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Article *in* Phytomedicine Plus · February 2022

DOI: 10.1016/j.phyplu.2022.100239

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Phytomedicine Plus 2 (2022) 100239

Contents lists available at ScienceDirect

Phytomedicine Plus

journal homepage: www.sciencedirect.com/journal/phytomedicine-plus

An overview about apitherapy and its clinical applications

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ARTICLE INFO

Keywords:
Apitherapy
Honey
Propolis
Bee venom
Bee pollen
Royal jelly

ABSTRACT

Background: Humanity has benefited from bee products over the centuries for treating and preventing various illnesses, and apitherapy has been employed in several countries as a complementary medicine. This review aimed to discuss scientific research and clinical trials using bee products and their relationship with apitherapy.
Methods: Scientific researches based on studies carried out *in vitro* using different cell cultures, and *in vivo* studying mice or other experimental animals are discussed. Clinical trials using bee products are also documented.
Results: The most common applications of bee products in apitherapy are presented, as well as cases of allergy to bee products and apitherapy for treating allergies. Standardization of bee products and their use in research and apitherapy are discussed.
Conclusion: Apitherapy is practiced in some parts of the world, bringing benefits for healthy individuals and patients, with no clear consensus on its application according to the world regions or a prevalent use of bee product and treated disease. Different recommendations regarding the use of bee products are found and people ingest different amounts of bee products once or several times a day. Although we have advanced a lot about the knowledge of bee products, it is imperative to exploit their potential and standardize their use, communicating the results in scientific and alternative events to reinforce the exchange of information between beekeepers, researchers, apitherapists, nutritionists, physicians, sellers and consumers of bee products. If not, we will always be working separately, without complementing our expertise.

Abbreviations
8-OHDG: 8-hydroxy-2′-deoxyguanosine;
API: approximal plaque index;
BV: bee venom;
CHX: chlorhexidine;
COVID-19: coronavirus disease 2019;
DFU: diabetic foot ulcer;
DH: dental hypersensitivity;
eBV: essential BV;
H_2O_2: hydrogen peroxide;
HbA1c: hemoglobin A1c;
HDL: high-density lipoprotein;
HOMA-IR: homeostasis model assessment of insulin resistance;
hs-CRP: high sensitive C-reactive protein;
LDL: low-density lipoprotein;
MCP-1: monocyte chemoattractant protein-1;
MDR: multi-drug resistant;
MRSA: methicillin-resistant *Staphylococcus aureus*;
PHP: patient hygiene performance;
RJ: royal jelly;
SOD: superoxide dismutase:
T2DM: type 2 diabetes mellitus;
TG: triglycerides;
TLR: Toll-like receptor;
VIT: venom immunotherapy.

Introduction

Bees produce a large number of products that contain bioactive constituents like honey, propolis, royal jelly, bee pollen, beeswax, and bee venom, which have been used by different civilizations for centuries to treat various illnesses (Al Naggar et al., 2021).

The investigation of natural products has gained prominence in

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https://doi.org/10.1016/j.phyplu.2022.100239
Received 19 September 2021; Received in revised form 20 January 2022; Accepted 9 February 2022
Available online 12 February 2022

recent times to prevent or treat several diseases. Interest in bee products and in apitherapy has also increased (J.D. Lee et al., 2005; Fratellone, 2015; Bognadov, 2020; Doko et al., 2020). Apitherapy is the treatment with bees or their products as therapeutic/prophylactic agents to prevent diseases or control their progression. Nowadays, apitherapy is part of complementary and integrative medicine in many countries. Moreover, due to their nutrients, the consumption of bee products as nutraceutical and dietary supplements has increased (Pasupuleti et al., 2017; Al Naggar et al., 2021).

Research on the pharmacological activity of bee products has increased in recent decades, disclosing numerous biological properties. *In vitro* and *in vivo* studies as well as clinical trials have shown that bee products can be indicated to treat various diseases and for the health balance and homeostasis (Kwon et al., 2001; Zhu and Wongsiri, 2008; White and Nezvesky, 2009; Jull et al., 2015; Tasca et al., submitted). In addition, bee products are constantly used in food, cosmetics and by the pharmaceutical industry, in the search for new drugs (Berretta et al., 2020).

Apitherapy has been employed in several countries and Brazil stands out not only for the diversity of resources for bees, but for research on bee products. Using the Web of Science database, Şenel and Demir (2018) performed a bibliometric study of apitherapy in complementary medicine literature between 1980 and 2016. Brazil ranked first on the publication number followed by the USA, China, Japan and Turkey. According to their score, the most productive countries in apitherapy were Switzerland, Croatia and Bulgaria.

There is no clear consensus on the application of apitherapy according to the world regions. In addition, people confuse information gained from popular knowledge with scientific experiments. Apitherapy is more than that. Thus, this review aimed to discuss scientific research based on studies carried out *in vitro* using different cell cultures, and *in vivo* studying mice, rats or other experimental animals. Clinical trials using bee products are also documented, although the mechanisms of action involved in their activity are not always reported. In an attempt to bridge the gap between beekeepers, apitherapists and the scientific evidence of research on bee products, we aimed at analyzing the practice of apitherapy globally and combine traditional knowledge with the scientific evidence. Special attention was given to clinical trials, types of interventions, and outcomes.

The PubMed database (https://PubMed.ncbi.nlm.nih.gov/) was used to assess the therapeutic studies involving bee products, searching for the biological activity of each bee product. The following keywords were assessed: "honey biological activity", "propolis biological activity", "bee venom biological activity", "bee pollen biological activity", "bee bread biological activity", "royal jelly biological activity", "apilarnil biological activity", and "beeswax biological activity".

The inclusion criteria for selecting the manuscripts were: only manuscripts dealing with the biological activity of each product were included. Exclusion criteria: manuscripts related to bee product chemical composition, reviews, research focused on isolated compounds and products from stingless bees were discarded. Some manuscripts were rejected for other reasons, such as citing a particular bee product without investigating its biological activity, articles discussing information superficially and those outside the scope. Although there is a lot of information on the internet sites, the abstracts of scientific events, personal communications and unpublished data were avoided. Otherwise, we could include general information without confirmation or credibility (Fig.1).

The number of manuscripts published until 2020 is shown in Table 1.

The importance of beehive products for bees

Before discussing the benefits of apitherapy, it is relevant to understand the importance of bee products for the bees and for the beehive. The bees themselves chemically synthesize beeswax, bee venom, and royal jelly, while honey, propolis, bee pollen, and bee bread result from the modification of plant-derived material by bees (Al Naggar et al., 2021).

Honey comes from the floral nectar or secretions from living parts of plants, which are collected and transformed by bees. It is deposited, dehydrated, stored and left in the honeycomb to mature. Honey is one of the main source of energy for bees, containing mainly carbohydrates and minor substances such organic acids, proteins, minerals and vitamins (Jones, 2009; Quicazán and Zuluaga, 2016). Knowledge of honey

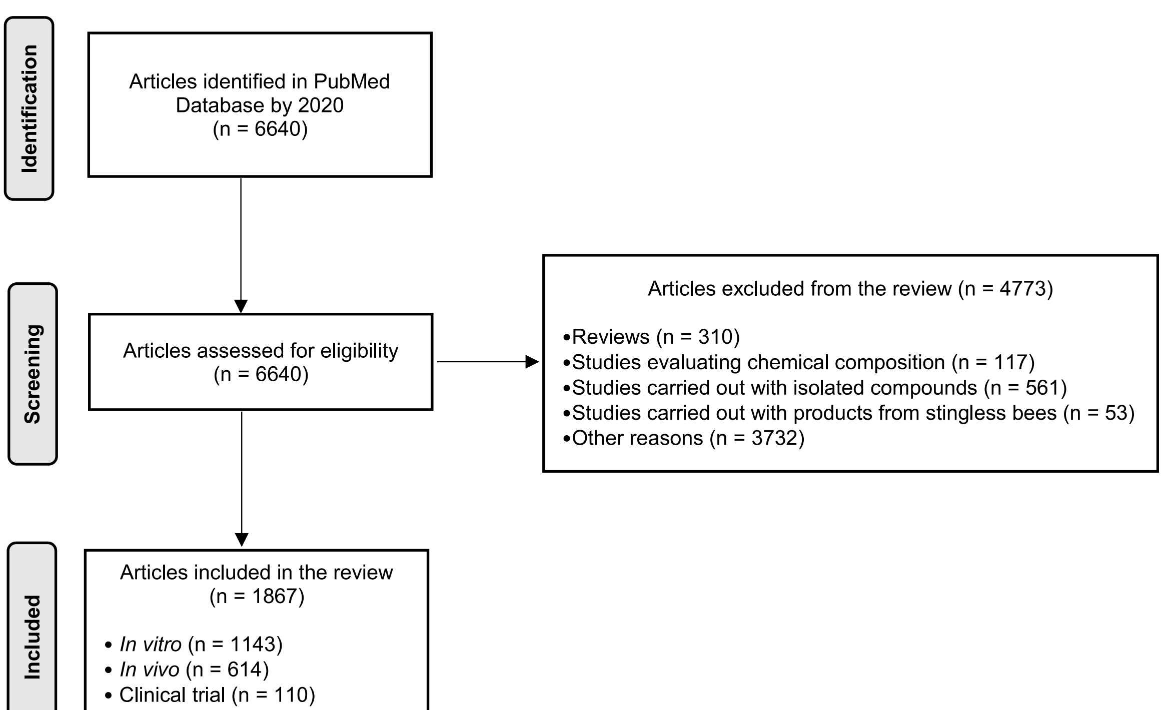

Fig. 1. Flowchart for identifying and selecting the articles included in the review.

Table 1
Number of published articles related to bee products' biological activity, assessing in vitro and in vivo assays and clinical trials.

Bee product	Number of manuscripts	Included manuscripts*	In vitro assays	In vivo assays	Clinical trials
Honey	1418	248	172	51	25
Propolis	1545	987	655	309	23
Bee venom	3020	453	232	175	46
Bee pollen	223	48	26	22	0
Bee bread	198	5	5	0	0
Royal jelly	173	93	49	38	6
Beeswax	40	28	4	14	10
Apilarnil	10	10	–	5	–

* Only manuscripts dealing with the biological activity of each product were included, discarding those related to their chemical composition, reviews, research focused on isolated compounds and products from stingless bees.

composition according to the phytogeography where it was produced guarantees its authenticity and adds value to the food. The huge amount of honey-related data requires multivariate statistical analysis specifically to discriminate the origin of honeys (Quicazán and Zuluaga, 2016).

Within the hive, bees store their food and the queen lays hundreds of eggs daily, which become larvae, pupae and adult bees. Thus, the hive needs to be protected from predators and microorganisms. Propolis is involved in the beehive protection. It is composed of substances secreted by plants, exudates and resins, and this material is chewed, mixed with salivary secretions, and wax. Propolis is applied in thin layers on the inner walls of the hive to sterilize the environment, reducing the entry of the hive, covering cracks or openings, and strengthening the thin edges of the combs. Propolis is also used to embalm dead invaders within the hive. Therefore, propolis is a building material and a protective agent in the hive, playing an important role in the social immunity of bees (Bankova et al., 2016; Goblirsch et al., 2020).

In addition to the protection afforded by propolis, bees produce bee venom (BV) and sting through their inoculation device (a stinger). The stinger has evolved from the laying apparatus and only females are able to sting. BV is a complex material produced by the poisonous gland located in the abdominal cavity (Ali, 2012).

