Propolis: chemical diversity and challenges in quality control

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Abstract Propolis is a resinous natural product produced by honeybees using beeswax and plant exudates. The chemical composition of propolis is highly complex, and varies with region and season. This inherent chemical variability presents several challenges to its standardisation and quality control. The present review was aimed at highlighting marker compounds for different types of propolis, produced by the species Apis mellifera, from different geographical origins and that display different biological activities, and to discuss strategies for quality control. Over 800 compounds have been reported in the different propolises such as temperate, tropical, birch, Mediterranean, and Pacific propolis; these mainly include alcohols, acids and their esters, benzofuranes, benzopyranes, chalcones, flavonoids and their esters, glycosides (flavonoid and diterpene), glycerol and its esters, lignans, phenylpropanoids, steroids, terpenes and terpenoids. Among these, flavonoids (> 140), terpenes and terpenoids (> 160) were major components. A broad range of biological activities, such as anti-oxidant, antimicrobial, anti-inflammatory, immunomodulatory, and anticancer activities, have been ascribed to propolis constituents, as well as the potential of these compounds to be biomarkers. Several analytical techniques, including non-separation and separation methods have been described in the literature for the quality control assessment of propolis. Mass spectrometry coupled with separation methods, followed by chemometric analysis of the data, was found to be a valuable tool for the profiling and classification of propolis samples, including (bio)marker identification. Due to the rampant chemotypic variability, a multiple-marker assessment strategy considering geographical and biological activity marker(s) with chemometric analysis may be a promising approach for propolis quality assessment.

Keywords Propolis · Phytochemistry · Marker compounds · Quality control · Standardisation

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COVID-19 Coronavirus disease
Folk medicine plays a vital role in the human health care systems of many countries around the globe, and has done so since antiquity. In traditional systems of medicine, thousands of plants and their derived products, such as propolis, are reported to have significant medical value, but most remain untested in new drug discovery approaches. Propolis (bee glue) is a resinous, sticky, coloured material with a characteristic smell that is prepared by honeybees, using beeswax and plant exudates (Sforcin 2016). The colour of propolis depends largely on the plant source and collection time (Chen et al. 2004), and varies from green to red to dark brown, with dark brown being the most common (Lotti et al. 2010; Kasote et al. 2017). Honeybees use propolis as a construction material for sealing openings and cracks in their beehive, also to avoid the entry of intruders, and to maintain aseptic conditions within the beehive (Bankova et al. 2002; Salatino et al. 2005). Commercial propolis is produced mainly by the honeybee, Apis mellifera, although small amounts are derived from stingless bee species (Kasote 2017; Kasote et al. 2019).

The chemical composition of propolis is highly complex and changeable. It generally comprises a vegetable resin and balsam (up to 70%), beeswax (< 10% to 87%), volatile organic compounds (< 1% to 3%), pollen, and other substances, representing compound classes such as aliphatic acids and their esters, aromatic acids and their esters, flavonoids and other plant phenolics, terpenoids, carbohydrates, amino acids, vitamins (B1, B2, B6, C, and E), and minerals (aluminum, antimony, calcium, cesium, copper, iron, lanthanum, manganese, mercury, nickel, silver, vanadium, and zinc) (Burdock 1998; De Almeida and Menezes 2002; Cunha et al. 2004; Anjum et al. 2019; Salatino and Salatino 2021).

Since approximately 300 BC, propolis has been used in traditional Egyptian medicine as a therapeutic agent (Banskota et al. 1998; Hegazi and Abd El Hady 2002). The use of propolis to accelerate wound-healing and for other conditions, were also recorded in archaic Greek, Roman, and Georgian folk medicine (Salatino et al. 2005; Sforcin and Bankova 2011). In modern time, the use of propolis in pharmaceutical and food preparations has been increasing, due to its wide range of therapeutic and health-promoting activities, which include anti-oxidant, antibacterial, antifungal, anti-inflammatory, antiviral, immunomodulatory, hepatoprotective, anti-allergic, septic wound healing, antitumour and antidiabetic activities (Banskota et al. 2002; Oršolić et al. 2006; Schnitzler et al. 2010; Adewumi and Ogunjinmi 2011; Shi et al. 2012b; Bhaduria 2012; Wu et al. 2012; Chan et al. 2013; Przybyłek and Karpinski 2019; Pobiega et al. 2019; Nandre et al. 2021). Recently, it was reported that Brazilian and Egyptian propolis can be regarded as a safe and effective adjunct therapy to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Siveira et al. 2021; H Elwakil et al. 2021), which caused a global pandemic referred to as coronavirus disease 2019 (COVID-19) that is still not under control.
Despite its promising therapeutic and health-promoting potential, the use of propolis as a drug or herbal supplement has not been officially accepted in most countries, due to its inconsistent composition. The phytochemistry of propolis varies according to the region and season, and this may be the biggest hurdle impeding the standardisation and quality control of this substance. The availability of comprehensive information regarding the possible phytochemical composition of propolis samples from different specific places of origin, including qualitative and quantitative biomarker data, will aid in the quality control of propolis. Several review articles have been published in the context of the phytochemistry of different types of propolis, the factors affecting the phytochemistry, related health benefits of propolis, and the problems associated with chemical standardisation (Salatino et al. 2011; Farooqui and Farooqui 2012; Bankova et al. 2014; Pobiega et al. 2019; Shahinozzaman et al. 2021). However, comprehensive information regarding the diverse range of phytochemicals, specific geographical and biological marker compounds, and the analytical techniques used for the standardisation and quality control of propolis, has not been collectively and comprehensively compiled. Hence, the approach taken in this review was to summarise the phytochemical content of propolis from all over the world, according to compound classes, and, where possible, link it to the botanical source and place of origin. Moreover, herein, marker compounds that characterise the geographic origin and biological activities are collated, the existing quality control strategies are discussed, and future research perspectives are proposed.

