Chemopreventive and Chemotherapeutic Effect of Propolis and Its Constituents: A Mini-review

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Propolis is a bee wax rich in various phytocomponents and traditionally used to treat various ailments. Propolis is reported to possess an array of biological properties including anti-inflammatory, antioxidant, anti-cancer, and anti-diabetic as well as cardioprotective, hepatoprotective, renoprotective, and derma protective activities. A plethora of studies confirmed that propolis is effective against various types of cancer including head and neck, lung, liver, brain (glioma), pancreas, kidney, prostate, skin (melanoma), breast, oral, esophagus, gastric, colorectal, and bladder cancers. However, many researchers have demonstrated that propolis displays potent chemoprotective/chemopreventive or anti-cancer activity against only a few types of cancers like oral, gastrointestinal, dermal (melanoma), breast, and prostate cancers. Therefore, this mini-review only summarizes the chemopreventive/chemotherapeutic activities of propolis and its updated underlying mechanisms. Taken together, propolis displays potent chemoprotective or anti-cancer effect due to the presence of various phytocomponents which contribute to pro-apoptotic, cytotoxic, anti-proliferative (cell cycle arrest), anti-metastatic, anti-invasive, anti-angiogenic and anti-genotoxic or anti-mutagenic properties along with antioxidant, immunomodulatory, and anti-inflammatory functions. Hence, propolis could be used as an adjuvant for treating various cancers along with standard chemotherapeutic drugs. However, many large-scale clinical studies are needed to justify such applications.

Key Words Propolis, Anti-cancer, Adjuvant therapy, Apoptosis, Chemotherapeutic drugs

INTRODUCTION

Propolis (bee wax/glue) is a resinous product collected by a bee (Apis mellifera) from plants to cementing the beehives and acts as an insulating or protecting material. Propolis is rich in phytocomponents (polyphenols-flavonoids and phenolic acids) which have numerous therapeutic properties [1,2]. Propolis is traditionally used in the management of various abnormal or pathological conditions which include sore throat, stomach ulcer, oral mucositis, skin rashes, eczemas, bacterial/viral/fungal infection (anti-microbial), and breast cancer [3,4]. Currently, in the market, there are different types of propolis based on their origin. The popular propolis types are Brazilian, Taiwanese, Chinese, Okinawa, Indian, Turkish, Polish, Greece, Cuban, and African. They also differ from one another in a color (red/brown/yellow/green) and texture, depending on the origin of place (geographical) as well as climate [5,6].

The composition of propolis depends on the location (plant source-phytogeography) and collection time (season/climate condition) [7]. The major components include resin (40%-50%), wax (25%-30%), essential oils/fatty acids (8%-10%), bee pollen (3%-5%), organic acids and amino acids (1%-3%), and vitamins and mineral (1%) [8-10]. Propolis contains more than 300 different types of components especially polyphenols (flavonoids, flavones, flavonols, and phenolic acids). The major active components of propolis include caffeic acid phenethyl ester (CAPE), galangin, chrysins, nemorosone, propolin G, artemisinin C, cardanol, cardol, pinocembrin, pinobanksin, chicoric acid, and ohenolic acids (caffeic acid, ferulic acid, cinnamic and coumaric acid) as well as luteolin, apigenin, myricetin, naringenin, kaempferol, quercetin, polysaccharide, tannins, terpenes, sterols and aldehydes [8,11-13]. Studies have also
shown that the presence of various organic acids/amino acids, vitamins (C, A, B complex) and minerals (Ca, P, Mg, Fe, K, and Si) along with the aforementioned active polyphenols makes propolis a special therapeutic as well as a health care product. Hence, propolis can be used as a functional food as well as complementary and alternative medicine [7,14,15].

