REVIEW ARTICLE

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Propolis: The Role of Propolis in Cancer

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Abstract

Propolis is a resinous natural product produced by honey bees by mixing collected buds and exudates of plants with bee wax. Bees use propolis to protect themselves against wind and rain by using it to construct and repair hives. Propolis has a wide range of biological effects as it is a mixture of natural substances, and it is widely used for its anti-inflammatory, anti-oxidant, immunomodulatory, and anti-cancer effects. Propolis has been used in traditional medicine since time immemorial. Research studies on the anti-tumor effects of propolis extracts and components such as flavonoids, phenolic acids, and their esters demonstrate their potential to be used in the development of new anti-tumor agents. Propolis shows an anti-carcinogenic effect against cancers of the brain, head and neck, skin, breast, liver, pancreas, kidney, bladder, prostate, colon, and blood. In-vivo and in-vitro studies have shown that propolis has cytotoxic, anti-genotoxic or anti-mutagenic, anti-proliferative, anti-angiogenic, anti-metastatic, and proapoptotic properties. Its main mechanisms in cancer treatment can be explained as prevention of metastasis, arrest of the cell cycle, induction of apoptosis and alleviation of harmful side effects caused by chemotherapy. The beneficial effects of natural products on human health have been reported in studies to prevent tumor formation and/or suppress the growth of tumors into cancer. In this review, detailed information about the properties, biological effects, and anti-cancer effects of propolis was given by reviewing current literatures.

Keywords: Anti-cancer, apitherapy, cytotoxicity, propolis.

INTRODUCTION

Owing to the many negative impacts such as the side effects of drugs used in medicine, the decrease in the effectiveness of drugs and economic losses, the tendency to use natural/herbal drugs in disease conditions treatment has increased (Doğan and Hayoğlu, 2012; Yücel et al., 2014). For this reason, honey, pollen, propolis, poison and bee bread, which are bee products, have become used in complementary medicine (Yücel et al., 2014; Onbaşılı et al., 2019).

Propolis, whose bioactive substances are beneficial to human health, ranks first among the supplements (Sağdıç et al., 2020). The term propolis is of Greek origin: "pro" means "in front of / for" and "polis" means "city". So it means going ahead/forward for the defense of the city (deGrood, 2013). The constituents enhancing the biological activity of propolis are; phenolic acids and flavonoids. These substances are important for human health due to their having different biological effects such as metal chelation, modulation of enzymatic activity, and free radical scavenging properties. Studies have shown that the polyphenols contained in propolis strengthen the immune system, protect the heart, and prevent cancer (Memmedov et al., 2017).

Cancer is derived from the Greek word 'canker' or 'carcinos' and means crab. Hippocrates coined the term tumor based on its resemblance to the swollen veins around the tumor on the legs of a crab. The term 'oncos', which means swelling, was used by the Greek doctor Galen (Baykara, 2016). Cancer is a group of diseases that are characterized by uncontrolled cell division and can spread throughout the body (Baskar et al., 2014).

In today's cancer treatment; surgery, chemotherapy, radiotherapy, hormone therapy, and immunotherapy are the main approaches adopted. These treatment methods are usually supported by other complementary and alternative treatments such as herbal medicines (Monteiro et al., 2014). Due to the limited effectiveness of synthetic drugs in cancer treatment, the scientific world has not been indifferent to herbal medicines in traditional treatment methods, and studies on the medicinal use of plants have increased in recent years (Bozyel et al., 2019).

In addition, many studies have shown that the use of herbal medicines or natural substances in conjunction with chemotherapeutic drugs increases anti-tumor effects and/or reduces their toxicity (Monreiro et al., 2014).

Propolis

Propolis is the general name of a complex lipophilic, resinous mixture collected from the buds and exudates of various plants by honey bees (*Apismellifera L.*). This material is mixed with the β-glycosidase enzyme found in the saliva of the bees, partially digested and added to bee wax to form raw propolis, which they use as a thin layer on the inner walls of their hive or other spaces where they live (de Groot, 2013). Numerous plant species secrete highly anti-microbial resins to protect vegetative tips, young leaves, and injured tissues. These secretions are the raw material of propolis, and propolis forms the basis of colony-level immunity for honey bees (Bankova et al., 2018). Bees use the propolis they produce to protect and strengthen their hives (to close cracks and holes, reduce the hive entrance hole, to prevent moisture loss), to maintain aseptic conditions and appropriate temperature in

