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Review of the anticancer activities of bee products

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PEER REVIEW

Peer reviewer

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Comments

Having read through the present manuscript, I could interpret that the authors dealt with the bee products from the honeybees species belonging to the subfamily Apinae, which contains less than 10 species. There are two types of beekeeping in the world. One is called Apiculture which keeps Apinae bees. The other is Meliponiculture where bees belonging to the subfamily Meliponinae, which contains about 400 species. Meliponinae bees also produce honey and propolis which have been utilized for people widely in tropical and subtropical areas.
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ABSTRACT

Bee products have long been used in traditional medicine. The raw materials, crude extracts and purified active compounds from them have been found to exhibit interesting bioactivities, such as antimicrobial, anti-inflammatory and antioxidant activities. In addition, they have been widely used in the treatment of many immune-related diseases, as well as in recent times in the treatment of tumors. Bee product peptides induce apoptotic cell death *in vitro* in several transformed (cancer) human cell lines, including those derived from renal, lung, liver, prostate, bladder and lymphoid cancers. These bioactive natural products may, therefore, prove to be useful as part of a novel targeted therapy for some types of cancer, such as prostate and breast cancer. This review summarizes the current knowledge regarding the *in vivo* and *in vitro* potential of selective bee products against tumor cells.

KEYWORDS

Bee products, Cancer cells, Chrysin, Flavonoid, Inflammatory, Propolis

1. Introduction

Bees are flying insects in the order Hymenoptera and are closely related to wasps and ants. Asides their important ecological and economic role in the pollination of natural and commercial plant species[1], respectively, they are also known commercially for their role in producing natural products. In addition to honey, commercial bee products also include beeswax, bee pollen, royal jelly and propolis[2]. Each of these different bee products are, or are becoming, economically important and additionally are known to have several potent bioactivities. Indeed, bee products have been used in traditional medicine throughout society. For instance, bee pollen is reported to boost energy and

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stamina[3], propolis to help maintain good health[4], royal jelly to support the immune system and increase energy[5], whilst honey, mainly used as a natural sweetener in every food culture, is also used traditionally used for treatment of burns, sore throats and as an antiseptic[6]. More recent studies have found that several bee products have a potential anticancer activity *in vitro* and *in vivo*[7].

Several recent studies have reported that some natural bee products inhibit tumour cell growth and metastasis and induce apoptosis of cancer cells[8], suggesting the potential application of these natural compounds (or their active components) as part of an alternative medical treatment of human tumours[7]. When chemo- and radio-therapy are used systemically or over a broad directed tissue area to kill cancerous cells, they also typically harm healthy cells in the process causing undesirable side effects that limit the treatment (duration and/or dose) and effectiveness, or in the worst cases can kill the patient faster than the cancer would have done. Accordingly, research for alternative anticancer drugs has become a popular topic, especially for natural products. Natural products are viewed as generally being weaker but much safer. There is some element of validity in this approach in that, although some natural products are as toxic to normal cells, others do not directly interact with the cells but rather activate the immune system and so rely on the natural immune discrimination between healthy and infected or transformed cells. Alternatively, some natural products differentially act upon transformed and normal cells. Moreover, natural sources are a rich and largely untapped resource of potentially new agents against such diseases. For example, the origin of mostly current anticancer drugs is in one way while the rest are from natural sources[9], yet the diversity of such natural compounds remains relatively unknown. Although relatively few of the actual isolated compounds advance to become clinically effective drugs in their own right, they may serve as a template for the preparation of more efficacious analogues using total or combinatorial synthesis, or manipulation of biosynthetic pathways[9].

During the past two decades, the simple and polyphenolics plus peptides from bee products have started to attract more attention for their potential use in cancer therapy. This review aims to summarize the anticancer activity of bee products.

2. Honey and cancer

For centuries, honey has been known for its medicinal and health promoting properties. Honey is a complex produced by various species of honey bees (*Apis* sp.) from the nectar of plant blossoms or the exudates of plant phloem feeding insects (honeydew), or a mixture of both. These differences in direct and indirect (via phytophagous insect exudates) botanical sources, as well as the different foraging strategies of different bee isolates/species give rise to the seasonal, biogeographic (regional) and species specific variations in different honeys[10]. Although honey is principally a concentrated aqueous solution of inverted sugars (glucose and fructose), it aslo containes other saccharides, amino acids, organic acids, vitamins, minerals, antioxidants, flavonoids, phenolic acids and carotenoids [11-13]. Of the various kinds of phytochemicals present in honey, the phenolic and flavonoid content are relatively high and are comprised of simple and polyphenols, such as acacetin, apigenin, caffeic acid, caffeic acid phenethyl ester (CAPE), chrysin, galangin, kaemfereol, pinocembrin, pinobanksin and quercetin[14] that contribute to its antioxidant activity[12,15,16]. Flavanoids typically have anticancer properties[17] because of their antioxidant activity and also their related ability to alter many signalling pathways, including stimulation of tumor necrosis factor-alpha (TNF-α), inhibition of cell proliferation, induction of apoptosis, and cell cycle arrest[18-22]. Honey is thought to exhibit a broad spectrum of therapeutic properties in addition to an antioxidant activity, including an antimicrobial activity[19,23-25], cytostatic and anti-inflamatory activity[24]. Of interest here, however, is that honey can provide the basis for the development of novel therapeutics for patients with soft and hard (tumour) tissue cancers, especially jungle honey (wild honey collected from forest regions). In addition to affecting the chemotactic induction of neutrophils and reactive oxygen species[26], jungle honey has been shown to posses a significant antitumor activity *in vitro* against human breast, cervical, oral and osteosarcoma cancer derived cell lines[27,28]. However, the *in vivo* or *in vitro* effect of honey on hormone-dependent human cancers, such as breast, endometrial and prostate cancers, as well as solid tumour cancers *in vivo*, remains largely unknown. Honey has moderate anti-tumour activity and anti-metastatic effects against renal cell carcinoma and rat and murine tumours[22,29-31], and potentiated the effect of standard chemotherapy with 5-flourouracil or cyclophosphamide[32]. Some of the principal phytochemicals in honey (epigallocatechin-gallate, lycopene, genistein and resveratrol) have been used for treatment of prostate cancer [33,34], although the exact relative composition will vary between different regional, season and botanical source of the honey. There is increasing evidence to support that honey is a natural anti-inflammatory, antimicrobial, anticancer agents and potential for healing chronic ulcers and wounds[35]. Whilst the antibacterial effects of neat or high concentration honey are likely to be largely due to its osmotic potential, the *in vitro* and *in vivo* anti-cancer effects are usually seen at much lower concentrations (e.g. IC_{50} values of 100-200 μg/mL) even before systemic dilution in the tissue and so are more likely to reflect the actual bioactivities of its trace components. To this end, honey is known to contain caffeic acid, CAPE and flavonoid aglycones that downregulate many cellular enzymatic pathways, including protein tyrosine kinases, cyclooxygeneses and ornithine decarboxylase[36]. However, it should be born in mind that in addition to the above anti-proliferation and anti-metastic effects plus the induction of apoptosis in tumour cells, honey has, in contrast, been reported to induce the proliferation of malignant cells, albeit that this was