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## Review

Propolis characterization and antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*: A review

Sarra Bouchelaghem

Department of General and Environmental Microbiology, Institute of Biology, University of Pécs, Ifjúság str. 6, 7624 Pécs, Hungary



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## ABSTRACT

Propolis is a plant-based sticky substance that is produced by honeybees. It has been used traditionally by ancient civilizations as a folk medicine, and is known to have many pharmaceutical properties including antioxidant, antibacterial, antifungal, anti-inflammatory, antiviral, and antitumour effects. Worldwide, researchers are still studying the complex composition of propolis to unveil its biological potential, and especially its antimicrobial activity against a variety of multidrug-resistant microorganisms. This review explores scientific reports published during the last decade on the characterization of different types of propolis, and evaluates their antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*. Propolis can be divided into different types depending on their chemical composition and physical properties associated with geographic origin and plant sources. Flavonoids, phenols, diterpenes, and aliphatic compounds are the main chemicals that characterize the different types of propolis (Poplar, Brazilian, and Mediterranean), and are responsible for their antimicrobial activity. The extracts of most types of propolis showed greater antibacterial activity against Gram-positive bacteria: particularly on *S. aureus*, as well as on *C. albicans*, as compared to Gram-negative pathogens. Propolis acts either by directly interacting with the microbial cells or by stimulating the immune system of the host cells. Some studies have suggested that structural damage to the microorganisms is a possible mechanism by which propolis exhibits its antimicrobial activity. However, the mechanism of action of propolis is still unclear, due to the synergistic interaction of the ingredients of propolis, and this natural substance has multi-target activity in the cell. The broad-spectrum biological potentials of propolis present it as an ideal candidate for the development of new, potent, and cost-effective antimicrobial agents.

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E-mail address: [bouchelaghem24sarra@gmail.com](mailto:bouchelaghem24sarra@gmail.com)<https://doi.org/10.1016/j.sjbs.2021.11.063>

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## 1. Introduction

*Staphylococcus aureus* is a Gram-positive bacterium that is often found in the respiratory tract and the skin, while *Candida albicans* is mostly detected in the mucous membranes and in the gastrointestinal tract (Lee et al., 2019). *S. aureus* and *C. albicans* are ubiquitous opportunistic pathogens and important nosocomial strains that can cause mild to severe illnesses (Todd and Peters, 2019). The widespread use of antimicrobial drugs and the ability of certain microbes to acquire accessory genes that can cause diversity in microbes' phenotype and resistance mechanisms has led to an unprecedented crisis of antimicrobial resistance (Aslam et al., 2018). Besides this, multidrug-resistance-carrying superbugs have increased overall mortality and morbidity rates from such infections several-fold (Fair and Tor, 2014; Frieri et al., 2017). Microorganisms acquire antimicrobial resistance by means of several underlying mechanisms, including the synthesis of enzymes that degrade the active part of antibiotics, drug efflux, modifying antibiotic binding sites, and biofilm formation (Munita and Arias, 2016). *S. aureus* and *C. albicans* have been found to form persistent biofilms on abiotic surfaces or within a host. The interaction between these biofilms is a precursor to increased drug tolerance, immune evasion, and virulence, with the outcome of this being increased mortality (Todd and Peters, 2019). For the last few decades, scientific communities have been in search of new, cost-effective, and potent antimicrobial agents to treat infections caused by multidrug-resistant strains (Aslam et al., 2018).

Natural plant-based products and synthetic chemistry are two main fields to which scientific attention has shifted in the quest to develop potent antimicrobial agents to treat and prevent infectious diseases (Abreu et al., 2012; Anand et al., 2019). Propolis is produced from the balsamic secretions of the flowers, branches, shells, leaves, barks, and buds of various plants. Honeybees (*Apis mellifera*) extract and transform this sticky substance by aid of their salivary secretions and beeswax into propolis (Elnakady et al., 2017). Propolis protects hives from moisture and predators, sealing cracks, and keeps the inner temperature of the hive warm. Since ancient times, propolis has been used as a traditional folk medicine, alone or in combination with other natural substances, to treat wounds (Rojczyk et al., 2020). The literature makes evident that propolis possesses several biological properties, including antibacterial, antiviral, antiprotozoal, antifungal, anticancer, antioxidant, antitumour, and antimutagenic activities (Elnakady et al., 2017; Ezzat et al., 2019; Kujumgiev et al., 1999; Silva et al., 2019). Several scientific reports have been published on the cytotoxicity, antioxidant and antimicrobial potential of different types of propolis (de Marco et al., 2017; López et al., 2015; Mello and Hubinger, 2012). Free-radical scavenging and antimicrobial activities have presented propolis as an ideal food preservative and supplement in various food industries (Grecka and Szweda, 2021; Guzmán and Cruz, 2017). Moreover, the solvent chosen for propolis extraction can act to enhance its pharmacological potential. Ethanol extracts of propolis are more effective and show higher levels of antimicrobial activity compared to water, ester, and chloroform fractions (Wagh, 2013).

Propolis has attracted the attention of scientists searching for an alternative therapeutic drug against infectious diseases and multidrug-resistant bacteria since the 1970 s. Researchers' interest in this complex substance has increased in recent decades based on further investigation of the chemical composition of propolis (Toreti et al., 2013). However, the standardization of propolis

extracts and their use in clinical treatment remains a challenge (Silva-Carvalho et al., 2015; Toreti et al., 2013). Therefore, this study seeks to review scientific reports published during the last decade on the characterization of different types of propolis around the world, their chemical composition, and to evaluate their antimicrobial activity against *S. aureus* and *C. albicans*.

## 2. Chemical composition

Propolis is currently gaining the attention of scientific communities due to its wide-ranging biological application. It is a highly complex substance, and several factors influence its chemical composition, including the plant sources surrounding beehives, honeybee species, method of collection, geographical and climatic variation, collecting seasons, altitudes, and adequate lighting (Bueno-Silva et al., 2017; López and Sawaya, 2012). Propolis is a sticky substance that contains 50% plant resins, 30% wax, 10% essential oils, 5 % pollen, and 5% other organic compounds (Brown, 1989). More than 400 compounds had been identified in poplar-type propolis by 2014 (Ristivojević et al., 2015). This list of compounds is still increasing, and the propolis samples collected from different parts of the world had revealed 850 components up to 2018 (Šturm and Ulrih, 2019). The known components of propolis are grouped into chemical classes that include: alcohols, alkanes, volatile oils, aromatic acids, amino acids, vitamins, sugars and sugar alcohols, terpenoids, fatty acids, hydrocarbons, wax esters, flavonoids, chalcones, phenols, glycerol derivatives, aldehydes, trace elements, small proportions of minerals, and ketones (Ahangari et al., 2018; Šturm and Ulrih, 2019). These categories include various active compounds, such as flavones, caffeic acid, isovanillin, vanillin, butanoic acid, malic acid, alanine, benzoic acid, coumaric acid, gentisic acid, ferulic acid, vanillic acid, pinocembrin, pinobanksin, galangin, thymol, luteolin, terpenes, lignans, myricetin, decanoic acids, chrysin, quercetin, and kaempferol (Kurek-Górecka et al., 2013; Šturm and Ulrih, 2019). The therapeutic properties of propolis are mainly attributed to volatiles (Bankova et al., 2014; Jihene et al., 2018), flavonoids, and phenolic compounds which are well known as antioxidant and antimicrobial active ingredients (da Silva et al., 2006; Kurek-Górecka et al., 2013). Chrysin is a plant flavone extracted from the leaves of *Passiflora caerulea*, and it is found in honey and propolis (Mani and Natesan, 2018). The anticancer and cytotoxicity activities of propolis are related mainly to chrysin (Celińska-Janowicz et al., 2018; Seetharaman et al., 2017). Some studies report that chrysin has antimicrobial properties based on its ability to destroy the integrity of the microbial cell wall and cell membrane (Celińska-Janowicz et al., 2018; Mani and Natesan, 2018). Besides, this other polyphenols (such as caffeic acid, ferulic acid, and *p*-coumaric acid) in propolis affect DNA biosynthesis in cancer cells (Liu et al., 2014; Suresh Babu et al., 2006; Vardar-Ünlü et al., 2008). Genistein is one of the natural isoflavones detected in propolis (Gargouri et al., 2019; Volpi and Bergonzini, 2006), and is mainly found in *Glycine max* L. and *Trifolium* species. It has received widespread attention due to its chemotherapeutic activity against different types of cancer, mainly by altering apoptosis (Spagnuolo et al., 2015), and reduction in chronic inflammatory disorders (Vanden Braber et al., 2018). It enhances the immune response of macrophages against *C. albicans* (Cui et al., 2016), and acts as an antibacterial agent against *S. aureus* (Choi et al., 2018). Pinocembrin is one of the primary flavonoids abundant in poplar-type propolis. Its pharmacological activities

**Table 1**  
Chemical characterization of different types of propolis, geographic distribution, botanical origin, and biological activities.