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the hive (Vagish-Kumar, 2014). Its chemical composition is very variable as it depends on the local flora (plant source), samples from different geographical and climatic areas, collection time (season/climate), and bee species. Currently, more than 500 chemical compounds present in this natural product have been identified (Huang et al., 2014). Although these compounds vary depending on the content, the composition of propolis in general; contains macronutrients such as a resin (50%), bee wax (8-30%), plant wax (6%), essential oils (10-14%), pollen (5%), and tannin (10%) (Anjum et al., 2019). The substances identified in the propolis belong to the following groups of chemically similar compounds: polyphenols (flavonoids, flavones, flavonols, and phenolic acids); benzoic acids and their derivatives; cinnamic alcohol, cinnamic acid, and derivatives; sesquiterpene and triterpene hydrocarbons; benzaldehyde derivatives; other acids and related derivatives; alcohols, ketones and heteroaromatic compounds; terpene and sesquiterpene alcohols and their derivatives; aliphatic hydrocarbons; minerals; sterols and steroid hydrocarbons; sugars and amino acids, and low amounts of volatile compounds produced by plants. It is thought that the sugars are produced by chance during the preparation of propolis and/or the bees pass over the resin. Some compounds are common to all propolis samples and determine their characteristic properties (Wagh, 2013; Chiu et al., 2020). In addition to vitamins (A, B, and C complex), some essential elements such as magnesium (Mg), calcium (Ca), iron (Fe), nickel (Ni) and zinc (Zn) were also found (de Groot, 2013).

Worker bees (12-21 days old) collect propolis from the tops of trees in summer or spring, and in autumn when the weather is nice, and use it immediately in the required areas (Kumova et al., 2002). Raw propolis collected from the hive cannot be used as it is. At this point, the extraction method and selection of solvent to be used for extraction determine the chemical composition (the amount and quality of the bioactive components of the final product). Generally, the maceration technique and 70% ethanol are used for extraction (Sağdıç et al., 2020). Propolis has low solubility in water. Due to that, the amount of phenolic compounds in propolis extracted with water is 10 times lower than in those extracted with ethanol (Kubiliene et al., 2015). In recent years, different extraction methods have been tried. However, only water-soluble propolis preparations have been produced which yield final products which do not contain alcohol and its derivatives (Sağdıç et al., 2020).

Currently, there are different types of propolis in the market according to their origin (Chiu et al., 2020). Brazil, especially China, ranks first in propolis production. It is processed and distributed to the world market from Japan. Other countries producing propolis are Canada, Uruguay, Chile, Argentina, and Eastern European countries. In addition, the annual production of propolis is around 200 tons and it is reported that its production started in 1984 (Doğan and Hayoğlu, 2012).

Biological Effects of Propolis

The main components of propolis are wax, resin, and volatile substances. Bees obtain plant material for the preparation of propolis by cutting pieces of plant tissue or from plant secretions. The biological activity of propolis is based on these plant-derived substances (Salantino et al., 2005). Bee wax is a crystalline substance synthesized from honey sugars by the wax glands in the abdomen of the worker bees during the colony growth phase in late spring (Cornara et al., 2017). Yellow, soft, and highly absorbable waxes contain esters, acids, higher fatty alcohols, and sometimes free hydrocarbons. While bee wax is stable and highly resistant to moisture, it is unstable to heat and mechanical pressures (Ahangari et al., 2018). Resin contains most of the compounds found in alcohol extracts. On the other hand, propolis contains other components such as pollen and amino acids (Salantino et al., 2005).

Epidemiological data support the knowledge that natural products, dietary phenols and polyphenols are not toxic and have beneficial effects on human health (Carocho and Ferreira, 2013). Compounds responsible for the biological effects of propolis are aromatic acids and esters, especially, flavonoids. Propolis show anti-bacterial activity and inhibition of bacterial RNA-polymerase by showing a synergistic effect with different compounds; was reported that they provide mixtures of pinocembrin, galangin and caffeic acid phenyl ester (CAPE) (Albayrak and Albayrak, 2008). It has been shown that different plants rich in polyphenols exhibit anti-cancer effects on cell lines, providing higher anti-cancer effects compared to synthetic compounds (Carocho and Ferreira, 2013). Products from the beehive, such as honey, pollen, royal jelly, and propolis, are extremely beneficial for use as both healthy foods and medicinal products in apitherapy (Münstedt and Bogdanov, 2009). However, the therapeutic application and use of these products in the pharmaceutical industry are still limited. The main reason for this is the variability in the chemical composition of propolis resulting from geographical differences, as bees use different plants in different ecosystems (Daleprane and Abdalla, 2013). Understanding the mechanism of these natural products will contribute to the development of more specific preventive strategies against cancer development (Toshiya et al., 2012).