Phytochemical composition and chemogeographical variation

Propolis is a very rich source of a wide range of bioactive compounds. Numerous factors, such as the origin, time of collection, plant sources visited by the bees, and bee species, determine the chemical composition of propolis (Tagliacollo and Orsi 2011; Huang et al. 2014). Although it was reported earlier (Huang et al. 2014) that about 300 phytoconstituents, such as polyphenols, esters of phenolic acids, flavonoids, sesquiterpene, diterpenes, triterpenes, lignans, prenylated benzophenones, aldehydes, steroids, and coumarins, are present in propolis samples from various parts of the world, this number has increased to more than 800 (Šturm and Ulrih 2019). Polyphenols are the most abundant constituents of the majority of propolis samples (Bankova et al. 1995), and are represented mainly by phenolic acids and their esters, and flavonoids. Brazilian red and green propolis were reported to contain proanthocyanidins (condensed tannins), which is quite rare (Mayworm et al. 2014). By 2014, approximately 140 flavonoids had been reported in propolis, and these mainly include compounds from nine classes, namely; flavones, flavonols, flavanones including prenylflavanones, isoflavones, isoflavanones, isoflavans, neoflavonoids, pterocarpans (Table S1; Fig. 1). Until 2011, it was believed that flavonoid glycosides are uncommon in propolis obtained from A. mellifera (Salatino et al. 2011). However, since then, at least 55 flavonoid glycosides were reported in propolis samples from Serbia, the UK, Portugal and Brazil (Šturm and Ulrih 2019). Similarly, diterpene glycosides, such as diterpene rhamnosides, were reported in propolis from El Salvador (Popova et al. 2001a).

Nearly 160 terpenes, including terpenoids, have been reported in propolis. These primarily includes monoterpenes, sesquiterpenes, diterpenes, triterpenes, monoterpenoids, diterpenoids, and triterpenoids (Table S1; Fig. 2). The occurrence of nitrogenous compounds, such as alkaloids and cyanogens, was also considered to be unusual in propolis obtained from A. mellifera (Salatino et al. 2011). Nonetheless, several alkaloids and alkaloid derivatives, such as pagicerine, demecolcine, papaverine, aspidospermidine, morphinan-6-one-2-ol, thebaine, N,O-dimethyl stephine, morpholine, 5(4H)-thebenidinone, 4-(phenylthioxomethyl)morpholine, 4-methyl-2,6-bis(4-morpholylmethyl)phenol, 3-[(trimethylsilyl)oxy]4,5a-epoxy-14-hydroxy-17-(2-propenyl)morphinan-6-one and nicotinaldehyde semicarbazone were reported from Algerian propolis (Soltani et al. 2017). However, as this is the only communication of alkaloids in propolis and they have been detected by GC–MS, and there is no report on isolation of alkaloids from propolis so far, this information should be corroborated by further research.

The volatile oil composition of propolis is comparatively low (typically less than 1%, rarely 2–3% of the total weight of the propolis sample) and generally comprises mono- or sesquiterpenoids, prenylated
acetophenones and other volatile organic compounds (Bankova et al. 1998, 2014; Sun et al. 2012). Despite the relatively low concentrations, their characteristic aroma and significant biological activity make them indispensable for propolis characterisation, and profiles of the volatiles can be useful to differentiate propolis samples from different geographical regions (Kaškonienė et al. 2014; Bankova et al. 2014).

Samples from temperate zones can be classified as one of two types, based on the presence of representative amounts of β-eudesmol (40–60%) or benzyl benzoate (20–40%) in the volatile fraction (Petri et al. 1988; Pavlovic et al. 2020). Bankova et al. (2014) reviewed the chemical compositions of propolis volatiles from various regions and reported that, other than the usual chemical diversity, most of the European propolis samples are rich in sesquiterpenes, while samples from temperate zones contain mainly monoterpenes in their volatile fractions.

The chemical composition of propolis is largely dependent on the flora frequented by the bees in the vicinity of their hives (Lotti et al. 2010; Righi et al. 2011). The chemistry of propolis samples from different parts of the world has been extensively studied, and notably, was found to be unique to specific geographical zones, in many cases. In general, there have been attempts to classify samples from around the globe according to their chemical composition and floral origin (Fig. 3). Poplar (temperate), Birch, Tropical, Mediterranean and Pacific are the main recognised classes of propolis (Salatino et al. 2011).

