

## A Comprehensive Review on Chemical Compounds, Biological Actions and Potential Health Benefits of Stingless Bee Propolis

(Ulasan Komprehensif Komponen Kimia, Tindakan Biologi dan Potensi Manfaat Kesehatan Propolis Kelulut)

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### ABSTRACT

Propolis mainly comprises of resins, waxes, essential oils, pollens, and impurities collected from various parts of plants such as leaf buds, mucilage, gums, and lattices. Stingless bees had been noted to produce higher amount of propolis than honey bees since they use propolis to build their nests, which makes them valuable and economical. However, very little is known about the properties of stingless bee propolis compared to honey bees'. Therefore, this review aims to highlight the chemical composition, biological actions, health benefits including some promising future research and directions of stingless bee propolis. Recent studies had shown that the chemical composition of propolis may vary according to factors such as bee species, seasonality, location and floral preferences. These compounds play a major role in the biological and medical efficacy exhibited by the propolis. Stingless bee propolis is also known to display potent therapeutic and biological properties such as antioxidant, antimicrobial, antifungal and many more that could be used to treat diseases, infections and disorders effectively. The insights provided in this review may helpfully enhance the utility of stingless bee propolis for their therapeutic and health benefits in the food, pharmacological and medicinal sectors, some which are yet to be fully discovered.

Keywords: Biological activity; chemical composition; health benefit; propolis; stingless bee

### ABSTRAK

Propolis terdiri daripada resin, lilin, minyak pati, debunga dan campuran yang diambil daripada pelbagai bahagian tumbuhan seperti tunas daun, lendir, damar dan kekisi. Kelulut dilaporkan menghasilkan propolis yang lebih tinggi daripada lebah madu kerana propolisnya digunakan untuk membina sarang, menjadikan propolis kelulut lebih berharga dan berekonomi. Walau bagaimanapun, sangat sedikit diketahui tentang propolis kelulut berbanding lebah madu. Oleh itu, kajian ini menyoroti komposisi kimia, tindakan biologi, manfaat kesihatan termasuk arah penyelidikan propolis kelulut pada masa hadapan. Kajian baru telah menunjukkan bahawa komposisi kimia propolis adalah berbeza mengikut faktor seperti spesies kelulut, musim, lokasi dan pilihan bunga. Sebatian ini memainkan peranan penting dalam keberkesanan biologi dan perubatan yang dipamerkan oleh propolis. Propolis kelulut juga dilaporkan mempunyai ciri terapeutik dan biologi yang berkesan seperti antioksidan, antimikrob, antikulat dan banyak lagi yang boleh digunakan untuk merawat penyakit, jangkitan serta gangguan dengan berkesan. Pemahaman yang disediakan dalam ulasan ini diharap dapat membantu meningkatkan kegunaan propolis kelulut untuk manfaat terapeutik dan kesihatan dalam sektor makanan, farmakologi dan perubatan yang masih belum diteroka sepenuhnya.

Kata kunci: Aktiviti biologi; kelulut; komposisi kimia; manfaat kesihatan; propolis

### INTRODUCTION

According to the Food and Agriculture Organization (FAO), stingless bees or meliponines are one of the longest evolved bees that can be found in the tropical regions worldwide, and the art and science of stingless beekeeping

is known as meliponiculture. Nowadays, there are about 24 genus, 28 subgenus and 500 known species of stingless bees worldwide, with new ones being identified each year (Kumar et al. 2020). Stingless bees provide services that are very invaluable and crucial to the ecosystem, such as by pollinating crops and help to maintain the biodiversity.

Furthermore, stingless bees are also able to pollinate smaller flowers such as sunflowers, *Ixora*, sensitive plants and paper flowers due to their little figures which cannot be done by the relatively bigger-sized honey bees (Jalil et al. 2017; Kumar et al. 2020).

Meliponiculture products are on high demand nowadays and there are various stingless bees by-products that can be obtained and utilized, namely honey, royal jelly, bee bread, cerumen, pollen, beeswax, and propolis to name a few (Chidi & Odo 2017). The study of stingless bee products is very important as they contain multitudinal benefits and opportunities that can be applied and put to use in numerous industrial sectors such as the food, medical and pharmacological areas among others. Propolis is one of the most valuable bee products with a lot of great potentials that can be benefited from and we are yet to make the most of. Therefore, this review aims to focus on the properties and health potentials that can be derived from the propolis of the stingless bee.

