


REVIEW

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# Propolis: An update on its chemistry and pharmacological applications

Rajib Hossain<sup>1</sup>, Cristina Quispe<sup>2</sup>, Rasel Ahmed Khan<sup>3</sup>, Abu Saim Mohammad Saikat<sup>4</sup>, Pranta Ray<sup>5</sup>, Damira Ongalbek<sup>6</sup>, Balakyz Yeskaliyeva<sup>6</sup>, Divya Jain<sup>7</sup>, Antonella Smeriglio<sup>8\*</sup>, Domenico Trombetta<sup>8</sup>, Roghayeh Kiani<sup>9\*</sup>, Farzad Kobarfard<sup>10,11</sup>, Naheed Mojangi<sup>12</sup>, Parvaneh Saffarian<sup>9</sup>, Seyed Abdulmajid Ayatollahi<sup>10,13</sup>, Chandan Sarkar<sup>1</sup>, Mohammad Torequl Islam<sup>1</sup>, Dilhun Keriman<sup>14</sup>, Arserim Uçar<sup>14\*</sup>, Miquel Martorell<sup>15,16\*</sup>, Antoni Sureda<sup>17</sup>, Gianfranco Pintus<sup>18,19</sup>, Monica Butnariu<sup>20</sup>, Javad Sharifi-Rad<sup>10\*</sup>  and William C. Cho<sup>21\*</sup>

## Abstract

Propolis, a resinous substance produced by honeybees from various plant sources, has been used for thousands of years in traditional medicine for several purposes all over the world. The precise composition of propolis varies according to plant source, seasons harvesting, geography, type of bee flora, climate changes, and honeybee species at the site of collection. This apinary product has broad clinical applications such as antioxidant, anti-inflammatory, antimicrobial, anticancer, analgesic, antidepressant, and anxiolytic as well as immunomodulatory effects. It is also well known from traditional uses in treating purulent disorders, improving the wound healing, and alleviating many of the related discomforts. Even if its use was already widespread since ancient times, after the First and Second World War, it has grown even more as well as the studies to identify its chemical and pharmacological features, allowing to discriminate the qualities of propolis in terms of the chemical profile and relative biological activity based on the geographic place of origin. Recently, several *in vitro* and *in vivo* studies have been carried out and new insights into the pharmaceutical prospects of this bee product in the management of different disorders, have been highlighted. Specifically, the available literature confirms the efficacy of propolis and its bioactive compounds in the reduction of cancer progression, inhibition of bacterial and viral infections as well as mitigation of parasitic-related symptoms, paving the way to the

\*Correspondence: antonella.smeriglio@unime.it; t.kiani2020@yahoo.com; kerimanarserim@gmail.com; mmartorell@udec.cl; javad.sharifirad@gmail.com; chocs@ha.org.hk

<sup>8</sup> Department of Chemical, Biological, Pharmaceutical and Environmental Sciences (ChiBioFarAm), University of Messina, Viale Ferdinando Stagno d'Alcontres 31, 98166 Messina, Italy

<sup>9</sup> Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

<sup>10</sup> Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>14</sup> Food Processing Department, Vocational School of Technical Sciences, Bingöl University, Bingöl, Turkey

<sup>15</sup> Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción, Chile

<sup>21</sup> Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong

Full list of author information is available at the end of the article



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use of propolis as an alternative approach to improve the human health. However, a more conscious use of propolis in terms of standardized extracts as well as new clinical studies are needed to substantiate these health claims.

**Keywords:** Anticancer, Antioxidant, Anti-inflammatory, Bee glue, Bioactive compounds, Food preservative

## Introduction

The name "propolis" derives from two terms of Greek origin, "pro" and "polis", which literally mean "in favor of the city" [1]. In fact, propolis, which is a sticky, gummy, and balsamic material collected from plants, is used by bees (*Apis mellifera* L.) to coat the hive and protect it from diseases caused by fungi, yeast, and bacteria as well as from predators [2]. In particular, propolis derives from a resin that is found mainly in the buds and bark of poplars, birches and conifers in general. The foraging bees collect these resins obtaining a mixture of resinous substances, pollen, waxes, and enzymes [3, 4]. Propolis is commonly employed by bees as building material and sealer [5] by maintaining homeostasis, reducing vibrations, keeping airflow, defend the colony against squatters, and prevent putrefaction [6]. It consists of granules of various sizes and shades of color (yellow, red, and dark brown) depending on its botanical source, while its smell is strongly aromatic [7]. Its consistency is hard and crumbly in nature, but as soon as it is handled and slightly heated, it becomes viscous and sticky, melting at temperatures around 70 °C [8].

Propolis has been the topic of several research conducted around the world in recent decades, and its chemical composition and biological properties have been widely explored [9–15]. The most common uses of propolis are as immunostimulant, as an aid to prevent colds thanks to its antibacterial and antiviral action, as a natural remedy in case of skin problems due to its soothing and healing effect, also in the oral cavity to treat small ulcers and canker sores, to relieve redness and itching of the urinary tract and finally to restore the balance of the gastric mucosa [16–18].

Recently, some mechanisms of action have been suggested paving the way to new clinical applications. The aim of this study is to provide a comprehensive review of these recent findings, discussing the current state of propolis research as well as the future prospectives.

## History of propolis

In the long and rich history of human beekeeping, apiary products have been widely used due to their recognized beneficial properties. In particular, the traditional use of propolis is known since 300 B.C. The Egyptians worshiped the bee and used propolis in the mummification process [19]. It was also well known to the priests who, at that time, monopolized medicine and chemistry [1]. Bees

played an essential role in Greek and Roman religious traditions assuming many symbolic meanings and being featuring in many stories of the Greek and Roman gods. Among them, one tells of Zeus (Jupiter for Romans), who, to escape his father, the god Cronus, was hidden in a secret cave by his mother and fed thanks to the honey of the sacred bees. Probably due to this story, one of Zeus' names was "*Melissaaios*", or "bee-man". According to this legend, it was Zeus himself, who gave the bees their bright gold color and to made them strong enough to withstand the cold and winds.

In traditional Georgian medicine, some ailments were treated using propolis ointments. There was also the custom of putting a propolis cake on the navel of the newborn. During the Anglo-Boer War [2] and World War II, doctors used propolis to heal wounds efficiently. Finally, in the USRR, the orthodox medicine recognized the therapeutic use of propolis (30% alcohol solution) already in 1969 [20]. Propolis was a key component in the Greek fragrance polyanthus, which included propolis, olibanum, styrax, and fragrant plants [21]. It has been extolled by more than 15 Greek and Roman writers (beside honey and wax) such as Aristotele in its "*Historia Animalium*" and Hippocrates, who is known to have employed propolis to treat wounds and ulcers [21]. Moreover, Dioscorides, in his main book "*De materia Medica*", outlined the medicinal applications of propolis, by citing also honey, wax, and different honey wines as medicines [22]. The bee and propolis were likewise highly esteemed by the Romans. Just think of Pliny the Elder, who discussed it, enhancing its multiple therapeutic applications as purifying agent, tumors dispersant, calming agent for tendon pains and for its healing properties [23].

## Traditional uses

Propolis has long been used as a bactericidal, antiviral, and antifungal drug in folk medicine to treat inflammations in several body areas worldwide [24]. It was used for skin regeneration, wound healing, and as local anesthetic and, in this sense, it was found in nearly all home first-aid kits [25]. Propolis has also been advised in folk medicine for the treatment of purulent disorders, as it has been shown to improve wound healing and relieve many types of discomfort. Craftsmen utilized propolis also for no-health purposes such as windows sealer, impregnant for valuable timber objects, varnish and repairing instrument [26]. The alternative and complementary medicine

used different propolis-based preparations such as sprays, ointments, and powders (mainly consisting of tinctures and ethanolic extracts) for the treatment of colds, flu, bronchial asthma, and other human ailments [27] such as gastric disorders [28]. Moreover, propolis is still used as an active substance in some dietary supplements, cosmetics, and even medicinal sweets. Unlike honey and bee pollen, it has no nutritional value, but exerts a very strong and multidirectional biotic effect [29]. Propolis has recently become popular in food and beverages as a way to boost health and prevent illness [30, 31]. It is still used to treat wounds and burns, as well as sore throats, dental caries, and stomach ulcers [32]. For years, propolis ethanolic extract has been known to have anti-inflammatory properties and used as an immunomodulatory agent [24, 33]. It can be used for various purposes in endodontics and would have a promising role in dentistry [28]. Researchers used nanoparticles to test the usage of propolis for various purposes. The use of nanoparticle-based delivery methods has the potential to make hydrophobic compounds like propolis dispersible in aqueous media, avoiding the problems associated with poor solubility [34].

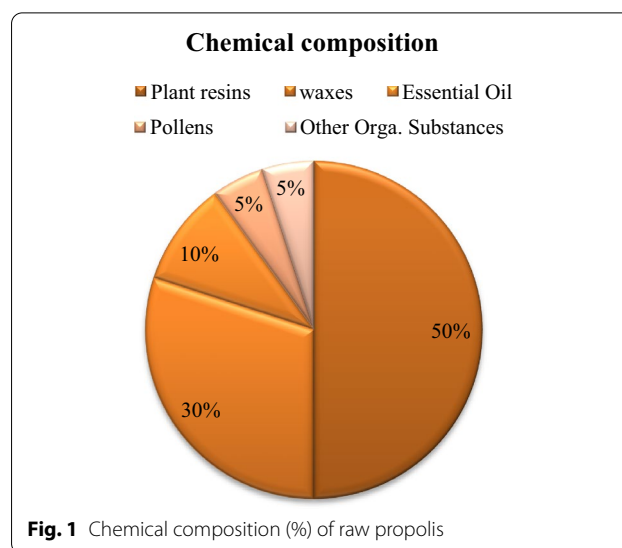
### Chemical composition and physical properties

It is well-known that a medicinal plant demonstrates a pharmacological effect thanks to its chemical constituents. Raw propolis contains not only plant resins, but also waxes, essential oil, pollens, and other organic substance in different percentage as depicted in Fig. 1. Thanks to this multitude of components, it consists of a rather complex chemical profile as reported in Table 1. Many studies reported that propolis contains, in particular, phenolic acids, flavonoids, ketones, aldehydes, chalcones, dihydrochalcones, terpenoids, amino acids, aliphatic acids, aromatic esters and acids, carbohydrates, vitamins, metals, and also beeswax [35–40].

The color and melting point of propolis varies according to area and the plant source [4]. Propolis melts on 60 °C to 70 °C while some of its kinds melt on 100 °C [4, 26]. Ethanol is the best suitable solvent to obtain commercially extracts of propolis but is also used methanol, chloroform, ether and acetone [4, 26, 41].

### Compounds isolated from propolis

According to literature up to now about 300 different chemicals components have been determined in propolis of different sources [4, 9, 42–44]. Moreover, the major chemical constituents are varied in amount and type and depend on the extraction process associated with the extraction solvents. Recently, Bankova et al. [45] reviewed classical and modern methods of extraction of propolis such as maceration, Soxhlet, ultrasound-assisted



and microwave-assisted extraction, supercritical CO<sub>2</sub> extraction, high-pressure methods, and the application of different solvents. The authors concluded that ultrasound-assisted extraction is the best optimal method, considering into account extraction time and extraction yield, and concerning the solvents, mixtures of water and ethanol are most effective.

Propolis has a very rich and complex chemical composition, which varies according to several parameters such as plant source, seasons harvesting, geography, type of bee flora, climate changes, and honey bee species at the collection site [15, 44, 46, 47]. Indeed, more than 300 different compounds have been isolated and identified from this natural product. Many studies conducted on various propolis samples have shown that the main secondary metabolites are phenolic substances, especially flavonoids, belonging to different sub-classes such as flavanones, flavones, flavonols and dihydroflavonols, which constitute more than 50% of the propolis weight [4, 9, 42–44]. These compounds, generally present in the plant kingdom as glycosides, are mostly present in propolis as aglycones, probably due to the action of bees'enzymes (glucosidase) during harvesting and transport. Other phenolic compounds found abundantly in propolis are hydroquinones, caffeic acids and related esters and phenolic aldehydes [48]. Propolis has also proved to be a rich source of essential elements such as magnesium, nickel, calcium, iron, zinc, cesium, manganese, silver, copper, aluminum, vanadium, vitamins B, C and E [49], as well as amino acids [50]. In addition, in propolis, some non-phenolic substances belonging to different classes such as aliphatic acids, coumarins, aliphatic and aromatic hydrocarbons, terpenoids, steroids and isoprenylated benzophenones, have also been found. The chemical

**Table 1** Chemical composition of raw propolis

Class	Compounds
Alcohols	Benzene methanol, cinnamyl alcohol, glycerol; <i>a</i> -glycerophosphate; hydroquinone; isobutenol, phenethyl alcohol; prenyl alcohol [176, 177, 353]
Aldehydes	Benzaldehyde; caproialdehyde; <i>p</i> -hydroxybenzaldehyde; isovanillin; protocatechuic aldehyde; vanillin [176, 353–356]
Aliphatic acids and aliphatic esters	Acetic acid; angelic acid; butyric acid; crotonic acid; fumaric acid; isobutyric acid; methylbutyric acid; isobutyl acetate; isopentyl acetate; isopentenyl acetate [176]
Amino acids	Alanine; $\beta$ -alanine; $\alpha$ -aminobutyric acid; 6-aminobutyric acid; arginine; asparagine; aspartic acid; cysteine; glutamic acid; glycine; histidine; hydroxyproline; isoleucine; leucine, lysine; methionine; ornithine; phenylalanine; proline; pyroglutamic acid, sarcosine; serine; threonine, tryptophan; tyrosine; valine [49, 50, 176, 357]
Aromatic acid	<i>p</i> -Anisic acid; benzoic acid; caffeic acid; cinnamic acid; coumaric ( <i>-o,m,p</i> ) acid; 3,4-dimethoxycinnamic acid; ferulic acid; gallic acid; gentisic acid; hydroxycinnamic acid; <i>p</i> -hydroxybenzoic acid; isoferulic acid; 4-methoxycinnamic acid; protocatechuic acid; salicylic acid; vanillic acid; veratric acid [176, 177, 353–356, 358, 359]
Aromatic esters	Benzyl acetate, benzyl benzoate, benzyl caffeate, benzyl coumarate; benzyl-3,4-dimethoxycinnamate; benzyl ferulate; benzyl isoferulate; benzyl salicylate; butenyl caffeate; butyl caffeate; cinnamyl benzoate; cinnamyl caffeate; butyl caffeate; cinnamyl coumarate; cinnamyl isoferulate; ethyl benzoate; ethyl caffeate; methyl benzoate; 2-methyl-2-butenyl caffeate; 3-methyl-2-butenyl caffeate; 3-methyl-3-butenyl caffeate; 3-methyl-3-butenyl coumarate; 3-methyl-2-butenyl ferulate; 3-methyl-3-butenyl ferulate; 2-methyl-2-butenyl isoferulate, 3-methyl-3-butenyl isoferulate; methyl salicylate; phenyl ethyl caffeate; phenyl ethylcoumarate; phenyl-ethyl isoferulate; pentyl caffeate; pentenyl caffeate, pentenyl ferulate; prenyl caffeate; prenyl coumarate; prenyl ferulate; prenyl isoferulate [176, 177, 353, 358, 359]
Chalcones and dihydrochalcones	Alpinetin chalcone; naringenin chalcone; pinobanksin chalcone, pinobanksin-3-acetate chalcone; pinocembrin chalcone; pinostrobin chalcone; sakuranetin chalcone; 2',4',6'-trihydroxy-4'-methoxychalcone; 2',6'-dihydroxy-4'-methyldihydrochalcone; 2',4',6'-trihydroxydihydrochalcone [176, 177, 353, 359]; 3,4,2',3'-tetrahydroxychalcone [360], isoliquiritigenin, 4,4'-dihydroxy-2'-methoxychalcone; 4,2',4'-alpha-tetrahydroxydihydrochalcone, 2',4'-dihydroxychalcone [361]
Flavanones	Naringenin; pinobanksin; pinobanksin-3-acetate; pinobanksin-3-butyrate; pinobanksin-3-hexanoate, pinobanksin-3-methyl ether; pinobanksin-3-pentanoate; pinobanksin-3-pentenoate; pinobanksin-3-propanoate; pinocembrin; pinostrobin; sakuranetin; 3,7-dihydroxy-5-methoxyt-lavanone; 2,5-dihydroxy-7-methoxyflavanone [49, 176, 177, 355, 359, 362–364]; 5,7-dihydroxy-6-methoxy-2,3-dihydroflavonol-3-acetate [365], 5-methoxy-3-hydroxyflavanone [366], (2 <i>R</i> , 3 <i>R</i> )-3,6,7-trihydroxyflavanone [367], alnustinol, (2 <i>R</i> ,3 <i>R</i> )-3,7-dihydroxy-6-methoxyflavanone, garbanzol, (2 <i>R</i> ,3 <i>R</i> )-3,7-dihydroxyflavanone, (2 <i>S</i> )-dihydrooroxylin A, (2 <i>S</i> )-dihydrobaicalein, (2 <i>S</i> )-nNaringenin, (2 <i>S</i> )-7-hydroxy-6-methoxyflavanone, (2 <i>S</i> )-liquiritigenin, (2 <i>S</i> )-7-hydroxyflavanone [361], sophoraflavanone A, solophenol A, bonannione A [368], sigmoidin B, propolin E, propolin B, propolin A [369], 5,7,3',4'-tetrahydroxy-2'-C-geranyl-6-prenylflavanone, 5,7,3',4'-tetrahydroxy-2'-C-geranylflavanone, 5,7,3',4'-tetrahydroxy-6-C-geranylflavanone, 5,7,3',4'-tetrahydroxy-5'-C-geranylflavanone [48]; 3',4',6-trihydroxy-7-methoxy flavanone [367], (2 <i>R</i> ,3 <i>R</i> )-6[1-(4'-hydroxy-3'-methoxyphenyl) prop-2-en-1-yl]-pinobanksin-3-acetate, (2 <i>R</i> ,3 <i>R</i> )-6[1-(4'-hydroxy-3'-methoxyphenyl) prop-2-en-1-yl] pinobanksin [370], (2 <i>R</i> ,3 <i>R</i> )-3,5-dihydroxy-7-methoxyflavanone 3-(2-methyl)-butyrate [97]; 7- <i>O</i> -prenylpinocembrin, 7- <i>O</i> -prenylstrobopinin [371]; pinobanksin-5-methyl-ether-3- <i>O</i> -pentanoate, hesperitin-5,7-dimethyl ether [366], (2 <i>S</i> )-5,7-dihydroxy-4'-methoxy-8-prenylflavanone [368], 3- <i>O</i> -[( <i>S</i> )-2-methylbutyryl] pinobanksin [372]
Flavones and flavonols	Acacetin; apigenin; apigenin-7-methyl ether; chrysin, fisetin; galangin; galangin-3-methyl ether; izalpinin; isorhamnetin; kaempferide; kaempferol; kaempferol-3-methyl ether; kaempferol-7-methyl ether; kaempferol-7,4'-dimethyl ether; pectolinarigenin; quercetin; quercetin-3,7-dimethyl ether; ramnetin; ramnocitrin, tectocrisin [49, 176, 177, 353–356, 364]; luteolin [373]; 6-cinnamylchrysin [372]; 3',5-dihydroxy-4',7-dimethoxy flavones [374]; hexamethoxy flavones [375]; (7 <i>R</i> )-8-[1-(4'-hydroxy-3'-methoxyphenyl) prop-2-en-1-yl] chrysin [97]; (7 <i>R</i> )-8-[1-(4'-hydroxy-3'-methoxyphenyl)prop-2-en-1-yl]-galangin [97]; macarangin [376]; 2'-geranylquercetin, 8-(8'-hydroxy-3',8'-dimethyl-oct-2'-enyl)-quercetin, 2'-(8'-hydroxy-3',8'-dimethyl-oct-2'-enyl)-quercetin [368]
Isoflavones	4',7-dimethoxy-2'-isoflavonol, medicarpin, homopterocarpin, 7,4'-dihydroxyisoflavone [377], calycosin [361], 5,7-dihydroxy-4'-methoxyisoflavonoid, 7-hydroxy-4'-methoxyisoflavonoid [378], 7,3'-dihydroxy-6,5'-methoxyisoflavonoid, 6,7,3'-trihydroxy-4'-methoxyisoflavonoid, 7,3',4'-trihydroxy-5'-methoxyisoflavonoid, odoratin [367]; biochanin [379], (3 <i>R</i> )-4'-Methoxy-2',3,7-trihydroxyisoflavone, (3 <i>S</i> )-ferreirin, (3 <i>S</i> )-violanone, (3 <i>S</i> )-vestitone, 2'-hydroxybiochanin A, pratensein, biochanin A, xenognosin B, formononetin, daidzein [361]

**Table 1** (continued)

Class	Compounds
Flavans and Isoflavans	8-[( <i>E</i> )-4-phenylprop-2-en-1-one]-(2 <i>R</i> ,3 <i>S</i> )-2-(3,5-dihydroxyphenyl)-3,4-dihydro-2 <i>H</i> -2-benzopyran-5-methoxyl-3,7-diol, 8-[( <i>E</i> )-4-phenylprop-2-en-1-one]-(2 <i>S</i> ,3 <i>R</i> )-2-(3,5-dihydroxyphenyl)-3,4-dihydro-2 <i>H</i> -2-benzopyran-5-methoxyl-3,7-diol, 8-[( <i>E</i> )-4-phenylprop-2-en-1-one]-(2 <i>R</i> ,3 <i>S</i> )-2-(3-methoxyl-4-hydroxyphenyl)-3,4-dihydro-2 <i>H</i> -2-benzopyran-5-methoxyl-3,7-diol [380]; 3-hydroxy-5,6-dimethoxyflavan [381]; (3 <i>S</i> )-vestitol, (3 <i>S</i> )-isovestitol, (3 <i>S</i> )-7- <i>O</i> -methylvestitol, (3 <i>S</i> )-mucronulatol [361]; 7,4'-dihydroxy-2'-methoxyisoflavone [378]; neovestitol [379]
Open-chain neoflavonoids and other flavonoids	( <i>S</i> )-4-methoxydalbergione, ( <i>S</i> )-3,4'-dihydroxy-4-methoxydalbergione, ( <i>S</i> )-3'-hydroxy-4-methoxydalbergione [367], neoflavonoid 1–10 [382], ( <i>Z</i> )-1-(2'-methoxy-4',5'-dihydroxyphenyl)-2-(3-phenyl)propene, 1-(3',4'-dihydroxy-2'-methoxyphenyl)-3-(phenyl)propane [381], 2-(2,4'-dihydroxyphenyl)-3-methyl-6-methoxybenzofuran, 2,6-dihydroxy-2-[(4-hydroxyphenyl)methyl]-3-benzofuranone [361]
Hydrocarbon esters ethers, hydroxyl and keto waxes	Heneicosane; hentriacontane; heptacosane; hexacosane; nonacosane; pentacosane; tricosane; tripentacontane; tritriacontane; dotriacontyl hexadecanoate; dotriacontyl-[( <i>Z</i> )-octadec-9-enoate]; hexacosyl hexadecanoate; hexacosyl-[( <i>Z</i> )-octadec-9-enoate]; octacosylhexa decanoate; octacosyl-[( <i>Z</i> )-octadec-9-enoate] tetracosyl-hexadecanoate; tetracosyl-[( <i>Z</i> )-octadec-9-enoate]; tetratriacontyl-hexadecanoate tetratriacontyl-[( <i>Z</i> )-octadec-9-enoate]; triacontyl-hexadecanoate; triacontyl-[( <i>Z</i> )-octadec-9-enoate] [177, 353, 383, 384]
Pterocarpins (a type of neoflavonoid)	(6 <i>aR</i> ,11 <i>aR</i> )-4-methoxymedicarpin, 6 <i>a</i> -ethoxymedicarpin, 3,10-dihydroxy-9-methoxypterocarpan [361], 3,4-dihydroxy-9-methoxypterocarpan, 3-hydroxy-8,9-dimethoxypterocarpan, 3,8-dihydroxy-9-methoxypterocarpan, 4'-methoxy-5'-hydroxyvesticarpan, homopterocarpan, 4-hydroxy-medicarpin, medicarpin [378]
Fatty acids	Arachid acid; behenic acid; cerotic acid; lauric acid; linoleic acid; lignoceric acid; montanic acid; myristic acid; oleic acid; palmitic acids; stearic acid [177, 353, 359, 383]
Ketones	Acetophenone; <i>p</i> -acetophenolacetophenone; dihydroxy-acetophenone; methylacetophenone; hept-5-en-2-one; 6-methylketone [177, 353, 359]
Terpenoids and other compounds	$\alpha$ -Acetoxibetulenol; $\beta$ -bisabolol; 1,8-cineole; $\alpha$ -copaene; cymene; limonene; pterostilbene; styrene; xanthoreol; xylitol; naphthalene; 4-hexanolactone; sesquiterpene alcohol; sesquiterpene diol [49, 177, 353, 354, 363]; linalool [385], trans- $\beta$ -terpineol [386], camphor [387]; junipene [386], $\gamma$ -elemene, $\alpha$ -ylangene, valencene [385], 8- $\beta$ H-cedran-8-ol, 4- $\beta$ H,5 $\alpha$ -eremophil-1(10)-ene, $\alpha$ -bisabolol, $\alpha$ -eudesmol, $\alpha$ -cadinol [388], patchoulene, manoyl oxide, ferruginol, ferruginolone, 2-hydroxyferruginol, 6/7-hydroxyferruginol, semperviol, abietic acid, 18-succinyloxyabietadiene, 18-succinyloxyhydroxyabietatriene, 18-hydroxyabiet-8,11,13-triene, imbricataloic acid, diterpenic acid, neoabiatic acid, labda-8(17),12,13-triene, hydroxydehydroabiatic acid, dihydroxyabieta-8,11,13-triene, 13(14)-dehydrojunicedric acid, dehydroabiatic acid, 18-hydroxyabieta-8,11,13-triene [389], junicedric acid, 14,15-dinor-13-oxo-8(17)-labden-19-oic acid, tran-communal, palmitoyl isocupressic acid, oleoyl isocupressic acid, 13-hydroxy-8(17),14-labdadien-19-oic acid, 15-oxolabda-8(17),13( <i>E</i> )-dien-19-oic acid, pimaric acid, totarolone [390]; lupeol alkanooates, lupeol, 24-methylene-9,19-ciclolanostan-3 $\beta$ -ol [391], lupeol acetate, lanosterol, germanicol acetate, germanicol, $\beta$ -amyrin acetate, $\beta$ -amyron, $\alpha$ -amyrin acetate, $\alpha$ -amyron [392], lanosterol acetate [375], (2 <i>Z</i> ,2 <i>E</i> )-3-Oxocycloart-22,24-dien-26-oic acid, (2 <i>E</i> )-3-oxo-27,28-dihydroxycycloart-24-en-26-oic acid [393], 3,4-seco-cycloart-12-hydroxy-4(28),24-dien-3-oic acid, cycloart-3,7-dihydroxy-24-en-28-oic acid [390], 3-oxo-triterpenic acid methyl ester [394]; 2 <i>H</i> -cyclopentacyclo octene,4,5,6,7,8,9-hexahydro-1,2,2; 3-tetramethyl; germanicol; dimethyl-1,3,5,6-tetramethyl-[1,3-(1 <i>C</i> 2)] bicycle; dodeca-1,3,5,6,8,10-hexaene-9,10-dicarboxylate; spiro[benzo[ <i>a</i> ]cyclopenta [3, 4] cyclobuta[1,2- <i>c</i> ]cycloheptene-8(5 <i>H</i> ),2'-[1,3]dioxane]; 6,7,7 $\beta$ ,10 $\alpha$ -tetrahydro-1; 14-methyl-cholest-7-en-3-ol-15-one; (3 $\alpha$ ,4 $\alpha$ )- 4-methyl-stigmast-22-en-3-ol [28]
Lignans	Tetrahydrojusticidin B, 6-methoxydiphyllin, phyllamricin C [376]
Phenylpropanoids	<i>cis</i> -3-Methoxy-4-hydroxycinnamic acid, <i>trans</i> -3-methoxy-4-hydroxycinnamic acid [395]; 3-prenyl cinnamic acid allyl ester, <i>p</i> -methoxycinnamic acid, dihydrocinnamic acid, 3-methyl-2-butenyl isoferulate, 3-methyl-3-butenyl caffeate, hexadecyl caffeate [396]; 3-prenyl-4-hydroxycinnamic acid, 3,5-diprenyl-4-hydroxycinnamic acid [397]; methyl( <i>E</i> )-4-(4'-hydroxy-3'-methylbut-( <i>E</i> )-2'-enyloxy) cinnamate [398]; tetradecenyl caffeate (isomer), tetradecenyl caffeate [375]; 2-methyl-2-butenyl ferulate [48]
Chlorogenic acids	4-Feruloyl quinic acid [399]; 5-feruloyl quinic acid [373]; 3,4,5-tri- <i>O</i> -caffeoylquinic acid [400]
Stilbenes	5'-Farnesyl-3'-hydroxyresveratrol [368]; schweinfurthin A, B [376]; 5,4'-dihydroxy-3'-methoxy-3-prenyloxy- <i>E</i> -stilbene, 3,5,3',4'-tetrahydroxy-2-prenyl- <i>E</i> -stilbene, 3,5,4'-trihydroxy-3'-methoxy-2-prenyl- <i>E</i> -stilbene, 5,3',4'-trihydroxy-3-methoxy-2-prenyl- <i>E</i> -stilbene, 5,4'-dihydroxy-3,3'-dimethoxy-2-prenyl- <i>E</i> -stilbene, 5,4'-dihydroxy-3-prenyloxy- <i>E</i> -stilbene, 3,4'-dihydroxy- <i>E</i> -stilbene, 3,4'-dihydroxy-3,5-dimethoxy- <i>E</i> -stilbene, diprenylated dihydrostilbene, 3,5-dihydroxy-2-prenyl- <i>E</i> -stilbene, 4-prenyldihydroresveratrol, 3-prenylresveratrol [398]; (+)-pinoresinol dimethyl ether, (+)-pinoresinol, (+)-syringaresinol [361]

**Table 1** (continued)

Class	Compounds
Other phenolics	8-(Methyl-butanechromane)-6-propenoic acid, 3-hydroxy-2,2-dimethyl-8-prenylchromane-6-propenoic acid, 2,2-dimethyl-8-prenylchromene-6-propenoic acid, 2,2-dimethylchromene-6-propenoic acid, 2,2-dimethyl-6-carboxyethyl-2 <i>H</i> -1-benzopyran, 2,2-dimethyl-6-carboxyethyl-8-prenyl-2 <i>H</i> -1-benzopyran [401]; nemorosone, 7-epi-clusianone, xanthochymol, gambogone, hyperibone A [402]; 5-pentadecylresorcinol, 5-(8' <i>Z</i> ,11' <i>Z</i> -heptadecadienyl)-resorcinol, 5-(11' <i>Z</i> -heptadecenyl)-resorcinol, 5-heptadecylresorcinol [95]; 1,3-bis(trimethylsilyloxy)-5,5-proylbenzene, 3,4-dimethylthioquinoline, 4-oxo-2-thioxo-3-thiazolidinepropionic acid, D-glucofuranuronic acid, dofuranuronic acid, 3-quinolinecarboxamine [403], baccharin [20], suberosin, tschimgin, tschimganin, bornyl <i>p</i> -hydroxybenzoate, bornyl vanillate, ferutinin, teferin, ferutanol <i>p</i> -hydroxybenzoate, ferutanol vanillate [387]; 2-acetoxy-6- <i>p</i> -methoxybenzoyl jaeschkeanadiol, 2-acetoxy-6- <i>p</i> -hydroxybenzoyl jaeschkeanadiol [404]
Steroids	Calinasterol acetate; $\beta$ -dihydrofucosterol acetate; ucoosterol acetate; stigmasterol acetate [178]
Sugars	Fructofuranose-1; fructofuranose-2; $\alpha$ -D-glucopyranose; $\beta$ -D-glucopyranose [177, 353, 358]; galactitol, gluconic acid, galacturonic acid and 2-O-glycerylgalactose [394]

composition of propolis is closely related to the place of origin, the time of harvest and the plant source from which it derives, and it is for this reason it is difficult to achieve a univocal classification of the chemical substances and therapeutic properties of this natural product. Moreover, these remarkable qualitative-quantitative phytochemical differences related to its geographical distribution that diversify and characterize propolis, make it unique both from chemical and biological point of view. For example, Tunisian propolis is distinguished by the presence of characteristic methoxyylated flavonoids, such as quercetin 3,7,3'-trimethyl ether and myricetin 3,7,4',5' tetramethylether from *Cistus* spp., Cistaceae, leaf exudates [51], while a study carried out on New Zealand propolis has shown that hydroflavonoids such as pinocembrin and pinobanksin and make up about 70% of the total flavonoids from *Populus nigra* L., Salicaceae, bud exudates [52].

In the Uruguayan and the Chinese [53], however, these hydroflavonoids are present in less than 10%; while in Brazil they make up as much as 50% [49, 54, 55]. In the Chinese and Uruguayan varieties, the predominant flavonoids are substantially flavones and flavonols [53]. Extensive comparisons have been made on the chemical composition between propolis samples from Europe, South America and Asia [49], and from this point of view, it was possible to establish that European and Chinese propolis mainly abound in various species of flavonoids, phenolic acids and relative esters, while the predominant compounds of Brazilian propolis are terpenoids and prenylated derivatives of *p*-coumaric acid [49, 54, 55], such as artemillin C of Brazilian green propolis from the plant *Baccharis dracunculifolia* DC, Asteraceae, in southeastern and western-central Brazil [56, 57]. Therefore, there is a considerable difference between propolis originating in tropical areas (South America) with respect to those

of temperate areas (Europe). Indeed, the first one is characterized by substances with a hydroxycinnamic acid nucleus (C<sub>6</sub>-C<sub>3</sub> backbone), whereas in the second one the flavonoid (C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> backbone) composition predominates [49]. In Fig. 2, the 2D structures of the main isolated compounds from propolis were depicted, whereas the main compounds isolated from African, American, Australian and Asian propolis were reported in Tables 2, 3, 4, 5, and 6.

Propolis from Egypt reported to possess constituent of *P. nigra* and esters of caffeic acid and long-chain fatty alcohols including tetradecanol, hexadecanol and dodecanol [9]. Cuban propolis is mainly from *Clusia rosea* Jacq. and contains polyisoprenylated benzophenone which is distinct from both European and Brazilian propolis [2, 9]. Birch propolis from Russia contained flavonols and flavones from *Betula pendula* Roth. Anjum et al. [4].

### Analytical techniques

Each propolis type is characterized by the specific proportion of the dominant plant material. Various chromatographic techniques were used for evaluation of the botanical origin of propolis samples such as high performance thin-layer chromatography [58], high-performance liquid chromatography (HPLC) [59–61], gas chromatography-mass spectrometry (GC-MS) [62], capillary electrophoresis [63], microscopic techniques [64]. Furthermore, structure elucidation techniques such as direct analysis in real time (DART) mass spectrometry [52], nuclear magnetic resonance (NMR) [65], and infrared spectroscopy (IR) [66] have been applied to screen compositional differences between propolis samples supplied from various origins.

Using high-performance thin-layer chromatographic (HPTLC) fingerprinting analyses to explore the chemical composition of propolis, studies have confirmed the

Chrysin  $R^1=H, R^2=OH, R^3=H, R^4=H, R^5=H$

Galangin  $R^1=OH, R^2=OH, R^3=H, R^4=H, R^5=H$

Tectochrysin  $R^1=H, R^2=OCH_3, R^3=H, R^4=H, R^5=H$

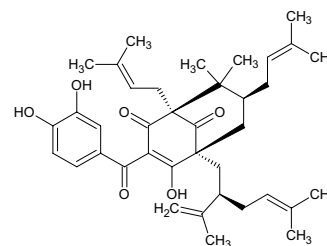
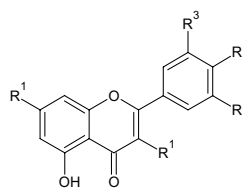
Apigenin  $R^1=H, R^2=OH, R^3=H, R^4=OH, R^5=H$

Kaempferol  $R^1=OH, R^2=OH, R^3=H, R^4=OH, R^5=H$

Isorhamnetin  $R^1=OH, R^2=OH, R^3=OCH_3, R^4=OH, R^5=H$

Luteolin  $R^1=H, R^2=OH, R^3=OH, R^4=OH, R^5=H$

Myricetin  $R^1=OH, R^2=OH, R^3=OH, R^4=OH, R^5=OH$

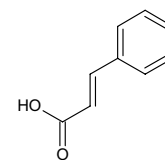
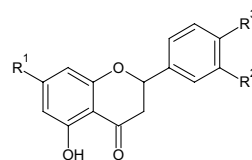


Xanthocymol

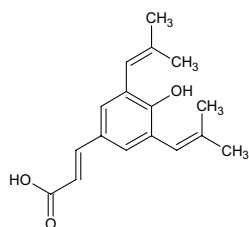
Pinocembrin  $R^1=OH, R^2=H, R^3=H$

Naringenin  $R^1=OH, R^2=OH, R^3=OH$

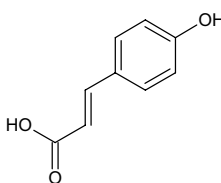
Hesperetin  $R^1=OH, R^2=OH, R^3=OCH_3$



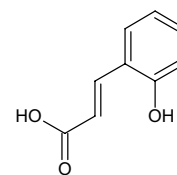
Cinnamic Acid



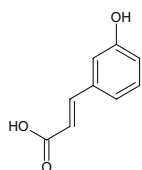
Artepillin C



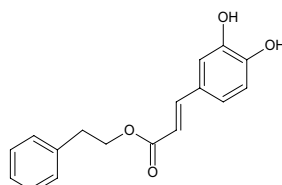
p-Coumaric ACid



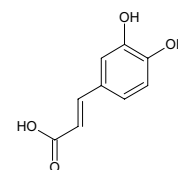
o-Coumaric ACid



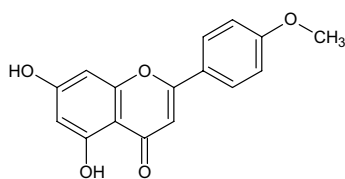
m-Coumaric Acid



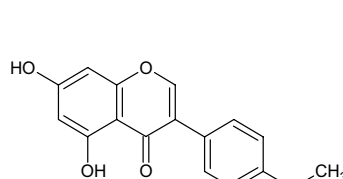
Caffeic Acid Phenylethyl ester (CAPE)



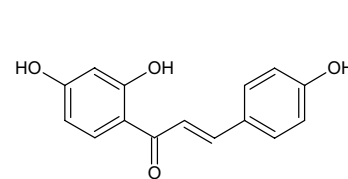
Caffeic Acid



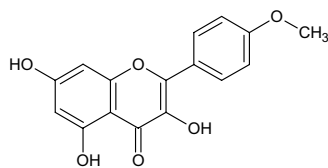
Acacetin



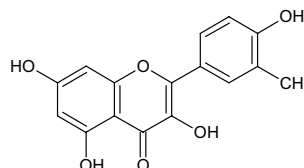
Biochanin A



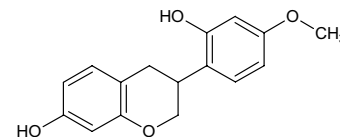
Isoliquiritigenin



Kaempferide



Quercetin



Vestitol

Fig. 2 Isolated compounds from propolis

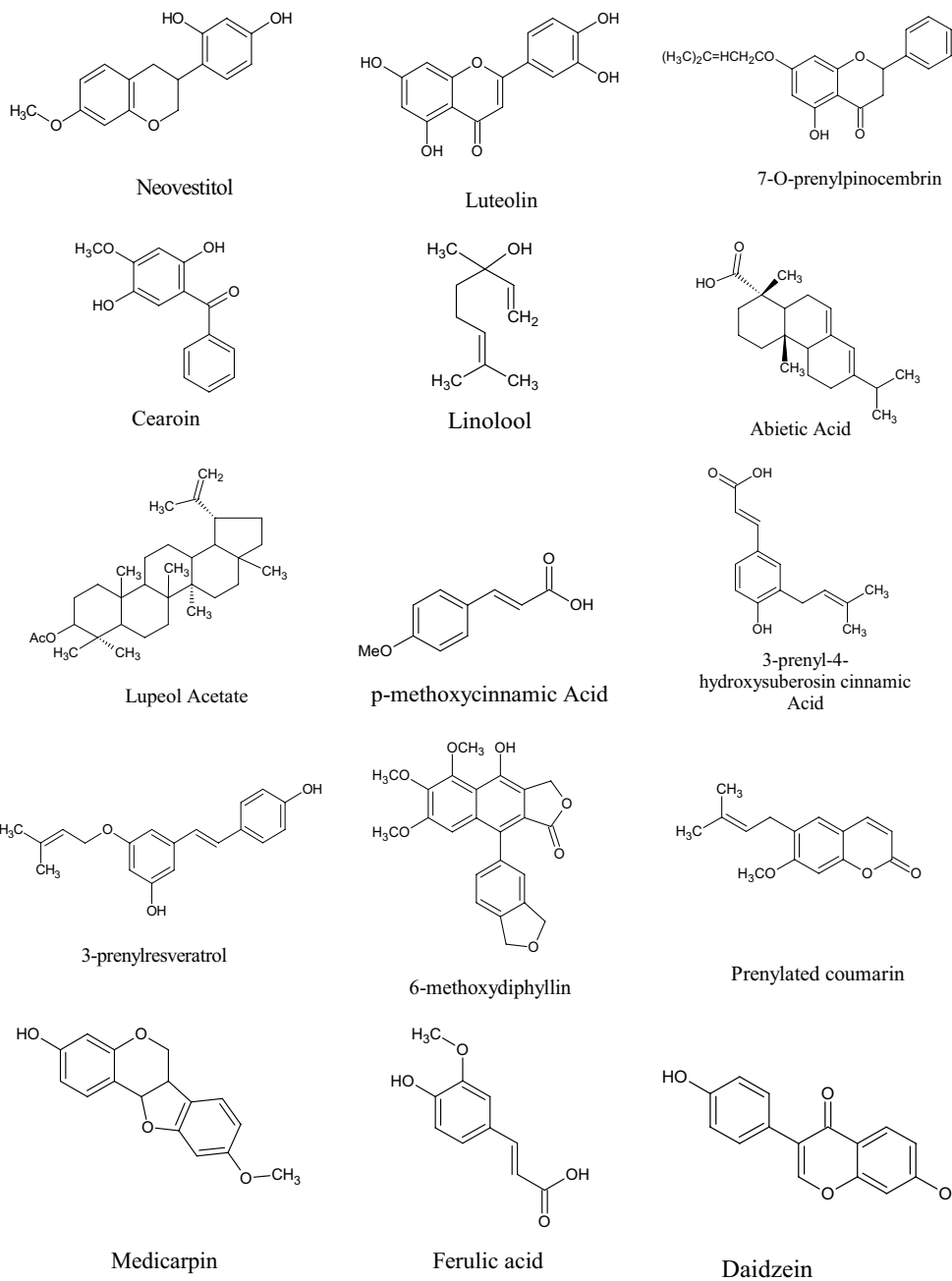


Fig. 2 continued



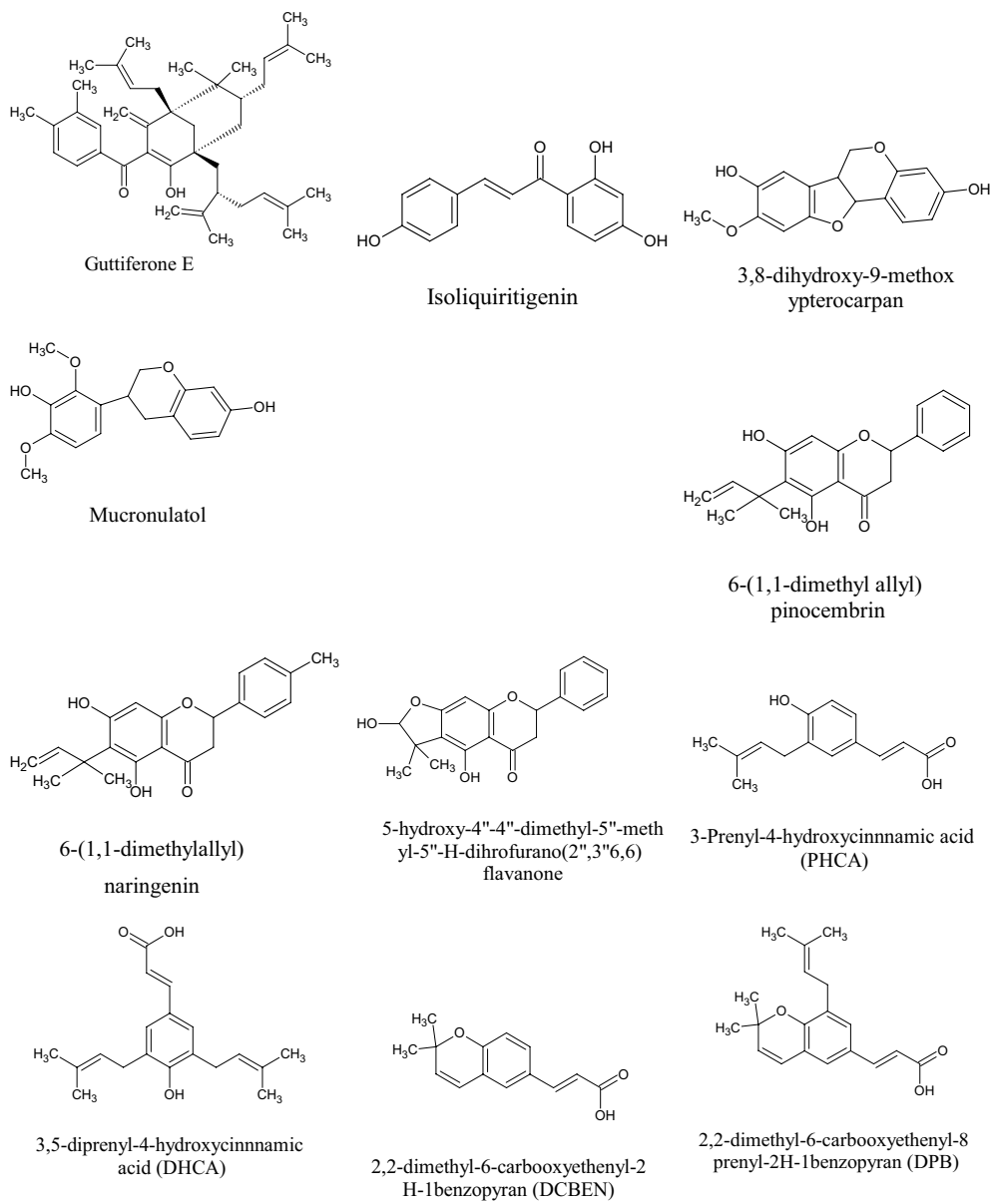
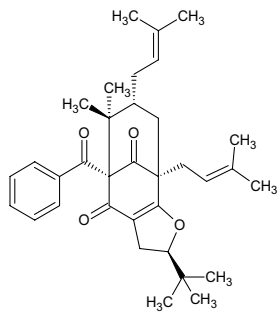
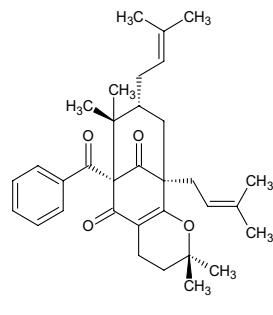


