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REVIEW

Emerging Adjuvant Therapy for Cancer: Propolis and its Constituents

Seema Patel

Bioinformatics and Medical Informatics Research Center, San Diego State University, San Diego, CA, USA

ABSTRACT. Propolis is a bee-metabolized resinous substance (bee glue) from plant sap and gums. It has been in usage as a healing agent since antiquity, yet has not garnered global popularity as a health promoter. Its biological effects, which range from antimicrobial, antioxidant, anti-inflammatory, antidiabetic, dermatoprotective, anti-allergic, laxative and immunomodulatory to anticancer, have been validated. Propolis has shown efficacy against brain, head and neck, skin, breast, liver, pancreas, kidney, bladder, prostate, colon and blood cancers. The inhibition of matrix metalloproteinases, anti-angiogenesis, prevention of metastasis, cell-cycle arrest, induction of apoptosis and moderation of the chemotherapy-induced deleterious side effects have been deduced as the key mechanisms of cancer manipulation. The components conferring antitumor potentials have been identified as caffeic acid phenethyl ester, chrysin, artepillin C, nemorosone, galangin, cardanol, etc. These compounds target various genetic and biochemical pathways of cancer progression. Depending on the botanical sources and the geographical origin, biological activities of propolis vary. Despite phenomenal development in cancer research, conventional therapy falls short in complete malignancy management. The findings obtained so far build hope that propolis as a complementary medicine may address the lacunae. This review documents the recent advances and scope of amendement in cancer remediation with adequate emphasis on the mechanistic aspect of propolis.

KEYWORDS. anticancer, apoptosis, caffeic acid phenethyl ester, chrysin, propolis

BACKGROUND

Quintessential healthiness of honey is universally acknowledged but that of propolis is sparsely known (Alvarez-Suarez, Giampieri and Battino, 2013). Propolis is another bee-processed product of plant origin with comparable yet distinctly different ameliorative properties. Bees gather this resinous secretions from buds, flowers, leaves, barks and latex of plants to seal, strengthen and disinfect their hives. Propolis is brown, green, red, black or white in hue and sticky or brittle in structure. For

Address correspondence to: Dr. Seema Patel, Bioinformatics and Medical Informatics Research Center, San Diego State University, 5500 Campanile Dr San Diego, CA 92182, USA (E-mail: Patel3@rohan.sdsu.edu).

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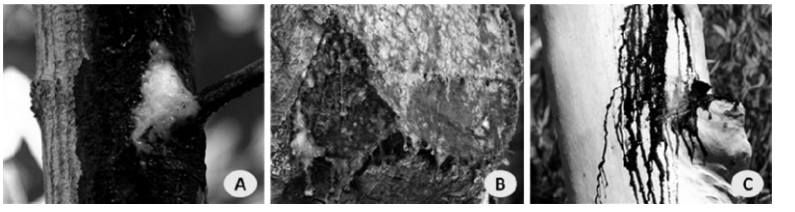

FIGURE 1. Potential sources of propolis (A) Sweetgum, (B) Pine, (C)Eucalyptus.

the gooey property and synthesis by bees, it's often called 'bee glue' or 'bee putty'. The composition varies depending on the botanical source and the geographical areas. The plant resources are too diverse, the chief being pine, poplar, oak, chestnut, sweetgum, birch, eucalyptus, willow, elm, acacia, coin vine *etc* (Figure 1). Literature survey reveals that propolis is harvested across the globe viz. Thailand, Taiwan, China, India, Iraq, Turkey, Greece, Cuba, Tunisia, Croatia, Egypt, Brazil, Portugal, Mexico and Caribbean countries.

In folk medicine, it is used as an antibiotic substitute. Ancient healers used it to cure wound, ulcers, cold, fever and infections (Toreti, Sato, Pastore and Park, 2013). Propolis is discovered to be rich in polyphenols, flavonoids, aminoacids and minerals. It is sold as dietary supplement in health food stores, as capsules, ointments or liquid extracts (Al-Hariri, 2011). A growing body of experimental proofs support the healthy roles of propolis spanning from antioxidant, anti-inflammatory, antimicrobial, skin emollient, laxative, antidiabetic, and immunomodulator, to most remarkable anticancer.

Cancer inhibition by propolis is so far the most startling finding. Cancer is a multifactorial disease, triggered by genetic aberrations and environmental mutagens and their hostile interactions. Antitumor properties of propolis have been attributed to the bolstered antioxidant status, augmented immune-surveillance, suppression of proliferation, reduction in the cancer stem cell populations, blockage of specific oncogene signalling pathways, anti-angiogenesis, modulation of the tumour microenvironment, valorization of chemotherapeutics and alleviation of side effects induced by drugs (Meneghelli, Joaquim, Flix, Somensi, Tomazzoli and da Silva, 2013). In this review, the current state of knowledge and prospects of propolis as cancer therapeutic have been explored.

Preparation and Chemical Profile

After harvesting from honeycomb, propolis is fragmented for optimal functional ingredient recovery. Water, ethanol, hexane, dichloromethane or dimethyl sulfoxide-based solvent extraction yields the bioactive-rich fractions. Apart from the conventional extraction techniques involving maceration and Soxhlet, supercritical fluid extraction, microwave-assisted extraction and sonication have proved effective in maximum bioactive acquisition (Biscaia and Ferreira, 2009, Khachaananda, Tragoolpua, Chantawannakul and Tragoolpua, 2013, Trusheva, Trunkova and Bankova, 2007). Propolis consists of a complex combination of resin (45%), wax and fatty acids (30%), essential oils (10%), pollen (5%) and organic compounds (10%) (Chen et al., 2009) (Figure 2). The key constituents of propolis have

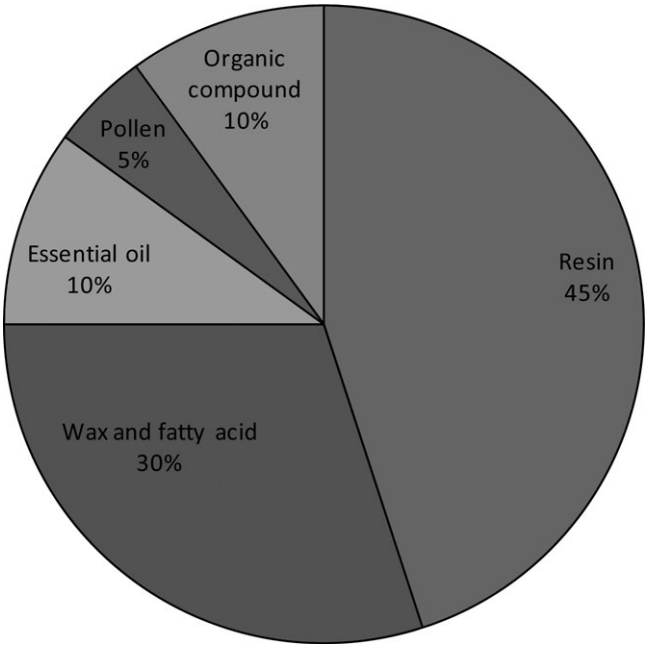

FIGURE 2. The common class of compounds in propolis.