Bee pollen is the main source of proteins for bees. This product results from the agglutination of flower pollen by worker bees using nectar and salivary substances, which is deposited inside the hive. In addition to protein, pollen has a nutritional source of lipids, vitamins, minerals and certain carbohydrates (Serra Bonvehí and Jordá, 1997; Campos et al., 2016). Bees also produce a pollen-based product that, after collection and storage inside the hive, is transformed into "bee bread" by microorganisms through a lactic acid fermentation (Del Risco-Ríos et al., 2012; Anderson et al., 2014).

Worker bees produce royal jelly (RJ) through their hypopharyngeal and mandibular glands. RJ is a viscous substance, whitish to yellow, and with an acidic taste. Its complex composition includes proteins, fatty acids, sugars, and minerals (Simúth, 2001). RJ is used for a short period in the diet of larvae and for the entire life of the queen (Campos et al., 2016).

Bees produce beeswax as a construction material for their combs using the ceriferous glands located in the ventral part of the abdomen. The honeycomb is intended not only for storage of honey, pollen and RJ but also for laying eggs and for young bee development (Eshete and Eshetie, 2018). Wax production is at its highest in the growth phase of the colony. It contains mainly esters of higher fatty acids and alcohols. Besides esters, beeswax contains small amounts of hydrocarbons, free acids, alcohols and other substances (Bognadov, 2004).

Apitherapy in a nutshell

The beginning of the relationship between men and bees may have evolved in the early days of our ancestors, and the interaction with bees must have occurred even before *Homo sapiens* (Boesch et al., 2009). Ethnographic documents and rock art demonstrated that non-human primates employed tools to access the hives (Crittenden, 2011). In fact, the history of bees and their products can be traced back to archeological excavations, rupestri paintings, hieroglyphics, and temples (Zhu and Wongsiri, 2008; Crittenden, 2011).

The first documentation of beekeeping started when humans began raising their own bees, engineering artificial cavities in which bees could live and make their products. Honey, pollen and bee larvae were part of the diet of the first members of the genus *Homo* (Crittenden, 2011). Primitive men learned to look for hives and were certainly the first to receive apitherapy due to bee stings. Honey has been used for thousands of years, as observed in several religious texts including the Veda (Hindu scriptures), Quran and the Bible (Ali, 2012).

Apitherapy has been empirically explored in ancient China and Egypt. Romans and Greeks used bee products for medicinal purposes. It is traditionally recognized in many countries, like Romania, Lithuania, Slovenia, Bulgaria, Germany, Switzerland, Nigeria and others (Ayansola et al., 2012; Trumbeckaite et al., 2015). The current level of medical science and technology is not available for everyone everywhere. Apitherapy is accessible for human health and it is worth popularizing and spreading apitherapy as it is a simple and effective method of heath care, as a bee colony is like a "pharmaceutical factory" (Zhu and Wongsiri, 2008).

Apitherapy is based on the traditional knowledge provided by some civilizations aiming to restore body homeostasis. It is a branch of alternative medicine and, although the value of allopathic medicine is well recognized, the approach of apitherapy on healing is integrative (Habryka et al., 2016). It may comprise the use of hive products alone or in combination with medicinal plants and their derivatives (api-pharmacopeia), as well as clinical protocols incorporating the use of the api-pharmacopeia and/or the bees (api-medicine) (Gupta and Stangaciu, 2014). Apitherapy has been applied to treat illnesses (arthritis, infections, multiple sclerosis) and their symptoms, as well as pain and injuries like wounds and burns; however, the treatment requires patience and perseverance and must be adapted to each individual, due to different individual biological reactions (Habryka et al., 2016).

Hellner et al. (2008) reported the use of apitherapy among German beekeepers, describing the guidelines proposed by Dr Stefan Stangaciu, one of the protagonists in the apitherapy field. According to Dr Stangaciu's recommendations, it is important to test for allergies due to bee products. Small doses can be used to treat bee product allergies (as in pollen, bee venom and honey allergy). The dosage of bee products must be gradually increased and established with accuracy according to the age, weight, condition of each patient, and time of application. Different vehicles can be used to reach the affected area: liquids (tea, water, juices), creams/ointments, suppositories, injections and through inhalation. The duration of treatment may vary according to the patient's biorhythm and disease. Each patient is considered unique and therefore receives an individual treatment, especially to treat chronic diseases, what requires perseverance. It is assumed that bee products have a synergistic effect, especially when combined with a healthy lifestyle; moreover, not all people react similarly to the treatments and a gradual approach is encouraged (Hellner et al., 2008).

In Brazil, apitherapy tends to be an expanding practice and has become part of the National Policy of Integrative and Complementary Practices (PNPIC – Ministry of Health, Regulation 702, March 21, 2018). PNPIC is in agreement with the Ministry of Health and the influence of international parameters, national health conferences related to social demands, teaching and research, entry on the political agenda, federal leadership and challenges to institutionalization. PNPIC has expanded since its institutionalization in 2006, monitoring Brazilian practices.

According to data obtained in 2019, PNPIC was available in 17,335 services of the Health Care Network supplied in 4297 counties (Brasil, 2020a).

PNPIC aims to stimulate natural mechanisms to prevent disease and promote health through effective and safe practices, with the goal of integrating the human being with the environment and society as a holistic approach. PNPIC comprises apitherapy, homeopathy, medicinal plants and herbal medicines, traditional Chinese medicine, acupuncture, anthroposophical medicine, and other practices adopted in the national public health system (SUS) (Brasil, 2021).

Resistance from the biomedical society and disputes of interest challenged this process in Brazil. Despite the advance in the dissemination of the practices, the actions of the federal management were not accompanied by significant changes in the training of professionals and in the hegemonic health practice (Silva et al., 2020a).

Recently, in the State of Santa Catarina (south of Brazil), health professionals were recommended to apply integrative and complementary treatments (including apitherapy) to treat patients with the coronavirus disease 2019 (COVID-19) during the pandemic, as a complementary, individualized and moderate intervention (Brasil, 2020b).

Apitherapy is a growing practice worldwide and effective in alleviating a wide spectrum of diseases (Grassberger et al., 2013; Basa et al., 2016). Currently, apitherapy has been proven as a scientific-based practice since bee products may provide nutrients and active substances, restoring health and vital energy. In general, beekeepers do not consider themselves as apitherapists, although most of them have reported benefits using bee products (Hellner et al., 2008).

Depending on the source, the chemical composition of bee products may vary and consequently their therapeutic actions (Chen et al., 2000; Aljaghwani et al., 2021).

The quality of the products used in apitherapy is subject to factors such as soil, climate, methods of harvesting and storage, and the botanic sources. Thus, it is important to establish the conditions in which the products were obtained, to not expose the patient to risks of contamination and to improve the results.

However, important questions can be raised concerning apitherapy. How were parameters established by civilizations using the bee products, with regard to their origin, amount or concentration, type of extraction or preparation, and other practical issues? Apitherapy probably started empirically and led to interesting applications. The traditional knowledge is extremely important and useful, and has been the basis of scientific research. On the other hand, as research has advanced a lot in recent decades, has this scientific knowledge been used by apitherapists? How have apitherapists standardized the use of bee products and their applications? Although people think that natural products do not pose risks, are there adverse effects or any interaction between bee products and drugs commonly used to treat diseases?

Once again, we highlight the need for establishing a better communication between beekeepers, apitherapists, researchers, nutritionists, physicians, sellers and consumers of bee products.

Bee product research and its application in apitherapy

Honey

Honey is a viscous and aromatic product, with a variable composition depending on its botanical source. Bees utilize plants medicinal properties to make honey; therefore, the identification of honey is closely related to its botanical origin (Stangaciu et al., 2015). In general, honey is composed of sugars (fructose, glucose, sucrose, maltose, isomaltose, maltulose, threalose, maltotriose, melezitose and others), water, and enzymes (invertase, α- and β-amilase, glucose oxidase, catalase). Proteins and amino acids are found in low quantities, as well as vitamins (mainly B and C), some minerals (Na, K, Ca, Mg, Fe, Cu, Mn and Zn), pollen grains and other phytochemicals. Some characteristics such as color, smell and flavor depend on floral sources, geographic regions, seasonal factors and bee species involved in honey production. It is also affected by climate conditions, handling and storage (Silva et al., 2016; Almeida-Muradian et al., 2020).

People around the world have empirically used honey as a medicine to treat a variety of diseases. Studies have demonstrated the nutritional value of honey and its therapeutic properties, such as antioxidant, antimicrobial, antiparasitic, anti-inflammatory, antitumor, cardiovascular protector and mainly as a healing product (Khan et al., 2017).

One of the most explored characteristic of honey for medicinal purposes is its antioxidant action (Dżugan et al., 2018), due to the activity of polyphenolic compounds (phenolic acids and flavonoids), vitamins C and E, and enzymes (catalase, peroxidase). Polyphenolic compounds are also involved in honey anti-inflammatory and anticancer effects (Ranneh et al., 2019; Waheed et al., 2019; Biluca et al., 2020).

Honey antibacterial potential is closely linked to its low water content and the presence of glucose oxidase, preventing bacterial growth, even destroying microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from infected wounds (Mama et al., 2019).

Swellam et al. (2003) investigated honey effects against bladder cancer *in vitro* and *in vivo*: honey reduced the proliferation of T24 and MBT-2 cell lines *in vitro*; moreover, honey both intralesional injected or orally given inhibited tumor growth in mice.

Honey has been indicated alone or in combination with other products such as pollen and propolis. El-Guendouz et al. (2017) analyzed the effects of *Capparis spinosa* honey and propolis administration for 21 days, verifying that this combination exerted a diuretic action in rats.

Clinical trials revealed honey capacity for wound healing. Moghazy et al. (2010) investigated honey potential as a topical treatment for diabetic foot ulcer (DFU). Diabetic individuals with infected foot wounds received honey dressings for 3 months, resulting in significant healing of mild ulcers but not of ulcers with exposed bone and insufficient vascularity. This was attributed to honey antimicrobial effects creating a barrier and preventing the entry of microorganism, stimulating the epithelialization and leading to rapid absorption of edema from the wound and surrounding area.

Imran et al. (2015) evaluated the healing effect of Beri honey-impregnated dressing on DFU (179 participants in the honey-dressing group and 169 in the control). The honey-treated group showed a more efficient healing (75.97% over an average of 18 days) compared to the saline control (57.39% over an average of 29 days).

Malhotra et al. (2017) carried out a randomized study to assess the role of Manuka honey in surgical wounds on the eyelids of 55 patients for 4 months. Scars treated with Manuka honey had less stiffness and less pain than controls. In addition, patients treated with Manuka honey exhibited a decreased tendency for skin distortion and the scar was less palpable.

Nijhuis et al. (2012) compared the clinical effect of two topical treatments in patients with symmetrical intertrigo in large skin folds: a standard therapy with zinc oxide ointment and a honey cream. Both treatments were effective; however, honey-treated patients reported less complaints of itching.

Fakhr-Movahedi et al. (2018) conducted a clinical trial with 68 hospitalized patients with acute coronary syndrome in Iran, verifying the effects of a milk-honey mixture twice a day for three days improving sleep quality due to the glucose content in honey that can lead to tryptophan absorption in the brain.