Propolis samples originating from temperate zones (West Asia, North Africa, Europe and North America, parts of Argentina, New Zealand) reportedly have similar phytochemical compositions and are predominantly rich in flavonoids and phenolic acid esters, which are almost absent in those originating from tropical regions (Cuesta-Rubio et al. 2007). The propolis obtained from of North-Russia, and mountainous regions of Switzerland and Italy were characterised by phenolic glycerides, namely dicoumaroyl acetyl-, diferuloyl acetyl-, feruloyl coumaroyl acetyl- and caffeoyl coumaroyl acetyl glycerol (Pavlovic et al. 2020) coming from Populus tremula which grows at colder climate and higher altitudes than P. nigra. In contrast, propolis obtained from tropical regions (particularly South America) are dominated by prenylated p-coumaric acid derivatives, flavonoids, benzophenones, lignans and terpenes (Popova et al. 2009). Polyprenylated benzophenones and lignans are characteristic of samples from tropical regions (Fig. 4). The observed chemical composition variation between propolis from temperate and tropical zones has been attributed to differences in vegetation sources (Burdock 1998; Banskota et al. 2000). Samples from Mediterranean countries, such as Croatia, Algeria, Greece (Island of Evia), and Cyprus, exhibit a somewhat mixed chemical profile, distinguished by high concentrations of diterpenoids and the absence (or very low concentrations) of flavonoids (Trusheva et al. 2007; Popova et al. 2010b). Pacific propolis samples obtained from Taiwan and Japan (Okinawa) were found to contain predominantly prenylated flavanones, which is probably linked to the botanical source, Macaranga tanarius (Shahinozzaman et al. 2021). The chemical composition of samples from New Zealand showed resemblance to samples originating from Europe and North America (Markham et al. 1996).
Fig. 2 Terpenes and terpenoids reported in propolis
Despite characteristic phytochemical similarities of propolis from within the same geographical zone, region-specific uniqueness and variation in chemical composition have also been observed. This phenomenon is most probably related to region-specific flora. An excellent example is Brazilian propolis, which has been classified into 12 different groups based on the geographical origin, plant source, and chemical composition (Park et al. 2000, 2002). The Brazilian propolis derived from bees frequenting Baccharis plant species contains mainly prenylated derivatives of \( p \)-coumaric acid, sesquiterpenes, acetophenones, diterpenes and lignans (Bankova 2005a, 2005b; Piccinelli et al. 2005). In addition, prenylated and straightforward \( p \)-coumaric acids, are unique to Brazilian green propolis (Fig. 5). Green and brown Brazilian propolis are the most common among the above-mentioned types of propolis. Green propolis, which is derived from Baccharis dracunculifolia,
is found to be rich in prenylated phenylpropanoids, chlorogenic and benzoic acids, as well as triterpenoids (Righi et al. 2011). In contrast, Dalbergia ecastaphylum is the source for red propolis; the pigments retusapurpurin A and B are responsible for this characteristic red colour (Piccinelli et al. 2011). This type contains isoflavonoids, prenylated benzophenones (from flowers of Clusia spp.) and naphthoquinone epoxide (Trusheva et al. 2006). Similar to Brazilian propolis, phytochemical variation has also been reported amongst Cuban propolis (Cuesta-Rubio et al. 2007). Based on their physicochemical characteristics, they are further divided into three types; brown, yellow, and red (Piccinelli et al. 2011). Polyisoprenylated benzophenones from the flowers of Clusia nemorosa and triterpenoids are the main components of brown and yellow propolis, respectively, whereas the red type contains mainly chalcones, pterocarpanes, isoflavans, and isoflavones originating from the resin of Clusia and Dalbergia species (Piccinelli et al. 2005, 2011). In addition to Brazil and Cuba, samples from other countries on the South American continent, including Chile, Venezuela, Argentina, and Uruguay, have also been well studied. Chilean propolis reportedly contains several classes of compounds, such as phenylpropanes, benzaldehydes, dihydrobenzofurans, benzopyrans and lignans (Valcic et al. 1998, 1999). It has been reported that Chilean propolis originates from the species Eucalyptus and Ricinus and five native Chilean species, namely; Baccharis linearis, Buddleja globosa, Peumus boldus, Quillaja saponaria and Salix humboldtiana (Montenegro et al. 2001). Similar to samples from Brazil, Venezuelan propolis contains polyisoprenylated benzophenones, its plant sources are the flowers of Clusia major and Clusia minor (Tomás-Barberán et al. 1993; Cuesta-Rubio et al. 2007). Larrea nitida is the plant source for Andean Argentinian propolis, which contains characteristic epoxy lignans (Agüero et al. 2010).

The bud exudates of poplar trees are the main floral source of propolis from temperate regions (North America, Europe, and West Asia); hence, propolis samples obtained from this region are generally termed Poplar propolis (Bankova et al. 2002). This propolis contains poplar bud phenolics, such as flavonoid aglycones (flavones and flavanones) and phenolic acids, and their esters (Bankova et al. 2002). Uruguayan propolis has a chemical composition similar to propolis of European and Chinese origin, which explains its classification into the Poplar class (Kumazawa et al. 2002). Populus nigra bud secretions are the major resin source for propolis from various European countries, such as France, Great Britain, Spain and Bulgaria (Bankova et al. 1992). However, some chemical variations have been observed among the same and different countries. This could be due to the other vegetal sources of resins for “Poplar-type” propolis, such as different Pinus spp., Prunus spp., Acacia spp. and also Betula pendula, Aesculus hippocastanum and Salix alba (Dezmirean et al. 2021). Variation in the chemical compositions of samples from various European countries has been reported, namely Bulgaria, Italy, and Switzerland; even though they displayed the characteristic typical chemical patterns of Poplar propolis (Bankova et al. 2000).

Portuguese propolis was found to contain a dimer of a p-coumaric ester derivative, together with four unique methylated, esterified, and/or hydroxylated derivatives of common poplar flavonoids, in addition to six unusual derivatives of pinocembrin/pinobanksin, including phenylpropanoid acid derivatives (Falcão et al. 2013). Propolis from the Canary Islands showed the presence of furofuran lignans, which are uncommon in European and Mediterranean propolis (Bankova et al. 1998). In addition to the typical compounds in Poplar-types, Australian and Canadian products contained chalcones, which are uncommon in propolis from temperate regions (Christov et al. 2006; Tran et al. 2012). The observed chemical composition of Russian propolis differ from that of Poplar propolis. This finding may be due to its different plant sources, namely Betula verrucosa and P. tremula (Christov et al. 2006). Consequently, phenylpropanoids, cinnamic acid esters, phenylpropanoid glycerides and sesquiterpenols, along with flavonoids and chalcones, were reported in Russian propolis samples (Isidorov et al. 2014).

Mediterranean propolis, obtained from counties on the Mediterranean Sea present a somewhat mixed and characteristic diterpene composition. Two chemotypes have been identified in the abovementioned Mediterranean countries; one rich in esters of phenolic acids (benzyl, phenylethyl and pentenyl caffeates) and flavonoids (pinocembrin, pinobanksin, pinobanksin-3-O-acetate, galangin)—e.g. the typical poplar type, and the second type abundant in diterpenes, including
totarol, 13-epi-manool, iso-agatholal, agathadiol, communic acid, junicedric acid, 13-epi-cupressic acid, isocupressic acid (Popova et al. 2008; Piccinelli et al. 2013). The buds of poplars and *Cupressus sempervirens* resin are the main source of the phenolic and characteristic diterpene composition, respectively, of Mediterranean propolis (Velikova et al. 2000; Popova et al. 2011). The non-volatile fraction of Mediterranean propolis was characterised by the presence of phenolic acids and their esters and flavonoids. However, diterpenes were also reported in propolis samples from countries including Italy, Croatia, Malta, Greece, Turkey, Cyprus, Egypt, Libya, Algeria and Morocco (El-Guendouz et al. 2019).