been characterized as phenolic acids, flavonoids, terpenes, alcohols, sugars, esters etc. High performance liquid chromatography-mass spectrometry (HPLC-MS) and ultra-high performance liquid chromatography-mass spectrometry (UPLC-MS) analyses have identified the predominant bioactive components to be chrysin (5, 7-dihydroxyflavone), caffeic acid phenethyl ester (CAPE), artepillin C, nemorosone, galangin, cardanol, cardol, quercetin, kaempferol and p-coumaric acid (Figure 3). Chrysin, artepillin C, galangin, quercetin and kaempferol belong to flavonoid class; CAPE is an ester of caffeic acid, nemorosone is a benzophenone, cardanol and cardol are phenolic lipids and p-coumaric acid is a phenolic acid. Baccharin and drupanin, the phenolic acids (cinnamic acid derivatives) isolated from Brazilian propolis have been reported to be crucial antiangiogenic factors (Hattori et al., 2011). Also, vitamin A, B_1, B_2, B_3 and minerals viz. Ca, Mg, Fe, Zn, K, P, Si, Mn, Co, Cu have been detected in propolis. An informative tabular presentation of the propolis components and their chemical classes has been published (Sawicka, Car, Borawska, Nikliński and 2012).

Anticancer Properties

Cancer-related morbidity and mortality pace is unprecedented. Surgical removal of tumour or resorting to chemo-, radio- and immunotherapy are common ways to fight cancers. But, resistance towards these conventional curative regimens have summoned for discovery of novel approaches of treatment. Complementary and alternative medicine (CAM) has emerged as a supportive strategy (Ernst and Cassileth, 1998). Propolis as an emergent CAM has demonstrated efficacy against a range of cancers *viz*. head and neck, brain and spinal cord, blood, skin, breast, pancreas, liver, colon, prostate, kidney and bladder. It elicits antitumor response

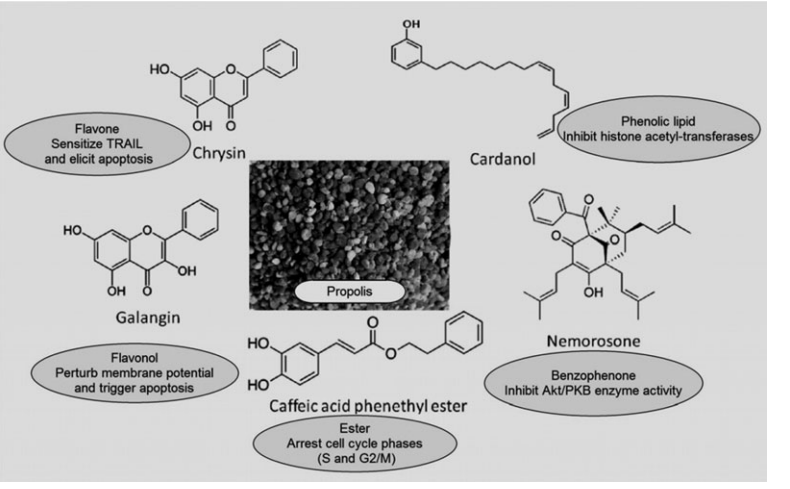

FIGURE 3. Major anticancer compounds isolated from various propolis.

alone or in conjunction with other drugs. The tumour blocking effects of propolis extracts and their constituents have been reviewed (Watanabe, Amarante, Conti and Sforcin, 2011). Apoptosis, cell-cycle arrest and interference with metabolic pathways have been recognized as the underlying mechanisms. Further, the antiproliferative action of propolis, CAPE and chrysin in restraining tumour progression has been reviewed (Sawicka, Car, Borawska and Nikliński, 2012). A host of high throughput tools (viz. flow cytometry, mass spectrometry and nuclear magnetic resonance) have proved the anticancer potency of propolis. The active anticancer components have been presented in Table 1. The pathways intervened by various geographically-distinct propolis has been elucidated in Figure 4.

Brain and Spine

It was observed that rat C6 glioma cells treated with CAPE results in morphological anomalies and boosts the expression of glial differentiation marker proteins (glial fibrillary acidic protein and S-100β). Also, it arrests the motility and invasion of the C6 glioma cells. Further, it was discerned that CAPE inhibits the activity of matrix metalloproteinases (MMP) and induces the expression of RhoB, a tumor suppressor (Lin, Liang, Lee, Chuang and Tseng, 2010). MMPs are a family of zinc-dependent neutral endopeptidases that disintegrate extracellular matrix and basement membranes, expediting tumour progression. Propolin G, isolated from Taiwanese green propolis extract was used to develop an anticancer agent NBM-HD-3, a histone deacetylase inhibitor (HDACis). Rat C6 glioma and human glioblastoma DBTRG-05MG cell lines were subjected to the HDACis. NBM-HD-3 treated cells were analyzed by a barrage of tools. It was found to increase phosphatase and tensin homolog (PTEN) and protein kinase B (Akt) protein levels significantly, while decreasing phospho-PTEN and phospho-Akt levels markedly. The modulation enhances tumour suppressor by down-shifting Akt/PKB signaling pathway. NBM-HD-1 exerted antagonistic effect on the cancer cells between

TABLE 1. The Cancer Cells Studied and the Underlying Mechanism of Action of Propolis

Cancer	Types of Cells	Bioactive Compound	Mechanisms	Rerferences
Brain	Rat glioma C6	CAPE	Inhibit the activity of matrix metalloproteinases	Lin, Liang, Lee, Chuang & Tseng (2010)
	Human glioblastoma *U87MG*	Prenylflavanone	Induce the expression of RhoB	Huang et al. (2011)
			Increase PTEN and AKT protein levels, while decreasing phospho-PTEN and phospho-AKT levels	Huang et al. (2012)
			Increase the expressions of tumour-suppressor gene p53	Markiewicz-Zukowska et al. (2013)
			Attenuate NF-κB nuclear localization	
Head and neck	Human squamous carcinoma FaDu Oral submucosal fibroblast OSF Neck metastasis of gingival carcinoma GNM Tongue squamous cell carcinoma TSCCa	CAPE and its ethyl analogue	Caspase 3 cleavage and apoptosis	Hehlgans, Lange, Eke, Kammerer, & Cordes (2011)
Skin	Murine B16-F1	Chrysin	Stimulate IL-2, IL-10 expression	Missima, Pagliarone, Orsatti, Araujo, & Sforcin (2010)
	Human melanoma A375	Galangin	Downregulate ERK 1/2 and activate p38 MAP kinases	Pichichero, Cicconi, Mattei, & Canini (2011)
	Murine B16F10			Zhang, Lan, Huang, & Hua (2013)
Breast	Human breast adenocarcinoma MCF-7 and	Nemorosone	Estrogen-like activity	Popolo et al. 2009
	MDA-231	CAPE	Block the cell cycle in the G_0G_1 phase	Seda Vatansever et al. (2010)
			Express pERK1/2 and pAkt	Popolo et al. (2011)
			Decrease dihydropyrimidine dehydrogenase protein level	Sobočanec et al. (2011)
			Induce cell cycle arrest, apoptosis	Wu et al. (2011)
			Reduce expression of growth and transcription factors	

