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BIOCHEMICAL MECHANISMS OF REALIZATION OF ANTITUMOR EFFECTS OF PROPOLIS

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Abstract. In recent years, interest in natural products such as alternative sources of pharmaceuticals for numerous chronic diseases, including tumors, has been renewed. Propolis, a natural product collected by honeybees, and flavonoid propolis-related components modulate all steps of the cancer progression process. Anticancer activity of propolis and its compounds relies on various mechanisms: cell-cycle arrest and attenuation of cancer cells proliferation, reduction in the number of cancer stem cells, induction of apoptosis, modulation of oncogene signaling pathways, inhibition of matrix metalloproteinases, prevention of metastasis, anti-angiogenesis, anti-inflammatory effects accompanied by the modulation of the tumor microenvironment (by modifying macrophage activation and polarization), epigenetic regulation, antiviral and bactericidal activities, modulation of gut microbiota, and attenuation of chemotherapy-induced deleterious side effects. Ingredients from propolis also ”sensitize“ cancer cells to chemotherapeutic agents, likely by blocking the activation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). In this review, we summarize the current knowledge related to the the effects of flavonoids and other polyphenolic compounds from propolis on tumor growth and metastasizing ability, and discuss possible molecular and cellular mechanisms involved in the modulation of inflammatory pathways and cellular processes that affect survival, proliferation, invasion, angiogenesis, and metastasis of the tumor.

Keywords: cancer, propolis, polyphenolic/flavonoid compounds, molecular targets, chemoprevention, epigenetic and genetic mechanisms, cancer therapy.

Introduction. Despite the tremendous research efforts and rapid development of novel therapies and miracle drugs, cancer is the second leading cause of death in the world. As a hyperproliferative disorder, cancer induces morphological transformation, disturbs apoptotic signaling, and drives uncontrolled proliferation, invasion,

angiogenesis, and metastasis spreading. It also includes a number of genetic and epigenetic modifications that affect the regulation of cell proliferation and survival, such as deregulated CpG dinucleotide methylation and aberrant histone acetylation that can impair the immunogenic potential of cancer cells. During the multistage processes of tumor formation, cancer cells acquire specific properties that differentiate them from healthy cells: resistance to growth inhibition, growth-factor independent proliferation, ongoing replication, escape from apoptosis, migration, invasion, formation of metastasis, and support of angiogenesis [1-7].

It is estimated that the number of new cancer cases reached 19.3 million, together with 10 million deaths, in 2020. The most diagnosed cancer is female breast cancer (11.7% of all cases) and is closely followed by lung cancer (11.4%). Prostate cancer (7.3%) and non-melanoma of skin (6.2%) and colon cancer (6%) are the rest of the top five most commonly diagnosed cancers. Lung cancer is the most common cause of death (18% of all cancer deaths), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers [2]. According to Aggarwal [4], most of all cancer cases (90–95%) are attributable to lifestyle, while 5-10% are associated with faulty genes. So far, more than 500 different genes have been identified contributing to tumor development and progression, suggesting that multitarget drugs would be advantageous as a treatment option in cancer therapy. This brings us to honeybee products such as propolis and its polyphenolic compounds, which are able to target multiple gene products and could be considered as promising candidates in cancer prevention and treatment.

Treatment with bee products (apitherapy), as an alternative medicine practice, has been used since ancient times and is increasingly appreciated as a medical support by many scientific authorities worldwide. Bee products, of which the most researched are honey, propolis, pollen, and royal jelly, are recognized as nutritious food and health products in apitherapy. Their biological effects are mostly attributed to phenolic compounds. Results of previous research suggest that honeybee products and their flavonoid components are particularly promising as antitumor [8-19], immunomodulatory [20-26], and radioprotective [27-34] agents. Results of epidemiological studies also support the important contribution of foodstuffs of vegetable origin in the prevention of numerous illnesses, including cancer [35-39].

The aim of the study. The study of natural compounds and synthetic chemicals that may be useful for cancer prevention and cancer treatment.

Materials and Methods. Analysis of systematic reviews on the chemical components of propolis and study of their antitumor properties.

Results and Discussion. Propolis is one of the most researched hive products, the richest in polyphenolic/flavonoid components. It is a "golden product of the hive" with a wide range of biological activities. Based on that, in recent years, interest in the health effects of honeybee propolis has been revived. The results of many studies indicate that propolis possesses a wide spectrum of activities including antibacterial, antifungal, cytostatic, wound healing, antitumor, anti-diabetic, anti-allergic, and anti-inflammatory [35-44].