Chinese propolis samples are reported to have a similar composition to that of European propolis. However, propolis samples obtained from Taiwan, Japan and the Solomon Islands reportedly contain some components that are not generally observed in propolis from other regions, such as Europe and Brazil (Kumazawa et al. 2008). These products are termed Pacific propolis and are characteristically rich in prenylated flavanones (Popova et al. 2010a). The fruit of *M. tanarius* are reportedly the resin source (Kumazawa et al. 2008; Popova et al. 2010b). Similar to Pacific propolis, Indonesian and Myanmar (Burmese) propolis were found to contain prenylflavanones and cycloartane-type triterpenes (Li et al. 2009; Trusheva et al. 2011). *Macaranga tanarius* and *Mangifera indica* were identified as the plant sources for Indonesian propolis (Trusheva et al. 2011).

Samples obtained from Nepal were rich in neo-flavonoids, isoflavones, flavanones and pterocarpans (Awale et al. 2005; Shrestha et al. 2007). Five different coloured products (brown, green, green–brown, red, and red–brown) were reported among Indian samples; most displayed a chemical composition similar to those originating from temperate regions. Moreover, it was proposed that Indian samples be classified into two groups, northern and southern state propolis samples (Kasote et al. 2017).

Available literature data was summarised in the form of a heat map to assist in understanding the chemical composition variation and uniqueness within propolis samples from different countries of the world (Fig. 6). Interestingly, it became evident that the chemical composition of propolis samples from temperate and subtropical climatic zones are very similar. However, no specific chemical composition similarity was revealed within samples from tropical or subtropical regions.

**Analytical methods employed in propolis quality control**

Propolis is an important therapeutic and health-promoting agent that is usually consumed in the form of extracts or fractions. Thus, the setting of definite quality control parameters is a prerequisite for the marketing of propolis as a medicine and health supplement. This step will help to ensure its uniform quality, stability and therapeutic efficacy. However, in reality, the qualitative and quantitative standardisation of propolis is difficult, due to its complex and varying chemical composition. Therefore, to guarantee the quality of propolis, it is necessary to have detailed information regarding the overall complex and varying chemistry of propolis, and the existing quality control strategies.

Propolis is not consumed in its natural form due to the presence of some inert material. Instead, it is generally purified with solvents to remove the inert material and to enrich the polyphenolic content (Pobiega et al. 2019). Numerous solvents, including water, ethanol, methanol, chloroform and hexane, have been used for the preparation of extracts and fractions; however, the use of diluted ethanol (70%) is most common (Pietta et al. 2002; Alencar et al. 2007; Cvek et al. 2007; Miguel and Antunes 2011; Sforcin and Bankova 2011; Elbaz and Elsayad 2012). Moreover, oils and natural deep eutectic solvents (NADES) have demonstrated promising potential (Bankova et al. 2021). Cvek et al. (2007) optimised the extraction conditions with respect to time, temperature, and concentration of extraction solvent, and found 80% ethanol and one hour at room temperature to yield the best results. In contrast, Pietta et al. (2002) reported that multi-step extraction with ethanol is a more suitable procedure to obtain dewaxed propolis that is rich in polyphenolics. The method of extraction was found to be a crucial step that defines not only the quality, but also the yield of the bioactive constituents of propolis. To date, various modern techniques, in addition to conventional maceration and Soxhlet extraction have been employed to increase the yield of the extract. Compared to the traditional maceration extraction method, MAE (microwave assisted
extraction) and ultrasonic extraction (UE) provide high yields in a short timeframe and are less labour-intensive (Trusheva et al. 2007). Similarly, high-hydrostatic-pressure extraction (HHPE) has also been employed to concentrate flavonoids from propolis, and was found to be more effective than the conventional extraction methods in terms of time, efficiency and yield (Shouqin et al. 2005). Furthermore, bioactivity-guided selective fractionation of the hydroalcoholic extracts of propolis has also been conducted using both conventional and unconventional techniques, such as supercritical carbon dioxide extraction (Paviani et al. 2010). A recent review (Bankova et al. 2021) evaluated data generated from classical (maceration and Soxhlet) and modern (ultrasound-assisted and microwave-assisted extraction, supercritical CO2 extraction, high-pressure methods) propolis extraction methods, as well as potential large-scale applications.

Its region-specific chemical composition is one of the characteristic properties of propolis. Almost all types of reported propolis samples are unique and rich in a diversity of phytochemicals. The determination and identification of these unique and prominent

**Fig. 6** Heat map showing chemical composition variation within propolis samples studied from different countries of world. The yellow colouring indicates the presence, and the brown colouring, the absence, of specified compound classes. Temperate and subtropical climatic zone countries reflect a similar chemical composition. However, no distinct chemical composition is evident within tropical and subtropical climatic zone countries. (Color figure online)
constituents of propolis could be vital for its standardisation and chemical quality control (Fernandes-Silva et al. 2013). Several analytical techniques, including non-separation [ultraviolet spectroscopy (UV), near-infrared (NIR) and nuclear magnetic resonance (NMR) spectroscopy] and separation [gas chromatography (GC), high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), and HPTLC (high-performance thin-layer chromatography) methods have been described in the literature for the analysis of propolis (Pellati et al. 2011). NMR spectroscopy is an important non-separation technique that has been used frequently to characterise propolis extracts. Several flavonoids from various fractions of Chinese propolis have been structurally elucidated using carbon-13 (13C) NMR after purification (Zhou et al. 1999). Proton (1H) NMR has been extensively applied to prepare chemical profiles of various propolis extracts, prepared from the Brazilian, Chinese, Greek and Indian-propolis. In combination with chemometric analysis, these datasets were used to classify propolis samples based on their chemical proximity (Maraschin et al. 2016; Kasote et al. 2017; Wang et al. 2020; Stavropoulou et al. 2021). A particular advantage of NMR in the chemical characterisation of propolis is that it helps to identify isomeric compounds (Pavlovic et al. 2020). Using similar chemometric techniques to that applied to the 1H NMR datasets, NIR spectroscopy data was used to classify Egyptian propolis into three types, namely the (O), (G) and (B) types (Shawky and Ibrahim 2018).