‘Pro’ is the Greek word for ‘the entrance to’ and ‘polis’ stands for ‘city’ or ‘community’, and the word ‘propolis’ can be translated to ‘city’s guardian’ for its important role in protecting the hives (Ahangari et al. 2018; Wagh 2013). Propolis, which is also known as ‘bee glue’, is natural resinous substances collected by the bees from various parts of plants such as the mucilage, resins, gum, leaf buds, lattices and exudates (Anjum et al. 2018; Wagh 2013). Propolis mainly contributes to the defense part of the hives by acting as a sealant to seal the holes and cracks around the hives, regulates the internal hive temperature, smoothens the inside wall and for prevention against invaders as well as weathering of the hive. Besides, propolis also acts as a disinfectant due to its anti-microbial property and helps to protect and antisepticise the internal hive environment from dead pests and microorganisms (Devequi-Nunes et al. 2018; Kocot et al. 2018).

Propolis is generally made up of 50% resinous substance, 30% wax, 10% essential oil and aromatic oil, 5% pollen and 5% impurities, and its extracts is known to have numerous applications due to its components and biological properties such as antibacterial, antifungal, anti-inflammatory, antioxidant and many more (Kraikongjit et al. 2017). Some species of the stingless bees add clay or soil into the propolis and therefore cause it to differ slightly from the propolis of the honey bees in term of its mineral and soil content. However, it has been observed that both types display similar functions and roles to the beehives (Lavinias et al. 2019). The stingless bees would collect some of the plant resinous substances with their mouthparts, moisten them with their tongues, turn them to pellets using their mandibles and transfer the propolis to the corbiculae on the hind legs to be carried or transported to the hive (Çelemlı 2012).

It has been noted that the process of resins or propolis collection of stingless bees is similar to the honey bees, though honey bees would usually mix them

with wax to form cement, covering the cracks and holes in nests as well as strengthening the comb and beeswax (Simone et al. 2009). According to Santos et al. (2009), the glandular secretion from the stingless bee salivary and intramandibular glands that can be traced in propolis during resin collection and storage play an important role in maintaining the propolis state of viscosity as well as lubricating the mandibles. However, it has been proven that there are barely any changes made by the bees to the resins collected, and therefore, propolis is also sometimes considered to be a good herbal medicine (Meyerowitz 2000). The stingless bees would use the propolis to construct their whole hives while the honey bees’ nests are usually made up of beeswax coated with propolis as the sealants. Therefore, the antimicrobial activities of the stingless bees propolis may seep into its honey, which also able to exude antimicrobial effect as well (Miyata et al. 2019).

Besides, studies conducted have shown that the stingless bees are also able to produce propolis of higher quantity and quality as opposed to the other bees. According to Hasan et al. (2014), lack of a sting on stingless bees such as *Trigona* sp. most likely causes the higher quantity of propolis production, which acts as their defense mechanism compared to honey bees. Moreover, Ismail et al. (2018) had also reported that the stingless bee propolis contain higher antioxidant level compared to its honey as well as propolis derived from other stinging bees in their finding. Their propolis extracts are also said to be more potent in exhibiting effective biological effects than those collected from the honey bees (Agussalim et al. 2015; Ibrahim et al. 2016). Therefore, this review aims to explore and provide some insights on the chemical compounds, biological activities and health importance of stingless bee propolis extracts in order to enhance the understanding and utility of propolis in near future.

#### CHEMICAL COMPOSITIONS OF STINGLESS BEES PROPOLIS

The chemical compositions of propolis may vary according to the plant source available, bee species, seasonality and climatic state of the propolis collection site (Anjum et al. 2019; López et al. 2020). The knowledge of chemical compositions present in propolis is essential in order to understand its biological activities. Several compounds that had been identified from the propolis of the stingless bees are such as the amino acids derived from the bees, chalcone collected during propolis production and preparation, flavanones together with flavones that accounts for its antimicrobial effects, aldehydes, ketones, terpenoids, alcohols as well as hydrocarbons resulting from the bee metabolism (Çelemlı 2012).