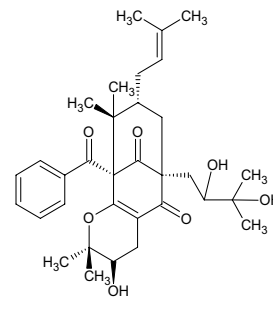
Fig. 2 continued



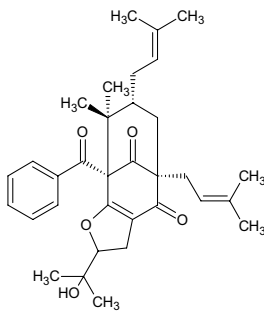
Hyperibone B



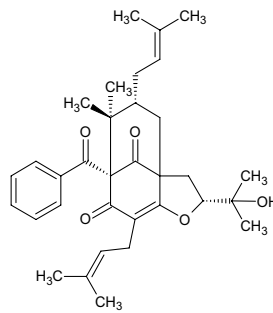
Propolone A



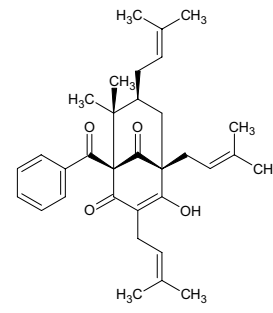
Propolone B



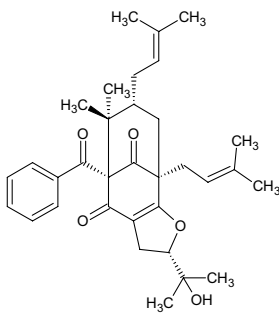
Propolone C



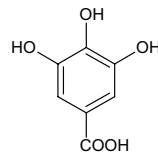
Propolone D



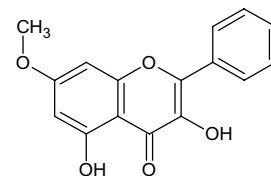
Nemorosone



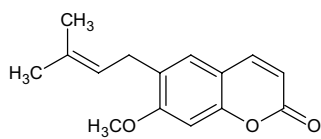
Garcinielliptone I



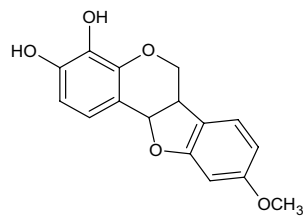
Gallic acid



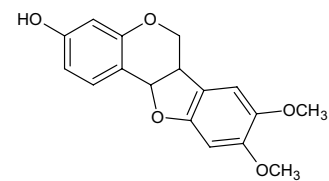
Izalpinin



Prenylated coumarin



(6aR,11aR)-3,4-Dihydroxy-9-methoxypterocarpan



(6aR,11aR)-3-Hydroxy-8,9-dimethoxypterocarpan

Fig. 2 continued

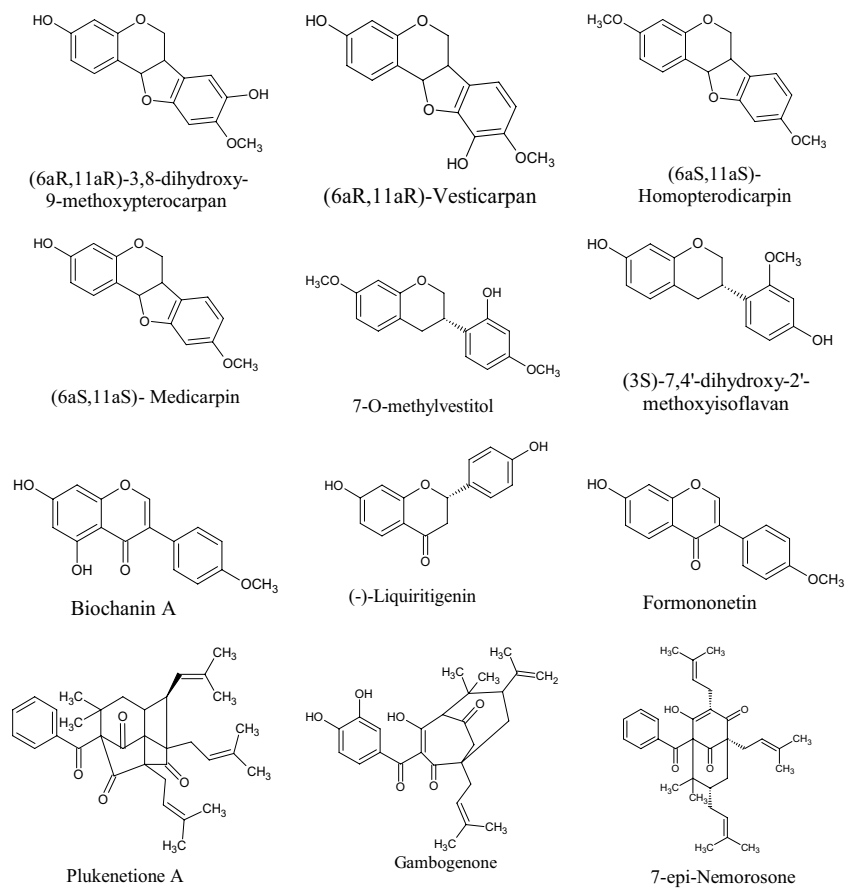


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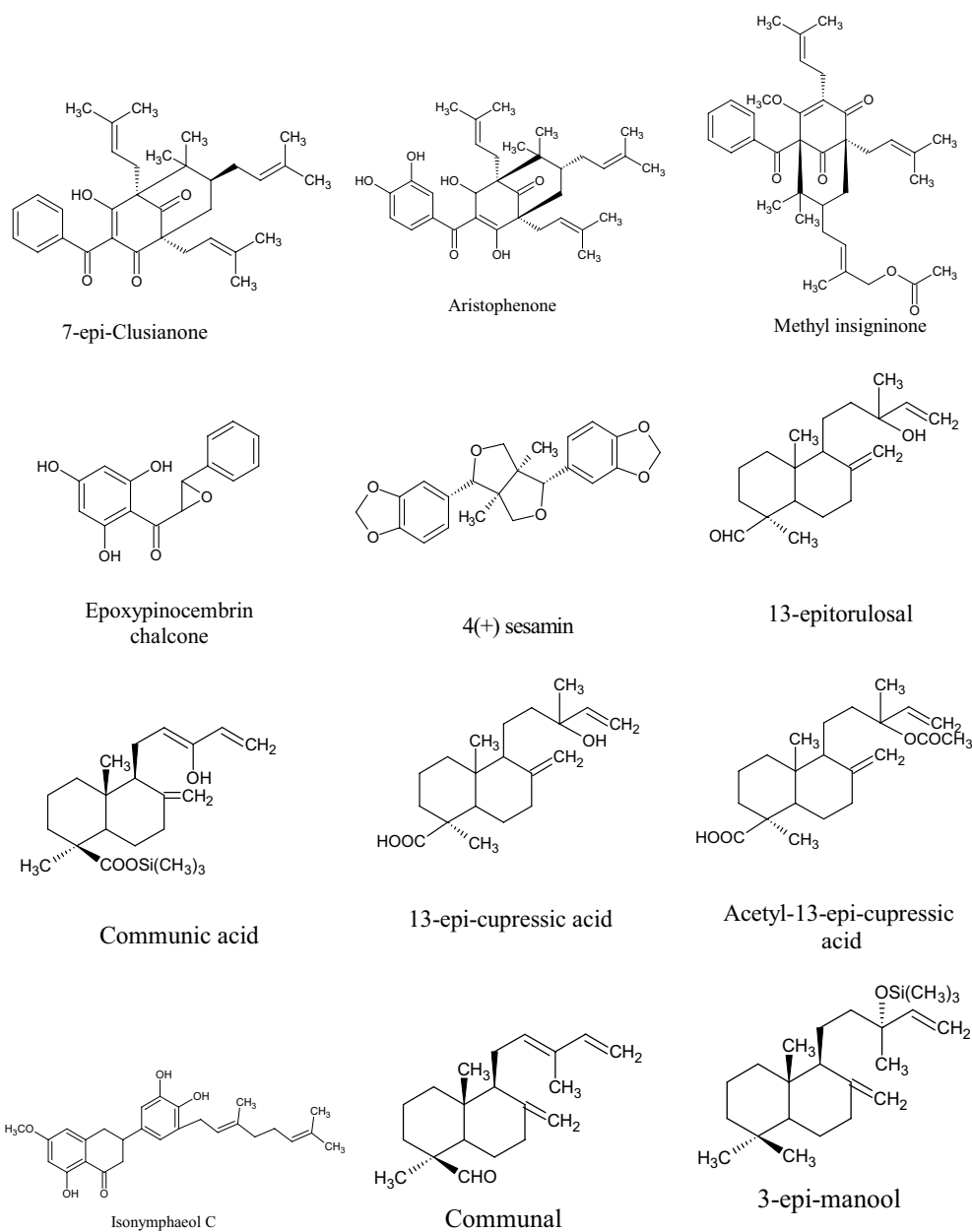
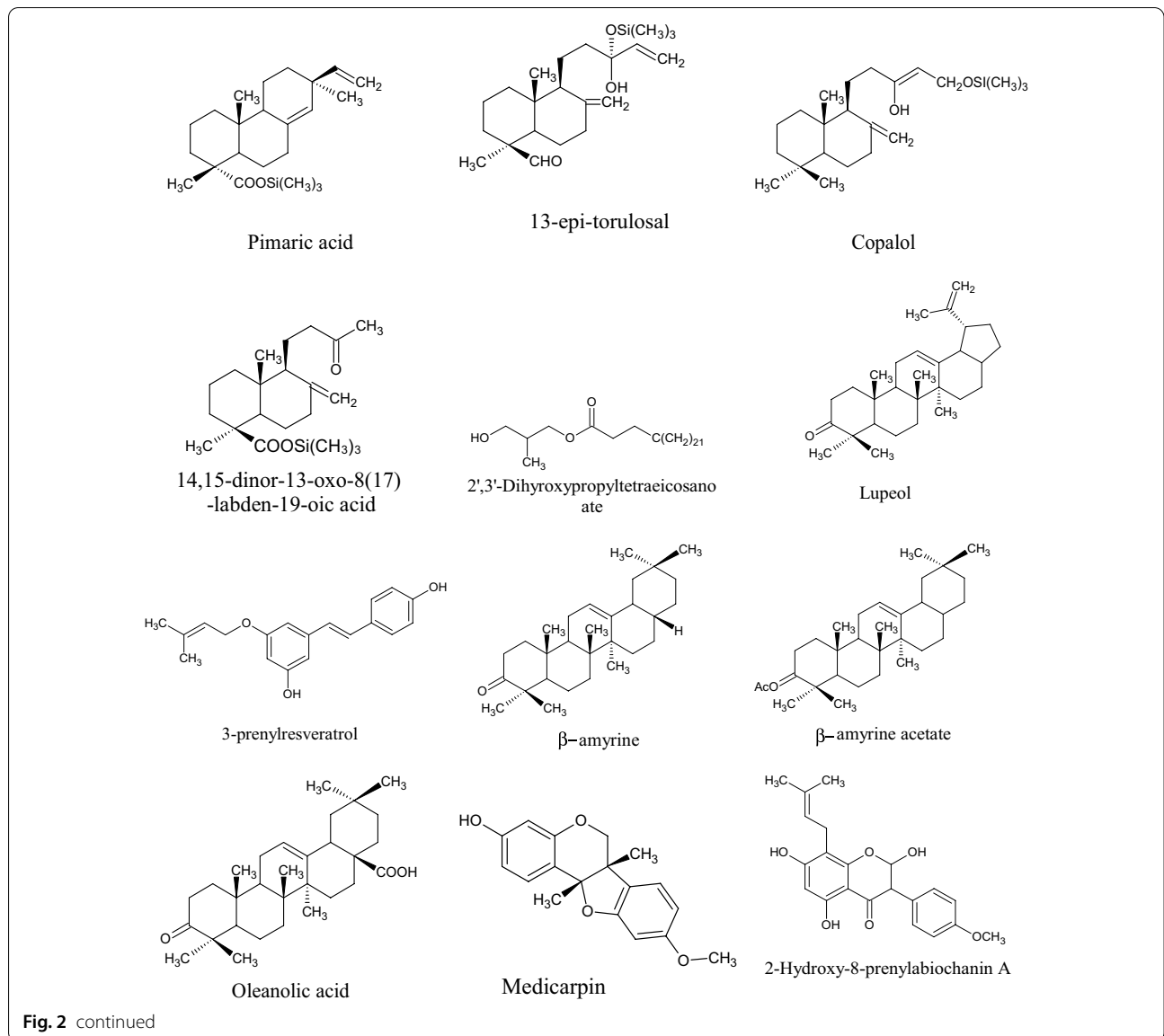


Fig. 2 continued



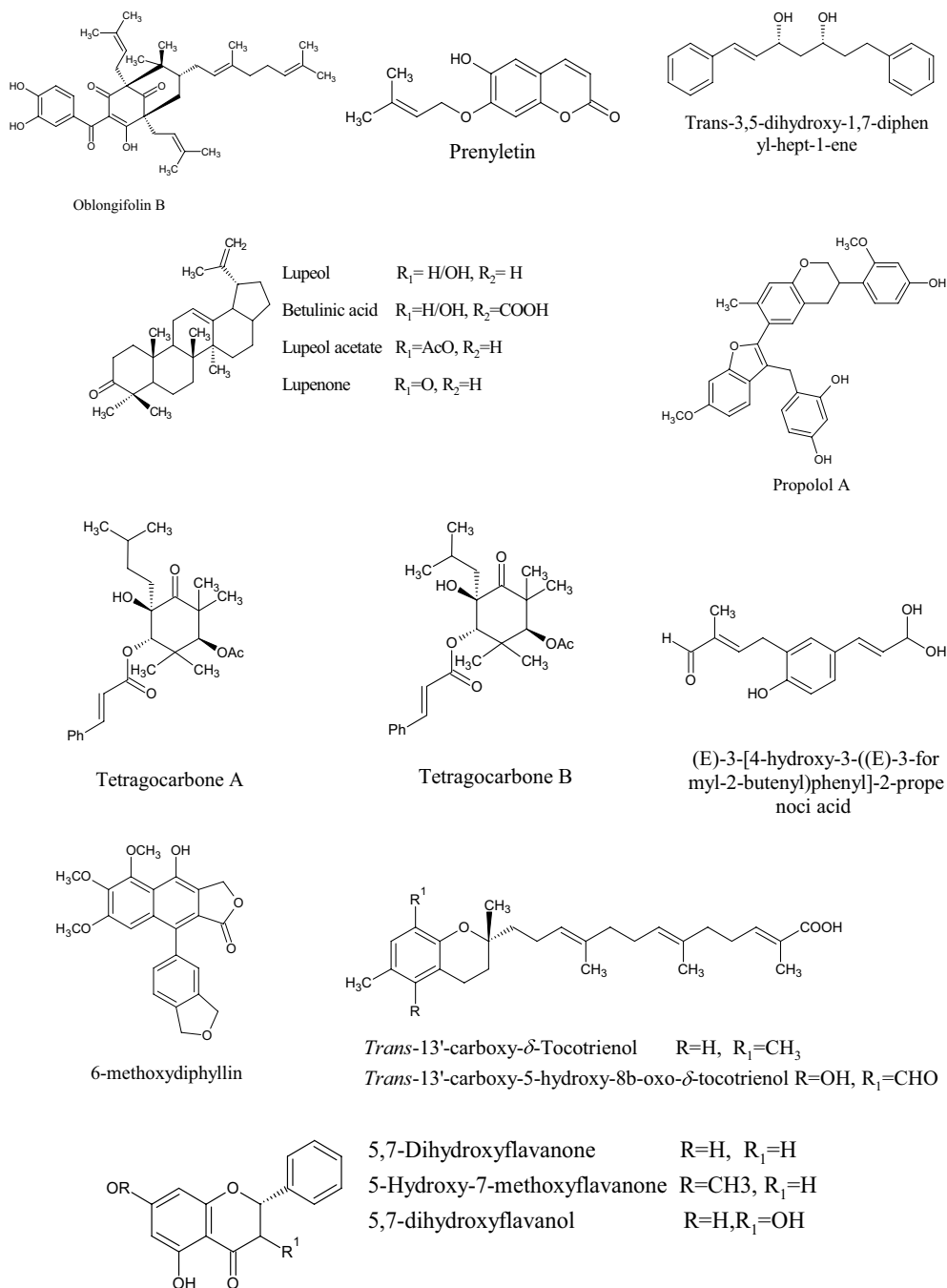


Fig. 2 continued

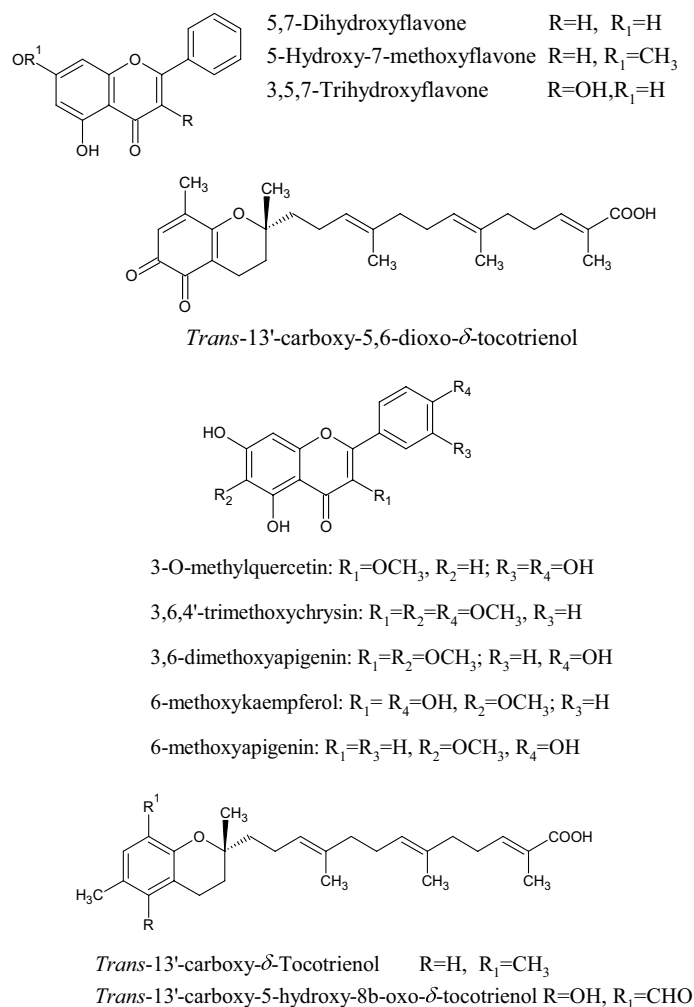


Fig. 2 continued

existence of two different subtypes of European propolis, as orange and blue types (O-type and B-type), originating from *P. nigra* and *Populus tremulas* L., respectively. Green type (G-type) propolis is distinguished by its mixture of light orange, dark green, and blue bands. 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. For instances, HPTLC profiles of plant resins as potential botanical sources of propolis, were compared with profiles of Turkish propolis extracts [58]. Based on phenolics fingerprint, O-type of Turkish propolis showed similarity with *P. nigra* buds, while B-type has similar HPTLC pattern with *P. tremula* bud.

Recently, a reversed-phase HPLC-ESI-TOF-MS analysis of an ethyl acetate extract of propolis prepared from *Apis mellifera* beehives using liquid-liquid extraction was described. Two flavonoids, galangin

and apigenin, were identified as the major constituents present in this bee glue, which were responsible for the inhibitory activity in head and neck squamous cell carcinoma on the key enzymes matrix metalloproteinase (MMP)-2 and MMP-9 that destroyed the basement membrane and degrade the extracellular matrix, leading to tumor invasion Niyomtham et al. [59].

## Pharmacological activities

### Antioxidant activity

The screening of the biological activity of bee products has attracted considerable attention due to their health benefits. Bee products including propolis, are considered to be a potential source of naturally occurring antioxidant and antimicrobials [67–72].

Several antioxidant tests such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP),

**Table 2** Compounds isolated from African propolis

Country	Compound	Class	References
Cameroon	Lupenone, $\alpha$ -amyrin, $\beta$ -amyrin, methyl-3 $\beta$ ,27-dihydroxycycloart-24-en-26-oate, oleanolic acid, $\beta$ -amyrin acetate, lupeol, betulinic acid, lupeol acetate, $\psi$ -taraxasterol-acetate, taraxasterol acetate, lanosterol, 3 $\alpha$ -hydroxy-olean-12-en-30-ol, $\alpha$ -amyrone, $\beta$ -acetoxy-amyrin, bacchara 12,21 dien3 $\beta$ -ol, betulinic aldehyde and erythrodiol	Terpenoid	[405, 406]
	3-Undecylphenol, 3-tetradecylphenol, 3-pentadecylphenol, 3-hexadecylphenol, 3-heptadecylphenol, 3-nonadecylphenol, 3-((100 z)-pentadecenyl)-phenol, 3-((120 z)-pentadecenyl)-phenol, 3-((80 z)-heptadecenyl)-phenol, 3-((120 z)-heptadecenyl)-phenol, 3-((140 z)-heptadecenyl)-phenol, 3-((130 z)-nonadecenyl)-phenol, 3-((140 z)-nonadecenyl)-phenol, 5-pentadecylresorcinol, 5-hexadecylresorcinol, 5-heptadecylresorcinol, 5-((100 z)-pentadecenyl)-resorcinol, 5-((80 z)-heptadecenyl)-resorcinol, 5-((110 z)-heptadecenyl)-resorcinol, 5-((120 z)-heptadecenyl)-resorcinol, 5-((140 z)-hheptadecenyl)-resorcinol, 5-((140 z)-nonadecenyl)-resorcinol	Phenolic lipids	[407]
Cameroon	$\alpha$ -Terpineol and 1,8-terpineol	Monoterpene alcohols	[406]
	Ethyl palmitate	Fatty acid ester	
Congo	Lonchocarpol a, 6,8-diprenyl-aromadendrin and lespedezaflavanone C	Diprenyl-flavonoids	
	Lonchocarpol A and 6,8-diprenyl-eriodictyol	Diprenyl-flavonoids	
Cameroon	10-O-Eicosanyl glycerol, deperoxidized derivative of plukenetione C	Miscellaneous	[405, 408]
Egyptian	2,3-dihydroxy-4-methyl-octanoic acid		[409]
	hexacosanoic acid; 3,4- dimethoxy-cinnamic acid; 3-methyl-3-butenyl-trans-caffeate ester, tectochrysin		
Egyptian	5-hydroxy-7-methoxy isoflavone		
	Isonymphaeol C	Prenylated flavonoid	[409]
Libya/Nigeria/cameroon	Cycloartanol, mangiferolic acid, mangiferonic acid, ambolic acid, 27-hydroxymangiferonic acid	Cycloartane triterpene	[405]
Nigeria	Ambonic acid		[410]
Libya	13-Epitorulosol, acetylisocupressic acid, agathadiol, isocupressic acid, isoagatholal	Diterpene	[411]
Cameroon	2-Hydroxy-8-prenylbiochanin A	Flavonoid	
Libya	Taxifolin-3-acetyl-4'methyl ether		
Nigeria	3,8-Dihydroxy-9-methoxy-pterocarpan, astrapterocarpan, vesticarpan, vestitol, broussonin B, calycosin, liquiritigenin, pinocembrin, isosativan, 2'-hydroxy-7,4'-dimethoxyisoflavan, medicarpin	Flavonoid	[411]
Algeria	Pectolinarigenin; 6,7-dihydroxy-7,4'-dimethoxyflavone (ladanein), acacetin, quercetin, 3-O-methyl-quercetin, kaempferol, chrysin, tectochrysin, galangin, myricetin-3,7,40,50-tetramethyl ether, apigenin, pectolinarigenin, pilosin, ladanein, pinocembrin, pinobanksin, pinobanksin-3-acetate, pinobanksin-3-(E)-caffeate, pinostrobin, genistein, (E)-resveratrol, tyrosol	Flavonoid	[412, 413]
	pimaric acid, totarol, 18-hydroxy-cis-clerodan-3-en-15-oic acid, cistadiol, isoagatholal, imbricatolonic acid, cupressic acid, isocupressic acid, torulosol, agathadiol, torulosal	Miscellaneous	[413]
		Terpenoids	[412, 413]
	caffeic acid, prenyl caffeate, methyl caffeate, isopentyl caffeate, 2-methyl-2-butenyl (E)-caffeate, 3-methyl-3-butenyl-(E)-caffeate, phenethyl-(E)-caffeate (CAPE), <i>p</i> -coumaric acid, <i>p</i> -coumaric acid methyl ester, cinnamic acid (isoferulic acid, caftaric acid, caftaric acid methyl ester, (+)-chicoric acid, (+)-chicoric acid methyl ester,	Phenylpropanoids	[412–414]
Egypt	Isoferulic acid	Phenylpropanoids	[415]
	Chrysin, tectochrysin, galangin, pinocembrin, pinostrobin, quercetin-3,7-di-o-methyl ether, 3-methoxy-5,7,40-trihydroxyflavone, 3,30-dimethoxy-5,7,40-trihydroxyflavone, izalpinin, isonymphaeol C, isonymphaeol B, isonymphaeol D, nymphaeol B,	Flavonoids	[409, 415]
Nigeria	3 $\beta$ -Cycloartenol, 3 $\beta$ -cycloartenol-26-oic acid, 3 $\alpha$ -cycloartenol-26-oic acid, $\beta$ -amyrin acetate,	Terpenoids	[416]
	Macarangin, 8-prenylNaringenin, pinocembrin, nymphaeol b, liquiritigenin, calycosin, (3S)-vestitol	Flavonoids	[417]
	Ambonic acid, mangiferonic acid, $\alpha$ -amyrin	Terpenoids	[405, 410]
	Medicarpin, riverinol, gerontoxanthone h, 6-deoxy- $\gamma$ -mangostin, 1,7-dihydroxy-3-o-(3-methylbut-2-enyl)-8-(3-methylbut-2-enyl) xanthone	Miscellaneous	[410]
	8-prenylNaringenin, 6-prenylNaringenin, propolin d, macarangin	Prenylated flavonoid	[405, 410]
	Gerontoxanthone H, 6-deoxy- $\gamma$ -mangostin; 1,7-dihydro-3-o-(3-methylbut-2-enyl)-8-(3-methylbut-2-enyl) xanthone	Xanthone	



**Table 2** (continued)

Country	Compound	Class	References
Libya	13-Epitorulosal, acetyl-13-epi-cupressic acid, 13-epi-cupressic acid	Diterpenes	[418]
	Sesamin	Lignin	
	Taxifolin-3-acetyl-4'-methyl ether	Flavanonol	
	13-Epitorulosolol	Diterpene	
	Demethylpiperitol, 5'-methoxypiperitol	Lignan	
	Cycloartanol, mangiferolic acid, mangiferonic acid, ambolic acid, 27-hydroxymangiferonic acid	Cycloartane triterpene	
	Cardol	Resorcinol	
	Agathadiol, isocupressic acid, isoagatholal, acetylisocupressic acid	Diterpene	
	bilobol		
Libya	Demethylpiperitol, 5'-methoxypiperitol	Lignan	[411]
Nigeria	Riverinol	Benzofuran	
Cameroon	Triacetyl $\rho$ -coumarate	Coumarin	
	Arachic/arachidic acid ethyl ester (PEN <sub>4</sub> )	Alkylphenol	
Libya/Cameroon	Cardol	Alkylresorcinol	
Cameroon	1'-O-Eicosanyl glycerol	Acylglycerol	[405]
Nigeria	Oleic acid; propyl stearate	Fatty acid and ester	[410]
Cameroon	Hexatriacontanoic acid, 2',3'-dihydroxypropyltetraeicosanoate	Fatty acid	[411]
Zambian and Tanzanian	6(1,1, dimethyl allyl) pinocembrin; 6(1,1, dimethyl allyl) naringenin; 5-hydroxy-4'',4''-dimethyl-5''-methyl-5''-H-dihydrofuranol [2'',3'',6,7] flavanone	Flavanone	[419]
Mediterranean	Copalol; 3-epi-manool; communal; 14,15-dinor-13-oxo-8(17)-labden-19-oic acid; pimaric acid; 13-epi-torulosal; communic acid;	Diterpene	[389]
Cameroon	2-Hydroxy-8-prenylabiochanin A, 2,3'-dihydroxypropyltetraeicosanoate, $\beta$ -amyrine, oleanolic acid, $\beta$ -amyrine acetate, lupeol, betulinic acid, lupeol acetate, lupenone	Isoflavonol	[219]
Kenya	Tetrahydrojusticidin B, phyllamyricin C, and 6-methoxydiphyllin	Arylnaphthalene lignan	[376]
Kenya	Macarangin, schweinfurthin A and B	Geranylated flavonol (geranylstilbenes)	[376]
Kenya	Phyllamyricin C, tetrahydrojusticidin B, 6-methoxydiphyllin	Micellaneous	[376]
Cameroon	(E)-5-(2-(8-hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-chromen-6-yl) vinyl)-2-(3-methylbut-2-en-1-yl) benzene-1,3-diol; 5-((E)-3,5-dihydroxystyryl)-3-((E)-3,7-dimethylocta-2,6-dien-1-yl) benzene-1,2-diol;	Prenylated stilbenes	[408]

iron-chelating activity (ferrozine assay), cupric ions reducing antioxidant power (CUPRAC), hydroxyl radical scavenging ability, lipid peroxidation inhibition, N,N-dimethyl-*p*-phenylenediamine (DMPD), O<sub>2</sub> scavenging ability, H<sub>2</sub>O<sub>2</sub> scavenging ability,  $\beta$ -carotene bleaching, superoxide anion radical scavenging ability have been used to evaluate the in vitro antioxidant activity of propolis [43, 67, 73]. These tests have different mechanisms, reaction environments, principles, charged radicals, and use difference reference compounds. Therefore, the antioxidant ability of natural compounds is generally evaluated with at least two or more antioxidant methods. Besides this, the phenolic content and composition of natural products is determined and correlated with the antioxidant capability in order to validate the obtained results [42, 74].

The extraction method greatly influences the type and quantity of bioactive compounds, because their solubility also depends on the solvent type and polarity [75, 76]. The antioxidant efficacy of propolis extracts (ethanol and water) as well as that of its fractions has been already reported in several studies [7, 43, 67, 77]. Ahn et al. [67] evaluated the antioxidant activity of ethanol extracts of propolis from various Chinese areas using the DPPH, TEAC and  $\beta$ -carotene bleaching assays. Chinese propolis extracts showed strong antioxidant activity with a positive correlation with the high total phenols content, such as flavonoids and phenolic acid esters, identified by HPLC coupled with a photodiode array (PDA) and mass spectrometry (MS) detection [60]. There are many other reports concerning the antioxidant potential of ethanol extract of propolis [44, 78, 79]. In addition, there are also some reports about the antioxidant capacity of water

**Table 3** Compounds isolated from American propolis

Country	Compound	Class	References
Brazil	$\beta$ -Amyrin, glutinol	Triterpenoid	[420]
Bolivia	Cycloart-24-en-3 $\beta$ -ol, cycloart-24-en-3 $\beta$ ,26-diol, 24(E)-Cycloart-24-en-26-ol-3-one, cycloart-24-en-3-one, lupeol, cycloartenone	Cycloartane triterpene	[421]
Brazil	Liquiritigenin, isoliquiritigenin, formononetin, vestitol, neovestitol, medicarpin, 7-O-neovestitol, 3-O-methylquercetin, 3,6,4'-trimethoxychrysin, 3,6-dimethoxyapigenin, 6-methoxykaempferol, 6-methoxyapigenin, 5,7-dihydroxy-2-(3,4-dihydroxy)-4-h-chromen-4-one, dihydrokaempferide	Flavonoid	[103, 422, 423]
	3-O-Methylquercetin, 3,6,4'-trimethoxychrysin, 3,6-dimethoxyapigenin	Flavones	[103]
	6-methoxyapigenin, 6-methoxykaempferol		
	3-Prenyl-4-hydroxycinnamic acid, 3,5-diprenyl-4-hydroxycinnamic acid, 2,2-dimethyl-6-carboxyethyl-2-H-1-benzopyran, 2,2-dimethyl-6-carboxyethyl-2-8-prenyl-2H-1-benzopyran	Polyphenol	[397]
	nemorosone, gambogone, 7-epi-Nemorosone, 7-epi-clusianone, methylinsiginone, aristophenone, hyperibone B	Polyisoprenylated benzophenones	[95, 424] [425]
	Propolonones A, propolonones B, propolonones C, propolol A	Flavonoid derived dimer	[102]
	(E)-3-[4-Hydroxy-3-((E)-3-formyl-2-butenyl)phenyl]-2-propenoic acid, 3,4-dihydroxy-5-prenyl-(E)-cinnamic acid, capillartemisins A, 2,2-dimethylchromene-6-(E)-propenoic acid	Cinnamic acid derivative	[423]
Chile	5,7-Dihydroxyflavanone, 5-hydroxy-7-methoxyflavanone, 5,7-dihydroxyflavanol, 5,7-dihydroxyflavone, 5-hydroxy-7-methoxyflavone, 3,5,7-trihydroxyflavone	Flavonoid	[426]
Colombian	Trans-13'-carboxy-5-hydroxy-8 $\beta$ -oxo- $\delta$ -tocotrienol, trans-13'-carboxy-5,6-dioxo- $\delta$ -tocotrienol, trans-13'-carboxy- $\delta$ -tocotrienol	d-Tocotrienol	[427]
Central Chilean Matorral	Prenyletin, trans-3,5-dihydroxy-1,7-diphenyl-hept-1-ene, acacetin, izalpinin, kaempferide	Phenolic	[428]
Cuba/ Brazil	Propolone A, propolone B, propolone C, propolone D	Polyisoprenylated Benzophenones/ Flavonoid	[102, 424, 429]
Cuba	Gallic acid, isoliquiritigenin, liquiritigenin, formononetin, biochanin A, (3S)-7,4'-dihydroxy-2'-methoxyisoflavan, 7-O-methylvestitol, (6aS,11aS)-medicarpin, (6aS,11aS)-homopterodocarpin, (6aR,11aR)-vesticarpin, (6aR,11aR)-3,8-dihydroxy-9-methoxypterocarpan, (6aR,11aR)-3-hydroxy-8,9-dimethoxypterocarpan, (6aR,11aR)-3,4-dihydroxy-9-methoxypterocarpan	Isoflavonoids	[378]
	Plukenetione A	Polyprenylated acylphloroglucinol	[430]
Mexican	Pinocembrin, pinobanksin chrysin, galangin-5-methylether, isorhamnetin, pinobanksin-5-methylether, alpinetin, alpinone, pinostrobin, kaempferide	Flavonoid	[431]
Ecuador	Naringenin, Sakuranetin, Eupatolitin, Rhamnazin		[432]
Chile	Pinocembrin, chrysin		[433]
Bolivia	Kaempferol 3-methyl ether, kaempferol 7-O-methyl ether		[421]
Brazil	2-Phenoxychromone	Benzopyran derivative	[434]
Bolivia	Cinnamic acid	Phenyl propanoid	[421]
	3-Prenyl- <i>p</i> -coumaric acid (drupanin)	Coumarin	
	Benzyl benzoate	Benzyl ester	
Brazil	Guttiferone E, oblongifolin B	Polyprenylated benzophenone	[434]
	2-Phenoxychromone	Flavones	[103]
Chile	(E)-3-Hydroxy-1,7-diphenylhept-1-ene-5-acetate, (E)-5-hydroxy-1,7-diphenylhept-1-ene-3-acetate	Diarylheptanoid	[435]

**Table 4** Compounds isolated from Australian propolis

Country	Compound	Class	References
Pitcairn Island	3-oxo-cycloart-24e-en-21,26-diol-21,26-diacetate, 3-oxo-cycloart-24e-en-21,26-diol, 3-oxo-cycloart-24e-en-21,26-diol-21-acetate, 3-oxo-cycloart-24e-en-21,26-diol-26-acetate, 3-oxo-cycloart-24-en-26-al	Triterpenoid	[436, 437]
Australia	7,8,18-Trihydroxyserrulat-14-ene, 5,18-epoxyserrulat-14-en-7,8-dione, (18 <i>RS</i> )-5,18-epoxyserrulat-14-en-8,18-diol	Diterpene	[12]
Pitcairn Island	Abietinal	Diterpene	[436, 437]
Fiji Island	Glyasperin	Flavonoid	[438]
Kangaroo Island	( <i>E</i> )-4-(3-Methyl-2-buten-1-yl)-3,4',5-trihydroxy-3'-methoxystilbene, ( <i>E</i> )-2-(3-methyl-2-buten-1-yl)-3,4',5-trihydroxystilbene (2-prenylresveratrol), ( <i>E</i> )-2,4-bis(3-methyl-2-buten-1-yl)-3,3',4',5-tetrahydroxystilbene ( <i>E</i> )-2-(3-methyl-2-buten-1-yl)-3-(3-methyl-2-butenyloxy)-3',4',5-trihydroxystilbene, ( <i>E</i> )-2,6-bis(3-methyl-2-buten-1-yl)-3,3',5,5'-tetrahydroxystilbene ( <i>E</i> )-2,6-bis-(3-methyl-2-buten-1-yl)-3,4',5-trihydroxy-3'-methoxystilbene	Stilbene	[398, 439, 440]
Fiji Islands	Solomonin B, solomonin C Glyasperin A, kumatakenin, macarangin, mangiferolic acid	Stilbene Flavonid	[438]