Yousaf et al. (2019) determined the antibacterial activity of Pakistan Beri honey in 90 patients with infected wounds compared to silver sulfadiazine. Beri honey not gamma-irradiated improved wound healing better than gamma-irradiated Beri honey and silver sulfadiazine, decreasing the bacterial load and reducing the length, width and depth of patients' wounds. The authors attributed the antibacterial properties of honey to the acidic nature presence of hydrogen peroxide and high osmosis.

Besides exerting an effective healing effect, honey displays an antibacterial action, promoting positive effects on infectious diseases such as mucositis. Oral mucositis is one of the most worrying side effects treating head and neck cancer with radiotherapy. Jayalekshmi et al. (2016) analyzed the effect of honey (15 ml) on oral mucositis in 28 patients after radiotherapy. A significant difference in the degree of oral mucositis was observed between the experimental and control group after 4, 5 and 6 weeks. Moreover, 64.28% in the control developed grade III oral mucositis *versus* 7.14% in the experimental group.

Charalambous et al. (2018) demonstrated the efficiency of a thyme honey rinse to control radiation-induced oral mucositis in 72 patients with head and neck cancer. Weekly evaluations were carried out for 7 weeks and repeated 6 months later, revealing that thyme honey exerted beneficial effects on oral mucositis due to cellular and tissue differentiation restoring the integrity of the epithelium and contributing to patients' quality of life.

Ramasamy et al. (2019) evaluated 40 participants with head and neck cancer, completing chemotherapy and/or radiotherapy in Malaysia and receiving Tualang honey daily (20 mg) for 8 weeks. Honey improved their fatigue and quality of life.

Honey also exerts cardiovascular protection due to its polyphenols by improving endothelial function, inhibiting platelet aggregation, reducing inflammatory responses and oxidation of low-density lipoprotein (LDL), acting as an antioxidant and reducing oxidative stress (Hossen et al., 2017).

Kas'ianenko et al. (2011) evaluated the effectiveness of treating patients with atherogenic dyslipidemia applying bee products (honey, pollen, and bee bread). Honey in combination with pollen exerted a hypolipidemic effect: the total cholesterol decreased by 18.3% and LDL by 23.9%.

Rasad et al. (2018) conducted a clinical trial to investigate the effect of honey consumption compared to that of sucrose on the lipid profile in 60 healthy young individuals. The honey-treated group received 70 g of honey/day and the second group received 70 g of sucrose/day. Fasting blood sugar, systolic blood pressure and basal diastolic blood pressure did not differ between the groups but honey consumption decreased total cholesterol, triglycerides (TG) and LDL and increased the high-density lipoprotein (HDL), while sucrose intake increased total cholesterol, TG and LDL and decreased HDL. Honey contains antioxidants such as beta-carotene, vitamin C, uric acid and minerals that play a role in lipid metabolism, increasing the catabolism of fats and consequently reducing their serum levels.

Ab Wahab et al. (2018) investigated the long-term effects of 20 g/day of Tualang honey *versus* 20 g/day of honey cocktail (mix of honey, bee bread and royal jelly) on cardiovascular markers and anthropometric measurements of 100 women in post-menopause. The parameters were analyzed after 6 and 12 months. After 12 months, there was a significant decrease in diastolic blood pressure and a reduction in fasting blood sugar in the Tualang honey-treated group compared to the honey cocktail.

In addition, honey has been used in cosmetics, facial wash, skin moisturizer, and hair conditioner, and for treating pimples (Ediriweera and Premarathna, 2012).

Table 2 shows honey effects in some clinical studies.

With regard to the use of honey in apitherapy, data indicated honey potential for ulcer and wound healing, treatment of oral mucositis and cardiovascular protection. Honey exerts an anti-inflammatory action and promotes tissue reepithelialization, accelerating healing and pain relief. Honey can be a substrate for probiotic bacteria and displays benefits for the gut microbiota modulation (Mohan et al., 2017). Honey has been also employed to treat eye diseases, piles, eczema, throat infection, cough, bronchial asthma, tuberculosis, hepatitis, dizziness, fatigue, constipation, worm infestation, gastrointestinal diseases. More recently, the positive effects of honey treating neurological diseases, diabetes mellitus, and cancer have been reported (Fratellone, 2015; Samarghandian et al., 2017).

However, one may verify that there is no definitive conclusion about the origin of honey, intake period, amount, times a day and other conditions to obtain the same effects.

Propolis

Propolis is a resinous product made by bees from different parts of plants, such as tree bark and leaf buds, mixing salivary secretions and beeswax. The Greek word propolis means "defense of the city", because bees use it to seal holes and protect the hive against the entrance of water and intruders (Burdock, 1998).

The biological activities of propolis vary according to its chemical composition (Sforcin, 2016), which is extremely complex and depends on the botanical source and the geographical location where it was produced (Bankova et al., 2016). Numerous botanical species have been described as propolis sources, such as poplar, birch, palm, pine, alder, willow, *Baccharis dracunculifolia* and *Dalbergia ecastophyllum* (Toreti et al., 2013). Its composition may include aromatic aldehydes, alcohols, amino acids, esters, diterpenes, sesquiterpenes, lignans, fatty acids, vitamins and minerals (Braakhuis, 2019).

Propolis has been used in folk medicine since ancient times for a wide variety of purposes. Egyptians used propolis to embalm cadavers and prevent putrefaction. Greeks and Romans used propolis as a mouth disinfectant and for treating wounds, due to its antiseptic and healing properties. Incas used propolis as an anti-pyretic agent; Persians used it to treat eczemas, myalgia, and rheumatism. During the Second world war, propolis was used to treat tuberculosis and for wound healing (Silva-Carvalho et al., 2015).

The greatest amount of scientific work on bee products is about propolis. In fact, propolis has never gone out of fashion over time and is currently employed in cosmetics, health food and beverages, extracts,

Table 2
Clinical trials with honey: main approaches, types of trial, subjects and groups, types of intervention and main outcomes.

Approach	Trial	Number of subjects/ groups	Honey intervention	Main outcomes	Authors
Diabetic foot ulcer	Randomized	Honey dressing (n = 179) Saline dressing (n = 169)	Honey dressing 120 days	↑ healing efficiency	Imran et al. (2015)
Eyelid surgical wound healing	Randomized single-blind	n = 46 (29 women, 17 men)	Manuka honey twice a day 6 weeks	↓ tendency for skin distortion scar less palpable	Malhotra et al. (2017)
Cardiovascular parameters and anthropometric measurements of postmenopausal women	Randomized double-blind two-armed parallel	Tualang honey (n = 49) Honey cocktail (n = 49)	Tualang honey 20 g/day honey cocktail 20 g/day 6 and 12 months	↓ diastolic blood pressure ↓ fasting blood sugar	Ab Wahab et al. (2018)

capsules and mouthwash.

In vitro studies using cell culture assays revealed an abundance of propolis properties, such as antioxidant, antimicrobial (especially its antibacterial action), antitumor, anti-inflammatory and immunomodulatory, among others (Sforcin, 2016; Santiago et al., 2018; Conte et al., 2021a). Lately, propolis potential to be included in the treatment of COVID-19 has been reported, including several mechanisms and perspectives (Berretta et al., 2020; Ripari et al., 2021; Silveira et al., 2021).

Regarding *in vivo* studies, a wide variety of propolis activities has been described, *e.g.* antipsoriatic (Ledón et al., 1997), estrogenic (Song et al., 2002), antihypertensive (Mishima et al., 2005a), immunomodulatory (Sforcin et al., 2005; Orsatti et al., 2010), analgesic (Paulino et al., 2006), hepatoprotective (Bhadauria et al., 2008), antidiabetic and hypolipidemic (El-Sayed et al., 2009), anti-inflammatory (Butnariu et al., 2011), antitumor (Badr et al., 2011), anti-nephrotoxic (Garoui et al., 2012), antidepressant and anxiolytic (Reis et al., 2014), anti-allergic (Yasar et al., 2016), neuroprotective (Nanaware et al., 2017), antioxidant (Bazmandegan et al., 2017), antiurolithiasis (López-Cabanillas et al., 2017), wound and burn healing (Balata et al., 2018), photoprotective (Batista et al., 2018) and others.

Propolis has been also studied using different models of diseases or biological disorders, including asthma (Sy et al., 2006), insulin resistance (Zamami et al., 2007), chronic gastric ulcers (Belostotskiĭ et al., 2009), sciatic nerve injury (Barbosa et al., 2016), lung damage (Saddiq et al., 2016), colitis (Wang et al., 2018), chronic apical periodontitis (Yuanita et al., 2019), ovary injury (Geyikoglu et al., 2019), cerebral injury (Abdel-Rahman et al., 2020), among others.

In this review, we focused on clinical trials using propolis as a preventive or therapeutic intervention for different biological purposes. Clinical trials carried out with propolis started in dentistry (Poppe and Michaelis, 1986; Silveira et al., 1988; Gafar et al., 1989). Oral hygiene has a wide influence on health and quality of life, since toxins and inflammatory mediators may migrate from the infectious site into the bloodstream, leading to diseases. There are numerous toothpastes and mouthwashes with different compositions on the market and natural ingredients are gaining popularity, especially propolis, which has a positive impact on oral hygiene (Piekarz et al., 2017).

Mahmoud et al. (1999) and Askari and Yazdani (2019) evaluated propolis action against dental hypersensitivity (DH), one of the most frequent complaints in dental practice, characterized by acute pain. The former study was carried out with 26 women followed up for 4 weeks after propolis use, obtaining a high satisfactory rate (85%) on DH (Mahmoud et al., 1999). Askari and Yazdani (2019) studied 67 women and 29 men divided into 4 groups of treatment lasting 3 months: 1) 10% ethanolic extract of propolis, 2) 30% ethanolic extract of propolis, 3) Single Bond Universal dentin bonding agent, 4) placebo (distilled water). Both propolis extracts (10 and 30%) were equally effective and more efficient than placebo. Although dentin bonding exerted a fast relieving effect on DH, it was equally efficient as propolis in the long-term. A possible mechanism involved in propolis action on DH is the occlusion of the dentinal tubule (Kripal et al., 2019).

Santos et al. (2008) analyzed the clinical efficacy of a Brazilian propolis gel (10% ethanolic solution) in patients with denture stomatitis. The volunteers received a miconazole gel – Daktarin ($n = 15$) or a propolis-based gel ($n = 15$) applied 4 times/day for a week. Due to its anti-inflammatory activity, propolis was effective in treating denture stomatitis and had a similar efficacy to Daktarin: all patients presented a complete clinical remission of palatal edema and erythema.

Dental implants and oral surgeries favor the invasion of bacteria and inflammatory reactions. Brazilian propolis was also evaluated in toothpaste or gel formulation, both as a 3% ethanolic extract. Morawiec et al. (2013) analyzed patients who received implant-supported oral rehabilitation, using a propolis-based toothpaste ($n = 8$) or placebo ($n = 8$). The toothpaste was applied twice a day for at least 2 min and subjects were followed-up for 8 weeks. Propolis improved oral health, decreased the approximal plaque index (API), and promoted qualitative/quantitative changes in oral bacteria. Morawiec et al. (2015) evaluated the propolis-based gel during postoperative procedure, including the third molar extraction and short endosseous implant installation. Subjects in propolis ($n = 7$) or placebo ($n = 7$) groups were followed up for 5–6 weeks. Propolis reduced *Neisseria* spp. and *Bifidobacterium* spp., and eliminated *Streptococcus acidominimus, Streptococcus oralis, Staphylococcus epidermidis, Veillonella parvula, Bifidobacterium breve, Bifidobacterium longum*, and *Lactobacillus acidophilus*. These studies suggest propolis as a natural alternative or additive to chemicals for individuals with a high risk of periodontal problems associated to implants and in the postoperative period of oral surgery procedures, probably due to propolis' antimicrobial and anti-infllammatory properties (Morawiec et al., 2013, 2015).