Type	Region	Main compounds	Plant source	Activity	Cell used	Reference	
Green propolis	Brazil	Apigenin	<i>Baccharis dracunculifolia</i>	Antibacterial	<i>Bacillus Subtilisn</i>	(Bezerra et al., 2020; Búfalo et al., 2009; Chen et al., 2018; Corrêa et al., 2020; Ferreira et al., 2017; Roberto et al., 2016)	
	Taiwan	Artepillin C Caffeic acid Chrysin Cinnamic acid Ferulic acid Kaempferide Narigenin Pinobanksin Rutin	<i>Eucalyptus citriodora</i> <i>Araucaria angustifolia</i> <i>Mimosa tenuiflora</i>	Antibiofilm Antioxidant	<i>Escherichia coli</i> <i>Listeria monocytogenes</i> MRSA MSSA <i>Pseudomonas aeruginosa</i>		
Red propolis	Brazil Cuba	Artepillin C	<i>Dalbergia ecastophyllum</i> Clusia sp. ( <i>C. scrobiculata</i> , <i>C. minor</i> , <i>C. major</i> , and <i>C. rosea</i> )	Antibacterial	HEp-2		(Alencar et al., 2007; Andrade et al., 2017; Cuesta-Rubio et al., 2007; Dantas Silva et al., 2017; Machado et al., 2016; Piccinelli et al., 2011; Regueira Neto et al., 2017; Rufatto et al., 2018)
		Biochanin A		Antibacterial	<i>Bacillus subtilis</i>		
		Flavone		Antioxidant	<i>Enterococcus faecalis</i>		
		Homopterocarpin			<i>Enterococcus</i> sp.		
		Liquiritigenin			<i>Escherichia coli</i>		
		Lupeol			<i>Klebsiella</i> sp.		
		Medicarpin			MRSA		
		Methyl abietate			<i>Pseudomonas aeruginosa</i>		
		Methyl o-orsellinate		Antiparasitic	<i>Streptococcus mutans</i>		
		Naringenin		Antitumour	<i>Trypanosoma cruzi</i> epimastigotes Y		
Neovestitol		HCT-116					
Pterocarpan		SF-295					
Vestitol		HL-60					
$\beta$ -amyryn		OVCAR-8					
Brown propolis	Brazil Cuba	Artepillin C	<i>B. dracunculifolia</i> <i>C. rosea</i>	Anti-mycoplasma	<i>Mycoplasma</i> sp. ( <i>M. bovis</i> , <i>M. gallisepticum</i> , <i>M. genitalium</i> , <i>M. hominis</i> , <i>M. hyorinis</i> , <i>M. penetrans</i> , and <i>M. pneumoniae</i> )	(Andrade et al., 2017; Cuesta-Rubio et al., 2007; Dantas Silva et al., 2017; de Oliveira Dembogurski et al., 2018; do Nascimento Araújo et al., 2020; Machado et al., 2016)	
		Baccharin		Antibacterial	<i>Enterococcus</i> sp.		
		Caffeic acids		Antibiofilm	<i>Staphylococcus aureus</i>		
		Chlorogenic acids		Antioxidant			
		Drupanin		Antiparasitic	<i>Trypanosoma cruzi</i> epimastigotes Y		
		Kaempferide		Antitumour	<i>Trichomonas vaginalis</i>		
		Kaempferol			OVCAR-8		
		<i>p</i> -coumaric					
		Phenylpropanoid					
		Polyisoprenylated benzophenones					
Prenylated phenylpropanoids							
Mediterranean propolis	Greek Cyprus Malta Sicily Bulgaria Turkey Greece Algeria Croatia Morocco	Communic acid	<i>Cupressus sempervirens</i> <i>Pinus species</i>	Antibacterial	<i>Enterobacter cloacae</i>	(El-Guendouz et al., 2016; Piccinelli et al., 2013; Popova et al., 2010; Velikova et al., 2000; Popova et al., 2012)	
		Diterpenic acids		Antibiofilm	<i>Escherichia coli</i>		
		Hydroxyditerpenic acid		Antioxidant	<i>Klebsiella. pneumoniae</i>		
		Imbricataloic			MRSA		
		Isoagatholal			<i>Pseudomonas aeruginosa</i>		
		Isocupressic acid			<i>Staphylococcus epidermidis</i>		
		Pimaric acid			<i>Streptococcus mutans</i>		
		Pinocembrin		Antifungal	<i>Streptococcus viridans</i>		
					<i>Candida albicans</i>		
					<i>Candida tropicalis</i>		
		<i>Candida glabrata</i>					

Table 1 (continued)

Type	Region	Main compounds	Plant source	Activity	Cell used	Reference
Yellow propolis	Cuba	Acetyl triterpenes	Undetermined	Antibacterial	<i>Staphylococcus aureus</i>	(Cuesta-Rubio et al., 2007; Machado et al., 2016; Márquez Hernández et al., 2010; Monzote et al., 2012)
	Brazil	Flavanones Lanostane Lupane Oleanane Polymethoxylated Sterols Triterpenic alcohols Ursane		Antifungal Antiprotozoal	<i>Trichophyton rubrum</i> <i>Leishmania infantum</i> <i>Plasmodium falciparum</i> <i>Trypanosoma brucei</i> <i>Trypanosoma cruzi</i>	
Poplar propolis	Mostly from Eurasian regions*	Acetyloxycaffeate	<i>Populus</i> sp. ( <i>P. nigra</i> L., <i>P. tremuloide</i> , and <i>P. alba</i> L.)	Antifungal	<i>Aspergillus fumigatus</i> <i>Candida glabrata</i> <i>Candida albicans</i> <i>Fusarium</i> sp.	(Boisard et al., 2020, 2015; de Marco et al., 2017; Dezmirean et al., 2017; Popova et al., 2007; Ristivojević et al., 2020; Vardar-Ünlü et al., 2008; Wang et al., 2014)
		Caffeic acid Chrysin Dihydroflavonols Galangin Henolics Phenylpropanoids Pinobanksin Pinocembrin Prenyl caffeate Salicylic acid		Antibacterial Antibiofilm Antioxidant	<i>Acinetobacter baumannii</i> <i>Bacillus cereus</i> <i>Enterococcus</i> sp. <i>Escherichia coli</i> <i>Lactobacillus acidophilus</i> <i>Listeria</i> sp. <i>Mycobacterium smegmatis</i> <i>Pseudomonas aeruginosa</i> <i>Salmonella enteritidis</i> <i>Staphylococcus</i> sp. <i>Streptococcus</i> sp.	
				Anti-inflammatory	Murine macrophage RAW 264.7 HEK-293 T and HEK-293	

(MRSA) Methicillin-Resistant *Staphylococcus aureus*. (MSSA) Methicillin-Sensitive *Staphylococcus aureus*. (HEp-2) Human epidermoid carcinoma. (HCT-116) Colorectal carcinoma. (SF-295) Human glioblastoma. (HL-60) Human leukaemia. (OVCAR-8) Human ovarian carcinoma. (MRC-5) Human simian virus 40-immortalised lung fibroblasts. (HEK-293 T and HEK-293) Human embryonic kidney cells.\* England, France, Italy, Switzerland, Germany, Poland, New Zealand, Russia, Bulgaria, Macedonia, Estonia, Latvia, Lithuania, Slovakia, Slovenia, Serbia, Ukraine, Hungary, Syria, Turkey, Iran, Argentina, Canada, Chile, China, Korea, Uruguay, Uzbekistan, and the USA.

have been well studied, including anti-inflammatory, antioxidant (Rasul et al., 2013) and antibacterial action against *S. aureus*, *Escherichia coli*, and *Klebsiella pneumonia* (Tundis et al., 2019), and antifungal against *Penicillium italicum* (Peng et al., 2012). Malic acid is a chemical found in fruits and used as a flavouring in drinks and foods, and has shown antimicrobial activity against a wide range of bacterial strains of *Listeria monocytogenes*, *Salmonella enteritidis* and *Escherichia coli* (Raybaudi-Massilia et al., 2009). Propolis also contains vanillin, glycerol, and glycolic acid, which are used in other fields like cosmetic products and food additives, due to their anti-aging, antimicrobial, antiviral, and antioxidant properties (Boonchird and Flegel, 1982; Talla et al., 2017). In addition, propolis comprises certain components that are still not well known to have any antimicrobial activity, including fatty acids and sugars. Propolis has long been confirmed as an interesting pharmaceutical agent: however, its biological activity is associated with the synergistic activity of many classes of its active ingredients (Kujumgiev et al., 1999).

### 3. Types of propolis

To date, several types of propolis have been identified based on chemical composition and plant origin, the most famous of which are poplar-type (Eurasian) propolis, Brazilian green and red propolis, and Mediterranean propolis (Table 1). The huge heterogeneity in the chemical composition of propolis needs to be carefully analysed to ensure that the appropriate type of propolis is used, for safer and more effective treatment. The process of standardization and homogenization is extremely challenging and requires innovative, cost-effective, and efficient technologies such as high-performance liquid chromatography (Bruschi et al., 2003; Cuesta-Rubio et al., 2007), thin-layer chromatography (Milojković-Opsenica et al., 2016), liquid chromatography and gas chromatography coupled with other powerful techniques such as mass spectrometry (Asgharpour et al., 2020; Cheng et al., 2013; Falcão et al., 2013; Popova et al., 2010), and nuclear magnetic resonance (Cuesta-Rubio et al., 2007; Kasote et al., 2017). The chemical composition of poplar-type propolis is well studied among different types of propolis and offers an ideal standardization model (Bankova, 2005). Propolis varies in colour from dark yellow, to greenish-brown, to red, due to its age and nearby plant sources, while terpenes and phenolic compounds are accountable for its distinctive scent (Devequi-Nunes et al., 2018). Using high-performance thin-layer chromatographic fingerprinting analyses to explore the chemical composition of propolis, studies have confirmed the existence of two different subtypes of European propolis, as orange and blue types (O-type and B-type), originating from *Populus nigra* and *Populus tremulas*, respectively (Degirmencioglu et al., 2019; Milojković Opsenica et al., 2016; Ristivojević et al., 2015). On the other hand, green type (G-type) propolis is distinguished by its mixture of light orange, dark green, and blue bands (Ristivojević et al., 2015). O-type propolis is characterized by quercetin, while B-type corresponds mostly to galangin, caffeic acid, feruloyl, and *p*-coumaroyl derivatives. G-type corresponds to apigenin or naringenin. However, some German propolis samples have been classified as of mixed type (Morlock et al., 2014). Brazilian propolis has been classified into 12 types, based on physical and chemical properties and geographical locations, but only three species of plant sources have been identified: namely *Populus* sp., *Hyptis divaricate*, and *Baccharis dracunculifolia* (Alencar et al., 2007; Silva et al., 2008). Green and red Brazilian propolis types are well known compared to newer types like yellow and brown propolis, which still need further characterization (Machado et al., 2016). The Mediterranean type has distinctive chemical

properties, and is exceptionally rich in diterpenes and their derivatives (Popova et al., 2012).

### 4. Geographic distribution and botanical origin of propolis

The literature highlights the crucial role played by geographic region in types of propolis (Table 1), mainly due to climatic variation and different ethnobotanical flora by region (Bueno-Silva et al., 2017). Poplar, alder, willow, elm, birch, horse-chestnut, beech, and conifer tree species are popular sources for the finest quality propolis (Toreti et al., 2013). *P. nigra*, commonly known as the poplar, is widely distributed in Europe and North America, Asia, and New Zealand (Dezmirean et al., 2021). Russian birch propolis collected from *Betula verrucosa* is different from poplar propolis, and comprises flavonols and flavones (Bankova, 2005). *Dalbergia ecastophyllum*, *Clusia scrobiculata*, *Clusia minor*, *Clusia major*, and *Clusia rosea* are the plant sources for the red propolis that is widely distributed in Brazil, Cuba, Mexico, China and Venezuela, and is characterized by polyisoprenylated benzophenones as active phytochemicals (Rufatto et al., 2017). Similarly, the leaf resin of *Baccharis dracunculifolia* accounts for the collection of Brazilian propolis and contains a variety of phytochemicals, including flavonoids, lignans, *p*-coumaric acid, diterpenes, acetophenone, and higher concentrations of artemillin C (Anjum et al., 2019). Certain phytochemicals such as sesquiterpenoid compounds including ledol, germacren D, and spatulenol are limited to tropical regions. Also, a Mediterranean propolis type is found in Greek, Cyprus, Croatia, Egypt, Algeria, Morocco, and Malta, whose main compounds are diterpenes most probably originating in the coniferous plant of the genus *Cupressaceae* (El-Guendouz et al., 2018; Ezzat et al., 2019; Piccinelli et al., 2013; Popova et al., 2012, 2010). Propolis samples from different geographic origins were investigated for their antibacterial and antifungal properties. Significantly, all the propolis samples were active against *S. aureus* and *C. albicans*, despite the great differences in the plant origins between the samples from the temperate and tropical zones (Table 1).

