



## Composition and functional properties of propolis (bee glue): A review

Syed Ishtiaq Anjum<sup>a</sup>, Amjad Ullah<sup>a</sup>, Khalid Ali Khan<sup>b,c</sup>, Mohammad Attaullah<sup>d</sup>, Hikmatullah Khan<sup>a</sup>, Hussain Ali<sup>e</sup>, Muhammad Amjad Bashir<sup>f</sup>, Muhammad Tahir<sup>g</sup>, Mohammad Javed Ansari<sup>h,i</sup>, Hamed A. Ghramh<sup>b,c,j</sup>, Nuru Adgaba<sup>h</sup>, Chandra Kanta Dash<sup>k,\*</sup>

<sup>a</sup> Department of Zoology, Kohat University of Science and Technology, Kohat 26000, Khyber Pakhtunkhwa, Pakistan

<sup>b</sup> Unit of Bee Research and Honey Production, Faculty of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia

<sup>c</sup> Department of Biology, Faculty of Science, King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia

<sup>d</sup> Department of Zoology, University of Malakand, Chakdara 18800, Dir Lower, Khyber Pakhtunkhwa, Pakistan

<sup>e</sup> Entomology Section, Agricultural Research Institute (ARI), Tarnab, Peshawar, Khyber Pakhtunkhwa, Pakistan

<sup>f</sup> Department of Plant Protection, Faculty of Agriculture Sciences, Ghazi University, Dera Ghazi Khan 32200, Punjab, Pakistan

<sup>g</sup> Faculty of Marine Sciences, Lasbela University of Agriculture, Water and Marine Sciences, Uthal, Baluchistan, Pakistan

<sup>h</sup> Bee Research Chair, Department of Plant Protection, College of Food and Agriculture Sciences, King Saud University, Riyadh, Saudi Arabia

<sup>i</sup> Department of Botany, Hindu College Moradabad, 244001, India

<sup>j</sup> Research Center for Advanced Materials Science (RCAMS), King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia

<sup>k</sup> Department of Entomology, Faculty of Agriculture, Sylhet Agricultural University, Sylhet 3300, Bangladesh

### ARTICLE INFO

#### Article history:

Received 16 July 2018

Revised 10 August 2018

Accepted 14 August 2018

Available online 17 August 2018

#### Keywords:

Propolis

Chemical composition

Physical properties

Antimicrobial activities

Biomedical applications

### ABSTRACT

Propolis is a natural substance collected by honey bees from various plants such as, poplar, palm, pine, conifer secretions, gums, resins, mucilage and leaf buds. It is collected and brought very painstakingly by honey bees to be used for sealing cracks and crevices occurring in their hives. Originally, it as an antiseptic meant for preventing bee-hive from microbial infections along with preventing decomposition of intruders. Additionally, propolis has been used in folk medicine for centuries. The biological characteristics of propolis depend upon its chemical composition, plant sources, geographical zone and seasons. More than 300 compounds have been identified in propolis such as, phenolic compounds, aromatic acids, essential oils, waxes and amino acids. Many scientific articles are published every year in different international journals, and several groups of researchers have focused their attention on the chemical compounds and biological activity of propolis.

© 2018 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### Contents

1. Introduction . . . . .	1696
2. History of propolis . . . . .	1696
3. Physical properties of propolis . . . . .	1696
4. Composition of propolis . . . . .	1697
4.1. Gross composition of propolis . . . . .	1697
4.2. Geographical origin of propolis and composition . . . . .	1698
5. Biomedical application of propolis . . . . .	1699
5.1. Anti-bacterial activity of propolis . . . . .	1699

\* Corresponding author.

E-mail address: [chandra.ento.sau@hotmail.com](mailto:chandra.ento.sau@hotmail.com) (C.K. Dash).

Peer review under responsibility of King Saud University.



<https://doi.org/10.1016/j.sjbs.2018.08.013>

1319-562X/© 2018 Production and hosting by Elsevier B.V. on behalf of King Saud University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

5.2.	Anti-fungal activity of propolis . . . . .	1699
5.3.	Anti-tumoural activity of propolis . . . . .	1699
5.4.	Anti-protozoal activity of propolis . . . . .	1700
5.5.	Anti-inflammatory activity of propolis . . . . .	1700
5.6.	Hepatoprotective activity of propolis . . . . .	1700
5.7.	Dental action of propolis . . . . .	1700
5.8.	Anti-oxidant activity of propolis . . . . .	1700
5.9.	Anti-viral activity of propolis . . . . .	1701
5.10.	Wound healing activity of propolis . . . . .	1701
5.11.	Anti-cancer activity of propolis . . . . .	1701
6.	Conclusion . . . . .	1701
	References . . . . .	1701

## 1. Introduction

The word propolis has been derived from Greek in which the morpheme ‘Pro’ means “in front of” or “at the entrance to”) and the morpheme ‘polis’ means ‘community’ or ‘city’ (Aminimoghdamfarouj and Nematollahi, 2017; Chandna et al., 2014; Yumnam et al., 2017) which means hive defensive substance (Al-Hariri, 2011; Aminimoghdamfarouj and Nematollahi, 2017; Bankova et al., 2000; Burdock, 1998; Castaldo and Capasso, 2002; Fokt et al., 2010; Ota et al., 2001; Parolia et al., 2010; Ramos and Miranda, 2007; Sabir, 2017; Sforcin, 2016; Toreti et al., 2013; Wagh, 2013) Propolis is collected by worker-bees, from numerous plant resinous secretions (Banskota et al., 2001b; Ciftci-Yilmaz et al., 2017) such as mucilage, gums, resins (Bankova et al., 1992) and lattices and also from leaf buds (Harfouch et al., 2016; Marcucci, 1995; Özcan, 1999; Walker and Crane, 1987) of different plant species like palm, pine, alder, poplar, beech, conifer and birch (Zheng et al., 2017) and then mixed with salivary and enzymatic secretions (Sforcin, 2007). It is also called “Bee-glue” which is a natural resin (wax-like) substance (Abdulrhman et al., 2012; Tosi et al., 1996) present in bee hives and used by Honey bees as a cementing material to close open spaces and cracks occurring in their hives (Ahmed et al., 2017; Bankova et al., 2002; Bankova et al., 2000; Castaldo and Capasso, 2002; El Hady and Hegazi, 2002; Grange and Davey, 1990; Hegazi et al., 2000; Koo and Park, 1997; Kuropatnicki et al., 2013; Marcucci, 1995; Park et al., 1998; Shinohara et al., 2002; Sung et al., 2017; Toreti et al., 2013; Viuda-Martos et al., 2008; Wagh, 2013). Honey bees use propolis not only to protect their hives, by blocking the cracks, sealing the spaces and smoothening the internal walls of their hives but they also use it as an antiseptic (Akbay et al., 2017; Al-Hariri, 2011; Alonso-Salces et al., 2017; Fernández et al., 2004; Greenaway et al., 1990; Kasiotis et al., 2017; Rajpara et al., 2009; Sabir and Sumidarti, 2017; Seidel et al., 2008; Shouqin et al., 2005; Uzel et al., 2005) to protect the bees larvae, honey stores and comb from microbial infections (Açıkgöz et al., 2005; Drescher et al., 2017; Omar et al., 2017; Rufatto et al., 2017; Sforcin, 2016; Simone-Finstrom et al., 2017). It is also applied to those areas of the hive where the comb is attached to an object so as to create germ-free, smooth surface (Sforcin, 2007; Simone-Finstrom and Spivak, 2010). The reason is that honey bees live together, and therefore infection occurring in one bee can spread quickly in the whole colony (Aminimoghdamfarouj and Nematollahi, 2017; Kuropatnicki et al., 2013; Seeley and Morse, 1976; Simone-Finstrom et al., 2017; Visscher, 1980). In addition, it is also used by honey bees to prevent decomposition of the carcass of the intruder in the hives (Kumar et al., 2008; Shinohara et al., 2002) and to maintain internal hive temperature (Moreira et al., 2008; Yuksel and Akyol, 2016) around 35 °C (El Sohaimy and Masry, 2014; Pasupuleti et al., 2017). Similarly, propolis prevents entry of water to the hive which maintains constant humid-

ity and also serves as a control over the air flow towards the hive (Afrouzan et al., 2017; Kuropatnicki et al., 2013).

Propolis was identified and used by man since long (Kuropatnicki et al., 2013; Lotfy, 2006). Currently propolis is used as an anti-bacterial, anti-inflammatory, anti-viral (Sforcin et al., 2017), anti-oxidant, anti-protozoal, anesthetic, anti-tumoural, anti-cancer, anti-fungal (Rajpara et al., 2009; Sforcin, 2016), anti-septic, anti-mutagenic, anti-hepatotoxic in addition to being used for cytotoxic activity, etc. (Toreti et al., 2013).