The effects of a toothpaste containing ethanolic extract of Polish propolis 1.5% associated with *Melaleuca alternifolia* oil 1% was assessed for 4 weeks in patients ($n = 25$) compared to placebo ($n = 26$). The toothpaste promoted a significant API reduction and modified the sulcus-bleeding index. Besides, it maintained the microbiome balance and eliminated microorganisms causing diseases in the gingiva and tooth tissue (Piekarz et al., 2017).

Santiago et al. (2018) evaluated a mouthwash containing propolis compared to chlorhexidine (CHX) in the control of dental plaque. Subjects were divided into four double-blind groups ($n = 10$): 1) placebo mouthwash; 2) mouthwash containing propolis 2.6%; 3) mouthwash with CHX 0.12%; 4) mouthwash with CHX 0.06% + propolis 1.3%. After assessment of oral health, dental plaques were removed and participants were prescribed to use the mouthwash the very same night. The rinses were performed daily after the last tooth brushing for 1 min during 14 consecutive nights. Individuals who used the mouthwash containing propolis in combination or not with CHX showed a similar Patient Hygiene Performance (PHP) index to CHX alone. Moreover, this product exerted an antibacterial action *in vitro*, exhibiting a positive action to control causative agents for caries.

Propolis is also effective in child dental treatment. Neto et al. (2020) analyzed 24 children without caries, using a Brazilian propolis varnish 1%, 2.5%, 5% or 10%. All treatments reduced *Streptococcus mutans*, achieving the best result at 2.5%. Propolis can eliminate microorganisms directly, damaging the cytoplasmic membrane, affecting the permeability of cell membrane, inhibiting microorganism motility and viability, inhibiting nucleic acid and protein synthesis, affecting microorganisms' growth and activity (Silva-Carvalho et al., 2015; Oryan et al., 2018). Besides, propolis may destroy microorganisms indirectly by stimulating the immune system to eliminate them (Sforcin and Bankova, 2011). Conti et al. (2016) reported that propolis increased the bactericidal activity of dendritic cells against *Streptococcus mutans*.

Propolis intervention in diabetic subjects has been also investigated. Henshaw et al. (2014) investigated propolis effects on DFU healing, evaluating 24 subjects with diabetes mellitus type 1 or 2, presenting a DFU for ≥4 weeks. Aqueous propolis was applied topically for 6 weeks or less if the ulcer healed. After 1 and 3 weeks, propolis reduced the wound area. After 4, 5 and 6 weeks, the percentage of patients with ulcers fully healed was significantly higher in the propolis group. No adverse effects were reported, suggesting that topical use of propolis is well tolerated and enhance wound closure. Some mechanisms of propolis action in wound healing have been reported: reduced concentration of free radicals; modulation of fibronectin expression; increased collagen; activation of anti-inflammatory and anti-oxidant pathways; inhibition of myeloperoxidase activity; acceleration of tissue repair by stimulating glycosaminoglycan leading to wound closure (Oryan et al., 2018).

Zhao et al. (2016) and Gao et al. (2018) conducted clinical trials with type 2 diabetes mellitus (T2DM) patients using 900 mg propolis/day for 18 weeks. Although different samples were tested, propolis increased the levels of reduced glutathione (GSH) and IL-6, decreasing lactate dehydrogenase (LDH). Zhao et al. (2016) observed an increased IL-1β and reduced TNF-α and carbonyls levels. Among the studies' limitations, the authors speculated a too high dose of propolis was used and appropriate doses need to be investigated before clinical applications (Zhao et al., 2016; Gao et al., 2018).

Afsharpour et al. (2019) evaluated 62 patients with T2DM using a higher propolis dose (1500 mg/day) for 8 weeks. After treatment, fasting blood sugar, two-hour postprandial glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and hemoglobin A1c (HbA1c) decreased in the propolis group. In addition, propolis increased the total antioxidant capacity (TAC), glutathione peroxidase and superoxide dismutase (SOD). Propolis may control glycemic levels due to the stimulation of glucose uptake by peripheral tissues, inhibiting its release into the bloodstream and reducing its absorption in the gut, probably due to flavoinoids and their antioxidant activity. Flavonoids increase the production of antioxidants and interact with free radicals, leading to more stable and less reactive radicals. Other mechanisms presented by propolis include the reduction of inflammatory mediators, increased adiponectin levels and inhibition of carbohydrate digestive enzymes, such as α-amylase and α-glycosidase (Afsharpour et al., 2019). These findings open perspectives to include propolis as a supplement for T2DM patients, aiming to increase the standard drug's effectiveness and improve the antioxidant status.

Zakerkish et al. (2019) evaluated T2DM patients randomized in propolis (1000 mg/day – $n = 50$) or placebo ($n = 44$) groups for 90 days. Propolis reduced HbA1c, insulin, HOMA-IR, homeostasis model assessment of β-cell function, high sensitive C-reactive protein (hs-CRP) and TNF-α. Besides, a reduced ALT, AST and urea was observed in the propolis group, with increased HDL levels. These findings indicated that Iranian propolis displayed beneficial effects on T2DM individuals and may be useful for preventing liver and renal dysfunction.

Other studies involving inflammatory conditions have been also reported. Khayyal et al. (2003) analyzed patients with mild to moderate asthma suffering for 2–5 years. They received propolis ($n = 22$) or placebo ($n = 24$) sachets suspended in water once a day for 2 months. Each sachet contained constituents equivalent to 2 ml of 13% aqueous propolis extract. Both treatments decreased prostaglandins and increased the anti-inflammatory cytokine IL-10. Propolis reduced the incidence and severity of nocturnal attacks and improved the ventilatory function, what was associated with reduced levels of TNF-α, ICAM-1, IL-6, IL-8, leukotriene D4. As propolis decreased these mediators production, it may be effective as an adjuvant therapy and may be useful during the routine management of bronchial asthma.

Gambelunghe et al. (2003) investigated whether propolis and honey could influence testosterone urinary concentration. Healthy male subjects were divided into a group consuming 4 tablets of propolis (1280 mg) + 20 g of honey every morning for 21 days ($n = 10$) and a group without any intervention ($n = 10$). No alterations were seen in testosterone levels, concluding that propolis/honey consumption at the doses commonly used as an oral supplementation did not affect hormonal equilibrium in men.

Imhof et al. (2005) reported an improvement in vaginal smears and well-being of patients with recurrent vaginal infections ($n = 54$) after using a 5% aqueous propolis solution as a vaginal douche for 7 days (30 ml/day), suggesting that propolis may be an alternative for chronic vaginal infection. García-Larrosa and Alexe (2016) reported that an intervention with reticulated gelatin (125 mg), hibiscus (100 mg) and propolis (100 mg) twice a day for 5 days ($n = 30$ vs. 30 placebo) improved urinary tract infection and reduced the need of antibiotic treatment. As above mentioned, propolis has a remarkable antimicrobial action. Its isolated components may be responsible for its specific activities (*e.g.* lignans are mainly associated with antibacterial activity, benzoic acid with antimycotic action, quercetin with antiviral action, while caffeic acid is associated to all these properties). Antibacterials and antimycotics successfully eliminate harmful microorganisms; however, they may be associated with multidrug resistance, side effects and high recurrence rates, making propolis an interesting alternative for treating infections (Imhof et al., 2005).

According to Jasprica et al. (2007), propolis effect on human health seems to be time and gender-dependent. Healthy nonsmoking adults were randomized in a control ($n = 7$ men and 13 women) or study ($n = 12$ men and 15 women) group. The study group received a powdered propolis extract (0.65 g of dry propolis containing 2.5% of total flavonoids – 3 doses/day). In men, propolis decreased malondialdehyde concentration after 15 days, increased SOD activity and changed red blood cell parameters (red blood cell count, hemoglobin, mean corpuscular volume, red cell distribution width) after 30 days of treatment. No alterations were seen in women, what can be explained by hormonal variation and uncoordinated menstrual cycles in volunteer women, since estrogens are also powerful antioxidants (Jasprica et al., 2007).

Ishikawa et al. (2012) evaluated the effects of Brazilian propolis capsules (containing 165 μmol artepillin C and 150 μmol other phenolics) on the risk of developing colon cancer. Patients with adenoma polyps removed recently from the colon were randomized in propolis ($n = 15$) or placebo ($n = 16$) groups, receiving three capsules/day for 3 months. Propolis increased creatine phosphokinase activity in the blood and cyclin D1 mRNA levels (a marker of tumor cell proliferation) in the sigmoid colon mucosa. Data showed no evidence that propolis was effective in preventing alterations during the early stages of colon cancer. *In vitro* studies have demonstrated the antitumor action of propolis and its constituents through different mechanisms. It inhibits cell growth and proliferation; increases the percentage of cells in the G0/G1 phase; induces apoptosis; regulates cyclin D1 and B1 and increases the cyclin dependent kinase inhibitors p21, p27, and p16; promotes nucleosomal DNA fragmentation; induces antiangiogenic effects; inactivates the signaling pathways ERK1/2 and PAK1, and reduces cell migration (Silva-Carvalho et al., 2015). These findings reinforce the importance of communication between basic research and clinical practice.

Veiga et al. (2018) evaluated the antifungal action of propolis in patients with mild to moderate toenail onychomycosis, with no previous antifungal treatment. Volunteers ($n = 16$) were instructed to thoroughly clean, brush and polish their nails, applying two drops of a 10% ethanolic extract of propolis on the affected area twice a day. After 6 months, 56.25% of the patients presented a complete mycological and clinical cure, 31.25% showed partial improvement and 12.5% showed no improvement. In addition to its antifungal activity, propolis was able to reach the deep layers of the nail, favoring the treatment of onychomycosis. The therapeutic effectiveness of topically medicines is related to their diffusion rate, as filamentous fungi reach the deepest layers of the nail. Propolis is an adhesive material, prolonging its interaction with the substrate. Moreover, the polarity and chemical composition of propolis allow for good retention and permeation. Few options are available to treat onychomycosis and a low efficacy of medication is reported, indicating promising research on propolis in this field.

Regarding propolis antiviral action, Vynograd et al. (2000) verified that patients with recurrent chronic genital herpes using a 3% propolis ointment ($n = 30$) 4 times/day for 10 days presented better results of healing the genital lesions and reduction of local symptoms, compared to the group treated with acyclovir ($n = 30$) and placebo ($n = 30$). Samet et al. (2007) observed a less frequent recurrence of aphthous stomatitis in patients using propolis (500 mg/day – $n = 10$) for 6 months compared to placebo ($n = 9$) and a better quality of life.

Our group evaluated propolis effects on asymptomatic HIV-infected people treated with antiretroviral therapy. The patients received capsules of propolis (500 mg/day; $n = 20$) or placebo ($n = 20$) for 3 months. Data indicated that propolis intake is safe and may be an alternative for improving the immune response and reducing inflammation in asymptomatic HIV patients (Conte et al., 2021b; Tasca et al., submitted).

