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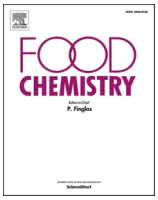

Food-grade delivery systems of Brazilian propolis from *Apis mellifera*: From chemical composition to bioactivities *in vivo*

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ABSTRACT

Brazilian propolis from *Apis mellifera* is widely studied worldwide due to its unique chemical composition and biological properties, such as antioxidant, antimicrobial, and anti-inflammatory. However, although many countries produce honey, another bee product, the consumption of propolis as a functional ingredient is linked to hydroethanolic extract. Hence, other food uses of propolis still have to be incorporated into food systems. Assuming that propolis is a rich source of flavonoids and is regarded as a food-grade ingredient for food and pharmaceutical applications, this review provides a theoretical and practical basis for optimising the bioactive properties of Brazilian propolis, encompassing the extraction processes and incorporating its bioactive compounds in the delivery systems for food applications. Overall, pharmacotechnical resources can optimise the extraction and enhance the chemical stability of phenolic compounds to ensure the bioactivity of food formulations.

1. Introduction

In recent decades, the population's dietary pattern has shown increased consumption of highly processed fast foods, which has generated concern about the population's future health and quality of life (Elizabeth et al., 2020). On the other hand, consumers are increasingly looking for foods known as functional that benefit one or more physiological functions and provide health to individuals (Galanakis, 2021; Baker et al., 2022). Among the foods with this characteristic of functionality are medicinal foods and those from bees: honey, propolis, and royal jelly (Giampieri et al., 2022).

Bees (*Apis mellifera* L.) can produce other high-value-added products besides honey (Viteri et al., 2021), such as royal jelly and propolis. Bee products have been known for centuries for their nutritional capacity and as additives in health promotion (Martinello and Mutinelli, 2021). In addition, numerous activities have already been reported as anti-inflammatory, antioxidant, and antimicrobial (Valverde et al., 2023). Among bee products, propolis is one of the most popular and used as a remedy in traditional medicine (Pasupuleti et al., 2017). Propolis is composed mainly of plant parts, including exudates, unexpanded buds, and beeswax (Salatino et al., 2021). At least 500 chemical compounds have already been identified in propolis, including polyphenols, terpenes, aldehydes, aromatic alcohols, fatty acids, and steroids, which are essential organic compounds commonly found as secondary plant metabolites (Šuran et al., 2021). These properties make propolis an ideal candidate for use as a functional ingredient in foods, in addition to its well-known use as a nutraceutical (Viteri et al., 2021).

Foods' functional and physical properties are related to their constituents and processing methods (Galanakis, 2021). Since propolis is resinous and needs to be transformed into an extract before

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consumption, the extraction step must include methods with a high yield and able to recover the bioactive compounds (Patra et al., 2022). Indeed, it is known that variations in extraction, including the type of solvent, temperature conditions, maceration and extraction technique, and time can be decisive for the functionality of a food (Putnik et al., 2018) and may be customised based on each food's chemical composition.

Propolis' quality traits depend highly on the botanical source and the extraction methods used in processing (Pu et al., 2023a; Pu et al., 2023b). In this context, Brazilian propolis types have been arousing attention worldwide due to their phytochemical profiles, which differ from the European and Chinese propolis that generally contain mainly flavones, flavonols, flavanones, and dihydro flavonols (Popova et al., 2004). Green propolis from southern Brazilian, e.g., contains high contents of prenylated hydrocinnamic acids, while red propolis from mangroves outstands by its high levels of isoflavonoids and chalcones (Silva et al., 2008; Teixeira et al., 2005).

Following the growing demand for nutraceuticals and functional foods, researchers and food industries have accelerated their efforts in developing processing technologies to preserve products' qualitative, active, and nutritional characteristics (Galanakis, 2021). However, some of these biologically active compounds in the extracts require optimisation, proper absorption, and tissue distribution (Altemimi et al., 2017). In this way, it becomes essential to make a good choice in the delivery system (Tai et al., 2020; Gareev et al., 2022). Pharmacotechnical resources can have different approaches, such as liposomes, microemulsions, nanoparticles, and even precursors for liquid crystal systems (Tai et al., 2020; Gareev et al., 2022). The encapsulation systems of natural products in different drug delivery systems can favour biological activity, stability, and bioavailability, hence the need to review and properly evaluate (Tavares et al., 2022). Trying to incentivise a more widespread of propolis in food applications, in this review (Fig. 1), we discuss the botanical origin and functional properties of Brazilian propolis, compare different extraction procedures for bioactive compounds, and present different delivery systems to make the inclusion of Brazilian propolis as a functional ingredient in foods.

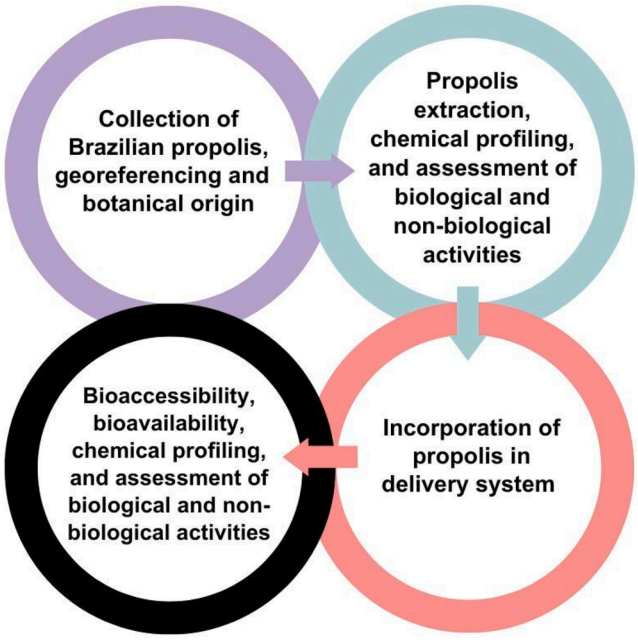

Fig. 1. Flowchart of this review: collection processes, botanical identification, and georeferencing of Brazilian propolis followed by the application of techniques to obtain the extract, chemical profiling analysis, incorporation of extracts delivery systems for food use, and finally, studies of bioaccessibility, epithelial transport (bioavailability) and assessment of biological and non-biological activities.

2. Phytochemical composition and botanical origin of Brazilian propolis

The ecosystem where propolis is collected directly affects its phytochemical composition since the main components of propolis are materials collected by the bees (e.g., exudates, apical buds, and young leaves) from plant genera typical of each biome. The botanical origins of propolis produced in Brazil vary greatly. Brazil has continental dimensions with 8,511,965 km^2 comprising diverse ecosystems such as mangroves, savannas (*Cerrado*), rain forests (Atlantic Forest and Amazon), natural grasslands (Pampa), and the Caatinga, with distinct hot-and-dry-adapted species, (Salatino et al., 2021). Fig. 2 and Table 1 show the locations where some Brazilian propolis samples are produced and their main bioactive compounds and botanical origins.

Commercially, the green propolis from the southeast, mainly produced in the states of Minas Gerais and São Paulo, is the most important one. The primary botanical origin of this propolis is apical buds and young leaves of *Baccharis dracunculifolia* BC. (Asteraceae), a native species widely spread in Cerrado areas of southeast Brazil (Teixeira et al., 2005). The main constituents of this type of propolis are prenylated derivatives of cinnamic acid – 3,5-diprenyl-4- hydroxycinnamic acid (artepillin C), 3-prenyl-4-dihydroxycinnamoloxycinnamic acid (baccharin), and 3-prenyl-4-hydroxycinnamic acid (drupanin) – and flavonoids – aromadendrin-4′-O-methyl-ether and kaempferide (Costa et al., 2018). The green propolis collected in southeast Brazil and its primary botanical origin (*B. dracunculifolia*) also contains terpenes, including volatile sesquiterpenes (e.g., spathulenol and nerolidol), which are helpful to attract the bees (Rodrigues et al., 2020). Other volatiles were identified in the green propolis from the Minas Gerais region, including 2,3-dihydrobenzofuran, and 2,5-dimethyl-γ-oxo-benzenebutanoic acid (Ribeiro et al., 2022).

Another Brazilian green propolis from the Caatinga (northeast region) was recently investigated (Ferreira et al., 2017; Son et al., 2022). This green propolis derives from *Mimosa tenuiflora* (Willd.) Poir. (Fabaceae) parts, and is mainly constituted of flavonols, and flavanones, including santin, viscosine, axillarin, kaempferide, and tamarixetin (Son et al., 2022), as well as chalcones, e.g., dihydroxydimethoxychalcone (Ferreira et al., 2017).

The red propolis from mangroves (northeast region) has been arousing the attention of the international market and is produced with exudates of *Dalbergia ecastaphyllum* (L.) Taub. (Fabaceae). This plant species is source of the main constituents of Brazilian red propolis, which are isoflavonoids, including formononetin, liquiritigenin, vestitol, neovestitol, biochanin A, and medicarpin, as well as isoliquiritigenin, which is a chalcone (Aldana-Mejía et al., 2021; Morais et al., 2021; Silva et al., 2008). The Brazilian red propolis also contains unique flavonoid dimers, including propolols, propolonones, and propolones, with cytotoxic activity against cancer cells (Banzato et al., 2020). Other constituents are polyprenylated benzophenones, mainly guttiferone E and oblongifolin B, and triterpenoids from *Symphonia globulifera* L.f. (Clusiaceae), which is a native species from the Atlantic Forest of seaside areas surrounding the mangroves (Ccana-Ccapatinta et al., 2020). Among the volatile compounds found in a sample of red propolis from the Bahia state, there were α-copaene, anethole, α-cubebene, methyl eugenol, α-bergamotene, β-caryophyllene, and elemicin (Ribeiro et al., 2022).