GC–MS is a powerful analytical technique that has been extensively used for the identification of both the volatile and the semi-volatile constituents of propolis for the last few decades (Bankova et al. 1995; Naik et al. 2013; Cruz et al. 2020). The use of GC–MS for the analysis of the volatile components of propolis is more common, and over 100 volatile constituents have been identified from propolis using GC–MS. Both volatile and semi-volatile compounds can be determined in propolis using this technique (Paviani et al. 2010; Nunes and Guerreiro 2012; Bankova et al. 2014; Balogun et al. 2020; Ribeiro et al. 2021). Spectroscopic data obtained from GC–MS analyses were processed with the help of multivariate analysis techniques and used to classify propolis samples according to regions and seasons. In addition, metabolic profiles were related to the biological activities (Nunes and Guerreiro 2012; Pavlovic et al. 2020; Ghallab et al. 2021).

Application of GC–MS to non-volatile propolis constituents is possible after derivatization (silylation). Non-volatile propolis constituents are mostly identified using liquid chromatography–mass spectrometry (LC–MS). This superior separating technique was used to identify 76 polyphenols in the ethanolic extracts of Portuguese samples from different geographical locations (Falcão et al. 2013). Chemical profiling is an important qualitative analysis parameter; LC–MS was used to demonstrate the chemical fingerprinting of propolis from different regions. The ethanolic extracts of propolis samples from Argentina, Italy, and Spain have approximately the same total ion chromatogram (TIC) profile due to the presence of the same molecular species, as determined using the online HPLC–ESI/MS technique (Volpi and Bergonzini 2006). In contrast, some researchers reported characteristic TIC profiles for samples from Azerbaijan, China, Ethiopia and Kenya (Volpi 2011). Chemometric analysis of the LC–MS data, involving the construction of unsupervised principal component analysis (PCA) and supervised orthogonal projection to latent structures-discriminant analysis (OPLS-DA) models, was found to be a valuable tool for the classification of propolis samples and for the identification of marker compounds in various types of propolis. Both the LC–MS chromatographic profiles and the 1H- and 13C NMR spectral data of the secondary metabolites of Cuban samples were used to classify them into different types, namely brown, red, and yellow Cuban propolis (Cuesta-Rubio et al. 2007). Chemometric analysis of ultra-performance liquid chromatography–mass spectrometry (UPLC–MS) data, generated from 39 South African propolis, revealed two distinct groups based on the sample chemistry. Moreover, the majority of the samples were phytochemically congruent with propolis from temperate regions (Kasote et al. 2014). Recently, 67 marker compounds, belonging to chemical classes, namely flavonoids, stilbenes, terpenoids, acid derivatives, steroid derivatives, and some miscellaneous components, were identified in propolis samples from Australia, China and Brazil using UPLC–MS in combination with chemometric analysis (Bhuyan et al. 2021). Capillary electrophoresis coupled to mass spectrometry (CE–MS), an important technique that provides selective information with
regard to analytes, has also been used for the analysis of complex propolis extracts, but this technique is far less common (Gómez-Romero et al. 2007).

Similar to LC–MS, TLC/HPTLC (thin layer chromatography/high-performance thin-layer chromatography) have also been used for fingerprinting, as well as for the qualitative and quantitative determination of the individual components of propolis. The floral and geographic origins of Romanian samples were identified using TLC fingerprinting and imaging (Sârbu and Moț 2011). Similarly, reversed-phase high-performance thin-layer chromatography (RP-HPTLC), reversed-phase HPLC and GC–MS, were collectively used to identify the botanical origin and chemical composition of Brazilian samples (Daugsch et al. 2007). The HPTLC fingerprints of 35 Egyptian samples, obtained after derivatisation and fluorescence detection (FLD) at \( \lambda \) 366 nm, were analysed using multivariate data analysis (Shawky and Ibrahim 2018). The data were used to identify nine marker compounds for the different sample clusters. Using the HPTLC-bioautography-MS technique, pinobanksin, pinocembrin, and caffeic acid were identified in South African propolis, as antibacterial, antifungal and anti-quorum components, respectively (Kasote et al. 2015).

Due to the complex chemical compositions, the quantitative determination of the chemical constituents in propolis samples has not attracted much interest. Hence, spectroscopic and chromatographic analysis methods, in addition to the use of reference standards, are a more routine and valid method for the analysis of propolis samples. A single reference-standard-based chemical standardisation method is not appropriate for propolis; hence, the need to identify multiple standards for various propolis types, according to their corresponding chemical profiles, has been proposed (Popova et al. 2010a). A validated spectrophotometric method was developed to quantify total flavones, flavonols, flavanones, dihydroflavonols and total phenolics, based on aluminum chloride complexation (Popova et al. 2004). Similarly, a DNP (dinitrophenylhydrazine) spectrophotometric method was reported to quantify prenylated flavanones in Pacific-type propolis from Taiwan (Popova et al. 2004). For routine analyses of Macaranga-type propolis, a HPLC-based method for quantifying propolins C, D, F and G was recommended for samples from Taiwan (Popova et al. 2010a).

**Challenges in propolis quality control: biomarker selection**

Propolis has received increasing attention from researchers over the last few decades, due to its broad spectrum of therapeutic activities and potential commercial applications in food, cosmetic, and health care preparations. The therapeutic potential of various types of propolis with different chemical compositions has been assessed worldwide. However, these data have not resulted in the universal acceptance of propolis as an authenticated drug or health-promoting product in international food and healthcare markets. For this, the lack of common uniform quality control parameters for propolis is an important contributing factor. The missing link between the marker compound(s) for propolis and respective therapeutic potential is one of the major hurdles in quality control.

In general, marker compounds for herbal products are selected based on their uniqueness, abundance and/or specific biological activity. However, the complex and variable chemistry of propolis prevents the compilation of uniform propolis quality control parameters, although multiple-marker-compound-targeted approach that enables the characterising of propolis types would be appropriate to ensure quality products. Potential marker compounds related to geographical origin and bioactivity, according to the propolis type, are summarised in Table 1.