## 2. History of propolis

Propolis was used by man as a traditional medicine since 300 BC (Ghisalberti, 1979; Seidel et al., 2008; Sung et al., 2017; Trusheva et al., 2007; Uzel et al., 2005; Veiga et al., 2017). Researchers stated that the healing activities of propolis were identified by Roman (Machado et al., 2017) and Greek doctors (Elnakady et al., 2017; Ferreira et al., 2017) as well as other scientists, such as Dioscorides, Galen, Aristoteles and Pliny (Castaldo and Capasso, 2002; Crane, 1997; Dobrowolski et al., 1991; Toreti et al., 2013). Similarly, physicians used propolis efficiently for the treatment of injuries during Anglo-Boer battle (De Castro, 2001; Sforcin, 2007) as well as in World War II (Lotfy, 2006; Ramos and Miranda, 2007). Early Egyptians used propolis to preserve their corpses from decomposition (Martinotti and Ranzato, 2015; Sawicka et al., 2012; Zabaïou et al., 2017) and to heal wounds (El Sohaimy and Masry, 2014; Parolia et al., 2010; Sforcin, 2007), because they were aware of the putrefactive properties of propolis (Ahuja and Ahuja, 2011; Castaldo and Capasso, 2002; Lotfy, 2006; Sforcin, 2016; Wagh, 2013). Furthermore, propolis was recognized as an anti-bacterial agent during 17th and 20th century in Europe (Toreti et al., 2013; Wagh, 2013). In England, Propolis was recognized as a better medicine for the treatment of wounds during 17th century (Kuropatnicki et al., 2013; Monti et al., 1983; Murray and Pizzorno Jr., 2005). Similarly in China, propolis was recognized as an anti-cancer and anti-infection medicine (Chan et al., 2013). The first scientific report about propolis, its composition and chemical actions was announced to the public in 1908 (Fokt et al., 2010; Helfenberg, 1908). In 17th century used as for varnishing (Fokt et al., 2010; Martinotti and Ranzato, 2015).

## 3. Physical properties of propolis

The color of propolis varies according to area and the plant source (Ahmed et al., 2017; De Castro, 2001; Lotfy, 2006; Özcan, 1999; Sawicka et al., 2012). It melts on 60 °C to 70 °C while some of its kinds melt on 100 °C (Martinotti and Ranzato, 2015; Ramos and Miranda, 2007; Wagh, 2013). Hard at low while soft at high temperature (Açıkgöz et al., 2005; Burdock, 1998; Fokt et al., 2010; Hausen et al., 1987; Kuropatnicki et al., 2013; Marcucci,

1995; Martinotti and Ranzato, 2015; Parolia et al., 2010; Wagh, 2013). It is extracted commercially with suitable solvents i.e. ethanol, methanol, chloroform, ether and acetone but Ethanol is the best (Martinotti and Ranzato, 2015; Ramos and Miranda, 2007; Trusheva et al., 2007). The biological activity of propolis sample varies, due to its different geographical origin (Wagh, 2013). It is found commercially in the form of dentifrices, lozenges, mouth rinses, creams, gels, cough syrups, wine, cake, powder, soap, chewing gums and tablets (Chandna et al., 2014; Parolia et al., 2010; Rajpara et al., 2009; Wagh, 2013) as well as candies, shampoos, chocolate bars, skin lotions, toothpastes (Ferreira et al., 2017; Yumnam et al., 2017), antiseptic mixtures (Ramos and Miranda, 2007) and is also used for the preservation of flesh (Chan et al., 2013). The estimated colony collection per year is 150–200 g (Krell, 1996; Kuropatnicki et al., 2013; Martinotti and Ranzato, 2015).

#### 4. Composition of propolis

Chemically propolis is composed of more than 180 different types of chemicals (Kuropatnicki et al., 2013) and season to season. Propolis is collected both in temperate zone and tropical zones and slightly different (Popova et al., 2004; Simone-Finstrom and Spivak, 2010).

As a result more than 300 different components have been identified in propolis (Ahuja and Ahuja, 2011; Al-Hariri, 2011; Banskota et al., 2001b; Chan et al., 2013; De Barros et al., 2008;

De Castro, 2001; Drescher et al., 2017; El Sohaimy and Masry, 2014; Fokt et al., 2010; Kuropatnicki et al., 2013; Rajpara et al., 2009; Ramos and Miranda, 2007; Sforcin, 2007; Sforcin, 2016; Toreti et al., 2013; Viuda-Martos et al., 2008). In general, propolis contains polyphenol (flavonoids, phenolic acids and esters) (Hegazi et al., 2000; Król et al., 2013; Kumar et al., 2008), phenolic aldehydes and ketones, etc. (Christov et al., 2005; Cuesta-Rubio et al., 2007; da Silva Frozza et al., 2013; Elnakady et al., 2017; Nagy et al., 1988). The percentage of these substances is as follows: resins and vegetable balsam 50%, Bee wax 30%, pollen 5%, essential and aromatic oils 10%, and some other substances which include organic compounds as well (Abdulkhali et al., 2017; Al-Hariri, 2011; Bosio et al., 2000; Boukraâ and Sulaiman, 2009; Burdock, 1998; Chandna et al., 2014; El Sohaimy and Masry, 2014; Fokt et al., 2010; Funari and Ferro, 2006; Kumar et al., 2008; Kuropatnicki et al., 2013; Lotfy, 2006; Martinotti and Ranzato, 2015; Park et al., 2002a, 2002b; Parolia et al., 2010; Pietta et al., 2002; Rajpara et al., 2009; Ramos and Miranda, 2007; Rufatto et al., 2017; Sabir and Sumidarti, 2017; Sforcin, 2007; Sforcin, 2016; Toreti et al., 2013; Uzel et al., 2005; Viuda-Martos et al., 2008; Wagh, 2013). The percentage of diverse material present in propolis depends upon the time of its collection and also on the geographical origin (Afrouzan et al., 2017; Bueno-Silva et al. (2017); Cuesta-Rubio et al., 2007; Kustiawan et al., 2017; Silva et al., 2017; Wagh, 2013).

##### 4.1. Gross composition of propolis

Compounds	References
<b>Flavonoids, flavanones, flavones &amp; flavonols:</b>	Walker and Crane (1987)
Islapinin, Ermanin, Pectolinarigenin, Sakuranetin, Isosakuranetin, Quercetin-3,3'-dimethyl ether, 3-acetyl pinobanksin, Betuletol, Isorhamnetin, Kaempferide, Rhamnazin, Rhamnetin, Alnusin, Alpinetin, Alnusitol, Pinostrobin, Pinocebrin, Chrysin, Tectochrysin, Acacetin, Rhamnocitrin, Quercetin, Galangin, Apigenin, Pinobanksin, Kaempferol,	
Rutin, Catechin, Luteolin, Naringenin	Lotfy (2006)
<b>Benzoic acid and derivatives:</b>	Walker and Crane (1987)
Benzoic acid, Salicylic acid, Gentisic acid, Gallic acid, Phenylmethyl ester of benzoic acid, Phenylmethyl ester of salicylic acid, Trans-coniferyl benzoate, Trans-p-coumaryl benzoate, Protocatechuic acid	
<b>Benzaldehyde derivatives:</b>	Abdulkhali et al. (2017), Akbay et al. (2017), Marcucci (1995), Walker and Crane (1987)
Vanillin, Caproic aldehydes, Isovanillin p-hydroxybenzaldehyde, Protocatechualdehyde	
<b>Cinnamyl alcohol, cinnamic acid &amp; its derivatives:</b>	Walker and Crane (1987)
Cinnamyl alcohol, Hydrocaeffic acid, Isoferulic acid, Cinnamic acid methyl ester, Cinnamic acid ethyl ester, Cinnamylidene acetic acid, Cinnamic acid, Caffeic acid, Ferulic acid	
<b>Aliphatic hydrocarbons:</b>	
Eicosine, 1-octadecene, Tricosane, Pentacosane, Eicosane, Heneicosane	
<b>Sugar:</b>	
d-ribofuranose, d-fructose, d-glucitol, d-gulose, Talose, Sucrose, d-glucose	
<b>Vitamins:</b>	Kuropatnicki et al. (2013)
B1, B2(complex), B6, C, E	
<b>Nicotinic acid, Pantothenic acid</b>	
<b>Chalcones &amp; dihydrochalcones</b>	
Alpinetin chalcone, Naringenin chalcone, Pinobanksin chalcones, Pinobanksin-3-acetate chalcone, Pinostrobin chalcone, Pinocebrin chalcones, Sakuranetin chalcone, 2',6',a-trihydroxy-4'-methoxy chalcone, 2',6, dihydroxy-4'-methoxydihydro chalcone, 2',4',6-trihydroxydihydro chalcone	Marcucci (1995)

(continued on next page)

(continued)