In addition to the above-mentioned benefits, a recent study evaluated a possible interaction between commonly used drugs and a Brazilian propolis extract. Healthy nonsmoking volunteers ($n = 16$) ingested propolis (125 mg/8 h) for 15 days, totalizing 375 mg/day. Before and after propolis intake, the subjects were orally given a capsule containing caffeine (10 mg), losartan (2 mg), omeprazole (2 mg), metoprolol (10 mg), midazolam (0.2 mg) and fexofenadine (10 mg). Propolis did not alter the major CYP enzymes involved in drug metabolism, and the magnitude of the changes in the area under the plasma concentration-time curve values were <20%, considered safe regarding potential interactions involving such enzymes (Cusinato et al., 2019).

Zhu et al. (2018) evaluated elderly people living at a high altitude ingesting six capsules/day of propolis (0.83 g) or a placebo for 24 months, assessing 30 patients in each group. Propolis improved the Mini-Mental State Examination scores and decreased inflammatory cytokines. Indeed, IL-1β, TNF-α and IL-6, are associated with increased cognitive decline, suggesting that early intervention of propolis may reduce inflammation and protect against cognitive decline.

Silveira et al. (2019) observed a lower proteinuria and urine excretion of monocyte chemoattractant protein-1 (MCP-1) levels in patients with chronic kidney disease (CKD) using propolis (500 mg/day for 12 months, $n = 18$ propolis *vs.* 14 placebo). Mechanisms related to propolis antiproteinuric effects have not been fully elucidated but they may be associated with lower oxidative stress and reduced renal infiltration by macrophages. MCP-1 high levels are correlated with CKD progression and its urinary excretion is associated with inflammatory aggression in renal tissue. This data indicates propolis benefits for patients with CKD.

Recently, Silveira et al. (2021) demonstrated the benefits of propolis as an adjunct treatment for adults hospitalized with COVID-19. Patients were allocated into three groups: the standard care ($n = 42$); standard care + propolis 400 mg/day ($n = 40$); standard care + propolis 800 mg/day ($n = 42$). Patients receiving propolis over 7 days had a follow up for a further 28 days after admission. Interestingly, the duration of hospitalization post-intervention was shorter in both propolis groups compared to control. In the higher propolis dose (800 mg/day), a lower rate of acute kidney injury was observed in comparison to controls, concluding that propolis may contribute in reducing the impact of COVID-19. Propolis components have inhibitory effects on ACE2 and TMPRSS2, which are required for SARS-CoV-2 entry into host cells. Its compounds also inhibit PAK1 pathway involved in the lung inflammation. In addition, propolis is a strategy to reduce the strong inflammation during the COVID-19 as it regulates Jak2/STAT3, NF-kB and inflammasome pathways, blocking the production of pro-inflammatory cytokines (Berretta et al., 2020).

Propolis has shown benefits for healthy individuals. Diniz et al. (2020) conducted a clinical trial with 34 participants receiving propolis (375 or 750 mg/day) during 7 days. Both propolis doses decreased 8-isoprostanes levels (a biomarker for lipid peroxidation) and increased SOD activity. Propolis 750 mg/day decreased 8-hydroxy-2′-deoxyguanosine (8-OHDG – a biomarker for DNA oxidation) and the dose 375 mg/day increased GSH, indicating propolis potential in reducing oxidative stress.

In general, propolis is considered as safe, well tolerated and nontoxic unless when administered in high amounts, with rare adverse effects (Braakhuis, 2019). Importantly, propolis is considered safer than many synthetic medicines (Toreti et al., 2013). However, cases of hypersensitivity, especially topical application, have already been reported and it is important to seek medical advice before using it (Braakhuis, 2019).

Based on these clinical trials, propolis is a promising product in the treatment of several diseases, as seen in Table 3. In addition, it is a low-cost treatment easily obtained and consumed. However, its effectiveness as an adjuvant treatment for some clinical conditions still needs investigation. It is noteworthy that its activity depends on its botanical origin, and that different compounds may be responsible for different activities. However, we strongly believe that propolis biological activities cannot be attributed to a specific compound, but to a synergism between its constituents.

In apitherapy, propolis has been used not only externally but also internally to treat a great variety of diseases due to its abundance of constituents. Propolis has been indicated for flu and cold symptoms, skin disorders (wounds, burns, and acne), psoriasis, otorhinolaryngologic, gynecologic, obstetric and proctologic diseases, preventing caries and treating gingivitis or stomatitis (Fokt et al., 2010). Propolis is indicated simultaneously with other bee products to reduce chronic inflammation. It can be used as an inhalation mixed with honey and saline solution. Medicine containing propolis exerts a positive effect in treating infections caused by antibiotic-resistant pathogens. Ayansola et al. (2012) reported that propolis has been used in Nigeria against measles and ringworm. Propolis has been used to heal wounds, bedsores and burns in post-traumatic and postoperative individuals (Fratellone, 2015; Habryka et al., 2016).

In general, it is safe and may be also consumed by healthy individuals or patients, showing no interaction with medications (Cusinato et al., 2019). However, no consensus can be seen on propolis preparation, doses, intake period and other conditions to obtain the same effects using propolis samples from different geographic regions.

Bee venom

BV is a transparent liquid utilized for the defense of the hive. Its composition comprises biologically active molecules like melittin, apamine, phospholipase 2, histamine, dopamine, norepinephrine, and others (Ali, 2012; Oršolić, 2012).

BV anti-inflammatory action has been reported due to its protective effects on the pathological mechanisms involved in liver injury (Park et al., 2011, 2012), airway inflammation (Choi et al., 2013) and inflammatory acne (An et al., 2014; Lee et al., 2014b), probably due to its

Table 3
Clinical trials with propolis: main approaches, types of trial, subjects and groups, types of intervention and main outcomes.

Approaches	Trial	Number of subjects/ groups	Propolis intervention	Main outcomes	Authors
Type 2 diabetes mellitus	Randomized double-blind placebo controlled	Placebo ($n = 30$) Propolis ($n = 30$)	Capsules 1500 mg/day 8 weeks	↓ fasting blood sugar ↓ 2-hp, insulin, HOMA-IR and HbA1c ↑ antioxidant capacity ↑ GPx and SOD	Afsharpour et al. (2019)
COVID-19 (Hospitalized patients)	Randomized controlled open-label single-center	Propolis 400 mg + standard care ($n = 40$) Propolis 800 mg/day + standard care ($n = 42$) control (standard care alone – $n = 42$)	Capsules 400 mg/day or 800 mg/day 7 days (followed for 28 days after admission)	Both doses: ↓ length of hospital stay 800 mg: ↓ acute kidney injury	Silveira et al. (2021)
HIV-infected people under antiretroviral therapy	Randomized double blind parallel-group placebo-controlled	Placebo ($n = 20$) Propolis ($n = 20$)	Tablets 500 mg/day 3 months	↑ Foxp3 expression ↑ CD4+ T cell proliferation ▪ Positive correlation: IL-10 and $CD4^+$ T cell count ▪ Negative correlation: IL-10 and IFN-γ	Conte et al. (2021)

main component, melittin (Lee and Bae, 2016). In fact, melittin suppresses the signal pathways of Toll-like receptor (TLR)−2, TLR-4, CD14, NEMO and PDGFRβ, affecting the activation of p38, ERK1/2, AKT, PLCγ1 and the translocation of NF-kB into the nucleus, decreasing the expression of pro-inflammatory cytokines and other mediators (Lee and Bae, 2016). However, melittin toxicological effects (mainly erythrocyte lysis) have been already demonstrated (Walsh et al., 2011), reducing the possibility of using purified melittin in clinical therapies unless there is a structural modification in this molecule. On the other hand, nontoxic concentration of melittin and its synergism with other molecules in BV may explain the low toxicity of apitherapy using bee stings and BV diverse applications (Hegazi et al., 2015).

In the neuroscience field, it has been reported that apamine – a BV neuropeptide, is able to act as a selective antagonist to the SK family of calcium-sensitive potassium channels, suggesting its therapeutic benefits and a novel strategy in improving attention deficit in patients with Alzheimer's disease (Proulx et al., 2020). BV has been studied using an experimental mouse model of Parkinson's disease, which is characterized by loss of dopaminergic neurons in the substantia nigra. BV's phospholipase 2 exerted a neuroprotective activity, suggesting its potential for treating Parkinson's disease and other diseases associated with neuroinflammation (Kim et al., 2019). Indeed, patients who received BV acupuncture twice a week for 12 weeks during conventional treatment showed less symptoms, revealing that the combined treatment with BV acupuncture is a promising adjunct therapy for Parkinson's disease (Doo et al., 2015). However, apamine toxicological effects have already been demonstrated *in vivo* (Lallement et al., 1995) and the adverse effects of phospholipase 2 are discussed in a section below.

BV antimicrobial action has been investigated *in vitro*. It is worth highlighting BV activity against the multi-drug resistant (MDR) bacterial strains MRSA and *Acinetobacter baumannii* (Giacometti et al., 2003; Rodríguez-Hernández et al., 2006; Al-Ani et al., 2015; Choi et al., 2015; Bardbari et al., 2018). This is an interesting finding since the occurrence of MDR bacteria is increasing due to their resistance to conventional antibiotics. Biofilm-producing bacteria such as MRSA and other MDR strains were also sensitive to BV and melittin (Picoli et al., 2017). BV antimicrobial action has been evaluated against HIV replication (Wachinger et al., 1998; Fenard et al., 1999, 2001; Uzair et al., 2018) and other viruses (Baghian and Kousoulas, 1993; Ramadan et al., 2009; Hassan et al., 2015; Han et al., 2020). Dehghani et al. (2020) assessed physicochemical properties, post-modification sites, and interactions between melittin and HIV proteins, revealing its interaction with the viral capside and protease.

Importantly, BV can be used to prevent or treat COVID-19 in beekeepers. Apitherapists at the epicenter of the SARS-CoV-2 pandemic did not acquire the disease even though treating infected patients (Yang et al., 2020). On the other hand, a study conducted in Germany reported different results and the authors did not support the protective effects of BV against this virus (Männle et al., 2020), although there is evidence indicating the beneficial role of BV and other bee products against SARS-CoV-2 infection (Block, 2020; Lima et al., 2021). Likewise, it was proposed that BV therapy could mitigate the effects of the H1N1 pandemic (Singla and Bhat, 2010).

Regarding tumor cells, Ceremuga et al. (2020) reported that melittin decreased the viability of leukemia cell lines (acute lymphoblastic leukemia CCRF-CEM and chronic myelogenous leukemia K-562) but not of peripheral blood mononuclear cells, by inducing apoptosis in leukemia cells. The preserved leukocyte viability using concentrations of melittin that inhibit the proliferation of tumor cells indicates a selective/differential effect on these cells.

With respect to clinical trials, Eltaher et al. (2015) conducted a double-blind clinical trial with a BV injection to treat recalcitrant localized plaque psoriasis, concluding that it was efficient and safe. The risk of anaphylaxis for treatment with BV seems to be low. In fact, Cosme et al. (2019) reported their findings with BV ultra-rush therapy over twenty years in 129 patients, showing no anaphylaxis during treatment and most of the systemic reactions were mild, with no adrenaline treatment required. Similarly, a double-blind clinical trial using a BV injection to treat Parkinson's disease has shown to be safe and effective in non-allergic patients. Maybe a higher frequency of administration and increasing individual doses may increase the success of treatment (Hartmann et al., 2016).