The phytochemical uniqueness and variation in propolis samples from different places of world have been reported, and which provide an opportunity to propose geographical markers for their standardisation. Such marker(s) could be a single compound or a group of compounds that are supposedly unique to, and abundant in, certain types of propolis. However, there is a need to consider the physicochemical properties and phytochemical variations between different propolis types during the establishment of geographical markers. For example, Brazilian and Cuban propolis exhibit different physicochemical properties within their sub-types. Similarly, Canadian propolis showed the presence of chalcones, in addition to the typical Poplar-type chemical composition.

A broad range of biological activities, such as antioxidant, antimicrobial, anti-inflammatory, immunomodulatory, and anticancer activities, have been ascribed to propolis and its isolated chemical constituents (Oršolić et al. 2004; Okutan et al. 2005;
| Geographical zone | Major plant source(s) | Country of origin | Key compounds | Markers compounds and bioactivity | References |
|-------------------|------------------------|-------------------|---------------|----------------------------------|------------|
| Temperate         | Birch                  | Russia, Poland    | Flavones and flavonols different from Poplar-type | Bioflavonoids (anti-oxidant activity) | Gromenko et al. (2008) and Sforcin and Bankova (2011) |
|                   | Poplar-\( \text{Populus tremuloides, P. trichocarpa} \) | Canada            | Aliphatic acids, aromatic acids, chalcones, flavonols and flavanones | Benzyl hydroxybenzoate (anti-oxidant); Cinnamic acid (anti-oxidant); Dihydrochalcones (anti-oxidant); Galangin (anti-inflammatory, antifungal); \( p \)-Hydroxyacetophenone (anti-oxidant) | Blonska et al. (2004) and Christov et al. (2006) |
|                   |                        | Britain, China, Germany, France, India, Italy, Netherlands, New Zealand, Portugal, South Africa, Spain, Switzerland, Uruguay, USA | Cinnamic acid, caffeic acid, \( p \)-coumaric acid, flavanones, flavones and flavanols | Benzyl caffeate (antiproliferative); Caffeic acid (immunomodulatory, anti-quorum sensing, anti-oxidant); Caffeic acid phenethyl ester (immunomodulatory antitumor, anti-oxidant, anti-diabetic, anti-inflammatory; neuroprotective); Chrysin (anti-oxidant, anti-inflammatory, anticancer); Cinnamic acid (antifungal); \( p \)-Coumaric acid (antifungal); Cinnamyl caffeate (antiproliferative); 3,4-Dimethoxy cinnamic acid (antifungal); Ferulic acid (antifungal); Galangin (antifungal); Kaempferol (anti-inflammatory, antifungal); Morin (antifungal); Naringenin (antifungal); Pinobanksin (antibacterial); Pinocembrin (antioxidant antifungal); Quercetin (immunomodulatory, antimetastatic, anti-inflammatory); Rhamnetin (cytotoxic) | Banskota et al. (2002), Blonska et al. (2004), Márquez et al. (2004), Oršolić et al. (2004), Park et al. (2004), Okutan et al. (2005), Oršolić et al. (2006), Quiroga et al. (2006), Sha et al. (2009), Güro et al. (2011), Sawicka et al. (2012), Silva et al. (2013), Kasote et al. (2015) and Kasote et al. (2017) |
| Sub-tropical      | Poplar (\( P. nigra, P. x euramericana, P. canadensis \)–China) | Turkey            | Aliphatic and aromatic acids, alcohols, fatty acid esters, hydrocarbons, flavones, flavonols and ketones | Caffeic acid and its esters (antimicrobial); Galangin (anti-inflammatory); Chrysin (anti-oxidant, anticancer, anti-inflammatory); Quercetin (immunomodulatory, antimetastatic) | Kartal et al. (2003), Blonska et al. (2004), Oršolić et al. (2004), Üzel et al. (2005), Duran et al. (2011) and Sawicka et al. (2012) |
| Geographical zone | Major plant source(s) | Country of origin | Key compounds | Markers compounds and bioactivity | References |
|-------------------|-----------------------|-------------------|---------------|----------------------------------|------------|
| Lepidosperma spp., Acacia paradoxa | Australia | Cinnamic acid esters, chalcones, flavonols and stilbenes | Prenylated cinnamate (anti-oxidant); Stilbenes (anti-oxidant) | Abu-Mellal et al. (2012) and Tran et al. (2012) |
| Poplar, unknown source of triterpenes | Egypt | Aliphatic, aromatic acid, chalcones, flavones, flavonols and their esters, and triterpenes | Chrysin (anti-oxidant, anticancer, anti-inflammatory); Aromatic acid esters (anti-oxidant, antimicrobial, antiviral); Triterpenoids (anti-oxidant, antimicrobial, antiviral) | Abd El Hady and Hegazi (2002), Hegazi and Abd El Hady (2002) and Sawicka et al. (2012) |
| Ferula spp., Poplar | Iran | Caffeic acid phenethyl ester, flavonols, mono- and sesquiterpene esters of benzoic acids, prenylated coumarin and suberosin | Kaempferol (anti-inflammatory); Mono- and sesquiterpene esters of benzoic acids (antibacterial) | Blonska et al. (2004) and Trusheva et al. (2010) |
| Poplar, unknown source of triterpenes | Jordan | Aromatic acid, flavones, flavanones and sesquiterpenoids | Chrysin (anti-oxidant, anticancer, anti-inflammatory) | Shaheen et al. (2011) and Sawicka et al. (2012) |
| Cupressus sempervirens, minor source—poplar (Mediterranean) | Greece, Algeria, Croatia, Cyprus, Malta | Diterpenes, aromatic acids and their esters, flavonols and flavanones | Diterpenes (antimicrobial) | Velikova et al. (2000), Sahinler and Kaftanoglu (2005), Popova et al. (2009), Popova et al. (2010b) and Popova et al. (2011) |
| Dalbergia sissoo | Nepal | Flavanones, isoflavones, neo-flavonoids and pterocarpsans | Neo-flavonoids (inhibition of nitric oxide production) | Awale et al. (2005) and Shrestha et al. (2007) |