Propolis (bee glue) is a resinous mixture collected by honeybees from leaf buds and tree sap. It is used by honeybees for sealing holes in honeycombs, and to smooth out the inside walls, reinforcing the structural stability of the hive and protecting the hive entrance from intruders. Raw propolis typically contains 50% plant resin, 30% beeswax, 10% essential and aromatic oil, and 5% pollen. The rest are various organic compounds, and some micro and macro minerals. Overall, in propolis from different geographical areas, over 800 compounds have been identified. These include phenolic acids, flavonoids (flavones, flavanones, flavonols, dihydroflavonols, and chalcones), terpenes, lignans, amino acids, fatty acids, vitamins, and minerals [40, 41]. Besides geographical location, the chemical profile of propolis also depends on plant sources and bee species. The main chemical components of propolis are fatty and aliphatic acids (24-26%), flavonoids (18-20%), and sugars (15-18%). Compounds that are present in less than 10% are aromatic acids (5-10%), esters (2-6%), vitamins (2-4%), alcohol and terpenes (2-3.3%), microelements (0.5-2.0%), and others (21-27%) [40-43].

Molecular targets modulated by propolis and its flavonoids include transcription factors, growth factors and their receptors, cytokines, enzymes, and genes participating in the regulation of cell proliferation, and apoptosis [3-14].

Growing data [3-7, 13, 14] suggest that propolis and its polyphenolic/flavonoid compounds are multitarget agents in cancer prevention. Possible molecular targets underlying effects of propolis and flavonoids on different stages of carcinogenesis, as well as protective effects against tumors. The modulation of oncogenes, tumor suppressor genes, and intracellular signaling pathways inhibits cell proliferation and induces transformation, angiogenesis, and apoptosis, which have been proposed as the key mechanisms of the chemopreventive action of diverse polyphenolic compounds.

Flavonoids and other phenolic compounds may inhibit activities of telomerase [45-50], matrix metalloproteinases [3-7, 51, 52], angiotensin-converting enzyme [53], and sulfotransferase [54]. They also may interact with sirtuins [55] and cellular drug transport systems [56-58], compete with glucose for transport across the membrane [59-61], interfere with cyclin-mediated cell cycle regulation [1-4], and modulate

platelet function [62]. Furthermore, isoflavones and lignans found in propolis act as phytoestrogens and modulate hormone-dependent carcinogenesis in animals [63-65]. Finally, it must be emphasized that flavonoids are recognized as xenobiotics, which are visible by their rapid metabolism, and their detrimental effects have been observed in vitro and in vivo [50, 66, 67].

Numerous literature data suggest that non-nutritious dietary ingredients, such as flavonoids, may affect the composition of the intestinal microbiota [68-70]. These data emphasize the relationship between flavonoid intake and diverse inflammation-associated chronic conditions such as certain forms of cancers, including colorectal, breast, lung, and liver cancer. The effect of dietary intake on gut microbiota is, at least partially, determined by the metabolism of flavonoids by the gut microbiota. In particular, gut microbiota may regulate cancer processes by affecting genetic instability, sensitivity to host immune response, progression, and therapy efficacy [71]. It has been demonstrated that gut microbiota may affect tumor development and modify interactions with the immune system. Gut dysbiosis represents an imbalance between the number and diversity of the commensal and pathogenic bacterial communities and the production of diverse microbial antigens and metabolites. As the immune system and the gut microbiota work together to preserve intestinal homeostasis, alteration of microbiota composition may lead to immune dysregulation, promoting chronic inflammation and tumor development. In addition, gut microorganisms and their toxic metabolites may reach other body parts via the circulatory system and disturb the physiological conditions of the host and the release of various bioactive molecules, which may impact inflammation and tumorigenesis in specific organs. On the other hand, specific ingredients and substances from Lactobacillus and Bifidobacterium strains demonstrated anticancer effects through their antiproliferative, proapoptotic, and antioxidant activities. Regarding antioxidative action, these strains can express and secrete GSH and antioxidant enzymes (SOD, CAT, and GPx), scavenge free radicals, release antioxidants of small molecular weight and exopolysaccharides, and chelate metal ions, preventing deleterious effects of various carcinogens. These activities reduce oxidative stress, lipid peroxidation, and oxidative damage of DNA and proteins, promote DNA repair, and may help to reduce the risk of cancer development [72].

Mechanisms are speculated to be involved in cancer prevention and therapy using prebiotics: modification of gut microbiota, enhancement of gut barrier functions, protective effect on DNA damage of intestinal epithelium and degradation of potential carcinogens, and stimulation of immune system and anti-inflammatory properties.

Acting as prebiotics, propolis and its polyphenolic/flavonoid components stimulate the immune system, reducing inflammatory responses and oxidative stress.