BV has shown to be effective in treating patients with systemic sclerosis (Hwang and Kim, 2018) and chronic pain (Shin et al., 2012; Seo et al., 2013).

BV may be used in apitherapy for different purposes (Hegazi et al., 2015) and injections may occur directly with the bee sting or by applying BV with a needle at acupuncture points (acupoints). Acupuncture is a historical practice accepted worldwide for treating pain and the release of endogenous neuropeptides is involved in its analgesic effect (Han, 2004). Typically, BV is administered in acupoints a few times a week, depending on the treatment goals. Among its various activities, the anti-inflammatory action in arthritis treatment (J.Y. Lee et al., 2005), pain relief and antitumor activity stands out (Son et al., 2007).

However, some precautions are needed: (i) the concentration of BV compounds may change depending on the season in which the bees produce it (Danneels et al., 2015); (ii) some isolated BV molecules may exert cytotoxic effects; (iii) each individual allergic response must be carefully observed before starting any treatment, following strictly the desensitization protocol (discussed in a section bellow); and (iv) the application of BV (with bee sting or needles) may exert different activities depending on the concentration of its active compounds. These differences may explain the failure or success of BV therapy.

Lee et al. (2014a) published a systematic review of clinical trials using BV therapy for rheumatoid arthritis. Zhang et al. (2018) described other possible BV therapeutic applications: to treat liver fibrosis and atherosclerosis. Table 4 shows BV effects in some clinical studies.

In apitherapy, the bee sting has been employed to treat numerous health conditions such as arthritis, autoimmune diseases (multiple sclerosis and systemic lupus erythematosus), and post-herpetic neuralgia by exerting an anti-inflammatory action (Fratellone, 2015). In Nigeria, BV has been used to treat malaria, rheumatism, arthritis, body pain, high blood pressure, headache and stroke (Ayansola et al., 2012). In addition, BV beneficial role in disorders of the muscular system, skin diseases such as psoriasis and dermatitis has also been observed. Although compounds isolated from BV may present a cytotoxic action, it can be assumed that BV itself can be useful for treating some inflammatory conditions without leading to adverse effects, since its constituents may act synergistically according to their concentrations in BV, through different pathways.

Nonetheless, it can be noticed that further investigation is needed to standardize the conditions of using bee venom for specific treatments.

Bee pollen

Bee pollen is obtained after pollen harvest by honeybees from different entomophilous plant species, mixed with nectar and enzymes from the salivary glands. Bee pollen can be collected using pollen traps placed in front of the hive's entrance and its consumption has increased due to its nutritional value (Denisow and Denisow-Pietrzyk, 2016).

Although there is a large range between the minimum and maximum values of chemical compounds in bee pollen due to the variation of geographic origin and botanical sources visited by bees (Campos et al., 2010), its major components include proteins, essential amino acids, carbohydrates, lipids, fatty lipids, phenolic compounds, vitamins (B complex, C and E), calcium, phosphorus, magnesium, sodium, potassium, iron, copper, zinc, manganese, and selenium (Xi et al., 2018). This diverse composition makes bee pollen a noteworthy option as a diet supplement. In spite of controversy due to pollens tough shell which may or may not be breached and digested by humans, maceration and water or ethanol extracts are recommended to improve digestibility for

Table 4
Clinical trials with bee venom acupuncture: main approaches, types of trial, subjects and groups, types of intervention and main outcomes.

Approach	Trial	Number of subjects/ groups	Bee venom intervention	Main outcomes	Authors
Chronic low back pain	Randomized sham-controlled triple-blind	Control ($n = 30$) Bee venom ($n = 30$)	Injection of 0.1 ml/ point twice a week for 4 weeks	↓ chronic low back pain	Shin et al. (2012)
Recalcitrant localized plaque psoriasis (RLPP)	Randomized double-blind	Apitherapy ($n = 25$) Placebo ($n = 25$)	Injection of 0.05 to 0.1 ml of commercial BV (Epivac®) once a week for 3 months	↓ RLPP ↓ TNF-α	Eltaher et al. (2015)
Parkinson's disease (PD)	Prospective open-label study	$n = 11$ (7 men and 4 women) with idiopathic PD	0.1 ml diluted to 0.005% twice a week for 12 weeks	↑ gait speed ↑ Parkinson's disease quality of life questionnaire (PDQL) ↑ motor symptoms	Doo et al. (2015)

obtaining therapeutic effects (Kroyer and Hegedus, 2001; Campos et al., 2010).

In addition to its nutritious properties, bee pollen exhibits antioxidant, cardioprotective, hepatoprotective, anti-inflammatory, antibacterial, anticancer, immunostimulant and antianaemic activity (Rzepecka-Stojko et al., 2015).

Several *in vitro* studies focused on evaluating the antioxidant activity of bee pollen, indicating its potential to prevent free radical-mediated diseases. Samples containing a high content of phenolic compounds exhibit a high free radical scavenging capacity. Bee pollen exerts an anti-inflammatory action both *in vitro* and *in vivo*, what suggests that its consumption is associated to therapeutic properties; moreover, it can be indicated as a potential anti-inflammatory ingredient in functional food or nutraceutical formulation (Kim et al., 2015; Araújo et al., 2017; F. Li et al., 2019).

Regarding bee pollen's antimicrobial activity, its effects on both Gram-positive (*S. aureus, S. epidermidis, Listeria monocytogenes*) and Gram-negative bacteria (*Escherichia coli, Salmonella enterica, Pseudomonas aeruginosa*, among others) have been assessed. However, Gram-negative bacteria were more resistant to pollen action than the Gram-positive ones, most likely due to the extra layer membrane. This property may be attributed to flavonoids such as quercetin and kaempferol glucoside present in bee pollen, which are known to possess antibacterial activity (Graikou et al., 2011; Fatrcová-Šramková et al., 2013; Pascoal et al., 2014).

Its antifungal activity against *Candida, Zygosacharomyces* and *Aspergillus* species has been reported (Graikou et al., 2011; Morais et al., 2011; Fatrcová-Šramková et al., 2016). Sancho-Galán et al. (2019) used bee pollen as a *Saccharomyces*' yeast growth activator, enhancing its development and the wine's characteristics.

Most research investigating the anti-inflammatory action of bee pollen was performed both *in vitro* and *in vivo* Liberal et al., 2016. *In vitro* tests aimed to identify the inflammatory mediators or signaling pathways inhibited by bee pollen. It was observed that bee pollen inhibited COX-2 activity and NO production, as well as supressed MAPK and NF-κB signaling pathways (Maruyama et al., 2010; Q. Li et al., 2019; Lopes et al., 2019, 2020).

In vivo studies presented a wide variety of approaches. Some studies were carried out by inducing paw edema in rats, and bee pollen was successful in attenuating inflammation, probably by activating the ERK-CREB or the Akt-GSK-3β signaling pathways (Maruyama et al., 2010). Bee pollen improved cognitive impairment induced by cholinergic blockade in mice (Liao et al., 2019). Diets containing bee pollen improved muscle mass and metabolism in old undernourished rats (Salles et al., 2014). Bee pollen exerted a protective role against diabetes-induced pituitary testicular axis dysfunction in rats, what may be attributed to the improved insulin secretion and β cell function as well as to the enchancement of the testicular antioxidant defense system (Mohamed et al., 2018). Bee pollen supplementation prevented changes in blood parameters in elderly horses during autumn (Kędzierski et al., 2020). Bee pollen protected coronary arteries by limiting the development of atherosclerosis (Rzepecka-Stojko et al., 2017). Propolis and bee pollen were used as an alternative to zinc bacitracin (a banned antibiotic growth promoter) and improved the reproductive performance of rabbits, with a positive effect on growth performance and economic efficiency in rabbit breeding (Attia et al., 2019). Carbaryl caused a negative impact on oxidative stress markers and serum biochemical variables in rats, which were alleviated after bee pollen administration (Eraslan et al., 2009).

Thus, literature demonstrates that bee pollen is an important food supplement not only because of its nutritional composition but also due to its therapeutic properties. Due to the way pollen is processed by bees, it becomes a product rich in enzymes and probiotics, making it useful for intestinal disorders such as ulcerative colitis, constipation and diarrhea, reducing inflammation and intestinal permeability (Habryka et al., 2016).

Pollen has been prescribed in apitherapy to increase muscle mass. It has been applied for treating prostate disorders (prostatitis and benign prostatic hypertrophy) and in geriatrics in general, for anorexia (to maintain a good nutritional status), autoimmune diseases (thyroiditis, multiple sclerosis, lupus and celiac disease), memory loss, and cancer (Fratellone, 2015). Moreover, bee pollen has beneficial effects on lipid metabolism in the liver and exerts an immunomodulatory action, increasing the body's resistance to infection (Habryka et al., 2016).

It should be taken into account that obtaining pollen depends on the plant source available for collection by bees and therefore different samples can be gathered.

Bee bread

Bee bread is obtained by mixing pollen with nectar and saliva and packing it in the hive, where it undergoes a chemical change due to the action of enzymes from microorganisms over time (Vásquez and Olofsson, 2009; Del Risco-Ríos et al., 2012; Anderson et al., 2014). This process facilitates the transformation of the stored pollen and the final product is acidic (pH=4) and contains 40–50% simple sugars (Nagai et al., 2004; Markiewicz-Żukowska, 2013; Anderson et al., 2014; Sobral et al., 2017).

Bee bread is more efficiently absorbed by the human body than pollen, because the pollen envelope is dissolved during processing, favoring the absorption of vitamins (Habryka et al., 2016). The biochemical transformations play a vital role in releasing nutrients and bioactive substances whithin the pollen grain (Atkin et al., 2011).

Bee bread contains approximately 20% protein, 3% lipids, 24–35% carbohydrates, 3% minerals and vitamins, in addition to essential amino acids and vitamins (C, B1, B2, E, H, P, nicotinic acid, folic acid and pantothenic acid), phenolic compounds acting as natural antioxidants, and pigments (Zuluaga et al., 2015). It also contains many biological active compounds such as sucrase, amylase, phosphatase, flavonoids, carotenoids and hormones (Nagai et al., 2004).

Bee bread exerted antioxidant and cytotoxic effects on U87MG glioblastoma cells (Markiewicz-Żukowska et al., 2013).

Due to the proportion of bee bread's constituents, it is a good supplement for vitamin deficiency (Habryka et al., 2016). In fact, bee bread has been consumed as a diet supplement and its flavonoid content may exert an antitumor activity, with no toxicity for normal cells (Sobral et al., 2017). Therefore, apitherapy has recommended bee bread because of its nutrient content. According to Bogdanov (2020), it can improve digestion and intestinal disorders, as it is a source of probiotics, indicated to restore the intestinal microbiome, specifically in patients who have undergone colonoscopy or who are receiving antibiotic therapy.

It is imperative to publicize the usefulness of this bee product.

Royal jelly

RJ is secreted by hypopharyngeal and mandibular glands of worker bees. The queen bee is fed only with RJ, unlike workers who receive it only for a short period, implying a significant difference in the lifestyle of bees. Despite coming from the same diploid genome, the queen bee is twice as large, has a specialized anatomy for reproduction and lives up to 5 years, different from worker bees, which only lives for few weeks. These facts indicate that RJ promotes health and longevity (Kamakura, 2011; Buttstedt et al., 2013); moreover, it is considered an anti-aging nutraceutical, improving fertility and body composition (Ali and Kunugi, 2020).

