeneity among trials was assessed using the Chi-square test, and the extent of inconsistency was measured by I^2 statistics.[58]

RESULTS

After screening around 15,573 articles, only two full-text papers were selected for further review. The abstraction process and reasons for exclusion are detailed in Figure 2. Table 5 summarizes the details of the studies reviewed. Two studies[59,60] were random *in vivo* studies. One

Table 4: Study design; participants; intervention; outcome criteria

	Inclusion criteria	Exclusion criteria
Study design	Mixed method	All review articles, irrelevant articles, articles on chemical properties and optimization, *in vitro* activities, exclude tentative identification of bioactive compounds with *in vitro* activities, exclude *in vivo* activities with no information on bioactive compounds, exclude *in vivo* activities on different pharmaceutical preparation, exclude paper that uses propolis in combination with other agent, exclude studies due to absence in scoring rat dental caries by Keyes' method, exclude *in vivo* activities other than caries development/dental caries development
Participants Intervention	Pathogen-free female wistar rats Propolis extract and their fractions delivered to pathogen-free female wistar rats/pup, infected with *S. sobrinus* and S. *mutans*	
Outcomes	Role of the bioactive composition of propolis extract/fractions in caries development	

S. sobrinus=Streptococcus sobrinus, S. mutans=Streptococcus mutans

Table 5: Studies included in the systematic review

Author, year	Country	Sample size in each group (n)	Study groups	Identified bioactive compounds	Identification method	Conclusions
Duarte, 2006	Brazil	12	Crude propolis (EEP), hexane fraction (EEH), the vehicle control ethanol 80%	Benzenepropanoic acid, methyl ester, trans-caryophyllene, a-humulene, nerolidol, myristic acid, 1,2-benzenedicarboxylic acid, bis (2-methylpropyl) ester, palmitic acid, methyl ester, hexadecanoic acid, methyl ester, linoleic acid, methyl ester, oleic acid, methyl ester, stearic acid, methyl ester, behenic acid, methyl ester, 1,2-benzenedicarboxylic acid, bis (2-ethylhexyl) ester	GC-MS	Oleic acid, linoleic acid, palmitic acid and stearic acid found in nonpolar bioactive hexane fraction of propolis and was able to reduce the incidence and severity of sulcal surface caries (P<0.05)
Silva, 2013	Brazil	13	NV (800 |ag/mL), 250 ppm fluoride and vehicle control (20% ethanol, v/v)	NV	GC-MS	NV containing fraction isolated from Brazilian red propolis as effective as fluoride in reducing the development of carious lesions *in vivo*

NV=Neovestitol-vestitol

study on the *in vitro* and *in vivo* effects of isolated fractions of Brazilian propolis on caries development was removed due to the absence of scoring rat dental caries by Keyes' method.[61] SYRCLE's RoB tool for animal studies is used in this study as mentioned in Table 7. In both of the studies, there was lack of information about the conditions of the animal house, animal loss during the study, attempt to blind the researcher, validity and reliability measures, and missing data reported as mentioned in Figure 1. The hexane fraction of Brazilian propolis (type 6) was compared with the control ethanol 80% in Duarte *et al.* experimentation, whereas neovestitol-vestitol containing fraction isolated from Brazilian red propolis was compared with the control (fluoride) in Bueno-Silva *et al.* experiment. The comparison was made between smooth surface caries and sulcal caries. The subgroups were divided into slight, moderate and severe according to Keyes' method. In the assessment of potential publication bias, visual inspection of the funnel plot in smooth surface caries and sulcal caries revealed a roughly symmetrical distribution of studies as shown in Figures 3 and 4, respectively. The overall effect in smooth surface caries and sulcal caries was found statistically significant ($P = 0.006$). Heterogeneity test in general on smooth surface caries (I^2 = 36%) and sulcal caries (I^2 = 65%) differed comparatively. Therefore, smooth surface caries showed low heterogeneity as compared to sulcal caries, whereas in both cases, there was no heterogeneity within the groups (i.e., slight, moderate, and severe). Chi-square test, df values and I^2 statistics of every individual group are mentioned in Figures 5 and 6.