(Continued on next page)

TABLE 1. The Cancer Cells Studied and the Underlying Mechanism of Action of Propolis *(Continued)*

Cancer	Typesof Cells	Bioactive Compound	Mechanisms	Rerferences
Liver	Human hepatoma Hep-3B cells	Chrysin Nymphaeol	Reduce expression of COX-2 and NFkB p65 Increase expression of p53, Bax and caspase 3	Khan Devaraj, & Devaraj, 2011 Chen et al. (2012)
Pancreas	Human pancreatic PANC-1	Phenylallylflavanones	Cause necrotic-type morphological changes	Li, He, Awale, Kadota, & Tezuka (2011)
Kidney	Human renal carcinoma A-498	CAPE	Modulate oxidative processes	Valente, Baltazar, Henrique, Estevinho, & Carvalho (2011)
Bladder	Transitional cell carcinoma TCC	Caffeic acid, naringin, chrysin and quercetin	Induce cytotoxicity	Dornelas et al. (2012a), (2012b)
Prostate	Human prostatic adenocarcinoma LNCaP, PC-3 and DU-145	CAPE Epi-nemorosone	Augment the activity of NF-κB Downregulate cyclins D1/D3 and CDK 4/6 Inhibit AKR1C3-mediated cancer	Szliszka et al. (2011a) Szliszka et al. (2011b) Barlak et al. (2011) Diaz-Carballo et al. (2012) Chuu et al. (2012) Endo et al. (2012)
Colon	Human colon carcinoma HCT-15, HCT116, HT29 and SW480	Chrysin	Increase the cellular mRNA levels of p21CIP1 and p53 Arrest at the G2/M phase of the cell cycle Increase p53 and decrease Ki-67 expression Modulate glycolytic metabolism of tumor cells	Ishihara, Naoi, Hashita, Itoh, & Suzui (2009) Pratsinis, Kletsas, Melliou, & Chinou (2010) Sulaiman et al. (2012) Valenca et al. (2013)
Blood	Human T cell lymphoblast-like cell CCRF-CEM Human promyelocytic leukemia HL-60 Human erythromyeloblastoid leukemia K562	CAPE	Decrease the hTERT expression Downregulate Bcl-2 and activate Bax	Cogulu et al. (2009) Avci et al. (2011) Sulaiman et al. (2012) Franchi et al. (2012)

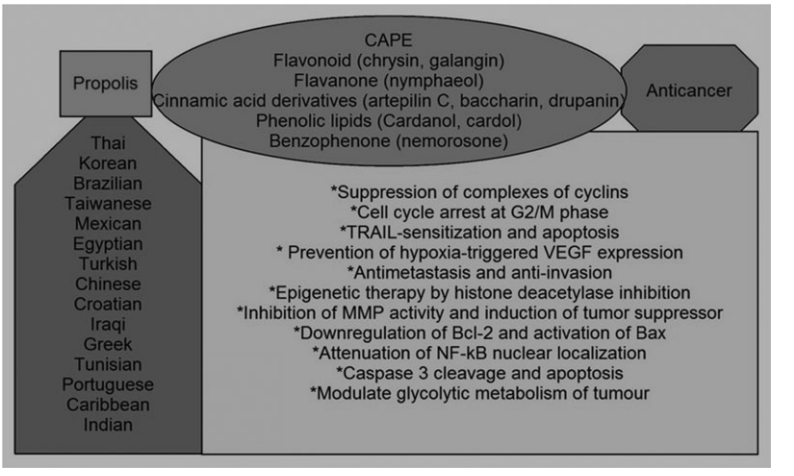

FIGURE 4. Most-studied propolis for cancer therapeutics, their key constituents and the modes of cancer inhibition.

1 and 4 h at a dose of 17 μM (Huang et al., 2011). Further, the activity against rat glioma cells in a xenograft model was reconfirmed (Huang et al., 2012). The cyclin-dependent kinase inhibitor 1A (p21) gene expression had markedly increased while cyclin B1 and D1 gene (overexpression of these genes lead to uncontrolled cancer cell growth) expressions had decreased. NBM-HD-1 increased the expressions of tumour-suppressor gene p53 in a dose-dependent manner and exhibited potent antitumor activity. The combinatory impact of propolis ethanolic extract and temozolomide (drug to treat aggressive brain tumors) on human glioblastoma U87MG cell line growth was investigated. The concomitant usage of both components resulted in a higher extent of growth inhibition than individual actions. The co-treatment led to a double attenuation of NF-κB nuclear localization, promoting the inhibition of the cancer cells (Markiewicz-Żukowska et al., 2013).

Head and Neck

The radio-sensitizing capacity of propolis was evaluated in human head and neck squamous carcinoma FaDu cells (Hehlgans, Lange, Eke, Kammerer and Cordes, 2011). It significantly reduced cell growth and clonogenic survival (ability of a cell to proliferate indefinitely), in a time- and concentration-dependent manner. Propolis-induced apoptosis and caspase 3 cleavage, increased phosphorylation of extracellular signal regulated kinase 1/2 (ERK1/2), protein kinase B/Akt1 and focal adhesion kinase (FAK). A 3h pre-treatment with propolis amplified the radiation sensitivity of cancer cells significantly. The effect of alcoholic extract of green propolis was evaluated against chemically-induced epithelial dysplasia in rat tongues. When administered orally for 20 weeks at a dose of 100–300 mg/kg, the protective role against the lingual carcinogenesis was observed (Cavalcante et al., 2014). CAPE treatment suppressed cell proliferation and colony formation of human oral squamous carcinoma TW2.6 cells. The mechanism of inhibitory action was tracked. CAPE decreased G1 phase cell population, increased G2/M phase cell popula-

tion, and induced apoptosis in TW2.6 cells. The treatment reduced the protein abundance of Akt, Akt1, Akt2, Akt3, phospho-Akt Ser473, phospho-Akt Thr 308, GSK3β, FOXO1, FOXO3a, phospho-FOXO1 Thr24, phospho-FoxO3a Thr32, NF-κB, phospho-NF-κB Ser536, Rb, phospho-Rb Ser807/811, Skp2, and cyclin D1, while increasing the cell cycle inhibitor p27Kip. Co-treatment with CAPE and 5-fluorouracil exhibited additive anti-proliferation of TW2.6 cells. Dose-dependent inhibitory effect was perceived (Kuo et al., 2013).

