Chemical Science International Journal

24(2): 1-6, 2018; Article no.CSIJ.44457
ISSN: 2456-706X
(Past name: American Chemical Science Journal, Past ISSN: 2249-0205)

Therapeutic Effects of Propolis: Review Article

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Authors' contributions

This work was carried out in collaboration between both authors. Author RA wrote the manuscript. Author SK managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CSJI/2018/44457
Editor(s):
(1) Dr. Dimitrios P. Nikolelis, Professor, Department of Chemistry, Athens University, Greece.
Reviewers:
(1) Giuseppe Pipicelli, Italy.
(2) Daohong Chen, Yiling Pharma Research Institute, China.
(3) Yoshiji Ohta, Fujita Health University School of Medicine, Japan.
Complete Peer review History: http://www.sciencedomain.org/review-history/26599

Review Article

Received 21 July 2018
Accepted 02 October 2018
Published 10 October 2018

ABSTRACT

The term apitherapy refers to the medical use of bee products, including honey, propolis, royal jelly, pollen, beeswax and, most notably, bee venom. For example, propolis is known to exhibit antiviral, immunomodulatory, anti-inflammatory and anticancer effects. Growing importance is being attached to the discovery of medications derived from natural sources. The purpose of this review is to provide a detailed analysis of the bioactive compounds in propolis and their biological effects, beneficial or deleterious.

Keywords: Propolis; apitherapy; therapeutic effect.

1. INTRODUCTION

The resin collected by bees from flowers and other plant tissues is mixed with wax and pollen to yield a highly malleable substance known as propolis, used for hive repair and other purposes [1]. The chemical composition of propolis depends on its geographical and floral origins. Raw propolis may consist of more than 300 different compounds, notably triterpenes (50% w/w), waxes (25–30%), volatile mono- and sesquiterpenes (8–12%), responsible for its distinctive odor, and phenolics (5–10%) [2]. European and Asian propolis contains simple

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phenolic acids [3], while lignans represent the principal compounds in propolis from tropical regions [4]. Caffeic acid phenethyl ester (CAPE) is an important phenolic present in European, Asian and American propolis [5]. Brazilian green propolis is distinguished by the presence of 3,5-dipenyl-4-hydroxycinnmamic acid, artepillin C, in addition to other prenylated cinnamic acids and cafeic acid derivatives [6]. Other frequently detected constituents of propolis include organic acids, ketones, aldehydes, hydrocarbons, and minerals [7].

1.1 Antioxidant Activity

Propolis has the highest phenolic content of all bee products, and has therefore been the subject of intensive research in terms of antioxidant and radical scavenging properties [8]. Various compounds contained in propolis, including pinocembrin, chrysin, and pinobanksin, exhibit powerful antioxidant and antiradicalic activities [1]. 1,1-Diphenyl-2-picrylhydrazyl radical (DPPH) and oxygen radical absorbance capacity (ORAC) tests have identified pinobanksin-3-acetate as one of the most potent antioxidant constituents of propolis [9]. Cao et al. reported a DPPH scavenging activity of ethanol extract of Chinese propolis (EECP) of 47.71 ± 1.34 µg/mL. However, EECP exhibited a weaker effect than α-tocopherol (38.23 ± 0.39 µg/mL). The ferric reducing power of EECP in that study was 1.73 ± 0.09 mmol Trolox/g, but was closer to that of α-tocopherol (1.57 ± 0.04 mmol Trolox/g) [10].