Other than that, studies done have also reported that the major common chemical components identified in the hydroalcoholic extracts of honey bees propolis

can also be found in the propolis extracts of the stingless bees, with flavonoids found more frequently in the latter (Lavinias et al. 2019; Salatino et al. 2019). Moreover, they had also noted that the flavonoids in the honey bees (*Apis mellifera*) propolis are usually not glycosylated since honey bees hydrolyzed the glycosides using glycosidases in their saliva, as compared to the glycosylated propolis of the stingless bees (*M. interrupta*) that may not contain glycosidase in their saliva and therefore unable to hydrolyze the glycosides.

Furthermore, studies done by Pino et al. (2006) from Mexico and de Souza et al. (2018) from Brazil had also

managed to identify certain volatile components that can only be detected or found in essential oil extracted from the propolis of either honey bees (*Apis mellifera*) or stingless bees (*Melipona beecheii* and *Frieseomelitta longipes*) only. According to de Souza et al. (2018) in their finding, only sesquiterpenes can be found in *A. mellifera* propolis, while both monoterpenes and sesquiterpenes were present in the stingless bee propolis oil extract. However, there is far more research done on the volatile components of honey bees propolis than those of the stingless bees to compare. Table 1 provides the list of some chemical compounds present in the propolis extracted from both honey and stingless bees as well as their differences.

TABLE 1. Similarities and differences of some volatile components found in honey and stingless bees propolis extract

Honey bees and stingless bees		
Compound class	Compound	
Sesquiterpene	$\alpha$ -copaene	
	$\alpha$ -humulene	
	$\beta$ -bisabolene	
	$\beta$ -caryophyllene	
	$\delta$ -cadinene	
Monoterpene	$\alpha$ -pinene	
	trans-verbenol	
Carboxylic Acid	isopentyl acetate	
	3-methyl-2-butenyl acetate	
Ketone	2-heptanone	
Aldehyde	nonanal	
	octanal	
Honey bees	Compound class	Stingless bees
decanal	Aldehyde	pyridine
phenylacetaldehyde		carboxaldehyde
heptacosane	Alkane	1-undecene
pentacosane		
<i>cis</i> - $\alpha$ -bergamotene	Monoterpene	$\alpha$ -phellandrene
geranyl linalool		$\alpha$ -pinene oxide
neryl linalool		$\delta$ -3-carene
<i>trans</i> -sabinene hydrate		<i>cis</i> -limonene oxide
		trans-p-mentha-2
		8-dien-1-ol
$\alpha$ -cadinene	Sesquiterpene	$\alpha$ -dehydro-ar-himachalene
$\gamma$ -gurjunene		$\beta$ -vetivenene
ar-curcumene		germacrene A
cadina-1		germacrene D
<i>cis</i> -calamenene		
cyperene		
kaur-16-ene	Diterpene	manool
manoyl oxide	Triterpene	diploptene
$\alpha$ -bisabolol	Sesquiterpene alcohol	spathulenol
$\beta$ -eudesmol		$\alpha$ -cadinol

Besides, it has been reported that the presence of highly hydrophobic totarol, hinokiol derivative, artepillin C methyl ester and isocupressic acid in the Brazilian stingless bee, *M. quadrifasciata quadrifasciata*, propolis ethanolic extract may justify the antimicrobial, antibacterial, antioxidant and anti-inflammatory effects exhibited by the propolis extract (Torres et al. 2018). Other than that, terpenoids such as eusdemol and guaiol, and phenolic acids such as gallic acid, pterostilbene and protocatechuic acid found in the ethanolic extract of the Philippine stingless bee (*Tetragonula biroi*) propolis has been proven to mediate anticancer activity by restricting growth, initiate apoptosis and G1 phase arrest (Desamero et al. 2019). Furthermore, a study conducted by Wang et al. (2018) using Australian *Tetragonula carbonaria* species resided on the *Corymbia* trees has shown that their propolis hexane extract also possesses an anti-deterrent property that can be commercialized as ant repellents. This is due to the non-volatile and non-polar chemical compounds present in the propolis.