Another commercially Brazilian propolis is collected in rainforests (southern region) with the native *Araucaria angustifolia* (Bertol.) Kuntze (Araucariaceae). When produced under the roles of organic certification, this propolis has a milder taste and flavour when compared with other types of propolis (Tiveron et al., 2016). The main constituents of *Araucaria* sp. propolis, comprising 78 % of the total dried extract mass, are diterpenes such as isocupressic acid, 13-*epi*-cupressic acid, *epi*-13-torulosol, communic acid, and abietic acid from *A. angustifolia*, as shown in Table 1 (Santos et al., 2021a; Tazawa et al., 2016). The volatile compounds present in this propolis are mainly monoterpenes, especially

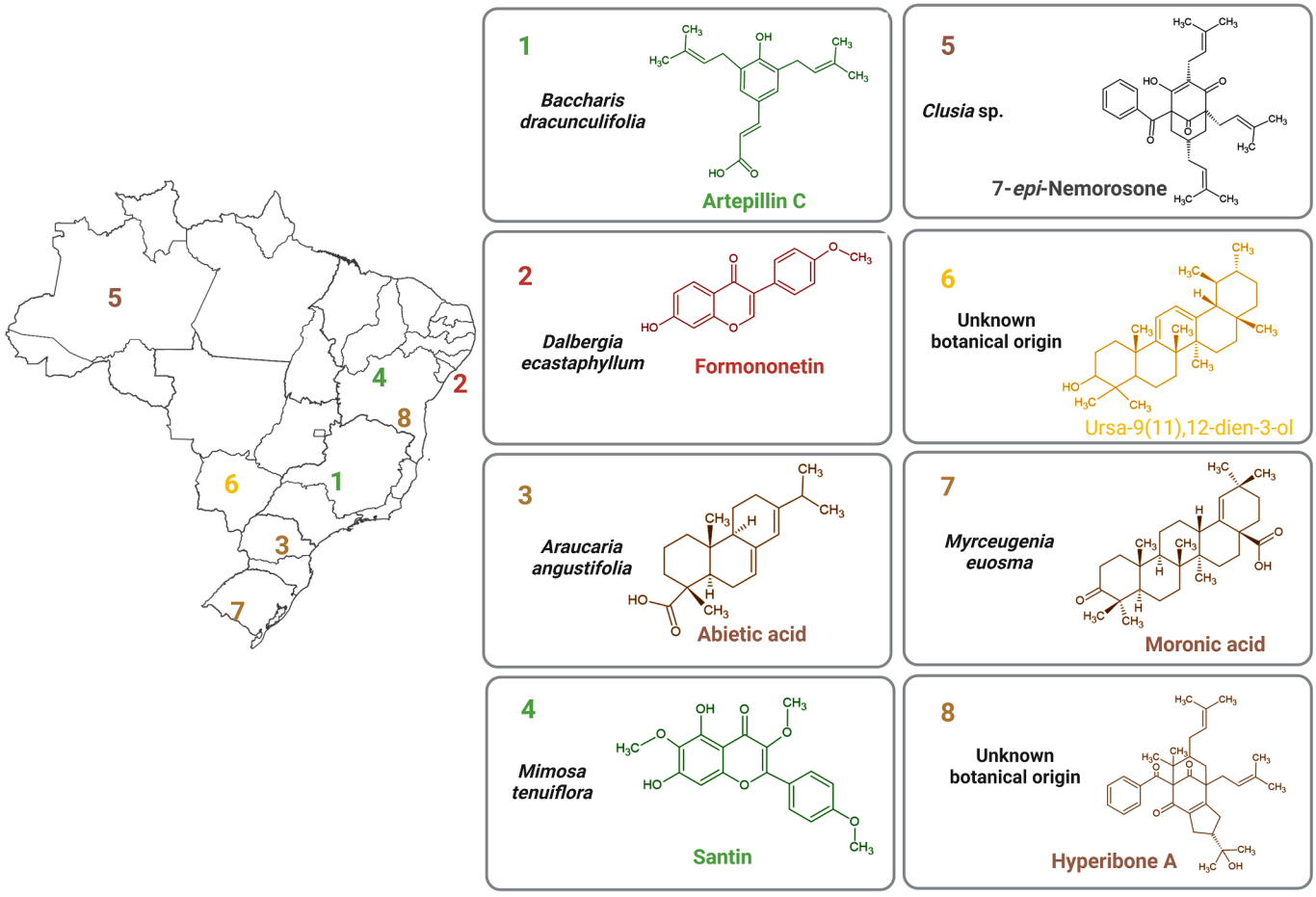

Fig. 2. Illustrative representation of the locations where some Brazilian propolis are produced, with the respective structural formula of major phytochemicals and botanical origins, when known. https://www.pucrs.br/mct/plantas-extintas-e-o-herbario-do-mct-pucrs/

α-pinene, and β-pinene, which are also present in Uruguayan and South African propolis and may come from *Araucaria* sp. and *Pinus* sp. as well (Ribeiro et al., 2022; Sartori et al., 2021).

Other propolis produced in Brazilian biomes from native plants are not yet commercially relevant, and there are few studies on their singular phytochemical compositions. Moreover, the studies generally focused on identifying bioactive compounds, by liquid chromatography coupled with mass spectrometry or nuclear magnetic resonance, with fewer quantitative studies to assess the levels of these compounds for under-explored Brazilian propolis types. The yellow propolis from the Pantanal biome of the state of Mato Grosso do Sul had fifteen triterpenoids identified in it, including α- and β-amyrin, ursadienol, lupenone, oleanone, and botulin, as well as steroids (e.g., lanosterol) of unknown botanical origin (Machado et al., 2016a). A propolis produced in Teresina city, state of Piauí (northeast region) was found to be constituted by cycloartane triterpenoids, such as isomangiferolic, mangiferolic, mangiferonic, ambonic and ambolic acids (Silva et al., 2005). Based on bees' observation and similar reported phytochemical profiles, the authors suggested the *Mangifera indica* as a possible botanical origin of this propolis.

Another Brazilian propolis with a peculiar phytochemical profile was collected in the south, close to the border with Uruguay, and its central botanical origin is likely to be *Myrceugenia euosma* (O. Berg) Legrand (Myrtaceae) (Ito et al., 2001). Among the compounds isolated from this propolis, moronic acid was the primary chemical compound, followed by melliferone, an uncommon triterpenoid, anwuweizonic and betulonic acids, and aromatic compounds.

The *Clusia* sp. black propolis from the Amazon Forest (collected in Manaus city in northwest Brazil) contains prenylated benzophenones identified as main constituents, especially 7-*epi*-nemorosone, 7-*epi*-clusianone, xanthochymol, and gambogenone (Ishida et al., 2011). Prenylated benzophenones, including hyperibone A, were isolated from propolis collected in the Atlantic Forest (northeast region), which are also linked to coming from *Clusia* sp. (Castro et al., 2009).

The notable variation in the phytochemical composition of Brazilian propolis has made it necessary to put efforts into the indication of geographical origin. In this context, it is essential to mention the importance of referring to the geographical origin of a studied propolis sample, especially from complex biomes, such as those found in Brazil. Referencing the collection location makes possible the investigation of botanical sources of propolis. It is helpful to decipher the relations between bees and the environment surrounding the beehives, which allow the pollination of flowering plant species that affect biodiversity and food security, as well as the biological properties of propolis. The variations in the phytochemical profile of each type of Brazilian propolis from each location have also been studied. Differences in the phytochemical profile were found according to the geographical region.

For the red propolis collected in the Brazilian northeast, studies have shown that seasonality has an impact on concentrations of major phenolic compounds, with accumulation of some compounds during the rainy season, between March and May, and lower concentrations during the drought season, in September (Aldana-Mejía et al., 2021; Nascimento et al., 2019; Bueno-Silva et al., 2017). For samples from Canavieiras city, Bahia state, the concentrations varied greatly throughout a year: e.g., formononetin (0.2–2.6 g/100 g), liquiritigenin (0.2–2.1 g/100 g), vestitol (2.1–19.5 g/100 g), neovestitol (1.0–6.9 g/100 g), medicarpin (1.5–14.6 g/100 g), and isoliquiritigenin (0.2–2.4 g/100 g), as shown in Table 1 (Aldana-Mejía et al., 2021). Conversely, although

Table 1
Summary of the main chemical compounds found in Brazilian propolis.