Pinocembrin, one of the major water-insoluble flavonoids in propolis, inhibited EMT and metastasis by preventing NF-κB translocation to MMP promoter sites. Furthermore, at non-cytotoxic concentrations, pinocembrin suppressed the TGF-β1-induced cell-matrix adhesion, invasion, and migration of human retinoblastoma Y-79 cells. It attenuated the TGF-β1-induced expression of vimentin, N-cadherin, and αvβ3 integrin, reduced the expression of MMP-2 and MMP-9, inhibited the activation of focal adhesion kinase (FAK) and phosphorylation of p38α, and decreased nuclear levels and the DNA binding activity of NF-κB and degradation of inhibitor of κBα (IκBα).

Numerous polyphenolic components from propolis show the inhibition of telomerase activity, including resveratrol, genistein, quercetin, curcumin, apigenin, daidzein, gallic acid, ellagic acid, luteolin-7-0-glucoside, etc., which may add new therapeutic value to cancer treatment by inhibiting hTERT and hTR, telomerase substrates, and their associated proteins [73].

Similar studies have confirmed the inhibitory effect of resveratrol and pterostilbene, a natural analog of resveratrol, on telomerase activity, together with the down-regulation of hTERT expression in various cancer cell lines, which ultimately induced senescence through the DNA damage response. Tannic acid also reduced telomerase activity, cell viability, and cell count in human breast (MCF-7) and human colon cancer cell lines. Likewise, quercetin reduced telomerase activity, down-regulated hTERT expression, and induced apoptosis, thus preventing the growth of various cancer cell lines (lung, stomach, colon, nasopharyngeal, laryngeal, and breast) [74].

Conclusions. Antitumorigenic properties of propolis rely on powerful antioxidant and anti-inflammatory effects, regulation of the cell cycle arrest and proliferation, apoptosis/autophagy, angiogenesis, invasions, metastasis spreading processes, and the ability to regulate epigenetic mechanisms and blood glucose levels. Results presented here indicate that honeybee propolis and its polyphenolic components might be useful adjuvants in the control of tumor growth in vitro and in vivo. The potential anticancer effects of propolis and its polyphenolic/flavonoid compounds can be summarized into the following cellular and molecular mechanisms of action: suppression of cancer/precancerous cell proliferation via direct cytotoxic effect or via its immunomodulatory effect; reduction in cancer stem cell populations; inhibition of the specific oncogene signaling pathways; antiangiogenic effects; modulation of the tumor microenvironment; inhibition of the cellular glucose uptake and metabolism in the cancer cell, and finally; as a supplementary or complementary

approach to conventional anticancer therapies. Current research shows that propolis and its components inhibit multiple signaling pathways essential for the initiation, progression, and metastasis of cancer.

Propolis and its flavonoids may act on pathways involved in the prevention of metastatic progression, inhibition of NF-κB translocation, modulation of gene expression, inactivation of MMPs, and induction of tumor suppressors, acting as histone deacetylase inhibitors for epigenetic therapy and overcoming the TRAIL resistance of cancer cells.

The use of nanoparticulate drug carriers may help to resolve current challenges in drug delivery to the cancer cells, including improvement in drug solubility and stability, extending the half-life of anticancer agents in the blood, reduction in the adverse effects in non-target organs, and aiding in the delivery of high concentrations of anticancer drugs to the site of the disease, providing more effective treatments and better results. Hopefully, propolis can become an attractive and promising agent for cancer prevention and treatment.

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BIOLOGICALLY ACTIVE SUBSTANCES OF FUNGI AND ALGAE AS POTENTIAL PHARMACOLOGICAL AGENTS

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Abstract. Many species of fungi including lichenized fungi (lichens) and algae have the ability to biosynthesize biologically active compounds. They produce, among others, polysaccharides with anticancer and immunostimulatory properties. Presents the characteristics of the most important bioactive compounds produced by fungi and algae. Based on the example of the selected species of mushrooms, lichens and algae, the therapeutic properties of the secondary metabolites that they produce and the possibilities of their use are presented. The importance of fungi, especially large-fruited mushrooms, lichens and algae, in nature and human life is discussed, in particular, with regard to their use in the pharmaceutical industry and their nutritional value. The natural organisms, such as fungi, lichenized fungi and algae, could be used as supplementary medicine, in the form of pharmaceutical preparations and food sources. Further advanced studies are required on the pharmacological properties and bioactive compounds of these organisms.

Keywords: algae, fungi, lichens, mushrooms, biologically active compounds, functional food, pharmaceuticals sources.

Introduction. Mushrooms and algae play a significant role both in nature and in the human economy. About 700 species of fungi have been found to have therapeutic properties [1], so they may be a good source of biologically active compounds for use in the pharmaceutical industry. Many species of edible mushrooms, lichens and algae