Other than that, phenolic acids such as caffeic acid and *p*-coumaric acid as well as flavonoids such as naringenin, hesperitin, kaempferol, baicaline, quercetin and myricetin had also been identified in the ethanolic extract of Malaysian *Geniotrigona thoracica* propolis, as shown in Figure 1, which are essential to control the oxidative stress in the human body by exerting antioxidant effects in order to balance them out (Salim et al. 2018). The study had also shown that the chemical compositions of the Malaysian propolis extract are comparable and may sometimes even be superior to that of other places in terms of its total flavonoids, phenolics compound and antioxidant capacity. On top of that, dos Santos et al. (2017) had also been able to identify terpenoids, flavanones and phenolic heterosides which were commonly found in the honey bee propolis but was rarely reported in *Melipona* geopropolis. These compounds are usually found in apicultural plants and therefore might suggest that *Melipona* sp. and *Apis* sp. may share the same plants to produce propolis.

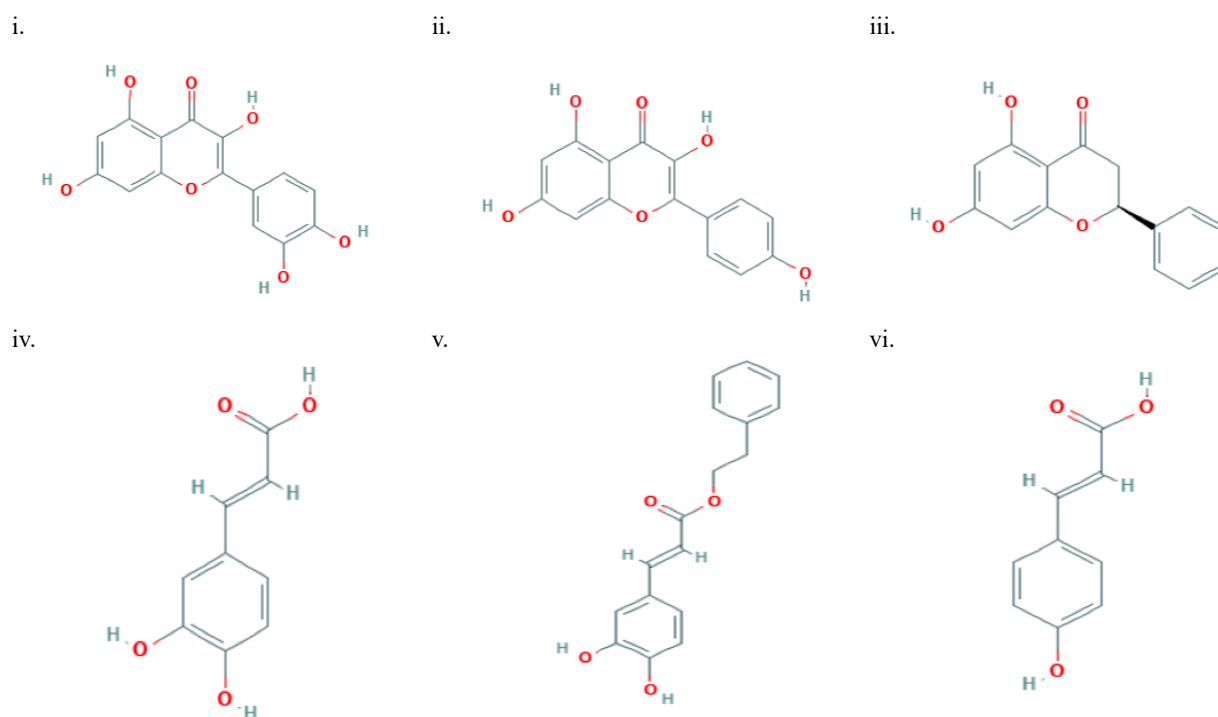


FIGURE 1. Some common chemical compounds and structures identified in Malaysian propolis are such as: i) Quercetin ii) Kaempferol iii) Pinocembrin iv) Caffeic acid v) Caffeic acid phenethyl ester (CAPE) and vi) *p*-coumaric acid (PubChem Compound Data Base)

BIOLOGICAL ACTIVITIES OF STINGLESS BEES PROPOLIS  
ANTIBACTERIAL ACTIVITY

The volatile components of propolis, such as the essential oils, play an important part in the biological activities of the propolis. Studies on the components and biological properties of the volatiles present in the propolis are still quite limited, especially those performed using oils extracted from the propolis of the stingless bees. Volatiles components obtained from the propolis of the stingless bees have demonstrated the ability to enhance the immune systems of the elders by improving the activity of the

lymphocytes and reducing the potential of diseases such as influenzas (Sena-Lopes et al. 2018). Other than that, it was also noted that extracts of several stingless bee species from all over the world are able to inhibit pathogens and can be used for pharmacological uses such as for antibacterial purposes effectively. Antibacterial activity of the propolis has also been found to be directly correlated with its amount of flavonoid and phenolic concentration (Afrouzan et al. 2018). Table 2 shows the antibacterial activity of the stingless bee propolis ethanolic extract from several countries.