### 5. Antibacterial and antifungal activities

#### 5.1. Anti-staphylococcal activity

Due to the development of microbial resistance against various antibiotics (Aslam et al., 2018), there has been a growing interest in identifying effective antimicrobial agents obtained from various natural products (Guzmán and Cruz, 2017). Propolis is one of the most promising sources of bioactive compounds to show antimicrobial activity (AL-Ani et al., 2018). The antibacterial potential of propolis varies considerably from one bacterial strain to another, and depending on the propolis sample used (Almuhayawi, 2020). In many scientific studies, propolis and its derivatives have shown significant antibacterial activity against *Escherichia coli*, *S. aureus*, *Streptococcus* species, *Salmonella typhi*, *Enterococcus* species, *Bacillus* species, and *Pseudomonas aeruginosa* (Anjum et al., 2019; Przybyłek and Karpiński, 2019; Rufatto et al., 2017). Literature suggests that alcohol fractions of propolis possess significant antibacterial activity against Gram-positive as compared to Gram-negative bacteria (Przybyłek and Karpiński, 2019). In Lu et al.'s (2005) study, an ethanolic extract of Taiwanese propolis showed high levels of antibacterial activity against *S. aureus* with a minimum inhibitory concentration (MIC) of lower than 3.75 to 60 µg/mL, and a minimum bactericidal concentration (MBC) which ranged between 7.5 and 120 µg/mL, hence being found to be effective. The same study confirmed the influence of season and area of the collected samples on propolis activity. In addition, the age of bacterial cells, a temperature of 37 °C, and an acidic pH enhanced the

antibacterial activity of the propolis extract (Lu et al., 2005). The highest anti-staphylococcal activity levels of ethanolic extract of propolis (EEP) after Taiwanese propolis was recorded for samples collected from Turkey, Oman, and Ireland, with MIC values of 8, 42, and 80  $\mu\text{g/mL}$ , respectively (AL-Ani et al., 2018; Popova et al., 2013; Uzel et al., 2005). Some Brazilian propolis samples showed a very broad range of MIC, from 31.2  $\mu\text{g/mL}$  to higher than 1024  $\mu\text{g/mL}$ , against *S. aureus* strains (Bueno-Silva et al., 2017; Regueira Neto et al., 2017). An ethanolic extract of Chilean propolis inhibited the growth of Gram-positive bacteria only, and showed very weak antibacterial activity against *Streptococcus pyogenes* and *S. aureus* (ATCC 25923), with an MIC of 200–26900  $\mu\text{g/mL}$ . Interestingly, the total phenolic content of Chilean propolis was not correlated with the MIC values (Bridi et al., 2015). An antibacterial study of Mediterranean propolis samples was carried out by the disc diffusion method against Gram-positive and Gram-negative bacteria and oral pathogens. It is noteworthy that the diterpene content in the EEP samples was directly proportional to antimicrobial activity against all tested bacteria. Moreover, the samples showed particularly strong activity on Gram-positive bacteria (*S. aureus*, *Staphylococcus epidermidis*, *Streptococcus mutans*) (Graikou et al., 2016). Further studies on propolis samples collected from Mediterranean areas confirmed the effectiveness of EEP on *S. epidermidis*, *S. aureus* and methicillin-resistant *S. aureus* (MRSA) using a disc diffusion assay at a concentration range of 100 to 1000  $\mu\text{g/mL}$ , with an inhibitory zone of 4.6–21.4 mm (Béji-Srairi et al., 2020; Benhanifia et al., 2014; Nedji and Loucif-Ayad, 2014), and MBC values of 980 and 1220  $\mu\text{g/mL}$  on *S. aureus* ATCC 6538 and MRSA strains respectively (El-Guendouz et al., 2018). Interestingly the Tunisian EEP showed strong antibacterial activity on Gram-negative bacteria (Béji-Srairi et al., 2020). Chloroform fractions of Brazilian red propolis (BRP) have shown antibacterial activities against *S. aureus* and *Streptococcus mutans*, with MIC values ranging from 25 to 50  $\mu\text{g/mL}$  (Alencar et al., 2007). Another study investigated the antimicrobial potential of methanol, acetate and hexane fractions of BRP against reference strains including *S. aureus* (ATCC 13,150 and 25,923), *S. epidermidis* (ATCC 12228) and *Pseudomonas aeruginosa*, showing significant antibacterial activity at MIC values ranging from 128 to 512  $\mu\text{g/mL}$  (Neves et al., 2016). Similarly, ethanolic extracts of Polish propolis (EPPP) have shown antibacterial activity against *S. aureus* (ATCC 25,923 and ATCC 29213) with MIC values ranging from 128 to 512  $\mu\text{g/mL}$ , and weak bactericidal activity with MBC values from 512 up to 4096  $\mu\text{g/mL}$ . However, *S. epidermidis* ATCC 12,228 was more susceptible at MIC and MBC values in the range of 32 and 512  $\mu\text{g/mL}$  (Grecka et al., 2019). Siritwong et al. (2016) found that some propolis compounds modulated resistance to conventional antibiotics, with quercetin for example showing synergistic effects with amoxicillin and reduced resistance in amoxicillin-resistant *S. epidermidis* to  $\beta$ -lactam antibiotics (Siritwong et al., 2016).

Infections caused by biofilms are causing challenges, as eradication of biofilms with conventional antibiotics is becoming more difficult (Arciola et al., 2018). Several reports have shown that antibiotics are often ineffective in eradicating biofilms (Daikh et al., 2020). Use of ethanolic extracts of Brazilian brown propolis was investigated with mature biofilms of *S. aureus*, and the results included a reduction of 93% of the viability of the cells present in the biofilms at 125  $\mu\text{g/mL}$ . However, total biofilm biomass eradication was insignificant (de Oliveira Dembogurski et al., 2018). Algerian propolis exhibited a difference in biofilm inhibition across *S. aureus* ATCC 29213, *S. aureus* ATCC 33862, and MRSA strains based on the extraction solvent used and the origin of the propolis samples. A petroleum ether extract of Algerian propolis eradicated 40–80% of 48 h-old biofilm at a concentration of 300  $\mu\text{g/mL}$  (Daikh et al., 2020). At an MIC value of 360  $\mu\text{g/mL}$ , Moroccan propolis extract significantly reduced the virulence of *S. aureus* ATCC 6538

and MRSA. Furthermore, continued exposure to propolis treatments did not lead to the development of bacterial resistance (El-Guendouz et al., 2018). EPPP has shown antibiofilm activity against reference strain of *S. epidermidis* ATCC 35,984 with the MBEC<sub>50</sub> (minimal biofilm eradication concentration that causes a total of 50% reduction in biofilm) equivalent to an MIC value of 128  $\mu\text{g/mL}$  (Grecka et al., 2020). A study by Wojtyczka and colleagues found moderate inhibition of *S. epidermidis* biofilm with 780 to 1560  $\mu\text{g/mL}$  of EEP after 24 h incubation (Wojtyczka et al., 2013b). However, *S. aureus* biofilms were completely inactivated with 2  $\mu\text{g/mL}$  EEP after 40 h' treatment, indicating that activity is dependent on treatment time (Ambi et al., 2017). Grecka et al. revealed the high efficiency of EEP in the eradication of MSSA biofilms incubated for 24 h at 37 °C, with equal values of MIC and MBEC<sub>50</sub> (64–128  $\mu\text{g/mL}$ ). It was concluded that the antibiofilm activity of propolis was its most clinically beneficial aspect (Grecka et al., 2019). The antibiofilm activity of Russian propolis ethanol extracts (RPEE) on mature biofilm has been reported by Bryan et al., using MTT assay. Their study showed a 50% decreased viability of *S. aureus* at a high concentration (5% w/v) of RPEE. However, at fairly high RPEE concentrations (20% w/v), confocal and scanning electron microscopy images indicated complete cell lysis of bacterial biofilms after 18 h treatment (Bryan et al., 2015). Generally, propolis may be an excellent candidate for combating nosocomial diseases and eradicating biofilm on medical equipment caused by *S. aureus* (El-Guendouz et al., 2018).

## 5.2. Anti-candida activity

The increasing number of fungal infections is a troublesome problem in particular for immunocompromised patients (Gucwa et al., 2018). The genus *Candida* refers to a fungus that forms part of the individual's microbiota, and is largely present in areas of mucous membrane such as the oral and vaginal cavity (Capoci et al., 2015). *Candida albicans* and other species are opportunistic pathogens which have been recorded as the most frequent cause of candidiasis (Gucwa et al., 2018) and candidemia (Mutlu Sariguzel et al., 2016). Furthermore, many hospital-acquired infections are associated with the ability of microorganisms to adhere to human cells (Capoci et al., 2015), and to form biofilms in implanted orthodontics, catheter materials, and other medical devices (Gucwa et al., 2018). Thus, the formation of biofilm by *C. albicans* is one of several virulence factors responsible for infectious disease, and increases the risk of periodontal disease (Siqueira et al., 2015), vulvovaginal candidiasis (Capoci et al., 2015), and the development of various mechanisms of resistance against antifungal agents (Bezerra et al., 2020).

Some studies have supported the importance of using natural products such as propolis to treat fungal infections caused by *Candida* species. Although the antimicrobial activity of propolis has been investigated over recent years as an alternative for conventional therapeutic strategies, the antifungal activity of propolis is still underestimated, and therefore needs more evaluation to determine its therapeutic role. An ethanolic extract of Turkish propolis showed the highest antifungal activity against 76 *Candida* isolates (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata*) that were isolated from the blood cultures of intensive care unit patients, with an MIC range of 0.185 to 3  $\mu\text{g/mL}$  (Mutlu Sariguzel et al., 2016). Among 19 *Candida* species, *C. albicans*, *C. glabrata*, and *C. tropicalis* were isolated from chronic periodontitis cases, and about 42% of *C. albicans* isolates were resistant to fluconazole. However, all *Candida* species were sensitive to alcoholic extract of BRP. Fungistatic (MIC) and minimum fungicidal concentration (MFC) activities of propolis extract on *C. albicans* were observed in the range of 32–64  $\mu\text{g/mL}$  and 64–512  $\mu\text{g/mL}$ , respectively (Siqueira et al., 2015). Ethanolic extract of BRP showed MIC and

MFC at 256  $\mu\text{g/mL}$  on all yeast cells (*C. albicans*, *C. tropicalis*, and *C. neoformans*): however, hexane, acetate, and methanol fractions of the same samples of propolis showed antifungal activity at MIC values ranging between 32 and 1024  $\mu\text{g/mL}$  (Neves et al., 2016). Propolis samples collected from Tunisia exhibited intense antifungal activity against all tested *Candida* species (*C. albicans* ATCC 90028, *C. glabrata* ATCC 90030, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258) at a concentration of 250  $\mu\text{g/mL}$  (Béji-Srairi et al., 2020). Moreover, other studies suggest that the crude extract of any natural product displaying MIC lower than 500  $\mu\text{g/mL}$  is a promising substance (Duarte et al., 2007; Tiveron et al., 2016). Different BRPs showed an MIC in the range of 250–1000  $\mu\text{g/mL}$  using the serial microdilution method on *C. albicans* (López et al., 2015). Most likely, extraction method affects the activity of propolis: an ethanolic extract of French poplar-type propolis showed considerable activity against *C. albicans* at an MIC equal to 31.25  $\mu\text{g/mL}$  (Boisard et al., 2015).