With these properties, propolis is used in traditional medicine in a well-known and effective way in the treatment of various diseases (Krol et al., 2013). In addition, research on propolis in recent years has shown the breadth of its biological activities such as anti-cancer, anti-septic, anti-inflammatory, anti-oxidant, anti-bacterial, anti-fungal, anti-neoplastic, hepatoprotective, cardioprotective, and immunomodulatory (Anjum et al., 2018).

Cancer and Propolis

Cancer is a complex collection of different genetic diseases linked by common features (Luo et al., 2009). In other words, cancer is a condition that occurs when the cell begins to divide uncontrollably, that is to say, without complying with the mechanisms that control the rate of proliferation (Nema et al., 2013). The factors responsible for the development of cancer are classified as exogenous and endogenous. The former refers to nutritional habits (food storage and preparation), socio-economic status, lifestyle, physical agents, and chemical compounds. Endogenous factors include inflammation and immune system damage caused by uncertain conditions (eg, ulcerative colitis, pancreatitis, etc.), genetic make-up, age, endocrine imbalance, and physiological status (Oliveira et al., 2007).

In cancer treatment, surgery, chemotherapy, radiotherapy, hormone therapy, and immunotherapy are the main approaches adopted (Monteiro et al., 2014). In recent years many chemotherapeutic agents have been developed, and although they are useful in cancer treatment, many side effects have been encountered.

Therefore, great emphasis is placed on promising natural products to provide safer and more effective anti-cancer agents, in order to improve already existing anti-cancer agents, and to develop new ones with no and/or fewer side effects (Desai et al., 2008). One of these natural products is propolis (Anjum et al., 2019).

Propolis contains biologically active substances like; caffeic acid, CAPE, artepillin C, quercetin, naringenin, resveratrol, galangin, and genistein which are known to be promoters that stimulate cell proliferation or apoptosis (Kurek-Górecka et al., 2014). Propolis shows an anti-carcinogenic effect against cancers of the brain, head and neck, skin, breast, liver, pancreas, kidney, bladder, prostate, colon, and blood (Patel, 2016). In addition, flavonoids consumed with food have a direct effect on the proliferation, differentiation, and apoptosis of cancer cells, especially, gastrointestinal system-related cancers, and this is due to their direct impact on digestion (Kurek-Górecka et al., 2014). Cell cycle arrest, anti-angiogenesis, prevention of metastasis, induction of apoptosis, and alleviation of harmful side effects caused by chemotherapy are shown as the key mechanisms of the anti-tumor effect of propolis (Patel, 2016).

Cancers that need nutrients and oxygen supply can only grow 2-3 mm without forming new vessels. Tumor cells spend a long and silent period around the capillaries until they begin to multiply uncontrollably. They begin to multiply and grow rapidly with the formation of new vessels (local small blood vessels, angiogenesis) (Aktaş and Akbulut, 2014). Angiogenesis is a multi-step process in which new blood vessels are formed. This tightly regulated process includes migration, proliferation, and differentiation of endothelial cells. Angiogenesis occurs in more than 80 diseases characterized by persistent and inappropriate blood vessel development, particularly many types of cancer and inflammatory diseases such as atherosclerosis. Events related to the pathophysiology of angiogenesis, associated cytokines, and growth factors may lead to poor prognosis in many diseases (Daleprane and Abdalla, 2013). Keshavarz et al. (2009) reported that green propolis extracts containing artepillin-C and CAPE significantly reduced the number of new vessels formed, and the production of the vascular endothelial growth factor by endothelial cells. Different steps of angiogenesis can be affected by propolis and its constituents. Daleprane and Abdalla (2013) reported that Brazilian propolis and its main constituent artepilin-C can inhibit the proliferation of human umbilical vein endothelial cells as well as endothelial cell migration, and capillary formation by suppressing angiogenesis in a dose-dependent manner. Suppression of angiogenesis may inhibit the spread of the disease (Sforcin, 2016).