Compounds	References
<b>Amino acids:</b>	
Alanine, $\beta$ -alanine, $\alpha$ -amino butyric acid, $\delta$ -amino butyric acid, Arginine, Asparagine, Aspartic acid, Cystine, Cystein, Glutamic acid, Glycine, Histidine, Hydroxyproline, Isoleucine, Leucine, Lysine, Methionine, Ornithine, Phenylalanine, Proline, Pyroglutamic acid, Sarcosine, Serine, Threonine, Tryptophane, Tyrosine, Valine	
<b>Esters:</b>	<a href="#">El Hady and Hegazi (2002)</a>
Methyl palmitate, Cinnamyl- <i>trans</i> -4- coumarate, Ethyl palmitate, Stearic acid methyl ester, Phthalate ester, Benzyl benzoate, Benzyl- <i>trans</i> -4- coumarate, 3-Methyl-3-butenyl isoferulate, 3-Methyl-2-butenyl isoferulate, 3-Methyl-3-butenyl caffeate, 2-Methyl-2-butenyl caffeate, 3-Methyl-2-butenyl caffeate, Benzyl caffeate, Phenylethyl caffeate, Cinnamyl caffeate, Tetradecyl caffeate, Tetradecenyl caffeate, Tetradecenyl caffeate (isomer) <sup>b</sup> , Tetradecanyl caffeate <sup>b</sup> , Hexadecyl caffeate	
<b>Other acids and derivatives</b>	
Phenylmethyl ester of 14- methylpentadecanoic acid, Ethyl ester of palmitic acid, Myristic acid, Sorbic acid, Butyl-2-methylpropyle ester of Phthalic acid, Stearic acid, Methyl ester of alnustic acid	<a href="#">Walker and Crane (1987)</a>
<b>Alcohol, ketones, phenols and heteroaromatic compounds:</b>	
Benzyl alcohol, Hexadecanol acetate, Coumarine, Pterostilbene, Xanthorrhoeol, Scopoletol	
<b>Terpene, Sesquiterpene, alcohol &amp; derivatives:</b>	
Geraniol, Neroleol, $\beta$ -bisabolol, Guaiol, Farnisol, Dihydroeudesmol, $\alpha$ -acetoxybetulenol	
<b>Sesquiterpene &amp; Triterpene hydrocarbons:</b>	
$\beta$ -patchoulene, $\beta$ -bisabolene, Squalene, $\beta$ -bourbonene, Copaene, Calarene, Calamenene, Caryophyllene, Patchoulane, Selenene, Aromadendrene	
<b>Sterols &amp; steroid hydrocarbons:</b>	
Cholestrilene, Cholinasterol, Stigmasterol, $\beta$ -dihydrofucosterol, Lanosterol, Cholesterol	
<b>Minerals:</b>	
Sr, Ba, Cd, Sn, Pb, Ti, Ag, Co, Mo, Al, Si, V, Ni, Mn, Cr Na, Mg, Cu, Ca, Zn, Fe, K	<a href="#">Lotfy (2006)</a> , <a href="#">Pasupuleti et al. (2017)</a> , <a href="#">Walker and Crane (1987)</a>
<b>Enzymes:</b>	
Glucose-6-phosphatase, Acid phosphatase, Adenosine triphosphatase, Succinic dehydrogenase	
<b>Ketones:</b>	<a href="#">Marcucci (1995)</a>
Acetophenone, p-acetophenolacetophenone, Dihydroxy-acetope9i9inone, Methylacetophenone, Hept-5-en-2-one, 6-methylketone	
<b>Waxy acids:</b>	
Archid acid, Behenic acid, Cerotic acid, Lauric acid, Linoleic acid, Lignoceric acid, Montanic acid	
<b>Aliphatic acids &amp; aliphatic esters:</b>	
Acetic acid, Angelic acid, Butyric acid, Crotonic acid, Fumaric acid, Isobutyric acid, Methylbutyric acid, Isobutyl acetate, Isopentyl acetate, Isopentynyl acetate	
<b>Alcohol:</b>	
Benzene methanol, Cinnamyl alcohol, Glycerol, $\alpha$ -glycerophosphate, Phenethyl alcohol, Isobutenol, Hydroquinone, Prenyl alcohol	
<b>Aliphatic acids:</b>	<a href="#">El Hady and Hegazi (2002)</a>
Lactic acid, Hydroxyacetic acid, Malic acid, 5-Hydroxy-n-valeric acid, 2,3-Dihydroxypropanoic acid, Pentonic acid- 2-deoxy-3,5-dihydroxy- $\gamma$ -lactone <sup>b</sup> , Pentonic acid- 2-deoxy-3,5- dihydroxy- $\gamma$ -lactone (isomer) <sup>b</sup> , Succinic acid, 2,3,4,5-Tetrahydroxypentanoic acid- 1,4-lactone, 2,3,4,5-Tetrahydroxypentanoic acid- 1,4-lactone(isomer) <sup>b</sup> , Nonanoic acid, Palmitic acid, Oleic acid, Decanoic acid, Dodecanoic acid, Tetradecanoic acid, Heptadecanoic acid, Octadecenoic acid, Tetracosanoic acid, Eicosanoic acid, Hexacosanoic acid, 2- Hydroxy hexacosanoic acid <sup>b</sup>	

(continued)

Compounds	References
<b>Fatty acids (C7-C18 acids)</b>	
<b>Other compounds:</b>	
Phosphoric acid, 1,4-Dihydroxy benzene, 4-Hydroxy-benzaldehyde, 4-Hydroxy acetophenone, 1,2,4-trihydroxy butane, 1,2,3-trihydroxy butanal, 1,2,3-trihydroxy butanal (isomer) <sup>b</sup> , Myristicin, 2,4-bis(dimethyl benzyl)-6-tert-butyl phenol, 1,8-dihydroxy-3-methyl anthraquinone, Myristicin (isomer)	

#### 4.2. Geographical origin of propolis and composition

Poplar tree (*Populus nigra*), is found in North America, Europe, non-tropical regions of Asia as well as New Zealand. Propolis collected from Egypt was known to possess constituent of poplar tree as well as esters of caffeic acid and long-chain fatty alcohols including tetradecanol, hexadecanol and dodecanol (Bankova et al., 2000). Birch propolis collected from Russia in hold flavonols and Flavones (distinct from poplar propolis) of *Betula verrucosa* (plant source). Similarly, the main source of Brazilian propolis is *Baccharis dracunculifolia* leaf resin, including constituents, such as diterpenes, lignans, prenylated derivatives of *p*-coumaric acid as well as of acetophenone and flavonoids (distinct from poplar type). Brazilian propolis contains artepillin C in large amount as compared to CAPE (caffeic acid phenethyl ester) (Chan et al., 2013; Ferreira et al., 2017). There are some compounds, found only in tropical zones, e.g. sesquiterpenoids including germacren d, ledol and spatulenol (Bankova et al., 2000). The main source of Cuban propolis is *Clusia rosea*, and contains polyisoprenylated benzophenone which is distinct from both European and Brazilian propolis (Awale et al., 2008; Bankova, 2005; Bankova et al., 2000).

### 5. Biomedical application of propolis

Propolis use has great effect on human health and is used for various purposes. Nowadays, it is used as an antibacterial, antifungal, anti-inflammatory, antiviral, anesthetic, antioxidant (Boukraâ and Sulaiman, 2009; Omar et al., 2017), antitumoural, antiprotazoal, anticancer (Abdulrhman et al., 2012; Bankova et al., 2000; Bankova et al., 1992; Fokt et al., 2010; Koo and Park, 1997; Kuropatnicki et al., 2013; Popova et al., 2004; Rajpara et al., 2009; Ramos and Miranda, 2007; Sforcin, 2016) antihypertensive, anticarcinogenic and anti-hepatotoxic in addition to possessing cytotoxic activity, etc. (Toreti et al., 2013).

#### 5.1. Anti-bacterial activity of propolis

Propolis has a significant effect against bacteria such as *Enterococcus* spp., *Escherichia coli* and *Staphylococcus aureus* (AL-Waili et al., 2012; Grange and Davey, 1990; Kasiotis et al., 2017; Kujumgiev et al., 1999; Kuropatnicki et al., 2013; Martin and Pileggi, 2004; Sforcin et al., 2000; Silici and Kutluca, 2005). It also surfaced that, ethanolic extracts of propolis were more effective against gram-positive bacteria and showed limited effect against gram-negative bacteria (Ahuja and Ahuja, 2011; De Castro, 2001; Fokt et al., 2010; Grange and Davey, 1990; Harfouch et al., 2016; Lotfy, 2006; Martinotti and Ranzato, 2015; Uzel et al., 2005; Wagh, 2013) but only stop growth by gram-negative bacteria due to high concentration of propolis (Sforcin et al., 2000). The mode of action of propolis is due to the interaction between phenolic with other compounds such as pinocembrin, galangin, and pinobanksin (Castaldo and Capasso, 2002; Tosi et al., 1996; Wagh, 2013). Similarly, the antibacterial activity takes place due

to its active compounds such as, aromatic compounds (caffeic acid) and flavonoids (Parolia et al., 2010). Moreover, propolis acts as a bactericidal agent, to stop division of bacterial cell, destroy cell wall, bacterial cytoplasm (Parolia et al., 2010) and stop protein synthesis (Lotfy, 2006; Machado et al., 2017). The component of propolis such as Pinocembrin shows antibacterial activity towards *Streptococcus* spp. artepillin C, *p*-Coumaric acid and 3-phenyl-4-di hydrocinnamylcinnamic acid towards *Helicobacter pylori* and Apigenin strongly restrain bacterial glycosyltransferase (Martinotti and Ranzato, 2015).