Brazilian propolis type	Main compounds	Analytical method	Reference
Propolis from *Myrceugenia eousma* – Rio Grande do Sul, Brazil	Moronic acid, melliferone, anwuweizonic acid and betulonic acid	NMR ^{1}H and ^{13}C	Ito et al. (2001)
Propolis from *Mangifera indica* – Piauí, Brazil	Isomangiferolic acid, mangiferolic acid, mangiferonic acid, ambonic acid, ambolic acid	NMR ^{1}H and ^{13}C	Silva et al. (2005)
Propolis *from Clusia* sp. – Amazonas, Brazil	7-*epi*-Nemorosone, 7-*epi*-clusianone, xanthochymol and gambogenone	NMR ^{1}H and ^{13}C, HPLC/ESI/MS	Ishida et al. (2011)
Propolis (unknown botanical origin) – Mato Grosso do Sul, Brazil	α-Amyrin, β-amyrin, ursadienol, lupenone, oleanone and botulin	NMR ^{1}H and UPLC-ESI (−)-MS/MS	Machado et al. (2016a)
Green propolis from *Mimosa tenuiflora* – Rio Grande do Norte, Brazil	Quercetin-methyl ether, kaempferol-methyl ether, quercetin-dimethyl ether, dimethoxy-dihydroxychalcone, dihydroxy-trimethoxyflavone	RP-HPLC/DAD and HPLC-DAD-ESI-MS/MS	Ferreira et al. (2017)
Green propolis from *Baccharis dracunculifolia* – São Paulo, Minas Gerais and Paraná, Brazil	Artepillin C (4.6–5.0 %*), baccharin (2.0–2.3 %*), *p*-coumaric acid (1.0–1.4 %*), drupanin (0.06 %**), aromadendrin-4′-*O*-methyl-ether (0.05 %**) and kaempferide (0.06 %**)	NMR ^{1}H and ^{13}C, RP-HPLC-DAD	Rodrigues et al. (2020); Costa et al. (2018)
Brown propolis from *Araucaria angustifolia* – Paraná and Santa Catarina, Brazil	Coniferyl alcohol (0.04 %**), coniferyl aldehyde (0.02 %**), lariciresinol (0.02 %**), secoisolariciresinol (0.01 %**), balajaponin D (0.01 %**), pinoresinol (0.02 %**) and matairesinol (0.01 %**)	NMR ^{1}H and ^{13}C, RP-HPLC-DAD	Tiveron et al. (2020)
Red propolis from *Dalbergia ecastaphyllum* – Alagoas, Sergipe and Bahia, Brazil	Formononetin (0.2–2.6 g/100 g**), liquiritigenin (0.2–2.1 g/100 g**), calycosin (0.1–0.6 g/100 g**), vestitol (2.1–19.5 g/100 g**), neovestitol (1.0–6.9 g/100 g**), biochanin A (0.1–0.4 g/100 g**), medicarpin (1.5–14.6 g/100 g**), isoliquiritigenin (0.2–2.4 g/100 g**) and 7-*O*-methylvestitol (0.5–3.8 g/100 g**)	RP-HPLC-UV	Aldana-Mejía et al. (2021)
Brown propolis from *Araucaria angustifolia* – Paraná and Santa Catarina, Brazil	Isocupressic acid (10.78 %**), 13-*epi*-cupressic acid (14.50 %**), *epi*-13-torulosol (17.42 %**), *trans*-communic acid (6.58 %**), *cis*-communic acid (11.75 %**) and abietic acid (16.99 %**)	NMR ^{1}H and ^{13}C, RP-HPLC-DAD	Santos et al. (2021a)
Green propolis from *Mimosa tenuiflora* – Bahia, Brazil	Santin, ermanin, quercetin 3-methyl ether, viscosine, axillarin, isokaempferide, kaempferide and tamarixetin	NMR ^{1}H and ^{13}C, RP-HPLC-DAD	Son et al. (2022)

*% of hydroalcoholic extract made with ethanol:water (9:1; v/v). ** g/100 g of dried raw material.

the presence of guttiferones, which are minor constituents of red propolis, remained throughout the year, higher concentrations were found in samples collected during the drought season: e.g., from around 500 to 8.000 μg/100 mg extract for guttiferone E, and from about 20 to 3.000 μg/100 mg extract for guttiferone B (Nascimento et al., 2019).

The seasonal variation of southeastern Brazilian green propolis and its botanical origin was assessed in a Cerrado bee pasture, shedding light on how to increase the production of green propolis with standardised phytochemical composition (Rodrigues et al., 2020). Despite the insignificant variations in artepillin C (0.08–0.36 % w/w) and baccharin (0.04–0.17 % w/w) concentrations in hydroalcoholic extract of *Baccharis dracunculifolia* leaves, it was observed that female plants had higher terpene concentrations (as visually demonstrated in chromatograms), were visited by bees more often, and were less infested by galling insects when compared with male plants. Therefore, agricultural practices such as handling the seedlings of *Baccharis dracunculifolia* may increase the productivity of green propolis. Moreover, other studies on the effect of farming practices on the botanical origins of Brazilian propolis types should be encouraged.

Introducing non-native plants may affect the preference of *Apis mellifera* for resins sources and consequently change Brazilian propolis' phytochemical profile and biological activities. The introduction of *Populus* sp. in southern Brazil, e.g., led to the production of poplar propolis in that region (Park et al., 2002b). The Brazilian poplar propolis has a phytochemical profile similar to European and Chinese poplar propolis and contains the same chemical markers, including caffeic acid phenethyl ester and pinobanksin esters (Sartori et al., 2022). This fact highlights that other economic activities, e.g. the timber industry, may impact propolis types diversity, which may not be adequately measured.

3. Biological and non-biological activities of types of Brazilian propolis

In the following subsections, we describe the biological and non-biological activities of types of Brazilian propolis (Table 2).

3.1. Red propolis from Dalbergia ecastaphyllum

Brazilian propolis is widely known for its benefits to human health, and the classes of its bioactive compounds that stand out are flavonoids, lignans, benzophenones, and phenolic acids. Among the most studied propolis, red propolis (*Dalbergia ecastaphyllum)* from northeastern Brazil has significant antioxidant and antimicrobial activities (Freires et al., 2016). Alencar et al. (2007) studied the antimicrobial activity of red propolis. They found that the ethanol extract showed activity against *Staphylococcus mutans* (minimum inhibitory concentration, MIC 50–100 μg/mL and minimum bactericidal concentration, MBC 200–400 μg/mL) and *Staphylococcus aureus* (MIC 50–100 μg/mL and MBC 200–400 μg/mL). In that same study, the cytotoxic activity of red propolis was also demonstrated against HeLa cells and presented a half-maximal inhibitory concentration (IC_{50}) value of 7.45 μg/mL. In another study, Oldoni et al. (2011) isolated two isoflavones from red propolis, called namely vestitol and neovestitol, and a chalcone, isoliquiritigenin, and demonstrated that vestitol (39.5 %) had better antioxidant potential in a inhibit β-carotene consumption *in vitro* than neovestitol (21.4 %). Furthermore, the authors found that isoliquiritigenin was the most active for antimicrobial activity against *Staphylococcus aureus*, *Streptococcus mutans* and *Actinomyces naeslundii*, with lower MIC ranging from 15.6 to 62.5 μg/mL. The chemical sub-fraction containing vestitol and neovestitol was tested and showed a significant anti-biofilm effect. Its topical application by five weeks (800 μg/mL, twice daily) reduced the development of carious lesions in the rat model of dental caries (Bueno-Silva et al., 2013a).

The anti-inflammatory activity of red propolis has also been studied. A study by Bueno-Silva et al. (2016) demonstrated that the administration of subcutaneous red propolis mice with hydroethanolic extract (10 mg/kg) inhibited the influx of neutrophils in the peritoneum of mice challenged with carrageenan (inflammatory stimulus). Regarding the isolated compounds, Franchin et al. (2016a) tested the *in vitro* anti-inflammatory activity of the vestitol (3 or 10 μM) and found that this compound inhibits neutrophil chemotaxis induced by CXCL2/MIP-2 or leukotriene B4. In the culture of macrophages obtained from the peritoneum of mice and activated with LPS, vestitol (0.37 to 0.59 μM) also demonstrated its anti-inflammatory potential by suppressing the release

Table 2
Summary of biological and non-biological activities of types of Brazilian propolis.