**Table 5** Compound isolated from Asian propolis

Country	Compounds	Class	Refs.
Indonesia/Vietnam	Mangiferolic acid, cycloartenol, mangiferonic acid, ambonic acid, ambolic acid Cardol	Cycloartane triterpenoid Alkyresorcinol	[238, 441] [138]
Vietnam	23-Hydroxyisomangiferolic acid B, 23-hydroxyisomangiferolic acid A, 27-acetoxymangiferolic acid, (5 <i>R</i> ,8 <i>S</i> ,9 <i>S</i> ,10 <i>R</i> ,13 <i>R</i> ,14 <i>S</i> ,17 <i>R</i> ,20 <i>R</i> )-27-methoxycarbonyloxymangiferonic acid, 27-acetoxymangiferonic acid, lanosterol, cycloartenone, mangiferonic acid, 23-hydroxymangiferonic acid, 27-hydroxymangiferonic acid, (23 <i>E</i> )-27-nor-3β-hydroxycycloart-23-en-25-one, (24 <i>E</i> )-3βhydroxycycloart-24-en-26-al, 27-hydroxyisomangiferonic acid	Cycloartane triterpenoid	[442]
Thailand/Vietnam	3- <i>O</i> -Acetyl ursolic acid, ocotillone I, ocotillone II, ursolic aldehyde, oleanolic aldehyde, dip-terocarpol, cabralealactone, isocabralealactone	Triterpenoid	[441, 443]
Thailand	Methylpinoselinol	Lignan	[443]
Malaysia	20-Hydroxy-24-dammaren-3-one, β-panasinsene	Sesquiterpene	
Thailand/Vietnam	α-Mangostin, γ-mangostin, cochinchinone t, β-mangostin, gartanin, 8-deoxygartanin, 9-hydroxycalabaxanthone, mangostanol, mangostanin, garcinone B	Prenylated xanthone	[441, 443]
Vietnam	Hydroxyhopanone (13 <i>E</i> ,17 <i>E</i> )-polypoda-7,13,17,21-tetraen-3β-ol Lisofurvin, Dihydrobrasixanthone B, cochichinone A, cochichinone I, cochichinone J, cratoxylumxanthone B, α-mangostanin, pruniflorone S, 2-hydroxyl-6-(14' <i>Z</i> -nonadecenyl) benzoic acid	Micellaneuous Dihydrochromene Xanthone Alkenylphenol	[441] [441] [441] [444]

extracts of propolis [7]. The antioxidant activity of a water extract of propolis from Brazil was evaluated using the superoxide scavenging ability assay, the DPPH assay, and the hydroxyl radical scavenging ability assay. The extract showed the best free-radical scavenging ability against superoxide anion radical and hydroxyl radical at 50 and 100 µg/ml, respectively. Similarly, in the study of Gülçin et al. [43], who investigated the in vitro antioxidant activity of a water extract of propolis from Erzurum province of Turkey by using FRAP, CUPRAC, iron-chelating activity, H<sub>2</sub>O<sub>2</sub> and O<sub>2</sub> scavenging ability as well as DPPH and TEAC assays, the water extract showed an interesting

antioxidant profile. The aqueous extract was analyzed by HPLC and LC-MS/MS reporting a large number of antioxidative compounds such as caffeic acid, ferulic acid, syringic acid, ellagic acid, quercetin, α-tocopherol, pyrogallol, *p*-hydroxy benzoic acid, vanillin, *p*-coumaric acid, gallic acid, and ascorbic acid [43]. In the study conducted by Aldemir et al. [80], the effect of different solvents (ethanol, water and polyethylene glycol) on the antioxidant activity of propolis was determined using TEAC and FRAP methods. However, they did not find any statistically significant differences in the antioxidant activity between the different propolis extracts. In another

**Table 6** In vitro antimicrobial effects of some propolis extracts, doses, and studied microorganisms

Country/Region	Solvent	Dose/Concentration	Microorganism	Effect	References
Tunisia	Ethanol	10 µl	<i>Aspergillus flavus</i> , <i>Aspergillus niger</i> , <i>Streptococcus mutans</i> , <i>Penicillium nordicum</i> , <i>Penicillium expansum</i> , <i>Penicillium commune</i> , <i>Lactobacillus plantarum</i> , <i>Escherichia coli</i>	Growth inhibition	[83]
Chile	Ethanol	MIC, 256 to 1024 µg/ml	<i>Helicobacter pylori</i> ATCC 43,504, <i>Helicobacter pylori</i> 84C	Growth inhibition	[37]
Brazil	Ethanol	MIC 7.44 to 29.76 mg/ml	<i>Streptococcus mutans</i> ATCC 25,175, <i>Streptococcus sanguinis</i> ATCC 10,566, <i>Streptococcus salivarius</i> ATCC 7073, <i>Lactobacillus casei</i> ATCC 393	Growth inhibition	[93]
-	-	200 µl	<i>Streptococcus mutans</i> ATCC 25,175, <i>Streptococcus sanguinis</i> ATCC 10,566, <i>Candida albicans</i> ATCC 1023	Growth inhibition	[92]
Mexico	Ethanol	MIC 1.62 to 2.50 µg/ml	<i>Candida albicans</i> ATCC 10,231	Growth inhibition	[46]
Turkey	Ethanol–water (8:2)	0.25, 0.50, 1 mg/well	<i>Streptococcus sanguinis</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus mutans</i> , <i>Candida albicans</i>	Growth inhibition	[47]
Algeria	Ethanol–water	500 µg/ml	<i>Shewanellaputrefaciens</i> , <i>Photobacterium damsela</i> , <i>Vibrio harveyi</i>	Growth inhibition	[87]
India	Chloroform, ethanol, acetone	5,10,15 mg/ml	<i>Pseudomonas fluorescens</i> , <i>Pseudomonas citrea</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Vibrio cholera</i> , <i>Vibrio parahaemolyticus</i> , <i>Vibrio harveyi</i> , <i>Vibrio fischeri</i> , <i>Bacillus-substillus</i>	Growth inhibition	[76]
Brazil	Ethanol–Water	1.64 to ≥ 1024 µg/ml	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Growth inhibition	[445]
Russia	Ethanol	2 µg/ml	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i>	Anti-biofilm	[35]
Romania	Ethanol	10 mg/ml	<i>Paenibacillus larvae</i>	Growth inhibition	[88]
Argentina	Ethanol	MIC, 4.7 to 152 g GAE/ml	<i>Erwinia carotovorasppcarotovora</i> CECT 225, <i>Pseudomonas syringaepar tomato</i> CECT 126, <i>Pseudomonas corrugata</i> CECT 124, <i>Xanthomonas campestris pvarvesicatoria</i> CECT 792	Growth inhibition	[86]
Korea	Ethanol	0.036 to 2.3 mg/ml	<i>Bacillus cereus</i> , <i>Listeria monocytogenes</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas fluorescence</i>	Growth inhibition	[84]
Brazil	Ethanol	0.69 to 42.8 mg/ml	<i>Staphylococcus aureus</i> , <i>Staphylococcus intermedius</i> , <i>Malassezia pachydermatis</i>	Growth inhibition	[251]
Turkey	Ethanol	MIC, 4 to 512 mg/ml	<i>Peptostreptococcus anaerobius</i> , <i>Peptostreptococcus micros</i> , <i>Lactobacillus acidophilus</i> , <i>Actinomyces naeslundii</i> , <i>Prevotellaoralis</i> , <i>Prevotellamelaninogenica</i> , <i>Porphyromonasgingivalis</i> , <i>Fusobacterium nucleatum</i> , <i>Veillonellaparvula</i>	Growth inhibition	[38]
Brazil	Ethanol	0.4 to 0.5 mg	<i>Staphylococcus aureus</i> 209, <i>Escherichia coli</i> , <i>Candida albicans</i> 562	Growth inhibition	[446]

study, propolis extracts from different regions of Korea were evaluated and compared to extracts obtained from Brazilian propolis [79]. Korea propolis extracts, which contained the highest total phenols and flavonoids content, showed the highest antioxidant activity in the linoleic peroxidation and DPPH assays. Flavonoids present in propolis play a crucial role in photoaging and psoriasis [81].

Hochheim et al. [77] examined the antioxidant activity of methanol, water, 70% ethanol, dichloromethane, ethyl acetate and butanol extract fractions in native Brazilian bee *Melipona quadrifasciata* propolis. The authors found that the aqueous extract showed the best antioxidant potential, followed by methanol extract. Moreover, the methanol extract showed the highest radical scavenging capacity in the DPPH

assay with an  $IC_{50}$  value of  $151.37 \pm 7.9$   $\mu\text{g/ml}$  followed by ethyl acetate ( $IC_{50} = 311.47 \pm 8.2$   $\mu\text{g/ml}$ ), dichloromethane ( $IC_{50} = 489.8 \pm 0.0$   $\mu\text{g/ml}$ ), and butanol ( $IC_{50} = 588.8 \pm 0.0$   $\mu\text{g/ml}$ ) fractions. In addition, crude extracts and fractions showed different activity in the lipid peroxidation assay. Ethyl acetate fraction [ $64.93 \pm 0.6$  mg gallic acid equivalent (GAE)/g], showed the highest total phenols content followed by methanol extract ( $57.53 \pm 0.2$  mg GAE/g), aqueous extract ( $11.96 \pm 1.5$  mg GAE/g), dichloromethane fraction ( $8.10 \pm 0.3$  mg GAE/g), hydroalcoholic extract ( $4.87 \pm 0.2$  mg GAE/g), and was not observed in butanol fraction. On the contrary, the highest content of flavonoids was detected in the methanol extract [ $8.48 \pm 0.3$  mg quercetin equivalents (QUE)/g], followed by ethyl acetate fraction ( $4.23 \pm 0.5$  mg QUE/g), hydroalcoholic extract ( $3.99 \pm 0.4$  mg QUE/g), aqueous extract ( $3.67 \pm 0.3$  mg QUE/g), dichloromethane fraction ( $2.20 \pm 0.3$  mg QUE/g), and butanol fraction ( $0.78 \pm 0.2$  mg QUE/g).

In another study, twelve propolis samples from Greece, Greek island, and east Cyprus were analyzed for their antioxidant activity, as well as chemical composition [42]. The propolis ethanol extracts possessed potent DPPH scavenging activities from 0.33 to 1.11 mmol trolox equivalents (TE)/g extract and reducing power ability from 2.14 to 3.35 mmol ascorbic acid equivalent (AAE)/g. The antioxidant activity of propolis samples correlated with total phenol content as well as with the amount of the main identified compounds such as phenolic acids and their esters, anthraquinones, flavonoids and terpenes. Kumazawa et al. [74] performed an extensive study investigating the antioxidant potential of propolis collected from Argentina, Australia, Brazil, Bulgaria, Chile, China, Hungary, New Zealand, South Africa, Thailand, Ukraine, Uruguay, United States and Uzbekistan by using  $\beta$ -carotene bleaching and DPPH assays. HPLC-PDA and LC-MS analysis were also used to identify the major constituents of their ethanol extracts. All the propolis extracts exhibited significant free-radical scavenging activity against DPPH radical and inhibitory effects on  $\beta$ -carotene-bleaching, mainly attributable to the phenolic acids and flavonoids content. Regarding this, Lee et al. [68] isolated ten phenylpropanoic acid esters from ethanol extracts of Korean propolis. The antioxidant potential of these compounds, specifically caffeic acid phenethyl ester, caffeic acid benzyl ester, caffeic acid ethyl ester, ferulic acid benzyl ester, ferulic acid 3',3'-dimethylallyl ester, 3,4-dimethoxycaffeic acid cinnamyl ester, coumaric acid cinnamyl ester, coumaric acid benzyl ester, cinnamic acid phenethyl ester, and cinnamic acid cinnamyl ester, were investigated by DPPH and ABTS assays. Among the tested compounds, caffeic

acid phenethyl ester (CAPE), caffeic acid benzyl ester, and caffeic acid ethyl ester exhibited significant activity, ferulic acid benzyl ester, ferulic acid 3',3'-dimethylallyl ester had moderate activity, and the other compounds did not show any activity. Russo et al. [71] reported that the antioxidant activity of the propolis extract is mainly ascribable to CAPE and galangin. In particular, the results showed that propolis extract (with and without CAPE), galangin and CAPE exhibited a dose-dependent antioxidant activity. Moreover, CAPE possessed a higher antioxidant activity with respect to galangin. On the contrary, regarding Portugal propolis, the collected in Bornes region showed the highest antioxidant capacity with the following  $IC_{50}$  values than the propolis from Fundão region [82]. The values varied between  $IC_{50} = 6.22$   $\mu\text{g/ml}$  (Bornes) and  $IC_{50} = 52.00$   $\mu\text{g/ml}$  (Fundão) in DPPH assay, and  $IC_{50} = 9.00$   $\mu\text{g/ml}$  (Bornes) and  $IC_{50} = 55.00$   $\mu\text{g/ml}$  (Fundão) in CUPRAC assay. Moreover, the results obtained showed a positive correlation with the phenolic content of propolis extracts.

Ozdal et al. [36] determined the antioxidant activity of propolis collected in 11 different geographical areas of Turkey by using DPPH and CUPRAC methods. Moreover, the bioaccessibility of propolis samples in terms of total antioxidant capacity of propolis extracts after *in vitro* simulated gastrointestinal digestion was evaluated. The antioxidant capacity of samples recorded by DPPH method ranging from  $1370.6 \pm 198$  mg trolox equivalents (TE)/100 g and  $6332.9 \pm 114$  mg TE/100 g, whereas in CUPRAC assay the antioxidant capacity ranging from  $2461.6 \pm 278$  mg TE/100 g and  $8580.3 \pm 234$  mg TE/100 g. Moreover, for most samples, the antioxidant capacity of propolis recorded by both methods increased after *in vitro* gastrointestinal digestion from oral to intestinal phase.

Despite the little information available in literature, the content of bioactive compounds in propolis may be different in relation to the seasonal collection. The antioxidant ability of propolis collected in three different regions of Algarve in winter and spring (Serra do Algarve, Transição and Barrocal) as well as in South Portugal (Bornes and Fundão regions) were evaluated by using DPPH, TEAC, superoxide anion radical and metal-chelating activity assays [73]. Samples collected in winter showed the highest free-radical scavenging activity in DPPH assay ( $IC_{50} = 0.027$ – $0.031$  mg/ml) whereas samples collected in spring showed the highest metal-chelating activity. Moreover, propolis samples collected in Barrocal region possessed the higher radical scavenging capacity with respect to Serra do Algarve and Transição regions, without any correlation between seasonal variation and antioxidant assays.

Considering all these results, it is possible to affirm that the antioxidant activity of propolis is certainly correlated with its phytochemical profile, which can vary not only according to the pedoclimatic characteristics of the territory but also according to the harvest season. In any case, certainly, propolis has shown a strong antioxidant activity which supports its use as a replacement for many synthetic antioxidant agents such as butylatedhydroxyanisole, butylatedhydroxytoluene, and tertiary butyl hydroquinone.

### Antimicrobial activity

Propolis is also increasingly recognized for its antimicrobial (antibacterial/antifungal) properties. The antimicrobial efficiency of propolis mainly depends on its broad chemical diversity, extraction methods, applied concentration, collected season, region, and bee species. However, despite this variability, propolis maintained its functional properties [46, 75, 76, 83]. Because it contains many bioactive compounds, propolis possesses antibacterial and antifungal activity on a board range of microorganisms. Propolis extract was effective specifically on various foodborne pathogens [84], agricultural bacterial pathogens [85], phytopathogenic bacteria [86], marine opportunistic pathogenic bacteria [87] other than honeybee pathogens [88]. The antibacterial effects of propolis samples collected in different countries/regions around the world have been investigated by several studies grouped in Table 1. The antibacterial properties, either bactericidal or bacteriostatic, highlighted by *in vitro* studies, depends on concentration, treatment time, and bacterial mode of action [84], although the mechanism is often unknown. Propolis acts either by directly interacting with the microbial cells or by stimulating the immune system of the host cells [89]. The hypothesized mechanisms include the inhibition of bacterial adherence and division, decrease of bacterial mobility, disturbance of membrane potential, and increase in cell membrane permeability [47, 90]. These biological activities are strictly related to the presence of phenolic acids, flavonoids, terpene esters, chalcones, dihydrochalcones, terpenoids, aliphatic acids and esters, aromatic compounds, and metals [35]. As mentioned before, several factors play a key role on the propolis activity, being one of this the extraction method. For example, Gargouri et al. [83] demonstrated that ultrasonic extraction method increased notably the biological activity of the propolis extract with respect to the conventional liquid–liquid extraction method. Concerning the effect of the extraction method used, a study was conducted to evaluate different extraction solvents [75]. In particular, the antimicrobial efficacy of polyethylene glycol (PEG) 400, water, olive oil and the combination of them was investigated against *Staphylococcus aureus*

ATCC 25,923, *Escherichia coli* 25,922, *Pseudomonas aeruginosa* ATCC 27,853, *Klebsiella pneumoniae* ATCC 33,499, *Bacillus cereus* ATCC 8035, *Candida albicans* ATCC 60,193. Among them, PEG/olive oil/water, PEG/water, showed similar or a higher significant inhibition in comparison with the hydroalcoholic extract. From phytochemical point of view, caffeic acid, trans-*p*-cumaric acid, and galangin were determined in all extracts under investigations, whereas naringenin, kaempferol, and galangin were determined in PEG/olive oil/water and hydroalcoholic extracts. Selvaraj et al. [76] demonstrated the effect of different solvents (ethanol, chloroform, and acetone) on the propolis antibacterial activity. The ethanol extract, in particular, was found to be the most effective against microbial growth.

Moreover, the propolis composition varies also between bee species, which can modify its antimicrobial capacity. Ramón-Sierra et al. [46] reported the antifungal activity of ethanol extracts of propolis obtained from two different bee species (*Apis mellifera* and *Melipona beecheii*) against *C. albicans* ATCC 10,231. According to their findings, *M. beecheii* propolis extract showed a lower MIC with respect to the *A. mellifera* propolis extract. Furthermore, Campos et al. [91] reported that propolis ethanol extract of *Melipona orbignyi* (Hymenoptera, Apidae), very rich in aromatic acids, phenolic compounds, alcohols, terpenes, and sugars, is effective against *Staphylococcus aureus* and *C. albicans*.

The antibacterial activity of the various propolis samples also varied according to the collection region. Ristivojević et al. [47] compared the antimicrobial activity of forty-eight propolis ethanol extract from various Turkey regions against *Streptococcus sanguinis*, *Streptococcus pyogenes*, *Streptococcus mutans*, *C. albicans* as well as examined the phytochemical composition and antioxidant activity. They concluded that the samples with strongest antimicrobial activity contain the highest total phenols, total flavonoid as well as cinnamic, ferulic, caffeic, chlorogenic, and *p*-coumaric acid content. Similarly, the antimicrobial activity of propolis extracts from different regions of Korea was evaluated and compared to Brazil propolis [79]. Korea and Brazil propolis extracts showed high antimicrobial activity against *S. aureus*, *Bacillus subtilis*, *Salmonella Typhimurium* and *C. Albicans*, whereas they did not show any activity against *P. aeruginosa*. The Yeosu and Cheorwon extracts showed higher antibacterial activity with respect to Yangpyeong, mainly related to their higher total phenols and flavonoid contents. Ambi et al. [35] hypothesized that metals may be involved in the antimicrobial properties of Russian propolis, by testing a crude ethanol extract and a metal-free ethanol extract against *S. aureus* and *E. coli* biofilm formation. The crude ethanol extract was more active

than the metal-free ethanol extract on biofilm formation. However, at the same concentration, increasing the time exposure to 40 h, both extracts completely inhibit the *S. aureus* and *E. coli* biofilms. Several studies have been carried out also about the antimicrobial properties of propolis against oral cavities infections. Its efficacy was tested against several oral microorganisms such as *S. mutans* ATCC 25,175, *S. sanguinis* ATCC 10,566, *C. albicans* ATCC 1023 and *Lactobacillus casei* ATCC 393 [92, 93]. Propolis showed a good inhibitory activity on all oral pathogens, paving the way to an alternative application of this natural product to mouthwashes and toothpastes. From these studies, it can be highlighted that propolis antimicrobial potential varied according to its chemical composition. However, among extraction methods, solvent type and bee species, it may be concluded that floral diversity is the most responsible for the bioactivity of propolis.

### Anticancer activity

#### *In vitro* studies

**Cytotoxic, antioxidant and apoptotic effects** Cytotoxic and apoptotic effects have been described for propolis and correlated with its capacity to improve the antioxidant capacity in various disease states [94]. Castro et al. [95] isolated prenylated benzophenone and isoprenylated benzophenone from Brazilian propolis in order to evaluate their cytotoxic effects. They carried out an *in vitro* study using HeLa cervical cancer cells and they found that the both compounds exhibited good cytotoxic effects at 0.18  $\mu\text{M}$  concentration [95]. A study by Vukovic et al. [96] reported antioxidant, cytotoxic and pro-apoptotic activities of flavonoids derived from propolis in colon (HCT-116) and breast (MDA-MB-231) cancer cell lines at 115.68  $\mu\text{M}$ , 114.75  $\mu\text{M}$ , 66.86  $\mu\text{M}$ , and 50  $\mu\text{M}$  concentrations [96]. Flavones from Mexican propolis at 4.6  $\mu\text{M}$  concentration significantly triggered apoptosis-like morphological changes/cytotoxic effects in PANC-1 human pancreatic cell line [97]. Additionally, in a recent study, Rivero-Cruz et al. [98] revealed the cytotoxic activity of an ethanol extract of propolis (92.2  $\mu\text{g}/\text{ml}$ ) in glioblastoma cells cancer line. Another study by Alday et al. [99] evaluated the antiproliferative activity by using the flavonoids and derived esters isolated from propolis at various concentrations (49.1  $\mu\text{M}$ ; 52.1  $\mu\text{M}$ ; 67.0  $\mu\text{M}$ ; 49.9  $\mu\text{M}$ ; 51.3  $\mu\text{M}$ ; 76.6  $\mu\text{M}$ ) in B-cell lymphoma cell line. All the isolated compounds exhibited the antiproliferative activity through apoptotic induction [99]. The ethanolic extract of Turkish propolis at 76.9  $\pm$  2.9  $\mu\text{g}/\text{ml}$  concentration showed cytotoxic activity in human normal foreskin fibroblast cells at 31.7  $\pm$  0.26  $\mu\text{g}/\text{ml}$  concentration arresting the cell cycle in G1 phase, inducing endoplasmic reticulum stress, caspase activity, and apoptosis and reducing

mitochondrial membrane potential in Human adenocarcinomic alveolar basal epithelial (A549) cancer cell line [100]. In another study, the ethanol extract of Polish propolis displayed anti-proliferative and pro-apoptotic effect at 100  $\mu\text{M}$  concentration on HCT 116 colon cancer and Me45 malignant melanoma cells [101].

In a recent study, Banzato et al. [102] isolated rare flavanoid dimers, propolones A–D, with a 3-{3-[(2-phenylbenzofuran-3-yl)methyl]phenyl}chromane skeleton, and propolones A–C, with a 3-[3-(3-benzylbenzofuran-2-yl)phenyl]-chromane skeleton, as constituents of Brazilian red propolis by cytotoxicity-guided assays. Results of the chiral-phase HPLC analysis of these propolis dimers confirmed that they represented scalemic mixtures in which the (+)-enantiomers predominate. The bees that produce this type of red propolis feed on *Dalbergia ecastophyllum* (L.) Taub. Propolone B and propolone A display significant cytotoxic activities against an ovarian cancer cell line expressing a multiple drug resistance phenotype when compared with doxorubicin. They reported that the isolated compounds at 19.1  $\pm$  2.4  $\mu\text{M}$  and 29.9  $\pm$  3.4  $\mu\text{M}$  concentration exhibited suitable antiproliferative activity in ovarian cancer cell line [102].

Mitsui et al. [103] also isolated flavones from Brazilian propolis and performed an *in vitro* study to evaluate the activity of these isolated compounds. They reported that 3-methoxy-flavones, such as 3-*O*-methylquercetin (MCF-7: IC<sub>50</sub> 16.2  $\mu\text{M}$ ), 3,6-dimethoxyapigenin (MCF-7: IC<sub>50</sub> 31.0  $\mu\text{M}$ ), and 3,6,4'-trimethoxychrysin (MCF-7: IC<sub>50</sub> 17.1  $\mu\text{M}$ ), exhibited anti-proliferative effect and inhibited cell growth in DLD-1 (human colorectal adenocarcinoma), MCF-7 (human breast cancer), and A549 (human lung cancer) cancer cell lines. Interestingly, the novel 5,7-dihydroxy-2-[3,4-dihydroxyphenoxy-4*H*-chromen-4-one] also displayed an anti-proliferative effect on cancer cells (MCF-7: IC<sub>50</sub> 65.8  $\mu\text{M}$ ).

The extract of Sonoran Desert propolis at 22.4  $\pm$  1.3  $\mu\text{M}$  concentration displayed suitable antiproliferative activity against cancerous cell line M12.C3.F6 (murine B cell lymphoma). The antiproliferative activity through apoptosis induction was exhibited by pinobanksin and its ester derivatives, pinobanksin-3-*O*-propanoate, pinobanksin-3-*O*-butyrate, and pinobanksin-3-*O*-pentanoate [104]. Moreover, Catchpole et al. [105] evaluated the antiproliferative activity of a commercial New Zealand propolis tincture (Bio30™) reporting that the extract at 200  $\mu\text{g}/\text{ml}$  concentration exerted suitable antiproliferative activity in DLD-1 cells and anti-inflammatory potential (TNF- $\alpha$ , COX-1, COX-2). Phenolic compounds were responsible for these activities. New Zealand wax-free Bio30™ propolis tincture solids had very high levels of the dihydroflavonoids pinocembrin and pinobanksin-3-*O*-acetate, and high levels of the

dimethylallyl, benzyl and 3-methyl-3-butenyl caffeates relative to CAPE (caffeic acid phenethyl ester). Another study by Asgharpour et al. [106], described the capability of Iranian propolis to inhibit the proliferation of cancer cells. They isolated flavonoids and then, performed the *in vitro* test using various concentrations. The isolated compounds inhibited cancer cell proliferation at  $40 \pm 8.9 \mu\text{M}$  and  $195 \pm 14.9 \mu\text{M}$  concentrations, respectively in mouth epidermoid carcinoma (KB) cell line and, at  $98 \mu\text{M}$ , and  $195 \mu\text{M}$  concentrations, in skin squamous cell carcinoma (A431) cell line [106]. The ethanol extract of propolis from stingless bees *Tetragonisca fiebrigi* induced cell death by necrosis at 250 and 500  $\mu\text{g}/\text{mL}$  concentrations against K562 erythroleukemia cells [107]. Santos et al. [108] reported that the extract of Brazilian red propolis exerted antitumor activity at  $75.15 \pm 3.35$ , and  $70.81 \pm 4.18$  concentrations, respectively in diverse colon cancer cell lines.

In another study, Assumpcao et al. [109] described that the *p*-coumaric acid derived from propolis displayed cytotoxic activity at 17.02, 13.94, 22.85, and 23.55  $\mu\text{M}$  concentrations, respectively against triple-negative breast cancer cell lines. Besides, the ethanol extract of propolis inhibited the growth and proliferation of AGS human gastric cancer cells in a concentration range from 15 to 60  $\mu\text{g}/\text{ml}$  [110]. In addition, the ethanol extract of propolis displayed significant cytotoxic activity and induced apoptosis at 50 and 100  $\mu\text{g}/\text{ml}$  concentrations in human breast cancer and colon adenocarcinoma cell lines [111]. Khacha-ananda et al. [112] reported that the ethanol extract of propolis exerted cytotoxic and antiproliferative activity at a concentration of 80.96  $\mu\text{g}/\text{ml}$  in HeLa cells. A study by Ishihara et al. [113] demonstrated the effects of the ethanol extract of Chinese and Brazilian propolis using different concentrations *in vitro*. They found that the extract at concentration  $> 50 \mu\text{g}/\text{ml}$ , 38  $\mu\text{g}/\text{ml}$ , and 20  $\mu\text{g}/\text{ml}$  induced apoptosis via growth inhibitory activity in human colon carcinoma cell lines [113]. Turan et al. [114] utilized the ethanol extract of Turkish propolis to examine the cytotoxic activity. They reported that the propolis extract at  $20.7 \pm 3.4 \mu\text{g}/\text{ml}$  concentration showed the highest cytotoxic activity against PC-3 cell line preventing the proliferation of cancer cells [114]. It has been reported that propolis displayed suitable cytotoxic activity at 25 and 50  $\mu\text{g}/\text{ml}$  concentrations in human tongue squamous cell carcinoma cell line [115]. Besides, Lee et al. [116] described that propolis inhibited the proliferation of cells at 10  $\mu\text{g}/\text{ml}$  in human rectal and colon cancer cell. Another study by Markiewicz-Żukowska et al. [117] reported that propolis reduced the growth of U87MG glioblastoma cell via nuclear factor kappa B (NF- $\kappa$ B) pathway at concentration ranging from 10 to 100  $\mu\text{g}/\text{ml}$ .

Bhargava et al. [118] stated that the isolated artepillin C from Brazilian green propolis abrogated mortalin-p53 complex, causing the activation of p53 and the growth arrest of cancer cells at 275  $\mu\text{M}$  concentration in HT1080 (fibrosarcoma), A549 (lung carcinoma) and U2OS (osteosarcoma) human cell lines. In another study, Ishida et al. [119] examined the effects of isolated caffeic acid phenethyl ester from propolis on human cancer cells, SKOV3 (ovarian carcinoma), HT1080 (fibrosarcoma), A549 (lung carcinoma), HeLa (cervical carcinoma), U2OS (osteosarcoma), MCF7 and MDA-MB-231 (breast adenocarcinoma), reporting that this compound displayed suitable anticancer activity at 50  $\mu\text{M}$ . A recent study by Mohamed et al. [120] reported that the ethanol extract of propolis significantly inhibited the proliferation of MCF7 cells at 62.24  $\mu\text{g}/\text{ml}$ . Utispan et al. [121] reported that the propolis extract exerted cytotoxic activity and inhibited the proliferation of metastatic cells at  $76.33 \pm 1.24 \mu\text{g}/\text{ml}$  concentration in head and neck squamous cell carcinoma (HNSCC) cell lines. In a study, propolis at a concentration of 0.38  $\text{mg}/\text{mL}$  reduced the viability of K562 erythroleukemia tumour cell line [122]. Sun et al. [123] stated that the chrysin from propolis suppressed MDA-MB-231 breast cancer cell growth at 40  $\mu\text{M}$  and 60  $\mu\text{M}$  concentrations. In another study, Mutallip et al. [124] isolated pinobanksin-3-acetate from propolis, which inhibited the human colon cancer cell proliferation and induced apoptosis through up-regulation and down-regulation of multiple genes at 163.61  $\mu\text{g}/\text{ml}$  concentration. Motomura et al. [125] stated that the methanol extract of propolis induced the cell cycle arrest and apoptosis in HML cells U937 at 300–500  $\mu\text{g}/\text{ml}$ . It has been reported that the Brazilian red propolis produced apoptosis-like cell death and alleviated migration potential in carcinoma BCL-5637 cell line at 25, 50 and 100  $\mu\text{g}/\text{ml}$  [126]. High-resolution direct-infusion mass spectrometry (HR-DIMS) was used for chemical characterization of the red propolis extract. The main components were dereplicated as follows: *m/z* 257.0764 (liquiritigenin); 269.0769 (formononetin); 271.0921 (medicarpin); 285.0718 (biochanin A); 523.1641 (retusapurpurin B). Exact mass, fragmentation pathway, and isotopic ratio were used for confirmation. Salim et al. [127] demonstrated that the ethanol extract of Egyptian propolis revealed antioxidant and antitumoral activities at 38.48  $\mu\text{g}/\text{ml}$  in prostate cancer cell lines [127]. In addition, the ethanol extract of Brazilian green propolis induced apoptosis in human lung carcinoma cell line at 17.29  $\mu\text{g}/\text{ml}$  [128]. Sulaiman et al. [129] experimented the effects of Iraq propolis demonstrating that its extract exhibited suitable anti-tumor activity against HL-60 and HCT-116 cell lines at 25  $\mu\text{g}/\text{ml}$ .

Kamiya et al. [130] evaluated the effects of ethanol propolis extract. They observed that the extract at 10 and



**Table 7** Anticancer properties of propolis ethanol, water, methanol and hydroalcoholic extracts (EE, WE, ME and HAE, respectively) and their isolated compounds

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
Hyperibone A	HeLa tumor cells	IC <sub>50</sub> = 0.18 μM	In vitro	Cytotoxic	Brazil	[95]
Nemorosone	HeLa tumor cells	IC <sub>50</sub> = 3.3 μM	In vitro		Cuba	[95]
Luteolin	Human colon cancer (HCT-116)	IC <sub>50</sub> = 115.68 μM	In vitro	Cytotoxic/apoptosis	Serbia	[96]
Luteolin	Human triple negative breast cancer (MDA-MB-231) cell lines	IC <sub>50</sub> = 66.86 μM	In vitro			
Myricetin	Human triple negative breast cancer (MDA-MB-231) cell lines	IC <sub>50</sub> = 114.75 μM	In vitro	Inhibition of cell growth and apoptosis		
Galangin	Human colon cancer and human triple negative breast cancer cell lines	IC <sub>50</sub> = 50 μM	In vitro	Apoptosis		
EE	glioblastoma cells cancer line	IC <sub>50</sub> = 92.2 μg/mL	In vitro	Cytotoxic	Mexico	[98]
(7''R)-8-[1-(4'-Hydroxy-3'-methoxyphenyl) prop-2-en-1-yl] galangin	PANC-1 humanpancreatic cell line	IC <sub>50</sub> = 4.6 μM	In vitro	Apoptosis-like morphological changes/Cytotoxic		[97]
Chrysin, pinobanksin, pinobanksin-3-O-propanoate, pinobanksin-3-O-butyrate, pinobanksin-3-O-pentanoate, pinobanksin-3-O-hexanoate	B-cell lymphoma cell line	IC <sub>50</sub> = 49.1 μM; 52.1 μM; 67.0 μM; 49.9 μM; 51.3 μM; 76.6 μM	In vitro	Antiproliferative activity through apoptotic induction	Sonaran	[99]
Turkish propolis EE	Human adenocarcinomic alveolar basal epithelial (A549) cancer	IC <sub>50</sub> = 31.7 μg/mL	In vitro	Cell cycle arrest (G <sub>1</sub> phase), induction of endoplasmic reticulum stress, caspase activity, and apoptosis; decrease of mitochondrial membrane potential	Turky	[100]
Turkish EE	human normal foreskin fibroblast cells	IC <sub>50</sub> = 76.9 μg/mL	In vitro	Cytotoxic activity		
Turkish EE	Human adenocarcinomic alveolar basal epithelial (A549) cancer	31.7 and 57.1 μg/mL	In vitro	Increase of caspase activity; decrease of mitochondrial membrane potential; up-regulation CHOP mRNA expression; cell cycle arrest (G <sub>1</sub> phase)—apoptosis	Turky	[100]
EE	HCT 116 Colon Cancer and Me45 Malignant Melanoma Cells	IC <sub>50</sub> = 100 μM	In vitro	Anti-proliferative and pro-apoptotic Effect	Poland	
Propolone A-B	Ovarian cancer cell line	LC <sub>50</sub> = 19.1 μM and 29.9 μM	In vitro	Anti-proliferative	Brazil	[102]
Novel 2-phenoxochromone; 3-O-methylquercetin; 3,6,4'-trimethoxychrysin; 3,6-dimethoxy-pigenin	DLD-1 (human colon cancer), MCF-7 (human breast cancer) and A549 (human lung cancer) cancer cell lines	IC <sub>50</sub> = 65.8; 16.2; 17.1; 31.0 μM IC <sub>50</sub> = 174.4; 16.7; 50.5; 41.9 μM IC <sub>50</sub> = 81.9; 34.2; 19.9; 47.0 μM	In vitro	Anti-proliferative effect; cell growth inhibition	Brazil	[103]

**Table 7** (continued)

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
Sonoran Desert EE	Cancerous cell line M12.C3.F6 (murine B cell lymphoma)	IC <sub>50</sub> = 22.4 μM	In vitro	Antiproliferative	Sonoran Desert	[104]
Caffeic acid and pinocembrin	Human colorectal adenocarcinoma DLD-1 cells	IC <sub>50</sub> = 200 μM	In vitro	Antiproliferative	New Zealand	[105]
Ardabil EE and quercetin	Mouth epidermoid carcinoma (KB) cell line	IC <sub>50</sub> = 40 mM and 195 μM	In vitro	Cell proliferation inhibition	Iran	[106]
Ardabil EE and quercetin	Skin squamous cell carcinoma (A431) cell line	IC <sub>50</sub> = 98 μM, and 195 μM	In vitro	Cell proliferation inhibition	Iran	[106]
EE from stingless bees <i>Tetragonis-cafiabrigi</i>	K562 erythroleukemia cells	IC <sub>50</sub> = 250 and 500 μg/mL	In vitro	Necrosis	Brazil	[107]
Brazilian red EE	Colon cancer cell lines (human colorectal adenocarcinoma and human colorectal carcinoma)	IC <sub>50</sub> = 75.15 and 70.81 μg/mL	In vitro	Antitumor activity	Brazil	[108]
p-Coumaric acid	Four triple-negative breast cancer cell lines (BT-20, BT-549, MDA-MB-231, and MDA-MB-436 cells)	IC <sub>50</sub> = 17.02, 13.94, 22.85, and 23.55 μM	In vitro	Cytotoxic; decrease of cell viability	Brazil	[109]
(-)-Epigallocatechin-3-gallate	BT-20, BT-549, MDA-MB-231, and MDA-MB-436 cells,	IC <sub>50</sub> = 20.10, 19.16, 24.97 and 18.16 μM	In vitro	Cytotoxic; decrease of cell viability	Brazil	[109]
EE	AGS human gastric cancer cell	60, 30, and 15 μg/mL	In vitro	Cell growth and proliferation inhibition	Iran	[110]
	Human breast cancer, colon adenocarcinoma, epithelial colorectal adenocarcinoma, murine melanoma	50 and 100 μg/mL	In vitro	Cytotoxic/apoptosis	India	[111]
EE	HeLa cervical cancer cells	IC <sub>50</sub> = 80.96 μg/mL	In vitro	Cytotoxic/anti-proliferative effect	Thailand	[112]
	Human colon carcinoma cell lines CaCo2	IC <sub>50</sub> = 50 μg/ml	In vitro	Growth inhibitory activity by apoptosis	China	[113]
	Human colon carcinoma cell lines CaCo2	20 μg/ml	In vitro	Decrease of cells in G1, S and G2-M phases, modulation of p53 protein	China	[113]
	HCT116	38.9 μg/ml	In vitro	Growth inhibitory activity by apoptosis	Brazil	[113]
EE	Human colon carcinoma cell lines CaCo2	> 50	In vitro	Growth inhibitory activity by apoptosis	Brazil	[113]
Turkish EE	PC-3 cell line	IC <sub>50</sub> = 20.7 μg/mL	In vitro	Cytotoxic activity		[114]
Flavonoids and phenolic acid	Human tongue squamous cell carcinoma cell line	25 and 50 μg/mL	In vitro	Activation of caspases-3, -8 and -9		[115]
	Human rectal and colon cancer cell	10 μg/mL	In vitro	Proliferation inhibition		[116]
	Human U87MG glioblastoma cell	TMZ (10–100 μM), EE (10–100 μg/mL)	In vitro	Glioblastoma cell growth inhibition NF-κB activity down-regulation		[117]

**Table 7** (continued)

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
Artepillin C	HT1080 (fibrosarcoma), A549 (lung carcinoma) and U2OS (osteosarcoma) human cell lines	IC <sub>50</sub> = 275 μM	In vitro	Abrogation of mortalin-p53 complexes causing the activation of p53	Brazil	[118]
Caffeic acid phenethyl ester	Human cancer cells, SKOV3 (ovarian carcinoma), HT1080 (fibrosarcoma), A549 (lung carcinoma), HeLa (cervical carcinoma), U2OS (osteosarcoma), MCF7 and MDA-MB-231 (breast adenocarcinoma)	50 μM	In vitro	Down-regulation of mortalin and up-regulation of GADD45a and p53 tumor suppressor proteins	New Zealand	[119]
EE	MCF7 cells	IC <sub>50</sub> = 62.24 μg/mL	In vitro	Proliferation inhibition		[120]
DMEP-A-C	head and neck squamous cell carcinoma (HNSCC) cell lines	IC <sub>50</sub> = 76.33 μg/mL	In vitro	Cytotoxic activity; metastatic proliferation inhibition		[121]
<i>P. dryana</i> propolis	the K562 erythroleukemia tumour line	IC <sub>50</sub> = 0.38 mg/mL	In vitro	Cell viability decrease		[122]
Chyrin	MDA-MB-231 breast cancer cell	40 μM and 60 μM	In vitro	Up-regulation of p21 (waf1/cip1) gene expression and inhibition of histone deacetylase 8	China	[123]
Pinobanksin-3-acetate	xenograft animal model human colon cancer	90 mg/kg/day per os IC <sub>50</sub> = 163.61 μg/mL	In vitro	Cell growth suppression proliferation inhibition and apoptosis induction through up-regulation and down-regulation of multiple genes involved in cell apoptosis, cytokinetics, colorectal carcinogenesis, Wnt, and calcium signaling		[124]
ME	HML cells U937	300–500 μg/mL	In vitro	Dose-dependent decrease of Bcl-2 expression, no changes in Bax expression, apoptosis		[125]
Liquiritigenin, formononetin, medicarpin, biochanin A, retusapurpurin	Carcinoma BCL-5637	25, 50 and 100 μg/mL	In vitro	Increase of Bax/Bcl-2 ratio levels	Brazil	[126]
EE	Prostate Cancer cell lines PC-3	IC <sub>50</sub> = 38.48 μg/mL	In vitro	Slight increase on Bax mRNA	Egypt	[127]
EE	Human lung carcinoma cell line	1/4 IC <sub>50</sub> = 17.29 μg/mL	In vitro	Decrease of mitochondrial membrane potential by overexpression of pro-apoptotic genes (Bax and Noxa) and decrease of the Anti-apoptotic gene Bcl-XL	Brazil	[128]

**Table 7** (continued)

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
WE <sup>a</sup>	HL-60 and HCT-116 cell lines	25 µg/mL	In vitro	Increase of Bax	Iraq	[129]
EE	Breast Cancer lines MCF-7	10 and 20 µg/mL	In vitro	Increase of Bax mRNA and decrease of Bcl-2 mRNA	Brazil	[130]
EE	HEp-2 human laryngeal carcinoma cell	1/4 IC <sub>50</sub> = 14 and 16 µg/mL	In vitro	Down-regulation of Bcl-2 and Bcl-XL mRNA; Up-regulation of Bax; apoptosis	Brazil	[131]
ME	HML cells U937	100, 300 and 500 µg/mL	In vitro	Caspase-3 activation	Japan	[125]
EE	Breast Cancer lines MCF-7 and MDAMB-231	50, 100 and 200 µg/mL	In vitro	Caspase-3 activation	Chinese	[132]
EE	HeLa	Nan: 125 µg/mL 250 µg/mL	In vitro	Caspase-3 activation	Thailand	[133]
EE	Human tongue carcinoma cell line (CAL-27)	200 µg/mL	In vitro	Caspase-3, -8 and -9 activation	Poland	[115]
EE	Breast Cancer lines MCF-7	63, 125 and 250 µg/mL	In vitro	Activation of caspase-6 than caspases-8 and 9	Turkey	[134]
EE	Breast Cancer lines MCF-7	20 µg/mL	In vitro	Caspase-3 activation	China and Brazil	[130]
EE	HEp-2 human laryngeal carcinoma cell	IC <sub>50</sub> = 80 µg/mL	In vitro	Apoptosis due to ROS generation and caspase-3 activation	Brazil	[135]
EE	Human lung carcinoma cell line A549	35 µg/mL	In vitro	Mitochondrial membrane potential decrease and caspase activity increase	Turkey	[100]
EE	LNCaP prostate cancer cells	25–50 µg/mL	In vitro	Up-regulation of TRAIL-R2		[136, 137]
Cardol	SW620 human colorectal cancer cell line	IC <sub>50</sub> = 4.51 ± 0.76 µM	In vitro	Increase of caspase-3 and -9 activity and PARP; apoptosis; mitochondrial membrane potential decrease; antiproliferative effect; G <sub>0</sub> /G <sub>1</sub> cell cycle arrest	Indonesian propolis	[138]
EE	HUVECs	6.25–25 µg/mL	In vitro	Apoptosis in tube-forming endothelial cells through inactivation of survival signal ERK1/2	Chinese	[139]
EE	HUVECs	6.25–25 µg/mL	In vitro	Decrease of PC-PLC activity, p53 and ROS levels	Brazil	[140]