Brazilian propolis was more effective against Gram-positive bacteria as compared to Gram-negative ones (Salomao et al., 2008). Propolis show antibacterial activity against some aerobic bacteria such as, *Bacillus cereus*, *B. subtilis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Nocardia asteroides*, *Rhodococcus equi*, *Staphylococcus auricularis*, *S. epidermidis*, *S. capitis*, *S. haemolyticus*, *S. warnerii*, *S. mutans*, *S. hominis*, *Streptococcus cricetus*, *St. faecalis*, *St. pyogenes*, *St. pneumoniae*, *St. sobrinus* and *St. viridians* (Fokt et al., 2010).

#### 5.2. Anti-fungal activity of propolis

Propolis showed activity against different fungi (Acikelli et al., 2013; Aghel et al., 2014; AL-Waili et al., 2012; Alvareda et al., 2015; Franchin et al., 2016; Kartal et al., 2003; Marcucci, 1995). It was investigated that, propolis inhibit the aflatoxigenic fungi, and also decreases conidial growth in *Aspergillus flavus*. Propolis from different areas show activity against *Candida guilliermondii*, *C. guilliermondii*, *C. krusei*, *C. albicans*. In another investigation, a French propolis was effectively used against human fungal pathogen *C. albicans*, *C. glabrata*, *Aspergillus fumigates*. A constituent of propolis called pinocembrin shows activity against *Penicillium italicum*, which stops mycelial growth and acting on the pathogen respiration and energy homeostasis leading to the rupturing of cell membrane and metabolism disorder (Sforcin, 2016). Propolis also showed fungicidal effect against yeast (Sforcin et al., 2000). The presence of flavonoids in propolis shows fungicidal activity against *C. pelliculosa*, *C. parapsilosis*, and *Pichia ohmeri*, *C. famata*, *C. glabrata* (Wagh, 2013). Australian propolis showed antifungal activity towards *C. albicans*, due the greater amount of pinocembrin (Banskota et al., 2001b). It was reported that, constituents of propolis such as, 3-acetylpinobanksin, pinobanksin-3-acetate, pinocembrin, *p*-coumaric acid and caffeic acid out of 26 or more constituents show anti-fungal activity. Furthermore, caffeic acid showed antimycotic activity towards *Helminthosporium carbon* (Özcan, 1999). Propolis showed good result against *Mycobacteria*, *Candida*, *Trichophyton*, *Fusarium* as well as other skin infecting fungi (Fokt et al., 2010).

#### 5.3. Anti-tumoural activity of propolis

The components of propolis possess anti-tumoural property (Banskota et al., 2000; Callejo et al., 2001; Kimoto et al., 1998;

Komericki and Kränke, 2009; Su et al., 1995; Veiga et al., 2017) and components such as caffeic acid phenethyl ester (CAPE) (Castaldo and Capasso, 2002) and artemisin C were investigated, and found to possess anti-tumoural effects (Chan et al., 2013). These compounds of propolis are involved in the cell-cycle arrest, inhibition of matrix metalloproteinases, anti-angiogenesis effect and also inhibit disease transferring from one body part to another (Sforcin, 2016). Propolis has the ability to stop DNA synthesis in tumor cells, has the property to cause aging of tumor cells (Apoptosis) and possesses the capability to put into action the white blood cells for generating those agents which are able to regulate the function of B, T and natural killer cells respectively (Salomão et al., 2011; Wagh, 2013). Other compounds such as galangin, cardanol, nemorosone and chrysin are involved to prevent the rapid division of tumor cells (Sforcin, 2016). The cytotoxic activity of natural killer cell (NK) against murine lymphoma increased with the use of propolis for 3 days (Fokt et al., 2010; Sforcin, 2007). The presence of tumor suppresser proteins in Caffeic acid phenethyl ester causes the C6 glioma cells apoptosis (De Castro, 2001; Sforcin, 2016; Watanabe et al., 2011). Caffeic acid and esters as well as diterpenoids and phenolic compounds had the destructive capability against tumor cells. The anti-tumor effect of propolis is due to its polyphenolic constituents combined function (Sforcin, 2007). Decrease in the production of glutathione in tumor cell due to radiations, is consequently fulfilled by propolis, as the synthesis of glutathione in haematopoietic tissues (Chandna et al., 2014). Turkish propolis acts as an anti-tumor by enhancing program cell death it also showed retardation of leucine, thymidine and uridine from becoming cancer causing cells, by restraining the synthesis of DNA (Watanabe et al., 2011).

#### 5.4. Anti-protozoal activity of propolis

Antiprotozoal activity of propolis against many protozoan that cause diseases in human and other animals such as, giardiasis (Freitas et al., 2006), chagas disease, leishmaniasis (Duran et al., 2008), trichomoniasis, toxoplasmosis (De Castro, 2001; Salomão et al., 2011; Torres et al., 1990) has been reported (Aghel et al., 2014). However propolis showed antiprotozoal activity against *Leishmania donovani*, *Trypanosoma cruzi*, *Giardia lamblia*, *Trichomonas vaginalis*, *Toxoplasma gondii* and *G. duodenalis* (Aminimoghadamfarouj and Nematollahi, 2017; Fokt et al., 2010; Wagh, 2013). Some components of propolis showed antimicrobial activity such as, caffeic acid, chrysin, moronic acid, protocatechuic acid, p-coumaric acid, apigenin and other constituents as terpenoids, esters and phenols (Sforcin, 2016). Propolis show better activity (coccidostatic) toward *Chilomonas paramecium* (Marcucci, 1995). Dimethyl-sulphoxide extract and ethanolic extracts of propolis were more effective toward *Trypanosoma cruzi* while showed killing effect against *Trichomonas vaginalis* (Lotfy, 2006). Marcucci et al. (2001) separated 4 phenolic compounds from Brazilian propolis such as, 2,2-dimethyl-6-carboxyethenyl-2H-1-benzopyran, 3,5-diprenyl-4-hydroxycinnamic acid, 3-(2,2-dimethyl-8-prenylbenzopyran-6-yl) propenoic acid and 3,5-diprenyl-4-hydroxycinnamic acid, showing anti-microbial activity toward *Trypanosoma cruzi* (Banskota et al., 2001b; Marcucci et al., 2001).

#### 5.5. Anti-inflammatory activity of propolis

Propolis possess the anti-inflammatory capability due to the presence of flavonoids (de Groot, 2013; Dobrowolski et al., 1991; El-Guendouz et al., 2017; Franchin et al., 2016; Khayyal et al., 1993; Machado et al., 2017; Castaldo and Capasso, 2002; Martinotti and Ranzato, 2015; Parolia et al., 2010; Ramos and Miranda, 2007; Viuda-Martos et al., 2008). It controls NADPH-oxidase ornithine decarboxylase, myeloperoxidase activity, hyalur-

onidase from guinea pig mast cells and tyrosine-protein kinase (Lotfy, 2006). The mode of action of these compounds is that, to restrain leukotrienes and prostaglandins production by white blood cells (Machado et al., 2017) and retarding myeloperoxidase activity, ornithine decarboxylase, tyrosine-protein-kinase and NADPH-oxidase (Ramos and Miranda, 2007). CAPE and galangin, both are components of poplar propolis demonstrated the anti-inflammatory property and inhibit carrageenan pleurisy, carrageenan oedema and helpful arthritis inflammations in rats (Wagh, 2013). The effect of Brazilian propolis and Chinese on the pathogenesis of collagen-induced arthritis in mice was also reported (Sforcin, 2016). Propolis regulate those inflammatory substances which are produced in the cell, as a result of pressures, poisonous material or pathogenicity (Król et al., 2013).

#### 5.6. Hepatoprotective activity of propolis

Propolis acts as a hepatoprotective agent (Andrade et al., 2008; Banskota et al., 2001a; Khayyal et al., 1993; Peña, 2008; Prusotam and Four, 1996; Santos et al., 2002; Won Seo et al., 2003). It increases the glutathione level while stop lipid peroxidation and oxidized glutathione level. Consequently, propolis increase antioxidant activity against mercury induced-toxicity and acts as a hepatoprotective agent. Studies also showed that, extract of propolis possess protective role against CCL4-entice hepatorenal oxidative stress and resultant injury (Wagh, 2013). Propolis showed hepatoprotective effect toward liver damage in rats caused due to allyl alcohol CCL4 and paracetamol (Castaldo and Capasso, 2002; Tosi et al., 1996; Wagh, 2013). Banskota et al. (2001a) isolated phenolic components as well as diterpenic acids from Brazilian propolis, showing hepatoprotective property (Bankova, 2005; Banskota et al., 2001a).

#### 5.7. Dental action of propolis

Ethanolic extract of propolis collected from four different regions of Brazil and Turkey, were used against different anaerobic bacterial strains, such as *Actinomyces naeslundii*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Veillonella parvula*, *Lactobacillus acidophilus*, *Peptostreptococcus anaerobius*, *Peptostreptococcus micros*, *Prevotella oralis* and *Prevotella melaninogenica* gave result of low inhibitive and also low bacteriocidal activity through agar dilution method. Due to the presence of flavonoids, such as galangin, chrysin, pinobanksin, quercetin, naringenin, galangin and aromatic acids present in propolis are more effective against mouth abnormalities (especially dental diseases) (De Castro, 2001; Sforcin, 2016). It had significant role in dental pulp repairing (Chandna et al., 2014; Kuropatnicki et al., 2013). The combination of ethanolic extract of propolis with mouthwash and toothpastes enhanced the prevention of microbial infection as well as to treat inflammation of gums (De Castro, 2001; Pasupuleti et al., 2017).