Brazilian propolis type	Activities	Sample, bioactive compound, and major results	References
Red propolis from *Dalbergia ecastaphyllum*	Anti-inflammatory	Hydroethanolic extract (10 mg/kg) prevented neutrophil migration into the peritoneal cavity of mice; vestitol (3 or 10 μM) reduced neutrophil chemotaxis *in vitro*; vestitol (0.37 to 0.59 μM) suppressed cytokines in the culture of macrophages; neovestitol (10 mg/kg) inhibited chronic inflammation induced in mice; formononetin (10 mg/kg) inhibited oedema and leukocyte migration in rodents; daidzein (2, 4 and 8 mg/kg) reduced the migration of neutrophils and inflammatory cytokines in rats; isoliquiritigenin reduced the adhesion of neutrophils *in vitro*	Bueno-Silva et al. (2016); Franchin et al. (2016a); Bueno-Silva et al. (2022); Franchin et al. (2016b); Cavendish et al. (2015); Feng et al. (2015); Kumar et al. (2007)
	Antimicrobial	Ethanolic extract showed antimicrobial activity against *Staphylococcus mutans* (MIC 50–100 μg/mL and MBC 200–400 μg/mL) and *Staphylococcus aureus* (MIC 50–100 μg/mL and MBC 200–400 μg/mL) *in vitro*; isoliquiritigenin showed antimicrobial activity against *Staphylococcus aureus*, *Streptococcus mutans* and *Actinomyces naeslundii*, with lower MIC ranging from 15.6 to 62.5 μg/mL *in vitro*	Alencar et al. (2007); Oldoni et al. (2011)
	Antibiofilm	Chemical sub-fraction containing vestitol and neovestitol showed an anti-biofilm effect against *Staphylococcus mutans*, and its topical application (800 μg/mL, twice daily) reduced the development of carious lesions in rats	Bueno-Silva et al. (2013a)
	Antioxidant	Ethanolic extract (26 %), vestitol (39.5 %), neovestitol (21.4 %), and isoliquiritigenin (8.7 %) showed antioxidant potential in an inhibited β-carotene consumption *in vitro*	Oldoni et al. (2011)
	Cytotoxic	Ethanolic extract showed cytotoxic activity (IC_{50} 7.45 μg/mL) for the HeLa cells	Alencar et al. (2007)
Green propolis from *Baccharis dracunculifolia*	Anti-inflammatory	Ethanolic extract controlled oedema and cell influx *in vivo*; artepillin C (1–10 mg/kg) decreased paw oedema, neutrophil migration, and prostaglandin E2 levels in mice; *in vitro* artepillin C (10–30 μM) reduced NF-κB activity in the culture of HEK 293 cells; baccharin (500 or 1000 μg/kg) and *p*-coumaric (500 or 1000 μg/kg) reduced neutrophil infiltration, nitric oxide production, and protein extravasation after LPS stimulation in air pockets in mice	Paulino et al. (2006); Paulino et al. (2008); Ferreira et al. (2021)
	Neuroprotective	Ethanolic extract showed a neuroprotective effect in the HT22 cell culture	Takashima et al. (2019)
	Antimicrobial	Ethanolic extract showed antimicrobial activity (MIC90 246.3 μg/mL) against *Staphylococcus aureus in vitro*; aqueous extract of green propolis showed antimicrobial activity against the anaerobic bacteria *Fusobacterium nucleatum*, *Parvimonas micra*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Porphyromonas endodontalis* (MIC 55 mg/mL for all bacteria), an MMC 27.5 mg/mL for *Fusobacterium nucleatum* and *Parvimonas micra* and 55 mg/mL for *Prevotella intermedia in vitro*	Veiga et al. (2017); Assis et al. (2022)
	Antioxidant	Ethanolic extract (IC_{50} 13.09 μg/mL) showed antioxidant potential assessed by DPPH	Veiga et al. (2017)
	Gastroprotective	Administration (0.3, 3 or 10 mg/kg), the compounds artepillin C, drupanin, aromadendrin-4′-*O*-methyl-ether, and kaempferide showed gastroprotective activity in mice	Costa et al. (2018)
	Antiproliferative against tumor cells	Extract (IC_{50} 41.0 ± 4.5 μg/mL for U343), artepillin C (IC_{50} 20.1 ± 2.9 μg/mL for U343 cells) and baccharin (IC_{50} 13.0 ± 1.5 μg/mL for B16F10 cells) showed *in vitro* antiproliferative activity against tumor cells *in vitro*	Oliveira et al. (2014)
Propolis from *Clusia* sp.	Antimicrobial	Ethanolic extract showed antimicrobial activity against *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus mutans in vitro*	Ishida et al. (2011)
Brown propolis from *Araucaria* sp.	Antioxidant	Ethanolic extract of propolis 1 showed antioxidant potential in ABTS (1.02 ± 0.02 μmol TE*/mg), DPPH (0.30 ± 0.01 μmol TE/mg), ROO (1.95 ± 0.10 μmol TE/mg), O_2 (IC_{50} 1.05 ± 0.05 μg/mL) and HOCl (IC_{50} 0.11 ± 0.005 μg/mL) methods	Tiveron et al. (2016)
Brown propolis (unknown botanical origin)	Antimicrobial	Ethanolic extract brown propolis showed antimicrobial activity against *Staphylococcus aureus* (MIC 25–50 μg/mL and MBC 400–800 μg/mL); hyperibone A showed antimicrobial activity against microorganisms (MIC range 0.73–6.6 μg/mL and MBC range 2.92–106 μg/mL) *Streptococcus mutans*, *Streptococcus sobrinus*, *Streptococcus oralis*, *Staphylococcus aureus*, and *Actinomyces naeslundii*	Castro et al. (2009a); Castro et al. (2009b)
	Cytotoxic	Hyperibone A showed cytotoxic activity (IC_{50} 0.1756 μM) for the HeLa cells	Castro et al. (2009b)
Propolis from *Mimosa tenuiflora*	Antioxidant	Ethanolic extracts showed an antioxidant potential of 10% (municipality of Afonso Bezerra) and 13 % (municipality of Alto do Rodrigues) of quercetin activity by the DPPH and 15 % (both locations) by the β-carotene discolouration method	Ferreira et al. (2017)
Propolis from *Myrceugenia euosma*	Anti-HIV	Moronic acid showed anti-HIV activity (EC_{50} < 0.1 μg/mL, TI > 186) in HIV-1 infected H9 lymphocytes	Ito et al. (2001)

*TE - trolox equivalents.

of interleukin 1 beta (IL-1β), interleukin 1-alpha (IL-1α), granulocyte colony-stimulating factor (G-CSF), interleukin 10 (IL-10), and granulocyte–macrophage colony-stimulating factor (GM-CSF) and modulating the nuclear factor kappa B (NF-κB) pathway (Bueno-Silva et al., 2022). The anti-inflammatory activity of the compound neovestitol has also been proven (Bueno-Silva et al., 2013b). Furthermore, neovestitol (10 mg/kg/ subcutaneously) effectively inhibits chronic inflammation induced in mice by inhibiting interleukin 6 (IL-6) (Franchin et al., 2016b). Other isoflavones with anti-inflammatory activity in Brazilian red propolis are formononetin and daidzein. Cavendish et al. (2015) demonstrated that pre-treatment orally of mice with formononetin (10 mg/kg) induced a significant anti-inflammatory effect by inhibiting oedema and leukocyte migration. Regarding the studies with daidzein (2, 4 and 8 mg/kg/ intraperitoneally), its ability to inhibit the migration of neutrophils, the release of inflammatory cytokines, and the activation of NF-kB were found in rats (Feng et al., 2015). Finally, research has shown that the flavonoid isoliquiritigenin present in red propolis also can *in vitro* inhibit the inflammatory process by modulating the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) and reducing the adhesion of neutrophils (Kumar et al., 2007).

3.2. Green propolis from Baccharis dracunculifolia

Propolis from *Baccharis dracunculifolia* (green propolis) is also widely known for its health benefits, and its anti-inflammatory and antimicrobial effects are promising (Santos et al., 2022; Veiga et al., 2017). In the mice-induced inflammatory model, administering ethanol extract effectively controlled oedema and cell influx (Paulino et al., 2006). Later, artepillin C (1–10 mg/kg/intraperitoneal) was isolated from Brazilian green propolis and this compound's administration *in vivo* decreased paw oedema, neutrophil migration, and prostaglandin E2 levels in mice challenged with carrageenan. *In vitro*, the anti-inflammatory action of artepillin C (10–30 μM) occurred by inhibiting NF-κB (Paulino et al., 2008). Ferreira et al. (2021) demonstrated that baccharin (500 or 1000 μg/kg) and *p*-coumaric (500 or 1000 μg/kg) isolated from green propolis also showed anti-inflammatory activity by suppressing neutrophil infiltration, nitric oxide production, and protein extravasation after lipopolysaccharide (LPS) stimulation in air pockets in mice. In another study, the *in vitro* neuroprotective effect of green propolis ethanolic extract was demonstrated in HT22 cells (Takashima et al., 2019). The antimicrobial activity of green propolis was investigated against different microorganisms (Veiga et al., 2017; Assis et al., (2022). Veiga et al. (2017) demonstrated that green propolis ethanolic extract has antimicrobial activity (MIC90: 246.3 μg/mL) against *Staphylococcus aureus*. In another study, Assis et al. (2022) found that the aqueous extract of green propolis had *in vitro* antimicrobial action against the anaerobic bacteria *Fusobacterium nucleatum*, *Parvimonas micra*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Porphyromonas endodontalis* (MIC 55 mg/mL for all bacteria). In addition, the ethanolic extract (IC_{50} value of 13.09 μg/mL) demonstrated antioxidant potential assessed by 1,1-diphenyl-2-picryl hydrazyl radical (DPPH) (Veiga et al., 2017). Finally, other biological activities were also described for green propolis and isolated compounds (Oliveira et al., 2014; Costa et al., 2018; Zhao et al., 2016). A study by Oliveira et al. (2014) demonstrated that artepillin C (IC_{50} 20.1 ± 2.9 μg/mL for U343 cells) and baccharin (IC_{50} 13.0 ± 1.5 μg/mL for B16F10 cells) have significant *in vitro* antiproliferative activity against tumor cells. Costa et al. (2018) verified that oral administration (0.3, 3 or 10 mg/kg) of the compounds artepillin C, drupanin, aromadendrin-4′-*O*-methyl-ether, and kaempferide from green propolis could promote gastroprotective properties in mice, presenting different mechanisms of action.

Clinical studies with Brazilian green propolis were also performed. Silveira et al. (2021) studied adult patients hospitalised with COVID-19 and treated with standardised green propolis extract (EPP-AF®) as adjuvant therapy. Patients received an oral capsule dose containing 400 mg or 800 mg/day of green propolis for seven days. The authors found that the post-intervention hospitalisation time of patients with COVID-19 was shorter in the groups treated with green propolis at 400 mg or 800 mg/day. In addition, the group of patients who received the 800 mg dose had a lower rate of acute kidney injury (Silveira et al., 2021). Silveira et al. (2019) reinforce the protective effect of green propolis on the kidney. The authors found that supplementation with green propolis extract in tablets at 500 mg/day (35.5 mg of total flavonoids and 77.96 mg of total phenolic compounds) in patients with diabetic and non-diabetic chronic kidney disease reduced proteinuria.

The activity of green propolis was also evaluated in *Helicobacter pylori* infection (Coelho et al., 2007). The patients ingested 20 drops (thrice daily for seven days) of an alcoholic preparation of green propolis, and researchers found a minimal effect of green propolis on the *H. pylori* infection (Coelho et al., 2007). Zhao et al. (2016) studied the effect of green propolis on glucose metabolism and antioxidant function in patients with type 2 diabetes mellitus. In these studies, patients received ethanol extract of encapsulated green propolis (900 mg/day/ 18 weeks). It was observed that glutathione (GSH) and total serum polyphenols were increased. Serum carbonyls, lactate dehydrogenase activity, and serum tumor necrosis factor-alpha (TNF-α) were reduced in the group of patients who consumed green propolis (Zhao et al., 2016). Finally, Tasca et al. (2023) studied the beneficial effects of green propolis in patients with human immunodeficiency virus (HIV). Participants were randomly separated into two groups: propolis and placebo. The group of propolis patients consumed green propolis pills (500 mg/day) for three months. In both groups, patients (20–55 years old) were on regular antiretroviral therapy use for at least two years. At the end of the study, the researchers noted that there was a decrease in plasma malondialdehyde (MDA) and an increase in total antioxidant capacity, suggested by researchers that the use of green propolis might be beneficial for curbing the inflammatory and oxidative response in patients with HIV.