Ample amounts of data indicate that propolis displays an array of therapeutic functions, such as antioxidant/free-radical scavenging, anti-inflammatory, anti-microbial, anti-cancer, anti-ulcer, anti-allergic, and anti-diabetic activities as well as cardioprotective, hepatoprotective, renoprotective, and dermoprotective (wound healing) properties [8,12,16]. However, many scientists showed immense interest in the chemotherapeutic/chemopreventive activity of propolis due to the presence of phytonutrients which have multitargeted anti-cancer properties, such as pro-apoptotic, autophagy, cytotoxicity, anti-proliferative (cell cycle arrest), anti-migrative (anti-metastatic and, anti-invasive), anti-angiogenic and anti-genotoxic or anti-mutagenic (regulate tumor suppressor genes [TSG] and oncogenes) properties along with antioxidant, immunomodulatory and anti-inflammatory functions [10,12,17]. The common chemopreventive or anti-cancer activities of propolis are illustrated in Figure 1. In addition, propolis is well accepted and safe for human consumption and has been approved by the US Food and Drug Administration [18]. It has been reported that propolis exhibits potent anti-cancer/chemoprotective activity in many models (cell line/animal/human) of head and neck, lung, liver, brain, pancreas, kidney, prostate, skin, breast, oral, esophagus, gastric, colon, and bladder cancers through modulation of various signaling molecules. These include COX, lipoxygenase (LOX), inducible NOS, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), NF-κB, TSG (p53 and p21), mitogen-activated protein kinases (MAPKs), caspases, Bax/ Bcl2, TNF-related apoptosis-inducing ligand (TRAIL), and nuclear factor erythroid 2-related factor 2/heme oxygenase [11,16,17,19].

Propolis is reported to display potent chemoprotective activity against some malignancies like oral, gastrointestinal (GI), dermal (melanoma), breast, and prostate cancers [8,10,16,20,21]. This mini-review summarizes the chemopreventive activity of propolis and its updated detailed mechanism (based on in vitro and animal studies) with focus on the aforementioned cancers.

Chemopreventive effects on oral cancer and underlying mechanisms

Oral cancer is the most common cancer related to the head and neck cancer, which ranks the 6th frequent cancer globally. There are several types of oral cancers including oral squamous cell carcinoma (OSCC), verrucous carcinoma (VC), benign oral cavity tumor (gingiva/tongue), and minor salivary gland carcinoma. Of these, OSCC contributes to 90% to 92% of all types of oral cancer followed by VC and others. Epidemiological studies have revealed that the incidence of oral cancer is high in males than females, especially in developing countries. Moreover, Southeast Asian and Central Africans are highly prone to oral cancer due to increased consumption of chewing betel nut, smoking, and alcohol consumption [22,23]. Many researchers have inferred that propolis and its active components could considerably inhibit the proliferation of oral cancer cells, which was proven by using different cell lines like SCC15/25, CAL27, KB cells [11,18,24].

Treatment with propolis enriched with CAPE displayed potent chemotherapeutic activity by suppressing inflammatory cascade (downregulating COX-2 expression) and considerably altering immunological response (immunomodulatory activity) and subsequently suppressed the prostaglandin 2 synthesis in human oral epidermal carcinoma KB cells [11]. Anti-proliferative and cytotoxic activities were observed in various oral cancer cell lines after administration of various types of propolis and its active components [24,25]. Moreover, propolis and its components are reported to modulate cell cycle regulators like cyclin D, cyclin-dependent kinases (Cdk)-2/4/6, and cyclin-dependent kinase inhibitors, thereby arresting the progression of cancer cell cycle (G2/M phase) [18]. Also, propolis can modulate the expression of various TSGs (p53 and Rb) as well as downregulation of oncogenes.

Figure 1. The common chemopreventive or anti-cancer activity of propolis. TSG, tumor suppressor genes.
(MIFT and K-Ras) [18,26]. Propolis also exhibits potent anti-metastatic and anti-angiogenesis properties as revealed by suppressing MMPs-2/9 activity. This was attributable to downregulation of growth factors like EGF, vascular derived growth factor via alteration of Jun N-terminal kinase, ERK1/2, NF-κB, and Akt signaling [21,26]. Propolis could markedly trigger apoptosis by altering the expression of pro- and anti-apoptotic proteins as well as modulation of kinase C and inhibit tyrosine kinase signaling pathways [24,27]. Moreover, a study conducted by Kuo and colleagues [26] suggested that administration of CAPE would be a better adjuvant therapy in patients with OSCC as it inhibits human oral cancer TW2.6 cell proliferation and invasion/metastasis via downregulation of NF-κB and Akt signaling pathways. In 2018, Celinska-Janowicz et al. [28] reported that polyphenols present in the propolis (chrycin, coumarinic acid, caffeic acid, and ferulic acid) could trigger PRODH/POX (proline degradation/proline oxidase) dependent apoptosis by modulating proline turn over (utilization and degradation) and thus affecting collagen biosynthesis in human tongue squamous CAL-27 carcinoma cells.