Breast cancer is one of the deadliest cancers among women in the world. Multiple genetic changes enhance the initiation and progression of cancer cells. For example, activation of oncogenes and inactivation of tumor-suppressor genes result in the initiation of neoplastic tissues. Notably, cancer cells lose full control over cell growth regulatory signals resulting in abnormal proliferation while avoiding programmed cell death or apoptosis (Beauregard et al., 2015). Xuan et al. (2014) found that propolis has the potential for breast cancer therapy due to its anti-tumor activity by inducing apoptosis in EEP human breast cancer (MCF-7) cells. In another study, 1.56-100 µg / ml cisplatin, 0.08-5 µg / ml curcumin, and 2.5-160 µg / ml propolis were administered individually and in combination to MCF-7 cells, and IC_{50} doses were calculated after 48 hours. In a combinatorial study, in which apoptotic cell rates were also consistent with MTT findings, it was reported that the highest apoptotic cell rate was in the presence of cisplatin + curcumin + propolis ($p<0.001$), and hence, it had significant anti-cancer activities on MCF-7 breast cancer cells in-vitro (Yılmaz and Erdal, 2020). EEP of propolis samples collected from 7 different regions of Turkey in 2004 was applied to MCF-7 cells at concentrations of 0.5, 0.25, 0.125 and 0.063mg/ml and incubated for 48 hours. The findings of that study showed that the propolis extracts at all concentrations inhibited the growth of MCF-7 cells in a dose- and time-dependent manner. According to the results of the study, EEP5 and EEP6 at 0.125 mg/ml were more effective in inhibiting MCF-7 cell growth compared to the other extracts and dilutions (Vatansever et al., 2010)

Cancers of the digestive system are a group of malignancies that affect different organs of the digestive system. These include cancers of the esophagus, stomach, liver, pancreas, gallbladder, bowel (colorectal, duodenal), and anal (Chiu et al., 2020). The flavonoids in propolis have a direct effect on the proliferation, differentiation and apoptosis of cancer cells, especially gastrointestinal system cancers, due to their direct contact with digestion (Kurek-Górecka et al., 2014). In a study conducted by Vongsak et al. (2017), 20-2000 µg/ml of 3 methanol extracts of Thailand propolis (T. pagdeni, L. ventralis, and L. terminata) collected from the same orchard and dissolved in DMSO, and 2-200 µg/ml of doxorubicin were applied on colon adenocarcinoma (Caco-2), melanoma (SK-MEL-28), hepatocellular carcinoma (HepG2), papilloma carcinoma (KB), and normal human fibroblast cells. T. Pagdeni propolis extract showed cytotoxicity with IC_{50} values of 33.38 ± 3.30 in SK-MEL-28, 73.44 ± 2.37 in Caco-2, 80.81 ± 2.68 µg/ml in HepG2, 62.41 ± 2.70 in KB, and 228.75 ± 10.64 µg/ml in normal human fibroblast cells. The propolis extracts showed low cytotoxicity in the normal cells. In a study investigating the in vitro anticancer activity of EEP extract of corn propolis on DU-145, MCF-7, and Caco-2 cancer cell lines, IC_{50} values were found to be 26.5 ± 0.06 ug/ml, 11.95 ± 0.01 ug/ml, and 10.213 ± 0.07 µg/ml, respectively. These results are consistent with previous studies that the propolis component luteolin induces G2/M cell cycle arrest in human colon cancer cell lines. This study presented a comprehensive explanation of the proposed mechanism of action of propolis components in cancer and proposed this natural product as a potential source of Phyto-components that could be applied for cancer prevention and/or treatment. (Ibrahim and Al-Banna, 2021). Prostate cancer is the second cause of cancer-related deaths in men in Europe and the United States of America (USA). Among new cancer cases, it is estimated to be 12% in the EU and 29% in the USA. Risk factors for prostate cancer include age, ethnic group, diet, and hereditary susceptibility (Aus et al., 2005). In a study investigating the cytotoxic and apoptotic activities of hormone-sensitive LNCaP and hormone-resistant DU-145 prostate cancer cells, and the interaction between propolis-tumor necrosis; it was reported that modulation of the TRAIL apoptosis pathway may have an important potential for chemoprevention of prostate cancer and that, overcoming TRAIL resistance to propolis and its phenolic components maybe one of the mechanisms responsible for the cancer-preventive effects (Szliszka et al., 2011).