3.3. Other types of Brazilian propolis

Another Brazilian propolis that had its biological activities studied includes propolis from *Clusia* sp. that demonstrated significant antimicrobial activity against *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus mutans*, which was related to the presence of the compounds 7-*epi*-nemorosone, 7-*epi*-clusianone, xanthochymol, and gambogenone in its chemical composition (Ishida et al., 2011). Brazilian brown propolis from *Araucaria* presents numerous activities (Ribeiro et al., 2023; Santos et al., 2021a) with emphasis on *in vitro* antioxidant potential that is related to the presence of lignans (e.g., (+)-lariciresinol, (-)- secoisolariciresinol, and balajaponin D) and lignan precursors (coniferyl alcohol and coniferyl aldehyde) (Tiveron et al., 2016; Tiveron et al., 2020). Another ethanolic brown propolis extract demonstrated antimicrobial against *Staphylococcus aureus* (MIC 25–50 μg/mL and MBC 400–800 μg/mL) activity. However, the botanical origin of that brown propolis was unidentified (Duarte et al., 2006; Castro et al., 2009a). Castro et al. (2009b) isolated and identified the prenylated benzophenone, hyperibone A of brown propolis and confirmed its activity against the microorganisms (MIC 0.73–6.6 μg/mL; MBC 2.92–106 μg/mL) *Streptococcus mutans*, *Streptococcus sobrinus*, *Streptococcus oralis*, *Staphylococcus aureus*, and Actinomyces naeslundii and HeLa tumour cells (IC_{50} = 0.1756 μM). The action of propolis from *Mimosa tenuiflora* from northeast Brazil demonstrated *in vitro* antioxidant potential in the DPPH and β-carotene discolouration methods was attributed to the presence of phenolic compounds, mainly flavonoids (Ferreira et al., 2017). Finally, the compound moronic acid was isolated and identified in *Myrceugenia euosma* propolis. Its anti-HIV activity (concentration of agent that inhibits viral replication by 50% (EC_{50} < 0.1 μg/mL, therapeutic index, TI > 186) was shown in HIV-1 infected H9 lymphocytes (Ito et al., 2001).

4. Strategies for optimising the bioactive properties of Brazilian propolis for food applications

4.1. Production of Brazilian propolis extract

Crude propolis is unacceptable for direct consumption. Therefore, propolis has been commonly produced and consumed as aqueous or hydroethanolic extracts (Contieri et al., 2022). Moreover, propolis extracts have been used as ingredients in formulations of functional foods, cosmeceuticals, and pharmaceutical products (Irigoiti et al., 2021). Recently, the therapeutic application of natural polyphenols, such as those found in propolis, has been studied against some diseases, including COVID-19, due to their health benefits (Galanakis, 2020). In fact, the global market of healthy products has been continuously growing in the last years, with strategies to make it more sustainable in the hotspot. Among these strategies, there are the emerging, also known as non-conventional technologies with the potential to be used in the industry using green chemistry, less residue production, and the use of renewable resources (Galanakis, 2023).

Therefore, strategies to increase the retention and chemical stability of bioactive compounds from crude propolis in the extracts are timely needed. Aqueous propolis extracts are alternatives with no ethanolic smell and lower solubility issues. However, they generally do not show similar yield, composition, and bioactivities compared to hydroethanolic extracts (Cui et al., 2022) because of polarity; some phenolic compounds couldn't be extracted using water as a solvent. However, an extract of green propolis from southeast Brazil produced by alkaline hydrolysis and containing high amounts of only caffeic acid (71.76 ± 7.4 mg/g of extract) and *p*-coumaric acid (21.70 ± 1.6 mg/g of extract) showed higher antioxidant in the DPPH and ferric reducing antioxidant power (FRAP) assays, and antimicrobial activities against *Methicillin resistant S. aureus*, *S. epidermidis* and *K. pneumoniae* than ethanolic extracts containing artepillin C, and other chemical markers (Berretta et al., 2023). This extract was produced by maceration for one hour at room temperature in an aqueous solution containing NaOH (0.5 M), followed by acidification to pH 1.0 with hydrochloric acid (HCl), followed by partition with ethyl acetate.

Nonetheless, ethanol is currently the least toxic solvent able to extract phenolic compounds efficiently (Azmir et al., 2013), the essential bioactive compound from propolis, including the various types of Brazilian propolis (Park et al., 2002a). Moreover, ethanol is available to large-scale industries, is cheap, eco-friendly, food grade, and complies with current international legislation.

There are several techniques to produce propolis extracts. Regardless of the method employed, extraction performance is generally affected by process variables such as solvent polarity and its concentration, temperature, contact time, and solid–liquid ratio (Oldoni et al., 2015). At lower temperatures, beeswax in crude propolis can become solid, hampering the industrial extraction process by clogging the pipes. At the same time, some bioactive compounds can be degraded when the temperature and contact time between propolis and solvent are not carefully controlled (Contieri et al., 2022).

Traditionally, propolis balsam is a fraction soluble in hydroethanolic solutions with 70% ethanol (Ghisalberti, 1979). Industrially, maceration and Soxhlet are the methodologies more commonly reported. There are several studies on maceration process variations and their effects on different parameters, especially extraction yield and phytochemical profile of the obtained Brazilian propolis extracts. Most of them used the green propolis of the southeast or brown propolis of the south. A study with Brazilian green propolis from the southeast tested the effect of different conditions of maceration (at 20 g/100 mL, using 30–100 % ethanol as solvent (v/v) for 7–30 days), maceration with solvent renewal, Soxhlet (with absolute ethanol), and combinations of maceration or Soxhlet with wax removal by freezing (Cunha et al., 2004). Based on extraction yield and total phenolic content, the authors reported promising results for Soxhlet (58% and 13%, respectively). In comparison, the best results for maceration were obtained using at least 70 % ethanol as a solvent for at least 20 days (~60 % and 15 %, respectively). Although these results are very similar, the Soxhlet extraction has the advantage of being faster, taking just 24 h, compared to the maceration extraction. However, Soxhlet extraction has a downside to decomposing bioactive compounds due to the prolonged heat. Although no significant effect of light exposure was observed in this study, Arruda et al. (2020) observed the formation of degradation products of artepillin C and *p*-coumaric acid in extracts of Brazilian green propolis from southeast exposed to sunlight and high storage temperature (50 °C). These findings highlight the importance of using propolis extract's proper storage and transport conditions.

Extended maceration time (up to one year) was tested for Brazilian brown, green, and red propolis (Cunha et al., 2006). In summary, it was found that maceration time increased extraction yield (e.g., from 60.1 % in 20 days to 68.7 % in one year for a red propolis sample from Maranhão state). Nonetheless, the authors observed no changes in the phytochemical profile and the concentration of flavonoids and prenylated hydroxycinnamic acids when comparing 20 days with one year of maceration; thereby, extended maceration time seems to have a negligible effect on the extraction process of Brazilian propolis.

The effect of solvent type (ethanol, ethyl acetate, chloroform, hexane, and water) was investigated using Soxhlet extraction at fixed temperature and time (60 °C for 360 min) on the solubility of bioactive compounds of Brazilian green propolis (Biscaia & Ferreira, 2009). The authors observed that a higher yield was achieved by chloroform (73 % w/w), followed by ethanol (60 % w/w), and ethyl acetate (59.7 % w/w). Obviously, chloroform and ethyl acetate extracts cannot be used in food applications, so future studies on propolis should focus on using food-grade solvents to recover bioactive polyphenols from different propolis types.

Optimal extraction conditions by maceration of Brazilian brown propolis were obtained for the higher tested levels of extraction time (45 min), temperature (70 °C), and ethanol concentration (80 %) and allowed the recovery of phenolic acids such as caffeic acid (14.22 ± 0.53 mg/100 g of extract), *p*-coumaric acid (37.05 ± 1.90 mg/100 g of extract) and ferulic acid (15.44 ± 0.35 mg/100 g of extract) (Oldoni et al., 2015). Conversely, the optimal conditions to recover flavonoids (flavones, flavanones, isoflavonoids, flavonols, neoflavonoids) and polyprenylated benzophenones from Brazilian red propolis were the highest ethanol concentration and temperature tested (90 % and 80 °C), but the lower extraction time (30 min in 30–90 min), reaching a total phenolic content of 129.00 mg gallic acid equivalents/g propolis (Morais et al., 2021). The authors hypothesise that increased extraction time leads to oxidation, epimerisation, and degradation of Brazilian red propolis phytochemicals.

Therefore, the process variables of conventional extraction methods should be tailored to recover target compounds of each type of Brazilian propolis. Additionally, non-conventional techniques of extraction, regarded as green techniques, have been studied for Brazilian propolis aiming at reducing the use and amount of chemicals and maximising the concentration of target compounds while assuring safety (Contieri et al., 2022). Herein, we mention non-conventional methods as extraction methods that are not maceration or Soxhlet. Table 3 summarises the results of studies published in the last five years on non-conventional extraction techniques for producing Brazilian propolis extracts.

Among the non-conventional extraction techniques, supercritical fluid extraction (SFE), pressurised liquid extraction (PLE), ultrasound-assisted extraction (UAE), and microwave-assisted extraction (MAE) have been studied. The results have been compared to the conventional methods concerning efficiency parameters, such as spent time, selectivity of compounds of interest, and extraction yield in Brazilian propolis types (Reis et al., 2019; Devequi-Nunes et al., 2018; Monroy et al., 2017; Teixeira et al., 2023).

The SFE technique has been studied for over a century with different products. Because of several distinct properties that can be modulated in

Table 3
Summary of studies published in the last six years on non-conventional extraction techniques for producing Brazilian propolis extracts.