#### 5.8. Anti-oxidant activity of propolis

It was noted that, propolis had an antioxidant property due to its components galangin and pinocembrin (Ahn et al., 2004; Al-Hariri, 2011; El-Guendouz et al., 2017; Machado et al., 2017; Martinotti and Ranzato, 2015; Russo et al., 2002; Viuda-Martos et al., 2008). Due to higher polyphenols contents, the aqueous extract of propolis was more effective than ethanolic extracts. Galangin showed more activity in both extracts as compared to pinocembrin, due to structural difference in both (Wagh, 2013). The antioxidants had the ability to refuse free radical also prevent vitamin C, lipids and other compounds from destruction or oxidation. Because free radical and other factors are the primary cause of aging of cells and deterioration in such states as parkin-

son's disease, alzheimer's disease, arthritis, cancer, diabetes, cardiovascular diseases (Kuropatnicki et al., 2013) and also insufficient liver function. Components of propolis such as vanillin and phenolic acids had the capability to enter into the epidermis as well as dermis and protect them from free radicals, produced due to radiations or before maturation of dermal cells aging (Król et al., 2013). The mechanism of anti-oxidant property of propolis is due to phenolic compounds which donate hydrogen ions to free radicals to protect cell from oxidation reactions and also food storage from oxidation and poisoning. Propolis had the capability to remove free radicals, which are the primary cause of lipids, nucleic acids and proteins oxidation (Chandna et al., 2014). Portuguese Propolis had the antioxidant property and prevent lipid peroxidation in red blood cells of human (Zabaiou et al., 2017).

### 5.9. Anti-viral activity of propolis

It is known that, propolis showed antiviral activity (Amoros et al., 1992a; Amoros et al., 1992b), by inhibiting the virus entry into the cells, create disturbance in viral replication which cause destruction of RNA before or after its (RNA) release in the cells (Sforcin, 2016). Among other factors, propolis showed antiviral capability against genital herpes infection (HSV-2) (Kuropatnicki et al., 2013). Flavonoids which include kaempferol, acacetin, quercetin, galangin and chrysin were reported as a cytotoxic (Marcucci, 1995). Some other researcher reported a compound, separated from poplar propolis called 3-methyl-but-2-enyl caffeate inhibit titration and DNA synthesis of herpes simplex virus (type1) ex vivo. Another compound called isopentyl ferulated showed activity against influenza virus A1 Honey Kong (H3N2) ex vivo (Lotfy, 2006). Propolis showed antiviral activity against avian influenza virus, rift valley fever virus, newcastle disease virus, herpes bursal disease virus and influenza virus (El Hady and Hegazi, 2002).

### 5.10. Wound healing activity of propolis

Propolis components also has therapeutic capability of propolis on tissue repairing and regeneration of injury (Kuropatnicki et al., 2013). These are due to its immunomodulatory, anti-inflammatory and antimicrobial features (Martinotti and Ranzato, 2015; Sforcin, 2016). It was also noted that, propolis lower the quantity of free radicals in inflammatory injury and to increase collagen and its constituents development (Król et al., 2013; Martinotti and Ranzato, 2015). It accelerate different enzymatic reactions, metabolism of cells, blood circulation and also formation of collagen fibers, due to the presence of bioflavonoids, arginine, vitamin C, provitamin A, B complex as well as some minerals (Parolia et al., 2010).

### 5.11. Anti-cancer activity of propolis

Due to its antioxidant activity, propolis (ethanolic extract) of Indian stingless bees had capability of anticancer against four various cancer cell lines at various concentrations; which gave result of apoptosis and cytotoxic of these cancer cells (Król et al., 2013). Flavonoids in propolis stop breast cancers, lung cancer, oral cancer as well as esophagus, stomach, colorectal, prostate, and skin cancer (Martinotti and Ranzato, 2015). Brazilian propolis had the property of angiogenesis as well as stops the increase number of human umbilical vein endothelial cells (Zabaiou et al., 2017). Ethanolic extract of Brazilian propolis had the anti-cancer capability, examined upon 1,2 dimethylhydrazine which causing colon carcinogenesis in mice (Watanabe et al., 2011). The water extract of propolis from Thailand was examined by researchers, showed greater anti-cancer activity against colon carcinoma cell line SW620 as com-

pare to methanolic extract of propolis (Watanabe et al., 2011). Ethanolic extract of propolis had the cytotoxicity against HT-29 colon adenocarcinoma cells as well as toward HT-1080 human fibrosarcoma, however demonstrate no cytotoxicity toward typical human skin fibroblasts (Watanabe et al., 2011).

## 6. Conclusion

Propolis; a honey-bee hive product, possesses a wide range of pharmacological potentials including anti-bacterial, anti-fungal, anti-protozoal, hepatoprotective, anti-oxidant, anti-inflammatory, anti-viral, anti-cancer and anti-tumor properties. Besides, the addition of ethanolic extract of propolis in the composition of mouthwashes and toothpastes enhances the prevention of microbial infection and is effective in the treatment of gums inflammation. Moreover, the presence of bioflavonoids, arginine, vitamin C, provitamin A, B complex along with some minerals possesses wound healing property and therefore enhances injury cure. Instead of individual component, there may be combined action, which leads propolis to have diverse biological performance. Finally, the development of new propolis compounds from propolis coming from diverse geographical origins is vital in controlling various pathogenic diseases. The current literature review suggests that propolis may be explored further for its potential properties against human pathogen.

## References

- Abdulkhali, A., Hosseinzadeh, J., Ashori, A., Esmaeeli, H., 2017. Evaluation of the antibacterial activity of cellulose nanofibers/poly(lactic acid) composites coated with ethanolic extract of propolis. *Polym. Compos.* 38, 13–19.
- Abdulrhman, M., Samir Elbarbary, N., Ahmed Amin, D., Saeid Ebrahim, R., 2012. Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. *Pediatr. Hematol. Oncol.* 29, 285–292.
- Acikelli, A.H., Gustmann, S., Bardenheuer, W., Klein, J., Dembinski, U., Kohl, B., Yip, K. T., Nazif, A., Stoll, R., Strumberg, D., 2013. Flavonoids isolated from Caribbean propolis show cytotoxic activity in human cancer cell lines. *Int. J. Clin. Pharmacol. Ther.* 51, 51–53.
- Açikgöz, Z., Yücel, B., Altan, Ö., 2005. The effects of propolis supplementation on broiler performance and feed digestibility. *Arch. Geflügelk.* 69, 117–122.
- Afrouzan, H., Zakeri, S., Mehrizi, A.A., Molasalehi, S., Tahghighi, A., Shokrgozar, M.A., Es-haghi, A., Djadid, N.D., 2017. Anti-Plasmodial Assessment of Four Different Iranian Propolis Extracts. *Archives of Iranian Medicine (AIM)* 20.
- Aghel, S., Pouramir, M., Moghadamnia, A.A., Moslemi, D., Molania, T., Ghassemi, L., Motallebejad, M., 2014. Effect of Iranian propolis on salivary total antioxidant capacity in gamma-irradiated rats. *J. Dent. Res. Dent. Clin. Dent. Prospect.* 8, 235.
- Ahmed, R., Tanvir, E., Hossen, M.S., Afroz, R., Ahmmed, I., Rumpa, N.-E., Paul, S., Gan, S.H., Sulaiman, S.A., Khalil, M.I., 2017. Antioxidant properties and cardioprotective mechanism of Malaysian propolis in rats. *Evidence-Based Complement. Alternat. Med.*
- Ahn, M.-R., Kumazawa, S., Hamasaka, T., Bang, K.-S., Nakayama, T., 2004. Antioxidant activity and constituents of propolis collected in various areas of Korea. *J. Agric. Food. Chem.* 52, 7286–7292.
- Ahuja, V., Ahuja, A., 2011. Apitherapy-a sweet approach to dental diseases. Part II: propolis. *J. Adv. Oral Res.* 2, 1–8.
- Akbay, E., Özenirler, Ç., Çelemlı, Ö.G., Durukan, A.B., Onur, M.A., Sorkun, K., 2017. Effects of propolis on warfarin efficacy. *Kardiocirurgia I Torakocirurgia Polska= Polish J. Cardio-Thorac. Surg.* 14, 43.
- Al-Hariri, M.T., 2011. Propolis and its direct and indirect hypoglycemic effect. *J. Family Commun. Med.* 18, 152.
- Al-Waili, N., Al-Ghamdi, A., Ansari, M.J., Al-Attal, Y., Salom, K., 2012. Synergistic effects of honey and propolis toward drug multi-resistant *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* isolates in single and polymicrobial cultures. *Int. J. Med. Sci.* 9, 793.
- Alonso-Salces, R.M., Cugnata, N.M., Guaspari, E., Pellegrini, M.C., Aubone, I., De Piano, F.G., Antunez, K., Fuselli, S.R., 2017. Natural strategies for the control of *Paenibacillus* larvae, the causative agent of American foulbrood in honey bees: a review. *Apidologie*, 1–14.
- Alvareda, E., Miranda, P., Espinosa, V., Pardo, H., Aguilera, S., Paulino Zunini, M., 2015. 196 Antiinflammatory activity of phenolic compounds extracted from Uruguayan propolis and grape. *J. Biomol. Struct. Dyn.* 33, 129–129.
- Aminimoghaddamfarouj, N., Nematollahi, A., 2017. Propolis diterpenes as a remarkable bio-source for drug discovery development: a review. *Int. J. Mol. Sci.* 18, 1290.