The ability for morphological transition between yeast cells and hyphal forms is an important virulence factor for candidiasis that is caused mainly by *C. albicans* infection. MIC and MFC values of an ethanolic extract of Iranian propolis against fluconazole-resistant *C. albicans* isolates (from nails, the oral cavity, and vaginal cavity) ranged from 120.2 to 970.6  $\mu\text{g/mL}$  and 480.8 to 3900.4  $\mu\text{g/mL}$ , respectively. The sub-inhibitory concentrations (1/2 MIC and 1/4 MIC) significantly reduced germ tube formation (Haghdoost et al., 2016). The MFC was in a range comparable to the fungicidal activity of BRP, observed as 64–512  $\mu\text{g/mL}$  against *C. albicans* strains (Freires et al., 2016; Siqueira et al., 2015). Bezerra et al. found that the green propolis ethanolic extract showed significant antifungal activity, using disk diffusion assay, against *C. albicans* and *C. tropicalis*, with MIC values ranging from 2.5 to 250  $\mu\text{g/mL}$ , while *C. parapsilosis* was found to be less sensitive. The EEP exhibited antiadhesion activity at concentrations of 2.5 and 250  $\mu\text{g/mL}$  after 12 h, and highly significant antibiofilm activity (0.25–250  $\mu\text{g/mL}$ ) after 24 h and 48 h incubation, where a reduction of from more than 30% to 100% of colony-forming units (CFU) was observed for the three *Candida* species on surfaces of steel and acrylic resin of orthodontic material (Bezerra et al., 2020). Furthermore, propolis could be a promising anti-cariogenic agent, and has shown efficiency in reducing the CFU of *C. albicans* by between 33 and 79 % CFU in mature biofilm. Thus, propolis is considered a good oral antiseptic to prevent caries (Djais et al., 2019). Another study investigated the effect of Brazilian propolis extract in solution for anti-biofilm activity against 29 clinical isolates of *C. albicans* isolated from vaginal specimens. The EEP showed strong antibiofilm activity against all the isolates, with MIC values ranging between 68.35 and 546.87  $\mu\text{g/mL}$ , in which 75.8% of the total isolates died at a concentration of 546.87  $\mu\text{g/mL}$  (Capoci et al., 2015). A study by Gucwa et al. (2018) tested EPPP on biofilms from 34 clinical isolates of three species from the *Candida* genus, using MTT assay. Most of the EPPP samples showed high antibiofilm activity, and 50% of mature biofilm of *C. albicans* was eradicated at from 81  $\mu\text{g/mL}$  to more than 2540  $\mu\text{g/mL}$ . In addition, the biofilms of *C. krusei* and *C. glabrata* were less resistant to propolis treatment (Gucwa et al., 2018). More than 84% inhibition was found for the morphological transformation of *C. albicans* from yeast cell to hyphal forms after 2 h exposure to subinhibitory concentrations of EPPP. Excessive use of antimicrobial drugs often leads to resistance among microorganisms: hence the need to use higher and higher doses of drugs, which can be toxic to human cells. Gucwa et al. (2018) revealed a synergistic effect between the components of propolis and antifungal drugs (fluconazole and voriconazole) against *C. albicans*. This finding could be interesting from a clinical point of view. Therefore, propolis has potential use in modifying the adhesive properties of *C. albicans*, thus preventing the pathogen's ability to form biofilms (Feldman et al.,

2014). Additionally, propolis extracts could prevent yeast cells from forming biofilms while showing very low cytotoxicity in human cells (Capoci et al., 2015).

## 6. Mechanism of action

Propolis and some of its derivatives are responsible for either killing bacterial cells directly by interacting with them through different mechanisms, or by modifying the immune response of host cells (Almuhayawi, 2020). It is evident from the literature that several possible mechanisms might account for the lower antibacterial activity of propolis against Gram-negative bacteria. One possible reason could be the synthesis of a wide variety of hydrolytic enzymes by Gram-negative microorganisms (Grecka et al., 2019). These hydrolytic enzymes may interfere with the active components of propolis and result in the development of resistance (Bryan et al., 2015). Several underlying mechanisms have been proposed by different research groups regarding the antimicrobial activity of propolis, including the inhibition of cell division, nucleic acid synthesis, protein synthesis, impeding cytoplasmic membrane function, altering membrane permeability, reducing the ability to form biofilms, bacteriolysis, inhibiting the energy generation pathway, and reducing bacterial resistance towards certain conventional antibiotics (Przybyłek and Karpiński, 2019).

The effect of propolis on the bacterial cell membrane's integrity was assessed for *S. aureus* and *E. coli* by measuring the release of intracellular constituents into the medium. The results indicate that the ethanolic extract of Brazilian propolis causes irreversible damage to the bacterial cell membrane, leading to cell death (Torres et al., 2018). Due to the different quality, quantity, and ratios of each component of propolis, it is difficult to predict the predominant biological activity of this natural substance, as it is considered that these components act synergistically. The synergistic interaction between EEP and antibiotics on *S. aureus* and other microorganisms has been identified by the broth microdilution and disc diffusion methods, confirming the enhancement of the antimicrobial action of  $\beta$ -lactam antibiotics in the presence of propolis (Regueira Neto et al., 2017), through inhibition of  $\beta$ -lactamase enzymes and peptidoglycan synthesis. Therefore, propolis revealed synergistic interaction with antibiotics that act on inhibiting the cell wall, proteins synthesis, and ribosomes. The results further indicate that therapy with a combination of propolis and other drugs reduces the risk of developing multidrug-resistant microorganisms during treatment (Grecka et al., 2019; Grecka and Szweda, 2021; Regueira Neto et al., 2017; Wojtyczka et al., 2013a). A study by Ambi et al evaluated the activity of Russian propolis ethanol extract (RPEE) against *S. aureus* and *E. coli*. It was detected that RPEE causes cell lysis and bacterial cell membrane damage within mature biofilms at a concentration of 2–4  $\mu\text{g/mL}$ , and the authors state that the structural mechanism of action stems from antibacterial and anti-biofilm activities related to the duration of exposure to propolis (Ambi et al., 2017). It is remarkable that this propolis was found to have the ability to completely inactivate bacterial cells within the biofilm matrix after 18 h of treatment, demonstrating severe cell wall damage. Thus, the mechanism of action of RPEE is structural rather than functional (Bryan et al., 2015).

The fungal cell wall is the first barrier responsible for growth, adaptation, and permeability regulation of fungal pathogens during infection (Gucwa et al., 2018). Corrêa and colleagues found that Brazilian propolis damages the integrity of *C. albicans*' cell wall and cell membrane, and causes leakage of intracellular organelles. The study hypothesizes that the antifungal efficacy of propolis is due to the capacity of polyphenols to form a complex with soluble proteins by disrupting the synthesis of chitin, which leads to cell wall

disruption (Corrêa et al., 2020). After measurement of *C. albicans* growth in the presence and absence of an osmoprotectant (sorbitol), the results revealed that ethanolic extracts of polish propolis do not affect the cell wall. However, ergosterol and membrane depolarization assays suggest that the cell membrane might be a potential target for propolis (Gucwa et al., 2018).

A study by Aru et al. found that Turkish propolis extract caused an apoptotic effect on cancer cell lines, and promoted cell cycle arrest by activating the expression of cell cycle p21 proteins. Using MTS assay, the same propolis samples showed moderate anti-proliferative activity on cancer cell lines (Aru et al., 2019). Propolis-derived antiviral activity against human rhinovirus (HRV) was evaluated using sulforhodamine B assay and real-time reverse transcription-polymerase chain reaction. The results showed a significant decrease in HRV RNA replication into human epithelial adenocarcinoma cervix (HeLa) cell cultures. Kaempferol and *p*-coumaric acid may interfere with expression of intercellular adhesion molecules (Kwon et al., 2019).

These studies indicate that the mode of action of propolis is not determined by identifying the mode of action of its bioactive constituents separately, but that it is a complex interaction between all the compounds. Nevertheless, very little is currently known about the molecular mechanisms associated with the biological effects of propolis (Boisard et al., 2020), and the mechanisms underpinning its activity against microorganisms are still not clear. However, for a long time, it has been considered that the activities of propolis compounds against microorganisms are more related to the synergistic effect of polyphenols than to individual effects (Koo et al., 2000; Martins et al., 2002).

## 7. Conclusion

Propolis is an effective natural product that offers a wide variety of biological potentials, including antimicrobial activities, in addition to other pharmaceutical applications. The chemical composition of propolis is highly complex and varies from one geographical region to another. Despite the numerous studies dealing with this highly complex substance, it is currently challenging to standardize. It is established that the type of propolis varies depending on geographical origins and plant sources, with huge heterogeneity in chemical composition. Ethanol extracts of propolis are of great significance, exhibiting higher antibacterial and antifungal activities against multidrug resistant strains. Polyphenols, terpenes, and aromatic compounds are the major phytochemicals to show remarkable antimicrobial activities, and the activity of these chemicals can be based on a single action or synergistic interaction between several components. Finally, the current review recommends further study of the biological potentials and mechanisms of action of new types of propolis from diverse regions, for the prevention and control of human infectious diseases.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## References