Brazilian propolis type	Extraction method	Solvent	Extraction yield	Extracted compounds (mg of compound/g or mL of extract)	References
Green Propolis from *Baccharis dracunculifolia*- Minas Gerais, Brazil	Atmospheric pressure: stirred vessel – 50 °C, 150 rpm, for 30 min. Soxhlet – 78 °C for 180 min. High-pressure extraction: supercritical fluid extraction (SFE) and pressurised liquid extraction (PLE) at 50 °C and 250 bar for all steps	Stirred vessel and Soxhlet: Ethanol-H_2O mixtures with different proportions; SFE and PLE: CO_2, Ethanol 80 % (v/v) Ethanol absolute and water	53.5 % in the tree-step sequential extraction in high pressure (CO_2; water and ethanol), and 44.7 % in Soxhlet extraction with ethanol 80 %	Artepillin C: tree-step water (13 mg/g) and ethanol fraction (44 mg/g), Soxhlet (49.3 mg/g). *p*-coumaric acid: tree-step water (4.1 mg/g) and ethanol fraction (2.8 mg/g), Soxhlet (1.7 mg/g). Kaempferide: tree-step water (3.2 mg/g) and ethanol fraction (4.7 mg/g), Soxhlet (6.1 mg/g)	Monroy et al. (2017)
Green propolis from *Baccharis dracunculifolia* - Vitória da Conquista, Bahia, Brazil	Ethanolic extraction (70 °C for 30 min, under agitation) and supercritical fluid extraction (SF: 110, 50 °C, 350 bar, and co-solvent 1% ethanol)	Ethanol 80 % (v/v); liquid CO_2 and ethanol 1 % as co-solvent	Ethanolic extraction: 374.1 mg GAE/g of extract; Supercritical fluid extraction: 174.31 mg GAE/g of extract	Ethanolic extraction: catechin (76.7 mg/g); *trans*-ferulic acid (0.5 mg/g), and luteolin (4.25 mg/g).	Devequi-Nunes et al. (2018)
Brown propolis - Vitória da Conquista, Bahia, Brazil.	Ethanolic extraction (70 °C for 30 min, under agitation) and supercritical fluid extraction (SF: 110, 50 °C, 350 bar, and co-solvent 1% ethanol)	Ethanol 80 % (v/v); liquid CO_2 and ethanol 1 % as co-solvent	Ethanolic extraction: 249.28 mg GAE/g of extract; Supercritical fluid extraction: 113.41 mg GAE/g of extract	Ethanolic extraction: catechin (49.39 mg/g); *trans*-ferulic acid (0.1 mg/g), and luteolin (5.24 mg/g)	Devequi-Nunes et al. (2018)
Red Propolis from *Dalbergia ecastophyllum* (L) *Taub* - Canavieiras, Bahia, Brazil.	Ethanolic extraction (70 °C for 30 min, under agitation) and supercritical fluid extraction (SF: 110, 50 °C, 350 bar, and co-solvent 1% ethanol)	Ethanol 80 % (v/v); liquid CO_2 and ethanol 1 % as co-solvent	Ethanolic extraction: 481.59 mg GAE/g of extract; Supercritical fluid extraction: 171.33 mg GAE/g of extract	Ethanolic extraction: *trans*-ferulic acid (0.6 mg/g)	Devequi-Nunes et al. (2018)
Green Propolis from *Baccharis dracunculifolia*- Bambuí, Minas Gerais, Brazil	Supercritical fluid CO_2, performed at 50 °C and 300 bar using 1.5 g/min of an ethanol	ethanol 80 % (v/v) and ethanol absolute extraction	Ethanol 80 % extraction: 36 %; Ethanol extraction: 29 %	Ethanol 80% extraction: artepillin C (37.5 mg/g propolis); *p*-coumaric acid (8.4 mg/g propolis) and kaempferide (10.77 mg/g propolis). Ethanol absolute extraction: artepillin C (37.0 mg/g propolis); *p*-coumaric acid (1.14 mg/g propolis) and kaempferide (3.88 mg/g propolis)	Monroy et al. (2018)
Green Propolis from *Baccharis dracunculifolia*- Bambuí, Minas Gerais, Brazil	Ultrasound Bath (with different solvent concentrations, solid-solvent ratio, and extraction times)	Ethanol/distilled water (0–99 % ethanol v/v)	The extract was obtained by 99 % ethanol, 1:35 (w/v), for 20 min: 1615 mg GAE/g of crude propolis.	Artepillin C (807.6 mg/g) and *p*-coumaric acid (45.6 mg/g)	Cavalaro et al. (2019)
Green propolis, Brazil	Water Bath at 50 °C and in-room temperature (25–30 °C), for 3 h, under constant agitation.	Natural Deep Eutectic Solvents formulations, honey, and neat solvents	Water Bath Extracts- Total peak areas: Ethanol 70 % extract – 119 AU's; Choline chloride: propylene glycol 1:2 extract – 112 AU's; Choline chloride: DL-lactic acid: water 1:1:1—95 AU's	Artepillin C content: Ethanol 70% extract – 2.23 mg/mL; Choline chloride: propylene glycol 1:2 extract – 2.13 mg/mL; Choline chloride: DL-Lactic acid: water 1:1:1—1.8 mg/mL	Funari et al. (2019)
Red Propolis from *Dalbergia ecastophyllum* (L) Taub - Alagoas, Bahia, Rio Grande do Norte e Sergipe - Brazil.	Conventional process under agitation for 7 days at room temperature; and ultrasound-assisted extraction at 50 °C for 50 min	Ethanol 80 %	Alagoas propolis: conventional extraction - (1a) 307.63 and (2a) 398.31 mg GAE/g of extract; Ultrasound-assisted extraction - (1b) 337.72 and (2b) 380.73 mg GAE/g of extract	Formononetin: (1a) 6.54 mg/g, (1b) 6.15 mg/g, (2a) 12.67 mg/g and (2b) 13.64 mg/g; Kaempferol: (1a) 0.65 mg/g, (1b) 0.43 mg/g, (2a) 3.72 mg/g and (2b) 3.02 mg/g	Reis et al. (2019)
Green Propolis from *Baccharis dracunculifolia*- Minas Gerais, Brazil	Low-pressure extraction (LPE) and Supercritical fluid extraction (SFE), pre-treated with or without ultrasound	Ethanol 80% and CO_2 as supercritical fluid	LPE (ultrasound at 50 °C for 20 min) – 439.05 mg GAE/g of extract; SFE (at the same pre-treatment condition) – 194.12 mg GAE/g of extract	Quercetin (1.37 and 0.68 mg/g); Gallic acid (2.78 and 1.79 mg/g); Formononetin (7.77 and 4.76 mg/g); Kaempferol (0.91 and 2.51 mg/g); *p*-coumaric acid (8.10 and 0.0 mg/g); caffeic acid (2.19 and 0.19 mg/g); catechin (0.91 and 0.52 mg/g); epicatechin (0.48 and 0.31 mg/g); rutin (0.56 and 14.99 mg/g), of LPE and SFE respectively	Teixeira et al. (2023)

the technique application, it has been regarded as a promising alternative to conventional extraction techniques, mainly for herbal and natural products (Lang & Wai, 2001). The efficiency and biological potential of extraction using SFE (350 bar, 50 °C, S/F 110 – mass of CO_2/mass of propolis, 1 % ethanol as co-solvent, CO_2 flow: 6 g/min, total time: 2.5 h) and conventional low-pressure extraction (LPE) (ethanol 80 %, at 70 °C, for 30 min, under constant agitation) in brown, red and green Brazilian propolis were measured and compared (Machado et al., 2016b). The authors concluded that even though the conventional LPE of all propolis types tested showed higher biological potential, SFE showed a highly selective extraction of artepillin C and *p*-coumaric acid in brown and green propolis once the recovered content of these compounds was four times higher, the *p*-coumaric content in green propolis was 24.65 ± 0.24 μg/mL by LPE and 195.12 ± 6.12 μg/mL by SFE, and

in brown propolis, this content is just detected by SFE, equivalent to 5.05 ± 0.10 μg/mL. For the artepillin C content, the green and brown propolis showed 464.49 ± 9.23 μg/mL and 82.67 ± 6.12 μg/mL concentrations by LPE, and by SFE 845.05 ± 0.12 μg/mL and 315.96 ± 5.89 μg/mL respectively. Hence, the SFE was generally more efficient in extracting propolis bioactive compounds. However, the selectivity of compounds in SFE depends on extraction process conditions, as studied by Devequi-Nunes et al. (2018). These authors studied brown, green, and red Brazilian propolis extracted by SFE (350 bar, 50 °C, S/F 110 – mass of CO_2/mass of propolis, 1 % ethanol as co-solvent, CO2 flow: 6 g/min, total time: 60 min) and LPE (ethanol 80 %, at 70 °C, for 30 min, under constant agitation). As a result, the quantified compounds (catechin, *trans*-ferulic acid, and luteolin) were extracted more efficiently by LPE in all propolis profiles tested, representing 49.39 mg/g of extract and 76.70 mg/g of extract of catechin in brown and green propolis respectively, for the *trans* ferulic acid 0.10 mg/g of extract, 0.50 mg/g of extract and 0.60 mg/g of extract in brown, green and red propolis respectively, and for luteolin 5.24 mg/g of extract and 4.25 mg/g of extract in brown and green propolis respectively. None of these compounds could be quantified in the extracts obtained by SFE because they were below the detection levels. Therefore, the extraction conditions for each methodology should be optimised for each compound or class of compounds of interest.

SFE and sub-sequential pressurised liquid extractions (PLE) with other solvents, such as water and ethanol, are used to obtain rich-phenolic propolis extracts (Monroy et al., 2017). In this study, the Brazilian green propolis from Minas Gerais state was extracted using three steps of high-pressure extraction (1st step: CO_2 – 1.65 g/min; 2nd step: ethanol absolute pressurised liquid – 0.78 g/min; and 3rd step: pressurised water liquid – 1 g/mL; total time: 330 min; 250 bar; and 50 °C) showed the highest yield (i.e., 53.5 %). However, the second fraction, of ethanol 80 %, obtained in the two steps of high-pressure extraction (1st step: CO_2 – 1.65 g/min; 2nd step: ethanol 80 % pressurised liquid – 0.79 g/min; total time: 210 min; 250 bar; and 50 °C), showed the highest antioxidant potential when compared to the other fractions and extraction techniques. This two-step extraction method was also observed to produce purer extracts, according to the generated chromatogram peaks. This purity could be related to the higher antioxidant potential since the bioactive compounds associated with this activity might be free to scavenge the reactive species more efficiently.