TABLE 2. Antibacterial activity of ethanolic extract of stingless bee propolis

Location	Propolis	Finding	Reference
Brazil	<i>Melipona scutellaris</i>	Inhibited <i>Staphylococcus aureus</i> , <i>Streptococcus mutans</i> and MRSA strains successfully at concentration below 50 µg/mL	da Cunha et al. (2013)
India	<i>Trigona</i> sp.	Exhibited antibacterial activity against pathogens ( <i>S. aureus</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> ) due to the flavonoid and phenolic contents in propolis	Kasote et al. (2019)
India	<i>Trigona</i> sp.	Found that pathogens, especially <i>Staphylococcus</i> sp. and <i>Klebsiella</i> sp., are the most susceptible to the propolis extract	Choudhari et al. (2012)
Malaysia	<i>Heterotrigona itama</i>	Showed good inhibitory effect and antimicrobial activity especially against Gram positive bacteria such as <i>B. subtilis</i> and <i>S. aureus</i>	Akhir et al. (2017)
Brunei	<i>Heterotrigona itama</i>	Propolis extracts may be species dependent and are able to inhibit antibiotic resistant organisms ( <i>P. aeruginosa</i> , <i>S. aureus</i> , and <i>B. subtilis</i> ) better than common antibiotics (streptomycin and rifampicin) but ineffective against <i>E. coli</i>	Abdullah et al. (2019)

ANTIFUNGAL ACTIVITY

Besides, the stingless bee propolis is also widely known for its antifungal property. Ghisalberti (1960) has noted that antifungal activity exhibits by propolis could be due to bioactive and polar compounds, particularly phenols including phenolic acids, flavonoids and their esters

present in the propolis. A study done by Mendonça et al. (2015) showed that propolis extract with the lowest flavonoid and phenolic acid concentration yield lowest antifungal activity values. Table 3 shows several research done on the antifungal activity of stingless bee propolis extracts.

TABLE 3. Antifungal activity of stingless bee propolis extract

Location	Propolis	Finding	Reference
Malaysia	<i>Trigona thoracica</i>	Propolis is efficient in inhibiting growth of opportunistic and pathogenic fungi ( <i>C. albicans</i> and <i>C. neoformans</i> ) compared to the honey of rock bee ( <i>Apis dorsata</i> ) due to higher flavonoids and phenolics compounds found in the propolis	Shehu et al. (2016)
Mexico	<i>Melipona beecheii</i>	Ethanollic extract of <i>Melipona beecheii</i> is more effective in inhibiting <i>C. albicans</i> growth compared to honeybee ( <i>Apis mellifera</i> ) extract due to the different composition of phenolic compounds present in the propolis	Ramón-Sierra et al. (2019)
Brazil	<i>Melipona fasciculata</i>	Geopropolis was able to exhibit fungistatic effect on fungi-like organism ( <i>Pythium insidiosum</i> ) as well as had higher anti-microbial activity and flavonoids content than the Africanized honeybees propolis	Araújo et al. (2016)
Indonesia	<i>Tetragonula</i> sp.	Propolis extracted from the stingless bee could potentially be marketed as anti-Candida since it contained valuable anti-fungal compounds (curcumene, tetraline, thymol and <i>e-p</i> -coumaric acid) which can inhibit <i>Candida</i> sp. effectively	Farida et al. (2020)

## ANTICANCER ACTIVITY

Moreover, it has also been observed that the propolis derived from the stingless bee is capable of antiproliferative or anticancer activity by inducing programmed cell death or apoptosis on the tumor cells (da Cunha et al. 2013; Kustiawan et al. 2017). This finding also corroborates with the results gathered from a research carried out using propolis extract from the Indian *Trigona* sp. that exhibit powerful anticancer effect by inducing apoptosis and causing cell death, possibly due to the high antioxidant activity showed by the extract (Choudhari et al. 2013). The anticancer activity is mainly associated with the inhibitory activity effect and concentration of caffeic acid phenethyl ester (CAPE) and chrysin which are the active bioactive compounds found in the propolis (Sawicka et al. 2012). This showed that propolis may be used as a natural alternative for the chemotherapeutic agents used to treat cancer that may cause unwanted side effects.