- Abreu, A.C., McBain, A.J., Simões, M., 2012. Plants as sources of new antimicrobials and resistance-modifying agents. *Nat. Prod. Rep.* 29 (9), 1007. <https://doi.org/10.1039/c2np20035j>.
- Ahangari, Z., Naseri, M., Vatandoost, F., 2018. Propolis: Chemical composition and its applications in endodontics. *Iranian Endodontic Journal* 13. <https://doi.org/10.22037/iej.v13i3.20994>.
- Al-Ani, I., Zimmermann, S., Reichling, J., Wink, M., 2018. Antimicrobial activities of European propolis collected from various geographic origins alone and in combination with antibiotics. *Medicines* 5 (1), 2. <https://doi.org/10.3390/medicines5010002>.
- Alencar, S.M., Oldoni, T.L.C., Castro, M.L., Cabral, I.S.R., Costa-Neto, C.M., Cury, J.A., Rosalen, P.L., Ikegaki, M., 2007. Chemical composition and biological activity of a new type of Brazilian propolis: Red propolis. *Journal of Ethnopharmacology* 113 (2), 278–283. <https://doi.org/10.1016/j.jep.2007.06.005>.
- Almuhayawi, M.S., 2020. Propolis as a novel antibacterial agent. *Saudi Journal of Biological Sciences* 27 (11), 3079–3086. <https://doi.org/10.1016/j.sjbs.2020.09.016>.
- Ambi, A., Bryan, J., Borbon, K., Centeno, D., Liu, T., Chen, T.P., Cattabiani, T., Traba, C., 2017. Are Russian propolis ethanol extracts the future for the prevention of medical and biomedical implant contaminations? *Phytomedicine* 30, 50–58. <https://doi.org/10.1016/j.phymed.2017.03.006>.
- Anand, U., Jacobo-Herrera, N., Altemimi, A., Lakhssassi, N., 2019. A Comprehensive review on medicinal plants as antimicrobial therapeutics: potential avenues of biocompatible drug discovery. *Metabolites* 9, 258. <https://doi.org/10.3390/metabo9110258>.
- Andrade, J.K.S., Denadai, M., de Oliveira, C.S., Nunes, M.L., Narain, N., 2017. Evaluation of bioactive compounds potential and antioxidant activity of brown, green and red propolis from Brazilian northeast region. *Food Research International* 101, 129–138. <https://doi.org/10.1016/j.foodres.2017.08.066>.
- Anjum, S.I., Ullah, A., Khan, K.A., Attaullah, M., Khan, H., Ali, H., Bashir, M.A., Tahir, M., Ansari, M.J., Ghramh, H.A., Adgaba, N., Dash, C.K., 2019. Composition and functional properties of propolis (bee glue): A review. *Saudi Journal of Biological Sciences* 26 (7), 1695–1703. <https://doi.org/10.1016/j.sjbs.2018.08.013>.
- Arciola, C.R., Campoccia, D., Montanaro, L., 2018. Implant infections: adhesion, biofilm formation and immune evasion. *Nat. Rev. Microbiol.* 16 (7), 397–409. <https://doi.org/10.1038/s41579-018-0019-y>.
- Aru, B., Güzelmeric, E., Akgül, A., Demirel, G.Y., Kırmızıbekmez, H., 2019. Antiproliferative activity of chemically characterized propolis from Turkey and its mechanisms of action. *Chemistry & Biodiversity* 16 (7). <https://doi.org/10.1002/cbdv.v16.7.10.1002/cbdv.201900189>.
- Asgharpour, F., Moghadamnia, A.A., Kazemi, S., Nouri, H.R., Motalebnejad, M., 2020. Applying GC-MS analysis to identify chemical composition of Iranian propolis prepared with different solvent and evaluation of its biological activity. *Caspian. J. Intern. Med.* 11. <https://doi.org/10.22088/cjim.11.2.191>.
- Aslam, B., Wang, W., Arshad, M.I., Khurshid, M., Muzammil, S., Rasool, M.H., Nisar, M.A., Alvi, R.F., Aslam, M.A., Qamar, M.U., Salamat, M.K.F., Baloch, Z., 2018. Antibiotic resistance: a rundown of a global crisis. *IDR* 11, 1645–1658. <https://doi.org/10.2147/IDR.S173867>.
- Bankova, V., 2005. Chemical diversity of propolis and the problem of standardization. *Journal of Ethnopharmacology* 100 (1–2), 114–117. <https://doi.org/10.1016/j.jep.2005.05.004>.
- Bankova, V., Popova, M., Trusheva, B., 2014. Propolis volatile compounds: chemical diversity and biological activity: a review. *Chemistry Central Journal* 8, 28. <https://doi.org/10.1186/1752-153X-8-28>.
- Béji-Sraïri, R., Younes, I., Snoussi, M., Yahyaoui, K., Borchard, G., Ksouri, R., Frachet, V., Wided, M.K., 2020. Ethanolic extract of Tunisian propolis: chemical composition, antioxidant, antimicrobial and antiproliferative properties. *Journal of Apicultural Research* 59 (5), 917–927. <https://doi.org/10.1080/00218839.2020.1732572>.
- Benhanifia, M., Shimomura, K., Tsuchiya, I., Inui, S., Kumazawa, S., Mohamed, W., Boukraa, L., Sakharkar, M., Benbarek, H., 2014. Chemical composition and antimicrobial activity of propolis collected from some localities of Western Algeria. *Acta Alimentaria* 43 (3), 482–488. <https://doi.org/10.1556/AAlim.43.2014.3.16>.
- Bezerra, C.R.F., Borges, K.R.A., Alves, R. de N.S., Teles, A.M., Rodrigues, I.V.P., Silva, M. A.C.N. da, Nascimento, M. do D.S.B., Bezerra, G.F. de B., 2020. Highly efficient antibiofilm and antifungal activity of green propolis against *Candida* species in dentistry material. *bioRxiv* 2020.01.27.920959. <https://doi.org/10.1101/2020.01.27.920959>.
- Boisard, S., Le Ray, A.-M., Landreau, A., Kempf, M., Cassisa, V., Flurin, C., Richomme, P., 2015. Antifungal and antibacterial metabolites from a French poplar type propolis. *Evidence-Based Complementary and Alternative Medicine* 2015, 1–10. <https://doi.org/10.1155/2015/319240>.
- Boisard, S., Shahali, Y., Aumond, M.-C., Derbré, S., Blanchard, P., Dadar, M., Le Ray, A.-M., Richomme, P., 2020. Anti-AGE activity of poplar-type propolis: mechanism of action of main phenolic compounds. *International Journal of Food Science & Technology* 55 (2), 453–460. <https://doi.org/10.1111/ijfs.14284>.