Skin

Melanoma is the malignancy of pigment-producing melanocytes and it is a fatal form of skin cancer. The immunomodulatory effect of propolis on melanoma models of mice was investigated (Missima, Pagliarone, Orsatti, Arajo and Sforcin, 2010). Stress induced an expanded tumour area, while propolis-treated mice showed a melanoma development similar to the control. Propolis administration stimulated IL-2 and IL-10 production, which may be related to immunoregulatory effects. The biological activity of chrysin was tested on murine B16-F1 and human melanoma A375 cell lines. It was demonstrated that the flavone reduced melanoma cell proliferation and induced cell differentiation in both types of melanoma cells through synthesis and intracellular accumulation of heme precursor protoporphyrin IX. Also, elevation in the expression of porphobilinogen deaminase, the enzyme responsible for metabolism of porphyrin was noted. It induces cell death in both murine and human melanoma cells through caspase-dependent mechanisms, involving down-regulation of ERK 1/2 and activation of p38 MAP kinases. It implies that the induction of cell death by propolis could be a promising therapeutic approach in cancer therapy (Pichichero, Cicconi, Mattei and Canini, 2011). The effect of another major propolis constituent galangin on B16F10 murine melanoma cells was investigated. This flavonoid disrupted mitochondrial membrane potential, prompted apoptosis and lowered tumour cell viability. Apoptosis of the melanoma cells was caused by cleavage of procaspase-9, procaspase-3 and poly (ADP-ribose) polymerase (PARP). Moreover, galangin significantly induced the activation of phospho-p38 MAPK in a time and dose-dependent manner (Zhang, Lan, Huang and Hua, 2013).

Breast

Breast cancer is a heterogenous disease and this diversity often renders the existing therapies futile. However, a set of research findings has validated the oestrogen receptor positive (ERα+) as well oestrogen receptor negative (ERα-) breast cancer cell inhibitory potency of propolis. The antiproliferative activity of the ethanol extract of brown Cuban propolis was investigated on human breast cancer cell lines. The MTT assay showed a significant attenuation of ERα+ MCF-7 cell proliferation. Dose and time-dependent inhibition of cell growth in the G_1 phase of cell cycle was observed. Oestrogen-like activity of propolis was suggested from the findings (Popolo et al., 2009). Pertaining to this finding, efficacy of nemorosone, the polycyclic polyisoprenylated benzophenone in propolis for breast cancer suppression was investigated. Though, the benzophenone lacked anti-oestrogenic activity, it was capable of reducing the cell proliferation induced by 17-β-oestradiol (Camargo et al., 2013). It was further determined whether nemorosone, isolated

from Cuban propolis exerts anticancer effects on MCF-7 and MDA-MB-231 cells. It was confirmed to inhibit only ERα+ MCF-7 cells and not ERα- MDA-MB-231 cells. Nemorosone impeded MCF-7 growth by blocking the cell cycle in the G_0/G_1 phase. Moreover, the expression of phospho-ERK1/2 and phospho-Akt, considered to be the traits of non-genomic oestrogen signalling pathway were reduced in the treated MCF-7 cells (Popolo et al., 2011). The apoptotic effect of Turkish propolis extract on the caspase pathway of MCF-7 cells was investigated. Various doses of the extracts were incubated with the cancer cells during a 48h culture. MTT results showed that the extract at a dose of 0.125 mg/mL dilution induced apoptosis (Seda Vatansever et al., 2010). The antitumor properties of Croatian propolis were evaluated in mice injected with 4T1 mammary carcinoma. It was revealed that pre-treatment of mice with propolis in combination with 5-fluorouracil prolonged the suppressive effect of the drug on tumour growth and reduced the number of metastasis only in male mice. Propolis decreased dihydropyrimidine dehydrogenase protein level indicating higher sensitivity to 5-fluorouracil (Sobočanec et al., 2011). It was reported that CAPE inhibits both MCF-7 and MDA-231 tumour growth in a concentration dependent fashion, both in vitro and in vivo. It induces cell cycle arrest, apoptosis and reduces the expression of growth and transcription factors, including NF-κB. Notably, CAPE down-regulates mdr-1 gene, responsible for the resistance of cancer cells to chemotherapeutics. Further, CAPE dose-dependently suppresses vascular endothelial growth factor (VEGF) formation by MDA-231 cells, preventing capillary-like tubes development, implying repression of angiogenesis (Wu et al., 2011). The cancer-inhibitory property of water soluble derivatives of Egyptian propolis was evaluated against Ehrlich ascites carcinoma cells in mice. Administration of propolis by gastric intubations (50 mg/kg body weight) was followed by intraperitoneal injection of the cancer cells. After 11 consecutive days of propolis treatment, cancer cells shrunk in volume, diminished in total cell count and viability percentage. Immunological studies revealed a significant increase in the lymphocyte transformation rate and phagocytic activity in the group treated with propolis (Badr et al., 2014). It was investigated whether ethanol extracts of propolis and CAPE can induce apoptosis in MCF-7 cells. Brazilian red propolis significantly reduced the cancer cell viability through the induction of mitochondrial dysfunction, caspase-3 activity and DNA fragmentation. The action was believed to be due to endoplasmic reticulum stress-related signalling induction of CCAAT/enhancer-binding protein homologous protein (CHOP) (Kamiya, Nishihara, Hara and Adachi, 2012). Cancer stem cells are defiant towards drugs and notoriously associated with tumour recurrence, metastasis and high mortality. So, it was probed whether MDA-231 stem cells and mouse xenografts are susceptible to CAPE. It caused dose-dependent inhibition of daughter cell differentiation from the stem cells. Also, the stem cells significantly progressed from a quiescent state to replicating state, which enhanced their sensitivity towards drugs. Treatment of the cancer cells with CAPE for 4.5 days decreased CD44 protein (verified to promote metastasis) levels by 95% (Omene, Wu and Frenkel, 2012).;

Liver and Pancreas

The effect of chrysin on proliferation and apoptosis of diethylnitrosamine-induced early liver tumour development in rats was investigated. The gavage of chrysin