It is known that human pancreatic cancer cells such as PANC-1 show marked tolerance to nutritional starvation. Elimination of this situation is accepted as tolerance to

nutritional hunger, a new approach used in the development of anticancer drugs. From the analysis of a methanolic extract of Brazilian red propolis, 43 new compounds of propolis were isolated, and a cytotoxicity experiment was performed on PANC-1 cancer cells; According to the study, 10 µg/ml of the propolis extract incited PANC-1 cells-death (100% death) in the nutrient-deprived medium and that this pathway was not accompanied by DNA and was a necrotic pathway (Awale et al., 2008). In another study, the antiproliferative capacity of propolis EEP extract on Caco-2 and DU-145 human tumor cell lines were tested, and in KB, Caco-2, and DU-145 cells treated with EEP after 72 hrs incubation, cell viability was 9%, 45%, and 9%, respectively. The total phenol content of the ethanolic extract was found to be 63.88% equivalent to gallic acid. In the content analysis, the antioxidant activity of CAPE in propolis has been recently investigated and the results show that this compound acts as a direct radical scavenger. It has been reported that the capacity of ethanolic extract to prevent tumor cell growth by scavenging free radicals could be associated with its phenolic components, which may have a therapeutic approach in cancer treatment (Russo et al., 2004).

Skin cancer is one of the most common types of cancer, especially in the Caucasian population. A report by the World Health Organization shows that 0.1 million people are newly diagnosed with melanoma each year, and the death rate is climbing (Chiu et al., 2020). In a study investigating the preventive and/or therapeutic effect of EEP extract of Algerian Propolis in mice bearing B16F1 melanoma tumor, it was reported that EEP given after tumor formation increased the survival of mice by 30% and reduced tumor growth by 75%. It has been reported that preventive and curative EEP treatments reduced the invasiveness of B16F1 melanoma cells isolated from resected tumor by 55% and 40%, respectively, compared to control. Also, galangin, one of the most abundant flavonoids in propolis, significantly induced melanoma cell proliferation via autophagy/apoptosis in a dose-dependent manner. In conclusion, it was reported that EEP reduces melanoma tumor progression/dissemination and prolongs the survival of mice and that this complementary therapy can help melanoma patients when used under certain conditions where autophagy is not contraindicated (Benguedouar et al., 2015).

The standard treatment for primary tumors is a combination of therapies including surgery, local radiotherapy, and chemotherapy (Zitvogel et al., 2008). While chemotherapy is one of the most studied modalities in anti-cancer treatments, its effectiveness and safety remain a primary concern, as the toxicity and other side effects of chemotherapy are severe (Tan et al., 2011).

Micro-metastases of dormant tumor cells or cancer stem cells often lead to tumor recurrence and therapeutic failure, even if the tumor has been defeated by treatment. To win the battle against cancer, using just the right combination and program of chemotherapeutic agents is not enough to efficiently kill all cancer (stem) cells and keep the remaining tumor cells under control. It is also necessary to stimulate immune system regulation (Zitvogel et al., 2008).

Propolis can effectively minimize the toxicity damage to various organ systems, which is the side effect of chemotherapy. Improved functioning of the immune system has been demonstrated with propolis treatment (Damodaran, 2021). Although herbal supplements are not recommended for cancer patients by their oncologists, they use these supplements. Most oncologists strongly discourage using such agents due to the lack of evidence on benefits, lack of supporting scientific data, and concerns about possible drug interactions. In a study, 63-83% of cancer patients, especially breast cancer patients, used at least one type of alternative and natural treatment and 25-63% of them routinely used herbal and vitamin drugs on their own, despite medical advice (Omene et al., 2013).

CONCLUSION

Natural products are increasingly used around the world to treat various diseases, including cancer. Herbal medicines and phytochemicals should be made with chemically characterized, reproducible products for cancer prevention and/or treatment by modulating multimolecular targets of angiogenesis, metastasis, and serious adverse events. Compared to traditional drugs used in cancer treatment, the toxicity of medicinal plants should not be considered insignificant, and it should be taken into account that some plants can be extremely toxic and can cause deleterious effects to the health of patients. Therefore, the toxicity of herbal preparations should be evaluated and their applicability as a pharmacological drug should be ensured. (Monteiro et al., 2014). Propolis has attracted the attention of researchers for over 50 years due to its valuable pharmacological effects and potential to prevent and/or treat many diseases. It is only in recent years that scientists have begun to understand its importance for honey bees and as a component of their social immunity. Future work on propolis should be directed towards the development of procedures for standardization of propolis species and research on propolis from different geographical regions to chemically characterize it and explore plant resources. Studies on the biological and pharmacological effects of propolis should be performed only with chemically characterized and standardized propolis, in-vitro and in-vivo studies should be performed together with biological tests to obtain meaningful, reliable and reproducible results.

Conflict of Interest

The authors declared that there is no conflict of interest.

Authorship contributions

Concept: S.K., M.Ç., Design: S.K., M.Ç., Literature Search: S.K., M.Ç., Writing: S.K., M.Ç.

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