- Boonchird, C., Flegel, T.W., 1982. In vitro antifungal activity of eugenol and vanillin against *Candida albicans* and *Cryptococcus neoformans*. *Canadian Journal of Microbiology* 28 (11), 1235–1241. <https://doi.org/10.1139/m82-184>.
- Bridi, R., Montenegro, G., Nuñez-Quijada, G., Giordano, A., Fernanda Morán-Romero, M., Jara-Peoz, I., Speisky, H., Atala, E., López-Alarcón, C., 2015. International regulations of propolis quality: Required assays do not necessarily reflect their polyphenolic-related *In Vitro* Activities. *Journal of Food Science* 80 (6), C1188–C1195. <https://doi.org/10.1111/1750-3841.12881>.
- Brown, R., 1989. Hive products: Pollen, propolis and royal jelly. *Bee World* 70 (3), 109–117. <https://doi.org/10.1080/0005772X.1989.11099000>.
- Bruschi, M.L., Franco, S.L., Gremião, M.P.D., 2003. Application of an HPLC method for analysis of propolis extract. *Journal of Liquid Chromatography & Related Technologies* 26 (14), 2399–2409. <https://doi.org/10.1081/JLC-120023254>.
- Bryan, J., Redden, P., Traba, C., 2015. The mechanism of action of Russian propolis ethanol extracts against two antibiotic-resistant biofilm-forming bacteria. *Letters in Applied Microbiology* 62 (2), 192–198. <https://doi.org/10.1111/lam.12532>.
- 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. *Natural Product Research* 31 (11), 1318–1324. <https://doi.org/10.1080/14786419.2016.1239088>.
- Búfalo, M.C., Candeias, J.M.G., Sforcin, J.M., 2009. In Vitro Cytotoxic Effect of Brazilian Green Propolis on Human Laryngeal Epidermoid Carcinoma (HEp-2) Cells. *Evidence-Based Complementary and Alternative Medicine* 6 (4), 483–487. <https://doi.org/10.1093/ecam/nem147>.
- Capoci, I.R.G., Bonfim-Mendonça, P.d.S., Arita, G.S., Pereira, R.R.d.A., Consolaro, M.E. L., Bruschi, M.L., Negri, M., Svidzinski, T.I.E., 2015. Propolis is an efficient fungicide and inhibitor of biofilm production by vaginal *Candida albicans*. *Evidence-Based Complementary and Alternative Medicine* 2015, 1–9. <https://doi.org/10.1155/2015/287693>.
- Celińska-Janowicz, K., Zaręba, I., Lazarek, U., Teul, J., Tomczyk, M., Pałka, J., Miltky, W., 2018. Constituents of propolis: Chrysin, caffeic acid, p-coumaric acid, and ferulic acid induce PRODH/POX-dependent apoptosis in human tongue squamous cell carcinoma cell (CAL-27). *Front. Pharmacol.* 9, 336. <https://doi.org/10.3389/fphar.2018.00336>.
- Chen, Y.-W., Ye, S.-R., Ting, C., Yu, Y.-H., 2018. Antibacterial activity of propolis from Taiwanese green propolis. *Journal of Food and Drug Analysis* 26 (2), 761–768. <https://doi.org/10.1016/j.jfda.2017.10.002>.
- Cheng, H., Qin, Z.H., Guo, X.F., Hu, X.S., Wu, J.H., 2013. Geographical origin identification of propolis using GC-MS and electronic nose combined with principal component analysis. *Food Research International* 51 (2), 813–822. <https://doi.org/10.1016/j.foodres.2013.01.053>.
- Choi, H., Park, J.-S., Kim, K.-M., Kim, M., Ko, K.-W., Hyun, C.-G., Ahn, J.W., Seo, J.-H., Kim, S.-Y., 2018. Enhancing the antimicrobial effect of genistein by biotransformation in microbial system. *Journal of Industrial and Engineering Chemistry* 63, 255–261. <https://doi.org/10.1016/j.jiec.2018.02.023>.
- Corrêa, J.L., Veiga, F.F., Jarros, I.C., Costa, M.L., Castilho, P.F., de Oliveira, K.M.P., Rosseto, H.C., Bruschi, M.L., Svidzinski, T.I.E., Negri, M., 2020. Propolis extract has bioactivity on the wall and cell membrane of *Candida albicans*. *Journal of Ethnopharmacology* 256, 112791. <https://doi.org/10.1016/j.jep.2020.112791>.
- Cuesta-Rubio, O., Piccinelli, A.L., Campo Fernandez, M., Márquez Hernández, 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. <https://doi.org/10.1021/jf071296w>.
- Cui, S., Hassan, R., Heintz-Buschart, A., Bilitewski, U., 2016. Regulation of *Candida albicans* interaction with macrophages through the activation of HOG pathway by genistein. *Molecules* 21, 162. <https://doi.org/10.3390/molecules21020162>.
- da Silva, J.F.M., de Souza, M.C., Matta, S.R., de Andrade, M.R., Vidal, F.V.N., 2006. Correlation analysis between phenolic levels of Brazilian propolis extracts and their antimicrobial and antioxidant activities. *Food Chemistry* 99 (3), 431–435. <https://doi.org/10.1016/j.foodchem.2005.07.055>.
- Daikh, A., Segueni, N., Dogan, N.M., Arslan, S., Mutlu, D., Kivrak, I., Akkal, S., Rhoutati, S., 2020. Comparative study of antibiofilm, cytotoxic activity and chemical composition of Algerian propolis. *Journal of Apicultural Research* 59 (2), 160–169. <https://doi.org/10.1080/00218839.2019.1701777>.
- Dantas Silva, R.P., Machado, B.A.S., Barreto, G.d.A., Costa, S.S., Andrade, L.N., Amaral, R.G., Carvalho, A.A., Padilha, F.F., Barbosa, J.D.V., Umsza-Guez, M.A., Gupta, V., 2017. Antioxidant, antimicrobial, antiparasitic, and cytotoxic properties of various Brazilian propolis extracts. *PLoS ONE* 12 (3), e0172585. <https://doi.org/10.1371/journal.pone.0172585>.
- de Marco, S., Piccioni, M., Pagiotti, R., Pietrella, D., 2017. Antibiofilm and antioxidant activity of propolis and bud poplar resins versus *Pseudomonas aeruginosa*. *Evidence-Based Complementary and Alternative Medicine* 2017, 1–11. <https://doi.org/10.1155/2017/5163575>.
- de Oliveira Dembogurski, D.S., Silva Trentin, D., Boaretto, A.G., Rigo, G.V., da Silva, R. C., Tasca, T., Macedo, A.J., Carollo, C.A., Silva, D.B., 2018. Brown propolis-metabolomic innovative approach to determine compounds capable of killing *Staphylococcus aureus* biofilm and *Trichomonas vaginalis*. *Food Research International* 111, 661–673. <https://doi.org/10.1016/j.foodres.2018.05.033>.
- Degirmencioglu, H.T., Guzelmeric, E., Yuksel, P.L., Kirmizibekmez, H., Deniz, I., Yesilada, E., 2019. A new type of Anatolian propolis: Evaluation of its chemical composition, activity profile and botanical origin. *Chemistry & Biodiversity* 16, <https://doi.org/10.1002/cbdv.201900492> e1900492.
- Devequi-Nunes, D., Machado, B.A.S., Barreto, G.d.A., Rebouças Silva, J., da Silva, D.F., da Rocha, J.L.C., Brandão, H.N., Borges, V.M., Umsza-Guez, M.A., Lightfoot, D.A., 2018. Chemical characterization and biological activity of six different extracts of propolis through conventional methods and supercritical extraction. *PLoS ONE* 13 (12), e0207676. <https://doi.org/10.1371/journal.pone.0207676>.
- Dezmirean, D.S., Mărghitaș, L.A., Chirilă, F., Copaciu, F., Simonca, V., Bobiș, O., Erler, S., 2017. Influence of geographic origin, plant source and polyphenolic substances on antimicrobial properties of propolis against human and honey bee pathogens. *Journal of Apicultural Research* 56 (5), 588–597. <https://doi.org/10.1080/00218839.2017.1356205>.
- Dezmirean, D.S., Pașca, C., Moise, A.R., Bobiș, O., 2021. Plant Sources Responsible for the Chemical Composition and Main Bioactive Properties of Poplar-Type Propolis. *Plants* 10, 22. <https://doi.org/10.3390/plants10010022>.
- Djais, A.A., Jemmy, Putri, N., Rahmania Putri, A., Angky Soekanto, S., 2019. Description of *Streptococcus mutans*, *Streptococcus sanguinis*, and *Candida albicans* biofilms after exposure to propolis dentifrice by using OpenCFU method. *The Saudi Dental Journal* 32 (3), 129–134. <https://doi.org/10.1016/j.sdentj.2019.08.003>.
- do Nascimento Araújo, C., Mayworm, M.A.S., Yatsuda, R., Negri, G., Salatino, M.L.F., Salatino, A., Timenetsky, J., Campos, G.B., 2020. Chemical composition and antimycoplasmal activity of a brown propolis from southern Brazil. *J Food Sci Technol* 57 (11), 4228–4235. <https://doi.org/10.1007/s13197-020-04461-y>.
- Duarte, M.C.T., Leme, E.E., Delarmelina, C., Soares, A.A., Figueira, G.M., Sartoratto, A., 2007. Activity of essential oils from Brazilian medicinal plants on *Escherichia coli*. *Journal of Ethnopharmacology* 111 (2), 197–201. <https://doi.org/10.1016/j.jep.2006.11.034>.
- El-Guendouz, S., Aazza, S., Lyoussi, B., Bankova, V., Lourenço, J.P., Costa, A.M.R., Mariano, J.F., Miguel, M.G., Faleiro, M.L., 2016. Impact of Biohybrid Magnetite Nanoparticles and Moroccan Propolis on Adherence of Methicillin Resistant Strains of *Staphylococcus aureus*. *Molecules* 21, 1208. <https://doi.org/10.3390/molecules21091208>.
- El-Guendouz, S., Aazza, S., Lyoussi, B., Bankova, V., Popova, M., Neto, L., Faleiro, M.L., Miguel, M. da G., 2018. Moroccan Propolis: A natural antioxidant, antibacterial, and antibiofilm against *Staphylococcus aureus* with no induction of resistance after continuous exposure. *Evidence-Based Complementary and Alternative Medicine* 2018, 1–19. <https://doi.org/10.1155/2018/9759240>.
- Elnakady, Y.A., Rushdi, A.I., Franke, R., Abutaha, N., Ebaid, H., Baabbad, M., Omar, M. O.M., Al Ghamdi, A.A., 2017. Characteristics, chemical compositions and biological activities of propolis from Al-Bahah. *Saudi Arabia. Sci Rep* 7, 41453. <https://doi.org/10.1038/srep41453>.
- Ezzat, S.M., Khattaby, A.M., Abdelmageed, S., Abd Elaal, M.A., 2019. Cytotoxicity, antioxidant, anti-inflammatory activity, and GC-MS analysis of Egyptian propolis. *Comp Clin Pathol* 28 (6), 1589–1598. <https://doi.org/10.1007/s00580-019-02971-6>.
- Fair, R.J., Tor, Y., 2014. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem* 6, PMC514459. <https://doi.org/10.4137/PMC.514459>.
- Falcão, S.I., Vale, N., Gomes, P., Domingues, M.R.M., Freire, C., Cardoso, S.M., Vilas-Boas, M., 2013. Phenolic Profiling of Portuguese Propolis by LC-MS Spectrometry: Uncommon Propolis Rich in Flavonoid Glycosides: Phenolic Profiling of Portuguese Propolis. *Phytochem. Anal.* 24 (4), 309–318. <https://doi.org/10.1002/pca.2412>.
- Feldman, M., Al-Quntar, A., Polacheck, I., Friedman, M., Steinberg, D., Meijler, M.M., 2014. Therapeutic Potential of Thiazolidinedione-8 as an Antibiofilm Agent against *Candida albicans*. *PLoS ONE* 9, 8.
- 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. *Journal of the Science of Food and Agriculture* 97 (11), 3552–3558. <https://doi.org/10.1002/jsfa.8210>.
- Freires, I.A., Queiroz, V.C.P.P., Furlletti, V.F., Ikegaki, M., de Alencar, S.M., Duarte, M.C.T., Rosalen, P.L., 2016. Chemical composition and antifungal potential of Brazilian propolis against *Candida* spp. *Journal de Mycologie Médicale* 26 (2), 122–132. <https://doi.org/10.1016/j.mycmed.2016.01.003>.
- Frieri, M., Kumar, K., Boutin, A., 2017. Antibiotic resistance. *Journal of Infection and Public Health* 10 (4), 369–378. <https://doi.org/10.1016/j.jiph.2016.08.007>.
- Gargouri, W., Osés, S.M., Fernández-Muñoz, M.A., Sancho, M.T., Kechaou, N., 2019. Evaluation of bioactive compounds and biological activities of Tunisian propolis. *LWT* 111, 328–336. <https://doi.org/10.1016/j.lwt.2019.05.044>.
- Graikou, K., Popova, M., Gortzi, O., Bankova, V., Chinou, I., 2016. Characterization and biological evaluation of selected Mediterranean propolis samples. Is it a new type? *LWT - Food Science and Technology* 65, 261–267. <https://doi.org/10.1016/j.lwt.2015.08.025>.
- Grecka, K., Kuś, P.M., Okińczyc, P., Worobo, R.W., Walkusz, J., Szweđa, P., 2019. The Anti-*Staphylococcal* potential of ethanolic Polish propolis extracts. *Molecules* 24, 1732. <https://doi.org/10.3390/molecules24091732>.
- Grecka, K., Szweđa, P., 2021. Synergistic effects of propolis combined with 2-Phenoxyethanol and antipyratics on the growth of *Staphylococcus aureus*. *Pharmaceutics* 13, 215. <https://doi.org/10.3390/pharmaceutics13020215>.
- Grecka, K., Xiong, Z.R., Chen, H., Pełka, K., Worobo, R.W., Szweđa, P., 2020. Effect of ethanol extracts of propolis (EEPs) against *Staphylococcal* biofilm—microscopic studies. *Pathogens* 9, 646. <https://doi.org/10.3390/pathogens9080646>.
- Gucwa, K., Kuznierewicz, B., Milewski, S., Van Dijck, P., Szweđa, P., 2018. Antifungal activity and synergism with azoles of Polish propolis. *Pathogens* 7, 56. <https://doi.org/10.3390/pathogens7020056>.
- Guzmán, E.L., Cruz, F.J.M., 2017. Combinations of extracts of propolis and other compounds Against methicillin-resistant *Staphylococcus aureus*, in: El-Shemy, H.A. (Ed.), *Active Ingredients from Aromatic and Medicinal Plants*. InTech. <https://doi.org/10.5772/66219>