RJ is a white and viscous substance and its chemical composition comprises about 60% water, 20–40% protein, 15–30% carbohydrates, 3–8% lipids, 1.5–3% minerals and vitamins (Nagai and Inoue, 2004; Ramadan and Al-Ghamdi, 2012). RJ contains a wide number of bioactive substances, including 10-hydroxy-trans-2-decenoic acid (10H2DA; "royal jelly acid"), which displays an immunomodulatory action (Sugiyama et al., 2012). Royalactin is a functional component of RJ, which is involved in the morphological change from larva to queen, being the target of several studies. It is as an activator of a pluripotent gene network by modulating chromatin accessibility (Wan et al., 2018).

In preclinical assays, RJ exerted anti-inflammatory effects on peritoneal macrophages of mice, regulating the synthesis of pro-inflammatory cytokines. (Kohno et al., 2004). RJ beneficial effects in reducing neurodegeneration and the level of oxidative stress have been reported in rats, increasing the proliferation of neurons (Silva et al., 2020b). All studies involving animals indicated that RJ might counteract oxidative stress, neuroinflammation, and mitochondrial dysfunction, resulting in mitigation of neuronal damage and improving motor functioning in Parkinson's disease (Ali and Kunugi, 2020).

RJ showed a potent ability to improve hyperinsulinemia, insulin resistance and hypertension associated with insulin resistance in rats, via indirectly vascular control dysfunction regulated by adrenergic and CGRPergic nerves in the hyperinsulinemic state (Zamami et al., 2008).

Regarding clinical trials, a study conducted with 20 volunteers demonstrated RJ potential to regulate glucose metabolism, reducing glycemia probably due to an insulin-like activity (Münstedt et al., 2009). RJ may lower blood cholesterol: Chiu et al. (2017) evaluated 40 subjects with mild hypercholesterolemia who ingested RJ capsules (350 mg/capsule) for three months. RJ reduced total cholesterol and LDL with no hepatic or renal side effects by ameliorating the concentration of sex hormones like dehydroepiandrosterone sulfate in these individuals.

RJ has beneficial effects on hormonal regulation and on menopausal symptoms. Mishima et al. (2005b) demonstrated that RJ has an estrogenic activity, eliciting the full sequence of estrogenic action, interacting with ERs and stimulating mRNA expression of estrogen-responsive genes. Moreover, RJ beneficial effects on hormonal treatments are not only restricted to women: further, it is beneficial for treating male infertility. Al-Sanafi et al., (2007) conducted a clinical trial with 83 infertile patients, verifying that RJ increased sperm motility and testosterone levels.

Miyata et al. (2020) investigated the effects of RJ ingested by 33 patients with renal cell carcinoma (16 patients treated with RJ and 17 with a placebo), observing decreased levels of cytokines (TNF-α and TGF-β), which correlate with malignant transformation and occurrence of adverse events caused by anti-cancer therapies. TNF-α is involved in cancer-induced inflammation in the tumor microenvironment by regulating other molecules. TGF-β promotes chronic fatigue syndrome and cancer-induced cachexia including anorexia. In addition, RJ decreased the tumor size and counteracted adverse effects, anorexia and fatigue in such patients.

Given its rich composition of bioactive compounds, RJ displays plenty of health benefits in apitherapy, including antioxidant, anti-inflammatory, neurotrophic, hypotensive, antidiabetic, antirheumatic, anticarcinogenic, antifatigue, antiaging and antimicrobial activities. Fratellone (2015) reported RJ efficacy for wound healing and tissue repair, osteoporosis, as an immunomodulatory agent, regulating hormones, improving cognitive function, and reducing lipid levels. It is also indicated in contribution with treating diabetes, hypertension, cancer, skin disease, hyperlipidemia and neurodegenerative disease, such as in Alzheimer's and Parkinson's (Meng et al., 2017; Alu'datt et al., 2018; Ramanathan et al., 2018; Kunugi and Ali, 2019; Pan et al., 2019; Ali and Kunugi, 2020; Qiu et al., 2020).

In Europe, the European Food Safety Authority (EFSA) has not yet established a cause-effect relationship between the consumption of royal jelly and the claimed effects, although its beneficial effects for cancer treatment have been demonstrated by *in vivo* and *in vitro* studies (Miyata and Sakai, 2018).

Although demonstrating positive attributes, RJ is unfortunately not used globally.

Apilarnil

In the beehive, drones or male bees emerge from unfertilized eggs and are responsible for fertilizing the queen bee. Since ancient times, drone larvae have been included in people's diet (Bogdanov, 2011).

Apilarnil is obtained through homogenization, filtration and lyophilization of the drone larvae at the early stage of development, showing a milky consistency, yellowish gray color and a bitter taste. It contains many nutritional constituents, including proteins, carbohydrates, lipids, B complex vitamins, biotin, folic acid, inositol, choline, and a high content of micronutrients and macroelements (K, Mg, Na, P, Mn, Cu, Fe, Se). Compared to RJ, apilarnil contains a greater amount of free amino acids. Apilarnil is rich in steroid hormones such as testosterone, progesterone, estradiol, prolactin (Isidorov et al., 2016; Mărgăoan et al., 2017; Sawczuk et al., 2019), including E-dec-2-enedioic acid, which is similar to the estrogenic fatty acids isolated from RJ (Seres et al., 2013).

In vivo studies have shown apilarnil estrogenic activity, justifying its use in folk medicine and opening perspectives to be used in estrogen deficiency (Seres et al., 2013). Apilarnil stimulated sexual maturation of male broilers at an early age (Altan et al., 2013). Apilarnil increased the weight of seminal glands and epididymis, the ejaculated volume, the density of germ cells, and sperm mobility in pigs (Bolatovna et al., 2015). Apilarnil reduced the high levels of pro-inflammatory cytokines induced by sepsis in adult male rats, reduced the number of degenerated neurons, and exerted a neuroprotective effect preventing apoptosis (Hamamci et al., 2020). Further studies demonstrated that apilarnil might reduce oxidative stress and hepatic damage in rats (Doganyigit et al., 2020).

Apilarnil is used in complementary medicine to treat a variety of diseases and health conditions, including ovarian dysfunction and male infertility, thyroid and immune disorders, and malnutrition in children (Sidor and Dzugan, 2020). Apilarnil seems to exert an androgenic effect and literature revealed that it might be used for men with andropause problems (Erdem and Ozkok, 2017). Sidor and Dzugan (2020) highlighted that this underinvestigated bee product needs further investigation due to its benefits. In fact, few diet supplements are marketed and most patents are found mainly in Russia. However, due to its hormonal activity (Sawczuk et al., 2019), apilarnil safety should be investigated and further recommended as pharmaceutical products (Sidor and Dzugan, 2020).

Beeswax

Beeswax has been widely used in ancient times as a bargaining tool, in the preparation of death masks and embalming corpses, for writing tablets, and candle production. The majority of reports about beeswax stem from Egypt, Greece and Rome, demonstrating its utility as a commodity (Crane, 2015).

Beeswax is secreted as a liquid form by the wax glands located in the worker bees abdomen. Beeswax mainly contains hydrocarbons, free fatty acids, esters of fatty acids and fatty alcohol, as well as exogenous substances like pollen, propolis, and floral components. Beeswax composition may vary between bees due to genetic factors and diet (Fratini et al., 2016).

Beeswax displays antiviral effects (Hassan et al., 2015). Due to the characteristics of SARS-CoV-2, as it is an enveloped and single-stranded RNA virus, it may be sensitive to the antiviral effects of beeswax extracts (Lima et al., 2021).

An *in vivo* study demonstrated that a combination of beeswax, refined calcium hydroxide powder and sesame oil accelerated the healing of second-degree burns in rats (Ebrahimpour et al., 2020).

Due to its hydrophobic property, beeswax has a multitude of applications in cosmetics, craft and industrial products and in the food industry (Fratini et al., 2016). The production of beeswax-based dermocosmetics facilitates obtaining organic and nontoxic products for humans (Marquéz et al., 2019). Beeswax is an emulsifying and hardening agent and, in cosmetics, it is able to reduce transepidermal water loss from the skin, promoting hydration and a moisturized skin, especially for dry and chapped lips (Kasparaviciene et al., 2016). Beeswax can be incorporated into fabrics due to its biocidal properties against mold, resulting in practical applications for preventing cutaneous mycoses in patients from health and social care establishments (Szulc et al., 2020). Thus, beeswax is a protective barrier against external factors by forming a film on the skin surface (Kurek-Górecka et al., 2020).

A clinical trial including 90 patients with acute lymphoblastic leukemia and chemotherapy-induced oral mucositis revealed that the topical application of a mixture containing beeswax, honey and olive oil-propolis extract improved recovery time (Abdulrhman et al., 2012).

Ayansola et al. (2012) reported that beeswax has been used in Nigeria for treating frigidity in women and a weak erection in men. Ointments containing beeswax have been applied successfully in skin lesions, mainly burns. A mixture of beeswax, olive oil and *Alkanna tinctoria* (L.) Tausch was used to treat burns of 31 patients, whose pain and hospitalization time decreased, improving the epithelization (Gümüş and Özlü, 2017).

The potential of beeswax should be more widely explored.

Allergic reactions to bee products and apitherapy for treating allergic patients

This section reviews allergy in relation to bee products and their potential for treating allergic individuals.

Some bee products can trigger allergic reactions and anaphylaxis. The chemical complexity of these products is diverse and may include allergens depending on the season and phytogeography where they were collected. Thus, it is crucial to identify allergens and the risk of anaphylactic reactions before using bee products in complementary and alternative medicine (Gunawardana, 2017).

Sensitization to allergens found in bee products relies on their concentration and exposure frequency, beyond genetic predisposition. Therefore, it is suggested that those who are in frequent contact with beehive products could be prone to allergy. Indeed, beekeepers are more frequently exposed to stings and present a high risk for developing BV allergic reaction; however, only a small percentage of beekeepers develop severe anaphylaxis, because stings may act as natural immunotherapy by increasing serum BV-specific IgG4 instead of IgE (Bousquet et al., 1982; Carballo et al., 2017; Freedman et al., 2019).

BV is a causative agent for allergic reactions. In fact, bee sting allergy has been related to anaphylactic reactions and IgE-mediated hypersensitivity (Komi et al., 2018). BV allergy has been reported in children with asthma (Pearn and Hawgood, 1979). Ahn et al. (2016) studied the safety and efficiency of isolated and purified essential BV (eBV), demonstrating its anti-inflammatory effects *in vitro*. A clinical trial assessing 20 individuals revealed that eBV pharmacopuncture reduced local allergic reactions.

It is unlikely for propolis to induce allergic reactions (Shi et al., 2016), although atopic dermatitis was reported (Sforcin, 2007). Münstedt et al. (2007) reported that contact allergy to propolis is common among beekeepers, although they do not seem to recognize it as a problem or take measures to protect themselves. Allergic reaction have also been reported in people who do not work with bees (Hausen et al., 1987a) and a propolis component (1,1-dimethylallyl caffeic acid ester) was identified as a possible cause for allergies (Hausen et al., 1987b). During the 1980s, the incidence of allergy to propolis was 1.2–3.3% in Germany (Hegyi et al., 1990). From 1995–2002, 5.9% of 1255 children exhibited allergic reaction to propolis in Italy (Giusti et al., 2004). In addition to skin allergy, respiratory and gastrointestinal symptoms of propolis allergy have been also notified in Italy from 2002 until 2007 (Menniti-Ippolito et al., 2008). More recently, cases of contact allergy to propolis have been reported in Sweden (Nyman et al., 2020).