- Amoros, M., Sauvager, F., Girre, L., Cormier, M., 1992a. In vitro antiviral activity of propolis. *Apidologie* 23, 231–240.
- Amoros, M., Simões, C., Girre, L., Sauvager, F., Cormier, M., 1992b. Synergistic effect of flavones and flavonols against herpes simplex virus type 1 in cell culture. Comparison with the antiviral activity of propolis. *J. Nat. Prod.* 55, 1732–1740.
- Andrade, S.F., Silva Filho, A.A.D., Cunha, W.R., Nanayakkara, N., Bastos, J.K., 2008. Antileishmanial, antimalarial and antimicrobial activities of the extract and isolated compounds from *Austroplenckia populnea* (Celastraceae). *Zeitschrift für Naturforschung C* 63, 497–502.
- Awale, S., Li, F., Onozuka, H., Esumi, H., Tezuka, Y., Kadota, S., 2008. Constituents of Brazilian red propolis and their preferential cytotoxic activity against human pancreatic PANC-1 cancer cell line in nutrient-deprived condition. *Bioorg. Med. Chem.* 16, 181–189.
- Bankova, V., 2005. Recent trends and important developments in propolis research. *Evidence-Based Complement. Alternat. Med.* 2, 29–32.
- Bankova, V., De Castro, S., Marcucci, M., 2000. Propolis: recent advances in chemistry and plant origin. *Apidologie* 31, 3–15.
- Bankova, V., Dylugorov, A., Popov, S., Evstatieva, L., Kuleva, L., Pureb, O., Zamjansan, Z., 1992. Propolis produced in Bulgaria and Mongolia: phenolic compounds and plant origin. *Apidologie* 23, 79–85.
- Bankova, V., Popova, M., Bogdanov, S., Sabatini, A.-G., 2002. Chemical composition of European propolis: expected and unexpected results. *Zeitschrift für Naturforschung C* 57, 530–533.
- Banskota, A., Tezuka, Y., Adnyana, I., Ishii, E., Midorikawa, K., Matsushige, K., Kadota, S., 2001a. Hepatoprotective and anti-*Helicobacter pylori* activities of constituents from Brazilian propolis. *Phytomedicine* 8, 16–23.
- Banskota, A.H., Tezuka, Y., Adnyana, I.K., Midorikawa, K., Matsushige, K., Message, D., Huertas, A.A., Kadota, S., 2000. Cytotoxic, hepatoprotective and free radical scavenging effects of propolis from Brazil, Peru, the Netherlands and China. *J. Ethnopharmacol.* 72, 239–246.
- Banskota, A.H., Tezuka, Y., Kadota, S., 2001b. Recent progress in pharmacological research of propolis. *Phytother. Res.* 15, 561–571.
- Bosio, K., Avanzini, C., D'Avolio, A., Ozino, O., Savoia, D., 2000. In vitro activity of propolis against *Streptococcus pyogenes*. *Lett. Appl. Microbiol.* 31, 174–177.
- Boukraâ, L., Sulaiman, S.A., 2009. Rediscovering the antibiotics of the hive. *Recent Pat. Anti-Infect. Drug Discovery* 4, 206–213.
- Bueno-Silva, B., Marsola, A., Ikegaki, M., Alencar, S.M., Rosalen, P.L., 2017. The effect of seasons on Brazilian red propolis and its botanical source: chemical composition and antibacterial activity. *Nat. Prod. Res.* 31, 1318–1324.
- Burdock, G., 1998. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem. Toxicol.* 36, 347–363.
- Callejo, A., Armentia, A., Lombardero, M., Asensio, T., 2001. Propolis, a new bee-related allergen. *Allergy* 56, 579–579.
- Castaldo, S., Capasso, F., 2002. Propolis, an old remedy used in modern medicine. *Fitoterapia* 73, S1–S6.
- Chan, G.C.-F., Cheung, K.-W., Sze, D.M.-Y., 2013. The immunomodulatory and anticancer properties of propolis. *Clin. Rev. Allergy Immunol.* 44, 262–273.
- Chandna, P., Adlakha, V.K., Das, S., Singh, S., 2014. Complementary and Alternative Medicine (CAM): a review of propolis in dentistry. *Technology* 4, 6.
- Christov, R., Trusheva, B., Popova, M., Bankova, V., Bertrand, M., 2005. Chemical composition of propolis from Canada, its antiradical activity and plant origin. *Nat. Prod. Res.* 19, 673–678.
- Ciftci-Yilmaz, S., Azman, Z.N., Kosem, K., Gunduz, E., Grenman, R.G., 2017. Evaluating Antioxidant Capacity of Different Propolis Samples from Konya, Turkey and Their Inhibitory Effect on Head and Neck Cancer Cells. *BioRxiv* 183913.
- Crane, E., 1997. The Past and Present Importance of Bee Products to Man Bee Products. Springer, pp. 1–13.
- Cuesta-Rubio, O., Piccinelli, A.L., Campo Fernandez, M., Marquez Hernandez, I., Rosado, A., Rastrelli, L., 2007. Chemical characterization of Cuban propolis by HPLC–PDA, HPLC–MS, and NMR: the brown, red, and yellow Cuban varieties of propolis. *J. Agric. Food. Chem.* 55, 7502–7509.
- da Silva Frozza, A.C., Garcia, C.S.C., Gambato, G., de Souza, M.D.O., Salvador, M., Moura, S., Padilha, F.F., Seixas, F.K., Collares, T., Borsuk, S., 2013. Chemical characterization, antioxidant and cytotoxic activities of Brazilian red propolis. *Food Chem. Toxicol.* 52, 137–142.
- De Barros, M.P., Lemos, M., Maistro, E.L., Leite, M.F., Sousa, J.P.B., Bastos, J.K., de Andrade, S.F., 2008. Evaluation of antitumor activity of the main phenolic acids found in Brazilian Green Propolis. *J. Ethnopharmacol.* 120, 372–377.
- De Castro, S., 2001. Propolis: biological and pharmacological activities. Therapeutic uses of this bee-product. *Ann. Rev. Biomed. Sci.* 3, 49–83.
- de Groot, A.C., 2013. Propolis: a review of properties, applications, chemical composition, contact allergy, and other adverse effects. *Dermatitis* 24, 263–282.
- Dobrowolski, J.W., Vohora, S., Sharma, K., Shah, S.A., Naqvi, S., Dandiya, P., 1991. Antibacterial, antifungal, antiamebic, antiinflammatory and antipyretic studies on propolis bee products. *J. Ethnopharmacol.* 35, 77–82.
- Drescher, N., Klein, A.-M., Neumann, P., Yañez, O., Leonhardt, S.D., 2017. Inside honeybee hives: impact of natural propolis on the ectoparasitic mite varroa destructor and viruses. *Insects* 8, 15.
- Duran, G., Duran, N., Culha, G., Ozcan, B., Oztas, H., Ozer, B., 2008. In vitro antileishmanial activity of Adana propolis samples on *Leishmania tropica*: a preliminary study. *Parasitol. Res.* 102, 1217–1225.
- El-Guendouz, S., Al-Waili, N., Azza, S., Elamine, Y., Zizi, S., Al-Waili, T., Al-Waili, A., Lyoussi, B., 2017. Antioxidant and diuretic activity of co-administration of *Capparis spinosa* honey and propolis in comparison to furosemide. *Asian Pac. J. Trop. Med.*