(250 mg/kg) thrice a week for 3 weeks after induction of carcinogenesis, significantly reduced the number and size of nodules formed. Also, considerable decline in serum activities of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and γ-glutamyl transferse (γ-GT) was noticed. Expression of COX-2 and NF-kB p65 was significantly lowered whereas that of p53, Bax and caspase 3 increased at transcription and translation levels. An ebb in levels of β-arrestin (protein playing role in tumour progression) and the anti-apoptotic marker Bcl-xL was also noted (Khan, Devaraj and Devaraj, 2011). It was observed that nymphaeol, abundant in Taiwanese propolis exhibits cytotoxicity against broad range of cancer cell lines. Semi-synthetic modification (prenylation and dimerization) of the flavanone strengthened its efficacy against human hepatoma Hep-3B cells (Chen et al., 2012). Two phenylallylflavanones were isolated from the methanolic extract of Mexican propolis. Both compounds exhibited preferential cytotoxic activity against human pancreatic PANC-1 cells in a nutrient-deprived medium. Even though end-stage pancreas cancers are difficult to cure, intake of water extract of propolis has been reported to alleviate pain and serious symptoms in the patients (Li, He, Awale, Kadota and Tezuka, 2011). The effect of CAPE on epithelial-mesenchymal transition of PANC-1 cells was investigated. The over-expression of vimentin (a marker for the transdifferentiation) was attenuated by CAPE. Also, the alteration in cell morphology from polygonal to spindle was partially reversed. CAPE delayed the transforming growth factor β (TGF-β)-stimulated migration potential and inhibited the expression of transcriptional factor Twist 2 (known to promote tumour progression). CAPE suppressed the expression of Twist 2 and growth of PANC-1 xenografts in orthotopic pancreatic cancer model without significant toxicity (Chen et al., 2013).

Kidney and Bladder

Propolis and its constituents have exhibited ameliorative effect on kidney and bladder cancer. The possible chemo-preventive action of Portuguese propolis was determined. Renal carcinoma A498 cell line was treated with the extracts (0–100 μg/mL) and the evoked-cytotoxicity was determined by MTT assay. Selective lethality towards malignant cells compared to normal cells was conspicuous. In vitro cancerous growth inhibition by the extract occurred in a concentration-dependent manner (Valente, Baltazar, Henrique, Estevinho and Carvalho, 2011).

The effects of L-lysine-extracted green propolis and L- lysine alone for 40 weeks on carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN)-induced rat bladder carcinogenesis was determined. In the group treated daily with propolis 30 days prior to receiving BBN, carcinoma incidences were much lower than that of control (Dornelas et al., 2012). Further, the effects of water-soluble derivative of green propolis in bladder cancer angiogenesis in rats were assessed. After BBN abuse for 14 weeks, the rats were administered with the combination of propolis, L-lysine and celecoxib (anti-inflammatory drug). The microvascular density in bladder carcinomas was lower in rats receiving propolis compared to control (Dornelas et al., 2012).

Prostate

The activity of propolis has been verified against in vitro and in vivo prostate cancer instances. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is an endogenous anticancer agent in that it causes apoptosis of cancer cells. However, as a consequence of reckless chemotherapy, tumour cells are evolving and acquiring resistance towards TRAIL (Szliszka and Krol, 2013). The cytotoxic and apoptotic effects of Brazilian propolis ethanolic extract were examined against human prostate adenocarcinoma LNCaP cells. The extract sensitized TRAIL-resistant cancer cells and augmented their NF-κB activity. The co-treatment of cancer cells with 100 ng/mL TRAIL and 50 μg/mL propolis extract increased the percentage of apoptotic cells to about 66% and caused a significant disruption of membrane potential in LNCaP cells (Szliszka et al., 2011). Further, the cytotoxic and apoptotic effects of ethanolic extract of propolis was examined on hormone-sensitive LNCaP and hormone-resistant DU145 prostate cancer cell lines. The extract sensitized TRAIL to induce death in the cancer cells. The strongest cytotoxic effect on LNCaP cells was exhibited by apigenin, kaempferid, galangin and CAPE in combination with TRAIL (Szliszka et al., 2011). It was evaluated if protein expression profile in human prostate cancer PC-3 cell lines could be differentiated when incubated with dimethyl sulfoxide and water extracts of Turkish propolis. The antioxidant-rich extract at the dose of 20 μg/mL reduced the cell viability as determined by proteomic approach (surface enhanced laser desorption ionization time of flight mass spectrometry (SELDI-TOF MS) (Barlak et al., 2011). It was observed that nymphaeol, a key component in Taiwanese propolis exhibits cytotoxicity against prostate cancer cell lines. Further, their activities were improved via a semi-synthetic strategy. The potencies of the novel prenylated flavanones were assessed against PC-3 and DU-145 cell lines. Superior inhibition against PC-3 cell line was observed (Chen et al., 2012). The antitumor potential of 7-epi-nemorosone isolated from Caribbean propolis was determined against LNCaP cells. Flow cytometry revealed a significant accumulation of these cells in the sub-G_0/G_1, G_1 phase and depletion in the S phase. A concomitant down-regulation of cyclins D1/D3 and CDK 4/6 in LNCaP cells was detected by Western blot. Annexin-V-FITC labeling and caspase-3 cleavage assays showed that 7-epi-nemorosone induced the apoptotic events. Major signal transduction mediators p38 MAPK and Akt/PKB were down-regulated by the nemorosone (Daz-Carballo et al., 2012). The vigor of artepillin C from Brazilian green propolis in reducing TRAIL resistance of prostate cancer LNCaP cells was evaluated. Artepillin C increased the expression of TRAIL and decreased the activity of NF-κB. Further, it induced a significant activation of caspase-8 and caspase-3. Results showed that artepillin C sensitized the cancer cells by both extrinsic and intrinsic apoptotic pathways (Szliszka, Zydowicz, Mizgala and Krol, 2012). It was observed that CAPE dose-dependently suppressed the proliferation of LNCaP, DU-145, and PC-3 cells. On oral administration, it significantly inhibited the tumour growth of LNCaP xenografts in nude mice. The results suggest that CAPE can cure prostate and potentially other types of cancers that are guided by the phospho-70S6K and Akt signalling pathways (Chuu et al., 2012). The human aldo-keto reductase AKR1C3, also known as type-5 17β-hydroxysteroid dehydrogenase and prostaglandin F synthase has been suggested as a therapeutic target in the treatment of prostate cancer. The inhibition of AKR1C3

by Brazilian propolis-derived cinnamic acid derivatives was examined. A product baccharin emerged as a potent competitive inhibitor with high selectivity. Molecular docking and site-directed mutagenesis studies suggested that it causes AKR1C3-mediated cancer inhibition (Endo et al., 2012). The modulatory impact of CAPE on docetaxel and paclitaxel cytotoxicity in PC-3 cancer cells was investigated. Reduction in cyclin D1 and c-myc, decreased Bcl-2/Bax ratio and enhanced caspase-3 activity, drop in ER-α and insulin-like growth factor-1 receptor proteins were witnessed in the cancer cells. Synergistic action of CAPE with the drugs was demonstrated (Tolba et al., 2013).