**Table 7** (continued)

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
EE	HUVECs	3.13–25 µg/mL	In vitro	Angiogenesis suppression through inhibition of tube formation and proliferation; decrease of the number of newly formed vessels	Korean	[141]
HAE	HUVECs	100–200 µg/mL; 50–450 mg/Kg	In vitro	Inhibition of the tube-like structure formation (tubulogenesis)		[142]
EE	Carcinoma BCL-5637	25 and 50 µg/mL	In vitro	Cell migration inhibition	Brazil	[126]
EE	Breast Cancer line MDA-MB-231	25, 50, 100 and 200 µg/mL	In vitro	Cells migration inhibition	China	[132]
EE	Glioblastoma multiforme cell line U87MG	30 µg/mL	In vitro	Cell migration inhibition	Poland	[143]
EE	Human lung cancer A549 cell, melanoma cell line B16F10	1, 6, 12 and 30 µg/mL		Block of PAK1 and melanogenesis by down-regulation of intracellular tyrosinase activity	Japan	[144]
EE	Colon Tumorigenesis in male F344 rats	1% EE or WE, basal diet, 25 weeks	In vivo	Tumorigenesis decrease	Brazil	[145]
EE	Gastric cancer in Male Wistar rats	Enriched feed, 36 weeks	In vivo	Significantly decrease of IHC β-catenin positive tumors	Iran	[146]
EE	Bladder cancer in female Wistar rats	150 mg/Kg/day, intragastric, 40 weeks	In vivo	Chemo-preventive effects	Brazil	[147, 148]
EE	Dysplasia of tongue in male Wistar rats	100–400 mg/Kg, intraperitoneal, 20 weeks	In vivo	Tumor decrease	Iran	[149]
EE	Bladder Carcinogenesis in male F344 rats	0.125 to 1%, dietary administration, 32 weeks	In vivo	Enhances of BBN-initiated urinary bladder carcinogenesis via non-mutagenic mechanisms	Brazil	[150]
EE	Male Swiss albino mice	50 mg/Kg, gastric incubation, 7 days	In vivo	Tumor growth and proliferation inhibition; Increase of macrophages tumoricidal activity	Brazil; Zagreb, Croatia	[151]
EE	Male and female CBA inbred mice	50 or 150 mg/Kg, gauge administration, 3 days	In vivo	Suppression of tumor growth and metastases; Antimetastatic activity mediated by imm unomodulatory effects	Brazil, Zagreb, Croatia	[152, 153]

**Table 7** (continued)

Compound/extract	Model	Concentration/dose	Study type	Mechanism	Origin	References
EE	Female athymic Fox N1-nu/nu mice	500 or 1000 mg/Kg/day, p.o., 3 weeks	In vivo	Mitotic cell and Ki-67 expression decrease and increase in endoreduplications and p53 expression	Mosul, Iraq	[129]
EE	C57BL/6 male mice	200 mg/Kg, 14 days	In vivo	Transcription of stress stimulated Th1 cytokine (IL-2 and IFN- $\gamma$ ) and Th2 cytokine IL-10	Brazil	[154, 155]
EE	Female ICR mice	2.5 and 5%, oral administration, 6 days	In vivo	Suppressive effects on tumor-induced angiogenesis	Brazil	[156]
EE	OIRM in C57BL/6 mice	300 mg/Kg/day, subcutaneous administration, 5 days	In vivo	Suppression of retinal neovascularization	Brazil	[157]
EE	Female Swiss mice	500 mg/Kg/day, orally, 14 days	In vivo	Progressively increase of blood vessel number	Brazil	[158]
EE	Bladder cancer in female Wistar rats	150 mg/Kg/day, 40 weeks	In vivo	Decrease of microvascular density	Brazil	[159]

20 µg/ml induced apoptosis in MCF-7 cells [130]. Frión-Herrera et al. [131] demonstrated the cytotoxic effect of ethanol propolis extract on HEP-2 human laryngeal carcinoma cell. They reported that propolis extract at 14 and 16 µg/ml displayed cytotoxic effect and induced apoptosis [131]. Motomura et al. [125] reported that the methanol propolis extract at 100, 300 and 500 µg/ml arrested the cell cycle and induced apoptosis in human leukemic U937 cells. Xuan et al. [132] stated that the ethanol extract of Chinese propolis displayed antitumoral activity against breast cancer lines MCF-7 and MDAMB-231 at 50, 100 and 200 µg/ml. Besides, the ethanol extract of Thai propolis averted the proliferation of cancer cell via apoptosis in HeLa cell line at 125 µg/mL and 250 µg/ml [133]. Czyżewska et al. [115] described that the ethanol propolis extract exerted pro-apoptotic activity against human tongue carcinoma cell line (CAL-27) at a dose of 200 µg/ml. Moreover, Vatanserver et al. [134], in another study, stated that the ethanol extract of Turkish propolis induced apoptosis in MCF-7 cells at 63, 125 and 250 µg/ml via activating caspases. The ethanol extract of Brazilian propolis generated apoptosis in MCF-7 cells at 20 µg/ml [130]. It has been reported that the Brazilian propolis produced apoptosis through ROS generation in HEP-2 human laryngeal carcinoma cell at a dose of 80 µg/ml [135]. Demir et al. [100] used the ethanol extract of Turkish propolis to examine the antiproliferative and pro-apoptotic activity. They found that the propolis extract was able to alleviate mitochondrial membrane potential and enhance caspase activity in A549 cells at a concentration of 35 µg/ml [100]. Szliszka et al. [136, 137] reported that the ethanolic extract of Brazilian and Polish propolis induced apoptosis via upregulation of tumor necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) in LNCaP prostate cancer cells at 25–50 µg/ml [136, 137]. Cardol or 5-pentadecyl resorcinol, a compound isolated from *Trigona incisa* stingless bee propolis, displayed significant antiproliferative effect, alleviated mitochondrial membrane potential, and induced apoptosis at  $4.51 \pm 0.76$  µM concentration in SW620 human colorectal cancer cell line. Members of the Anarcadiaceae plant family are the source for this compound [138].

**Anti-angiogenic properties** Kunimasa et al. [139] demonstrated that the Brazilian propolis reduced angiogenesis by inducing apoptosis in human umbilical vein endothelial cells (HUVECs) at 6.25–25 µg/ml concentration. Another study by Park et al. [140] stated that the Brazilian propolis inhibited angiogenesis by preventing phosphatidylcholine-hydrolysing phospholipase C (PC-PLC) activity, p53 and ROS levels in HUVECs at 6.25–25 µg/ml concentration. The Korean propolis at 3.13–25 µg/ml concentrations suppressed angiogenesis through the inhibition of

tube formation and proliferation, decreasing the number of newly formed vessels in HUVECs [141]. Moreover, Meneghelli et al. [142] reported that the ethanol propolis extract at 100–200 µg/ml concentration averted the tube-like structure formation (tubulogenesis) in HUVECs.

**Cell migration** Red propolis induced an apoptosis-like cell death and attenuated cell migration in carcinoma BCL-5637 cell line at 25 and 50 µg/ml [126]. Xuan et al. [132], in in vitro studies, found that the green extract of propolis significantly alleviated the cells migration in breast cancer line MDA-MB-231 at 100 and 200 µg/ml. In another experimentation, Borawska et al. [143] revealed that the green propolis inhibited cells migration in glioblastoma multiforme cell line U87MG at 30 µg/ml. Finally, Taira et al. [144] evaluated the effects of ethanol propolis extract supplied by the Okinawa Yoho Bee-farm (Okinawa, Japan). They found that the propolis extract blocked the serine/threonine p21-activating kinase 1 (PAK1) and the melanogenesis by downregulating intracellular tyrosinase at 1, 6, 12 and 30 µg/ml. The main constituents were identified as prenylflavonoids by LC-MS and corresponded to nymphaeols A-C, isonymphaeol-B, and 3'-geranyl-naringenin.

#### **In vivo studies**

**Chemopreventive effects** Doi et al. [145] revealed that ethanol propolis extract alleviated colon tumorigenesis in male F344 rats. According to Alizadeh et al. [146], Iranian propolis remarkably prevented the immunohistochemistry positive for β-catenin positive tumors in female Wistar rats. In a female Wistar rat model, propolis extract exhibited chemo preventive activity against rat bladder carcinogenesis [147, 148]. In a report, Salehi et al. [149] examined the Iranian propolis chemo-preventive effects. They found that the propolis extract at 100–400 mg/kg dose alleviated tongue dysplasia in male Wistar rats [149]. In another report, Xie et al. [150] stated that the ethanol propolis extract increased the N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN)-induced carcinogenesis of urinary bladder through non-mutagenicity activity in male F344 rats.

**Immunomodulatory effects** Orsolić, Basić [151] reported that the ethanol propolis extract not only averted the tumor growth and proliferation but also enhanced the activity of tumoricidal macrophages. In another study, the ethanol propolis extract significantly suppressed the tumor growth and metastasis. In this study, the anti-metastatic activity was mediated by the immunomodulatory effects of propolis [152, 153]. Sulaiman et al. [129] reported that ethanol propolis extract at 500 or 1000 mg/kg increased the endoreduplication and p53 expression, with a reduction of mitotic cells and the Ki-67 expression in female

**Table 8** Anti-inflammatory properties of propolis ethanol and water extract (EE and WE, respectively) and their isolated bioactive compounds

Compound/extract	Origin	Concentration /Dose	Study type	Test system	Mechanism	References
Artepillin C	Brazil	25 $\mu$ M	In vitro	3 T3-L1 adipocytes	Inhibition of TNF- $\alpha$ Down regulation of adiponectin, increase of PPAR- $\gamma$ activity; inhibition of TNF- $\alpha$ -induced JNK signaling	[189]
	Brazil	500 mg/Kg, orally, 14 days	In vivo	Female Swiss mice	Decrease of inflammatory Cells, modulation of matrix remodeling	[190]
	Brazil	10 mg/Kg, single oral dose	In vivo	Male Swiss mice	Decrease of oedema, reduction of neutrophils number, decrease of prostaglandin E2 level	[191]
	Brazil	10 $\mu$ M 100 $\mu$ M	In vitro	RAW 264.7 cells	Reduction in NO synthesis	[191]
		50 $\mu$ M 100 $\mu$ M	In vitro	HEK 293 cells RAW 264.7 cells	Decrease of the NF- $\kappa$ B levels Inhibition of IL-1 $\beta$ , IL-3, IL-4, IL-5, IL-9, IL-12 p40, IL-13, IL-17, TNF- $\alpha$ , G-CSF, GM-CSF, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, KC and NF- $\kappa$ B pathway	[179]
Propolis extract	Brazil	30 $\mu$ g/mL 100 $\mu$ g/mL	In vitro	Peripheral leukocytes of human blood	Decrease cysteinyl leukotrienes and histamine	[192]
	-	10 mg/kg	In vivo	Carrageenan rat paw oedema rat model	Reduce prostaglandins, leukotrienes and histamine	[193]
EPE with CAPE		50 and 100 mg/Kg, orally, 7 days	In vivo	Carrageenin paw edema rat model	Inhibitory effect on granuloma and exudate formation	[194]
Propolis extracts	Cameroon	100–600 mg/Kg, 35 days	In vivo	Male Wistar rat model	Inhibit carrageenin oedema, carra- geenin pleurisy and adjuvant arthritis	[195]
Neovestitol and vestitol	Brazil	10 mg/Kg	In vivo	THP-1-derived macrophage cells	Inhibits pro-inflammatory IL-1 $\beta$ , TNF- $\alpha$ and IL-6, increase IL-10 and inhibition of purine nucleoside phosphorylase	[181]
Bulgarian Propolis	Bulgary	ID50 = 2.5 0.4 mg/kg-1	In vivo	Male Balb/c mice	Neutrophil migration	[197]
Apigenin	Bulgary	50 mg/Kg, intraperitoneally, 30 days	In vivo	Swiss male mice LPS- induced Male mice	Inhibit inflammatory cytokines, ERK1/2, NF- $\kappa$ B activation, and neutro- phil migration	[165] [204, 205]
Galangin		50 $\mu$ M	In vitro	RAW 264.7 murine macrophages	Inhibit inflammatory cytokines IL-1 $\beta$ and IL-6, and proinflammatory genes, such as iNOS, ERK1/2, NFKB p65 activa- tion, and neutrophil migration	[203, 206]



**Table 8** (continued)

Compound/extract	Origin	Concentration /Dose	Study type	Test system	Mechanism	References
pinoembrin		20 or 50 mg/kg ip	In vitro	RAW macrophage cells	Modulate the production of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-10 via inhibiting the phosphorylation of I $\kappa$ B $\alpha$ , ERK1/2, JNK and p38MAPK	[212]
Formononetin HERP		10 mg/Kg, orally 10 and 30 mg/Kg, orally	In vivo	Carrageenan-induced hindpaw oedema rat model	Inhibition of leukocyte migration and activation of NF- $\kappa$ B	[168]
Formononetin		10 mg/Kg	In vitro	INS-1 rat insulinoma cell line	Prevent IL-1 $\beta$ and cytokine-induced apoptotic signaling, reduce the Bax/Bcl-2 ratio and caspase-3 activity; activate NF- $\kappa$ B, decrease NO release	[210]
Neovestitol and vestitol		10 mg/kg	In vivo	LPS mice model	Inhibition of neutrophil migration, rolling and adhesion; inhibition of CXCL1/KC and CXCL2/MIP2 levels and neutrophil chemotaxis via blocking calcium influx	[198, 199]
Isoliquiritigenin		10 mg/mL	In vitro	Human primary endothelial cells	Inhibit adhesion of neutrophil, ICAM-1, VCAM1, E-selectin and TNF- $\alpha$ expression, translocation of the p65 subunit of NF- $\kappa$ B by blocking the phosphorylation and subsequent degradation of I $\kappa$ B $\alpha$	[213]
Daidzein		2, 4, 8 mg/Kg, ip	In vivo	Adult male Sprague-Dawley rats model	Inhibited macrophages and neutrophils infiltration, attenuated MPO activity, inhibited TLR4/MyD88 protein and NF- $\kappa$ B activation	[214]
Chinese propolis extract	China	15 $\mu$ g/mL	In vitro	RAW 264.7 cells	Inhibit the production of NO, IL-1 $\beta$ , and IL-6; suppress the phosphorylation of I $\kappa$ B $\alpha$ and AP-1; block the activation of NF- $\kappa$ B in TNF- $\alpha$ -stimulated HEK	[8]
Senegalese propolis EE	Senegal China	30 $\mu$ g/mL 25 and 100 mg/Kg, orally, 3 days	In vitro In vivo	J774.1 cells RAW 264.7 cells/endotoxemic mice	Inhibited iNOS Suppress the secretion of LPS-stimulated inflammatory cytokines, such as IL-6, IL-10, MCP-1, TNF- $\alpha$ and IL-12p70 production	[216] [447]
Propolis, coumaric and cinnamic acids		50 and 100 mg/well	In vivo/ vitro	Male BALB/c mice/ Peritoneal macrophages	Inhibited IL-10 and IL-6	[180]
Propolis extract		10 $\mu$ g/mL	In vitro	RAW 264.7 mouse macrophage cells	Inhibition of IL-1 $\beta$ , IL-6 and COX-2 mRNA expression	[211]

**Table 8** (continued)

Compound/extract	Origin	Concentration /Dose	Study type	Test system	Mechanism	References
2-Acetyl-1-coumaroyl-3-cinnamoyl-glycerol, (+)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, (-)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, 2-acetyl-1,3-dicinnamoylglycerol and (-)-2-acetyl-1-(E)-feruloyl-3-(3''(C),16'')-dihydroxy-palmitoylglycerol		10 and 100 μM	In vitro	Lipopolysaccharide (LPS)-stimulated RAW 264.7 mouse macrophage cells	Inhibitory effects on interleukin IL-1β, IL-6, and COX-2	[215]
3,3-Dimethylallyl caffeate in mixture with isopent-3-enyl caffeate		IC <sub>50</sub> = 0.49 μM	In vivo	Ear edema test in mice	Anti-inflammatory activity	[218]
Arachic acid ethyl ester		50.0 mg/Kg	In vivo	Carrageenan-induced paw edema, xylene-induced ear edema mice	Anti-inflammatory effect	[167]
Polyphenol-rich propolis extracts		100 mg of CPPE/Kg	In vitro	Lipopolysaccharide (LPS)-challenged mice/HEK 293 T cells	Suppressed NF-κB activation via inhibiting the ubiquitination of TRAF6; inhibitory effects on IκBα phosphorylation and p65 nuclear translocation; lowered serum IL-6, MCP-1, IFN-γ, TNF-α and IL-12p70	[208]
2-Hydroxy-8-prenylbiochanin A		IC <sub>50</sub> = 23.3 μg/mL	In vitro	Lipopolysaccharide (LPS) stimulated J774.2 mouse macrophages	NO inhibition	[219]
β-Amyrine acetate		IC <sub>50</sub> = 4.3 μg/mL			ROS inhibition	
Lupeol acetate		IC <sub>50</sub> = 1.1 μg/mL				
South Brazilian organic propolis	Brazil	0.1, 1, and 10 μg/mL	In vitro	RAW 264.7 macrophages	Decreased NF-κB activation and TNF-α release	[207]
3',4'-Dihydroxy-4-methoxydalbergione, 4-methoxydalbergion, cearoin, and chrysin	Nepal	30 μg/mL	In vitro	Bone marrow-derived mast cells (BMMC) and cell cultures	Inhibited IL-33-induced mRNA expression of inflammatory genes including IL-6, TNFα and IL-13 and activation of NF-κB	[182]
WE		50 mg/kg, i.p	In vivo	Male Wistar albino rats	Reduced ciliary body NF-κB/p65 immunoreactivity and AH levels of HIF-1α and TNF-α	[201]
EE		50 μL	In vitro	Hyaluronidase assay	Inhibited the hyaluronidase enzyme	[107]
Brazilian organic propolis	Brazil	10 μg/mL	In vivo	C57BL/16 SPF male mice	Reduced NF-κB activation, TNF-α release, and neutrophil migration	[448]
EE		1 mg/Kg	In vivo	Carrageenan-induced paw oedema in rats model	Decreased PGE <sub>2</sub> and NO levels, inhibited the IL-6 increase	[217]
Daidzein, formononetin A and biochanin A		4.68 μg/mL, 31.81 μg/mL, 9.58 μg/mL	In vivo	Adult male Wistar rats	Anti-inflammatory	[209]
Luteolin, galangin, quercetin		0.5 mg	In vivo	Croton oil-induced oedema in rats	Inhibited IL-1β and TNF-α	[202]
Lebanese propolis EE	Lebanon	30 μg/mL	In vitro	LPS-activated RAW monocytes	Inhibited COX-2 and iNOS protein expression, as well as PGE <sub>2</sub> and NO release	[222]

**Table 8** (continued)

Compound/extract	Origin	Concentration /Dose	Study type	Test system	Mechanism	References
Malaysian propolis	Malaysia	300 mg/kg b.w	In vivo	Male Sprague Dawley rats	Reduced malondialdehyde, NFκB (p65), TNF-α, IL-1β	[221]
CAPE		30 mg/kg	In vivo	High-fat diet-induced obesity in mice	Reduced the induction of the inflammatory pathway, c-jun-N-terminal kinase, NF-κB, COX-2 expression	[186]
		100 and 200 mM	In vitro	Human middle ear epithelial cells	Inhibited upregulation of TNF-α and COX-2	[185]
		$2.8 \times 10^{-4}$ –2.8 μg/mL	In vitro	Murine monocyte/macrophage J774 cell line	Inhibited COX-1 and COX-2	[184]
		30 mg/kg	In vivo	Gy gamma whole-body irradiation of rats	Decreased IL-6R, IL-6, IL-8, enhanced IL-10, suppressed cytokine signaling-3,	[223]
Caffeic acid		10 μg/mL	In vitro	Raw 264.7 macrophages	Inhibited NO production, p38 MAPK, JNK1/2 and NF-κB	[224]
EEP, chrysin, galangin, kaempferol quercetin		30 μg/mL	In vitro	J774A.1 macrophages	Suppressed both IL-1β mRNA ( $P < 0.02$ ) and iNOS mRNA ( $P < 0.001$ ) expression, decreased the IL-1β mRNA level and IL-1β protein concentration	[183]
Neovestitol		0.22 μM	In vitro	RAW264.7 murine macrophages	Inhibited NO production and reduced GM-CSF, IFN-γ, IL-1β, IL-4, TNF-α and IL-6 levels, increased IL-10 production, down-regulated genes related to nitric oxide production, NF-κB, IL-1β, and TNF-α signaling pathways	[200]
Okinawa propolis	Japan	200 μM	In vitro	RAW 264.7 cells	Reduced iNOS, COX-2, and PGE <sub>2</sub>	[220]

N1-nu/nu mice. According to Missima et al. [154, 155], the ethanol propolis extract stimulated cytokine production and thereby, displayed stress in C57BL/6 male mice at 200 mg/kg. An investigation by Doi et al. [145] reported the activation of NK cell cytotoxicity after the treatment with 500 mg/kg/day ethanol propolis extract in wild-type and RAG 2-deficient C57BL/6 mice.

**Anti-angiogenic effects** Ahn et al. [156] reported that the Brazilian propolis at 2.5 and 5% exerted suppressive effects against tumor-induced angiogenesis in female ICR mice. Moreover, an experiment carried out by Chikaraishi et al. [157] used green propolis extract to determine the angiogenic effects. In this study, they found that propolis at 300 mg/kg/day significantly alleviated the retinal neovascularization in C57BL/6 mice [157]. In another study, de Moura et al. [158] showed the anti-angiogenic effects of 500 mg/kg/day water propolis extract in female Swiss mice by morphometric analysis and evaluating the hemoglobin content. They reported that the number of blood vessels decreased gradually in the treated group in comparison to the control group [158]. Dornelas et al. [159] found that the microvascular density in bladder carcinomas was lower when applying propolis extract at the concentration of 150 mg/Kg/day in female Wistar rats. Anti-cancer properties of propolis ethanol, water, methanol and hydroalcoholic extracts and their isolated compounds are shown in Table 7.

### Analgesic effects

One of the most prevalent complaints seen in medical practice is pain [160]. Following tissue damage and/or injury, nociceptors (specialist peripheral sensory neurons) are triggered by noxious stimuli (chemical, mechanical, and thermal stimuli). Muscle, cutaneous tissues, connective tissues, arteries, viscera, and bone are all places where nociceptors may be found [161]. The release of inflammatory mediators, which can lower the threshold of nociception, and direct activation of nociceptive afferent fibers owing to pH lowering may both be involved in the acetic acid-induced nociceptive response [162]. Propolis red extract showed analgesic effect on mice model [163] via suppression of NF-kB [164]. Bulgarian propolis was reported to inhibit the contraction of trachea smooth muscle induced by histamine, capsaicin, and carbachol in vitro displaying analgesic effect [165]. Furthermore, Brazilian propolis exhibited anti-nociceptive effect and reduced paw oedema via activating the opioid receptors in rats [166]. Arachidonic acid ethyl ester, a bioactive substance isolated from Cameroonian propolis, reduced acute central pain sensation [167].

Propolis and its chemical constituents presented antinociceptive action on inflammatory and neurogenic pain

without motor side effects [168]. Also, one of the main chemical analogues of propolis, formononetin, showed antinociceptive effect [168]. Chinese propolis also showed central and peripheral antinociceptive properties due to the presence of flavonoids [169]. In the writhing model, propolis reduced the number of writhes, leading to antinociceptive effect [170].

Propolis demonstrated antinociceptive properties via two possible ways against acetic acid writhing model, i. by local peritoneal receptors; ii. by inhibition of prostaglandin synthesis or action [171, 172]. Furthermore, propolis was used to treat a wide variety of gynecologic, dental, and dermatological issues, where pain is a most frequent issue [173]. The release or production of mediators (e.g., serotonin, kinins, prostaglandin and aminoacids) from neurons or injured tissues is involved in the inflammatory process and in pain processing responses [174, 175].

A number of phytochemical constituents were identified in different propolis samples such as chalcones and dihydrochalcones [176, 177], flavanones, flavones and flavonols, hydrocarbons esters ethers, terpenoids, lignans, steroids [49, 178]. Brazilian red and green propolis, Chinese propolis, Bulgarian propolis, Iranian propolis and Cameroonian propolis have the ability to reduce pain sensation in mice/rat models [165, 167, 169, 170]. Brazilian propolis suppressed acetic acid-induced pain and increased the pain threshold reducing the nociceptive response [160]. As a result, the high flavonoids content in green Brazilian propolis could explain these anti-inflammatory properties [179]. Propolis extract promotes the down-regulation of pro-inflammatory cytokines (e.g., interleukin (IL)-1, TNF- $\alpha$ , and IL-6), inhibits the purine nucleoside phosphorylase, and increase the anti-inflammatory IL-10 according to previous results [180, 181]. Several investigations have tried to understand the processes behind the analgesic action of propolis [182]. Previous studies have established that propolis contains several polyphenols, terpenoids and lignans such as artemillin C, neovestitol, vestitol [165], pinocembrin, chrysin, galangin, kaempferol, quercetin, isoliquiritigenin, acetyl-1-coumaroyl-3-cinnamoylglycerol, (+)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, (-)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, 2-acetyl-1,3-dicinnamoylglycerol and (-)-2-acetyl-1-(E)-feruloyl-3-(3'',16'')-dihydroxy-palmitoylglycerol, 3,3-dimethylallyl caffeate, caffeic acid phenethyl ester, which showed anti-inflammatory properties in different experimental systems [183–186]. It has been reported that flavonoids suppressed the release of arachidonic acid and interact with GABA-ergic, serotonin and L-arginine–nitric oxide (NO) system [187].

### Anti-inflammatory activity

The anti-inflammatory activities of propolis are shown in Table 8. Propolis has great impact on inflammation [188], because it up-regulates or down regulates several inflammatory mediators [189]. A number of compounds were isolated from propolis, which have anti-inflammatory effects [190]. Artepillin C showed anti-inflammatory potential in adipocytes via down-regulation of adiponectin mediated by TNF- $\alpha$  and c-Jun N-terminal kinase (JNK) pathways [189], and decreasing inflammatory cells through modulation of matrix remodeling [190]. Furthermore, in an in vivo experimental model, artepillin C, reduced oedema by decreasing neutrophils, NO and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) release [191] and by down-regulation of the NF- $\kappa$ B pathway, which help to attenuate the release of pro-inflammatory cytokines such as TNF- $\alpha$  [191]. These data were confirmed by Szliszka et al. [179], who demonstrated that artepillin C have the ability to in vitro down-regulate the inflammatory chemokines IL-1 $\beta$ , IL-3, IL-4, IL-5, IL-9, IL-12 p40, IL-13, IL-17, TNF- $\alpha$ , G-CSF, GM-CSF, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES by modulating the NF- $\kappa$ B pathway [179]. Other studies reported that propolis extract and artepillin C decreased cysteinyl leukotrienes and histamine in peripheral leukocytes [192, 193]. Moreover, propolis extract inhibited granuloma and exudate formation [194]. Ethanol propolis extract with CAPE exerted anti-inflammatory effects in wistar rat model through inhibition of carrageenin oedema, pleurisy, and adjuvant arthritis [195]. Further studies showed that propolis extract accelerated the down-regulation process of pro-inflammatory cytokines release (e.g., IL-1 $\beta$ , TNF- $\alpha$  and IL-6), inhibited purine nucleoside phosphorylase and increased the anti-inflammatory IL-10 in macrophage cell line [180, 181]. Several inflammatory illnesses have been linked to excessive production of these mediators [196].

Vestitol, neovestitol, and Bulgerian propolis extract suppressed the neutrophil migration [165, 197]. Besides, in a lipopolysaccharide (LPS)-induced inflammatory mouse model, vestitol and neovestitol blocked neutrophil migration, rolling, and adhesion, as well as inhibiting the levels of the chemokines CXCL1/KC and CXCL2/MIP2 and neutrophil chemotaxis by preventing calcium influx [198, 199]. Neovestitol inhibited NO production and reduced GM-CSF, IFN- $\gamma$ , IL-1 $\beta$ , IL-4, TNF- $\alpha$  and IL-6 levels, increased IL-10 production and down-regulated genes related to NO production, NF- $\kappa$ B, IL-1 $\beta$ , and TNF- $\alpha$  signaling pathways [200].

Brazil propolis extract inhibited inducible nitric oxide synthase (iNOS) gene expression [164], TNF- $\alpha$  release, and neutrophil migration via reducing NF- $\kappa$ B activation [201]. Apigenin, luteolin, quercetin and galangin, active constituents isolated from propolis, down-regulated

inflammatory cytokines such as IL-1 $\beta$  and IL-6, TNF- $\alpha$  and inflammatory genes, such as iNOS, extracellular signal-regulated kinase 1/2 (ERK1/2) and NF- $\kappa$ B and inhibited neutrophil migration [202–206]. Formononetin also suppressed the activation of NF- $\kappa$ B pathway via ubiquitination of TRAF6 [168, 207, 208] and arrest IL-1 $\beta$ , cytokine-induced apoptotic signaling by blocking Bax/Bcl-2 ratio, caspase-3 activity and NO release, exerting anti-inflammatory effect [209, 210]. Furthermore, both IL-1 and iNOS mRNA expression were decreased by chrysin, galangin, kaempferol, and quercetin in macrophages [183].

Pinocembrin inhibited the phosphorylation of I $\kappa$ B $\alpha$ , ERK1/2, JNK, and p38/MAPK pathways, which controlled the production of inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, and IL-10) [180, 211, 212]. Isoliquiritigenin inhibited neutrophil adhesion, adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin expression and translocation of the p65 subunit of NF- $\kappa$ B by blocking the phosphorylation and subsequent degradation of I $\kappa$ B $\alpha$  in human primary endothelial cells [213]. Daidzein also blocked the activation of NF- $\kappa$ B, inhibiting macrophages and neutrophils infiltration in the inflammatory response. Furthermore, it attenuated myeloperoxidase (MPO) activity and MyD88 protein [209, 214].

Propolis extract from China also exerted anti-inflammatory properties via attenuating the production of NO, IL-1 $\beta$ , and IL-6 mediated by the phosphorylation of I $\kappa$ B $\alpha$ , AP-1 and NF- $\kappa$ B pathways [8, 215]. Senegalese propolis blocked the inflammatory gene iNOS [216]. Propolis extract and the isolated bioactives 2-acetyl-1-coumaroyl-3-cinnamoylglycerol, (+)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, (-)-2-acetyl-1-feruloyl-3-cinnamoylglycerol, 2-acetyl-1,3-dicinnamoylglycerol and (-)-2-acetyl-1-(*E*)-feruloyl-3-(3'',16'')-dihydroxy-palmitoylglycerol down-regulated the IL-1 $\beta$ , IL-6, cyclooxygenase (COX)-2 mRNA expression in mouse macrophage cells [211, 215]. Propolis aqueous extract decreased ciliary body NF- $\kappa$ B/p65 immunoreactivity as well as hypoxia inducible factor (HIF-1) and TNF- $\alpha$  levels in the aqueous humor [201]. Ethanol extract of propolis attenuated hyaluronidase enzyme [107]. Hu et al. [217] demonstrated that ethanol extract of propolis decreased PGE<sub>2</sub> and NO levels and inhibited IL-6 release in carrageenan-induced paw oedema in a rat model. Furthermore, a mixture of three bioactive compound isolated from Mexican propolis (3,3-dimethylallyl caffeate, isopent-3-enyl caffeate and arachic acid ethyl ester) reduced inflammation in ear and paw edema [167, 218]. Moreover, 2-hydroxy-8-prenylbiochanin A,  $\beta$ -amyrine acetate and lupeol acetate increased the NO inhibition in macrophages [219]. In bone

**Table 9** Antidiabetic effects of propolis extracts (PE) and their isolated bioactive compounds

Extract/Compound	Concentration	Study level	M/A	References
PE	IC <sub>50</sub> 3.77 μM	In vitro	α-Glucosidase inhibition	[220]
Chihuahua propolis	300 mg/kg/day, orally, 15 days	In vivo	Suppress Blood glucose levels	[234]
Astrapterocarpan, medicarpin, 8-prenylnaringenin	8.0, 5.0 and 4.0 mg/g	In vivo	α-Amylase and α-glucosidase inhibition	[228]
Propolis and bee pollen extracts	100–200 mg/Kg b.w., orally, 16 weeks	In vivo	Reduction of blood glucose and insulin resistance	[233]
PE	300 mg/Kg b.w., orally, 4 weeks	In vivo	Reduction of fasting blood glucose	[232]
PE	50–100 mg/Kg b.w., orally, 15 days	In vivo	Reduction of blood glucose	[231]
PE	300 mg/Kg b.w., orally, 15 days	In vivo	Reduction of blood glucose	[234]
PE	IC <sub>50</sub> 70.79 μg/mL	In vitro	α-Glucosidase inhibition	[227]
PE	IC <sub>50</sub> 0.09 mg/mL	In vitro	α-Amylase and α-glucosidase inhibition	[239]
PE	200–300 mg/Kg b.w./day, orally, 28 days	In vivo	Reduction of blood glucose, conservation of normal pancreatic cell architecture	[235]
PE	100 mg/Kg b.w., oral intubation, twice daily, 8 weeks	In vivo	Reduction of fasting blood glucose, reduction of glycated hemoglobin; restoration of hepatorenal functions	[236]
PE	200 mg/Kg b.w., orally, 5 weeks	In vivo	Reduction of serum glucose, reduction of oxidative stress parameters	[237]
PE	100–300 mg/Kg b.w., orally, 8 weeks	In vivo	Reduction of plasma level of insulin and HOMA-R index of insulin resistance	[229]
PE	1 mL/100 g, intragastrically, twice daily, 8 weeks	In vivo	Reduction of blood glucose, reduction of fructosamine, malonaldehyde and nitric oxide	[230]
PE	IC <sub>50</sub> 4.7 mg/mL	In vitro	Maltase and α -amylase inhibition	[400]
PE	1–2% w/w	In vivo	Reduction of cholesterol, triacylglycerol and ALT	[449]
PE	70 μL of 85% PE/animal, 60 days	In vivo	Increase of plasmatic HDL, prevention of LVH and arterial atherogenesis	[450]
PE	160 mg/Kg b.w., 14 weeks	In vivo	Reduction of total cholesterol and triglycerides, without any effect on HDL, decrease of atherosclerotic lesion development in aortic root	[451]
PE	250 mg/Kg b.w./day, orally, 4 weeks	In vivo	Normalisation of lipid profile/down-regulation of VCAM, FGF, VEGF and MMP-9 gene expression	[247]
PE	75 mg/Kg b.w., orally	In vivo	Reduction of total cholesterol, LDL and triglycerides	[266]
PE	0.05–0.5% w/w, orally, 8 weeks		Reduction of cholesterol and triglycerides/increase of PPARα protein level in the liver	[246]
CAPE	60 ng/mL	In vitro and in vivo	Increase of p-Akt and p-insulin receptor substrate (IRS)-1, inhibition of p-JNK, p-NF-κB p65, and nuclear translocation of p-NF-κB p6	[243]
PE conjugated with chitosan polyacrylic (CS-PAA) nanoparticles		In vivo	Suppress blood glucose levels	[245]
PE	300, 600 mg/Kg b.w., orally, 4 weeks	In vivo	Reduce glucagon, FBG level, and improve insulin and islet of Langerhans regeneration	[452]
Tectochrysin	60 μL/mL	In vitro	α-Glucosidase inhibition	[244]
PE	200, 600 mg/Kg b.w./day, orally, 6 weeks	In vivo	Decrease of glucose level	[453]
PE	100 g/Kg b.w., oral intubation, twice daily, 8 weeks	In vivo	Decrease of glucose level	[236]

**Table 9** (continued)

Extract/Compound	Concentration	Study level	M/A	References
PE	240 $\mu$ M	In vitro	Decrease the of G6Pase expression by inhibiting the autophosphorylation of GSK3 $\alpha$ and $\beta$ , which are involved in the activation of GSK3	[242]

marrow-derived mast cells (BMMC), 3',4'-dihydroxy-4-methoxydalbergione, 4-methoxydalbergion, cearoin, and chrysin isolated from Nepalese propolis, reduced the IL-33-induced activation of NF-kB [182]. Ethanol extract of Lebanese and Malaysian propolis induced anti-inflammatory reaction through blocking TNF- $\alpha$ , IL-1 $\beta$ , COX-2 PGE2, NO release and iNOS protein expression, as well as malondialdehyde (MDA) and NF-kB (p65) expression [220–222]. Furthermore, CAPE suppressed the activation of NF-kB p65, decreasing the inflammatory pathway. In addition, it reduced the expression of JNK, COX-1 and COX-2, and TNF- $\alpha$  in obese mice [184–186] and the release of IL-6 and IL-8, enhanced the anti-inflammatory cytokines IL-10 and suppressed the cytokine signaling-3 pathway [223]. Caffeic acid prevented macrophages from producing NO, via activating p38 MAPK, JNK1/2, and NF-kB [224].

#### Antidiabetic effects

Diabetes is a prevalent chronic metabolic health condition [225].  $\alpha$ -Amylase and  $\alpha$ -glucosidase are enzymes necessary for the uptake of glucose from starch or maltose.  $\alpha$ -glucosidase is essential for disaccharides hydrolysis and, suppressing this enzyme, it is possible to attenuate the blood glucose absorption [226]. Many drugs, that inhibit  $\alpha$ -glucosidase have been shown to reduce post-prandial hyperglycemic peaks, making them effective in the treatment of type 2 diabetes. However, a variety of side effects such as stomach pains or diarrhea may make it difficult for patients to stick to their treatment regimen [226]. As a result, natural compounds that inhibit  $\alpha$ -glucosidase might be promising therapeutic candidates for the treatment of diabetic mellitus. In this sense, propolis showed hypoglycemic effect by blocking  $\alpha$ -glucosidase ( $IC_{50}$  3.77  $\mu$ M) [220, 227]. Many compounds isolated from propolis such as astrapterocarpan, medicarpin and 8-prenylnaringenin exert antidiabetic effect via suppressing  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes in in vivo assays [228]. Furthermore, propolis extract reduced blood glucose levels in a dose-dependent manner [229–237]. The inhibitory impact of numerous triterpenes isolated from propolis such as cycloartenol, ambonic acid, mangiferonic acid and amboic acid on  $\alpha$ -glucosidase was investigated by

Pujirahayu et al. [238]. Mangiferonic acid showed the highest inhibitory impact on  $\alpha$ -glucosidase with an  $IC_{50}$  of 3.46  $\mu$ M [238]. Moreover, propolis and bee pollen extracts ameliorated the insulin resistance [233] as well as the  $\alpha$ -glucosidase and  $\alpha$ -amylase [239] activity, helping to reduce blood glucose.

The insulin receptor, acting like a tyrosine kinase receptor, shows a wide range of function in human body. Insulin receptor signal pathway helps to regulate glucose transporter in membranes of several cells including hepatocytes, adipocytes, and skeletal muscle cells for energy metabolism [240]. Insulin resistance can be caused by disruptions in various signaling pathways. Modulating insulin receptor signaling at various points along the intracellular route can improve insulin responsiveness in a variety of tissues and, reduce insulin resistance [240]. Several studies demonstrated that natural compounds may modulate the insulin receptor signal with promising results. Liu et al. [241] revealed that propolis with its main compounds galangin and pinocembrin can modulate insulin receptor signaling through regulating Akt/mammalian target of rapamycin (mTOR) signaling pathway [241]. Furthermore, these two phytochemicals attenuated insulin resistance via increasing the insulin sensitivity, Akt, and glycogen synthase kinase-3 (GSK3)  $\beta$  and decreasing insulin receptor substrate 1 (IRS-1) phosphorylation. Propolis inhibited the expression of glucose 6-phosphatase (G6Pase) by inhibiting the autophosphorylation of GSK3 $\alpha$  and  $\beta$ , which are involved in the activation of GSK3 [242]. In diabetes, IRS-1 phosphorylation has been established to be related to insulin signal transduction, hence galangin, and pinocembrin reinstate the sensitivity of insulin receptors and diminish insulin resistance [241]. Another study reported that CAPE increased the IRS-1. On the contrary, p-JNK, p-NF-B p65, and nuclear translocation of p-NF-B p6 were suppressed [243]. Tectochrysin (5-hydroxy-7-methoxyflavone) is a bioactive substance from propolis, which exerted hypoglycemic effect by blocking the  $\alpha$ -glucosidase enzyme [244]. Besides, propolis with chitosan polyacrylic (CS-PAA) nanoparticles diminished blood glucose levels [245]. Finally, propolis reduced body cholesterol and triglycerides levels and increased peroxisome proliferator activated receptor

alpha (PPAR- $\alpha$ ) protein expression in the liver [246]. In mice, an ethanol extract of propolis showed anti-hyperlipidemic and antioxidant activity and exhibited protective action on the cardiovascular system and hepatorenal functions [247]. Anvarifard et al. [248] recently reviewed the cellular mechanisms of Propolis on preserving renal functions. Antidiabetic effects of propolis extracts and their isolated bioactive compounds are shown in Table 9.

### Wound healing activity

Wound healing is a complex, multi-step process that can be hampered by a variety of internal and environmental causes [249]. Skin is one of the most prominent part of human body and acts as first line defence system. It can be perturbed by several factors including inflammation and bacterial infections and, these events often require long therapy to achieve a perfect healing [250]. According to recent findings, propolis aids wound healing in a time-dependent manner. The immunomodulatory [10], antimicrobial [251], antioxidant [252], analgesic, and anti-inflammatory [253] properties of propolis might account for accelerating the wound healing [254]. Vascular endothelial growth factor (VEGF), is a growth factor related to endothelial cell growth and migratory activation. VEGF promotes the growth of fibroblasts [255, 256], which play a pivotal role in the wound healing process [257]. Collagen deposition is an integral part of the healing process. It has been proved that propolis contributes also to increase the cell influx and collagen deposition [258].

Propolis has been shown in recent research to have a significant wound healing impact by up regulating the healing process at the tissue level. The preventive impact of propolis is mainly attributed to aminoacids, flavonoids, phenolic acids, terpenes, and vitamins [259]. Propolis extract displayed protective activity by regulating antioxidant-related genes including heme oxygenase 1 (HO-1), GCLM, GCLC in wounded tissue [260]. Propolis bioflavonoids improved immunity and induced the production of interferon by white blood cells or lymphocytes. In a rat experiment model, propolis also activated the thymus, the immune system's master gland, and healed wounds. Furthermore, it has a greater wound healing activity than silver sulfadiazine when used as a skin cream [261].