**Chemopreventive effects on GI cancers and underlying mechanisms**

GI cancer is a group of malignancies that affects the different organs of the digestive system. These include esophageal, gastric, liver, pancreas, gallbladder, intestinal (colorectal, duodenal), and anal cancers. As it combines many types of cancer, GI cancer is the most common form of cancer that affects both genders worldwide. The prevalence rate of GI cancer, especially colorectal cancer, is high in developing as well as developed countries [29,30]. Moreover, GI cancers are responsible for about 10% to 15% of total global cancer mortality, which is significantly higher than other types of cancer [31,32]. Propolis and its active components are reported to attenuate proliferation and migration (invasion) of various GI cell lines including HCT-15/116, HT-29, CT 26, SW-480/620, WiDr, CaCo2, AGS, KYSE-30, and NCI-N87 cell lines as well as in animal models [33,34].

Propolis shows anti-proliferative and cytotoxic activities (VEGF) in both animal and cell line models [35,36]. Propolis and its active ingredients can trigger both intrinsic and extrinsic apoptosis by modulating miRNA as well as via a TRAIL-dependent mechanism [34,37]. Moreover, different types of propolis and its active ingredients like genistein, chrysin, and CAPE upregulate various tumor suppressor genes like p53 as well as regulate cell cycle by modulating p21 mRNA expression, leading to induction of cell cycle arrest in the G2/M and G0/G1 phase in human colon cancer cells [38,39]. Brazilian propolis exerts anti-oxidant (free radical scavenging), immunomodulatory (macrophage and T lymphocytes activation) and anti-inflammatory effects in the gastric cancer model by downregulating Toll-like receptor 4 (TLR-4), glycogen synthase kinase 3 beta, and NF-κB signaling pathways [40]. Propolis triggers colon cancer cell death by increasing DNA condensation which accounts for the reduced proliferation rate and induction of apoptosis [41,42]. Propolis exhibits strong chemoprotective activity by modulation of the glycolytic metabolism of various cancer cells in a way to lower glucose availability, resulting in lower cell proliferation [10]. Also, propolis and CAPE may directly inhibit VEGF production and thus display anti-angiogenesis as well as inhibit MMP production and thus inhibit metastasis [43]. Studies have shown that propolis and its major ingredients can induce mitochondrial dysfunction by increasing reactive oxygen species (ROS) production and thus suppress proliferation and enhance apoptosis [44,45].

Skiba et al. [46], concluded that treatment with ethanolic extract of propolis (from Poland) could effectively inhibit Helicobacter pylori-induced gastric cancer by suppressing the expression of interleukin (IL)-8 in the gastric adenocarcinoma AGS cell line. Recently, a study conducted by Jafari-Ghahfarokhi and colleagues [47] has indicated that treatment with CAPE could effectively downregulate the mRNA expression of PLD1 gene responsible for phospholipase D production involved in AGS cell growth. Based on these findings, authors recommended that propolis (CAPE) can be used as adjuvant chemotherapy for gastric cancer. FrIon-Herrera et al. [48] have shown that Cuban propolis and its active component (nemorosone) can considerably abolish cell migration (metastasis and invasion) through modulation of the expression of E-cadherin, vimentin, and β-catenin in HT-29 and LoVo colorectal cell lines. Even the studies conducted in animals (rats) demonstrated that treatment with propolis and its active components can effectively suppress the tumor cell proliferation or tumor growth as well as trigger apoptosis [35,49,50].

**Chemopreventive effects on dermal or skin cancer or melanoma and underlying mechanisms**

Skin or dermal cancer is one of the most frequent types of cancer, especially in the Caucasian population. Skin cancer is classified into two types, malignant melanoma and non-malignant melanoma both of which are caused by chronic exposure to excessive UV light. Melanoma characterized by elevated/excess melanin production in melanocytes is one of the dangerous forms of skin cancer. Its incidence has considerably increased in recent times, especially due to climate changes, occupational exposure to UV, and a modified lifestyle pattern [51,52]. A report from World Health Organization shows that 0.1 million people are newly diagnosed with melanoma every year, and the mortality is also climbing [53]. Similar to other sections, many studies have confirmed that propolis and its active phytocomponents display a potent chemoprotective function against skin cancer or melanoma in different cell lines and animal models [54,55].