Colon

The anticancer activities of ethanol extracts of Chinese and Brazilian propolis were determined on human colon carcinoma HCT116, HT29 and SW480 cells. Both the extracts caused a marked dose-dependent growth inhibition. In HCT116 cell line, Chinese propolis extract induced apoptosis after 72h of treatment. Also, it caused a dose-dependent elevation in the cellular mRNA levels of p21CIP1 and p53 (Ishihara, Naoi, Hashita, Itoh and Suzui, 2009). It was observed that a diterpene manool identified in the butanolic extract of Greek propolis is selectively active against HT29 cells. The cancer cells were arrested at the G_2/M phase of the cell cycle (Pratsinis, Kletsas, Melliou and Chinou, 2010). The antitumour properties of Iraqi propolis were evaluated on HCT116 cell lines implanted on mice models. Oral administration of propolis, even at non-toxic doses was associated with increased endo-reduplications, higher p53 and diminished Ki-67 expression in tumour cells. Necrosis, characterized by dramatic swelling of cytoplasm and loss of membrane integrity, cell rupture and release of cellular contents were observed (Sulaiman et al., 2012). The in vitro antitumor activity of Portuguese propolis ethanolic extract was evaluated on the human colon carcinoma HCT15 cells. A conspicuous, dose- and time-dependent cytotoxic effect was observed, the maximum potency exerted by chloroform fraction. Modulation of glycolytic metabolism, as witnessed by a decline in glucose consumption and lactate production was elucidated to be the mechanism of action (Valena et al., 2013). Baccharin and drupanin worked in synergy against both intrinsic and extrinsic apoptotic signalling transduction in human colon cancer DLD-1 cells. The mechanisms were deduced to be the regulation of TRAIL death receptors DR4 and DR5 or Fas/ FasL pathway, and augmentation of miR-143 expression (the conserved miRNA that induces apoptosis) (Kumazaki et al., 2014).

Leukaemia

Telomerase reverse transcriptase is a catalytic subunit of the telomerase enzyme, playing critical role in cancer cell immortality. The in vitro effect of Manisa (Turkey) propolis on human telomerase reverse transcriptase of patient leukaemia cells was investigated. Different concentrations of propolis were administered to the bone marrow cell cultures of the patients. A significant decline in the reverse transcriptase expression level was observed at 60 ng/mL concentration of propolis (Cogulu et al., 2009). The apoptotic effects of CAPE were examined on human leukemic lymphoblasts CCRF-CEM cells. A time- and dose-dependent increment in the cytotoxic effect of the treated cells was observed. Enzyme-linked immunosor-

bant assay (ELISA) and acridine orange/ethidium bromide results showed that apoptotic cell population increased significantly. Also, there was remarkable loss of MMP in response to the compound (Avcı et al., 2011). The antitumour property of Iraqi propolis on HL-60 cells was evaluated. Antiproliferation was observed and the apoptosis was associated with the down-regulation of Bcl-2 (Sulaiman et al., 2012). The in vitro cytotoxic activities of Brazilian green and red propolis on human chronic myeloid leukaemia K562 cells were compared. After 48h incubation with the cells, red propolis conferred higher anticancer response compared to green propolis. When administered at equal dose (100 μg/mL), red propolis exerted cytostatic effect on K562 cells and stimulated apoptosis commensurate to Gleevec, a standard leukaemia drug (Franchi et al., 2012). The effect of honey, propolis and beewax mixture (4:2:1) was evaluated on leukaemia chemotherapy-induced oral mucositis through randomized controlled clinical trial and appreciable therapeutic effect was obtained. However, it remains obscure whether propolis contributed in antiinflammation or the honey was responsible for it (Abdulrhman et al., 2012).

Multiple Organs

Several studies have reported wide spectrum anticancer activity of propolis. The derivatives of Mexican propolis were evaluated against a panel of six cancer cell lines (murine colon 26L5 carcinoma, murine B16BL6 melanoma, murine Lewis lung carcinoma, human lung A549 adenocarcinoma, human cervix HeLa adenocarcinoma and human HT-1080 fibrosarcoma). A phenylpropanoid-substituted flavanol from propolis showed the most potent cytotoxicity against human lung adenocarcinoma A549 cells and human fibrosarcoma HT1080 cells, eliciting stronger effect than that of 5-fluorouracil (Li, Awale, Tezuka and Kadota, 2010). The antiproliferative activity of Thailand propolis ethanolic extract was evaluated against five cancer (human bronchogenic ChaGo, human gastric KATO-III, human colon SW620, human breast BT474 and human liver Hep-G2) and two normal (HS27 fibroblast and CH-liver) cell lines. The hexane fraction demonstrated the most potent anticancer activity which further increased with successive purification steps (Umthong, Phuwapraisirisan, Puthong and Chanchao, 2011) It was witnessed that pre-treatment with chrysin increases TRAIL-induced degradation of caspase 3, caspase 8 and PARP proteins. Morphological changes and appearance of sub-G_1 peak in HCT-116 and nasopharyngeal carcinoma CNE1 cells were observed (Li, Wang, Huang, Xiong, Chen, Ong, 2011). Tunisian propolis ethanol extract was tested for its antiproliferative effects on normal MRC-5 and cancer (HT29, A549, Hep2, raw 264.7, Vero) cell lines. MTT assay revealed that the extract possessed strong potency against all the studied cancer cell lines (Kouidhi, Zmantar, Bakhrouf, 2010). The anticancer activity of the ethanolic extract of Indian stingless bee propolis was investigated against MCF-7, HT-29, Caco-2 and B16F1cells. At 250 μg/mL concentration, cytotoxicity was observed against all the investigated cell lines. It's antioxidant components leading to early apoptosis of the cells was assumed to be the mode of action (Choudhari, Haghniaz, Rajwade, Paknikar, 2013). The TRAIL-sensitization effect of chrysin from Thai propolis was investigated against A549 and cervical cancer HeLa cell lines. Delving into the mechanism revealed that chrysin selectively decreases

the levels of Mcl-1 protein (a Bcl-2 family protein), by down-regulating its gene expression as determined by qRT-PCR. The proposed action of chrysin in enhancement of TRAIL-induced cell death by inhibition of STAT3 and suppression of Mcl-1 was supported by using a STAT3-specific inhibitor cucurbitacin-I (Lirdprapamongkol et al., 2013).