| Pacific (Macaranga tanarius) | Japan (Okinawa), Taiwan | Prenylflavanones | Propolin A (cytotoxic and anti-oxidant); Propolin B (cytotoxic and anti-oxidant); Propolin D (antimicrobial); Propolin G (antimicrobial, cytotoxic and anti-oxidant); Propolin H (antimicrobial) | Chen et al. (2003), Chen et al. (2004), Kumazawa et al. (2004), Kumazawa et al. (2007) and Raghukumar et al. (2010) |
| Tropical Poplar | Argentina | Aromatic acids and their esters, chalcone, epoxy lignans, flavones and flavonols | Chrysin (anticancer, anti-inflammatory); 2', 4'-Dihydroxychalcone (anti-oxidant and antibacterial); 2',4'-Dihydroxy 3'-methoxychalcone (anti-oxidant and antibacterial); Kaempferol (anti-inflammatory); Pinocembrin (antifungal); Quercetin (immunomodulatory, antimetastastic) | Blonska et al. (2004), Oršolić et al. (2004), Isla et al. (2005), Quiroga et al. (2006) and Agüero et al. (2011) |
| Geographical zone | Major plant source(s) | Country of origin | Key compounds | Markers compounds and bioactivity | References |
|-------------------|-----------------------|-------------------|---------------|----------------------------------|------------|
| Baccharis dracunculifolia | Brazil (Brazilian Green) | Benzoic and chlorogenic acids, prenylated phenylpropanoids (e.g. artepillin C) | Artepillin C (anti-tumor and anticancer, vaccine adjuvants); Baccharin (antitumor); Caffeic acid (anti-ulcer); Chrysin (anticancer, anti-inflammatory); Cinnamic acids (anti-ulcer); p-Coumaric acid (anti-ulcer); Coniferyl aldehyde (cytotoxic); Drupanin (antitumor); Ferulic acid (anti-ulcer); Kaempferide (cytotoxic); Quercetin (immunomodulatory, antimetastatic); 3,5,7-Trihydroxy-4'-methoxyflavanol (cytotoxic); | Bankova et al. (1996), Banskota et al. (1998), Blonska et al. (2004), Orsioli et al. (2004), Bankova (2005a), Mishima et al. (2005), Piccinelli et al. (2005), Trusheva et al. (2006), Awale et al. (2008), Li et al. (2008), Castro et al. (2009), Messerli et al. (2009), Fischer et al. (2010), Teixeira et al. (2010), Righi et al. (2011), Endo et al. (2012), Sawicka et al. (2012), Silva et al. (2013), Bueno-Silva et al. (2013) and Olegário et al. (2019) |
| Dalbergia ecastaphyllum, Clusia spp. | Brazil (Brazilian red) | Isoflavonoids, phenolics, prenylated benzophenones and triterpenoids | Hyperibone A (cytotoxic and antimicrobial); (6αR,11aR)-3,8-Dihydroxy-9-methoxypterocarpan (cytotoxic); Moronic acid (anti-HIV); Muconrolatol (cytotoxic); Neoestivitol (anti-inflammatory and antimicrobial); Vestitol (anti-inflammatory and antimicrobial) | |
| Araucaria angistifolia, Eucalyptus spp. | Brazil (Brazilian brown) | Ferulic acid, caffeic acid, 4-methoxycinnamic acid, 3,4-dimethoxycinnamic acid, 3-hydroxy-4-methoxybenzaldehyde, 3-methoxy-4-hydroxypropiofenone, 19-acetoxy-13-hydroxyyabda-8(17),14-diene, torotol, 7-oxodehydroabietaic acid, dehydroabietaic acid, communic acid, isopimaric acid, imbricataloic acid (antimicrobial) | Communicic acid (antimicrobial, antiplasmodial), isoimmaric acid (cytotoxic, antimicrobial), imbricalsoapic acid (antimicrobial) | |
| Mangifera indica, Macaranga tanarius | Indonesia | Alk(en)ylresorcinols, cycloartane-type triterpenes and prenyllflavanones | Prenyllflavanones (anti-oxidant, antimicrobial) | Trusheva et al. (2010) |
| Mangifera indica | Thailand | alk(en)ylresorcinols, anacardic acids, cycloartane-type triterpenes | Alk(en)ylresorcinols, anacardic acids (antibacterial) | Sanpa et al. (2017) |
| Mangifera indica | Myanmar | Cycloartane-type triterpenes | (2Z,3E)-3-Oxocycloart-22,24-dien-26-oic acid (cytotoxic); (2S)-5,7-dihydroxy-4'-methoxy-8,3'-diprenyllflavanone (cytotoxic) | Li et al. (2009) |
| Unknown | Chile | Benzaldehyde, benzopyran or dihydrobenzofuran and phenylpropane | Benzaldehyde, benzopyran or dihydrobenzofuran and phenylpropane (antimicrobial) | Valcic et al. (1999) |
| Geographical zone | Major plant source(s) | Country of origin | Key compounds | Markers compounds and bioactivity | References |
|-------------------|------------------------|-------------------|---------------|----------------------------------|------------|
| Dalbergia ecastaphyllum | Cuba (Cuban red) | | Isoflavones, isoflavanes, pterocarpans | **Isoflavonoids** (antibacterial and antifungal, anticancer) | Rubio et al. (1999), Hernández et al. (2005), Piccinelli et al. (2005), Monzote et al. (2012) and Díaz-Carballo et al. (2013) |
| Clusia rosea, Clusia nemorosa | Cuba (Cuban brown) | | Polyrenylated benzophenones | **Polyrenylated benzophenones** (antimicrobial, anticancer) | Popova et al. (2001b) |
| Unknown | El Salvador | | Chalcones and diterpene glycosides | | |
| Macaranga schweinfurthii | Kenya | | Arylnaphthalene, geranylstilbenes, geranyllavone and lignans | **Geranylstilbenes** (antibacterial); **Geranyllavon** (anti-oxidant) | Petrova et al. (2010) |
| Dalbergia unknown source | Mexico | | Diphenyl propanes, flavanones, isoflavans and pterocarpans | (2R,3R)-3,5-Dihydroxy-7-methoxyflavanone 3-(2-methyl)butyrate (cytotoxic); (2R,3R)-6-[1-(4'-Hydroxy-3'-methoxyphenyl)prop-2-en-1-yl]pinobanksin (cytotoxic); (2R,3R)-6-[1-(4'-Hydroxy-3'-methoxyphenyl)prop-2-en-1-yl]pinobanksin 3-acetate (cytotoxic); (7'R)-8-[1-(4'-Hydroxy-3'-methoxyphenyl)prop-2-en-1-yl]pinobanksin (cytotoxic); (7'R)-8-[1-(4'-Hydroxy-3'-methoxyphenyl)prop-2-en-1-yl]galangin (cytotoxic); Chrysin (cytotoxic); (2R,3S)-8-[4-Phenyprop-2-en-1-one]-4',7-dihydroxy-3',5-dimethoxyflavan-3-ol (cytotoxic) | Lotti et al. (2010) and Li et al. (2011) |
Monzote et al. 2012; Bueno-Silva et al. 2013). Both propolis solvent extracts and their isolated components have been found to exert promising bioactivities; however, the correlation between propolis quality and biological activity has not been investigated in enough depth.