Mast cells, characterized by inflammatory, proliferative, and remodeling phases, play important roles in wound healing. Mast cell enhance skin wound healing throughout the release of vasochemical mediators such as histamine, proteases, TNF- $\alpha$  and arachidonic acid metabolites [262], and promote the anticoagulant activity. Furthermore, mast cell attach leukocyte to the injured areas, and with macrophages, contribute to phagocytosis

and debridement [262]. Mast cells also help to enhance angiogenesis, fibroplasia and re-epithelialization [263]. Propolis used topically reduce the number of mast cells, favouring wound healing [264]. Isolated bioactive constituents from propolis, like CAPE and other active compounds reduced the levels of mast cell and improved surgical wound during acute inflammation phase [263]. Furthermore, CAPE attenuated histamine release and inflammatory cytokines in wounded tissue [265, 266]. Propolis and its components, such as chrysin and kaempferol, have anti-inflammatory properties [267]. Chrysin have the ability to inhibit inflammatory cytokines gene expression such TNF- $\alpha$ , IL-1, IL-4, and IL-6 in mast cells through NF- $\kappa$ B and caspase-1 related mechanistic pathways [267, 268]. Moreover, kaempferol can also inhibit degranulation and cytokine production by the activated mast cells [267] and improved wound healing capacity of propolis in experimental wound healing model.

Because oxidative stress occurs after wound, the antioxidant activities of propolis could favour tissue repair [269, 270]. Some studies reported that release of prooxidant mediators, such as reactive oxygen and nitrogen species, is linked to severe burns [270, 271]. Free radicals in burns disrupt the functionality of cellular membranes and intracellular organelles, and numerous inflammatory signaling processes, reducing the wound healing activity [271]. Hence, antioxidant compounds represent promising therapeutic agents for attenuating burn related injuries [270]. In several studies, it has been demonstrated that propolis exert antioxidant qualities, making it a viable alternative for regulating burn wound healing [71, 74, 272, 273]. Okinczyc et al. [273] reported that propolis from Eurasian areas have potential antioxidant activity. Propolis exert antioxidant activity in burn wound healing process due to its flavonoid and phenols content [274]. Mohammadzadeh et al. [274] stated that there is a strong relationship between the chemical composition of propolis and its antioxidant activity. The flavonoids (including flavones, flavonols, flavanones and dihydroflavonols) and other phenolics (mainly cinnamic acids and their esters) are able to scavenge free radicals [247, 275]. Polyphenolic compounds of propolis displayed a protecting role by reducing the proteins break down, and maintaining the integrity of cellular membrane decreasing peroxidation and hemolysis [272]. CAPE with some other polyphenols can upregulate the expression of aminopeptidase (AMP) gene, which helps re-epithelialize skin cell in chronic wound [276, 277] and reduce lipid peroxidation reducing the DNA and protein breakage [71]. In addition, propolis extract rich in galangin, has the ability to inhibit superoxide anion production and suppress oxidative stress in wound injuries [71].



**Table 10** Antiviral activity of propolis water, ethanol and hydroalcoholic extracts (WE, EE and HAE, respectively) and isolated compounds

Extract/Compound	Concentration /Dose	Test system	Results/Mechanisms	References
WE and EE	0–120 pfu (%)	HSV-1 on RC-37 cells	Affects viral infection cycle	[294]
WE and EE	0.00005–0.005 pfu (%)	HSV-2 on cells RC-37	Inhibition of HSV-2 plaque formation (IC <sub>50</sub> 0.0005% and 0.0004%, respectively)	[295]
0.5% WE	–	Rat and rabbit infected with HSV-1	50% inhibition of HSV infection	[296]
Mexican EE	250 µg/mL	<i>Canine distemper virus</i>	Inhibition of the virus nucleoprotein gene expression	[297]
5% HAE	–	<i>Influenza virus</i> in mice	Prevents influenza viral proliferation	[298]
Brazilian EE	50–100 µg/mL	HRV-2, HRV-3, and HRV-4 in HeLa cells	Block virus entrance into the cells, avoiding virus destruction and replication	[299]
Galangin, kaempferol, quercetin	0.05–1.0 µM	HSV-1	Reduce the viral titer by 2log <sub>10</sub>	[300]
3-methyl-but-2-enyl caffeate	6.25, 12.5, 25 and 50 µg/mL	HSV-1	Reduce the viral titer by 3log <sub>10</sub> and viral DNA synthesis by 32-fold	[301]
CAPE	5 µM	HTLV-1	Inhibits NF-κB activation during in vitro infection	[454]
Green propolis EE	5 mg	Suid herpesvirus type 1 (SuHV-1)	Increases humoral and cellular response in mice immunized with SuHV-1	[455]
Quercetin	5–25 µM 50 µM 1–50 µM	Rhinovirus (RV) Hepatitis C virus (HCV) Hepatitis B virus (HBV)	Inhibits rhinovirus replication in vitro and in vivo; Prevents up-regulation of diacylglycerol acyltransferase	[456] [457] [458]
Caffeic acid	IC <sub>50</sub> = 3.9 µM—100 mg/kg b.w. per os; 4 mM IC <sub>50</sub> = 7.2 and 8.5 µM on NA1 and NA2, respectively	HBV Influenza A virus (IAV)	(DGAT) required for HCV replication in vitro; Decreases heat shock proteins and HBV transcription levels in vitro	[277] [459] [460]
Rutin	Binding energy –8.97 kcal/mol (in silico)	SARS-CoV-2	Inhibitory potential on ACE2	[302]
Anatolia propolis EE, hesperetin (HE), pinocembrin (PI), CAPE	IC <sub>50</sub> = 0.57–1.14 µL, 16.88 mM, 29.53 mM, 79.09 mM; Binding energy to spike S1 protein: –7.28, –7.54, 7.17 respectively for HE, PI and CAPE	SARS-CoV-2	Binds spike S1 protein and ACE-2 receptor as both in vitro and in silico studies	[303]
Optimized liposomal formula of propolis, rutin and CAPE	IC <sub>50</sub> = 1.18 mM, ICM score: –92.8 and –67.8 against 3CL protease; ICM score: –94.3 and –77.8 against S1 spike protein	SARS-CoV-2	Bind COVID-3CL protease and S1 spike protein; inhibit the viral replication	[304]
Glyasperin A and broussonflavonol F	Binding affinity –7.8 kcal/mol	SARS-CoV-2	Bind SARS-CoV-2 main protease	[305]
Withaferin-A, Withanone and CAPE	Binding affinity: –5.6, –4.3 and –6.20 kcal/mol, respectively	SARS-CoV-2	Bind transmembrane protease serine 2 (TMPRSS2) in molecular docking studies	[306]

**Table 10** (continued)

Extract/Compound	Concentration /Dose	Test system	Results/Mechanisms	References
Withanone and CAPE	Binding affinity: -4.42 and -4.79 kcal/mol, respectively	SARS-CoV-2	Bind SARS-CoV-2 protease M <sup>pro</sup>	[307]
3-Methoxydaidzin (MD), neoblavaisoflavone, methylorhizopogonone A and genistin	Binding affinity: -7.7 for MD and -7.6 kcal/mol for other compounds against M <sup>pro</sup> ; -8.1, -8.2, -8.3, and -8.3 kcal/mol, respectively against spike protein S2	SARS-CoV-2	Bind main protease (Mpro) and spike protein subunit 2 (S2)	[308]
Glyasperin A, broussonflavonol F, sulabirins A, (2S)-5,7-dihydroxy-4'-methoxy-8-prenylflavanone and isorhamnetin	Docking score of -10.8, -9.9, -9.5, -9.3 and -9.2 kcal/mol respectively	SARS-CoV-2	ACE-2 inhibitors	[309]
2,2-Dimethyl-8-prenylchromene, Artepillin C, 3-Prenyl cinnamic acid allyl ester, Isocupressic acid, 1 3C-symphoreticolic acid, ellagic acid, syringic acid, caffeic acid phenethyl ester, p-coumaric acid, hesperetin, naringenin, kaempferol, quercetin, chrysin	Binding scores: -5.6—-7.8 kcal/mol against M <sup>pro</sup> , -5.3—-6.4 kcal/mol against RdRp	SARS-CoV-2	Main protease (M <sup>pro</sup> ) and RNA-dependent RNA polymerase (RdRp) enzymes	[310]

In association with nanoparticles (polymeric nanofibrous wound dressing of polyvinyl alcohol (PVA), propolis, showed significant potential tissue regeneration [278]. Furthermore, biogenic silver nanoparticles (Bio AgNP) with propolis showed antibacterial activity against Gram- and Gram+ bacteria stimulating fibroblast cell proliferation and heal wound in surgical sutures [279]. In a study, propolis extract incorporated in a biocompatible polyurethane-hyaluronic acid (PU-HA) nanofiber in wound dressing, displayed a potent activity favouring the fibroblast cells adhesion, deposition of collagen fibers and cell proliferation in wounded areas [280, 281]. A propolis mixture of two different geographical location evidenced better potential effect than individually on wound healing through re-epithelization process in rat chronic wound by bacterial inhibition [282]. It has been demonstrated that topical application of propolis paste (30%) showed a beneficial effect on cutaneous wound healing in dog experimental model [283]. Furthermore, propolis has dermal construction effect evidencing significant reduction in the wound surface area [30].

CAPE, a component of propolis, has immunosuppressive properties in T-cells, which play a significant role in the development of inflammatory disorders. CAPE also reduced both the expression of IL-2 gene and the production of IL-2 in activated T-cells [283]. Propolis also includes antiviral compounds such as 3-methyl-but-2-enyl caffeate, isopentyl ferulate, and moronic acid [5]. Additionally, together with ascorbic acid, propolis promoted wound healing in diabetic patients through dermal regeneration in a rat model [284].

Re-epithelialization is a critical phase in wound healing involving keratinocyte migration and proliferation [285]. Propolis along with its chemical constituents increases aquaporin-3 (AQP3) gene expression [254]. AQP3-facilitated water transport plays a pivotal role in cell migration and hyperproliferation and accelerates the healing of cutaneous wounds stimulating epidermal keratinocytes [254]. Therefore, in conclusion propolis from different countries heal wounds by regulating a plenty of signalling pathways including mast cell regulating via and AQP-3, VEGF, NF-kB and caspase-1 pathways.

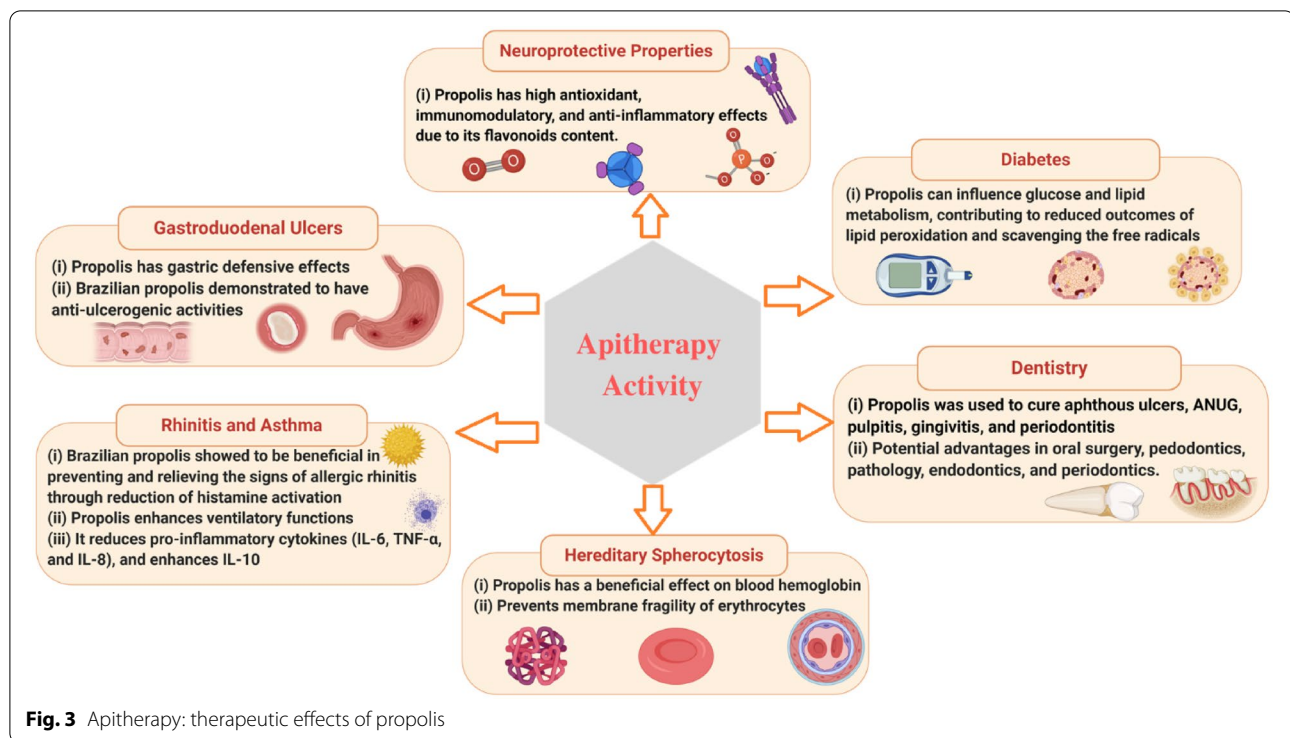
#### **Antiviral activity**

The world has witnessed the outbreak of several detrimental viral epidemics and/or pandemics since the creation of human civilization that have established a remarkable spotlight in the sectors of public health, education, and economy. The substantive example is the ongoing Covid-19 pandemic that nobly alters human lifestyle and creates a frenzied challenge for researchers to deliver safe, tolerable, and effective treatment strategies, including natural product therapy [286], experimental

drug candidates [287], and vaccines [287]. Various researchers in most of the countries are continuously trying to overcome this hectic challenge by computational technologies to determine predictable therapeutic responses at fast along with cost and time saving matters [288–290]. Regarding all kinds of viral issues, the alternative and complementary ethnomedical practices (i.e., plants, natural products, and natural compounds) in various holistic approaches led to the greatest concern in the direction of the therapeutic development throughout the world [286]. At the same time, to establish an appropriate therapeutic candidate, some non-clinical and pre-clinical studies before the clinical studies must be established and find out the satisfactory results that can lead to the clinical trial [291]. Based on these perspectives, some researchers began to investigate the antiviral properties of propolis and several isolated compounds.

Various propolis extracts (e.g., aqueous, ethanolic, and hydroalcoholic) at controllable laboratory condition have been found to exert substantial antiviral activity against several types of viruses such as *Herpes simplex* virus type 1 and 2 (HSV-1 and HSV-2), *Canine distemper* virus, *Human rhinovirus* type 2, 3 and 4 (HRV-2, HRV-3 and HRV-4), *Influenza virus* type A and B, *Parainfluenza* virus, *Human immunodeficiency virus* (HIV), and *Adenovirus* [292, 293]. Research findings demonstrated that aqueous and ethanol propolis extracts exhibited a strong antiviral activity against HSV-1 [294] and HSV-2 [295] on RC-37 cells by affecting viral plaque formation and viral infection cycle. On the other hand, 0.5% aqueous extract of propolis showed potent antiviral activity against HSV-1 infected rats and rabbits thorough prevention of virus absorption into the host and inhibition of an internal step(s) during the viral replication cycle [296]. In addition, ethanol Mexican propolis extract exerted antiviral activity against *Canine distemper* virus through the inhibition of the relative expression of the virus nucleoprotein gene [297]. It has been cited that a 5% alcoholic solution of propolis strongly prevented influenza viral proliferation in experimental influenza virus-infected mice [298]. Furthermore, the Brazilian propolis ethanolic extract adequately blocked the entry of viruses (HRV-2, HRV-3, and HRV-4) into the experimental HeLa cells protecting them from the virus destruction and reducing virus replication [299].

Some flavones and flavonols (especially galangin, kaempferol, and quercetin) extracted from propolis have been cited to exert antiviral activity against HSV-1 in variable doses [300]. Another investigation by Amoros et al. [301] reported that 3-methyl-but-2-enyl caffeate showed anti-HSV-1 activity through preventing the viral DNA synthesis. Finally, recent studies, showed that both propolis and its constituents had potential efficacy against



SARS-CoV-2 by modulating multiple pathogenic pathways [302–311]. Molecular docking studies have demonstrated high binding affinities of propolis compounds to several SARS-CoV-2 proteins, including 3C-like protease, papain-like protease, RNA-dependent RNA polymerase, the receptor-binding domain of the spike protein and helicase. Moreover, these studies showed a high affinity against the viral target angiotensin-converting enzyme 2 (ACE2). Among these compounds, the most promising one was the retusapurpurin A, which showed the best affinity for the most viral targets mentioned above inhibiting the viral entry by forming hydrogen bonds with amino acid residues within viral and human target proteins [312]. Table 10 shown the antiviral activity of propolis water, ethanol and hydroalcoholic extracts and isolated compounds.

#### Antidepressant and anxiolytic-like effects

Diverse studies have been reported the effects of propolis in the central nervous system (CNS) as a neuroprotector and in ameliorating alterations in behavior. Propolis extract (10–50 mg/kg) improved the locomotor activity and exert anxiolytic and antidepressant effects in vivo like diazepam, as observed by in vivo open field (OF), elevated plus-maze (EPM) and forced swimming tests, respectively [313]. Moreover, propolis extract decreased the NO release in response to swim stress induced in experimental model [313]. These pharmacological

effects are mainly attributed to its polyphenolic constituents such as flavonoids, phenolic acids and terpenes [314–316]. In the OF test, Lee et al. [317] revealed that propolis extract had an antidepressant-like effect without affecting locomotor function or spontaneous movement in a dose-dependent manner. Furthermore, they hypothesized that the antidepressant effect may be mediated by an elevation in hippocampal glucocorticoid receptor (GR) activity, which modulates the hypothalamic–pituitary–adrenal (HPA) axis by attenuating corticosterone response and, reducing c-fos neurons in brain tissue and lipid peroxidation in CNS. Moreover, CAPE, an active biocomponent of propolis, down-regulated c-fos levels in neurons, which relate with antidepressant-like effect [318]. Additionally, CAPE knocked down the expression of p38/MAPK signaling pathway, improving GR function and exerting antidepressant effect [69]. Chrysin, another active chemical constituents of propolis, exerted an antidepressant activity in vivo by elevating the brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), Na<sup>+</sup>, K<sup>+</sup>-ATPase, non-protein thiol (NPSH), corticosterone level [319] and down-regulated ROS levels [320]. Moreover, chrysin, as already demonstrated for the CAPE, exhibited antidepressant modulation via regulating the HPA axis [319]. Finally, chrysin contributed to reduce the stress by decreasing the release of several pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 [319].

A recent study had revealed that propolis extract drastically reduce cortisol (CORT), adrenocorticotrophic hormone (ACTH) and MDA and elevate superoxide dismutase (SOD) levels in a stressed mice model. Therefore, this study clearly demonstrated that propolis extract exerted anti-anxiety properties through the inhibition of the hyperfunction of the HPA axis and stimulation of antioxidation processes in nervous system [321]. In the OP test, however, anxiolytic-like agents led to an increase in central locomotion [322], and a diminution in grooming [323]. Propolis, on the contrary, increased locomotion in OF test [317, 321], thus the anxiolytic effect of propolis remains a bit controversial and further studies are needed to corroborate this hypothesis.

### Apitherapy

Apitherapy is a set of treatments aimed at recovering well-being, both in the human and veterinary fields, with products collected, processed, and secreted by bees including honey, propolis, pollen, bee venom, and royal jelly. Bee products are conventional drugs in several countries. The apitherapy has its origin in the pharmacy of Antique Egypt about 6000 years ago. Also, the ancient Greeks and Romans have used the ingredients of bees for various types of remedies [324, 325] (Fig. 3).

Propolis possess several helath properties including antiallergic, antimicrobial, antioxidant, cardioprotective effects, anti-cancer, anti-inflammatory, antiulcer, anti-tumor, hepatoprotective, neuroprotective and antidiabetic effects. The efficacy of neuroprotective flavonoids primarily depends on their high antioxidant, immunomodulatory and anti-inflammatory functions [217, 326–330]. In addition, an in vitro study showed that green propolis enhanced the differentiation, mitigation, and proliferation of stromal cells in bone marrow [331]. The therapeutic properties of the bioactive substances in propolis have been investigated in recent drug screening studies [290, 332, 333]. In dentistry, propolis was used to cure apthous ulcers, acute necrotizing ulcerative gingivitis, pulpitis, gingivitis, and periodontitis. Because of its medicinal and biological effects, propolis investigation has been expanded. Present dental propolis study includes a wide variety of areas and emphasizes the anti-inflammatory as well as antimicrobial activities of this bee product, notably in oral surgery, pedodontics, pathology, endodontics, and periodontics [334].

Diabetes is a metabolic condition defined by hyperglycemia as well as glycosuria attributed to complete or relative insulin insufficiency. Oxidative stress has been involved in the improvement of diabetic nephropathy. Most investigators showed the streptozotocin (STZ) exposure as a diabetes-inducing factor. One study revealed that propolis extract induced pancreatic  $\beta$ -cells

survival against STZ toxicity in rats [335]. Also, researchers found that the administration of water or ethanolic extract of propolis for seven weeks to STZ-induced diabetic rats influenced glucose and lipid metabolism, contributing to reduced outcomes of lipid peroxidation and scavenging the free radicals in diabetic rats [230]. However, it has been documented that the treatment with propolis for 8 weeks to 15% fructose-exposed rats, led to a decrease in body weight as well as insulin concentration without influencing blood glucose concentration [229].

Gastroduodenal ulcers may arise from the unbalance between inflammatory and protective processes in the stomach, such as alteration of the mucosal barrier, acid-pepsin secretion, cellular regeneration, mucus secretion, and epidermal growth factors [336]. It has been reported that propolis has gastric protective effects in mice at several doses (e.g., 50, 250, or 500 mg/kg) [337]. Also, the Brazilian propolis (50 mg/kg or 250 mg/kg) showed anti-ulcerogenic activities in different models [338]. Moreover, the authors investigated the impact of the essential oil derived from the most significant botanical source (*Baccharisdracun culifolia*) of the Brazilian green propolis on gastric ulcers, showing that it may be a successful therapeutic agent for the development of novel phytotherapeutic approach to treat gastric ulcers [339]. Recently, Boeing et al. [340] observed that the hydroalcoholic extract of red propolis from Northeastern Brazil displays gastroprotective property against ethanol/HCl-induced damage in mice.

Rhinitis is a form of sinusitis characterized by nasal congestion, purulence and sneezing due to bacterial or viral infections. It is a world health issue that affects people's work, education, sleep, and social lives [341, 342]. Brazilian propolis showed to be beneficial in preventing and relieving the signs of allergic rhinitis through the reduction of histamine release. The study showed that a single administration of 1 g/kg propolis was ineffective in preventing antigen-induced nasal rubbing and sneezing, but substantial improvement was described after continuous administration for 2 weeks at this dose [341]. Another respiratory tract disease to consider is asthma as an inflammatory disease of the airways related to overexposure to allergens characterized by congestion, inflammation, as well as repetitive movements and remodeling [343]. Khayyal et al. [344] observed that the daily administration of an aqueous sample of propolis (13%) to patients with mild to severe asthma for two months led to a decrease in night-time attacks and enhanced ventilatory functions. These improvements seemed to be related to a decrease in the release of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ , and IL-8) and an increase of the anti-inflammatory cytokine IL-10, [344].

Hereditary spherocytosis (HS) is an aberrant disease of red blood cells (RBCs). The disease is triggered by a mutation in the genes responsible for the production and maintenance of hemoglobin. Ordinary red blood cells are biconcave disks, and those with HS have a spherical shape (spherocytosis) [345–347]. A recent study evaluated the influence of the propolis extracts on the ability of the red blood cell membrane to retain ions. It has been observed that propolis had a beneficial effect on blood hemoglobin. This result has been attributed to the high content of phenolics in the propolis. The findings of the *in vitro* evaluation suggested that the membrane fragility improves in a patient's RBCs, and that the protective advantage of propolis was attributable to its antioxidant properties [348].

### Propolis as food preservative

The utilization of propolis in the human diet should be increased to take advantage of the benefits of its biological actions on human health. It also meets consumer demand for natural antioxidants and antimicrobials rather than synthetic food additives. Therefore, adding propolis to food products as a natural food additive and increasing food quality has become a trending topic [332]. Many of the compounds found in propolis have been utilized as functional food additives and are considered to be safe for human health [13, 30]. However, although propolis is generally considered safe, some people may experience side effects such as dermatitis [11].

Propolis is commonly used in food formulations such as oils, dairy, meat, seafood, fruits, and juice to extend the shelflife, to reduce lipid oxidation, and to provide health advantages to consumers [349]. Vargas-Sánchez et al. [350] observed that propolis extracts can be applied to increase lipid oxidation stability and to prevent microbial growth on beef patties during cold storage. Cottica et al. [351] reported that adding propolis aqueous extract to dairy beverages resulted in increased antioxidant capacity and lower aldehyde generation during storage with exposure to light. Considering that the use of propolis to coat quail eggs protected egg quality metrics, its use may help delay the loss of quality during storage [352].

### Conclusions and future directions

Propolis is a unique natural remedy, used since ancient times in traditional medicine, whose pharmacological properties are constantly updated. The present study summarized the known chemical profile of propolis until to date collecting data from multiple databases and shielding light also to the phytochemical differences due to the origin and grow pedo-climatic conditions. Summarizing, about 500 chemical compounds have been described till date, mainly belonging to the flavonoids, terpenoids and

phenolic acids classes. However, other secondary metabolites like alkaloids and iridoids were overlooked but have not been yet isolated. Available scientific literature confirms the efficacy of propolis and its bioactive components against bacterial and viral infections and cancer. However, the big problem about the study of therapeutic applications of propolis is its varied composition that depends on the flora of the area, the time of collection, weather conditions, environmental pollution, inclusion of polluting waxes, among others. This makes it difficult to define propolis for medicinal use since its composition varies greatly. Added to the above is the use of different extraction methodologies and solvents used in the different preclinical studies. To solve these problems in the future, standardization should be worked on by establishing exact chemical tests in order to control quality. Currently there is a problem of quality control in propolis products on the market. Apart from its innumerable health uses, some of which have been described recently, such as the possibility of using propolis extracts and its bioactive compounds against SARS-COV-2 infection, propolis can also be used for food preservation. However, further studies are needed to substantiate these claims, in particular, clinical studies with standardized extracts, in order to guarantee the reproducibility of the health properties observed and to translate on humans what observed in the numerous *in vitro* and animal studies.

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### Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. That is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and, confirming to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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#### Author details

<sup>1</sup>Department of Pharmacy, Life Science Faculty, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj, Dhaka 8100, Bangladesh. <sup>2</sup>Facultad de Ciencias de La Salud, Universidad Arturo Prat, Avda.

Arturo Prat 2120, 1110939 Iquique, Chile. <sup>3</sup>Pharmacy Discipline, Life Science School, Khulna University, Khulna 9280, Bangladesh. <sup>4</sup>Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh. <sup>5</sup>Department of Biomedical Engineering, Huazhong University of Science and Technology, Wuhan, China. <sup>6</sup>Faculty of Chemistry and Chemical Technology, Al-Farabi Kazakh National University, 050040 Almaty, Kazakhstan. <sup>7</sup>Department of Bioscience and Biotechnology, Banasthali Vidyapith, Rajasthan 304022, India. <sup>8</sup>Department of Chemical, Biological, Pharmaceutical and Environmental Sciences (ChiBioFarAm), University of Messina, Viale Ferdinando Stagno d'Alcontres 31, 98166 Messina, Italy. <sup>9</sup>Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran. <sup>10</sup>Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>11</sup>Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>12</sup>Department of Biotechnology, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran. <sup>13</sup>Department of Pharmacognosy and Biotechnology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>14</sup>Food Processing Department, Vocational School of Technical Sciences, Bingöl University, Bingöl, Turkey. <sup>15</sup>Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, Concepción, Chile. <sup>16</sup>Universidad de Concepción, Unidad de Desarrollo Tecnológico, UDT, 4070386 Concepción, Chile. <sup>17</sup>Research Group on Community Nutrition and Oxidative Stress, Laboratory of Physical Activity Sciences, and CIBEROBN - Physiopathology of Obesity and Nutrition, CB12/03/30038, University of Balearic Islands, Palma, Spain. <sup>18</sup>Department of Medical Laboratory Sciences, College of Health Sciences and Sharjah Institute for Medical Research, University of Sharjah, 22272 Sharjah, United Arab Emirates. <sup>19</sup>Department of Biomedical Sciences, University of Sassari, 07100 Sassari, Italy. <sup>20</sup>Chemistry & Biochemistry Discipline, University of Life Sciences King Mihai I from Timisoara, Calea Aradului 119, 300645 Timis, Romania. <sup>21</sup>Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong.

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## References

- Makashvili Z. Remarkable hive product: Propolis. Scientific data and suggestions concerning its composition, properties and possible use in therapeutics. In: From the history of Propolis. APIMONDIA standing commission on Bee keeping technology and equipment, Bucharest. 1978.
- Bankova V. Recent trends and important developments in propolis research. *Evid Based Complement Alternat Med*. 2005;2(1):29–32. <https://doi.org/10.1093/ecam/neh059>.
- Sforzin JM. Biological properties and therapeutic applications of propolis. *Phytother Res*. 2016;30(6):894–905. <https://doi.org/10.1002/ptr.5605>.
- Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H, Bashir MA, Tahir M, Ansari MJ, Ghramh HA, Adgaba N, Dash CK. Composition and functional properties of propolis (bee glue): a review. *Saudi J Biol Sci*. 2019;26(7):1695–703. <https://doi.org/10.1016/j.sjbs.2018.08.013>.
- Khalil ML. Biological activity of bee propolis in health and disease. *Asian Pac J Cancer Prev*. 2006;7(1):22–31.
- Simone-Finstrom M, Spivak M. Propolis and bee health: the natural history and significance of resin use by honey bees. *Apidologie*. 2010;41(3):295–311. <https://doi.org/10.1051/apido/2010016>.
- Nagai T, Inoue R, Inoue H, Suzuki N. Preparation and antioxidant properties of water extract of propolis. *Food Chem*. 2003;80(1):29–33. [https://doi.org/10.1016/S0308-8146\(02\)00231-5](https://doi.org/10.1016/S0308-8146(02)00231-5).
- Wang K, Ping S, Huang S, Hu L, Xuan H, Zhang C, Hu F. Molecular mechanisms underlying the *in vitro* anti-inflammatory effects of a flavonoid-rich ethanol extract from chinese propolis (poplar type). *Evid Based Complement Alternat Med*. 2013;2013: 127672. <https://doi.org/10.1155/2013/127672>.
- Bankova VS, de Castro SL, Marcucci MC. Propolis: recent advances in chemistry and plant origin. *Apidologie*. 2000;31(1):3–15.
- Sforzin JM. Propolis and the immune system: a review. *J Ethnopharmacol*. 2007;113(1):1–14. <https://doi.org/10.1016/j.jep.2007.05.012>.
- de Groot AC. Propolis: a review of properties, applications, chemical composition, contact allergy, and other adverse effects. *Dermatitis*. 2013;24(6):263–82. <https://doi.org/10.1097/der.000000000000011>.
- Huang S, Zhang CP, Wang K, Li GQ, Hu FL. Recent advances in the chemical composition of propolis. *Molecules*. 2014;19(12):19610–32. <https://doi.org/10.3390/molecules191219610>.
- Silva-Carvalho R, Baltazar F, Almeida-Aguiar C. Propolis: a complex natural product with a plethora of biological activities that can be explored for drug development. *Evid Based Complement Alternat Med*. 2015;2015: 206439. <https://doi.org/10.1155/2015/206439>.
- Sforzin JM, Bankova V. Propolis: is there a potential for the development of new drugs? *J Ethnopharmacol*. 2011;133(2):253–60. <https://doi.org/10.1016/j.jep.2010.10.032>.
- Stojanović S, Najman SJ, Bogdanova-Popov B, Najman SS. Propolis: chemical composition, biological and pharmacological activity – a review. *Acta Medica Medianae*. 2020;59(2):108–13. <https://doi.org/10.5633/amm.2020.0215>.
- McLoone P, Tabys D, Fyfe L. Honey combination therapies for skin and wound infections: a systematic review of the literature. *Clin Cosmet Investig Dermatol*. 2020;13:875–88. <https://doi.org/10.2147/ccid.S282143>.
- Zulhendri F, Chandrasekaran K, Kowacz M, Ravalía M, Kripal K, Fearnley J, Perera CO. Antiviral, antibacterial, antifungal, and antiparasitic properties of propolis: a review. 2021. *Foods*. <https://doi.org/10.3390/foods10061360>.
- Li Z, Li J, Wang G, Tao Y, Chang X, Xia H, Gui S. Reviewing propolis with multi-components in the treatment of oral diseases through multi-pathways and multi-targets. *Mini Rev Med Chem*. 2021;21(12):1406–20. <https://doi.org/10.2174/138957521666210126141314>.
- Wali AF, Mushtaq A, Rehman MU, Akbar S, Masoodi MH. In vitro anti-oxidant and antimicrobial activities of propolis from Kashmir Himalaya region. *Free Radicals Antioxidants*. 2016;6:51–7.
- Hegazi AG, Abd El Hady FK, Abd Allah FA. Chemical composition and antimicrobial activity of European propolis. *Z Naturforsch C J Biosci*. 2000;55(1–2):70–5. <https://doi.org/10.1515/znc-2000-1-214>.
- Cardinault N, Cayeux MO, Percie du Sert P. Propolis: origin, composition and properties. *Phytotherapie (Paris)*. 2012;10(5):298–304. <https://doi.org/10.1007/s10298-012-0733-y>.
- Ransome H. The Sacred Bee in Ancient Times and Folklore. London, UK. 1937.
- Bostock J, Riley HT. Pliny the Elder: The natural history. 1855.
- Wagh VD. Propolis: a wonder bees product and its pharmacological potentials. *Adv Pharmacol Sci*. 2013;2013:308249–308249. <https://doi.org/10.1155/2013/308249>.
- Stawiarz E, Dyduch J. The use of honey bee products of plant origin in apitherapy. *Episteme*. 2014;25:111–27.
- Martinotti S, Ranzato E. Propolis: a new frontier for wound healing? *Burns Trauma*. 2015;3:9. <https://doi.org/10.1186/s41038-015-0010-z>.
- Matuszewska E, Klupczynska A, Maciołek K, Kokot ZJ, Matysiak J. Multielemental analysis of bee pollen, propolis, and royal jelly collected in West-Central Poland. *Molecules*. 2021;26(9):2415.
- Ahangari Z, Naseri M, Vatandoost F. Propolis: chemical composition and its applications in endodontics. *Iran Endod J*. 2018;13(3):285–92. <https://doi.org/10.22037/iej.v13i3.20994>.
- Pasupuleti VR, Sannamugam L, Ramesh N, Gan SH. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxid Med Cell Longev*. 2017;2017:1259510–1259510. <https://doi.org/10.1155/2017/1259510>.
- Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem Toxicol*. 1998;36(4):347–63. [https://doi.org/10.1016/S0278-6915\(97\)00145-2](https://doi.org/10.1016/S0278-6915(97)00145-2).
- Ackermann T. Fast chromatographic study of propolis crude. *Food Chem*. 1991;42:135–8.
- Krol W, Scheller S, Czuba Z, Zydowicz G, Shani J, Mos M. Inhibition of neutrophils' chemiluminescence by ethanol extract of propolis (EEP) and its phenolic components. *J Ethnopharmacol*. 1996;55(1):19–25. [https://doi.org/10.1016/S0378-8741\(96\)01466-3](https://doi.org/10.1016/S0378-8741(96)01466-3).
- Song YS, Park EH, Hur GM, Ryu YS, Kim YM, Jin C. Ethanol extract of propolis inhibits nitric oxide synthase gene expression and enzyme activity. *J Ethnopharmacol*. 2002;80(2–3):155–61. [https://doi.org/10.1016/S0378-8741\(02\)00023-5](https://doi.org/10.1016/S0378-8741(02)00023-5).

34. Afrasiabi S, Pourhajbagher M, Chiniforush N, Bahador A. Propolis nanoparticle enhances the potency of antimicrobial photodynamic therapy against *Streptococcus mutans* in a synergistic manner. *Sci Rep*. 2020;10(1):15560–15560. <https://doi.org/10.1038/s41598-020-72119-y>.
35. Ambi A, Bryan J, Borbon K, Centeno D, Liu T, Chen TP, Cattabiani T, Traba C. Are Russian propolis ethanol extracts the future for the prevention of medical and biomedical implant contaminations? *Phytomedicine*. 2017;30:50–8. <https://doi.org/10.1016/j.phymed.2017.03.006>.
36. Ozdal T, Ceylan FD, Eroglu N, Kaplan M, Olgun EO, Capanoglu E. Investigation of antioxidant capacity, bioaccessibility and LC-MS/MS phenolic profile of Turkish propolis. *Food Res Int*. 2019;122:528–36. <https://doi.org/10.1016/j.foodres.2019.05.028>.
37. Romero M, Freire J, Pastene E, García A, Aranda M, González C. Propolis polyphenolic compounds affect the viability and structure of *Helicobacter pylori* in vitro. *Rev Bras*. 2019;29(3):325–32. <https://doi.org/10.1016/j.bjp.2019.03.002>.
38. Koru O, Toksoy F, Acikel CH, Tunca YM, Baysallar M, Uskudar Guclu A, Akca E, Ozkok Tuylu A, Sorkun K, Tanyuksel M, Salih B. *In vitro* antimicrobial activity of propolis samples from different geographical origins against certain oral pathogens. *Anaerobe*. 2007;13(3–4):140–5. <https://doi.org/10.1016/j.janaerobe.2007.02.001>.
39. Teixeira EW, Message D, Negri G, Salatino A, Stringheta PC. Seasonal variation, chemical composition and antioxidant activity of Brazilian propolis samples. *Evid Based Complement Alternat Med*. 2010;7(3):307–15. <https://doi.org/10.1093/ecam/nem177>.
40. Tzankova V, Aluani D, Yordanov Y, Kondeva-Burdina M, Petrov P, Bankova V, Simeonova R, Vitcheva V, Odjakov F, Apostolov A, Tzankov B, Yoncheva K. Micellar propolis nanoformulation of high antioxidant and hepatoprotective activity. *Rev Bras*. 2019;29(3):364–72. <https://doi.org/10.1016/j.bjp.2018.12.006>.
41. Trusheva B, Popova M, Bankova V, Simova S, Marcucci MC, Miorin PL, da Rocha PF, Tsvetkova I. Bioactive constituents of Brazilian red propolis. *Evid Based Complement Alternat Med*. 2006;3(2):249–54. <https://doi.org/10.1093/ecam/nel006>.
42. Kalogeropoulos N, Konteles SJ, Troullidou E, Mourtzinos I, Karathanos VT. Chemical composition, antioxidant activity and antimicrobial properties of propolis extracts from Greece and Cyprus. *Food Chem*. 2009;116(2):452–61. <https://doi.org/10.1016/j.foodchem.2009.02.060>.
43. Gülçin I, Bursal E, Sehitoglu MH, Bilsel M, Gören AC. Polyphenol contents and antioxidant activity of lyophilized aqueous extract of propolis from Erzurum. *Turkey Food Chem Toxicol*. 2010;48(8–9):2227–38. <https://doi.org/10.1016/j.fct.2010.05.053>.
44. Woźniak M, Mrówczyńska L, Waśkiewicz A, Rogoziński T, Ratajczak I. The role of seasonality on the chemical composition, antioxidant activity and cytotoxicity of Polish propolis in human erythrocytes. *Rev Bras*. 2019;29(3):301–8. <https://doi.org/10.1016/j.bjp.2019.02.002>.
45. Bankova V, Trusheva B, Popova M. Propolis extraction methods: a review. *J Apic Res*. 2021;60(5):734–43. <https://doi.org/10.1080/00218339.2021.1901426>.
46. Ramón-Sierra J, Peraza-López E, Rodríguez-Borges R, Yam-Puc A, Madera-Santana T, Ortiz-Vázquez E. Partial characterization of ethanolic extract of Melipona beecheii propolis and *in vitro* evaluation of its antifungal activity. *Rev Bras*. 2019;29(3):319–24. <https://doi.org/10.1016/j.bjp.2019.04.002>.
47. Ristivojević P, Dimkić I, Guzelmerić E, Trifković J, Knežević M, Berić T, Yesilada E, Milojković-Opsenica D, Stanković S. Profiling of Turkish propolis subtypes: Comparative evaluation of their phytochemical compositions, antioxidant and antimicrobial activities. *LWT*. 2018;95:367–79. <https://doi.org/10.1016/j.lwt.2018.04.063>.
48. Kumazawa S, Goto H, Hamasaka T, Fukumoto S, Fujimoto T, Nakayama T. A new prenylated flavonoid from propolis collected in Okinawa. *Japan Biosci Biotechnol Biochem*. 2004;68(1):260–2. <https://doi.org/10.1271/bbb.68.260>.
49. Marcucci MC. Propolis: chemical composition, biological properties and therapeutic activity. *Apidologie*. 1995;26(2):83–99. <https://doi.org/10.1051/apido:19950202>.
50. Gabrys J, Konecki J, Krol W, Scheller S, Shani J. Free amino acids in bee hive product (propolis) as identified and quantified by gas-liquid chromatography. *Pharmacol Res Commun*. 1986;18(6):513–8. [https://doi.org/10.1016/0031-6989\(86\)90146-3](https://doi.org/10.1016/0031-6989(86)90146-3).
51. Martos I, Cossentini M, Ferreres F, Tomás-Barberán FA. Flavonoid Composition of Tunisian Honeys and Propolis. *J Agric Food Chem*. 1997;45(8):2824–9. <https://doi.org/10.1021/jf9609284>.
52. Ristivojević P, Trifković J, Andrić F, Milojković-Opsenica D. Poplar-type Propolis: Chemical Composition. Botanical Origin and Biological Activity: *Natural Product Commun*; 2015. <https://doi.org/10.1177/1934578x1501001117>.
53. Markham KR, Mitchell KA, Wilkins AL, Daldy JA, Lu Y. HPLC and GC-MS identification of the major organic constituents in New Zealand propolis. *Phytochemistry*. 1996;42(1):205–11. [https://doi.org/10.1016/0031-9422\(96\)83286-9](https://doi.org/10.1016/0031-9422(96)83286-9).
54. Bankova V, Dylgerov A, Popov S, Marekov N. A GC/MS Study of the Propolis Phenolic Constituents. *Zeitschrift für Naturforschung C*. 1987;42(1–2):147–51. <https://doi.org/10.1515/znc-1987-1-224>.
55. Arruda C, Ribeiro VP, Mejía JAA, Almeida MO, Goulart MO, Candido ACBB, dos Santos RA, Magalhães LG, Martins CHG, Bastos JK. Green propolis: cytotoxic and leishmanicidal activities of artemillin c, p-coumaric acid, and their degradation products. *Rev Bras*. 2020;30(2):169–76. <https://doi.org/10.1007/s43450-020-00043-3>.
56. Beserra FP, Gushiken LFS, Hussni MF, Ribeiro VP, Bonamin F, Jackson CJ, Pellizzon CH, Bastos JK. Artemillin C as an outstanding phenolic compound of Brazilian green propolis for disease treatment: A review on pharmacological aspects. *Phytother Res*. 2020. <https://doi.org/10.1002/ptr.6875>.
57. Shahinozzaman M, Basak B, Emran R, Rozario P, Obanda DN. Artemillin C: A comprehensive review of its chemistry, bioavailability, and pharmacological properties. *Fitoterapia*. 2020;147: 104775. <https://doi.org/10.1016/j.fitote.2020.104775>.
58. Guzelmerić E, Ristivojević P, Trifković J, Dastan T, Yilmaz O, Cengiz O, Yesilada E. Authentication of Turkish propolis through HPTLC fingerprints combined with multivariate analysis and palynological data and their comparative antioxidant activity. *LWT*. 2018;87:23–32. <https://doi.org/10.1016/j.lwt.2017.08.060>.
59. Niyomtham N, Koontongkaew S, Yingyongnarongkul BE, Utispan K. Apis mellifera propolis enhances apoptosis and invasion inhibition in head and neck cancer cells. *PeerJ*. 2021;9: e12139. <https://doi.org/10.7717/peerj.12139>.
60. Vieira de Moraes D, Rosalen PL, Ikegaki M, de Souza Silva AP, Massarioli AP, de Alencar SM. Active Antioxidant Phenolics from Brazilian Red Propolis: An Optimization Study for Their Recovery and Identification by LC-ESI-QTOF-MS/MS. *Antioxidants (Basel)*. 2021. <https://doi.org/10.3390/antiox10020297>.
61. Bozkuş TN, Değer O, Yaşar A. Chemical characterization of water and ethanolic extracts of Turkish propolis by HPLC-DAD and GC-MS. *J Liq Chromatogr Relat Technol*. 2021;44(1–2):77–86. <https://doi.org/10.1080/10826076.2021.1883648>.
62. Park YK, Alencar SM, Aguiar CL. Botanical origin and chemical composition of Brazilian propolis. *J Agric Food Chem*. 2002;50(9):2502–6. <https://doi.org/10.1021/jf011432b>.
63. Silva BB, Rosalen PL, Cury JA, Ikegaki M, Souza VC, Esteves A, Alencar SM. Chemical composition and botanical origin of red propolis, a new type of Brazilian propolis. *Evid-Based Complement Altern Med*. 2008;5(3):313–6. <https://doi.org/10.1093/ecam/nem059>.
64. Salasa A, Mercadoc MI, Zampini IC, Ponessa GI, Isla MI. Determination of botanical origin of propolis from monte region of argentina by histo-logical and chemical methods. *Nat Prod Commun*. 2016;11(5):627–30.
65. Jiang X, Tian J, Zheng Y, Zhang Y, Wu Y, Zhang C, Zheng H, Hu F. A new propolis type from changbai mountains in north-east china: chemical composition. *Bot Origin Biol Act Mol*. 2019;24(7):1369.
66. Yang J, Chen LZ, Xue XF, Wu LM, Li Y, Zhao J, Wu ZB, Zhang YN. A feasibility study on the discrimination of the propolis varieties based on near infrared spectroscopy. *Guang Pu Xue Yu Guang Pu Fen Xi*. 2016;36(6):1717–20.
67. Ahn M-R, Kumazawa S, Hamasaka T, Bang K-S, Nakayama T. Antioxidant activity and constituents of propolis collected in various areas of Korea. *J Agric Food Chem*. 2004;52(24):7286–92. <https://doi.org/10.1021/jf048726s>.
68. Lee IK, Han MS, Kim DW, Yun BS. Phenylpropanoid acid esters from Korean propolis and their antioxidant activities. *Bioorg Med Chem Lett*. 2014;24(15):3503–5. <https://doi.org/10.1016/j.bmcl.2014.05.065>.