## ANTIOXIDANT ACTIVITY

Other than that, it has also been noted that the phenolics compound in the propolis is responsible for the antioxidant activity exhibited by the propolis extract. A study done using Meliponine propolis extract derived from stingless bees such as Malaysian and Bruneian *H. itama* as well as Vietnamese *Lisotrigona cacciae* showed high antioxidant activity because of their high phenolic contents and has the potential to be utilized as natural antioxidants (Abdullah et al. 2019; Georgieva et al. 2019). Sari et al. (2019) have also noted that the propolis extracts containing the highest phenolics compound displayed the highest antioxidant effects. Table 4 shows several studies of antioxidant activities of the stingless bee propolis from different places.

TABLE 4. Antioxidant activities of stingless bee propolis extracts

Location	Propolis	Finding	Reference
Malaysia	<i>Geniotrigona thoracica</i>	Malaysian stingless bee propolis exhibited the highest antioxidant effect (IC <sub>50</sub> =38.9 µg/mL), followed by honey (IC <sub>50</sub> =60 µg/mL) and beebread (IC <sub>50</sub> =64 µg/mL) including those reported from the honey bee ( <i>Apis mellifera</i> ) products	Ismail et al. (2018)
Brazil	<i>Melipona quadrifasciata quadrifasciata</i> <i>Tetragonisca angustula</i>	Antioxidant activity of propolis extract derived from <i>M. quadrifasciata quadrifasciata</i> is higher and more potent (IC <sub>50</sub> =241.8 µg/mL) than those collected from the propolis of <i>T. angustula</i> (IC <sub>50</sub> =2433.0 µg/mL) since it contained higher total phenol and flavonoid concentration	Torres et al. (2018)
Indonesia	<i>Homotrigona apicalis</i> <i>Wallacetrigona incisa</i> <i>Tetragonula fuscobalteata</i> <i>Tetragonula fuscibasis</i>	All of the stingless bee propolis methanolic extracts displayed good antioxidant property, with extract derived from <i>H. apicalis</i> propolis exhibited the highest activity due to the presence of chemical compounds such as flavonoids, terpenes, phytosterols, phenolics, tannins and tocopherol	Arung et al. (2020)
Brazil	<i>Melipona quadrifasciata anthidiodes</i> <i>Tetragona clavipes</i> <i>Scaptotrigona spp.</i>	The propolis extracts showed antioxidant activity and ethyl acetate and aqueous extracts of <i>M. anthidiodes</i> exhibited the highest activity compared to the other stingless bee propolis including green propolis and contain higher total polyphenol content out of all the extracts	Pazin et al. (2017)



#### ANTIDIABETIC ACTIVITY

On top of that, propolis from the stingless bees are also known to contain antidiabetic activity as reported in the study conducted by Ibrahim et al. (2016) using Malaysian *H. itama* that exhibits strong antidiabetic effect due to the amount of antioxidants and flavonoids content that are able to inhibit oxidative stress and lower the serum glucose level. This also corroborates with the findings of the study by Pujirahayu et al. (2019) which showed that the triterpenes isolated from the propolis of *Tetragonula sapiens* was able to inhibit  $\alpha$ -glucosidase successfully and therefore has the potential to be utilized as natural  $\alpha$ -glucosidase inhibitors in the future. Furthermore, a research done in Thailand has found out that the propolis extract derived from *Tetragonula pagdeni* is great in inhibiting  $\alpha$ -glucosidase activity due to its high phenolics compound and the mangostin derivatives present in the extract such as gamma-mangostin is also able to exhibit potent inhibitory activity (Vongsak et al. 2015).

#### ANTI-OBESITY ACTIVITY

Other than that, it has also been noted in numerous reports using mainly propolis extracted from the honeybees (*Apis mellifera*) in various places such as Brazil, Croatia, and Iran which exhibits propolis potential to be utilized as one of the natural treatments for obesity by reducing lipid content and preventing further weight gain in mice fed with high fat diet (Oršolic' et al. 2019; Sakai et al. 2017; Zakerkish et al. 2019). However, to date, there is a lack of information and studies done on the effect of the propolis derived from the stingless bees on obesity or weight loss.