Another application of the SFE is the use of the supercritical fluid CO_2 (SF-CO_2) as an anti-solvent (SAS) after some conventional extraction of propolis, like the Soxhlet methodology (Chen et al., 2009b; Chen, Lee, Lee, & Chang, 2009a; Wu et al., 2009). SAS aims to generate micronised particles of the solutes (like the Soxhlet previously extracted) by supersaturation in a high-pressure solution, and this can be effective for the propolis compounds obtained because most of the compounds have very low solubility in CO_2 (Chen et al., 2009a; Chen et al., 2009b). This process can obtain bioactive compounds of interest by flow rate and volume expansion control, like 3,5-diprenyl-4-hydroxycinnamic acid in Brazilian green propolis (Chen et al., 2009b; Chen, Lee, Lee, & Chang, 2009a; Wu et al., 2009), or remove the wax to enhance the concentration of phenolic compounds in the extracts. This SAS application to obtain bioactive compounds with a high yield shows high potential to be applied by the food and pharmaceutical industries (Chen et al., 2009a; Chen et al., 2009b).

UAE represents another non-conventional technique widely applied in propolis extraction, which is considered a fast and simple technique that requires fewer solvent volumes and low extraction temperatures (Nichitoi et al., 2023). Cavalaro et al. (2019) tested UAE to recover polyphenols from Brazilian green propolis. The authors used extraction time (5–45 min), solid-to-solvent ratio (1:10 – 1:50 w/v), and ethanol/distilled water concentration (0–99 % ethanol, v/v) as the independent variables, and the temperature was maintained at 25 °C in the throughout the process. The optimal experimental conditions to obtain the highest TPC value, artepillin C yield, and antioxidant potential were obtained using 99% ethanol, 1:35 propolis: solvent ratio (w/v) for 20 min.

The UAE methodology (50 °C for 20 min) was used as a pre-treatment, followed by a conventional method extraction (maceration with constant agitation for 30 min) with Brazilian green propolis from Minas Gerais state and Brazilian red propolis from Bahia state. This pre-treatment with UAE efficiently increased green propolis's total phenolic content (TPC) compared with the untreated extract. However, for the red propolis, the pre-treatment did not affect the TPC content compared to the untreated extract (Sokolonski et al., 2021). Hence, there is an indication that different propolis compounds may be affected differently by ultrasound-assisted extraction.

In addition to non-conventional techniques, some works have assessed the use of more sustainable alternative solvents to substitute the volatile organic solvents, such as hexane, methanol, and chloroform, that show high toxicity and present risks for the workers (Funari et al., 2019; Santos, Mesquita, Braga, & Rosso, 2021b). The use of ionic liquids and eutectic solvents to extract Brazilian red propolis from the Alagoas state with an ultrasonic probe (20 kHz at 400 W for 5 min) showed a promising potential when compared to the hydroethanolic (70 % and 95% v/v) extraction in the same conditions. It was observed that the 1-hexyl-3-methylimidazolium chloride ([C6mim]Cl) eutectic solvent (10:1 [C6mim]Cl: water) produced an extract with the highest content of total flavonoids (Santos et al., 2021b). Eutectic solvents are attractive alternatives for organic solvents since they are generally cheaper and show low toxicity and high biodegradability.

Funari et al. (2019) proposed the use of "natural deep eutectic solvents" (NADES) for Brazilian green propolis extractions (water bath for 3 h, at 50 °C or room temperature). It was observed that extracts obtained with NADES from choline chloride – propylene glycol (1:1 v/v) and choline chloride – lactic acid – water (1:1:1 v/v/v) showed great potential to replace extractions of ethanol: water (70:30 v/v), and propylene glycol, maintaining the proportions of artepillin C. To replace aqueous extraction, which presents low yield, using an aqueous solution of L-lysine at 50 °C showed a greater capacity in extracting the bioactive compounds, thus becoming a more effective alternative. Hence, studies comparing extraction techniques, especially non-conventional green technologies in different types of Brazilian propolis, should be encouraged to guide the establishment of more efficient protocols, which could be industrially scaled soon.

4.2. Incorporation of the Brazilian propolis into different delivery systems

Propolis extracts are widely used in food formulations to promote health (Irigoiti et al., 2021). Bioactive compounds, such as polyphenols, have been associated with reduced oxidative stress, inflammation, and the risk of cardiovascular disease (Galanakis, 2021). Brazilian propolis presents a complex bioactive composition, and a delivery system can provide phenolic compounds with stability, bioavailability, and favourable biological activity (Irigoiti et al., 2021). Table 4 summarises the types of Brazilian propolis and the use of different pharmacotechnical techniques in food science and technology. It is a fact that encapsulation technology is widely used in delivery system studies, as its application allows the coating of solid, liquid, or gaseous particles, which provides increased solubility, controlled release, and, in many cases, avoids undesirable effects of sensory changes in the product material. In addition, it can favour better storage of the material and reduce packaging and transport costs and shelf life. Countless excipients can be used in encapsulation, including gum Arabic, pectin, alginate, and maltodextrin (Tavares et al., 2022). Furthermore, drying the powders to form capsules by spray drying, freeze-drying, or spray-chilling may favour better material solubility. As a result of the advantages of the encapsulation process, Brazilian propolis has increasingly benefited from this technology. Andrade et al. (2018) proposed obtaining dry powders of brown, red, and green Brazilian propolis by spray-drying. Maltodextrin and gum Arabic were used separately for the material

Table 4
Summary of studies published in the last six years on the delivery system used in Brazilian propolis extracts/bioactive compounds and their applications.

Brazilian propolis type	Technology	Excipients/sample	Application	References
Red propolis from *Dalbergia ecastaphyllum* – Marechal Deodoro, Alagoas, Brazil.	Extract red propolis encapsulated by spray drying and freeze-drying	Guar gum, pectin, maltodextrin, carbopol, carboxymethylcellulose, stearic acid, and colloidal silicon dioxide in different proportions. Propolis extract at 75 %, 47.62 %, 76.93 %, or 64.94 %	Nutraceutical products	Almeida et al. (2017)
Green propolis from *Baccharis dracunculifolia* - Brazil	Green propolis encapsulated in a γ-cyclodextrin complex by then spray-dried	83 g of green extract and 250 g of γ-cyclodextrin (dry weight: 227 g) were added to 666 mL water	Diet	Rimbach et al. (2017)
Brown and green propolis – Bahia, Brazil; Red propolis - Sergipe, Brazil	Microcapsules containing spray dried powder obtained from Brazilian brown, green and red propolis	Maltodextrin and gum Arabic were dissolved separately in 0.2 g/mL water. The proportion of extract to the encapsulating material solution was 1: 0.67 w/v	Food and pharmaceutical	Andrade et al. (2018)
Green propolis from *Baccharis dracunculifolia* - Ouro Preto, Minas Gerais, Brazil	Ethanolic extract green propolis nano-emulsified	Corn oil (5.0% w/w), distilled water (84.0 % w/w), nonionic surfactants sorbitan monooleate (3.0% w/w), and polysorbate 80 (7.0 % w/w) and ethanolic propolis extract (1 % w/w)	Food preservative	Seibert et al. (2019)
Red propolis from *Dalbergia ecastaphyllum* – Canavieiras, Bahia, Brazil.	Probiotic yogurt with red propolis	Lactic culture-containing strains, the *L. acidophilus*, 1 × 10^6 CFU/g; *Bifidobacterium*, 1 × 10^6 CFU/g; and *Streptococcus thermophilus*. Red propolis extract (0.05 %, w/v; 0.046 %, w/w)	Food	Santos et al. (2019); Santos et al. (2020)
Green propolis from *Baccharis dracunculifolia* - Cruz das Almas, Bahia, Brazil	Sodium alginate bilayer coating incorporated with green propolis extract	The coating solution (300 mL) - sterile distilled water (262.5 mL), sodium alginate (3 g: final concentration of 1% v/v), glycerol (3 mL: final concentration of 1% w/v), and green propolis extract (37.5 mL: final concentration 25 mg/mL)	Food preservative	Cruz et al. (2021)
Red propolis from *Dalbergia ecastaphyllum*	Ethanolic extract Brazilian red propolis encapsulated by freeze-drying	Gum Arabic from the acacia tree and ethanolic extract Brazilian red propolis: carrier ratio 1:4 (w/w)	Food	Alencar et al. (2023)
Red propolis from *Dalbergia ecastaphyllum* – Maceió, Brazil	Brazilian red propolis extract encapsulated by spray-drying, spray-chilling, and using the combination of both techniques	Proportions 1:4 and 1:6 (ethanolic extract of red propolis: gum Arabic) - spray drying; proportions 1:4 and 1:6 (ethanolic extract of red propolis concentrated: fat) - spray-chilling	Food, feed, cosmetic, and pharmaceutical industries	Sá et al. (2023)
Green propolis from *Baccharis dracunculifolia* - Brazil	Microencapsulated propolis extract using a spray-drying process	Hydroethanolic propolis extract and gum Arabic (40:60 w/w)	Food, food supplements, hygiene and skin care products, and pharmaceutical formulations	Berretta et al. (2023)