Honey – the most commonly used bee product – is also related to allergy, causing serious problems due to systemic reactions. In general, allergy to honey is often associated to pollen and proteins secreted by pharyngeal and salivary glands of bees (Bauer et al., 1996). On the other hand, Alangari et al. (2017) reported honey efficacy in treating atopic dermatitis lesions.

Although some individuals are sensitive to bee products and develop allergic reactions, bee products are used in apitherapy for treating allergy, in an attempt to desensitize patients to these products. This is paradoxical since some bee products may be allergenic and, on the other hand, desensitize or alleviate allergic symptoms.

There are protocols to induce tolerance to BV (desensitization). Desensitization aims to decrease the symptoms of allergic reaction in individuals by increasingly inoculating doses of the allergen itself over time. Apitherapy using BV may be part of the treatment for desensitizing allergy to bee and wasp stings – the venom immunotherapy (VIT) (Pospischil et al., 2020).

Allergic reactions are related to the Th2 immunity profile and a possible explanation for VIT is the regulatory T cell (Treg) generation, attenuating an exacerbated immune response. VIT is a strategy to induce peripheral tolerance in allergen-specific Treg cells. Therefore, antigen-specific Treg cells regulate allergic/inflammatory reactions, increasing IL-10 and decreasing IgE production (Ozdemir et al., 2011; Rivas and Chatila, 2016; Sahiner and Durham, 2019). Moreover, VIT has been shown to be safe and effective in many patients (Goldberg et al., 2011; Ridolo et al., 2018).

Yocum et al. (1996) demonstrated VIT efficiency in a study conducted over ten years including 446 patients. There were no reports of urticaria, bronchospasm and other side effects; in addition, VIT impaired the release of preformed mediators from basophils (Jutel et al., 1996) and IgE or IgG antibody production (Boutin et al., 1994; Carballido et al., 1994).

VIT has been widely studied *in vitro* and *in vivo*, as well as in clinical trials. The mechanism of action involved in this therapy is the shifted Th2-mediated response to allergens to a Th1 dominant profile (McHugh et al., 1995; Košnik and Wraber, 2000), probably due to Th2 cell suppression by Treg cells during the treatment (Magnan et al., 2001). Treg cells may also regulate antigen presentation and the expression of co-stimulatory molecules. The co-stimulation of the ICOS receptor by its ligand (ICOSL) decreased after VIT (Bellinghausen et al., 2004). Regarding the adhesion molecule ICAM-1, responsible for the entry of effector cells into tissues exposed to allergens and upregulated in the endothelium by Th2 cytokines, Patella et al. (2011) observed a downregulated ICAM-1 expression in patients treated with BV.

These changes in the immune response profile, antigen presentation, cytokine and adhesion molecules production indicate that VIT may desensitize allergic subjects. A low incidence of allergic reactions to bee stings has been observed in beekeepers, evidence of this phenomenon occurring naturally, in contrast to allergic reactions to other products (Bousquet et al., 1982; Celikel et al., 2006).

Indeed, BV is able to protect against anaphylaxis by modulating mast cell-mediated inflammatory disorders (Kang et al., 2018), regulating Treg cells in experimental allergic asthma (Choi et al., 2013), reducing IgE and IL-4 production in experimental allergic rhinitis (Shin et al., 2014) and decreasing skin inflammation in mice (Sur et al., 2015). However, VIT may be ineffective in humans due to BV allergy, with no association between the duration of VIT and the frequency of VIT failure (Ruëff et al., 2013).

These findings provide scientific support for VIT not only for sting allergy but also for other Th2-mediated diseases such as asthma and rhinitis. VIT success or failure needs further investigation since the mechanisms for maintaining the tolerance of Treg cells remain unexplored (Rivas and Chatila, 2016). Reactive CD-1 T cells can recognize lipid-source antigens in BV (Subramaniam et al., 2016), what raises more questions about BV allergy and immunotherapy. Previous observations suggested that specific cytokines inducing allergic and nonallergic reactions could be related to the threshold of T cell activation (Blaser et al., 1998).

Propolis has shown to suppress mediators' release (leukotrienes and histamine) by leukocytes of patients with allergic rhinitis (Tani et al., 2010). In experimental models of allergic rhinitis, Brazilian green propolis inhibited histamine release (Shinmei et al., 2009; Shaha et al., 2018). Green propolis also decreased lung inflammation and increased the frequency of Treg cells in mice (Piñeros et al., 2020).

Green propolis and other propolis samples contain a flavonoid (chrysin) in their composition, which has been observed for attenuating atopic inflammation by suppressing keratinocyte reactivity (Choi et al., 2017), besides inhibiting IL-4 and IgE production, and mast cell degranulation (Nakamura et al., 2010). Changes in chrysin concentration in each propolis sample may be a possible explanation to why some samples do not trigger severe dermatitis. It is worthy reminding that flavonoids concentrations in propolis composition also rely on its geographical region of collection, vegetal sources and time of the year. Thus, propolis allergic and antiallergic action is related to the chemical composition of the sample used in each study. It is well known that propolis biological properties are related to the synergism between its constituents. Thus, propolis effectiveness in allergy or its side effects needs further investigation. It is recommended to identify the propolis samples that may cause allergy hence selecting allergenic samples, to characterize the allergens and in which concentrations they appear.

Although anaphylactic reaction and eosinophilic inflammation have been reported after bee pollen ingestion (Lin et al., 1989; Geyman, 1994), on the other hand, bee pollen has shown to inhibit mast cell degranulation *in vitro* and *in vivo*. *In vitro*, bee pollen reduced mast cell degranulation and TNF-α production by inhibiting IgE binding to its receptor on mast cells. Daily oral administration of bee pollen to mice reduced mast cell activation elicited by IgE and specific antigens (Ishikawa et al., 2008). In an experimental model of allergy, bee pollen decreased the migration of leukocytes to the lungs and the production of specific IgE and IgG (Medeiros et al., 2008).

As to RJ, it reduced the mRNA levels of histamine H1R receptor and IL-9 in an experimental model of rhinitis in rats (Shaha et al., 2018). In contrast, Hata et al. (2020) recommended caution in RJ ingestion by patients with a history of disease such as asthma and rhinitis due to a possible cross-reaction with other allergens.

Honey has been used to treat allergic diseases, such as allergic rhinitis and asthma, diminishing their symptoms (Habryka et al., 2016). Abbas et al. (2019) used a database to investigate honey therapeutic effects in asthmatic patients, observing its efficacy in combination with other substances. Yong et al. (2021) reported that honey might regulate the recruitment of inflammatory cells in cellular or animal models for studying allergic diseases.

As discussed in this review, evidence from studies point to the benefits of bee products for maintaining the health of individuals; in addition, they may be useful in the prevention or treatment of various diseases. Although bee products contain substances that may cause allergy, people may still be able to benefit from the antiallergic action of bee products as demonstrated above. It is important to highlight the complexity of this issue, reinforcing once again the need of a wide communication and exchange of information between researchers, apitherapists, beekeepers, physicians, nutritionists, sellers of bee products and consumers.

Conclusions and perspectives

Traditional knowledge provided by different civilizations regarding the application of bee products is extremely valuable, giving clues about their usefulness and preparation methods in treating and preventing several diseases. However, the chemical composition of each sample varies a lot depending on the plants around the hive, the geographic regions and climatic characteristics of the ecosystems, dictating specific biological properties. Thus, it is most unlikely to obtain the same outcomes using products from different regions due to the lack of homogeneity among the materials, procedures and production conditions, what makes it difficult to compare their effectiveness within the apitherapists' community.

This is an important issue revealing the need of a detailed standardization of harvesting, identification and preparation of formulations based on bee products whether for research or apitherapy. Apitherapists and researchers should apply/investigate the same samples produced in a given geographic region in order to evaluate their biological properties and therapeutic potential. Finally, a comparison of the efficacy of distinct bee products can be established.

Researches including *in vitro* assays have revealed important findings related to the biological properties of bee products and their mechanisms of action, despite this model limitation. *In vivo* assays have also provided information on the pharmacological activities of bee products. There are numerous methodologies and experimental conditions to carry out *in vitro* and *in vivo* assays, and it should be considered to compare the data. Nonetheless, both approaches have provided a scientific basis for conducting clinical trials in order to test the effectiveness of bee products in promoting human or animal health.

It is worth mentioning that the outcome obtained *in vitro* or *in vivo* cannot be automatically extrapolated to humans. Indeed, clinical trials provide a proper basis for apitherapists, in terms of preparation and recommendation of bee products for treatments. On the other hand, apitherapists should make their methods more widely available and spread their knowledge, in order to share the best standardization of their practice.

Several studies have shown that the combination of bee products with conventional medication may lead to positive results (Fernandez-Cabezudo et al., 2013; Erdem and Güngörmüş, 2014; Bartolomeu et al., 2016; Bernardino et al., 2018; Oliveira et al., 2016, 2019). Such approaches may include lower concentrations or doses of medicine such as antibiotics, chemotherapy, anti-inflammatory drugs and others, reaching the same effectiveness of the drug alone and minimizing side effects. These findings demonstrate that it is just a matter of adjusting the most efficient combination (bee product + drug) to obtain the expected outcome, benefiting from the biological properties of bee products and reducing drug adverse effects.

Clinical trials assessing bee products must include not only their activity but also the mechanisms involved in such effects, as apitherapy is not employed in many countries because physicians mention that no proven effects have been reported. Together, data showed the benefits of bee products and the clinical trials demonstrated their efficient action in the treatment of various diseases, both internally and externally; however, few authors explained the mechanisms of action involved in their clinical trials, and explanations can be found mainly about propolis, bee venom, honey and royal jelly.

Apitherapy is practiced in some parts of the world. After extensive search for information, we concluded that there is no clear consensus on the application of apitherapy according to the world regions or a prevalent use of bee product and treated disease. A subject that deserves attention is the different recommendations regarding the use of bee products by beekeepers, apitherapists and traders. Additionally, people ingest different amounts of bee products once or several times a day.

Although we have advanced a lot about the knowledge of bee products, we still need to expand and disseminate this knowledge for humanity's benefit, easier nowadays in the digital era. Thus, in order to exploit bee products potential and standardize their use, we highlight the importance of communicating the results in scientific and alternative events to reinforce the exchange of information between beekeepers, researchers, apitherapists, nutritionists, physicians, sellers and consumers of bee products. If not, we will always be working separately, without complementing our expertise.

Author contributions

Design of the study: Wilson Antonio Weis and José Maurício Sforcin. Writing, proofreading and editing: Wilson Antonio Weis, Nicolas Ripari, Fernanda Lopes Conte, Mariana da Silva Honorio, Arthur Alves Sartori, Ramon Hage Matucci, José Maurício Sforcin. All authors read and approved the final manuscript. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Author agreement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration of Competing Interests

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.

Acknowledgements

Authors are thankful for Prof. Christiaan Moora for assisting with the English.

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