#### HEALTH BENEFITS NEUROLOGICAL DISEASES

Propolis is known to contain a significant amount of antioxidants that can be very beneficial medically. It was reported that the antioxidants in the propolis could play an important role in contributing to its neuroprotective effects when tested using the mouse model of ischemic stroke. The study also further proved that propolis may help to improve neurological deficits or impairments caused by neurological diseases such as Alzheimer and Parkinson due to the present of CAPE that could help restore the antioxidant enzyme's activity (Bazmandegan et al. 2017; Kocot et al. 2018). Moreover, Silveira et al. (2020) had also noted that phenolic compounds such as CAPE and pinocembrin found in propolis had also been proven to be able to treat psychiatric and neurological diseases such as cerebral ischemia,

neuroinflammation, cognitive impairment, convulsion, anxiety, and depression effectively due to their potent anti-inflammatory and therapeutic properties. In other reports, it had also been stated that the honey collected from the stingless bees is also able to improve the spatial memory in mice significantly due to phenylalanine identified in the meliponini honey (Mustafa et al. 2019).

#### THERAPEUTIC EFFECT

Other than that, propolis extract can also be used for therapeutic purposes. Analgesics or pain killers are medicine used to relieve pain or discomfort. It has been noted that chemical analgesics consumed worldwide may cause negative effects besides having low therapeutic efficacy. Therefore, natural analgesics are developed using geopropolis extract and has been proven to be effective and potent in alleviating infection and inflammatory pain. Besides, propolis analgesic was also observed to have a similar effect produced by morphine (Brodkiewicz et al. 2018). Furthermore, studies have also shown that propolis-based cream and ointment containing terpenes, flavonoids and phenols are capable of healing burn wounds remarkably through cell proliferation and collagen type I production, due to its chemical components that are able to exert strong antimicrobial, immunomodulatory and antiseptic effects (Silva et al. 2019). Moreover, propolis extract is also known to have a potential therapeutic effect on anxiety and depression. A research done has also showed that propolis essential oil extracts can be used to reverse anxiety in mice caused by restraint stress through antioxidation enhancement and hypothalamic-pituitary-adrenal (HPA) axis hyperactivity inhibition successfully (Bankova et al. 2014).

#### ANTI-OBESITY SUPPLEMENT

Nowadays, high prevalence of overweight and obesity-related diseases worldwide have been documented and necessary precautions and treatments are very much needed in order to tackle the issue at hand. It had been reported that propolis could also be utilized in the diet industry as a natural anti-obesity treatment. It has been proven that the propolis and honey derived from the bees are able to reduce lipid accumulation and absorption as well as increase the feces weight in rats (Oršolic' et al. 2019; Sakai et al. 2017). According to Balica et al. (2021), phenolic and flavonoid constituents such as chrysin, galangin, and pinocembrin from propolis extracts contribute heavily to the anti-obesity effect exhibited by the propolis by activating receptors controlling appetite, energy regulation as well as lipocytes differentiation



in the body. Galangin found in propolis is also known to increase energy expenditure, enhance lipolysis and decrease lipid absorption in rats, which helps immensely in treating obesity and obesity-related illnesses (Kumar & Alagawadi 2013). These compounds had been deemed to be non-toxic and safe for consumption, thus makes supplements produced by propolis reliable, though more studies are needed to ensure safe and effective propolis administration.

#### ACE INHIBITORS

Other than that, it has also been proven that propolis exhibits good antihypertensive activity and can be used as natural angiotensin converting enzyme (ACE) inhibitor. This is because it is able to control hypertension effectively and lower the cardiovascular disease risk. It has also been noted that some of the current synthetic or chemical ACE inhibitors found over the counter can produce negative side effects such as coughing, angioedema and skin rashes. Furthermore, a study conducted in 2019 has also shown that the antihypertensive activity of the Tunisian propolis extract studied to be much higher and better than its honey (Gargouri et al. 2019; Osés et al. 2020). Flavonoids such as catechin are known to be great ACE inhibitors and past studies had shown that propolis containing higher amount of catechin and *p*-coumaric acid are able to exhibit better antihypertensive activity. Therefore, further research need to be conducted on the utilization and application of propolis from stingless bees as natural antihypertensive agents in the near future since propolis has limited allergic reactions as well as being readily and widely available to be extracted and utilized in the medicinal care.