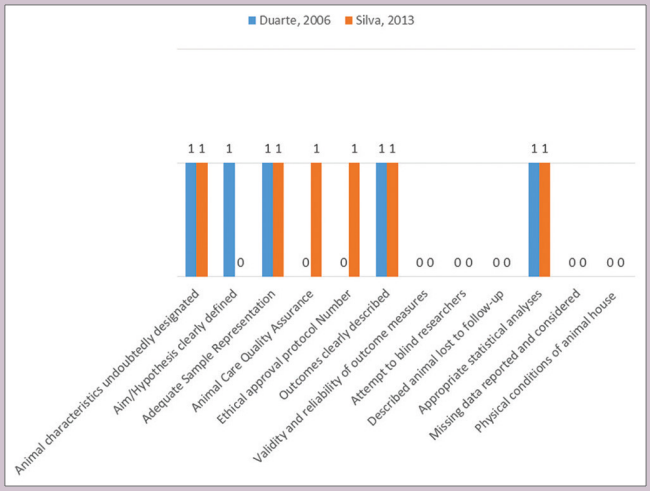

Figure 1: Methodological quality assessment of the two studies included in the meta--analysis (0 = no/not reported, 1 = yes)

DISCUSSION

The results of this meta-analysis suggest that fractional propolis is beneficial in preventing tooth decay. The reason for low heterogeneity in smooth surface caries is because of less potential for plaque attachment as compared to sulcal caries. Sulcal caries is the potential area between the tooth and gingival tissue. Hence, it is the target site for tooth decay.

The studies examined in this article are in concordance with the fact that propolis improves the oral health; however, these finding lacks validity because of less available studies. Moreover, there is a need to isolate identified bioactive compounds and evaluate their preclinical and clinical trial.

From the literature, it was also found that the identified bioactive compounds in propolis may possess antimicrobial properties. Nerolidol present in green tea possesses antimicrobial activity.[62,63] Trans-caryophyllene possesses antimicrobial activity against cariogenic bacteria.[64] α-Humulene exhibits antibacterial activity against *Streptococcus mutans*.[65] Myristic acid and palmitic acid exhibit antimicrobial activity against oral microorganisms such as *S. mutans*, *S. gordonii* and *S. sanguinis*.[66] Behenic acid has been used with dental fluoride foam as an emulsion stabilizer.[67] Neovestitol and vestitol exhibit anti-inflammatory and antimicrobial properties against *Actinomyces naeslundii*, *S. mutans*, *Staphylococcus aureus,* and *S. sobrinus*.[68-70]

Table 6: Study characteristics

Author, year	Study design	Intervention	Comparison group (s)	Statistical analysis	Software	Improvedoutcomes
Duarte, 2006	*In vivo* animal experimentation	Effect of chemical composition of propolis extract/fractions delivered to pathogen free female wistar rats infected with *S. sobrinus*	Crude propolis (EEP), hexane fraction (EEH), the vehicle control ethanol 80%	ANOVA, Tukey-Kramer HSD test	JMP version 3.1 software	Significant improvement when compared with the control group however unable to find substantial evidence of the role of identified bioactive compounds due to limitation as it require further investigation
Silva, 2013	*In vivo* animal experimentation	Effect of chemical composition of propolis extract/fractions delivered to pathogen free female wistar rats/pup infected with *S. mutans*	NV (800 ng/mL), 250 ppm fluoride and vehicle control (20% ethanol, v/v)	ANOVA, Tukey-Kramer HSD test for all pairs	BioEst version 5.0	Significant improvement when compared with the control group however unable to find substantial evidence of the role of identified bioactive compounds due to limitation as it require further investigation

Table 7: Results of SYRCLE's risk of bias tool for animal studies

Study (author, year)	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Duarte, 2006	Unclear	Yes	No	Unclear	Yes	Unclear	Unclear	Yes	Yes
Silva, 2013	Unclear	Yes	No	Unclear	Yes	Unclear	Unclear	Yes	Yes