An ample amount of experiments showed that propolis and its active compounds could display anti-proliferative, cy-
Lately, Misir et al. [73] have demonstrated that Turkish propolis displays various skin cancer or melanoma cell line [41,56,57]. Propolis can inhibit MMPs and trigger apoptosis, cell cycle arrest and autophagy by targeting the NLRP1 inflammatory signaling pathway [54,58]. Ozturk et al. [55] pointed out that the administration of propolis could suppress the production of pro-inflammatory cytokines as well as enhance the production of anti-inflammatory cytokines (IL-10) in the melanoma cell line. Zhang et al. [59], have demonstrated that propolis and its active components (galangin) initiate apoptosis and induce mitochondrial membrane potential loss through upregulating p38 mitogen-activated protein kinase (MAPK) and p62 as well as down-regulate tyrosinase activity (anti-melanogenesis) by modulating microphthalmia-associated transcription factor in B16F10 melanoma cells. Moreover, chrysin (an active ingredient of propolis) effectively stimulates apoptosis (Bax activation) by upregulating p38 MAPK and downregulating the ERK1/2 signaling pathway in A375 and B16-F1 melanoma cell lines [60]. Few animal studies also confirmed the chemotherapeutic properties of propolis against various skin cancer by inhibiting tumor proliferation as well as by triggering apoptosis and autophagy [36,61].

**Chemopreventive on breast cancer and underlying mechanisms**

Breast cancer is one of the common forms of malignancy in females, which contributes to almost half a million death every year. Also, the probability of developing breast cancer was increasing in recent times [62,63]. Statistical and epidemiological studies have shown that breast cancer prevalence among Asian and African women is significantly lower than Hispanic women. In addition, breast cancer incidence rates were also increasing in post-menopausal women than young women due to hormonal involvement [64,65]. Various breast cancer cell lines (MCF-7, MDA-MB-231, BT-474, and T47D-estrogen receptor) are used to examine the chemoprotective activity of propolis and its active components. Results are convincing as both crude extract of propolis as well as its active phytocomponents showed strong chemoprotective or anti-cancer activity in various cell lines [66,67].

Ethanolic extract of propolis and its active components (CAPE) are reported to exhibit antioxidant, cytotoxic, pro-apoptotic, autophagic, and anti-inflammatory activities in lipopolysaccharide stimulated MDA-MB-231 breast cancer cells by suppressing the TLR-4 signaling pathway [68-70]. Frión-Herrera and colleagues [71] demonstrated that treatment of breast cancer cells with propolis and its active ingredient (cardanol) triggered apoptosis (cytotoxicity) by modulation of PI3K/Akt, p38 MAPK, and ERK1/2 signaling pathways as well as by enhancing ROS generation and subsequent loss of mitochondrial potential. Propolis displays strong anti-proliferative and induces cell cycle arrest (G0/G1 and G2/M phase) by upregulating p21 and p27 expression [72]. Lately, Misir et al. [73] have demonstrated that Turkish propolis markedly alters the miRNA expression of tumor suppressors gene (miR 34, 15a, and 16-5p) as well as miR 21 and breast cancer gene (BRCA 1/2) in human breast cancer MCF-7 cells. Many studies have shown that propolis and its components can exert immunomodulatory (macrophage and Natural killer activation), anti-angiogenic (inhibit VEGF) and anti-metastatic properties in the breast cancer cell line model [10]. Jung et al. [74] have indicated that propolis and CAPE can effectively modulate estrogen receptor in MCF 7 and MDA 231 breast cancer cell lines. CAPE can potentially inhibit invasion/metastasis and cell motility in human breast cancer cells through blockage of voltage-gated sodium channels [75]. Moreover, a clinical study confirmed that propolis can effectively prevent oral mucositis in patients with breast cancer, who received doxorubicin and cyclophosphamide (chemotherapy). The above study indicates that propolis can also suppress the adverse events caused during chemotherapy and thus has its palliative property [76].