- Haghdoust, N.S., Salehi, T.Z., Khosravi, A., Sharifzadeh, A., 2016. Antifungal activity and influence of propolis against germ tube formation as a critical virulence attribute by clinical isolates of *Candida albicans*. *Journal of Mycologie Médicale* 26 (4), 298–305. <https://doi.org/10.1016/j.mycmed.2015.11.004>.
- Jihene, A., Karoui, I.J., Ameni, A., Hammami, M., Abderrabba, M., 2018. Volatile compounds analysis of Tunisian propolis and its antifungal activity. *JBM* 06 (06), 115–131. <https://doi.org/10.4236/jbm.2018.66009>.
- Kasote, D.M., Pawar, M.V., Bhatia, R.S., Nandre, V.S., Gundu, S.S., Jagtap, S.D., Kulkarni, M.V., 2017. HPLC, NMR based chemical profiling and biological characterisation of Indian propolis. *Fitoterapia* 122, 52–60. <https://doi.org/10.1016/j.fitote.2017.08.011>.
- Koo, H., Gomes, B.P.F.A., Rosalen, P.L., Ambrosano, G.M.B., Park, Y.K., Cury, J.A., 2000. In vitro antimicrobial activity of propolis and *Arnica montana* against oral pathogens. *Archives of Oral Biology* 45 (2), 141–148. [https://doi.org/10.1016/S0003-9969\(99\)00117-X](https://doi.org/10.1016/S0003-9969(99)00117-X).
- Kujumgiev, A., Tsvetkova, I., Serkedjieva, Y.u., Bankova, V., Christov, R., Popov, S., 1999. Antibacterial, antifungal and antiviral activity of propolis of different geographic origin. *Journal of Ethnopharmacology* 64 (3), 235–240. [https://doi.org/10.1016/S0378-8741\(98\)00131-7](https://doi.org/10.1016/S0378-8741(98)00131-7).
- Kurek-Górecka, A., Rzepecka-Stojko, A., Górecki, M., Stojko, J., Sosada, M., Świerczek-Zięba, G., 2013. Structure and antioxidant activity of polyphenols derived from propolis. *Molecules* 19, 78–101. <https://doi.org/10.3390/molecules19010078>.
- Kwon, M.J., Shin, H.M., Perumalsamy, H., Wang, X., Ahn, Y.-J., 2019. Antiviral effects and possible mechanisms of action of constituents from Brazilian propolis and related compounds. *Journal of Apicultural Research* 59 (4), 413–425. <https://doi.org/10.1080/00218839.2019.1695715>.
- Lee, R.A., Zurko, J.C., Camins, B.C., Griffin, R.L., Rodriguez, J.M., McCarty, T.P., Magadia, J., Pappas, P.G., 2019. Impact of infectious disease consultation on clinical management and mortality in patients with candidemia. *Clinical Infectious Diseases* 68, 1585–1587. <https://doi.org/10.1093/cid/ciy849>.
- Liu, Y., Song, X., He, J., Zheng, X., Wu, H., 2014. Synthetic derivatives of chrysin and their biological activities. *Med Chem Res* 23 (2), 555–563. <https://doi.org/10.1007/s00044-013-0711-4>.
- Lopez, B.-G.-C., de Lourenço, C.C., Alves, D.A., Machado, D., Lancellotti, M., Sawaya, A.C.H.F., 2015. Antimicrobial and cytotoxic activity of red propolis: an alert for its safe use. *Journal of Applied Microbiology* 119 (3), 677–687. <https://doi.org/10.1111/jam.12874>.
- López, B. G.-C., Sawaya, A.C.H.F., 2012. A review of the plant origins, composition and biological activity of red propolis. In: Gonçalves, R.E., Cunha Pinto, M. (Eds.), *Natural products: Structure, bioactivity and applications*. Nova Science Publishers, pp. 83–96.
- Lu, L.-C., Chen, Y.-W., Chou, C.-C., 2005. Antibacterial activity of propolis against *Staphylococcus aureus*. *International Journal of Food Microbiology* 102, 213–220. <https://doi.org/10.1016/j.ijfoodmicro.2004.12.017>.
- Machado, C.S., Mokoichinski, J.B., Lira, T.O.d., de Oliveira, F.d.C.E., Cardoso, M.V., Ferreira, R.G., Frankland Sawaya, A.C.H., Ferreira, A.G., Pessoa, C., Cuesta-Rubio, O., Monteiro, M.C., de Campos, M.S., Torres, Y.R., 2016. Comparative study of chemical composition and biological activity of yellow, green, brown, and red Brazilian propolis. Evidence-Based Complementary and Alternative Medicine 2016, 1–11. <https://doi.org/10.1155/2016/6057650>.
- Mani, R., Natesan, V., 2018. Chrysin: Sources, beneficial pharmacological activities, and molecular mechanism of action. *Phytochemistry* 145, 187–196. <https://doi.org/10.1016/j.phytochem.2017.09.016>.
- Márquez Hernández, I., Cuesta-Rubio, O., Campo Fernández, M., Rosado Pérez, A., de Oca, M., Porto, R., Piccinelli, A.L., Rastrelli, L., 2010. Studies on the Constituents of Yellow Cuban Propolis: GC-MS Determination of Triterpenoids and Flavonoids. *J. Agric. Food Chem.* 58, 4725–4730. <https://doi.org/10.1021/jf904527n>.
- Martins, R.S., Pereira, E.S.J., Jr, S.M.L., Senna, M.I.B., Mesquita, R.A., Santos, V.R., 2002. Effect of commercial ethanol propolis extract on the in vitro growth of *Candida albicans* collected from HIV-seropositive and HIV-seronegative Brazilian patients with oral candidiasis. *Journal of Oral Science* 44, 41–48. <https://doi.org/10.2334/josnusd.44.41>.
- Mello, B.C.B.S., Hubinger, M.D., 2012. Antioxidant activity and polyphenol contents in Brazilian green propolis extracts prepared with the use of ethanol and water as solvents in different pH values. *Int J Food Sci Technol* 47 (12), 2510–2518. <https://doi.org/10.1111/j.1365-2621.2012.03129.x>.
- Milojković Opsenica, D., Ristivojević, P., Trifković, J., Vovk, I., Lušić, D., Tešić, Ž., 2016. TLC fingerprinting and pattern recognition methods in the assessment of authenticity of poplar-type propolis. *J Chromatogr Sci* 54 (7), 1077–1083. <https://doi.org/10.1093/chromsci/bmw024>.
- Monzote, L., Cuesta-Rubio, O., Campo Fernandez, M., Márquez Hernandez, I., Fraga, J., Pérez, K., Kerstens, M., Maes, L., Cos, P., 2012. In vitro antimicrobial assessment of Cuban propolis extracts. *Mem. Inst. Oswaldo Cruz* 107 (8), 978–984. <https://doi.org/10.1590/S0074-02762012000800003>.
- Morlock, G.E., Ristivojević, P., Chernetsova, E.S., 2014. Combined multivariate data analysis of high-performance thin-layer chromatography fingerprints and direct analysis in real time mass spectra for profiling of natural products like propolis. *Journal of Chromatography A* 1328, 104–112. <https://doi.org/10.1016/j.chroma.2013.12.053>.
- Munita, J.M., Arias, C.A., 2016. Mechanisms of antibiotic resistance. *Microbiol Spectr* 4 (2). <https://doi.org/10.1128/microbiolspec.VMBF-0016-2015>.
- Mutlu Sariguzel, F., Berk, E., Koc, A.N., Sav, H., Demir, G., 2016. Antifungal activity of propolis against yeasts isolated from blood culture: In vitro evaluation. *Journal of Clinical Laboratory Analysis* 30 (5), 513–516. <https://doi.org/10.1002/jcla.21889>.
- Nedji, N., Loucif-Ayad, W., 2014. Antimicrobial activity of Algerian propolis in foodborne pathogens and its quantitative chemical composition. *Asian Pacific Journal of Tropical Disease* 4, 433–437. [https://doi.org/10.1016/S2222-1808\(14\)60601-0](https://doi.org/10.1016/S2222-1808(14)60601-0).
- Neves, M.V.M. das, da Silva, T.M.S., Lima, E.d.O., da Cunha, E.V.L., Oliveira, E.d.J., 2016. Isoflavone formononetin from red propolis acts as a fungicide against *Candida* sp. *Brazilian Journal of Microbiology* 47 (1), 159–166. <https://doi.org/10.1016/j.bjm.2015.11.009>.
- Peng, L., Yang, S., Cheng, Y.J., Chen, F., Pan, S., Fan, G., 2012. Antifungal activity and action mode of pinocembrin from propolis against *Penicillium italicum*. *Food Sci Biotechnol* 21 (6), 1533–1539. <https://doi.org/10.1007/s10068-012-0204-0>.
- Piccinelli, A.L., Lotti, C., Campone, L., Cuesta-Rubio, O., Campo Fernandez, M., Rastrelli, L., 2011. Cuban and Brazilian red propolis: Botanical origin and comparative analysis by high-performance liquid chromatography–photodiode array detection/electrospray ionization tandem mass spectrometry. *J. Agric. Food Chem.* 59, 6484–6491. <https://doi.org/10.1021/jf201280z>.
- Piccinelli, A.L., Mencherini, T., Celano, R., Mouhoubi, Z., Tamendjari, A., Aquino, R.P., Rastrelli, L., 2013. Chemical composition and antioxidant activity of Algerian propolis. *J. Agric. Food Chem.* 61 (21), 5080–5088. <https://doi.org/10.1021/jf400779w>.
- Popova, M., Dimitrova, R., Al-Lawati, H.T., Tsvetkova, I., Najdenski, H., Bankova, V., 2013. Omani propolis: chemical profiling, antibacterial activity and new propolis plant sources. *Chemistry Central Journal* 7, 158. <https://doi.org/10.1186/1752-153X-7-158>.
- Popova, M., Trusheva, B., Cutajar, S., Antonova, D., Mifsud, D., Farrugia, C., Bankova, V., 2012. Identification of the plant origin of the botanical biomarkers of Mediterranean type propolis. *Natural Product Communications* 7, 1934578X1200700. <https://doi.org/10.1177/1934578X1200700505>.
- Popova, M.P., Bankova, V.S., Bogdanov, S., Tsvetkova, I., Naydenski, C., Marazzan, G. L., Sabatini, A.-G., 2007. Chemical characteristics of poplar type propolis of different geographic origin. *Apidologie* 38, 306–306. <https://doi.org/10.1051/apido:2007013>.
- Popova, M.P., Graikou, K., Chinou, I., Bankova, V.S., 2010. GC-MS profiling of diterpene compounds in Mediterranean propolis from Greece. *J. Agric. Food Chem.* 58 (5), 3167–3176. <https://doi.org/10.1021/jf903841k>.
- Przybyłek, I., Karpiński, T.M., 2019. Antibacterial properties of propolis. *Molecules* 24, 2047. <https://doi.org/10.3390/molecules24112047>.
- Rasul, A., Millimouno, F.M., Ali Eltayb, W., Ali, M., Li, J., Li, X., 2013. Pinocembrin: A novel natural compound with versatile pharmacological and biological activities. *BioMed Research International* 2013, 1–9. <https://doi.org/10.1155/2013/379850>.
- Raybaudi-Massilia, R.M., Mosqueda-Melgar, J., Martín-Belloso, O., 2009. Antimicrobial activity of malic acid against *Listeria monocytogenes*, *Salmonella* Enteritidis and *Escherichia coli* O157:H7 in apple, pear and melon juices. *Food Control* 20 (2), 105–112. <https://doi.org/10.1016/j.foodcont.2008.02.009>.
- Regueira, M.S., Tintino, S.R., da Silva, A.R.P., Costa, M.d.S., Boligon, A.A., Matias, E.F.F., de Queiroz Balbino, V., Menezes, I.R.A., Melo Coutinho, H.D., 2017. Seasonal variation of Brazilian red propolis: Antibacterial activity, synergistic effect and phytochemical screening. *Food and Chemical Toxicology* 107, 572–580. <https://doi.org/10.1016/j.fct.2017.03.052>.
- Ristivojević, P., Stević, T., Starović, M., Pavlović, Š., Özcan, M.M., Berić, T., Dimkić, I., 2020. Phenolic composition and biological activities of geographically different type of propolis and black cottonwood resins against oral streptococci, vaginal microbiota and phytopathogenic *Fusarium* species. *Journal of Applied Microbiology* 129 (2), 296–310. <https://doi.org/10.1111/jam.14633>.
- Ristivojević, P., Trifković, J., Andrić, F., Milojković-Opsenica, D., 2015. Poplar-type propolis: Chemical composition, botanical origin and biological activity. *Natural Product Communications* 10, 1934578X1501001. <https://doi.org/10.1177/1934578X1501001117>.
- Roberto, M.M., Jamal, C.M., Malaspina, O., Marin-Morales, M.A., 2016. Antigenotoxicity and antimutagenicity of ethanolic extracts of Brazilian green propolis and its main botanical source determined by the *Allium cepa* test system. *Genet. Mol. Biol.* 39, 257–269. <https://doi.org/10.1590/1678-4685-gmb-2015-0130>.
- Rojczyk, E., Klama-Baryła, A., Łabuś, W., Wilemska-Kucharzewska, K., Kucharzewski, M., 2020. Historical and modern research on propolis and its application in wound healing and other fields of medicine and contributions by Polish studies. *Journal of Ethnopharmacology* 262, 113159. <https://doi.org/10.1016/j.jep.2020.113159>.
- Rufatto, L.C., dos Santos, D.A., Marinho, F., Henriques, J.A.P., Roesch Ely, M., Moura, S., 2017. Red propolis: Chemical composition and pharmacological activity. *Asian Pacific Journal of Tropical Biomedicine* 7 (7), 591–598. <https://doi.org/10.1016/j.apjtb.2017.06.009>.
- Rufatto, L.C., Luchtenberg, P., Garcia, C., Thomassigny, C., Bouttier, S., Henriques, J.A.P., Roesch-Ely, M., Dumas, F., Moura, S., 2018. Brazilian red propolis: Chemical composition and antibacterial activity determined using bioguided fractionation. *Microbiological Research* 214, 74–82. <https://doi.org/10.1016/j.micres.2018.05.003>.
- Seetharaman, P., Gnanasekar, S., Chandrasekaran, R., Chandrakasan, G., Kadarkarai, M., Sivaperambal, S., 2017. Isolation and characterization of anticancer flavone chrysin (5,7-dihydroxy flavone)-producing endophytic fungi from *Passiflora incarnata* L. leaves. *Ann Microbiol* 67 (4), 321–331. <https://doi.org/10.1007/s13213-017-1263-5>.