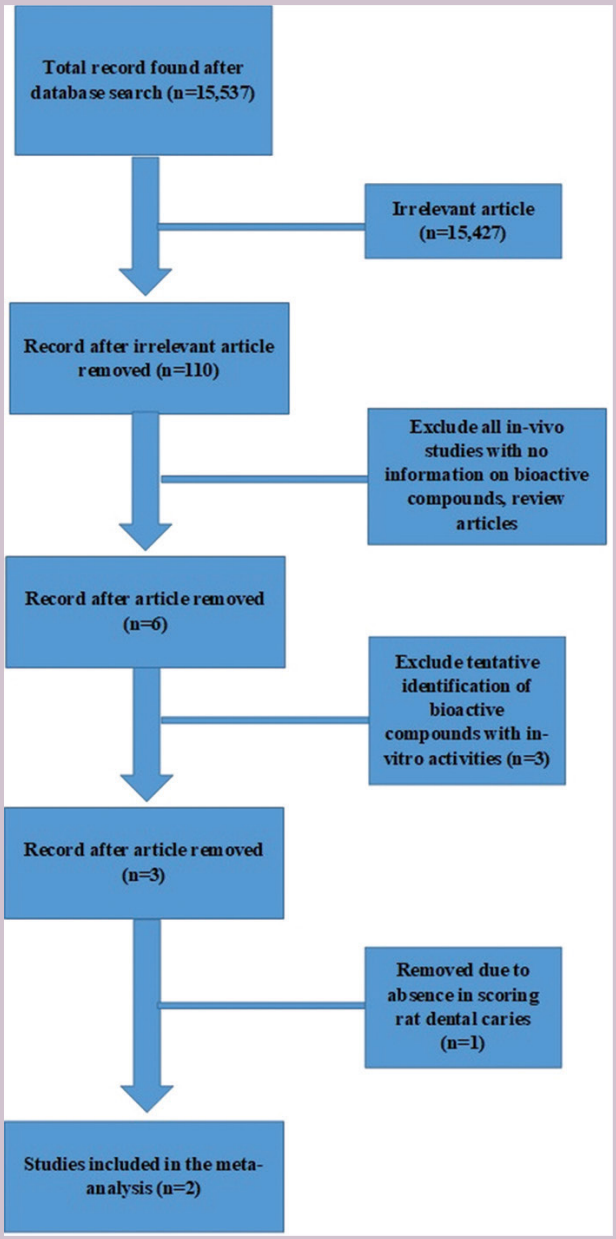

Figure 2: Summary of search strategy

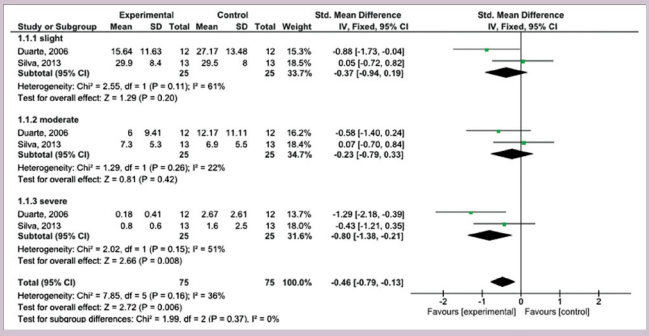

Figure 3: Forest plot in smooth surface caries

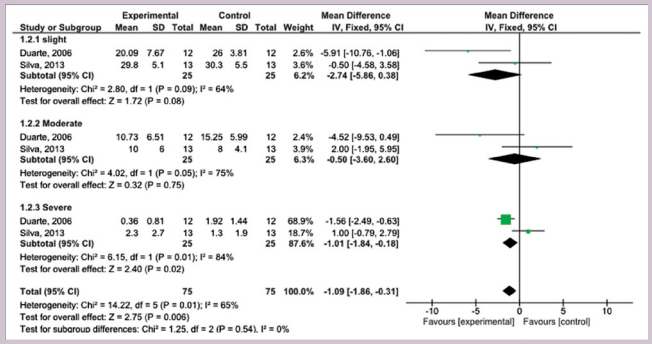

Figure 4: Forest plot in sulcal caries

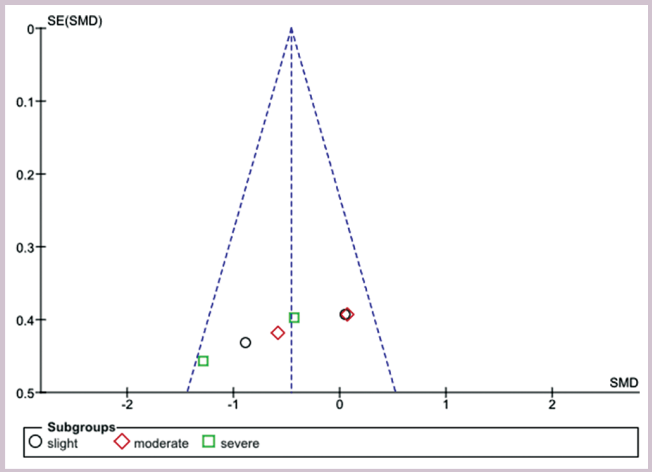

Figure 5: Funnel plot showing overall standardized mean difference in smooth surface caries