**Chemopreventive on prostate cancer and underlying mechanisms**

Prostate cancer is the fifth most common cancer globally (second most common in men), and its prevalence rate is increasing significantly in recent times especially in western countries. Prostate cancer is the second leading cause of death from cancer owing to its high metastasis rate, which accounts for 4% of all global cancer death rates. It is an androgen-dependent tumor but progresses very slowly without any notable symptoms [16,77]. The incidence of prostate cancer is higher in Caucasians than Asians, but the mortality rates are higher in black than white population [78]. Moreover, prostate cancer cells are highly resistant to apoptosis and autophagy. Hence, treating the prostate cancer cells is quite hard and thus a new therapeutic strategy should be developed by focusing more on anti-inflammatory and antioxidative drugs. Existing evidence has conferred that propolis and its active components can strongly suppress the proliferation and migration as well as enhance apoptosis in various prostate cancer cell lines like LNCaP, PC-3, PANC-1, and DU-145 [77,79].

Propolis and its components display strong anti-proliferative activity via suppression of proliferating cell nuclear antigen and vascular cell adhesion molecule 1 in human prostate PC-3 cancer cells [80]. Also, propolis supplementation could significantly arrest the cell cycle in prostate cancer cells by modulation of the expression of cyclin A, B, and D1, and Cdk as well as p21 [79,81]. Moreover, propolis can induce apoptosis by decreasing the cellular levels of apoptosis inhibitor proteins including cellular inhibitor apoptosis protein 1/2 (cIAP-1/2) [81,82]. Meanwhile, Szliszka et al. [83] reported that the treatment with propolis (apigenin, galangin, CAPE, and kaempferin) significantly improved TRAIL (death receptor)-mediated apoptosis in prostate cancer cells. Propolis and its derivatives (chrysin and CAPE) were proven to enhance
apoptosis of androgen-independent prostate cancer cells (PC-3) by increasing ROS production as well as suppressed their proliferation by down-regulating ERK1/2 and PI3K/Akt signaling [84,85].

Ozturk and his colleagues [55] have reported that propolis and its active ingredients can suppress ROS production due to antioxidant and anti-inflammatory activities associated with suppression of COX-2/LOX and NF-κB signaling. Moreover, this study demonstrated that propolis possessing 5-α reductase inhibitory activity effectively inhibited prostate cancer cell proliferation. Propolis and its components (genistein) were reported to enhance expression of TSGs, such as p53 and p16 as well as demethylation of p16 and MGMT genes in various prostate cancer cell lines [86]. CAPE has been reported to inhibit prostate cancer cell invasion and metastasis through activation of the non-canonical Wnt-signaling pathway [87]. CAPE can synergistically act with docetaxel and paclitaxel (standard chemotherapeutic drugs) and significantly decrease cell proliferation by triggering cell cycle arrest and subsequently initiating apoptosis in PC-3 prostate cancer cells [86].

Clinical studies and adjuvant therapy of propolis
Propolis and its active components have potent chemotherapeutic properties in various cancer cells and in animal studies. However, only few clinical trials have been conducted with propolis and its active components against limited cancer conditions (polyp), but the results are not convincing [88,89]. Moreover, propolis has poor bioavailability owing to low water solubility and hence can be delivered using nanoparticles (carriers-Ag-silica/Au) or by encapsulation [89], which might enhance the chemopreventive activity. Many studies have confirmed that propolis (safe and well-tolerated) can be recommended as an adjuvant agent against various cancers as it might potentiate either standard chemotherapy or radiotherapy (palliative) while suppressing the adverse effects induced by the standard chemotherapeutic drugs [10,76,88,89]. Figure 2 illustrates the in-depth chemopreventive or anti-cancer effects of propolis and its components against oral, GI, skin, breast, and prostate cancers.

CONCLUSION AND FUTURE PROSPECTIVE
Overall, this mini-review highlights the chemopreventive and chemotherapeutic activities of propolis and its detailed mechanism against oral, dermal/skin (melanoma), breast, prostate and GI cancers. Propolis displays potent chemoprotective effects due to the presence of various phytocomponents (CAPE, galangin, chrysin, artepillins C, and nemorosone) which contributes to pro-apoptotic, cytotoxicity, anti-proliferative, anti-angiogenic and anti-genotoxic properties along with antioxidant, immunomodulatory and anti-inflammatory functions. Therefore, propolis might be recommended for...
adjuvant therapy along with conventional chemotherapeutic drugs to either potentiate their efficacy or to minimize adverse effects. However, many large-scale clinical studies should be conducted with crude propolis extract and its active components (individually or mixture at different ratios) to validate their use in human populations.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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