- El Hady, F.K.A., Hegazi, A.G., 2002. Egyptian propolis: 2. Chemical composition, antiviral and antimicrobial activities of East Nile Delta propolis. *Zeitschrift für Naturforschung C* 57, 386–394.
- El Sohaimy, S., Masry, S., 2014. Phenolic content, antioxidant and antimicrobial activities of Egyptian and Chinese propolis. *Am.-Eurasian J. Agric Environ. Sci* 14, 1116–11124.
- Elnakady, Y.A., Rushdi, A.I., Franke, R., Abutaha, N., Ebaid, H., Baabhad, M., Omar, M. O., Al Ghamdi, A.A., 2017. Characteristics, chemical compositions and biological activities of propolis from Al-Bahah, Saudi Arabia. *Sci. Rep.* 7.
- Fernández, S.G., Luaces, E.L., Madoz, S.E., Alemán, E.A., Apiñániz, M.A., Purroy, A.I.T., 2004. Allergic contact stomatitis due to therapeutic propolis. *Contact Dermatitis* 50, 321–321.
- Ferreira, J.M., Fernandes-Silva, C.C., Salatino, A., Negri, G., Message, D., 2017. New propolis type from north-east Brazil: chemical composition, antioxidant activity and botanical origin. *J. Sci. Food Agric.*
- Fokt, H., Pereira, A., Ferreira, A., Cunha, A., Aguiar, C., 2010. How do bees prevent hive infections? The antimicrobial properties of propolis. *Curr. Res. Technol. Educ. Top. Appl. Microbiol. Microbial. Biotechnol.* 1, 481–493.
- Franchin, M., Cólón, D.F., Castanheira, F.V., da Cunha, M.G., Bueno-Silva, B., Alencar, S.M., Cunha, T.M., Rosalen, P.L., 2016. Vestitol isolated from Brazilian red propolis inhibits neutrophils migration in the inflammatory process: elucidation of the mechanism of action. *J. Nat. Prod.* 79, 954–960.
- Freitas, S., Shinohara, L., Sforcin, J., Guimarães, S., 2006. In vitro effects of propolis on *Giardia duodenalis* trophozoites. *Phytomedicine* 13, 170–175.
- Funari, C.S., Ferro, V.O., 2006. Análise de própolis. *Ciência e Tecnologia de Alimentos* 26, 171–178.
- Ghisalberti, E., 1979. Propolis: a review. *Bee World* 60, 59–84.
- Grange, J., Davey, R., 1990. Antibacterial properties of propolis (bee glue). *J. R. Soc. Med.* 83, 159–160.
- Greenaway, W., Scaysbrook, T., Whatley, F., 1990. The composition and plant origins of propolis: a report of work at Oxford. *Bee World* 71, 107–118.
- Harfouch, R.M., Mohammad, R., Suliman, H., 2016. Antibacterial activity of syrian propolis extract against several strains of bacteria in vitro.
- Hausen, B., Wollenweber, E., Senff, H., Post, B., 1987. Propolis allergy. (II). The sensitizing properties of 1, 1-dimethylallyl caffeic acid ester. *Contact Dermatitis* 17, 171–177.
- Hegazi, A.G., Abd El Hady, F.K., Abd Allah, F.A., 2000. Chemical composition and antimicrobial activity of European propolis. *Zeitschrift für Naturforschung C* 55, 70–75.
- Helfenber, K., 1908. The analysis of beeswax and propolis. *Chemiker Zeitung* 31, 987–998.
- Kartal, M., Yıldız, S., Kaya, S., Kurucu, S., Topçu, G., 2003. Antimicrobial activity of propolis samples from two different regions of Anatolia. *J. Ethnopharmacol.* 86, 69–73.
- Kasiotis, K.M., Anastasiadou, P., Papadopoulos, A., Machera, K., 2017. Revisiting Greek Propolis: chromatographic Analysis and Antioxidant Activity Study. *PLoS ONE* 12, e0170077.
- Khayyal, M., El-Ghazaly, M., El-Khatib, A., 1993. Mechanisms involved in the antiinflammatory effect of propolis extract. *Drugs Exp. Clin. Res.* 19, 197–203.
- Kimoto, T., Arai, S., Kohguchi, M., Aga, M., Nomura, Y., Micallef, M.J., Kurimoto, M., Mito, K., 1998. Apoptosis and suppression of tumor growth by artemillin C extracted from Brazilian propolis. *Cancer Detect. Prev.* 22, 506–515.
- Komericki, P., Kränke, B., 2009. Maculopapular exanthem from propolis: case report and review of systemic cutaneous and non-cutaneous reactions. *Contact Dermatitis* 61, 353–355.
- Koo, M.H., Park, Y.K., 1997. Investigation of flavonoid aglycones in propolis collected by two different varieties of bees in the same region. *Biosci. Biotechnol. Biochem.* 61, 367–369.
- Krell, R., 1996. Value-added Products from Beekeeping. *Food & Agriculture Org.*
- Król, W., Bankova, V., Sforcin, J.M., Szliszka, E., Czuba, Z., Kuropatnicki, A.K., 2013. Propolis: properties, application, and its potential. *Evidence-Based Complement. Alternat. Med.*
- Kujumgiev, A., Tsvetkova, I., Serkedjieva, Y., Bankova, V., Christov, R., Popov, S., 1999. Antibacterial, antifungal and antiviral activity of propolis of different geographic origin. *J. Ethnopharmacol.* 64, 235–240.
- Kumar, N., Mueen Ahmad, K.K., Dang, R., Husain, A., 2008. Antioxidant and antimicrobial activity of propolis from Tamil Nadu zone. *J. Med. Plants Res.* 2, 361–364.
- Kuropatnicki, A.K., Szliszka, E., Krol, W., 2013. Historical aspects of propolis research in modern times. *Evidence-Based Complement. Alternat. Med.*
- Kustiawan, P.M., Lirdprapamongkol, K., Palaga, T., Puthong, S., Phuwapraisrisan, P., Swasti, J., Chanchao, C., 2017. Molecular mechanism of chud, isolated from *Trigona incisa* stingless bee propolis, induced apoptosis in the SW620 human colorectal cancer cell line. *BMC Pharmacol. Toxicol.* 18, 32.
- Lotfy, M., 2006. Biological activity of bee propolis in health and disease. *Asian Pac. J. Cancer Prev.* 7, 22–31.
- Machado, B., Pulcino, T.N., Silva, A.L., Tadeu, D., Melo, R.G.S., Mendonça, I.G., 2017. Propolis as an alternative in prevention and control of dental cavity. *Immunity* 19, 24.
- Marcucci, M., Ferreres, F., Garcia-Viguera, C., Bankova, V., De Castro, S., Dantas, A., Valente, P., Paulino, N., 2001. Phenolic compounds from Brazilian propolis with pharmacological activities. *J. Ethnopharmacol.* 74, 105–112.
- Marcucci, M.C., 1995. Propolis: chemical composition, biological properties and therapeutic activity. *Apidologie* 26, 83–99.
- Martin, M.P., Pileggi, R., 2004. A quantitative analysis of Propolis: a promising new storage media following avulsion. *Dent. Traumatol.* 20, 85–89.