In general, it is expected that propolis with different chemical compositions would have different bioactivities. However, existing reports on the chemistry-dependent biological activity of propolis are controversial. Propolis samples from temperate and tropical zones showed similar antibacterial, antifungal, and antiviral activities, despite their diverse chemical compositions (Kujumgiev et al. 1999). Conversely, Brazilian propolis observed stronger bactericidal activity than that from Bulgaria, and these authors attributed this region-wise dissimilar bactericidal potential to their different chemical compositions (Orsi et al. 2005). The probable reason for these conflicting results could be differences in propolis quality-defining parameters, such as the available plant source, climatic conditions and extraction conditions. The antibacterial activities of propolis samples from different geographical climatic zones, such as tropical, subtropical and temperate, against a range of Gram-positive and Gram-negative bacteria were comparatively investigated and found that propolis samples from tropical regions had varying activity profiles, which may be due to the climatic characteristics and the available resin plant sources of the collection sites (Seidel et al. 2008). In addition, variations in bioactivity have also been observed within similar geographical climatic zone countries (Seidel et al. 2008). Samples from Austria, Germany, and France display diverse antimicrobial activities, despite some similarities in their qualitative composition. These researchers attributed this variation in antimicrobial activity to the predominant chemical compounds (Hegazi et al. 2000). The findings of this study further showed that phenylethyl-trans-caffeate, benzyl ferulate, and galangin are predominant in German propolis, whereas benzyl caffeate and pinocembrin are predominant in French and Austrian samples.

It is important to note that these differences could be due to a large extent to the difference in extraction procedures and protocols for performing biological tests.
In addition to crude propolis extracts, the chemical compounds isolated from propolis samples have been found to be encouraging with respect to their biological potential. In fact, most of the chemical compounds isolated were reported to have specific biological activity (Table 1). Caffeic acid phenethyl ester (CAPE) and chrysin from temperate propolis, and artemillin C from Brazilian propolis, have been extensively studied and show promising therapeutic potential in the treatment of cancer, degenerative diseases, and other pathologies (Okutan et al. 2005; Messerli et al. 2009; Li et al. 2011). These compounds could have significance in the biological-activity-marker-based standardisation of temperate and Brazilian propolis, respectively. Moreover, other types of propolis also exhibit the presence of specific bioactive compounds that could be used as biological marker compounds for the standardisation of the respective propolis types (Table 1).

**Conclusions and future perspectives**

In most cases, one or more analytical markers based on its uniqueness, abundance and specific bioactivity, are assigned for the quality assessment of a herbal product. However, in the case of propolis, more than 800 different phytoconstituents have been reported in samples from around the world, and these are found to vary with geography and season. Furthermore, available literature reports have not demonstrated whether the specific therapeutic potential of propolis is associated with a certain chemical entity. Therefore, there is a need to adapt a quality control strategy for propolis standardisation which will include quantitative botanical, geographical, and biological activity marker(s). Chromatographic fingerprinting methods, such as LC and HPTLC, are other tools that can provide valuable information regarding the origin of samples. Considering this, we propose that these techniques be emphasised as primary quality control parameters for propolis standardisation.

To date, researchers have only considered two major geographical zones, temperate and tropical, for the classification of propolis. We propose that propolis obtained from subtropical zones, including the Mediterranean and Pacific regions, exhibit a somewhat mixed chemical composition, and should be studied in greater detail.

Various techniques, such as HPTLC, GC–MS, LC–MS, CE–MS, and NMR, have been found to be useful for establishing the chemical profiles of propolis samples. However, due to the complex and variable chemical composition of propolis, there is a need to strengthen the propolis quality assessment techniques and use defined solvent extraction methods to improve overall efficacy of methods. Chemometric techniques have been successfully used in herbal drug quality control; and have been found to be promising for the quality assessment of propolis. These techniques can also be valuable for unravelling the link between the composition and the bioactivity, including to understand synergetic interactions. Multivariate statistical tools, such as cluster heat maps, PCA, and linear discriminant analysis, were used to classify different Portuguese samples according to their botanical/geographical origin (Dias et al. 2012). According to their geographical origin and the local flora, the fuzzy divisive hierarchical clustering approach was employed for the discrimination and fingerprinting of Romanian samples (Sârbu and Moț 2011). Vibrational spectroscopic techniques (infrared, NIR Raman spectroscopy and hyperspectral imaging), combined with chemometric techniques, may also be powerful techniques for the quality assessment of large numbers of samples in a short time (Sandasi et al. 2011; Shikanga et al. 2013).

However, these studies were performed on propolis samples from a relatively small territory and remain of limited regional importance. Their results can hardly be used with respect to propolis from other geographic regions without analysis of a new sample set. Chemometric approaches have a promising potential but the results should be discussed and used with caution.

In conclusion, propolis contains more than 800 different chemical components with complex and varying chemistry, and hence, the maintenance of its quality at one global or regional platform remains challenging. A multiple-marker assessment strategy with chemometric analysis may be a promising approach for propolis quality assessment.

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Declarations

Conflict of interest  The authors declare no competing interests.

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