1.2 Antimicrobial Activity

Propolis has been demonstrated to exhibit variable activity against numerous bacteria, fungi, and viruses [11,12]. It has been shown to exhibit antibacterial activity against a broad spectrum of gram-positive strains, but very little against gram-negative strains [13,14]. *Salmonella* spp. and *Listeria monocytogenes* (the causative agent of listeriosis) are two major food-borne pathogen bacteria. *Salmonellae*, from the family *Enterobacteriaceae*, are gram-negative, facultative anaerobic, and non-spore forming. The most common food-borne disease caused by *Salmonella* spp. and its serotypes is salmonellosis. Animal products such as meat, eggs, milk, and their derivatives are particularly implicated in outbreaks of human salmonellosis [15,16]. *Salmonella enteritidis* (*Salmonella enterica* subsp. *enterica serovar* Enteritidis) is one of the most commonly isolated serotypes in foods, and has been particularly linked to raw, insufficiently cooked, or contaminated eggs and egg products. The incidence of gastrointestinal infections due to *S. enteritidis* is believed to be increasing [17,18]. *L. monocytogenes* is a gram-positive, facultative anaerobic, non-spore forming bacterium, with known psychotropic properties. It is present in much of the natural environment, and is therefore also found in various animal and vegetable products. Common sources of *L. monocytogenes* include various thermally processed or ready-to-eat foods, including raw and pasteurized dairy products (particularly milk and cheese), uncooked vegetables, fermented sausages containing raw meat, cooked or uncooked poultry, raw meat, and raw or smoked fish [16-19]. Chen et al. reported that propolis extracts exhibit an antibacterial effect against *S. aureus*. The average MIC and MBC values of organic propolis extract for *S. aureus* were 10 µg/mL and 20 µg/mL, respectively. In the same study, propolin C exhibited the lowest MIC (1.25 µg/mL to 10 µg/mL) against gram-positive strains of *S. aureus*, *B. subtilis*, *L. monocytogenes*, and *P. larvae*, a low MIC value indicating high antimicrobial activity [20].

1.3 Immunomodulatory Activity

Propolis exhibits immunomodulatory effects on human peripheral blood mononuclear cells (PBMC). These largely derive from its effects on monocytes and on pathogen-recognizing receptors [21,22]. Toll-like receptors (TLRs) are thought to be particularly responsible for the capacity of cells with innate immunity to recognize pathogen-associated molecular patterns (PAMPs) and to eradicate invading microbial pathogens. These receptors are expressed by various antigen presenting cells (APCs), including monocytes/macrophages, dendritic cells and B cells, and also by neutrophils, T cells, and natural killer cells. They are also significantly involved in the development of adaptive immunity. Additionally, they perform a known function in fungi recognition, specifically reported in the context of *Candida albicans*, by inducing the production of a number of cytokines [23]. Sampietro et al. reported that partially purified propolis extracts (PPEs) were effective as chemotactic agents. In that study, the neutrophil phagocytic activity of PPEs was determined as 270 ± 10% [24].

1.4 Anti-inflammatory Activity

Anti-inflammatory properties of propolis have been described in various studies, and are

probably associated with the presence of phenolic acids. CAPE is a potent anti-inflammatory component, capable of specifically targeting nuclear Factor kappa B (NF-κB) signaling [25]. It has also been shown to modulate extracellular-signal-regulated kinase (ERK) and mitogen activated protein kinase (MAPK) signaling in T cells and mastocytes [26], as well as regulating the phosphatidylinositol-3-kinase/Akt (PI3K/Akt) pathway in a number of human cell lines [27]. Various potential downstream effects of these anti-inflammatory mechanisms have also been postulated, such as the downregulation of key inflammatory enzymes, including cyclooxygenase, matrix metalloproteinases, and inducible nitric oxide synthase [25,27]. Mouthwash products make particular use of the anti-inflammatory properties of propolis. Antigingivitis activity has been attributed to phenolics, particularly to CAPE [27]. Zhao et al. reported decreased TNF-α (16.4 ± 9.1 pg/mL) in subjects with type 2 diabetes mellitus treated with Brazilian propolis [28]. Wang et al. reported that PPE affected the production of IL-10, an important anti-inflammatory cytokine. That study reported an oral IL-10 concentration of 312 ± 65 pg/mL in 25 mg of PPE from China, compared to the LPS group (IL-10 concentration: 229 ± 48 pg/mL) [29].

1.5 Wound Healing and Skin Protection

Animal experiments and clinical trials have reported that propolis exhibits ameliorative effects on diabetic foot ulcers and other tissue injuries [30]. The wound healing activities of propolis are facilitated by the immunomodulatory, antioxidant and antiseptic activities of its natural ingredients [31]. In one study, the topical application to excision wounds in rats of Indian propolis containing flavonoids, phenolic acids and terpenes was reported to upregulate hydroxyproline, hexosamine, uronic acid, nucleic acids and protein levels in wounded tissue, similarly to nitrofurazone [32]. Several studies have concluded that propolis accelerates the healing process at various stages of tissue repair and reduces recovery times [33,34,35]. One study showed that propolis accelerated wound closure from the initial stage [36].