encapsulation process. The authors detected the presence of artepillin C (4.78–4.39 mg/g of propolis microparticles), kaempferide (0.26—–0.44 mg/g of propolis microparticles), *p*-coumaric acid (2.87–3.05 mg/g of propolis microparticles), and chlorogenic acid (0.64–1.03 mg/g of propolis microparticles) compounds in the obtained powders from the green propolis type. On the other hand, powders from red propolis contained luteolin (1.27–1.29 mg/g of propolis microparticles), naringenin (0.61–0.66 mg/g of propolis microparticles), biochanin A (0.27–0.29 mg/g of propolis microparticles), and pinocembrin (0.23–0.28 mg/g of propolis microparticles). In addition, the microparticles presented spherical shapes, smooth surfaces, amorphous characteristics, low water activity, humidity, high solubility, good encapsulation efficiency, and hygroscopic. Regarding the antioxidant potential, a better free radical scavenging activity (DPPH and ABTS) of encapsulated propolis was verified compared to the Brazilian propolis extract. The results reinforce that the encapsulation of Brazilian propolis and the retention of phenolic compounds can favour its application in food formulations, such as in food preservation or as an additive for health benefits in the elimination of free radicals (Galanakis, 2018; Galanakis, 2021). In another study, Berretta et al. (2023) obtained microcapsules containing green propolis by drying the emulsion prepared with hydroethanolic extract concentrate and gum Arabic (40:60) by spray-dryer. It was verified that the microcapsules with green propolis retained a more significant number of propolis bioactive substances (artepillin C, *p*-coumaric acid, 3,5 dicaffeoylquinic acid, 4,5 dicaffeoylquinic acid, aromadendrin-40 -O-methyl-ether, drupanin, caffeic acid, chrysin, baccharin, and galangin) and preserved the chemical profile of the original propolis extract, considered by the authors to be a great advantage in maintaining the already known functional benefits of hydroethanolic propolis extracts. In addition, the propolis microcapsules showed attenuated aroma, flavour, and less intense colour; they could be used in liquid formulations requiring a smoother taste. Regarding bioactive potential, the propolis chemical antioxidant capacity was negatively affected by the microencapsulation (DPPH and FRAP), which was hypothesised to occur due to less access of reagents to the encapsulated extract *in vitro*. Concerning the antimicrobial activity, propolis microcapsules showed the lowest antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) (MBC 6.88 ± 0.02 mg propolis dry matter/mL), and similar activity against *Staphylococcus epidermidis* (MBC 10.31 ± 4.84 mg propolis dry matter/mL) and *Klebsiella pneumoniae* (MBC 20.62 ± 9.67 mg propolis dry matter/mL) compared to the polar propolis fraction (MBC 3.44 ± 0.00 mg propolis dry matter/mL - *Staphylococcus epidermidis*; 3.44 ± 0.00 mg propolis dry matter/mL - *Klebsiella pneumoniae*) and soluble propolis dry extract (MBC 6.89 ± 0.01 mg propolis dry matter/mL - *Staphylococcus epidermidis*; MBC 6.89 ± 0.01 mg propolis dry matter/mL - *Klebsiella pneumoniae*). Despite its unusual use in food formulations, Rimbach et al. (2017) encapsulated Brazilian green propolis with γ-cyclodextrin, and its application in the study was directed as a supplement for mice on a diet rich in fats and carbohydrates. The authors studied the profile of endogenous antioxidant and inflammatory biomarkers in the liver of mice. They found that TNF-α and serum amyloid P mRNA levels decreased with treatments containing propolis encapsulated in the γ-cyclodextrin complex.

Comparative studies have been reported in the literature assessing spray drying, freeze-drying, and spray-chilling techniques in delivery systems. Almeida et al. (2017) studied microcapsules with Brazilian red propolis for potential application as a nutraceutical. In this study, the authors submitted the microcapsules to spray drying and freeze-drying processes using different types of excipients for coating (guar gum,

pectin, maltodextrin, carbopol, carboxymethylcellulose, stearic acid and colloidal silicon dioxide in different proportions) and the concentrations of red propolis incorporated in the microcapsules were 75 %, 48 %, 77 % and 65 %. The authors verified that microencapsulation of red propolis leads to a higher concentration of flavonoids (20.50 to 40.79 mg/100 mg of the microcapsules). The antioxidant potential was similar between red propolis tinctures A and B (IC_{50} 6.95 μg/mL e 7.48 μg/mL), spray-dried microcapsules (IC_{50} 8.89–15.63 μg/mL) and freeze-dried microcapsules (IC_{50} 11.83–23.36 μg/mL). The antimicrobial effect against *Staphylococcus aureus* and *Pseudomonas aeruginosa* was evidenced for tinctures and microcapsules (spray-drying and freeze-drying) containing red propolis, with greater sensitivity to Gram-positive bacteria. In another study, the authors encapsulated red propolis extract using spray-drying, spray-chilling, and using the combination of both techniques with the following concentrations of extract and excipient: ethanolic extract red propolis: gum Arabic for spray dryer (proportions 1:4 w/w) and ethanolic extract of red propolis concentrated: fat for spray-chilling (proportions 1:6 w/w) (Sá et al., 2023). The techniques used in this research for encapsulation preserved the antioxidant compounds (phenolic compounds and total flavonoid) in red propolis in the period (60 days), and the conditions evaluated, as well as the powders, showed low moisture content and water activity, suitable for food applications. In the *in vitro* simulated release test, the particles obtained by spray drying showed their formononetin release peak in the oral phase, with a drop in molecule concentration in the following steps (gastric and small intestinal phases). On the other hand, the coated particles by spray chilling showed higher release in the intestinal phase. Therefore, these results indicate that microencapsulation influences the release kinetics of bioactive compounds (Sá et al., 2023).

When considering propolis in food-grade applications, the bioavailability of the bioactive compounds in human plasma is pivotal. After digestion and interaction with the gut microbiome, original compounds and their metabolites must reach the plasma and tissues to exert any beneficial effect. *In vitro*, these crucial steps, namely simulated digestion, interaction with microbiome, metabolisation, and transport of bioactive compounds, can be accurately assessed using different 2-dimensional and 3-dimensional cell models (Granato, 2023). Alencar et al. (2023) reinforced the importance of evaluating the release kinetics of encapsulated red propolis compounds and intestinal permeability using Caco-2 cells in a monolayer. In this study, the authors encapsulated the ethanolic extract of red propolis using gum Arabic from an acacia tree as a coating. The results showed that all bioactive compounds of red propolis (eight isoflavones, one flavanone, and one chalcone) were bioaccessible and that their stability was greater for encapsulated propolis, possibly due to the formation of bonds between the isoflavonoid aglycones of the red propolis and the polysaccharides from gum Arabic, thereby increasing water solubility. On the other hand, red propolis encapsulation negatively affected Caco-2 cell transport of phenolic compounds, and *in vitro* antioxidant and anti-inflammatory (macrophages culture) potential.

The delivery system for Brazilian propolis has also been applied to improve the conservation of foods such as fish. Cruz et al. (2021) developed a bilayer sodium alginate coating incorporated with green propolis. The authors found that the antioxidant and antimicrobial activities of green propolis extract in *Colossoma macropomum* fillets extended the shelf life of the fish by 11 days, reducing microbial deterioration and improving physicochemical parameters, such as oxidation, moisture, and pH. Finally, the authors reported that the *C. macropomum* fillets had good sensory acceptance, making green propolis an excellent alternative as a natural preservative for fish, reducing the need for preservatives. In another study, researchers proposed a nanoemulsion to carry Brazilian green propolis as a food preservative (Seibert et al. 2019). The authors carried out a sequential extraction of propolis with solvents of different polarities (hexane, ethyl acetate, and ethanol), and the ethanolic extract was selected and incorporated into the nanoemulsion. It was verified that the nanoemulsion developed by the phase inversion technique was stable under thermal stress and centrifugation conditions. In addition, the antioxidant potential (DPPH and ABTS) and antimicrobial activity against Gram-positive bacteria were also maintained. These results indicated that the nano-emulsion could be used as a food preservative, preventing degradation and masking the unpleasant taste of green propolis (Seibert et al. 2019). Finally, researchers have also considered using 0.05 % red propolis extract in probiotic yoghurt to replace potassium sorbate (Santos et al. 2019). The extract was obtained with 70 % ethanol in water with subsequent complete solvent evaporation. Promising results were verified with propolis in yoghurt, as it maintained microbiological stability for at least 28 days and concentrations of total phenolic compounds higher than commercial yoghurt, providing better *in vitro* antioxidant potential. Another significant study result is that adding red propolis did not change the pH, acidity, fatty acid profile, chemical composition, and shelf life compared to commercial yoghurt. These studies, therefore, demonstrate the versatility of Brazilian propolis and bioactive compounds for use in food formulations, which can provide food preservation and health benefits due to their biological effects.

5. Challenges and perspectives

Research to optimise the bioactive properties of Brazilian propolis for food applications has evolved considerably, and delivery systems may provide compounds with optimal stability, bioavailability, and biological activities. In addition, the proper process for obtaining propolis extract and bioactive compounds is a fundamental step for developing a suitable nutraceutical or food ingredient. Studies on the applicability of Brazilian propolis to foods should consider the importance of the research reproducibility, and to achieve this objective, it is crucial to consider the standardisation of the sample, that is, obtain its georeferencing, its botanical origin, when known, and carry out the chemical profile analysis, at least with the main significant compounds. In addition, the *in vitro* bioaccessibility and intestinal permeability tests provide central results for evaluating the digestion behaviour of the compounds in the gastrointestinal tract (mouth, stomach, and intestine) and absorption into the bloodstream to predict bioavailability and effective bioactivity. Studies have focused mainly on Brazilian *green (Baccharis dracunculifolia)* and red (*Dalbergia ecastaphyllum*) propolis. Therefore, novel studies carried out with the other under-explored types of Brazilian propolis should be encouraged, mainly due to the chemical complexity and richness of bioactive compounds found in the samples according to Brazil's collection site and region. Finally, the incentive for assessing and applying new delivery systems using different excipients in Brazilian propolis and innovative extraction techniques are of considerable importance for its successful use by the food industry.

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Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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