69. Lee MS, Kim YH, Lee BR, Kwon SH, Moon WJ, Hong KS, Song YS, Morita K, Hahm DH, Shim I, Her S. Novel antidepressant-like activity of caffeic acid phenethyl ester is mediated by enhanced glucocorticoid receptor function in the hippocampus. *Evid Based Complement Alternat Med*. 2014;2014: 646039. <https://doi.org/10.1155/2014/646039>.
70. Mak K-K, Tan J, Marappan P, Baliyepalli MK, Choudhury H, Ramamurthy S, Pichika MR. Galangin s potential as a functional food ingredient. *J Funct Foods*. 2018;23:78.
71. Russo A, Longo R, Vanella A. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. *Fitoterapia*. 2002;73(Suppl 1):S21–29. [https://doi.org/10.1016/S0367-326X\(02\)00187-9](https://doi.org/10.1016/S0367-326X(02)00187-9).
72. Martinello M, Mutinelli F. Antioxidant Activity in Bee Products: A Review. *Antioxidants (Basel)*. 2021. <https://doi.org/10.3390/antiox10010071>.
73. Miguel MG, Nunes S, Dandlen SA, Cavaco AM, Antunes MD. Phenols and antioxidant activity of hydro-alcoholic extracts of propolis from Algarve. *South Portugal Food Chem Toxicol*. 2010;48(12):3418–23. <https://doi.org/10.1016/j.fct.2010.09.014>.
74. Kumazawa S, Hamasaka T, Nakayama T. Antioxidant activity of propolis of various geographic origins. *Food Chem*. 2004;84(3):329–39. [https://doi.org/10.1016/S0308-8146\(03\)00216-4](https://doi.org/10.1016/S0308-8146(03)00216-4).
75. Kubiliene L, Laugaliene V, Pavilonis A, Maruska A, Majiene D, Barcauskaite K, Kubilius R, Kasparaviciene G, Savickas A. Alternative preparation of propolis extracts: comparison of their composition and biological activities. *BMC Complement Altern Med*. 2015;15(1):156. <https://doi.org/10.1186/s12906-015-0677-5>.
76. Selvaraj R, Priyadarshini F, Jayaprakash P, Selvaraj R, Kanakarajan S, Kamalanathan A. Phytochemical profiling and antibacterial activity of propolis. *Int J Sci Res*. 2018;7:6.
77. Hochheim S, Guedes A, Faccin-Galhardi L, Rechenchoski DZ, Nozawa C, Linhares RE, Filho HHS, Rau M, Siebert DA, Micke G, Cordova CMMd. Determination of phenolic profile by HPLC–ESI-MS/MS, antioxidant activity, *in vitro* cytotoxicity and anti-herpetic activity of propolis from the Brazilian native bee *Melipona quadrifasciata*. *Rev Bras*. 2019;29(3):339–50. <https://doi.org/10.1016/j.bjp.2018.12.010>.
78. Calegari MA, Ayres BB, dos Santos Toniai LM, de Alencar SM, Oldoni TLC. Fourier transform near infrared spectroscopy as a tool for predicting antioxidant activity of propolis. *J King Saud Univ Sci*. 2020;32(1):784–90. <https://doi.org/10.1016/j.jksus.2019.02.006>.
79. Choi YM, Noh DO, Cho SY, Suh HJ, Kim KM, Kim JM. Antioxidant and antimicrobial activities of propolis from several regions of Korea. *LWT Food Sci Technol*. 2006;39(7):756–61. <https://doi.org/10.1016/j.lwt.2005.05.015>.
80. Aldemir O, Yildirim HK, Sözmen EY. Antioxidant and anti-inflammatory effects of biotechnologically transformed propolis. *J Food Process Preserv*. 2018. <https://doi.org/10.1111/jfpp.13642>.
81. Rivera-Yañez CR, Ruiz-Hurtado PA, Mendoza-Ramos MI, Reyes-Reali J, García-Romo GS, Pozo-Molina G, Reséndiz-Albor AA, Nieto-Yañez O, Méndez-Cruz AR, Méndez-Catalá CF, Rivera-Yañez N. Flavonoids Present in Propolis in the Battle against Photaging and Psoriasis. *Antioxidants (Basel)*. 2021. <https://doi.org/10.3390/antiox10122014>.
82. Moreira L, Dias LG, Pereira JA, Estevinho L. Antioxidant properties, total phenols and pollen analysis of propolis samples from Portugal. *Food Chem Toxicol*. 2008;46(11):3482–5. <https://doi.org/10.1016/j.fct.2008.08.025>.
83. Gargouri W, Osés SM, Fernández-Muñoz MA, Sancho MT, Kechaou N. Evaluation of bioactive compounds and biological activities of Tunisian propolis. *LWT*. 2019;111:328–36. <https://doi.org/10.1016/j.lwt.2019.05.044>.
84. Kim Y-H, Chung H-J. The effects of Korean propolis against foodborne pathogens and transmission electron microscopic examination. *New Biotechnol*. 2011;28(6):713–8. <https://doi.org/10.1016/j.nbt.2010.12.006>.
85. Basim E, Basim H, Özcan M. Antibacterial activities of Turkish pollen and propolis extracts against plant bacterial pathogens. *J Food Eng*. 2006;77(4):992–6. <https://doi.org/10.1016/j.jfoodeng.2005.08.027>.
86. Ordóñez RM, Zampini IC, Moreno MIN, Isla MI. Potential application of Northern Argentine propolis to control some phytopathogenic bacteria. *Microbiol Res*. 2011;166(7):578–84. <https://doi.org/10.1016/j.micres.2010.11.006>.
87. Soltani EK, Cerezuela R, Charef N, Mezaache-Aichour S, Esteban MA, Zerroug MM. Algerian propolis extracts: Chemical composition, bactericidal activity and *in vitro* effects on gilthead seabream innate immune responses. *Fish Shellfish Immunol*. 2017;62:57–67. <https://doi.org/10.1016/j.fsi.2017.01.009>.
88. Mihai CM, Mărghițaș LA, Dezmirean DS, Chirilă F, Moritz RF, Schläns H. Interactions among flavonoids of propolis affect antibacterial activity against the honeybee pathogen *Paenibacillus larvae*. *J Invertebr Pathol*. 2012;110(1):68–72. <https://doi.org/10.1016/j.jip.2012.02.009>.
89. Bouchelaghem S. Propolis characterization and antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*: A review. *Saudi Journal of Biological Sciences*. 2022;29(4):1936–46. <https://doi.org/10.1016/j.sjbs.2021.11.063>.
90. Przybyłek I, Karpiński TM. Antibacterial properties of propolis. *Molecules (Basel, Switzerland)*. 2019;24(11):2047. <https://doi.org/10.3390/molecules24112047>.
91. Campos JF, dos Santos UP, Macorini LF, de Melo AM, Balesieri JB, Paredes-Gamero EJ, Cardoso CA, de Picoli SK, dos Santos EL. Antimicrobial, antioxidant and cytotoxic activities of propolis from *Melipona orbignyi* (Hymenoptera, Apidae). *Food Chem Toxicol*. 2014;65:374–80. <https://doi.org/10.1016/j.fct.2014.01.008>.
92. Djas AA, Putri N, Jemmy PAR, Darwita RR, Bachtiar BM. Effect of Propolis on *Streptococcus mutans* Biofilm Formation. *Pesquisa Brasileira em Odontopediatria e Clínica Integrada*. 2019;19(1):1–9. <https://doi.org/10.4034/pboci.2019.191.138>.
93. Martins ML, Monteiro ASN, Guimarães JEC, Guimarães M, da Silva RF, Cabral LM, Farah A, dePaula J, Romanos MTV, Maia LC, Cavalcanti YW, Fonseca-Gonçalves A. Cytotoxic and antibacterial effect of a red propolis mouthwash, with or without fluoride, on the growth of a cariogenic biofilm. *Arch Oral Biol*. 2019;107: 104512. <https://doi.org/10.1016/j.archoralbio.2019.104512>.
94. Coskun ZM, Ersoz M, Gecili M, Ozden A, Acar A. Cytotoxic and apoptotic effects of ethanolic propolis extract on C6 glioma cells. *Environ Toxicol*. 2020;35(7):768–73. <https://doi.org/10.1002/tox.22911>.
95. Castro ML, Nascimento AMD, Ikegaki M, Costa-Neto CM, Alencar SM, Rosalen PL. Identification of a bioactive compound isolated from Brazilian propolis type 6. *Bioorg Med Chem*. 2009;17(14):5332–5. <https://doi.org/10.1016/j.bmc.2009.04.066>.
96. Vukovic NL, Obradovic AD, Vukic MD, Jovanovic D, Djurdjevic PM. Cytotoxic, proapoptotic and antioxidative potential of flavonoids isolated from propolis against colon (HCT-116) and breast (MDA-MB-231) cancer cell lines. *Food Res Int*. 2018;106:71–80. <https://doi.org/10.1016/j.foodres.2017.12.056>.
97. Li F, Awale S, Tezuka Y, Esumi H, Kadota S. Study on the constituents of Mexican propolis and their cytotoxic activity against PANC-1 human pancreatic cancer cells. *J Nat Prod*. 2010;73(4):623–7. <https://doi.org/10.1021/np900772m>.
98. Rivero-Cruz JF, Granados-Pineda J, Pedraza-Chaverri J, Perez-Rojas JM, Kumar-Passari A, Diaz-Ruiz G, Rivero-Cruz BE. Phytochemical constituents, antioxidant, cytotoxic, and antimicrobial activities of the ethanolic extract of Mexican brown propolis. *Antioxidants (Basel)*. 2020. <https://doi.org/10.3390/antiox9010070>.
99. Alday E, Valencia D, Carreño AL, Picerno P, Piccinelli AL, Rastrelli L, Robles-Zepeda R, Hernandez J, Velazquez C. Apoptotic induction by pinobanksin and some of its ester derivatives from Sonoran propolis in a B-cell lymphoma cell line. *Chem Biol Interact*. 2015;242:35–44. <https://doi.org/10.1016/j.cbi.2015.09.013>.
100. Demir S, Aliyazicioglu Y, Turan I, Misir S, Mentese A, Yaman SO, Akbulut K, Kilinc K, Deger O. Antiproliferative and proapoptotic activity of Turkish propolis on human lung cancer cell line. *Nutr Cancer*. 2016;68(1):165–72. <https://doi.org/10.1080/01635581.2016.1115096>.
101. Kubina R, Kabała-Dzik A, Dziedzic A, Bielec B, Wojtyczka RD, Buldak RJ, Wysznińska M, Stawiarska-Pięta B, Szaflarska-Stojko E. The ethanolic extract of Polish propolis exhibits anti-proliferative and/or pro-apoptotic effect on HCT 116 colon cancer and me45 malignant melanoma cells *in vitro* conditions. *Adv Clin Exp Med*. 2015;24(2):203–12. <https://doi.org/10.17219/acem/31792>.
102. Banzato TP, Gubiani JR, Bernardi DI, Nogueira CR, Monteiro AF, Juliano FF, de Alencar SM, Pilli RA, Lima CAD, Longato GB, Ferreira AG, Foglio MA, Carvalho JEd, Vendramini-Costa DB, Berlinck RGS. Antiproliferative Flavonoid Dimers Isolated from Brazilian Red Propolis. *J Nat Prod*. 2020;83(6):1784–93. <https://doi.org/10.1021/acs.jnatprod.9b01136>.
103. Mitsui T, Hotta S, Tazawa S, Arai Y, Kato K, Ichihara K. Chemical constituents of Brazilian Propolis from the state of Bahia and their growth

- inhibitory activities against cancer cells. *Biosci Biotechnol Biochem*. 2018;82(3):417–21. <https://doi.org/10.1080/09168451.2018.1427550>.
104. Alday E, Valencia D, Garibay-Escobar A, Domínguez-Esquivel Z, Piccinelli AL, Rastrelli L, Monribot-Villanueva J, Guerrero-Analco JA, Robles-Zepeda RE, Hernandez J, Velazquez C. Plant origin authentication of Sonoran Desert propolis: an antiproliferative propolis from a semi-arid region. *Naturwissenschaften*. 2019;106(5–6):25. <https://doi.org/10.1007/s00114-019-1620-2>.
  105. Catchpole O, Mitchell K, Bloor S, Davis P, Suddes A. Antiproliferative activity of New Zealand propolis and phenolic compounds vs human colorectal adenocarcinoma cells. *Fitoterapia*. 2015;106:167–74. <https://doi.org/10.1016/j.fitote.2015.09.004>.
  106. Asgharpour F, Moghadamnia AA, Zabihi E, Kazemi S, Ebrahimzadeh Namvar A, Gholinia H, Motallebnejad M, Nouri HR. Iranian propolis efficiently inhibits growth of oral streptococci and cancer cell lines. *BMC Complement Altern Med*. 2019;19(1):266–266. <https://doi.org/10.1186/s12906-019-2677-3>.
  107. Campos JF, Santos UPd, Rocha PdSd, Damião MJ, Balestieri JBP, Cardoso CAL, Paredes-Gamero EJ, Estevinho LM, de Picoli SK, Santos ELd. Antimicrobial, antioxidant, anti-inflammatory, and cytotoxic activities of propolis from the stingless Bee *Tetragonisca fiebrigii* (Jataí). *Evid-Based Complement Altern Med*. 2015;2015: 296186. <https://doi.org/10.1155/2015/296186>.
  108. Santos DAd, Munari FM, Frozza COdS, Moura S, Barcellos T, Henriques JAP, Roesch-Ely M. Brazilian red propolis extracts: study of chemical composition by ESI-MS/MS (ESI+) and cytotoxic profiles against colon cancer cell lines. *Biotechnol Res Innov*. 2019;3(1):120–30. <https://doi.org/10.1016/j.biori.2019.02.001>.
  109. Assumpcao JHM, Takeda AAS, Sforzin JM, Rainho CA. Effects of propolis and phenolic acids on triple-negative breast cancer cell lines: potential involvement of epigenetic mechanisms. *Molecules*. 2020. <https://doi.org/10.3390/molecules25061289>.
  110. Amini-Sarteshnizi N, Mobini-Dehkordi M, Khosravi-Farsani S, Teimori H. Anticancer activity of ethanolic extract of propolis on AGS cell line. *J Herbm Ed Pharmacol*. 2015;4(1):29–34.
  111. Choudhari MK, Haghniaz R, Rajwade JM, Paknikar KM. Anticancer Activity of Indian Stingless Bee Propolis: An *In Vitro* Study. *Evid-Based Complement Alternat Med*. 2013;2013: 928280. <https://doi.org/10.1155/2013/928280>.
  112. Khacha-ananda S, Tragoolpua K, Chantawannakul P, Tragoolpua Y. Antioxidant and anti-cancer cell proliferation activity of propolis extracts from two extraction methods. *Asian Pac J Cancer Prev*. 2013;14(11):6991–5. <https://doi.org/10.7314/apjcp.2013.14.11.6991>.
  113. Ishihara M, Naoi K, Hashida M, Itoh Y, Suzui M. Growth inhibitory activity of ethanolic extracts of Chinese and Brazilian propolis in four human colon carcinoma cell lines. *Oncol Rep*. 2009;22(2):349–54.
  114. Turan I, Demir S, Misir S, Kilinc K, Mentese A, Aliyazicioglu Y, Deger O. Cytotoxic effect of turkish propolis on liver, colon, breast, cervix and prostate cancer cell lines. *Trop J Pharma Res*. 2015. <https://doi.org/10.4314/tjpr.v14i5.5>.
  115. Czyzewska U, Siemionow K, Zaręba I, Miltyk W. Proapoptotic activity of propolis and their components on human tongue squamous cell carcinoma cell line (CAL-27). *PLoS ONE*. 2016;11(6):e0157091–e0157091. <https://doi.org/10.1371/journal.pone.0157091>.
  116. Lee SH, Kim DC, Lee JY, Moonjae C, Hwang WI. A study on the anticancer activity of propolis. *Prev Nutr Food Sci*. 2000;5(1):54–7.
  117. Markiewicz-Zukowska R, Borawska MH, Fiedorowicz A, Naliwajko SK, Sawicka D, Car H. Propolis changes the anticancer activity of temozolomide in U87MG human glioblastoma cell line. *BMC Complement Altern Med*. 2013;13:50. <https://doi.org/10.1186/1472-6882-13-50>.
  118. Bhargava P, Grover A, Nigam N, Kaul A, Dopi M, Ishida Y, Kakuta H, Kaul SC, Terao K, Wadhwa R. Anticancer activity of the supercritical extract of Brazilian green propolis and its active component, artemillin C: Bioinformatics and experimental analyses of its mechanisms of action. *Int J Oncol*. 2018;52(3):925–32. <https://doi.org/10.3892/ijo.2018.4249>.
  119. Ishida Y, Gao R, Shah N, Bhargava P, Furune T, Kaul SC, Terao K, Wadhwa R. Anticancer activity in honeybee propolis: functional insights to the role of caffeic acid phenethyl ester and its complex with  $\gamma$ -Cyclodextrin. *Integr Cancer Ther*. 2018;17(3):867–73. <https://doi.org/10.1177/1534735417753545>.
  120. Mohamed WAS, Ismail NZ, Omar EA, Abdul Samad N, Adam SK, Mohamad S. GC-MS evaluation, antioxidant content, and cytotoxic activity of propolis extract from peninsular Malaysian stingless bees, *tetragona apicalis*. *Evid Based Complement Alternat Med*. 2020;2020:8895262. <https://doi.org/10.1155/2020/8895262>.
  121. Utispan K, Chitkul B, Koontongkaew S. Cytotoxic activity of propolis extracts from the stingless bee *trigona sirindhornae* against primary and metastatic head and neck cancer cell lines. *Asian Pac J Cancer Prev*. 2017;18(4):1051–5. <https://doi.org/10.22034/apjcp.2017.18.4.1051>.
  122. Bonamigo T, Campos JF, Oliveira AS, Torquato HFV, Balestieri JBP, Cardoso CAL, Paredes-Gamero EJ, de Picoli SK, Dos Santos EL. Antioxidant and cytotoxic activity of propolis of *Plebeia droryana* and *Apis mellifera* (Hymenoptera, Apidae) from the Brazilian Cerrado biome. *PLoS ONE*. 2017;12(9): e0183983. <https://doi.org/10.1371/journal.pone.0183983>.
  123. Sun LP, Chen AL, Hung HC, Chien YH, Huang JS, Huang CY, Chen YW, Chen CN. Chrysin: a histone deacetylase 8 inhibitor with anticancer activity and a suitable candidate for the standardization of Chinese propolis. *J Agric Food Chem*. 2012;60(47):11748–58. <https://doi.org/10.1021/jf303261r>.
  124. Mutallip A, Abulizi A, Abiban A, Sheng L, Buweihailiqiemu A, Amina M, Takigchi Y, Yamaguchi T, Yimit R. Anticancer activity of propolis flavonoid pinobanksin-3-acetate against human colon cancer in vitro. *Int J Biosci*. 2015;7(2):4555.
  125. Motomura M, Kwon KM, Suh SJ, Lee YC, Kim YK, Lee IS, Kim MS, Kwon DY, Suzuki I, Kim CH. Propolis induces cell cycle arrest and apoptosis in human leukemic U937 cells through Bcl-2/Bax regulation. *Environ Toxicol Pharmacol*. 2008;26(1):61–7. <https://doi.org/10.1016/j.etap.2008.01.008>.
  126. Beghini KR, Moura de Leon PM, Thurow H, Schultze E, Campos VF, Martins Rodrigues F, Borsuk S, Dellagostin OA, Savegnago L, Roesch-Ely M, Moura S, Padilha FF, Collares T, Pêgas Henriques JA, Seixas FK. Brazilian red propolis induces apoptosis-like cell death and decreases migration potential in bladder cancer cells. *Evid Based Complement Alternat Med*. 2014;2014: 639856. <https://doi.org/10.1155/2014/639856>.
  127. Salim EI, Abd El-Magid AD, Farara KM, Maria DS. Antitumoral and anti-oxidant potential of egyptian propolis against the PC3 Prostate Cancer Cell Line. *Asian Pac J Cancer Prev*. 2015;16(17):7641–51. <https://doi.org/10.7314/apjcp.2015.16.17.7641>.
  128. Frión-Herrera Y, Díaz-García A, Ruiz-Fuentes J, Rodríguez-Sánchez H, Sforzin JM. Brazilian green propolis induced apoptosis in human lung cancer A549 cells through mitochondrial-mediated pathway. *J Pharm Pharmacol*. 2015;67(10):1448–56. <https://doi.org/10.1111/jphp.12449>.
  129. Sulaiman GM, Ad'hiah AH, Al-Sammarrak KW, Bagnati R, Frapolli R, Bello E, Ubaldi S, Romano M, Panini N, Scanziani E, Pezzolato M, Erba E, D'Incalci M. Assessing the anti-tumour properties of Iraqi propolis in vitro and in vivo. *Food Chem Toxicol*. 2012;50(5):1632–41. <https://doi.org/10.1016/j.fct.2012.01.022>.
  130. Kamiya T, Nishihara H, Hara H, Adachi T. Ethanol extract of Brazilian red propolis induces apoptosis in human breast cancer MCF-7 cells through endoplasmic reticulum stress. *J Agric Food Chem*. 2012;60(44):11065–70. <https://doi.org/10.1021/jf303004n>.
  131. Frión-Herrera Y, Díaz-García A, Ruiz-Fuentes J, Rodríguez-Sánchez H, Maurício Sforzin J. Mechanisms underlying the cytotoxic effect of propolis on human laryngeal epidermoid carcinoma cells. *Nat Prod Res*. 2018;32(17):2085–91. <https://doi.org/10.1080/14786419.2017.1363749>.
  132. Xuan H, Li Z, Yan H, Sang Q, Wang K, He Q, Wang Y, Hu F. Antitumor Activity of Chinese Propolis in Human Breast Cancer MCF-7 and MDA-MB-231 Cells. *Evid Based Complement Alternat Med*. 2014;2014: 280120. <https://doi.org/10.1155/2014/280120>.
  133. Khacha-Ananda S, Tragoolpua K, Chantawannakul P, Tragoolpua Y. Propolis extracts from the northern region of Thailand suppress cancer cell growth through induction of apoptosis pathways. *Invest New Drugs*. 2016;34(6):707–22. <https://doi.org/10.1007/s10637-016-0392-1>.
  134. Vatanserver HS, Sorkun K, Ismet Deliloğlu Gurhan S, Ozdal-Kurt F, Turkoz E, Gencay O, Salih B. Propolis from Turkey induces apoptosis through activating caspases in human breast carcinoma cell lines. *Acta Histochem*. 2010;112(6):546–56. <https://doi.org/10.1016/j.acthis.2009.06.001>.
  135. da Silva LM, Frión-Herrera Y, Bartolomeu AR, Gorgulho CM, Sforzin JM. Mechanisms involved in the cytotoxic action of Brazilian propolis and caffeic acid against HEP-2 cells and modulation of P-glycoprotein

- activity. *J Pharm Pharmacol*. 2017;69(11):1625–33. <https://doi.org/10.1111/jphp.12789>.
136. Szliszka E, Sokół-Łętowska A, Kucharska AZ, Jaworska D, Czuba ZP, Król W. Ethanol Extract of Polish Propolis: Chemical Composition and TRAIL-R2 death receptor targeting apoptotic activity against prostate cancer cells. *Evid Based Complement Alternat Med*. 2013;2013: 757628. <https://doi.org/10.1155/2013/757628>.
  137. Szliszka E, Zydowicz G, Janoszka B, Dobosz C, Kowalczyk-Ziomek G, Krol W. Ethanol extract of Brazilian green propolis sensitizes prostate cancer cells to TRAIL-induced apoptosis. *Int J Oncol*. 2011;38(4):941–53. <https://doi.org/10.3892/ijco.2011.930>.
  138. Kustiawan PM, Lirdprapamongkol K, Palaga T, Puthong S, Phuwapraisirisan P, Svasti J, Chanchao C. Molecular mechanism of cardol, isolated from *Trigona incisa* stingless bee propolis, induced apoptosis in the SW620 human colorectal cancer cell line. *BMC Pharmacol Toxicol*. 2017;18(1):32–32. <https://doi.org/10.1186/s40360-017-0139-4>.
  139. Kunimasa K, Ahn MR, Kobayashi T, Eguchi R, Kumazawa S, Fujimori Y, Nakano T, Nakayama T, Kaji K, Ohta T. Brazilian propolis suppresses angiogenesis by inducing apoptosis in tube-forming endothelial cells through inactivation of survival signal ERK1/2. *Evid Based Complement Alternat Med*. 2011;2011: 870753. <https://doi.org/10.1093/ecam/nep024>.
  140. Park SI, Ohta T, Kumazawa S, Jun M, Ahn MR. Korean propolis suppresses angiogenesis through inhibition of tube formation and endothelial cell proliferation. *Nat Prod Commun*. 2014;9(4):555–60.
  141. Xuan H, Zhu R, Li Y, Hu F. Inhibitory effect of chinese propolis on phosphatidylcholine-specific phospholipase C activity in vascular endothelial cells. *Evid Based Complement Alternat Med*. 2011;2011: 985278. <https://doi.org/10.1155/2011/985278>.
  142. Meneghelli C, Joaquim LS, Félix GL, Somensi A, Tomazzoli M, da Silva DA, Berti FV, Vealeirinho MB, Recouvreur Dde O, de Mattos Zeri AC, Dias PF, Maraschin M. Southern Brazilian autumnal propolis shows anti-angiogenic activity: an in vitro and in vivo study. *Microvasc Res*. 2013;88:1–11. <https://doi.org/10.1016/j.mvr.2013.03.003>.
  143. Borawska MH, Naliwajko SK, Moskwa J, Markiewicz-Żukowska R, Puścion-Jakubik A, Soroczyńska J. Anti-proliferative and anti-migration effects of Polish propolis combined with *Hypericum perforatum* L on glioblastoma multiforme cell line U87MG. *BMC Complement Altern Med*. 2016;16:367. <https://doi.org/10.1186/s12906-016-1351-2>.
  144. Taira N, Nguyen BC, Be Tu PT, Tawata S. Effect of Okinawa Propolis on PAK1 Activity, *Caenorhabditis elegans* Longevity, Melanogenesis, and Growth of Cancer Cells. *J Agric Food Chem*. 2016;64(27):5484–9. <https://doi.org/10.1021/acs.jafc.6b01785>.
  145. Doi K, Fujioka M, Sokuza Y, Ohnishi M, Gi M, Takeshita M, Kumada K, Kakehashi A, Wanibuchi H. Chemopreventive action by ethanol-extracted brazilian green propolis on post-initiation phase of inflammation-associated rat colon tumorigenesis. *In Vivo*. 2017;31(2):187–97. <https://doi.org/10.21873/invivo.11044>.
  146. Alizadeh AM, Afrouzan H, Dinparast-Djadid N, Sawaya AC, Azizian S, Hemmati HR, Mohagheghi MA, Erfani S. Chemoprotection of MNNG-initiated gastric cancer in rats using Iranian propolis. *Arch Iran Med*. 2015;18(1):18–23.
  147. Dornelas CA, Cavalcanti BC, Magalhães HI, Jamacaru FV, Furtado FN, Juanes Cde C, Melo Nde O, Moraes MO. Potential chemoprotective effects of green propolis, L-lysine and celecoxib on bone marrow cells and peripheral blood lymphocytes of Wistar rats subjected to bladder chemical carcinogenesis. *Acta Cir Bras*. 2014;29(7):423–8. <https://doi.org/10.1590/s0102-86502014000700003>.
  148. Dornelas CA, Fachine-Jamacaru FV, Albuquerque IL, Magalhães HI, Souza AJ, Alves LA, Almeida PR, Lemos TL, Castro JD, Moraes ME, Moraes MO. Chemoprevention with green propolis green propolis extracted in L-lysine versus carcinogenesis promotion with L-lysine in N-Butyl-N-[4-hydroxybutyl] nitrosamine (BBN) induced rat bladder cancer. *Acta Cir Bras*. 2012;27(2):185–92. <https://doi.org/10.1590/s0102-86502012000200015>.
  149. Salehi M, Motalebnejad M, Moghadamnia AA, Seyemajidi M, Khanghah SN, Ebrahimpour A, Molania T. An intervention airing the effect of iranian propolis on epithelial dysplasia of the tongue: a preliminary study. *J Clin Diagn Res*. 2017;11(7):67–70. <https://doi.org/10.7860/jcdr/2017/24887.10249>.
  150. Xie XL, Gi M, Fujioka M, Doi K, Yamano S, Tachibana H, Fang H, Kakehashi A, Wanibuchi H. Ethanol-extracted propolis enhances BBN-initiated urinary bladder carcinogenesis via non-mutagenic mechanisms in rats. *Food Chem Toxicol*. 2015;83:193–200. <https://doi.org/10.1016/j.fct.2015.06.007>.
  151. Orsolić N, Basić I. Water-soluble derivative of propolis and its polyphenolic compounds enhance tumoricidal activity of macrophages. *J Ethnopharmacol*. 2005;102(1):37–45. <https://doi.org/10.1016/j.jep.2005.05.036>.
  152. Orsolić N, Knezević AH, Sver L, Terzić S, Basić I. Immunomodulatory and antimetastatic action of propolis and related polyphenolic compounds. *J Ethnopharmacol*. 2004;94(2–3):307–15. <https://doi.org/10.1016/j.jep.2004.06.006>.
  153. Orsolić N, Sver L, Terzić S, Tadić Z, Basić I. Inhibitory effect of water-soluble derivative of propolis and its polyphenolic compounds on tumor growth and metastasizing ability: a possible mode of antitumor action. *Nutr Cancer*. 2003;47(2):156–63. [https://doi.org/10.1207/s15327914nc4702\\_8](https://doi.org/10.1207/s15327914nc4702_8).
  154. Missima F, Pagliarone AC, Orsatti C, Sforzin J. The effect of propolis on pro-inflammatory cytokines produced by melanoma-bearing mice submitted to chronic stress. *J ApiProd ApiMed Sci*. 2009;1:11–5.
  155. Missima F, Pagliarone AC, Orsatti CL, Araújo JP Jr, Sforzin JM. The Effect of propolis on Th1/Th2 cytokine expression and production by melanoma-bearing mice submitted to stress. *Phytother Res*. 2010;24(10):1501–7. <https://doi.org/10.1002/ptr.3142>.
  156. Ahn M-R, Kunimasa K, Ohta T, Kumazawa S, Kamihira M, Kaji K, Uto Y, Hori H, Nagasawa H, Nakayama T. Suppression of tumor-induced angiogenesis by Brazilian propolis: major component artemipillin C inhibits in vitro tube formation and endothelial cell proliferation. *Cancer Lett*. 2007;252(2):235–43.
  157. Chikaraishi Y, Izuta H, Shimazawa M, Mishima S, Hara H. Angiostatic effects of Brazilian green propolis and its chemical constituents. *Mol Nutr Food Res*. 2010;54(4):566–75. <https://doi.org/10.1002/mnfr.200900115>.
  158. de Moura SA, Ferreira MA, Andrade SP, Reis ML, Noviello Mde L, Cara DC. Brazilian green propolis inhibits inflammatory angiogenesis in a murine sponge model. *Evid Based Complement Alternat Med*. 2011;2011: 182703. <https://doi.org/10.1093/ecam/nep197>.
  159. Dornelas CA, Fachine-Jamacaru FV, Albuquerque IL, Magalhães HI, Dias TA, Faria MH, Alves MK, Rabenhorst SH, de Almeida PR, Lemos TL, Castro JD, Moraes ME, Moraes MO. Angiogenesis inhibition by green propolis and the angiogenic effect of L-lysine on bladder cancer in rats. *Acta Cir Bras*. 2012;27(8):529–36. <https://doi.org/10.1590/s0102-86502012000800003>.
  160. Al-Hariri MT, Abualait TS. Effects of green brazilian propolis alcohol extract on nociceptive pain models in rats. *Plants*. 2020;9(9):1102.
  161. Zakaria ZA, Abdul Rahim MH, Mohd Sani MH, Omar MH, Ching SM, Abdul Kadir A, Ahmed QU. Antinociceptive activity of petroleum ether fraction obtained from methanolic extract of *Clinacanthus nutans* leaves involves the activation of opioid receptors and NO-mediated/cGMP-independent pathway. *BMC Complement Altern Med*. 2019;19(1):79. <https://doi.org/10.1186/s12906-019-2486-8>.
  162. Ribeiro RA, Vale ML, Thomazzi SM, Paschoalato AB, Poole S, Ferreira SH, Cunha FQ. Involvement of resident macrophages and mast cells in the writhing nociceptive response induced by zymosan and acetic acid in mice. *Eur J Pharmacol*. 2000;387(1):111–8. [https://doi.org/10.1016/s0014-2999\(99\)00790-6](https://doi.org/10.1016/s0014-2999(99)00790-6).
  163. Ledón N, Casacó A, González R, Merino N, González A, Tolón Z. Antiprosoritic, anti-inflammatory, and analgesic effects of an extract of red propolis. *Zhongguo Yao Li Xue Bao*. 1997;18(3):274–6.
  164. Paulino N, Teixeira C, Martins R, Scremin A, Dirsch VM, Vollmar AM, Abreu SR, de Castro SL, Marcucci MC. Evaluation of the analgesic and anti-inflammatory effects of a Brazilian green propolis. *Planta Med*. 2006;72(10):899–906. <https://doi.org/10.1055/s-2006-947185>.
  165. Paulino N, Dantas AP, Bankova V, Longhi DT, Scremin A, de Castro SL, Calixto JB. Bulgarian propolis induces analgesic and anti-inflammatory effects in mice and inhibits in vitro contraction of airway smooth muscle. *J Pharmacol Sci*. 2003;93(3):307–13. <https://doi.org/10.1254/jphs.93.307>.
  166. Junior OD, Andreucci VC, da Silva Cunha IB, Araujo CEP, de Oliveira F, Marcucci MC. Investigation of the anti-inflammatory and analgesic

- activities of a sample of Brazilian propolis. *Acta Farm Bonaerense*. 2004;23(3):285–91.
167. Sokeng SD, Talla E, Sakava P, Fokam Tagne MA, Henoumont C, Sophie L, Mbafor JT, Tchuenguem Fohouo F-N. Anti-inflammatory and analgesic effect of arachidic acid ethyl ester isolated from propolis. *Biomed Res Int*. 2020;2020:8797284. <https://doi.org/10.1155/2020/8797284>.
  168. Lima Cavendish R, de Souza SJ, Belo Neto R, Oliveira Paixão A, Valéria Oliveira J, Divino de Araujo E, Berretta ESAA, Maria Thomazzi S, Cordeiro Cardoso J, Zanardo Gomes M. Antinociceptive and anti-inflammatory effects of Brazilian red propolis extract and formononetin in rodents. *J Ethnopharmacol*. 2015;173:127–33. <https://doi.org/10.1016/j.jep.2015.07.022>.
  169. Sun L, Liao L, Wang B. Potential antinociceptive effects of Chinese propolis and identification on its active compounds. *J Immunol Res*. 2018;2018:5429543. <https://doi.org/10.1155/2018/5429543>.
  170. Parandin R, Daroogari S. Anti-inflammatory and antinociceptive activities of the ethanolic extract of propolis in male mice and rats. *Zahedan J Res Med Sci*. 2019. <https://doi.org/10.5812/zjrms.84150>.
  171. Atta AH, Alkofahi A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. *J Ethnopharmacol*. 1998;60(2):117–24. [https://doi.org/10.1016/s0378-8741\(97\)00137-2](https://doi.org/10.1016/s0378-8741(97)00137-2).
  172. Adzu B, Amos S, Wambebe C, Gamaniel K. Antinociceptive activity of *Zizyphus spina-christi* root bark extract. *Fitoterapia*. 2001;72(4):344–50. [https://doi.org/10.1016/s0367-326x\(00\)00289-6](https://doi.org/10.1016/s0367-326x(00)00289-6).
  173. Castro SL. Propolis: biological and pharmacological activities. therapeutic uses of this bee-product. *Annu Rev Biomed Sci*. 2001;3:49–83. <https://doi.org/10.5016/1806-8774.2001v3p49>.
  174. Corrêa CR, Calixto JB. Evidence for participation of B1 and B2 kinin receptors in formalin-induced nociceptive response in the mouse. *Br J Pharmacol*. 1993;110(1):193–8. <https://doi.org/10.1111/j.1476-5381.1993.tb13791.x>.
  175. Malmberg AB, Yaksh TL. Cyclooxygenase inhibition and the spinal release of prostaglandin E2 and amino acids evoked by paw formalin injection: a microdialysis study in unanesthetized rats. *J Neurosci*. 1995;15(4):2768–76. <https://doi.org/10.1523/jneurosci.15-04-02768.1995>.
  176. Greenaway W, Scaysbrook T, Whatley FR. The composition and plant origins of propolis: a report of work at Oxford. *Bee World*. 1990;71(3):107–18. <https://doi.org/10.1080/0005772X.1990.11099047>.
  177. García-Viguera C, Greenaway WT, Whatley FR. Composition of propolis from two different Spanish Regions. *Zeitschrift für Naturforschung C*. 1992;47:634–7.
  178. Maciejewicz W, Daniewski M, Mielniczuk Z, Suprynowicz Z. Gas chromatography-mass spectrometry investigation of propolis-analysis of beta-steroids. *Acta Pol Pharm*. 1982;39(4):277–9.
  179. Szliszka E, Mertas A, Czuba ZP, Król W. Inhibition of Inflammatory Response by Artepillin C in Activated RAW264.7 macrophages. *Evid Based Complement Alternat Med*. 2013;2013:735176. <https://doi.org/10.1155/2013/735176>.
  180. Bachiega TF, Orsatti CL, Pagliarone AC, Sforzin JM. The effects of propolis and its isolated compounds on cytokine production by murine macrophages. *Phytother Res*. 2012;26(9):1308–13. <https://doi.org/10.1002/ptr.3731>.
  181. Alqarni AM, Niwasabutra K, Sahlan M, Fearnley H, Fearnley J, Ferro VA, Watson DG. Propolis Exerts an Anti-Inflammatory Effect on PMA-Differentiated THP-1 Cells via Inhibition of Purine Nucleoside Phosphorylase. *Metabolites*. 2019. <https://doi.org/10.3390/metabo9040075>.
  182. Funakoshi-Tago M, Okamoto K, Izumi R, Tago K, Yanagisawa K, Narukawa Y, Kiuchi F, Kasahara T, Tamura H. Anti-inflammatory activity of flavonoids in Nepalese propolis is attributed to inhibition of the IL-33 signaling pathway. *Int Immunopharmacol*. 2015;25(1):189–98. <https://doi.org/10.1016/j.intimp.2015.01.012>.
  183. Blonska M, Bronikowska J, Pietsz G, Czuba ZP, Scheller S, Krol W. Effects of ethanol extract of propolis (EEP) and its flavones on inducible gene expression in J774A1 macrophages. *J Ethnopharmacol*. 2004;91(1):25–30. <https://doi.org/10.1016/j.jep.2003.11.011>.
  184. Rossi A, Ligresti A, Longo R, Russo A, Borrelli F, Sautebin L. The inhibitory effect of propolis and caffeic acid phenethyl ester on cyclooxygenase activity in J774 macrophages. *Phytomedicine*. 2002;9(6):530–5. <https://doi.org/10.1078/09447110260573164>.
  185. Song JJ, Lim HW, Kim K, Kim KM, Cho S, Chae SW. Effect of caffeic acid phenethyl ester (CAPE) on H2O2 induced oxidative and inflammatory responses in human middle ear epithelial cells. *Int J Pediatr Otorhinolaryngol*. 2012;76(5):675–9. <https://doi.org/10.1016/j.ijporl.2012.01.041>.
  186. Bezerra RM, Veiga LF, Caetano AC, Rosalen PL, Amaral ME, Palanch AC, de Alencar SM. Caffeic acid phenethyl ester reduces the activation of the nuclear factor κB pathway by high-fat diet-induced obesity in mice. *Metabolism*. 2012;61(11):1606–14. <https://doi.org/10.1016/j.metabol.2012.04.006>.
  187. Azevedo MI, Pereira AF, Nogueira RB, Rolim FE, Brito GA, Wong DV, Lima-Júnior RC, de Albuquerque RR, Vale ML. The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Mol Pain*. 2013;9:53. <https://doi.org/10.1186/1744-8069-9-53>.
  188. Silva JC, Rodrigues S, Feás X, Estevinho LM. Antimicrobial activity, phenolic profile and role in the inflammation of propolis. *Food Chem Toxicol*. 2012;50(5):1790–5. <https://doi.org/10.1016/j.fct.2012.02.097>.
  189. Ikeda R, Yanagisawa M, Takahashi N, Kawada T, Kumazawa S, Yamaotsu N, Nakagome I, Hirono S, Tsuda T (2011) Brazilian propolis-derived components inhibit TNF-α-mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. *Biochim Biophys Acta*. 1810;7:695–703. <https://doi.org/10.1016/j.bbagen.2011.04.007>.
  190. de Moura SA, Negri G, Salatino A, Lima LD, Dourado LP, Mendes JB, Andrade SP, Ferreira MA, Cara DC. Aqueous extract of Brazilian green propolis: primary components, evaluation of inflammation and wound healing by using subcutaneous implanted sponges. *Evid Based Complement Alternat Med*. 2011;2011: 748283. <https://doi.org/10.1093/ecam/nep112>.
  191. Paulino N, Abreu SR, Uto Y, Koyama D, Nagasawa H, Hori H, Dirsch VM, Vollmar AM, Scremin A, Bretz WA. Anti-inflammatory effects of a bioavailable compound, Artepillin C. *Brazilian propolis Eur J Pharmacol*. 2008;587(1–3):296–301. <https://doi.org/10.1016/j.ejphar.2008.02.067>.
  192. Tani H, Hasumi K, Tatefuji T, Hashimoto K, Koshino H, Takahashi S. Inhibitory activity of Brazilian green propolis components and their derivatives on the release of cyclo-oxygenases. *Bioorg Med Chem*. 2010;18(1):151–7. <https://doi.org/10.1016/j.bmc.2009.11.007>.
  193. Khayyal MT, el-Ghazaly MA, el-Khatib AS. Mechanisms involved in the antiinflammatory effect of propolis extract. *Drugs Exp Clin Res*. 1993;19(5):197–203.
  194. Park E-H, Kim S-H, Park S-S. Anti-inflammatory activity of propolis. *Arch Pharmacol Res*. 1996;19(5):337–41. <https://doi.org/10.1007/BF02976375>.
  195. Borrelli F, Maffia P, Pinto L, Ianaro A, Russo A, Capasso F, Ialenti A. Phytochemical compounds involved in the anti-inflammatory effect of propolis extract. *Fitoterapia*. 2002;73(Suppl 1):S53–63. [https://doi.org/10.1016/s0367-326x\(02\)00191-0](https://doi.org/10.1016/s0367-326x(02)00191-0).
  196. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest*. 2007;117(5):1175–83. <https://doi.org/10.1172/jci31537>.
  197. Bueno-Silva B, Alencar SM, Koo H, Ikegaki M, Silva GV, Napimoga MH, Rosalen PL. Anti-inflammatory and antimicrobial evaluation of neovestitol and vestitol isolated from Brazilian red propolis. *J Agric Food Chem*. 2013;61(19):4546–50. <https://doi.org/10.1021/jf305468f>.
  198. Franchin M, Colón DF, Castanheira FV, da Cunha MG, Bueno-Silva B, Alencar SM, Cunha TM, Rosalen PL. Vestitol isolated from Brazilian red propolis inhibits neutrophils migration in the inflammatory process: elucidation of the mechanism of action. *J Nat Prod*. 2016;79(4):954–60. <https://doi.org/10.1021/acs.jnatprod.5b00938>.
  199. Franchin M, Colón DF, da Cunha MG, Castanheira FV, Saraiva AL, Bueno-Silva B, Alencar SM, Cunha TM, Rosalen PL. Neovestitol, an isoflavonoid isolated from Brazilian red propolis, reduces acute and chronic inflammation: involvement of nitric oxide and IL-6. *Sci Rep*. 2016;6:36401. <https://doi.org/10.1038/srep36401>.
  200. Bueno-Silva B, Rosalen PL, Alencar SM, Mayer MPA. Anti-inflammatory mechanisms of neovestitol from Brazilian red propolis in LPS-activated macrophages. *J Funct Foods*. 2017;36:440–7. <https://doi.org/10.1016/j.jff.2017.07.029>.
  201. Ertürküneer SP, Yaprak Saraç E, Göçmez SS, Ekmekçi H, Öztürk ZB, Seçkin İ, Sever Ö, Keskinbora K. Anti-inflammatory and ultrastructural effects of Turkish propolis in a rat model of endotoxin-induced uveitis. *Folia*