1.6 Anticancer Activity

Propolis consists of polyphenols, flavonoid aglycones, phenolic acids and their esters, and phenolic aldehydes and ketones. Its exact composition depends on the plants sampled, and is therefore also related to biogeographic and seasonal factors, and different bee species [37]. Caffeic acid, CAPE and quercetin suppress cancer cell growth [38]. One study demonstrated that the propolis-derived compound artepillin C induced cytotoxicity in carcinomas and malignant melanoma cells through apoptosis, abortive mitosis and mass necrosis. Such suppression of tumor growth may probably be attributed to propolis' own direct cytotoxicity, in addition to enhanced immunity [39] and lipid peroxidation suppression [40]. Research has also demonstrated the induction of apoptosis in human melanoma cells by three distinct propolins (A-C) [41]. Parameterized Model 3 (PM3), another propolis-based compound, has been shown to suppress the growth of MCF-7 breast cancer cells in vitro, and to induce apoptosis [42]. Propolis induces apoptosis pathways in cancer cells. CAPE and chrysin have been identified as principal agents responsible for these antiproliferative effects by modifying cancer-related gene expression. One previous study identified CAPE, one of the components of propolis, as the most potent agent, since 90% of cells were killed at a 30 μM concentration [43]. In one study of red propolis from Pernambuco (RP-PER) collected in the rainy season, RP-PER concentration values of 1000, 500, 250 and 125 μg/mL resulted in almost 100% fibroblast cell death. The IC_{50} value for RP-PER in that study was 48.09 μg/mL [44].

2. CONCLUSION

In addition to investigating the components of natural products, it is also important for these to be standardized. Materials exhibiting biological activities have frequently been discovered during the investigation of substances extracted from natural products regarded as possessing medical properties in traditional medicine. Numerous such products have been shown to possess chemopreventive properties. Experimental studies involving cultured cells and different animal models are gradually illuminating the probable mechanisms of action of these substances. The majority of these mechanisms appear to be associated with the ability to prevent, or at least to significantly inhibit the onset of carcinogenesis, or cell proliferation. Honey and propolis both have high phenolic compound contents. Both are also growing in popularity due to their perceived health benefits. In contrast to various other natural remedies, propolis still enjoys considerable popularity. Its pharmacologically active molecules consist of

flavonoids, phenolic acids, and their esters, which exhibit various effects on bacteria, fungi and viruses. Propolis is also known to exhibit antioxidant, antimicrobial, immunomodulatory, anti-inflammatory, and anticancer activities. However, the therapeutic function of propolis may vary depending on the countries or areas where it is collected. Laboratory studies suggest that CAPE has a significant impact on cancer chemoprevention. Research has identified several effect mechanisms for CAPE and its associated compounds. The antitumor activity of polyphenolic compounds such as CAPE was initially reported to involve direct cytotoxic effects on tumor cells in vitro. This was subsequently confirmed in various types of tumor in vivo. In particular, the effect on initiation was investigated using a rat hepatocarcinogenesis model. CAPE was found to exhibit a protective effect when administered in a single dose prior to initiation. The chemoprotective effect of CAPE was attributed to its anti-oxidative and free radical scavenging activities. CAPE has also recently been shown to exhibit a chemoprotective effect on the initiation stage by modifying cytochrome *P450* (CYP)-dependent diethylnitrosamine bioactivation and reducing levels of reactive chemical species, thus suppressing the initiation stage of carcinogenesis. However, despite the recent research into the biological activities of caffeic acid esters and other analogues, particularly focusing on their structures, much of the detail involved in those mechanisms is still uncertain. It is not improbable that several of the protective effects exhibited by CAPE and its associated compounds may involve shared chemoprotective mechanisms. The effect of changes to the structure of CAPE, which may illuminate the role of characteristics such as lipophilicity, anti-oxidative and free radical scavenging on chemoprotection, therefore needs to be tested in an in vivo setting. If CAPE analogue compounds do indeed have one or more mechanisms of action in common, and if preparation is simple, fast and involves no significant cost burden, then these analogue compounds may represent promising anticancer agents in addition to CAPE. Hepatocellular carcinoma is an aggressive tumor involving high mortality rates. In all likelihood, early detection will rely on determining its molecular pathogenesis.

Physicians should consider the potential benefits of propolis as an adjuvant therapy for cancer patients. This will in turn facilitate the development of therapeutic measures as drugs' mechanism of action become better understood.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/26599