Mechanisms of Therapeutic Action

As the above evidences show, the anticancer mechanisms of propolis vary widely viz. angiogenesis prevention, apoptosis induction, cell cycle arrest, antiproliferation (Novak et al., 2014). Further, the ameliorative role of propolis expands to potentiating chemotherapeutics and alleviating their adverse effects. It was observed that the Chinese red propolis and CAPE in particular showed strong suppressive effects against VEGF-induced angiogenesis. In vitro tube formation was hampered, so human umbilical vein endothelial cells (HUVEC) proliferation and migration was disrupted (Izuta et al., 2009). The angiogenesis-inhibition property of benzo[k,l]xanthene lignan, synthesized through the biomimetic dimerization of CAPE was evaluated. The lignan showed a dose-dependent inhibitory effect on new vessel growth in the angiogenesis bioassay and inhibited VEGF secretion in ovarian cell culture (Basini et al., 2012). Human aldo-keto reductases metabolize aldehydes and drugs containing carbonyl groups and are involved in inflammation and tumorigenesis. Inhibitors of a tumour marker AKR1B10 gene (encoding a aldo-keto reducatse enzyme) are regarded as promising cancer therapeutics. CAPE proved to be an effective inhibitor of these critical enzymes (Soda et al., 2012). The antiproliferative potency of crude hexane and dichloromethane extracts of propolis from Thailand was evaluated. Cardanol and cardol in the extract induced cytotoxicity and cell death of human ductal carcinoma (BT474), undifferentiated lung (Chaco), liver hepatoblastoma (HepG2), gastric carcinoma (KATO-III) and colon adenocarcinoma (SW620) cells (Teerasripreecha et al., 2012). Other studies have found that the cytotoxicity of these phenolic lipids is mediated through epigenetic mechanisms by inhibition of histone acetyl-transferases (Sung et al., 2008). The active fraction of Brazilian red propolis containing xanthochymol (a catechol) and formononetin (an isoflavone), exhibited antiproliferative effects towards B16F0 cell line and murine tumour xenografts by arresting cell cycle in the G2/M phase and inducing apoptosis. A daily extract dose of 10 mg/kg daily subdued the tumor (Novak et al., 2014).

Doxorubicin damages the anatomy of testis, causing infertility. In rat model, propolis when concurrently administered with the chemothearapeutic, cancelled the adverse effect on testis, verified in higher level of serum testosterone (Rizk, Zaki and Mina, 2014). A Portuguese propolis sample reinforced paclitaxel effect in MDA-MB-231 and DU145 cell lines (Silva-Carvalho et al., 2014). A polar derivative of propolis augmented macrophage cytoxic activity and sensitivity of Ehrlich ascites tumor cells implanted on mice to hyperthermal intraperitoneal chemotherapy. Further the propolis product abated toxicity of cisplatin towards normal cells (Oršolić et al., 2013).

It is increasingly advocated that the individual efficacy of the propolis key components be assessed for their anticancer effect. A recently published review depicts the anticancer mechanism and the targets of CAPE. The repertoire

included various transcription factors such as nuclear factor-κB, tissue necrosis factor-α, interleukin-6, cyclooxygenase-2, nuclear factor (erythroid-derived 2)-like 2 (Nrf2), inducible nitric oxide synthase (iNOS), nuclear factor of activated T cells, hypoxia-inducible factor-1α, and signal transducers and activators of transcription (Murtaza, Sajjad, Mehmood, Shah and Siddiqi, 2014). The effect of nemorosone on pancreatic xenograft tumours in mice was determined. At a dose of 50 mg/kg daily, nemorosone was rapidly absorbed from bloodstream and was monitored to quell the tumour. HPLC-MS detected the metabolites to be CYP3A4-independent oxidation products (Wolf, Hilger, Hoheisel, Werner and Holtrup, 2013)

The molecular intervention of propolis in cancer propagation is only sparsely unravelled. Overcoming of TRAIL-resistance by propolis and its polyphenols may be one of the mechanisms responsible for their cancer preventive effects (Szliszka and Krol, 2013).

Apart from the precise interference of cancer metabolism, the therapeutic effect of propolis stems from enhanced antioxidant status as well. The abundance of polyphenols and flavonoids endow propolis with free radical scavenging, lipid peroxidation prevention and myeloperoxidase inhibition properties. Convincing number of histological studies have shown that propolis is capable of combating a wide range of stressors and alleviating DNA damage in organs (liver, kidney). It has been inferred that the augmentation of antioxidant enzymes by propolis shields against the oxidizing abuses (Türkez, Geyikoğlu, Yousef, Toğar and Vançelik, 2013).

Geographical Origin and Dose-Response Relation

The bioactive composition of propolis depends on the geography and climate (Teerasripreecha et al., 2012). Apart from bee and floral diversity, the extraction methods vary in various regions, thus bioactive constitution and biological efficiency of propolis from different origin are distinct (Szliszka and Krol, 2013; Kurek-Grecka et al., 2014). As Table 2 indicates, propolis from various regions has different percentages of active compounds and they target different cancers.

Also, the dosage required for eliciting a particular response vary. At high concentration (50–100 μM) CAPE caused apoptosis while at low concentration (0–25 μM) it caused cell growth inhibition of rat C6 glioma cells (Sawicka, Car, Borawska and Nikliński, 2012). Out of 5, 10, 20 μg/mL, the latter resulted in the maximum loss of PC-3 cell viability, reaffirming the importance of dose determination. The dosage information for various in vitro and in vivo studies has been presented in Table 3. However, the phenolic compounds reserve in each propolis type is specific, so comparison of biological response does not hold much rationale.

Future Directions

Propolis has a complex structure and many of its components are yet to be identified. The geographical origin, botanical source and season of harvest impact its chemical makeup, so consistency of dosage needs to be ensured (Novak et al., 2014). Despite containing a plethora of bioactive constituents, the imbibition of propolis is challenged by low water solubility and poor stability against oxidation (Fan et al., 2014). To mend for this lacunae, the optimum bioavailability needs to be ensured. In this regard, structural modification is likely to offer better efficacy against cancers. Prenylation has been demonstrated