- Histochem Cytobiol. 2016;54(1):49–57. <https://doi.org/10.5603/FHC.a2016.0004>.
202. Du Toit K, Buthelezi S, Bodenstern J. Anti-inflammatory and antibacterial profiles of selected compounds found in South African propolis. *S Afr J Sci*. 2009;105:470–2.
203. Jung YC, Kim ME, Yoon JH, Park PR, Youn HY, Lee HW, Lee JS. Anti-inflammatory effects of galangin on lipopolysaccharide-activated macrophages via ERK and NF- $\kappa$ B pathway regulation. *Immunopharmacol Immunotoxicol*. 2014;36(6):426–32. <https://doi.org/10.3109/08923973.2014.968257>.
204. Cardenas H, Arango D, Nicholas C, Duarte S, Nuovo GJ, He W, Voss OH, Gonzalez-Mejia ME, Guttridge DC, Grotewold E, Doseff AI. Dietary apigenin exerts immune-regulatory activity in vivo by reducing NF- $\kappa$ B activity, halting leukocyte infiltration and restoring normal metabolic function. *Int J Mol Sci*. 2016;17(3):323. <https://doi.org/10.3390/ijms17030323>.
205. Zhang X, Wang G, Gurley EC, Zhou H. Flavonoid apigenin inhibits lipopolysaccharide-induced inflammatory response through multiple mechanisms in macrophages. *PLoS ONE*. 2014;9(9): e107072. <https://doi.org/10.1371/journal.pone.0107072>.
206. Santos EO, Kabeya LM, Figueiredo-Rinhel AS, Marchi LF, Andrade MF, Piatessi F, Paoliello-Paschoalato AB, Azzolini AE, Lucisano-Valim YM. Flavonols modulate the effector functions of healthy individuals' immune complex-stimulated neutrophils: a therapeutic perspective for rheumatoid arthritis. *Int Immunopharmacol*. 2014;21(1):102–11. <https://doi.org/10.1016/j.intimp.2014.04.014>.
207. Tiveron AP, Rosalen PL, Franchin M, Lacerda RC, Bueno-Silva B, Benso B, Denny C, Ikegaki M, Alencar SM. Chemical characterization and antioxidant, antimicrobial, and anti-inflammatory activities of south brazilian organic propolis. *PLoS ONE*. 2016;11(11): e0165588. <https://doi.org/10.1371/journal.pone.0165588>.
208. Wang K, Hu L, Jin X-L, Ma Q-X, Marcucci MC, Netto AAL, Sawaya ACHF, Huang S, Ren W-K, Conlon MA, Topping DL, Hu F-L. Polyphenol-rich propolis extracts from China and Brazil exert anti-inflammatory effects by modulating ubiquitination of TRAF6 during the activation of NF- $\kappa$ B. *J Funct Foods*. 2015;19:464–78. <https://doi.org/10.1016/j.jff.2015.09.009>.
209. Batista CM, Alves AVF, Queiroz LA, Lima BS, Filho RNP, Araújo AAS, de Albuquerque Júnior RLC, Cardoso JC. The photoprotective and anti-inflammatory activity of red propolis extract in rats. *J Photochem Photobiol B*. 2018;180:198–207. <https://doi.org/10.1016/j.jphotobiol.2018.01.028>.
210. Wang Y, Zhu Y, Gao L, Yin H, Xie Z, Wang D, Zhu Z, Han X. Formononetin attenuates IL-1 $\beta$ -induced apoptosis and NF- $\kappa$ B activation in INS-1 cells. *Molecules*. 2012;17(9):10052–64. <https://doi.org/10.3390/molecules170910052>.
211. Shi H, Yang H, Zhang X, Yu LL. Identification and quantification of phytochemical composition and anti-inflammatory and radical scavenging properties of methanolic extracts of Chinese propolis. *J Agric Food Chem*. 2012;60(50):12403–10. <https://doi.org/10.1021/jf3042775>.
212. Soromou LW, Chu X, Jiang L, Wei M, Huo M, Chen N, Guan S, Yang X, Chen C, Feng H, Deng X. In vitro and in vivo protection provided by pinocembrin against lipopolysaccharide-induced inflammatory responses. *Int Immunopharmacol*. 2012;14(1):66–74. <https://doi.org/10.1016/j.intimp.2012.06.009>.
213. Kumar S, Sharma A, Madan B, Singhal V, Ghosh B. Isoliquiritigenin inhibits I $\kappa$ B kinase activity and ROS generation to block TNF- $\alpha$  induced expression of cell adhesion molecules on human endothelial cells. *Biochem Pharmacol*. 2007;73(10):1602–12. <https://doi.org/10.1016/j.bcp.2007.01.015>.
214. Feng G, Sun B, Li TZ. Daidzein attenuates lipopolysaccharide-induced acute lung injury via toll-like receptor 4/NF- $\kappa$ B pathway. *Int Immunopharmacol*. 2015;26(2):392–400. <https://doi.org/10.1016/j.intimp.2015.04.002>.
215. Shi H, Yang H, Zhang X, Sheng Y, Huang H, Yu L. Isolation and characterization of five glycerol esters from Wuhan propolis and their potential anti-inflammatory properties. *J Agric Food Chem*. 2012;60(40):10041–7. <https://doi.org/10.1021/jf302601m>.
216. Inui S, Hosoya T, Yoshizumi K, Sato H, Kumazawa S. Phytochemical and anti-inflammatory properties of Senegalese propolis and isolated compounds. *Fitoterapia*. 2021;151: 104861. <https://doi.org/10.1016/j.fitote.2021.104861>.
217. Hu F, Hepburn HR, Li Y, Chen M, Radloff SE, Daya S. Effects of ethanol and water extracts of propolis (bee glue) on acute inflammatory animal models. *J Ethnopharmacol*. 2005;100(3):276–83. <https://doi.org/10.1016/j.jep.2005.02.044>.
218. Guzman-Gutierrez SL, Nieto-Camacho A, Castillo-Arellano JI, Huerta-Salazar E, Hernandez-Pasteur G, Silva-Miranda M, Arguello-Najera O, Sepulveda-Robles O, Espitia CI, Reyes-Chilpa R. Mexican propolis: a source of antioxidants and anti-inflammatory compounds, and isolation of a novel chalcone and epsilon-caprolactone derivative. *Molecules*. 2018. <https://doi.org/10.3390/molecules23020334>.
219. Tamfu AN, Sawalda M, Fotsing MT, Kouipou RMT, Talla E, Chi GF, Epana JJE, Mbafor JT, Baig TA, Jabeen A, Shaheen F. A new isoflavonol and other constituents from Cameroonian propolis and evaluation of their anti-inflammatory, antifungal and antioxidant potential. *Saudi J Biol Sci*. 2020;27(6):1659–66. <https://doi.org/10.1016/j.sjbs.2019.11.035>.
220. Shahinozaman M, Taira N, Ishii T, Halim MA, Hossain MA, Tawata S. Anti-inflammatory, anti-diabetic, and anti-alzheimer's effects of prenylated flavonoids from Okinawa Propolis: an investigation by experimental and computational studies. *Molecules*. 2018. <https://doi.org/10.3390/molecules23102479>.
221. Nna VU, Abu Bakar AB, Md Lazin M, Mohamed M. Antioxidant, anti-inflammatory and synergistic anti-hyperglycemic effects of Malaysian propolis and metformin in streptozotocin-induced diabetic rats. *Food Chem Toxicol*. 2018;120:305–20. <https://doi.org/10.1016/j.fct.2018.07.028>.
222. Zeitoun R, Najjar F, Wehbi B, Khalil A, Fayyad-Kazan M, Dagher-Hamalian C, Faour WH, El-Makhour Y. Chemical composition, antioxidant and anti-inflammatory activity evaluation of the lebanese propolis extract. *Curr Pharm Biotechnol*. 2019;20(1):84–96. <https://doi.org/10.2174/1389201020666190206201241>.
223. Linard C, Marquette C, Mathieu J, Pennequin A, Clarençon D, Mathé D. Acute induction of inflammatory cytokine expression after gamma-irradiation in the rat: effect of an NF- $\kappa$ B inhibitor. *Int J Radiat Oncol Biol Phys*. 2004;58(2):427–34. <https://doi.org/10.1016/j.ijrobp.2003.09.039>.
224. Búfalo MC, Ferreira I, Costa G, Francisco V, Liberal J, Cruz MT, Lopes MC, Batista MT, Sforcin JM. Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF- $\kappa$ B and MAPK activation in macrophages. *J Ethnopharmacol*. 2013;149(1):84–92. <https://doi.org/10.1016/j.jep.2013.06.004>.
225. Chinthammit C, Axon DR, Mollon L, Taylor AM, Pickering M, Black H, Warholak T, Campbell PJ. Evaluating the relationship between quality measure adherence definitions and economic outcomes in commercial health plans: a retrospective diabetes cohort study. *J Manag Care Spec Pharm*. 2021;27(1):64–72. <https://doi.org/10.18553/jmcp.2021.27.1.064>.
226. Chiba S. Molecular mechanism in alpha-glucosidase and glucoamylase. *Biosci Biotechnol Biochem*. 1997;61(8):1233–9. <https://doi.org/10.1271/bbb.61.1233>.
227. Vongsak B, Kongkiatpaiboon S, Jaisamut S, Machana S, Pattarapanich C. In vitro alpha glucosidase inhibition and free-radical scavenging activity of propolis from Thai stingless bees in mangosteen orchard. *Rev Bras*. 2015;25(5):445–50. <https://doi.org/10.1016/j.rbjp.2015.07.004>.
228. Alaribe CS, Esposito T, Sansone F, Sunday A, Pagano I, Piccinelli AL, Celano R, Cuesta Rubio O, Coker HA, Nabavi SM, Rastrelli L, Picerno P. Nigerian propolis: chemical composition, antioxidant activity and  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibition. *Nat Prod Res*. 2021;35(18):3095–9. <https://doi.org/10.1080/14786419.2019.1682576>.
229. Zamami Y, Takatori S, Koyama T, Goda M, Iwatani Y, Doi S, Kawasaki H. Effect of propolis on insulin resistance in fructose-drinking rats. *Yakugaku Zasshi*. 2007;127(12):2065–73. <https://doi.org/10.1248/yakushi.127.2065>.
230. Fuliang HU, Hepburn HR, Xuan H, Chen M, Daya S, Radloff SE. Effects of propolis on blood glucose, blood lipid and free radicals in rats with diabetes mellitus. *Pharmacol Res*. 2005;51(2):147–52. <https://doi.org/10.1016/j.phrs.2004.06.011>.
231. El Menyiy N, Al-Wali N, El Ghouizi A, El-Guendouz S, Salom K, Lyoussi B. Potential therapeutic effect of Moroccan propolis in hyperglycemia, dyslipidemia, and hepatorenal dysfunction in diabetic rats. *Iran J Basic Med Sci*. 2019;22(11):1331–9. <https://doi.org/10.22038/ijbms.2019.33549.8004>.

232. Nna VU, Abu Bakar AB, Ahmad A, Eleazu CO, Mohamed M. Oxidative Stress, NF-kappaB-Mediated Inflammation and Apoptosis in the Testes of Streptozotocin-Induced Diabetic Rats: Combined Protective Effects of Malaysian Propolis and Metformin. *Antioxidants* (Basel). 2019. <https://doi.org/10.3390/antiox8100465>.
233. Laaroussi H, Bakour M, Ousaadi D, Aboulghazi A, Ferreira-Santos P, Genisheva Z, Teixeira JA, Lyoussi B. Effect of antioxidant-rich propolis and bee pollen extracts against D-glucose induced type 2 diabetes in rats. *Food Res Int*. 2020;138(Pt B): 109802. <https://doi.org/10.1016/j.foodres.2020.109802>.
234. Rivera-Yañez N, Rodriguez-Canales M, Nieto-Yañez O, Jimenez-Estrada M, Ibarra-Barajas M, Canales-Martinez MM, Rodriguez-Monroy MA. Hypoglycaemic and antioxidant effects of propolis of chihuahua in a model of experimental diabetes. *Evid Based Complement Alternat Med*. 2018;2018:4360356. <https://doi.org/10.1155/2018/4360356>.
235. Babatunde IR, Abdulbasit A, Oladayo MI, Olasile OI, Olamide FR, Gbolahan BW. Hepatoprotective and pancreatoprotective properties of the ethanolic extract of nigerian propolis. *J Intercult Ethnopharmacol*. 2015;4(2):102–8. <https://doi.org/10.5455/jice.20150202023615>.
236. Zhu W, Chen M, Shou Q, Li Y, Hu F. Biological activities of chinese propolis and Brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. *Evid Based Complement Alternat Med*. 2011;2011:468529. <https://doi.org/10.1093/ecam/neaq025>.
237. el El-Sayed SM, Abo-Salem OM, Aly HA, Mansour AM. Potential antidiabetic and hypolipidemic effects of propolis extract in streptozotocin-induced diabetic rats. *Pak J Pharm Sci*. 2009;22(2):168–74.
238. Pujirahayu N, Bhattacharjya DK, Suzuki T, Katayama T. alpha-glucosidase inhibitory activity of cycloartane-type triterpenes isolated from indonesian stingless bee propolis and their structure-activity relationship. *Pharmaceuticals* (Basel). 2019. <https://doi.org/10.3390/ph12030102>.
239. Popova M, Lyoussi B, Aazza S, Antunes D, Bankova V, Miguel G. Antioxidant and alpha-Glucosidase Inhibitory Properties and Chemical Profiles of Moroccan Propolis. *Nat Prod Commun*. 2015;10(11):1961–4.
240. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. *Cold Spring Harb Perspect Biol*. 2014. <https://doi.org/10.1101/cshperspect.a009191>.
241. Liu Y, Liang X, Zhang G, Kong L, Peng W, Zhang H. Galangin and Pinocembrin from Propolis Ameliorate Insulin Resistance in HepG2 Cells via Regulating Akt/mTOR Signaling. *Evid Based Complement Alternat Med*. 2018;2018:7971842. <https://doi.org/10.1155/2018/7971842>.
242. Kang LJ, Lee HB, Bae HJ, Lee SG. Antidiabetic effect of propolis: reduction of expression of glucose-6-phosphatase through inhibition of Y279 and Y216 autophosphorylation of GSK-3 $\alpha$ / $\beta$  in HepG2 cells. *Phytother Res*. 2010;24(10):1554–61. <https://doi.org/10.1002/ptr.3147>.
243. Nie J, Chang Y, Li Y, Zhou Y, Qin J, Sun Z, Li H. Caffeic Acid Phenethyl Ester (Propolis Extract) Ameliorates Insulin Resistance by Inhibiting JNK and NF- $\kappa$ B Inflammatory Pathways in Diabetic Mice and HepG2 Cell Models. *J Agric Food Chem*. 2017;65(41):9041–53. <https://doi.org/10.1021/acs.jafc.7b02880>.
244. Salah NM, Souleman AMA, Shaker KH, Hawary SSE, El-hady FKA. Acetylcholinesterase, Alpha-Glucosidase and Tyrosinase Inhibitors from Egyptian Propolis. *Int J Pharmacogn Phytochem Res*. 2017;9:528–36.
245. Hegazy SS, Helmy H, Salama MS, Lotfy NM, Mahmoud DM. The Anti-Diabetic Effect of Nano-Encapsulated Propolis from *Apis mellifera* on Type 2 Diabetes. *Current Appl Sci Technol*. 2021;6:88–103.
246. Ichi I, Hori H, Takashima Y, Adachi N, Kataoka R, Okihara K, Hashimoto K, Kojo S. The beneficial effect of propolis on fat accumulation and lipid metabolism in rats fed a high-fat diet. *J Food Sci*. 2009;74(5):H127–131. <https://doi.org/10.1111/j.1750-3841.2009.01147.x>.
247. Daleprane JB, Freitas Vda S, Pacheco A, Rudnicki M, Faine LA, Dörr FA, Ikegaki M, Salazar LA, Ong TP, Abdalla DS. Anti-atherogenic and anti-angiogenic activities of polyphenols from propolis. *J Nutr Biochem*. 2012;23(6):557–66. <https://doi.org/10.1016/j.jnutbio.2011.02.012>.
248. Anvarifard P, Anbari M, Ostadrahimi A, Ardalan M, Ghoreishi Z. A comprehensive insight into the molecular and cellular mechanisms of the effects of Propolis on preserving renal function: a systematic review. *Nutr Metab (Lond)*. 2022;19(1):6. <https://doi.org/10.1186/s12986-021-00639-z>.
249. Rojczyk E, Kłama-Baryła A, Łabuś W, Wilemska-Kucharzewska K, Kucharzewski M. Historical and modern research on propolis and its application in wound healing and other fields of medicine and contributions by Polish studies. *J Ethnopharmacol*. 2020;262: 113159. <https://doi.org/10.1016/j.jep.2020.113159>.
250. Medellín-Luna MF, Castañeda-Delgado JE, Martínez-Balderas VY, Cervantes-Villagrana AR. Medicinal plant extracts and their use as wound closure inducing agents. *J Med Food*. 2019;22(5):435–43. <https://doi.org/10.1089/jmf.2018.0145>.
251. Cardoso RL, Maboni F, Machado G, Alves SH, de Vargas AC. Antimicrobial activity of propolis extract against *Staphylococcus coagulase* positive and *Malassezia pachydermatis* of canine otitis. *Vet Microbiol*. 2010;142(3–4):432–4. <https://doi.org/10.1016/j.vetmic.2009.09.070>.
252. Ramadan A, Soliman G, Mahmoud SS, Nofal SM, Abdel-Rahman RF. Evaluation of the safety and antioxidant activities of *Crocus sativus* and Propolis ethanolic extracts. *J Saudi Chem Soc*. 2012;16(1):13–21. <https://doi.org/10.1016/j.jscs.2010.10.012>.
253. Ramos IFdAS, Biz MT, Paulino N, Scremin A, Della Bona Á, Barletta FB, de Figueiredo JAP. Histopathological analysis of corticosteroid-antibiotic preparation and propolis paste formulation as intracanal medication after pulpectomy: an in vivo study. *J Appl Oral Sci*. 2012;20:50–6.
254. Martinotti S, Pellavio G, Laforenza U, Ranzato E. Propolis Induces AQP3 expression: a possible way of action in wound healing. *Molecules*. 2019. <https://doi.org/10.3390/molecules24081544>.
255. Li Z, Van Bergen T, Van de Veire S, Van de Vel I, Moreau H, Dewerchin M, Maudgal PC, Zeyen T, Spileers W, Moons L, Stalmans I. Inhibition of vascular endothelial growth factor reduces scar formation after glaucoma filtration surgery. *Invest Ophthalmol Vis Sci*. 2009;50(11):5217–25. <https://doi.org/10.1167/iovs.08-2662>.
256. Westergren-Thorsson G, Bagher M, Andersson-Sjöland A, Thiman L, Löfdahl CG, Hallgren O, Bjermer L, Larsson-Callerfelt AK. VEGF synthesis is induced by prostacyclin and TGF- $\beta$  in distal lung fibroblasts from COPD patients and control subjects: Implications for pulmonary vascular remodelling. *Respirology*. 2018;23(1):68–75. <https://doi.org/10.1111/resp.13142>.
257. Jacob A, Parolia A, Pau A, Davamani Amalraj F. The effects of Malaysian propolis and Brazilian red propolis on connective tissue fibroblasts in the wound healing process. *BMC Complement Altern Med*. 2015;15:294. <https://doi.org/10.1186/s12906-015-0814-1>.
258. Kyriakides TR, Zhu YH, Yang Z, Huynh G, Bornstein P. Altered extracellular matrix remodeling and angiogenesis in sponge granulomas of thrombospondin 2-null mice. *Am J Pathol*. 2001;159(4):1255–62. [https://doi.org/10.1016/s0002-9440\(10\)62512-6](https://doi.org/10.1016/s0002-9440(10)62512-6).
259. Iyyam Pillai S, Palsamy P, Subramanian S, Kandaswamy M. Wound healing properties of Indian propolis studied on excision wound-induced rats. *Pharm Biol*. 2010;48(11):1198–206. <https://doi.org/10.3109/13880200903578754>.
260. Cao XP, Chen YF, Zhang JL, You MM, Wang K, Hu FL. Mechanisms underlying the wound healing potential of propolis based on its *in vitro* antioxidant activity. *Phytomedicine*. 2017;34:76–84. <https://doi.org/10.1016/j.phymed.2017.06.001>.
261. Khorasgani A. A comparison of healing effects of propolis and silver sulfadiazine on full thickness skin wounds in rats. *Pak Vet J*. 2010;30(2):72–4.
262. Noli C, Miolo A. The mast cell in wound healing. *Vet Dermatol*. 2001;12(6):303–13. <https://doi.org/10.1046/j.0959-4493.2001.00272.x>.
263. Weller K, Foitzik K, Paus R, Syska W, Maurer M. Mast cells are required for normal healing of skin wounds in mice. *Faseb j*. 2006;20(13):2366–8. <https://doi.org/10.1096/fj.06-5837je>.
264. Barroso PR, Lopes-Rocha R, Pereira EM, Marinho SA, de Miranda JL, Lima NL, Verli FD. Effect of propolis on mast cells in wound healing. *Inflammopharmacology*. 2012;20(5):289–94. <https://doi.org/10.1007/s10787-011-0105-5>.
265. Cho MS, Park WS, Jung WK, Qian ZJ, Lee DS, Choi JS, Lee DY, Park SG, Seo SK, Kim HJ, Won JY, Yu BC, Choi IW. Caffeic acid phenethyl ester promotes anti-inflammatory effects by inhibiting MAPK and NF- $\kappa$ B signaling in activated HMC-1 human mast cells. *Pharm Biol*. 2014;52(7):926–32. <https://doi.org/10.3109/13880209.2013.865243>.
266. Nader MA. Caffeic acid phenethyl ester attenuates IgE-induced immediate allergic reaction. *Inflammopharmacology*. 2013;21(2):169–76. <https://doi.org/10.1007/s10787-012-0138-4>.
267. Nakamura R, Nakamura R, Watanabe K, Oka K, Ohta S, Mishima S, Teshima R. Effects of propolis from different areas on mast cell

- degranulation and identification of the effective components in propolis. *Int Immunopharmacol.* 2010;10(9):1107–12. <https://doi.org/10.1016/j.intimp.2010.06.013>.
268. Bae Y, Lee S, Kim SH. Chrysin suppresses mast cell-mediated allergic inflammation: involvement of calcium, caspase-1 and nuclear factor- $\kappa$ B. *Toxicol Appl Pharmacol.* 2011;254(1):56–64. <https://doi.org/10.1016/j.taap.2011.04.008>.
  269. Daleprane JB, Abdalla DS. Emerging roles of propolis: antioxidant, cardioprotective, and antiangiogenic actions. *Evid Based Complement Alternat Med.* 2013;2013: 175135. <https://doi.org/10.1155/2013/175135>.
  270. Parihar A, Parihar MS, Milner S, Bhat S. Oxidative stress and anti-oxidative mobilization in burn injury. *Burns.* 2008;34(1):6–17. <https://doi.org/10.1016/j.burns.2007.04.009>.
  271. Olczyk P, Ramos P, Komosińska-Vashev K, Stojko J, Piława B. Positive effect of propolis on free radicals in burn wounds. *Evid Based Complement Alternat Med.* 2013;2013: 356737. <https://doi.org/10.1155/2013/356737>.
  272. Valente MJ, Baltazar AF, Henrique R, Estevinho L, Carvalho M. Biological activities of Portuguese propolis: protection against free radical-induced erythrocyte damage and inhibition of human renal cancer cell growth in vitro. *Food Chem Toxicol.* 2011;49(1):86–92. <https://doi.org/10.1016/j.fct.2010.10.001>.
  273. Okinczyk P, Widelski J, Szperlik J, Zuk M, Mroczek T, Skalicka-Wozniak K, Sakipova Z, Widelska G, Kus PM. Impact of plant origin on Eurasian propolis on phenolic profile and classical antioxidant activity. *Biomolecules.* 2021. <https://doi.org/10.3390/biom11010068>.
  274. Mohammadzadeh S, ShariatiPanahi M, Hamedei M, Amanzadeh Y, Sadat Ebrahimi SE, Ostad SN. Antioxidant power of Iranian propolis extract. *Food Chem.* 2007;103(3):729–33. <https://doi.org/10.1016/j.foodchem.2006.09.014>.
  275. Najafi MF, Vahedy F, Seyyedini M, Jomehzadeh HR, Bozary K. Effect of the water extracts of propolis on stimulation and inhibition of different cells. *Cytotechnology.* 2007;54(1):49–56. <https://doi.org/10.1007/s10616-007-9067-2>.
  276. Niyonsaba F, Ushio H, Nakano N, Ng W, Sayama K, Hashimoto K, Nagaoka I, Okumura K, Ogawa H. Antimicrobial peptides human beta-defensins stimulate epidermal keratinocyte migration, proliferation and production of proinflammatory cytokines and chemokines. *J Invest Dermatol.* 2007;127(3):594–604. <https://doi.org/10.1038/sj.jid.5700599>.
  277. Wang T, Chen L, Wu W, Long Y, Wang R. Potential cytoprotection: antioxidant defence by caffeic acid phenethyl ester against free radical-induced damage of lipids, DNA, and proteins. *Can J Physiol Pharmacol.* 2008;86(5):279–87. <https://doi.org/10.1139/y08-029>.
  278. Alberti TB, Coelho DS, de Prá M, Maraschin M, Veleirinho B. Electrospun PVA nanoscaffolds associated with propolis nanoparticles with wound healing activity. *J Mater Sci.* 2020;55(23):9712–27. <https://doi.org/10.1007/s10853-020-04502-z>.
  279. Baygar T. Characterization of silk sutures coated with propolis and biogenic silver nanoparticles (AgNPs): an eco-friendly solution with wound healing potential against surgical site infections (SSIs). *Turk J Med Sci.* 2020;50(1):258–66. <https://doi.org/10.3906/sag-1906-48>.
  280. Eskandarinia A, Kefayat A, Gharakhloo M, Agheb M, Khodabakhshi D, Khorshidi M, Sheikhmoradi V, Rafienia M, Salehi H. A propolis enriched polyurethane-hyaluronic acid nanofibrous wound dressing with remarkable antibacterial and wound healing activities. *Int J Biol Macromol.* 2020;149:467–76. <https://doi.org/10.1016/j.jbiomac.2020.01.255>.
  281. Afonso AM, Gonçalves J, Luís Á, Gallardo E, Duarte AP. Evaluation of the In Vitro Wound-Healing Activity and Phytochemical Characterization of Propolis and Honey. *Appl Sci* 2020;10 (5):1845
  282. Al-Waili N. Mixing two different propolis samples potentiates their antimicrobial activity and wound healing property: a novel approach in wound healing and infection. *Vet World.* 2018;11(8):1188–95. <https://doi.org/10.14202/vetworld.2018.1188-1195>.
  283. Abu-Seida AM. Effect of propolis on experimental cutaneous wound healing in dogs. *Vet Med Int.* 2015;2015: 672643. <https://doi.org/10.1155/2015/672643>.
  284. Voss GT, Gularte MS, Vogt AG, Giongo JL, Vaucher RA, Echenique JVZ, Soares MP, Luchese C, Wilhelm EA, Fajardo AR. Polysaccharide-based film loaded with vitamin C and propolis: A promising device to accelerate diabetic wound healing. *Int J Pharm.* 2018;552(1–2):340–51. <https://doi.org/10.1016/j.jipharm.2018.10.009>.
  285. Hara-Chikuma M, Verkman AS. Aquaporin-3 facilitates epidermal cell migration and proliferation during wound healing. *J Mol Med (Berl).* 2008;86(2):221–31. <https://doi.org/10.1007/s00109-007-0272-4>.
  286. Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA, Mubarak MS. Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data. *Phytother Res.* 2020;34(10):2471–92. <https://doi.org/10.1002/ptr.6700>.
  287. Sarkar C, Mondal M, Torequl Islam M, Martorell M, Docea AO, Maroyi A, Sharifi-Rad J, Calina D. Potential Therapeutic Options for COVID-19: current status, challenges, and future perspectives. *Front Pharmacol.* 2020;11: 572870. <https://doi.org/10.3389/fphar.2020.572870>.
  288. Sarkar C, Jamaddar S, Mondal M, Khalifa ABR, Islam MT, Mubarak MS. Natural Products as Anti-COVID-19 Agents: An In Silico Study. *Coronaviruses.* 2021. <https://doi.org/10.2174/2666796701999201116124851>.
  289. Mondal M, Sarkar C, Jamaddar S, Khalifa ABR, Islam MT, Mahafzah A, Mubarak MS. Evaluation of the binding affinity of anti-viral drugs against main protease of SARS-CoV-2 through a Molecular Docking Study. *Infect Disord Drug Targets.* 2020. <https://doi.org/10.2174/1871526520666201207124408>.
  290. Lavinas FC, Macedo EHBC, Sá GBL, Amaral ACF, Silva JRA, Azevedo MMB, Vieira BA, Domingos TFS, Vermelho AB, Carneiro CS, Rodrigues IA. Brazilian stingless bee propolis and geopropolis: promising sources of biologically active compounds. *Rev Bras.* 2019;29(3):389–99. <https://doi.org/10.1016/j.bjbp.2018.11.007>.
  291. Sarkar C, Jamaddar S, Mollick B, Akter M, Ahmed T, Mahir M, Mondal M, Islam M. Importance and the unique aspects of modalities for conducting non-clinical and pre-clinical studies of compartmental and non-compartmental analysis. *Pharmacologyonline.* 2019;3:1–15.
  292. Bachevski D, Damevska K, Simeonovski V, Dimova M. Back to the basics: Propolis and COVID-19. *Dermatol Ther.* 2020;33(4):e13780–e13780. <https://doi.org/10.1111/dth.13780>.
  293. Magnavacca A, Sangiovanni E, Racagni G, Dell'Agli M. The antiviral and immunomodulatory activities of propolis: An update and future perspectives for respiratory diseases. *Med Res Rev.* 2022;42(2):897–945. <https://doi.org/10.1002/med.21866>.
  294. Schnitzler P, Neuner A, Nolkemper S, Zundel C, Nowack H, Sensch KH, Reichling J. Antiviral activity and mode of action of propolis extracts and selected compounds. *Phytother Res.* 2010;24(Suppl 1):S20–28. <https://doi.org/10.1002/ptr.2868>.
  295. Nolkemper S, Reichling J, Sensch KH, Schnitzler P. Mechanism of herpes simplex virus type 2 suppression by propolis extracts. *Phytomedicine.* 2010;17(2):132–8. <https://doi.org/10.1016/j.phymed.2009.07.006>.
  296. Huleihel M, Isanu V. Anti-herpes simplex virus effect of an aqueous extract of propolis. *Isr Med Assoc J.* 2002;4(11 Suppl):923–7.
  297. González-Búrquez MJ, González-Díaz FR, García-Tovar CG, Carrillo-Miranda L, Soto-Zárate CI, Canales-Martínez MM, Penieres-Carrillo JG, Cruz-Sánchez TA, Fonseca-Coronado S. Comparison between in vitro antiviral effect of mexican propolis and three commercial flavonoids against canine distemper virus. *Evid Based Complement Alternat Med.* 2018;2018:7092416. <https://doi.org/10.1155/2018/7092416>.
  298. Shevchenko LF, Chasovodtseva OA, Peschanskii AN. Inhibiting activity of propolis on the influenza virus. *Chem Abstr.* 1972;82:11.
  299. Kwon MJ, Shin HM, Perumalsamy H, Wang X, Ahn Y-J. Antiviral effects and possible mechanisms of action of constituents from Brazilian propolis and related compounds. *J Apic Res.* 2020;59(4):413–25. <https://doi.org/10.1080/00218839.2019.1695715>.
  300. Amoros M, Simões CM, Girre L, Sauvager F, Cormier M. 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.* 1992;55(12):1732–40. <https://doi.org/10.1021/np50090a003>.
  301. Amoros M, Lurton E, Boustie J, Girre L, Sauvager F, Cormier M. Comparison of the anti-herpes simplex virus activities of propolis and 3-methylbut-2-enyl caffeate. *J Nat Prod.* 1994;57(5):644–7. <https://doi.org/10.1021/np50107a013>.
  302. Guler HI, Tatar G, Yildiz O, Belduz AO, Kolayli S. Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by molecular docking study. *Arch Microbiol.* 2021;203(6):3557–64. <https://doi.org/10.1007/s00203-021-02351-1>.
  303. Guler HI, Sal FA, Can Z, Kara Y, Yildiz O, Belduz AO, Çanakci S, Kolayli S. Targeting CoV-2 Spike RBD and ACE-2 Interaction with Flavonoids of

- Anatolian Propolis by *in silico* and *in vitro* Studies in terms of possible COVID-19 therapeutics. *Turk J Biol.* 2021;45:530–48.
304. Refaat H, Mady FM, Sarhan HA, Rateb HS, Alaaeldin E. Optimization and evaluation of propolis liposomes as a promising therapeutic approach for COVID-19. *Int J Pharm.* 2021;592: 120028. <https://doi.org/10.1016/j.ijpharm.2020.120028>.
305. Sahlan M, Irdiani R, Flamandita D, Aditama R, Alfarraj S, Ansari MJ, Khayrani AC, Pratami DK, Lischer K. Molecular interaction analysis of Sulawesi propolis compounds with SARS-CoV-2 main protease as preliminary study for COVID-19 drug discovery. *J King Saud Univ Sci.* 2021;33(1): 101234. <https://doi.org/10.1016/j.jksus.2020.101234>.
306. Kumar V, Dhanjal JK, Bhargava P, Kaul A, Wang J, Zhang H, Kaul SC, Wadhwa R, Sundar D. Withanone and Withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. *J Biomol Struct Dyn.* 2020. <https://doi.org/10.1080/07391102.2020.1775704>.
307. Kumar V, Dhanjal JK, Kaul SC, Wadhwa R, Sundar D. Withanone and caffeic acid phenethyl ester are predicted to interact with main protease (M(pro)) of SARS-CoV-2 and inhibit its activity. *J Biomol Struct Dyn.* 2021;39(11):3842–54. <https://doi.org/10.1080/07391102.2020.1772108>.
308. Harisna AH, Nurdiansyah R, Syaife PH, Nugroho DW, Saputro KE, Firdayani PCD, Rochman NT, Maulana NN, Noviyanto A, Mardiyati E. *In silico* investigation of potential inhibitors to main protease and spike protein of SARS-CoV-2 in propolis. *Biochem Biophys Res.* 2021;26: 100969. <https://doi.org/10.1016/j.bbrep.2021.100969>.
309. Khayrani AC, Irdiani R, Aditama R, Pratami DK, Lischer K, Ansari MJ, Chinnathambi A, Alharbi SA, Almoallim HS, Sahlan M. Evaluating the potency of Sulawesi propolis compounds as ACE-2 inhibitors through molecular docking for COVID-19 drug discovery preliminary study. *J King Saud Univ Sci.* 2021;33(2): 101297. <https://doi.org/10.1016/j.jksus.2020.101297>.
310. Shaldam MA, Yahya G, Mohamed NH, Abdel-Daim MM, Al Naggar Y. *In silico* screening of potent bioactive compounds from honeybee products against COVID-19 target enzymes. *Environ Sci Pollut Res Int.* 2021;28(30):40507–14. <https://doi.org/10.1007/s11356-021-14195-9>.
311. Berretta AA, Silveira MAD, Córdor Capcha JM, De Jong D. Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease: Running title: Propolis against SARS-CoV-2 infection and COVID-19. *Biomed Pharmacother.* 2020;131: 110622. <https://doi.org/10.1016/j.biopha.2020.110622>.
312. Yosri N, Abd El-Wahed AA, Ghonaim R, Khattab OM, Sabry A, Ibrahim MAA, Moustafa MF, Guo Z, Zou X, Algethami AFM, Masry SHD, AlAjmi MF, Afifi HS, Khalifa SAM, El-Seedi HR. Anti-viral and immunomodulatory properties of propolis: chemical diversity, pharmacological properties, preclinical and clinical applications, and *in silico* potential against SARS-CoV-2. *Foods.* 2021;10(8):1776.
313. Reis JS, Oliveira GB, Monteiro MC, Machado CS, Torres YR, Prediger RD, Maia CS. Antidepressant- and anxiolytic-like activities of an oil extract of propolis in rats. *Phytomedicine.* 2014;21(11):1466–72. <https://doi.org/10.1016/j.phymed.2014.06.001>.
314. Lu Y, Wu C, Yuan Z. Determination of hesperetin, cinnamic acid and nicotinic acid in propolis with micellar electrokinetic capillary chromatography. *Fitoterapia.* 2004;75(3–4):267–76. <https://doi.org/10.1016/j.fitote.2003.12.026>.
315. Silva MdSSd, Citó AmdGL, Chaves MH, Lopes JAD. Triterpenóides tipo cicloartano de própolis de Teresina - PI. *Quim Nova.* 2005;28(5):801–4. <https://doi.org/10.1590/s0100-40422005000500013>.
316. Albuquerque IL, Alves LA, Lemos TLG, Monte FJQ, Braz-Filho R. Ácido canárico (3,4-seco derivado do lupano) em própolis do Ceará. *Quim Nova.* 2007. <https://doi.org/10.1590/s0100-40422007000400013>.
317. Lee MS, Kim YH, Park WS, Ahn WG, Park OK, Kwon SH, Morita K, Shim I, Her S. Novel antidepressant-like activity of propolis extract mediated by enhanced glucocorticoid receptor function in the hippocampus. *Evid Based Complement Alternat Med.* 2013;2013: 217853. <https://doi.org/10.1155/2013/217853>.
318. Ha J, Choi HS, Lee Y, Lee ZH, Kim HH. Caffeic acid phenethyl ester inhibits osteoclastogenesis by suppressing NF kappaB and downregulating NFATc1 and c-Fos. *Int Immunopharmacol.* 2009;9(6):774–80. <https://doi.org/10.1016/j.intimp.2009.03.001>.
319. Filho CB, Jesse CR, Donato F, Del Fabbro L, de Gomes MG, Goes ATR, Souza LC, Giacomeli R, Antunes M, Luchese C, Roman SS, Boeira SP. Neurochemical factors associated with the antidepressant-like effect of flavonoid chrysin in chronically stressed mice. *Eur J Pharmacol.* 2016;791:284–96. <https://doi.org/10.1016/j.ejphar.2016.09.005>.
320. Filho CB, Jesse CR, Donato F, Giacomeli R, Del Fabbro L, da Silva AM, de Gomes MG, Goes AT, Boeira SP, Prigol M, Souza LC. Chronic unpredictable mild stress decreases BDNF and NGF levels and Na(+), K(+)-ATPase activity in the hippocampus and prefrontal cortex of mice: antidepressant effect of chrysin. *Neuroscience.* 2015;289:367–80. <https://doi.org/10.1016/j.neuroscience.2014.12.048>.
321. Li YJ, Xuan HZ, Shou QY, Zhan ZG, Lu X, Hu FL. Therapeutic effects of propolis essential oil on anxiety of restraint-stressed mice. *Hum Exp Toxicol.* 2012;31(2):157–65. <https://doi.org/10.1177/0960327111412805>.
322. Prut L, Belzung C. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. *Eur J Pharmacol.* 2003;463(1–3):3–33. [https://doi.org/10.1016/s0014-2999\(03\)01272-x](https://doi.org/10.1016/s0014-2999(03)01272-x).
323. Moody TW, Merali Z, Crawley JN. The effects of anxiolytics and other agents on rat grooming behavior. *Ann N Y Acad Sci.* 1988;525:281–90. <https://doi.org/10.1111/j.1749-6632.1988.tb38613.x>.
324. Hellner M, Winter D, von Georgi R, Münster K. Apitherapy: usage and experience in german beekeepers. *Evid Based Complement Alternat Med.* 2008;5(4):475–9. <https://doi.org/10.1093/ecam/nem052>.
325. Zhu F, Wongsiri S. A Brief Introduction to Apitherapy Health Care. *J Thai Tradit Altern Med.* 2018;3:303–12.
326. Popova M, Dimitrova R, Al-Lawati HT, Tsvetkova I, Najdenski H, Bankova V. Omani propolis: chemical profiling, antibacterial activity and new propolis plant sources. *Chem Cent J.* 2013;7(1):158–158. <https://doi.org/10.1186/1752-153X-7-158>.
327. Díaz-Carballo D, Ueberla K, Kleff V, Ergun S, Malak S, Freistuehler M, Somogyi S, Kücherer C, Bardenheuer W, Strumberg D. Antiretroviral activity of two polyisoprenylated acylphloroglucinols, 7-epi-nemorosone and plukenetione A, isolated from Caribbean propolis. *Int J Clin Pharmacol Ther.* 2010;48(10):670–7. <https://doi.org/10.5414/cpp48670>.
328. Farooqui T, Farooqui A. Molecular mechanism underlying the therapeutic activities of propolis: a critical review. *Curr Nutr Food Sci.* 2010;6(3):186–99. <https://doi.org/10.2174/157340110792389136>.
329. Farooqui T, Farooqui AA. Beneficial effects of propolis on human health and neurological diseases. *Front Biosci (Elite Ed).* 2012;4:779–93. <https://doi.org/10.2741/418>.
330. Kurek-Górecka A, Rzepecka-Stojko A, Górecki M, Stojko J, Sosada M, Swierczek-Zieba G. Structure and antioxidant activity of polyphenols derived from propolis. *Molecules.* 2013;19(1):78–101. <https://doi.org/10.3390/molecules19010078>.
331. Elkhenany H, El-Badri N, Dhar M. Green propolis extract promotes *in vitro* proliferation, differentiation, and migration of bone marrow stromal cells. *Biomed Pharmacother.* 2019;115: 108861. <https://doi.org/10.1016/j.biopha.2019.108861>.
332. Pobjega K, Kraśniewska K, Gniewosz M. Application of propolis in antimicrobial and antioxidative protection of food quality – A review. *Trends Food Sci Technol.* 2019;83:53–62. <https://doi.org/10.1016/j.tifs.2018.11.007>.
333. Ueda T, Inden M, Shirai K, Sekine SI, Masaki Y, Kurita H, Ichihara K, Inuzuka T, Hozumi I. The effects of Brazilian green propolis that contains flavonols against mutant copper-zinc superoxide dismutase-mediated toxicity. *Sci Rep.* 2017;7(1):2882. <https://doi.org/10.1038/s41598-017-03115-y>.
334. Silva FB, Almeida JM, Sousa SM. Natural medicaments in endodontics – a comparative study of the anti-inflammatory action. *Braz Oral Res.* 2004;18(2):174–9. <https://doi.org/10.1590/s1806-83242004000200015>.
335. Matsushige K, Basnet P, Hase K, Kadota S, Tanaka K, Namba T. Propolis protects pancreatic  $\beta$ -cells against the toxicity of streptozotocin (STZ). *Phytomedicine.* 1996;3(2):203–9. [https://doi.org/10.1016/s0944-7113\(96\)80037-7](https://doi.org/10.1016/s0944-7113(96)80037-7).
336. Lima ZP, Severi JA, Pellizzon CH, Brito AR, Solis PN, Cáceres A, Girón LM, Vilegas W, Hiruma-Lima CA. Can the aqueous decoction of mango flowers be used as an antiulcer agent? *J Ethnopharmacol.* 2006;106(1):29–37. <https://doi.org/10.1016/j.jep.2005.11.032>.
337. de Barros MP, Sousa JP, Bastos JK, de Andrade SF. Effect of Brazilian green propolis on experimental gastric ulcers in rats. *J Ethnopharmacol.* 2007;110(3):567–71. <https://doi.org/10.1016/j.jep.2006.10.022>.