#### ORAL CARE TREATMENT

Besides, stingless bee propolis also has a vast use in dental or oral healthcare due to its known biological activities, which include antimicrobial, antifungal, anti-inflammatory, antioxidant as well as immunomodulatory effects. A study carried out showed that Brazilian geopropolis oral gel contains high flavonoid content and is able to prevent caries and candidiasis when treated in mice, including on cariogenic *Streptococcus mutans* biofilm (Liberio et al. 2011). Duailibe et al. (2007) have also noted that propolis derived from the stingless bees contains resin with high germicidal activity, which is very useful to be utilized in dental care to fight caries. Other than that, propolis-based mouthwashes had also been tested and proven to be less toxic than prescription mouthwashes such as chlorohexidine (Khurshid et

al. 2017). Propolis mouthwashes and toothpastes had been observed to produce less adverse effects and was considered a great alternative to chlorohexidine in preventing caries. Furthermore, it has also been reported that patients using propolis-based toothpastes do not experience any unfavourable side effects such as itching and allergy when treated against denture stomatitis caused by *Candida* sp. due to its potent antifungal properties (Al-Fahdawi 2015).

#### RESPIRATORY DISEASES

On top of that, meliponine propolis can also be used to treat respiratory problems such as asthma. It has been noted that prolonged use of glucocorticoids to treat asthma can cause immunosuppression. Therefore, stingless bee propolis extract was utilized and had successfully exhibited a significant effect on the pulmonary inflammation allergy inhibition in mice and potentially improving its immune response as well due to total phenols and phenolic acids present in the extract which aids in preventing asthma and allergy when administered orally (de Farias et al. 2014). Furthermore, propolis can also be used in treating pulmonary tuberculosis. It has been proven that the hydroethanolic extract of the propolis from stingless bees of *Trigona* sp. is able to help cure the disease since they have antibacterial, antioxidant, immunomodulatory, and antihepatotoxicity properties that can be used without affecting the patients treated negatively (Sulaeman et al. 2018). Besides, Speciale et al. (2006) had also reported that propolis extracts were able to fight bacterial strains such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes*, known to cause upper respiratory tract infections, due to combination of bioactive components in propolis and their potent antibacterial, antimicrobial and anti-inflammatory properties.

#### IMMUNOMODULATORS

Immunomodulators are substances used to activate or boost the immune function on damaged immune system. A study done using propolis derived from the Indonesian *Trigona* spp. had exhibited a significant increase in the phagocytic activity of macrophages (white blood cells) in rats infected with *S. aureus* when treated with the propolis extract. The result showed that the effect observed is more notable with increasing propolis concentration used (Kalsum et al. 2017). It was postulated that limonene, a monoterpene, in the propolis may be responsible for the immunomodulatory effect exhibited by the extract. According to Sulaeman et al. (2019),

*Trigona* sp. propolis had also been able to show excellent immunomodulatory effect on peritoneal macrophages by improving the phagocytosis process as well as the macrophage phagocytosis index, even in small doses. This is due to the presence of chemical components such as cinnamic acid, artemillin C and caffeic acid phenethyl ester in the stingless bee propolis studied that are known to activate macrophages effectively.

#### CONCLUSION

Propolis is a versatile stingless bee by-product that can be utilized and applied in various fields and industries, since it possesses numerous beneficial chemical components and biological activities. However, there are still limited reports and information regarding studies conducted on meliponine propolis available. More research is needed in order to unlock the full potential of the propolis in treating disorders and diseases such as obesity, diabetes, allergy, anxiety, and asthma. Some promising important prospective studies of stingless bees propolis are studies on the chemical compounds that can be found in the meliponine propolis, including its essential oil extracts, from more stingless bee species in order to provide information and data on the components and constituents that made up propolis. Knowledge on the health benefits of the propolis is also far from being exhaustive, especially on its potential applications and clinical trials in the health foods, nutritional supplements and pharmacological industry for better understanding of the effectiveness of the propolis extracts. Hopefully, this paper will be able to kick-start these possible research suggested above as well as other stingless bees related studies in the near future.

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