- Silva, B.B., Rosalen, P.L., Cury, J.A., Ikegaki, M., Souza, V.C., Esteves, A., Alencar, S.M., 2008. Chemical composition and botanical origin of red propolis, a new type of Brazilian propolis. *Evidence-Based Complementary and Alternative Medicine* 5 (3), 313–316. <https://doi.org/10.1093/ecam/nem059>.
- Silva, F.R.G., Matias, T.M.S., Souza, L.I.O., Matos-Rocha, T.J., Fonseca, S.A., Mousinho, K.C., Santos, A.F., 2019. Phytochemical screening and in vitro antibacterial, antifungal, antioxidant and antitumor activities of the red propolis Alagoas. *Braz. J. Biol.* 79, 452–459. <https://doi.org/10.1590/1519-6984.182959>.
- Silva-Carvalho, R., Baltazar, F., Almeida-Aguiar, C., 2015. Propolis: A complex natural product with a plethora of biological activities that can be explored for drug development. *Evidence-Based Complementary and Alternative Medicine* 2015, 1–29. <https://doi.org/10.1155/2015/206439>.
- Siqueira, A.B.S., Rodriguez, L.R.N.d.A., Santos, R.K.B., Marinho, R.R.B., Abreu, S., Peixoto, R.F., Gurgel, B.C.d.V., 2015. Antifungal activity of propolis against *Candida* species isolated from cases of chronic periodontitis. *Braz. oral res.* 29 (1), 1–6. <https://doi.org/10.1590/1807-3107BOR-2015.vol29.0083>.
- Siriwong, S., Teethaisong, Y., Thumanu, K., Dunkhunthod, B., Eumkeb, G., 2016. The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant *Staphylococcus epidermidis*. *BMC Pharmacol Toxicol* 17, 39. <https://doi.org/10.1186/s40360-016-0083-8>.
- Spagnuolo, C., Russo, G.L., Orhan, I.E., Habtemariam, S., Daglia, M., Sureda, A., Nabavi, S.F., Devi, K.P., Loizzo, M.R., Tundis, R., Nabavi, S.M., 2015. Genistein and cancer: Current status, challenges, and future directions. *Advances in Nutrition* 6, 408–419. <https://doi.org/10.3945/an.114.008052>.
- Šturm, L., Ulrih, N.P., 2019. Advances in the Propolis Chemical Composition between 2013 and 2018. A Review. *eFood* 1, 24–37. <https://doi.org/10.2991/efood.k.191029.001>.
- Suresh Babu, K., Hari Babu, T., Srinivas, P.V., Hara Kishore, K., Murthy, U.S.N., Rao, J. M., 2006. Synthesis and biological evaluation of novel C (7) modified chrysin analogues as antibacterial agents. *Bioorganic & Medicinal Chemistry Letters* 16 (1), 221–224. <https://doi.org/10.1016/j.bmcl.2005.09.009>.
- Talla, E., Tamfu, A.N., Gade, I.S., Yanda, L., Mbafor, J.T., Laurent, S., Elst, L.V., Popova, M., Bankova, V., 2017. New mono-ether of glycerol and triterpenes with DPPH radical scavenging activity from Cameroonian propolis. *Natural Product Research* 31 (12), 1379–1389. <https://doi.org/10.1080/14786419.2016.1253077>.
- Tiveron, A.P., Rosalen, P.L., Franchin, M., Lacerda, R.C.C., Bueno-Silva, B., Benso, B., Denny, C., Ikegaki, M., de Alencar, S.M., 2016. Chemical characterization and antioxidant, antimicrobial, and anti-inflammatory activities of South Brazilian organic oropolis. *PLoS ONE* 11, <https://doi.org/10.1371/journal.pone.0165588>.
- Todd, O.A., Peters, B.M., 2019. *Candida albicans* and *Staphylococcus aureus* Pathogenicity and Polymicrobial Interactions: Lessons beyond Koch's Postulates. *JoF* 5, 81. <https://doi.org/10.3390/jof5030081>.
- 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 Complementary and Alternative Medicine* 2013, 1–13. <https://doi.org/10.1155/2013/697390>.
- Torres, A.R., Sandjo, L.P., Friedemann, M.T., Tomazzoli, M.M., Maraschin, M., Mello, C.F., Santos, A.R.S., 2018. Chemical characterization, antioxidant and antimicrobial activity of propolis obtained from *Melipona quadrifasciata* *quadrifasciata* and *Tetragonisca angustula* stingless bees. *Braz J Med Biol Res* 51, <https://doi.org/10.1590/1414-431x20187118> e7118.
- Tundis, R., Frattaruolo, L., Carullo, G., Armentano, B., Badolato, M., Loizzo, M.R., Aiello, F., Cappello, A.R., 2019. An ancient remedial repurposing: synthesis of new pinocembrin fatty acid acyl derivatives as potential antimicrobial/anti-inflammatory agents. *Natural Product Research* 33 (2), 162–168. <https://doi.org/10.1080/14786419.2018.1440224>.
- Uzel, A., Sorkun, K., Öncü, Ö., Çoğulu, D., Gençay, Ö., Salih, B., 2005. Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. *Microbiological Research* 160, 189–195. <https://doi.org/10.1016/j.micres.2005.01.002>.
- Vanden Braber, N.L., Novotny Nuñez, I., Bohl, L., Porporatto, C., Nazar, F.N., Montenegro, M.A., Correa, S.G., 2018. Soy genistein administered in soluble chitosan microcapsules maintains antioxidant activity and limits intestinal inflammation. *The Journal of Nutritional Biochemistry* 62, 50–58. <https://doi.org/10.1016/j.jnutbio.2018.08.009>.
- Vardar-Ünlü, G., Silici, S., Ünlü, M., 2008. Composition and in vitro antimicrobial activity of populus buds and poplar-type propolis. *World J Microbiol Biotechnol* 24, 1011–1017. <https://doi.org/10.1007/s11274-007-9566-5>.
- Velikova, M., Bankova, V., Sorkun, K., Houcine, S., Tsvetkova, I., Kujumgiev, A., 2000. Propolis from the Mediterranean Region: Chemical Composition and Antimicrobial Activity. *Zeitschrift für Naturforschung C* 55, 790–793. <https://doi.org/10.1515/znc-2000-9-1019>.
- Volpi, N., Bergonzini, G., 2006. Analysis of flavonoids from propolis by on-line HPLC–electrospray mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis* 42 (3), 354–361. <https://doi.org/10.1016/j.jpba.2006.04.017>.
- Wagh, V.D., 2013. Propolis: A wonder bees product and its pharmacological potentials. *Advances in Pharmacological Sciences* 2013, 1–11. <https://doi.org/10.1155/2013/308249>.
- Wang, K., Zhang, J., Ping, S., Ma, Q., Chen, X., Xuan, H., Shi, J., Zhang, C., Hu, F., 2014. Anti-inflammatory effects of ethanol extracts of Chinese propolis and buds from poplar (*Populus×canadensis*). *Journal of Ethnopharmacology* 155 (1), 300–311. <https://doi.org/10.1016/j.jep.2014.05.037>.
- Wojtyczka, R., Dziedzic, A., Idzik, D., Kępa, M., Kubina, R., Kabała-Dzik, A., Smoleń-Dzirba, J., Stojko, J., Sajewicz, M., Wąsik, T., 2013a. Susceptibility of *Staphylococcus aureus* clinical isolates to propolis extract alone or in combination with antimicrobial drugs. *Molecules* 18, 9623–9640. <https://doi.org/10.3390/molecules18089623>.
- Wojtyczka, R., Kępa, M., Idzik, D., Kubina, R., Kabała-Dzik, A., Dziedzic, A., Wąsik, T.J., 2013b. In vitro antimicrobial activity of ethanolic extract of Polish propolis against biofilm forming *Staphylococcus epidermidis* strains. *Evidence-Based Complementary and Alternative Medicine* 2013, 1–11. <https://doi.org/10.1155/2013/590703>.