338. Barros MP, Lemos M, Maistro EL, Leite MF, Sousa JP, Bastos JK, Andrade SF. Evaluation of antiulcer activity of the main phenolic acids found in Brazilian Green Propolis. *J Ethnopharmacol*. 2008;120(3):372–7. <https://doi.org/10.1016/j.jep.2008.09.015>.
339. Jang MH, Piao XL, Kim JM, Kwon SW, Park JH. Inhibition of cholinesterase and amyloid-beta aggregation by resveratrol oligomers from *Vitis amurensis*. *Phytother Res*. 2008;22(4):544–9. <https://doi.org/10.1002/ptr.2406>.
340. Boeing T, Mejia JAA, Ccana-Ccapatinta GV, Mariott M, Vilhena M, de Andrade Fonseca Da Silva RdC, de Souza P, Mariano LNB, Oliveira GR, da Rocha IM, da Costa GA, de Andrade SF, da Silva LM, Bastos JK. The gastroprotective effect of red propolis extract from Northeastern Brazil and the role of its isolated compounds. *J Ethnopharmacol*. 2021;267:113623. <https://doi.org/10.1016/j.jep.2020.113623>.
341. Shinmei Y, Yano H, Kagawa Y, Izawa K, Akagi M, Inoue T, Kamei C. Effect of Brazilian propolis on sneezing and nasal rubbing in experimental allergic rhinitis of mice. *Immunopharmacol Immunotoxicol*. 2009;31(4):688–93. <https://doi.org/10.3109/08923970903078443>.
342. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold—high cost to society. *Allergy*. 2010;65(6):776–83. <https://doi.org/10.1111/j.1398-9995.2009.02269.x>.
343. Sy LB, Wu YL, Chiang BL, Wang YH, Wu WM. Propolis extracts exhibit an immunoregulatory activity in an OVA-sensitized airway inflammatory animal model. *Int Immunopharmacol*. 2006;6(7):1053–60. <https://doi.org/10.1016/j.intimp.2006.01.015>.
344. Khayyal MT, el-Ghazaly MA, el-Khatib AS, Hatem AM, de Vries PJ, el-Shafei S, Khattab MM. A clinical pharmacological study of the potential beneficial effects of a propolis food product as an adjuvant in asthmatic patients. *Fundam Clin Pharmacol*. 2003;17(1):93–102. <https://doi.org/10.1046/j.1472-8206.2003.00117.x>.
345. Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. *Lancet*. 2008;372(9647):1411–26. [https://doi.org/10.1016/s0140-6736\(08\)61588-3](https://doi.org/10.1016/s0140-6736(08)61588-3).
346. Satchwell TJ, Shoemark DK, Sessions RB, Toye AM. Protein 42: a complex linker. *Blood Cells Mol Dis*. 2009;42(3):201–10. <https://doi.org/10.1016/j.bcmd.2009.01.005>.
347. Trompeter S, King M-J. Hereditary spherocytosis. *Paediatr Child Health*. 2019;29(8):359–64. <https://doi.org/10.1016/j.paed.2019.05.006>.
348. Moreira LL, Dias T, Dias LG, Rogão M, Da Silva JP, Estevinho LM. Propolis influence on erythrocyte membrane disorder (hereditary spherocytosis): a first approach. *Food Chem Toxicol*. 2011;49(2):520–6. <https://doi.org/10.1016/j.fct.2010.11.042>.
349. Spinelli S, Conte A, Lecce L, Incoronato AL, Del Nobile MA. Microencapsulated propolis to enhance the antioxidant properties of fresh fish burgers. *J Food Process Eng*. 2015;38(6):527–35. <https://doi.org/10.1111/jfpe.12183>.
350. Vargas-Sánchez RD, Torrecano-Urrutia GR, Acedo-Félix E, Carvajal-Millán E, González-Córdova AF, Vallejo-Galland B, Torres-Llanez MJ, Sánchez-Escalante A. Antioxidant and antimicrobial activity of commercial propolis extract in beef patties. *J Food Sci*. 2014;79(8):C1499–504. <https://doi.org/10.1111/1750-3841.12533>.
351. Cottica SM, Sabik H, Bélanger D, Giroux HJ, Visentainer JV, Britten M. Use of propolis extracts as antioxidant in dairy beverages enriched with conjugated linoleic acid. *Eur Food Res Technol*. 2015;241(4):543–51. <https://doi.org/10.1007/s00217-015-2483-1>.
352. Akpınar GC, Canogullari S, Baylan M, Alasahan S, Aygun A. The use of propolis extract for the storage of quail eggs. *J Appl Poultry Res*. 2015;24(4):427–35. <https://doi.org/10.3382/japr/pfv043>.
353. Greenaway W, Scaysbrook T, Whatley FR. The analysis of bud exudate of *Populus x euramericana*, and of propolis, by gas chromatography–mass spectrometry. *Proc R Soc Lond B*. 1987;232(1268):249–72. <https://doi.org/10.1098/rspb.1987.0073>.
354. Vanhaelen M, Van Haelen Fastré R. Propolis. II: Identification par chromatographies haute-performance (liquide gaz-liquide et sur couches minces) des constituants. *Bioautographie des chromatogrammes des composés antibactériens*. Belgique apicole; 1979.
355. Vanhaelen M, Van Haelen Fastré R. Propolis. I: Origine, Micrographie, Composition Chimique Et Activité Thérapeutique. Belgique apicole; 1979.
356. Vanhaelen M, Vanhaelen-Fastré R. High-performance liquid, gas-liquid and thin-layer chromatography of naturally occurring flavonoids, phenolic and related compounds. *J Chromatogr A*. 1980;187:225–60.
357. Moreira TF. Composição química da própolis: vitaminas e aminoácidos. *Rev Bras*. 1986;1(1):12–9. <https://doi.org/10.1590/s0102-695x198600100003>.
358. García-Viguera C, Ferreres F, Tomás-Barberán FA. Study of Canadian Propolis by GC-MS and HPLC. *Zeitschrift für Naturforschung C*. 1993;48(9–10):731–5. <https://doi.org/10.1515/znc-1993-9-1009>.
359. Bankova V, Dylgerov A, Popov S, Evstatieva L, Kuleva L, Pureb O, Zamjansan Z. Propolis produced in Bulgaria and Mongolia: phenolic compounds and plant origin. *Apidologie*. 1992;23(1):79–85. <https://doi.org/10.1051/apido:19920109>.
360. Righi AA, Alves TR, Negri G, Marques LM, Breyer H, Salatino A. Brazilian red propolis: unreported substances, antioxidant and antimicrobial activities. *J Sci Food Agric*. 2011;91(13):2363–70. <https://doi.org/10.1002/jsfa.4468>.
361. Li F, Awale S, Tezuka Y, Kadota S. Cytotoxic constituents from Brazilian red propolis and their structure-activity relationship. *Bioorg Med Chem*. 2008;16(10):5434–40. <https://doi.org/10.1016/j.bmc.2008.04.016>.
362. Villanueva VR, Barbier M, Gonnet M, Lavie P. The flavonoids of propolis Isolation of a new bacteriostatic substance: pinocembrin (dihydroxy-5, 7 flavanone)]. *Ann Inst Pasteur (Paris)*. 1970;118(1):84–7.
363. Ghisalberti EL, Jefferies PR, Lanteri R, Matisons J. Constituents of propolis. *Experientia*. 1978;34(2):157–8. <https://doi.org/10.1007/bf01944648>.
364. Bankova VS, Popov SS, Marekov NL. A Study on Flavonoids of Propolis. *J Nat Prod*. 1983;46(4):471–4. <https://doi.org/10.1021/np50028a007>.
365. Tran VH, Duke RK, Abu-Mellal A, Duke CC. Propolis with high flavonoid content collected by honey bees from *Acacia paradoxa*. *Phytochemistry*. 2012;81:126–32. <https://doi.org/10.1016/j.phytochem.2012.06.002>.
366. Falcão SI, Vilas-Boas M, Estevinho LM, Barros C, Domingues MR, Cardoso SM. Phenolic characterization of Northeast Portuguese propolis: usual and unusual compounds. *Anal Bioanal Chem*. 2010;396(2):887–97. <https://doi.org/10.1007/s00216-009-3232-8>.
367. Shrestha SP, Narukawa Y, Takeda T. Chemical constituents of Nepalese propolis: isolation of new dalbergiones and related compounds. *J Nat Med*. 2007;61(1):73–6. <https://doi.org/10.1007/s11418-006-0024-8>.
368. Inui S, Shimamura Y, Masuda S, Shirafuji K, Moli RT, Kumazawa S. A new prenylflavonoid isolated from propolis collected in the Solomon Islands. *Biosci Biotechnol Biochem*. 2012;76(5):1038–40. <https://doi.org/10.1271/bbb.120021>.
369. Chen CN, Wu CL, Shy HS, Lin JK. Cytotoxic prenylflavanones from Taiwanese propolis. *J Nat Prod*. 2003;66(4):503–6. <https://doi.org/10.1021/np0203180>.
370. Li F, He YM, Awale S, Kadota S, Tezuka Y. Two new cytotoxic phenylallylflavanones from Mexican propolis. *Chem Pharm Bull (Tokyo)*. 2011;59(9):1194–6. <https://doi.org/10.1248/cpb.59.1194>.
371. Melliou E, Chinou I. Chemical analysis and antimicrobial activity of Greek propolis. *Planta Med*. 2004;70(6):515–9. <https://doi.org/10.1055/s-2004-827150>.
372. Usia T, Banskota AH, Tezuka Y, Midorikawa K, Matsushige K, Kadota S. Constituents of Chinese propolis and their antiproliferative activities. *J Nat Prod*. 2002;65(5):673–6. <https://doi.org/10.1021/np010486c>.
373. Cao YH, Wang Y, Yuan Q. Analysis of flavonoids and phenolic acid in propolis by capillary electrophoresis. *Chromatographia*. 2004;59:135–40. <https://doi.org/10.1365/s10337-003-0138-z>.
374. Maciejewicz W. Isolation of flavonoid aglycones from propolis by a column chromatography method and their identification by Gc-MS and Tlc Methods. *J Liq Chromatogr Relat Technol*. 2006;24(8):1171–9. <https://doi.org/10.1081/jlc-100103439>.
375. Hegazi AG, Hady FK. Egyptian propolis: 3 Antioxidant, antimicrobial activities and chemical composition of propolis from reclaimed lands. *Z Naturforsch C J Biosci*. 2002;57(3–4):395–402. <https://doi.org/10.1515/znc-2002-3-432>.
376. Petrova A, Popova M, Kuzmanova C, Tsvetkova I, Naydenski H, Muli E, Bankova V. New biologically active compounds from Kenyan propolis. *Fitoterapia*. 2010;81(6):509–14. <https://doi.org/10.1016/j.fitote.2010.01.007>.
377. Alencar SM, Oldoni TL, Castro ML, Cabral IS, Costa-Neto CM, Cury JA, Rosalen PL, Ikegaki M. Chemical composition and biological activity

- of a new type of Brazilian propolis: red propolis. *J Ethnopharmacol.* 2007;113(2):278–83. <https://doi.org/10.1016/j.jep.2007.06.005>.
378. Piccinelli AL, Campo Fernandez M, Cuesta-Rubio O, Márquez Hernández I, De Simone F, Rastrelli L. Isoflavonoids isolated from Cuban propolis. *J Agric Food Chem.* 2005;53(23):9010–6. <https://doi.org/10.1021/jf0518756>.
379. Campo Fernández M, Cuesta-Rubio O, Rosado Perez A, De Oca M, Porto R, Márquez Hernández I, Piccinelli AL, Rastrelli L. GC-MS determination of isoflavonoids in seven red Cuban propolis samples. *J Agric Food Chem.* 2008;56(21):9927–32. <https://doi.org/10.1021/jf801870f>.
380. Sha N, Guan SH, Lu ZQ, Chen GT, Huang HL, Xie FB, Yue QX, Liu X, Guo DA. Cytotoxic constituents of chinese propolis. *J Nat Prod.* 2009;72(4):799–801. <https://doi.org/10.1021/np900118z>.
381. Lotti C, Campo Fernandez M, Piccinelli AL, Cuesta-Rubio O, Márquez Hernández I, Rastrelli L. Chemical constituents of red Mexican propolis. *J Agric Food Chem.* 2010;58(4):2209–13. <https://doi.org/10.1021/jf100070w>.
382. Awale S, Shrestha SP, Tezuka Y, Ueda JY, Matsushige K, Kadota S. Neo-flavonoids and related constituents from Nepalese propolis and their nitric oxide production inhibitory activity. *J Nat Prod.* 2005;68(6):858–64. <https://doi.org/10.1021/np050009k>.
383. Seifert M, Haslinger E (1991) Über die Inhaltsstoffe der Propolis. II Liebig's Annalen der Chemie. 1991;2:93–7. <https://doi.org/10.1002/jlac.199119910118>.
384. Seifert M, Haslinger E (1989) Über die Inhaltsstoffe der Propolis. I Liebig's Annalen der Chemie. 1989;11:1123–6. <https://doi.org/10.1002/jlac.198919890279>.
385. Oliveira AP, França HS, Kuster RM, Teixeira LA, Rocha LM. Chemical composition and antibacterial activity of Brazilian propolis essential oil. *J Venomous Animals Toxins Trop Dis.* 2010;16(1):121–30. <https://doi.org/10.1590/s1678-91992010005000007>.
386. Melliou E, Stratis E, Chinou I. Volatile constituents of propolis from various regions of Greece – Antimicrobial activity. *Food Chem.* 2007;103(2):375–80. <https://doi.org/10.1016/j.foodchem.2006.07.033>.
387. Trusheva B, Todorov I, Ninova M, Najdenski H, Daneshmand A, Bankova V. Antibacterial mono- and sesquiterpene esters of benzoic acids from Iranian propolis. *Chem Cent J.* 2010;4:8. <https://doi.org/10.1186/1752-153x-4-8>.
388. Silici S, Kutluca S. Chemical composition and antibacterial activity of propolis collected by three different races of honeybees in the same region. *J Ethnopharmacol.* 2005;99(1):69–73. <https://doi.org/10.1016/j.jep.2005.01.046>.
389. Popova MP, Graikou K, Chinou I, Bankova VS. GC-MS profiling of diterpene compounds in Mediterranean propolis from Greece. *J Agric Food Chem.* 2010;58(5):3167–76. <https://doi.org/10.1021/jf903841k>.
390. Popova MP, Chinou IB, Marekov IN, Bankova VS. Terpenes with antimicrobial activity from Cretan propolis. *Phytochemistry.* 2009;70(10):1262–71. <https://doi.org/10.1016/j.phytochem.2009.07.025>.
391. Pereira AS, Nascimento EA, de Aquino NF. Lupeol alkanooates in Brazilian propolis. *Z Naturforsch C J Biosci.* 2002;57(7–8):721–6. <https://doi.org/10.1515/znc-2002-7-829>.
392. Márquez Hernández I, Cuesta-Rubio O, Campo Fernández M, Rosado Pérez A, de Oca M, Porto R, Piccinelli AL, Rastrelli L. Studies on the constituents of yellow Cuban propolis: GC-MS determination of triterpenoids and flavonoids. *J Agric Food Chem.* 2010;58(8):4725–30. <https://doi.org/10.1021/jf904527n>.
393. Li F, Awale S, Zhang H, Tezuka Y, Esumi H, Kadota S. Chemical constituents of propolis from Myanmar and their preferential cytotoxicity against a human pancreatic cancer cell line. *J Nat Prod.* 2009;72(7):1283–7. <https://doi.org/10.1021/np9002433>.
394. El-Hady FKA, Hegazi AG. Egyptian propolis: 2. Chemical composition, antiviral and antimicrobial activities of East Nile Delta propolis. *Z Naturforsch C J Biosci.* 2002;57(3–4):386–94. <https://doi.org/10.1515/znc-2002-3-431>.
395. Teixeira EW, Negri G, Meira RM, Message D, Salatino A. Plant Origin of Green Propolis: Bee Behavior, Plant Anatomy and Chemistry. *Evid Based Complement Alternat Med.* 2005;2(1):85–92. <https://doi.org/10.1093/ecam/neh055>.
396. Salatino A, Teixeira EW, Negri G, Message D. Origin and Chemical Variation of Brazilian Propolis. *Evid Based Complement Alternat Med.* 2005;2(1):33–8. <https://doi.org/10.1093/ecam/neh060>.
397. Marcucci MC, Ferreres F, García-Viguera C, Bankova VS, De Castro SL, Dantas AP, Valente PH, Paulino N. Phenolic compounds from Brazilian propolis with pharmacological activities. *J Ethnopharmacol.* 2001;74(2):105–12. [https://doi.org/10.1016/s0378-8741\(00\)00326-3](https://doi.org/10.1016/s0378-8741(00)00326-3).
398. Abu-Mellal A, Koolaji N, Duke RK, Tran VH, Duke CC. Prenylated cinnamate and stilbenes from Kangaroo Island propolis and their antioxidant activity. *Phytochemistry.* 2012;77:251–9. <https://doi.org/10.1016/j.phytochem.2012.01.012>.
399. dos Santos PA, de Miranda Pereira AF, Trugo LC, de Aquino Neto FR. Distribution of quinic acid derivatives and other phenolic compounds in Brazilian propolis. *Z Naturforsch C J Biosci.* 2003;58(7–8):590–3. <https://doi.org/10.1515/znc-2003-7-824>.
400. Matsui T, Ebuchi S, Fujise T, Abesundara KJ, Dopi S, Yamada H, Matsu-moto K. Strong antihyperglycemic effects of water-soluble fraction of Brazilian propolis and its bioactive constituent, 3,4,5-tri-O-caffeoylquinic acid. *Biol Pharm Bull.* 2004;27(11):1797–803. <https://doi.org/10.1248/bpb.27.1797>.
401. Marcucci MC, Ferreres F, Custódio AR, Ferreira MM, Bankova VS, García-Viguera C, Bretz WA. Evaluation of phenolic compounds in Brazilian propolis from different geographic regions. *Z Naturforsch C J Biosci.* 2000;55(1–2):76–81. <https://doi.org/10.1515/znc-2000-1-215>.
402. Trusheva B, Popova M, Koendhori EB, Tsvetkova I, Naydenski C, Bankova V. Indonesian propolis: chemical composition, biological activity and botanical origin. *Nat Prod Res.* 2011;25(6):606–13. <https://doi.org/10.1080/14786419.2010.488235>.
403. Syamsudin WS, Simanjunta P, Heffen WL. Chemical Composition of Propolis from Different Regions in Java and their Cytotoxic Activity. *Am J Biochem Biotechnol.* 2009;5(4):180–3. <https://doi.org/10.3844/ajbbsp.2009.180.183>.
404. Popova M, Trusheva B, Antonova D, Cutajar S, Mifsud D, Farrugia C, Tsvetkova I, Najdenski H, Bankova V. The specific chemical profile of Mediterranean propolis from Malta. *Food Chem.* 2011;126(3):1431–5. <https://doi.org/10.1016/j.foodchem.2010.11.130>.
405. Talla E, Tamfu AN, Gade IS, Yanda L, Mbafor JT, Laurent S, Elst LV, Popova M, Bankova V. New mono-ether of glycerol and triterpenes with DPPH radical scavenging activity from Cameroonian propolis. *Nat Prod Res.* 2017;31(12):1379–89. <https://doi.org/10.1080/14786419.2016.1253077>.
406. Papachroni D, Graikou K, Kosalec I, Damianakos H, Ingram V, Chinou I. Phytochemical analysis and biological evaluation of selected African propolis samples from Cameroon and Congo. *Nat Prod Commun.* 2015;10(1):67–70.
407. Kardar MN, Zhang T, Coxon GD, Watson DG, Fearnley J, Seidel V. Characterisation of triterpenes and new phenolic lipids in Cameroonian propolis. *Phytochemistry.* 2014;106:156–63. <https://doi.org/10.1016/j.phytochem.2014.07.016>.
408. Almutairi S, Eapen B, Chundi SM, Akhalil A, Siheri W, Clements C, Fearnley J, Watson DG, Edrada-Ebel R. New anti-trypanosomal active prenylated compounds from African propolis. *Phytochem Lett.* 2014;10:35–9. <https://doi.org/10.1016/j.phytol.2014.07.002>.
409. El-Bassuony A, AbouZid S. A new prenylated flavanoid with antibacterial activity from propolis collected in Egypt. *Nat Prod Commun.* 2010;5(1):43–5.
410. Omar R, Igoli JO, Zhang T, Gray AI, Ebiloma GU, Clements CJ, Fearnley J, Edrada Ebel R, Paget T, de Koning HP, Watson DG. The chemical characterization of nigerian propolis samples and their activity against *Trypanosoma brucei*. *Sci Rep.* 2017;7(1):923. <https://doi.org/10.1038/s41598-017-01038-2>.
411. Blicharska N, Seidel V. Chemical diversity and biological activity of african propolis. *Prog Chem Org Nat Prod.* 2019;109:415–50. [https://doi.org/10.1007/978-3-030-12858-6\\_3](https://doi.org/10.1007/978-3-030-12858-6_3).
412. Piccinelli AL, Mencherini T, Celano R, Mouhoubi Z, Tamendjari A, Aquino RP, Rastrelli L. Chemical composition and antioxidant activity of Algerian propolis. *J Agric Food Chem.* 2013;61(21):5080–8. <https://doi.org/10.1021/jf400779w>.
413. Boufadi YM, Soubhye J, Riazi A, Rousseau A, Vanhaeverbeek M, Nève J, Boudjeltia KZ, Van Antwerpen P. Characterization and antioxidant properties of six Algerian propolis extracts: ethyl acetate extracts inhibit myeloperoxidase activity. *Int J Mol Sci.* 2014;15(2):2327–45. <https://doi.org/10.3390/ijms15022327>.
414. Segueni N, Magid AA, Decarme M, Rhouati S, Lahouel M, Antonicelli F, Lavaud C, Hornebeck W. Inhibition of stromelysin-1 by caffeic

- acid derivatives from a propolis sample from Algeria. *Planta Med.* 2011;77(10):999–1004. <https://doi.org/10.1055/s-0030-1270713>.
415. Ibrahim R, Wan A, El-Din AA, Radwan M, Elshohly M, Metwally A. Isolation of eleven phenolic compounds from Propolis (Bee Glue) collected in Alexandria, Egypt. 2014. <https://doi.org/10.1055/s-0034-1382569>.
416. El Hady FA, Shaker KH, Imhoff JF, Zinecker H, Salah NM, Ibrahim AM. Bioactive Metabolites from Propolis Inhibit Superoxide Anion Radical, Acetylcholinesterase and Phosphodiesterase (PDE4). *Int J Pharm Sci Rev Res.* 2013;21:338–44.
417. Omar RM, Igoli J, Gray AI, Ebiloma GU, Clements C, Fearnley J, Ebel RA, Zhang T, De Koning HP, Watson DG. Chemical characterisation of Nigerian red propolis and its biological activity against *Trypanosoma Brucei*. *Phytochem Anal.* 2016;27(2):107–15. <https://doi.org/10.1002/pca.2605>.
418. Siheri W, Igoli JO, Gray AI, Nasciemento TG, Zhang T, Fearnley J, Clements CJ, Carter KC, Carruthers J, Edrada-Ebel R, Watson DG. The isolation of antiprotozoal compounds from Libyan propolis. *Phytother Res.* 2014;28(12):1756–60. <https://doi.org/10.1002/ptr.5194>.
419. Siheri W, Ebiloma GU, Igoli JO, Gray AI, Biddau M, Akrahalanont P, Alenezi S, Alwashih MA, Edrada-Ebel R, Muller S, Lawrence CE, Fearnley J, Watson DG, De Koning HP. Isolation of a novel flavanone and an alkylresorcinol with highly potent anti-trypanosomal activity from libyan propolis. *Molecules (Basel, Switzerland).* 2019;24(6):1041. <https://doi.org/10.3390/molecules24061041>.
420. Ito J, Chang FR, Wang HK, Park YK, Ikegaki M, Kilgore N, Lee KH. Anti-AIDS agents. 48.(1) Anti-HIV activity of moronic acid derivatives and the new melliferone-related triterpenoid isolated from Brazilian propolis. *J Nat Prod.* 2001;64(10):1278–81. <https://doi.org/10.1021/np010211x>.
421. Nina N, Quispe C, Jiménez-Aspee F, Theoduloz C, Giménez A, Schmeda-Hirschmann G. Chemical profiling and antioxidant activity of Bolivian propolis. *J Sci Food Agric.* 2016;96(6):2142–53. <https://doi.org/10.1002/jsfa.7330>.
422. Boeing T, Mejía JAA, Ccana-Ccapatinta GV, Mariott M, Vilhena M, de Andrade Fonseca Da Silva RC, de Souza P, Mariano LNB, Oliveira GR, da Rocha IM, da Costa GA, de Andrade SF, da Silva LM, Bastos JK. The gastroprotective effect of red propolis extract from Northeastern Brazil and the role of its isolated compounds. *J Ethnopharmacol.* 2021;267:113623. <https://doi.org/10.1016/j.jep.2020.113623>.
423. Tani H, Hikami S, Takahashi S, Kimura Y, Matsuura N, Nakamura T, Yamaga M, Koshino H. Isolation, identification, and synthesis of a new prenylated cinnamic acid derivative from Brazilian green propolis and simultaneous quantification of bioactive components by LC-MS/MS. *J Agric Food Chem.* 2019;67(44):12303–12. <https://doi.org/10.1021/acs.jafc.9b04835>.
424. Hernández IM, Fernandez MC, Cuesta-Rubio O, Piccinelli AL, Rastrelli L. Polyprenylated benzophenone derivatives from Cuban propolis. *J Nat Prod.* 2005;68(6):931–4. <https://doi.org/10.1021/np0495884>.
425. de Castro Ishida VF, Negri G, Salatino A, Bandeira MFCL. A new type of Brazilian propolis: Prenylated benzophenones in propolis from Amazon and effects against cariogenic bacteria. *Food Chem.* 2011;125(3):966–72. <https://doi.org/10.1016/j.foodchem.2010.09.089>.
426. Astudillo L, Avila F, Morrison R, Gutierrez M, Bastida J, Codina C, Schmeda-Hirschmann G. Biologically active compounds from Chilean propolis. *Boletín Sociedad Chilena Química.* 2000;45:577–81.
427. Popova MP, Trusheva BS, Nedialkov PT, Tsvetkova I, Pardo-Mora DP, Najdenski H, Torres-García OA, Sforzin JM, Bankova VS. New  $\Delta$ -tocotrienol derivatives from Colombian propolis. *Nat Prod Res.* 2020;34(19):2779–86. <https://doi.org/10.1080/14786419.2019.1590710>.
428. Muñoz O, Peña R, Ureta E, Montenegro G, Caldwell C, Timmermann B. Phenolic compounds of propolis from Central Chilean Matorral. *Zeitschrift für Naturforschung C J Biosci.* 2001;56:273–7. <https://doi.org/10.1515/znc-2001-3-417>.
429. Cuesta-Rubio O, Frontana-Urbe BA, Ramírez-Apan T, Cárdenas J. Polyisoprenylated benzophenones in Cuban propolis; biological activity of nemorosone. *Z Naturforsch C J Biosci.* 2002;57(3–4):372–8. <https://doi.org/10.1515/znc-2002-3-429>.
430. Díaz-Carballo D, Malak S, Bardenheuer W, Freistuehler M, Peter Reusch H. The contribution of plukenetione A to the anti-tumoral activity of Cuban propolis. *Bioorg Med Chem.* 2008;16(22):9635–43. <https://doi.org/10.1016/j.bmc.2008.10.019>.
431. Granados-Pineda J, Uribe-Urbe N, Garcia-Lopez P, Ramos-Godinez MDP, Rivero-Cruz JF, Perez-Rojas JM. Effect of Pinocebrin Isolated from Mexican Brown Propolis on Diabetic Nephropathy. *Molecules.* 2018. <https://doi.org/10.3390/molecules23040852>.
432. Cuesta-Rubio O, Campo Fernández M, Márquez Hernández I, Jaramillo CGJ, González VH, De Oca M, Porto R, Marrero Delange D, Monzote Fidalgo L, Piccinelli AL, Campone L, Rastrelli L. Chemical profile and anti-leishmanial activity of three Ecuadorian propolis samples from Quito, Guayaquil and Cotacachi regions. *Fitoterapia.* 2017;120:177–83. <https://doi.org/10.1016/j.fitote.2017.06.016>.
433. Valčić S, Montenegro G, Timmermann BN. Lignans from Chilean propolis. *J Nat Prod.* 1998;61(6):771–5. <https://doi.org/10.1021/np980017j>.
434. Aga H, Shibuya T, Sugimoto T, Kurimoto M, Nakajima S. Isolation and Identification of Antimicrobial Compounds in Brazilian Propolis. *Biosci Biotechnol Biochem.* 1994;58(5):945–6. <https://doi.org/10.1271/bbb.58.945>.
435. Nina N, Quispe C, Jiménez-Aspee F, Theoduloz C, Feresín GE, Lima B, Leiva E, Schmeda-Hirschmann G. Antibacterial activity, antioxidant effect and chemical composition of propolis from the Región del Maule. *Central Chile Molecules.* 2015;20(10):18144–67. <https://doi.org/10.3390/molecules201018144>.
436. Trusheva B, Georgieva K, Popova M, Uzunova V, Stoyanova T, Valcheva V, Tzoneva R, Bankova V. New Insights into Tropical Propolis: Propolis from Pitcairn Island. *J Apitherapy Nat.* 2018;1(3):30.
437. Georgieva K, Trusheva B, Uzunova V, Stoyanova T, Valcheva V, Popova M, Tzoneva R, Bankova V. New cycloartane triterpenes from bioactive extract of propolis from Pitcairn Island. *Fitoterapia.* 2018;128:233–41. <https://doi.org/10.1016/j.fitote.2018.05.024>.
438. Trusheva B, Stancheva K, Gajbhiye N, Dimitrova R, Popova M, Saraf R, Bankova V. Two New Prenylated Stilbenes with an Irregular Sesquiterpenyl Side Chain from Propolis from Fiji Islands. *Records Nat Products.* 2016;10:465–71.
439. Duke CC, Tran VH, Duke RK, Abu-Mellal A, Plunkett GT, King DI, Hamid K, Wilson KL, Barrett RL, Bruhl JJ. A sedge plant as the source of Kangaroo Island propolis rich in prenylated p-coumarate ester and stilbenes. *Phytochemistry.* 2017;134:87–97. <https://doi.org/10.1016/j.phytochem.2016.11.005>.
440. King DI, Hamid K, Tran VH, Duke RK, Duke CC. Kangaroo Island propolis types originating from two *Lepidosperma* species and *Dodonaea humilis*. *Phytochemistry.* 2021;188:112800. <https://doi.org/10.1016/j.phytochem.2021.112800>.
441. Thanh LN, Thoa HT, Oanh VTK, Phuong DTL, Van HT, Chi NQ, Giap TH, Oanh NTT, Hang NTM, Hung NV, Minh CV, Bankova V. Isolated xanthenes from *Isotrigona furva* propolis in Vietnam. *J Apither Nat.* 2018;1(3):74–74.
442. Nguyen HX, Nguyen MTT, Nguyen NT, Awale S. Chemical Constituents of Propolis from Vietnamese *Trigona minor* and their antiausterity activity against the PANC-1 Human Pancreatic Cancer Cell Line. *J Nat Prod.* 2017;80(8):2345–52. <https://doi.org/10.1021/acs.jnatprod.7b00375>.
443. Sanpa S, Popova M, Bankova V, Tunkasiri T, Eitssayeam S, Chantawanakul P. Antibacterial Compounds from Propolis of *Tetragonula laeviceps* and *Tetragona melanoleuca* (Hymenoptera: Apidae) from Thailand. *PLoS ONE.* 2015;10(5):e0126886. <https://doi.org/10.1371/journal.pone.0126886>.
444. Nguyen HX, Van Do TN, Nguyen MTT, Dang PH, Tho LH, Awale S, Nguyen NT. A New Alkenylphenol from the Propolis of Stingless Bee *Trigona minor*. *Natural Product Commun.* 2018;13(1):19345. <https://doi.org/10.1177/1934578X1801300121>.
445. Regueira MSN, Tintino SR, da Silva ARP, Costa MDS, Boligon AA, Matias EFF, de Queiroz BV, Menezes IRA, Melo Coutinho HD. Seasonal variation of Brazilian red propolis: antibacterial activity, synergistic effect and phytochemical screening. *Food Chem Toxicol.* 2017;107(Pt B):572–80. <https://doi.org/10.1016/j.fct.2017.03.052>.
446. Velikova M, Bankova V, Sorkun K, Houcine S, Tsvetkova I, Kujumgiev A. Propolis from the Mediterranean region: chemical composition and antimicrobial activity. *Z Naturforsch C J Biosci.* 2000;55(9–10):790–3. <https://doi.org/10.1515/znc-2000-9-1019>.
447. Wang K, Zhang J, Ping S, Ma Q, Chen X, Xuan H, Shi J, Zhang C, Hu F. Anti-inflammatory effects of ethanol extracts of Chinese propolis and buds from poplar (*Populus canadensis*). *J Ethnopharmacol.* 2014;155(1):300–11. <https://doi.org/10.1016/j.jep.2014.05.037>.
448. Nani BD, Sardi JCO, Lazarini JG, Silva DR, Massarioli AP, Cunha TM, de Alencar SM, Franchin M, Rosalen PL. Anti-inflammatory and

- anti-Candida Effects of Brazilian Organic Propolis, a Promising Source of Bioactive Molecules and Functional Food. *J Agric Food Chem*. 2020;68(10):2861–71. <https://doi.org/10.1021/acs.jafc.8b07304>.
449. Albokhadaim I. Influence of dietary supplementation of propolis on hematology, biochemistry and lipid profile of rats fed high cholesterol diet. *J Advan Veter Anim Res*. 2015;2(1):1. <https://doi.org/10.5455/javar.2015.b49>.
450. Silva DB, Miranda AP, Silva DB, D'Angelo LR, Rosa BB, Soares EA, Ramalho JG, Boriollo MF, Garcia JA. Propolis and swimming in the prevention of atherogenesis and left ventricular hypertrophy in hypercholesterolemic mice. *Braz J Biol*. 2015;75(2):414–22. <https://doi.org/10.1590/1519-6984.15313>.
451. Fang Y, Sang H, Yuan N, Sun H, Yao S, Wang J, Qin S. Ethanol extract of propolis inhibits atherosclerosis in ApoE-knockout mice. *Lipids Health Dis*. 2013;12:123. <https://doi.org/10.1186/1476-511x-12-123>.
452. Usman UZ, Abu Bakar A, Zin A, Mohamed M. LC-MS analysis and effects of Malaysian propolis on insulin, glucagon, pancreas and oxidative stress status in streptozotocin-induced diabetic rats. *J Med Biomed Res*. 2017;16:15–27.
453. Ugbaja RN, Fatokun TP, Akinloye DI, James AS, Onabanjo OO, Akinloye OA. Propolis ethanol extract abrogates hyperglycemia, lipotoxicity, and lowered hepatic poly (ADP-ribose) polymerase protein level in male albino rats. *J Diabetes Metab Disord*. 2021;20(1):683–96. <https://doi.org/10.1007/s40200-021-00800-8>.
454. Shvarzbeyn J, Huleihel M. Effect of propolis and caffeic acid phenethyl ester (CAPE) on NFκB activation by HTLV-1 Tax. *Antiviral Res*. 2011;90(3):108–15. <https://doi.org/10.1016/j.antiviral.2011.03.177>.
455. Fischer G, Conceição FR, Leite FP, Dummer LA, Vargas GD, Hübner Sde O, Dellagostin OA, Paulino N, Paulino AS, Vidor T. Immunomodulation produced by a green propolis extract on humoral and cellular responses of mice immunized with SuHV-1. *Vaccine*. 2007;25(7):1250–6. <https://doi.org/10.1016/j.vaccine.2006.10.005>.
456. Ganesan S, Faris AN, Comstock AT, Wang Q, Nanua S, Hershenson MB, Sajjan US. Quercetin inhibits rhinovirus replication in vitro and in vivo. *Antiviral Res*. 2012;94(3):258–71. <https://doi.org/10.1016/j.antiviral.2012.03.005>.
457. Rojas Á, Del Campo JA, Clement S, Lemasson M, García-Valdecasas M, Gil-Gómez A, Ranchal I, Bartosch B, Bautista JD, Rosenberg AR, Negro F, Romero-Gómez M. Effect of Quercetin on Hepatitis C Virus Life cycle: from viral to host targets. *Sci Rep*. 2016;6:31777. <https://doi.org/10.1038/srep31777>.
458. Cheng Z, Sun G, Guo W, Huang Y, Sun W, Zhao F, Hu K. Inhibition of hepatitis B virus replication by quercetin in human hepatoma cell lines. *Virology*. 2015;53(4):261–8. <https://doi.org/10.1007/s12250-015-3584-5>.
459. Utsunomiya H, Ichinose M, Ikeda K, Uozaki M, Morishita J, Kuwahara T, Koyama AH, Yamasaki H. Inhibition by caffeic acid of the influenza A virus multiplication in vitro. *Int J Mol Med*. 2014;34(4):1020–4. <https://doi.org/10.3892/ijmm.2014.1859>.
460. Xie Y, Huang B, Yu K, Shi F, Liu T, Xu W. Caffeic acid derivatives: a new type of influenza neuraminidase inhibitors. *Bioorg Med Chem Lett*. 2013;23(12):3556–60. <https://doi.org/10.1016/j.bmcl.2013.04.033>.

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