- Martinotti, S., Ranzato, E., 2015. Propolis: a new frontier for wound healing? *Burns Trauma* 3, 9.
- Monti, M., Bertt, E., Carminati, G., Cusini, M., 1983. Occupational and cosmetic dermatitis from propolis. *Contact Dermatitis* 9, 163–163.
- Moreira, L., Dias, L.G., Pereira, J.A., Estevinho, L., 2008. Antioxidant properties, total phenols and pollen analysis of propolis samples from Portugal. *Food Chem. Toxicol.* 46, 3482–3485.
- Murray, M., Pizzorno Jr, J., 2005. Bee products: pollen, propolis, and royal jelly. chapter.
- Nagy, M., Suchy, V., Uhrin, D., Ubik, K., Budesinsky, M., Grancai, D., 1988. Constituents of propolis of Czechoslovak origin. *V. Chem. Pap.* 42, 691–696.
- Omar, R., Igoti, J.O., Zhang, T., Gray, A.I., Ebiloma, G.U., Clements, C.J., Fearnley, J., Ebel, R.E., Paget, T., De Koning, H.P., 2017. The chemical characterization of Nigerian propolis samples and their activity against trypanosoma brucei. *Sci. Rep.* 7, 923.
- Ota, C., Unterkircher, C., Fantinato, V., Shimizu, M., 2001. Antifungal activity of propolis on different species of *Candida*. *Mycoses* 44, 375–378.
- Özcan, M., 1999. Antifungal properties of propolis. *Grasas Aceites* 50, 395–398.
- Park, Y.K., Alencar Matias, S., Scamparini Pippa, A.R., Aguiar Lima, C., 2002a. Própolis produzida no sul do Brasil, Argentina e Uruguai: Evidências fitoquímicas de sua origem vegetal. *Ciência Rural* 32.
- Park, Y.K., Alencar, S.M., Aguiar, C.L., 2002b. Botanical origin and chemical composition of Brazilian propolis. *J. Agric. Food. Chem.* 50, 2502–2506.
- Park, Y.K., Koo, M.H., Abreu, J.A., Ikegaki, M., Cury, J.A., Rosalen, P.L., 1998. Antimicrobial activity of propolis on oral microorganisms. *Curr. Microbiol.* 36, 24–28.
- Parolia, A., Thomas, M.S., Kundabala, M., Mohan, M., 2010. Propolis and its potential uses in oral health. *Int. J. Med. Med. Sci.* 2, 210–215.
- Pasupuleti, V.R., Sannugam, L., Ramesh, N., Gan, S.H., 2017. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxidative Med. Cell. Longevity*.
- Peña, R.C., 2008. Propolis standardization: a chemical and biological review. *Cien. Inv. Agr.* 35 (1): 17–26. *Ciencia e Investigación Agraria* 35, 11–20.
- Pietta, P., Gardana, C., Pietta, A., 2002. Analytical methods for quality control of propolis. *Fitoterapia* 73, S7–S20.
- Popova, M., Bankova, V., Butovska, D., Petkov, V., Nikolova-Damyanova, B., Sabatini, A.G., Marcuzzan, G.L., Bogdanov, S., 2004. Validated methods for the quantification of biologically active constituents of poplar-type propolis. *Phytochem. Anal.* 15, 235–240.
- Prusotam, B., Four, D.-O., 1996. Caffeoyl Quinic acid Derivatives from Propolis. *Biol. Pharm. Bull.* 19, 1479–1484.
- Rajpara, S., Wilkinson, M.S., King, C.M., Gawkrödger, D.J., English, J.S., Statham, B.N., Green, C., Sansom, J.E., Chowdhury, M.M., Horne, H.L., 2009. The importance of propolis in patch testing—a multicentre survey. *Contact Dermatitis* 61, 287–290.
- Ramos, A., Miranda, J.D., 2007. Propolis: a review of its anti-inflammatory and healing actions. *J. Venomous Anim. Toxins Incl. Trop. Dis.* 13, 697–710.
- Rufatto, L.C., Dos Santos, D.A., Marinho, F., Henriques, J.A.P., Ely, M.R., Moura, S., 2017. Red propolis: chemical composition and pharmacological activity. *Asian Pac. J. Trop. Biomed.*
- Russo, A., Longo, R., Vanella, A., 2002. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. *Fitoterapia* 73, S21–S29.
- Sabir, A., 2017. Prospect of using propolis in conservative dentistry and endodontic treatment (basic research vs clinical application)(prospek penggunaan propolis dalam bidang operative dentistry dan perawatan endodonti (penelitian dasar vs aplikasi klinis)). *Dentika Dent. J.* 18.
- Sabir, A., Sumidarti, A., 2017. Interleukin-6 expression on inflamed rat dental pulp tissue after capped with *Trigona* sp. propolis from south Sulawesi, Indonesia. *Saudi J. Biol. Sci.* 24, 1034–1037.
- Salomão, K., de Souza, E.M., Henriques-Pons, A., Barbosa, H.S., de Castro, S.L., 2011. Brazilian green propolis: effects in vitro and in vivo on *Trypanosoma cruzi*. *Evidence-Based Complement. Alternat. Med.*
- Salomao, K., Pereira, P.R.S., Campos, L.C., Borba, C.M., Cabello, P.H., Marcucci, M.C., De Castro, S.L., 2008. Brazilian propolis: correlation between chemical composition and antimicrobial activity. *Evidence-Based Complement. Alternat. Med.* 5, 317–324.
- Santos, F., Bastos, E., Uzeda, M., Carvalho, M., Farias, L., Moreira, E., Braga, F., 2002. Antibacterial activity of Brazilian propolis and fractions against oral anaerobic bacteria. *J. Ethnopharmacol.* 80, 1–7.
- Sawicka, D., Car, H., Borawska, M.H., Nikliński, J., 2012. The anticancer activity of propolis. *Folia Histochemica et Cytobiologica* 50, 25–37.
- Seeley, T., Morse, R., 1976. The nest of the honey bee (*Apis mellifera* L.). *Insectes Soc.* 23, 495–512.
- Seidel, V., Peyfoon, E., Watson, D.G., Fearnley, J., 2008. Comparative study of the antibacterial activity of propolis from different geographical and climatic zones. *Phytother. Res.* 22, 1256–1263.
- Sforcin, J., 2007. Propolis and the immune system: a review. *J. Ethnopharmacol.* 113, 1–14.
- Sforcin, J., Fernandes, A., Lopes, C., Bankova, V., Funari, S., 2000. Seasonal effect on Brazilian propolis antibacterial activity. *J. Ethnopharmacol.* 73, 243–249.
- Sforcin, J.M., 2016. Biological properties and therapeutic applications of propolis. *Phytother. Res.* 30, 894–905.
- Sforcin, J.M., Machado, B.A.S., 2017. Medical benefits of honeybee products. *Evidence-Based Complement. Alternat. Med.*
- Shinohara, R., Ohta, Y., Hayashi, T., Ikeno, T., 2002. Evaluation of antilipid peroxidative action of propolis ethanol extract. *Phytother. Res.* 16, 340–347.
- Shouqin, Z., Jun, X., Changzheng, W., 2005. High hydrostatic pressure extraction of flavonoids from propolis. *J. Chem. Technol. Biotechnol.* 80, 50–54.
- Silici, S., Kutluca, S., 2005. Chemical composition and antibacterial activity of propolis collected by three different races of honeybees in the same region. *J. Ethnopharmacol.* 99, 69–73.
- Silva, R.P.D., Machado, B.A.S., de Abreu Barreto, G., Costa, S.S., Andrade, L.N., Amaral, R.G., Carvalho, A.A., Padilha, F.F., Barbosa, J.D.V., Umsza-Guez, M.A., 2017. Antioxidant, antimicrobial, antiparasitic, and cytotoxic properties of various Brazilian propolis extracts. *PLoS ONE* 12, e0172585.
- Simone-Finstrom, M., Borba, R.S., Wilson, M., Spivak, M., 2017. Propolis counteracts some threats to honey bee health. *Insects* 8, 46.
- Simone-Finstrom, M., Spivak, M., 2010. Propolis and bee health: the natural history and significance of resin use by honey bees. *Apidologie* 41, 295–311.
- Su, Z., Lin, J., Prewett, M., Goldstein, N., Fisher, P., 1995. Apoptosis mediates the selective toxicity of caffeic acid phenethyl ester (CAPE) toward oncogene-transformed rat embryo fibroblast cells. *Anticancer Res.* 15, 1841–1848.
- Sung, S.-H., Choi, G.-H., Lee, N.-W., Shin, B.-C., 2017. External use of propolis for oral, skin, and genital diseases: a systematic review and meta-analysis. *Evidence-Based Complement. Alternat. Med.*
- Toreti, V.C., Sato, H.H., Pastore, G.M., Park, Y.K., 2013. Recent progress of propolis for its biological and chemical compositions and its botanical origin. *Evidence-Based Complement. Alternat. Med.*
- Torres, D., Holland, I., Palacio, E., 1990. Efecto de un extracto alcohólico de propóleos sobre el crecimiento de *Giardia lamblia* in vitro. *Rev. Cubana Cienc. Vet.* 21.
- Tosi, B., Donini, A., Romagnoli, C., Bruni, A., 1996. Antimicrobial activity of some Commercial Extracts of Propolis Prepared with different solvents. *Phytother. Res.* 10, 335–336.
- Trusheva, B., Trunkova, D., Bankova, V., 2007. Different extraction methods of biologically active components from propolis: a preliminary study. *Chem. Cent. J.* 1, 13.
- Uzel, A., Öncaç, Ö., Çoğulu, D., Gençay, Ö., 2005. Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. *Microbiol. Res.* 160, 189–195.
- Veiga, R., De Mendonça, S., Mendes, P., Paulino, N., Mimica, M., Lagareiro Netto, A., Lira, I., López, B.C., Negrão, V., Marcucci, M., 2017. Artepillin C and phenolic compounds responsible for antimicrobial and antioxidant activity of green propolis and *Baccharis dracunculifolia* DC. *J. Appl. Microbiol.* 122, 911–920.
- Visscher, P., 1980. Adaptations of honey bees (*Apis mellifera*) to problems of nest hygiene. *Sociobiology* 5, 249–260.
- Viuda-Martos, M., Ruiz-Navajas, Y., Fernández-López, J., Pérez-Álvarez, J., 2008. Functional properties of honey, propolis, and royal jelly. *J. Food Sci.* 73.
- Wagh, V.D., 2013. Propolis: a wonder bees product and its pharmacological potentials. *Adv. Pharmacol. Sci.*
- Walker, P., Crane, E., 1987. Constituents of propolis. *Apidologie* 18, 327–334.
- Watanabe, M.A.E., Amarante, M.K., Conti, B.J., Sforcin, J.M., 2011. Cytotoxic constituents of propolis inducing anticancer effects: a review. *J. Pharm. Pharmacol.* 63, 1378–1386.
- Won Seo, K., Park, M., Jung Song, Y., Kim, S.J., Ro Yoon, K., 2003. The protective effects of propolis on hepatic injury and its mechanism. *Phytother. Res.* 17, 250–253.
- Yuksel, S., Akyol, S., 2016. The consumption of propolis and royal jelly in preventing upper respiratory tract infections and as dietary supplementation in children. *J. Int. Ethnopharmacol.* 5, 308.
- Yumnam, R., Nandan, N., Kumar, N., Raj, S., Mannepalli, A., 2017. Effect of propolis in oral health. *J. Ayurveda Integr. Med. Sci.* 2, 186–192 (ISSN 2456-3110).
- Zabaiou, N., Fouache, A., Trousson, A., Baron, S., Zellagui, A., Lahouel, M., Lobaccaro, J.-M.A., 2017. Biological properties of propolis extracts: something new from an ancient product. *Chem. Phys. Lipids.*
- Zheng, Y.-Z., Deng, G., Liang, Q., Chen, D.-F., Guo, R., Lai, R.-C., 2017. Antioxidant activity of quercetin and its glucosides from propolis: a theoretical study. *Sci. Rep.* 7.