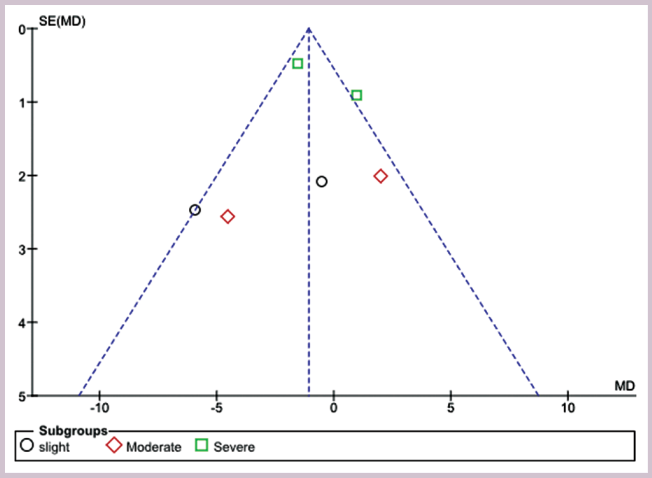

Figure 6: Funnel plot showing overall standardized mean difference in sulcal caries

On the other hand, the limitations of the present meta-analysis should be debatable. First, the outcomes of this study should be inferred as carefully optimistic because of the unavailability of data. Most of the studies on propolis are either on crude or extract. Second, there is a lack of literature on isolated bioactive compounds on propolis and moreover, most of the studies are limited to *in vitro* or *in vivo* studies. Animal studies need to be more robust and well defined. In general, there are a number of phytochemical studies on propolis, but these studies cannot proceed further for the isolation and evaluation of identified compounds for a clinical trial in tooth decay. From the literature, it was also found that there is no clinical report on identified compounds other than dental caries.

CONCLUSION

Existing evidence proposes that fractional propolis is beneficial in preventing tooth decay. However, there are few studies currently available that restrict the currently available evidence. No studies are available that have made an effort to isolate bioactive compounds and test those bioactive compounds either on animal model or under clinical trial. Moreover, there is a need for research in the standardization of propolis which results in variability in their bioactive compounds. The variation in bioactive compounds results in inconsistent results which is the reason for insignificant statistical results from the previous meta-analysis of a clinical trial performed on propolis. There is a need to isolate identified compounds and evaluate their clinical potential to validate the results and determine the final conclusion.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AEP: Aqueous extract propolis; **EPE:** Ethanolic propolis extract; **PCV:** Propolis based chitosan varnishes; **CP:** Chronic periodonti-tis; **DMt2**: Type 2 diabetes mellitus; **SRP:** Scaling and root planning; **HbA1c:** Hemoglobin A1c; **NMR:** Nuclear magnetic resonance spectroscopy; **ESI-MS:** Electrospray ionization-Mass spectroscopy; **HPLC:** High Performance Liquid Chromatography; **GCMS:** Gas chromatography–mass spectrometry; **UV:** Ultraviolet Spectroscopy; **LC-DAD:** Liquid chromatography with diode array detector; **N/A:** Not available.

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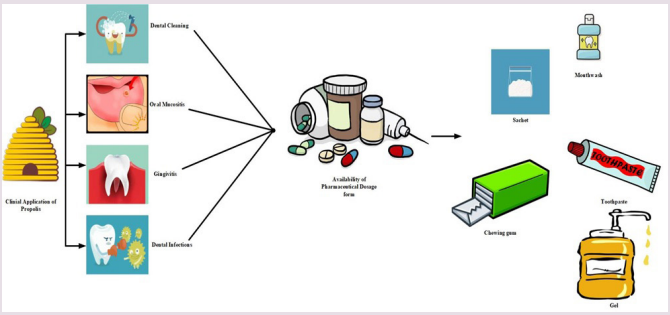
GRAPHICAL ABSTRACT



SUMMARY

Propolis produced by honeybee is geographic centric and difficult to standardize. The propose of current article is to evaluate the qualitative synthesis and meta-analysis of *in-vivo* studies of propolis in tooth decay.

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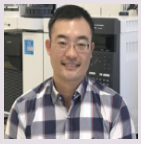

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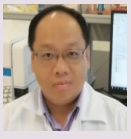

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