TABLE 2. Propolis from Various Geographical Region and Their Bioactive Compounds

Geographical Origin	Bioactive Compounds	Cancer	References
Thai	Cardanol and cardol	Liver	Terrasripreecha et al. (2012)
	Chrysin	Colon Gastric Lung Cervix	Lirdprapamongkol et al. (2013)
Taiwanese (green)	Nymphaeol	Brain cancer	Huang et al. (2012)
		Liver Prostate	Chen et al. (2012)
Iraqi	Phenolic acids and their esters	Colon Blood	Sulaiman et al. (2012)
Chinese	Cinnamic acids and their esters	Colon	Ishihara, Naoi, Hashita, Itoh, & Suzui (2009)
Greek	Diterpenes (Manool)	Colon	Pratsinis, Kletsas, Melliou, & Chinou (2010)
Cuban (brown)	Nemorosone	Breast	Popolo et al. (2009) Popolo et al. (2011)
Tunisian	Myricetin, quercetin	Lungs	Kouidhi, Zmantar, & Bakhrouf (2010)
		Colon	
Turkish	—	Prostate	Seda Vatansever et al. (2010) Barlak et al. (2011)
Croatian	Flavonoid aglycones	Breast	Sobočanec et al. (2011)
Egyptian	CAPE	Breast	Badr et al. (2011)
Brazilian	Artepillin C	Breast	Kamiya, Nishihara, Hara & Adachi (2012)
	Cinnamic acid derivatives (baccharin)	Prostate	Szliszka, Zydowicz, Mizgala, & Krol (2012) Endo et al. (2012)
Mexican	Phenylallylflavanones	Pancreas	Li, He, Awale, Kadota, & Tezuka (2011)
		Lungs Fibroblast	Li et al. (2010)
Portuguese	Flavonoid	Kidney	Valente, Baltazar, Henrique, Estevinho, & Carvalho (2011)
		Oral	Cavalcante et al. (2011)
Caribbean	Epi-nemorosone	Prostate	Diaz-Carballo et al. (2012)
Indian	—	Breast, Colon	Choudhari, Haghniaz, Raiwade, & Paknikar (2013)

to enhance cytotoxicity of nymphaeol (Chen et al., 2012). Efficacy augmentation through adequate purification, supercritical extraction and substitution of functional groups must be emphasized. Microemulsion has been verified to boost immunomodulatory effect of propolis flavonoids (Fan et al., 2014). It could be replicated for anticancer efficacy too. Blending with other natural anticancer agents, chemical drugs or innovative therapeutic paradigm could be undertaken for possible synergistic action. Some encouraging results of chemotherapeutic efficacy valorization (with 5-fluorouracil, temozolomide docetaxel and paclitaxel) has been verified and this could be used as starting point for further investigation. In combination with photodynamic therapy, propolis exerted better efficacy in lowering viability and proliferation of malignant human head and neck AMC-HN-4 cell lines (Ahn, Biswas and Chung, 2013)

TABLE 3. The *In Vitro* and *In Vivo* Dosage of Propolis and Its Constituents Effective in Eliciting Anticancer Responses

Propolis/ Constituent/ Mixture	Dose	*In vitro/ In vivo*	References
Green propolis	100–300 mg/kg	Rat tongue carcinogenesis	Cavalcante et al. 2011
Brown Cuban propolis	1–25 mg/mL	MCF-7 cell	Popolo et al. 2009
Turkish propolis	0.125 mg/mL	MCF-7 cell	Seda Vatansever et al. 2010
Egyptian propolis	50 mg/kg	Ehrlich ascites carcinoma mice	Badr et al. 2011
Portuguese propolis	100 μg/mL	Renal A498 cells	Valente et al. 2011
Brazilian propolis	50 μg/mL	Prostate LNCaP cells	Szliszka and Krol 2011
Turkish propolis	20 μg/mL	PC-3 prostate	Barlak et al. 2011
Chinese and Brazilian propolis	4–41 μg/mL	HCT116, HT29 and SW480 cell lines	Ishihara et al. 2009
Portuguese propolis	5–26 μg/mL	HCT15 cells	Valença et al. 2013
Turkish propolis	60 ng/mL	Acute lymphoblastic leukemia and chronic myeloid leukemia cells	Cogulu et al. 2009
Brazilian red propolis	100 μg/mL	Leukemia K562 cells	Franchi et al. 2012
Indian stingless bee propolis	250 μg/mL	MCF-7, HT-29, Caco-2 and B16F1cells	Choudhari et al. 2013
CAPE	5–100 μM/L	Human oral cancer TW2.6 cells	Kuo et al. 2013
	15 μM/L	MDA-231 and MCF-7 cells	Wu et al. 2011
	0–40 μM/L	MDA-MB-231 stem cells	Omene et al. 2012
	10 mg/kg	LNCaP xenografts in nude mice	Chuu et al. 2012
	10 μM/L	CCRF-CEM leukemic cells	Avcı et al. 2010
Chrysin	250 mg/kg	Liver tumor in mice	Khan et al. 201
Galangin	100 μM/L	Melanoma B16F10	Zhang et al. 2013
Anticancer agent with propolis as constituent NBM-HD-3	17 μM/L	Rat C6 glioma and human glioblastoma DBTRG-05MG	Huang et al. 2011

Efficacy assays against hitherto unexplored cancer cell lines must be performed. CAPE was documented to induce apoptosis in human cervical cancer lines by arresting S and G2 /M phase of cell cycle. The crucial role of the transcription factor E2F-1 in CAPE-mediated growth inhibition was verified by silencing it (Hsu et al., 2013).

Acquisition of resistance towards chemotherapy is a mounting issue in cancer therapy regime. Modulation of drug targets, activation of prosurvival pathways and ineffective induction of cell death have rendered the drugs ineffective (Holohan, Van Schaeybroeck, Longley and Johnston, 2013). Propolis cinnamic acid derivatives could cause apoptosis of drug-resistant human colon cancer DLD-1

cells. This efficacy merits further probing in order to tackle the bigger challenge of drug resistance (Kumazaki et al., 2014).

Another interesting facet to anticancer investigation of propolis would be to evaluate the contribution of each of its major functional component. Findings reporting the superior efficacy of the compound compared to the propolis as a whole are emerging. Artepillin C and baccharin exerted higher cytotoxicity than Brazilian green propolis (De Oliveira et al., 2014).

Pharmacokinetics of propolis has been an ill-investigated area till now. Only a few studies have delved into this aspect. The absorption of naringenin, an active constituent of Algerian propolis in rats was monitored. Hematological analysis revealed fast assimilation of naringenin from gut, indicating high bioavailability. At same dosing, naringenin in propolis was more efficiently imbibed compared to standard naringenin, assumed to be due to other flavonoids in propolis (Mesbah and Samia, 2011).

Side effects of propolis consumption like inflammation, dermatitis and other allergy have often been reported. So, safety evaluation is required before administration to patients. Any other detrimental consequences of propolis ingestion must be explored in order to develop complication-free CAM. Validated quality control and clinical trials are prerequisite for administration of propolis or its active ingredients to cancer patients (Chan, Cheung and Sze, 2013).

Role of the newest omics, metabolomics has started to be appreciated in developing metabolic signature of propolis sourced from diverse origins. Spectral analysis by mass spectrometry (mainly gas chromatography (GC – MS)) and nuclear magnetic resonance, assisted with chemometrics (principal component analysis, partial least square-discriminant analysis, random forest) and machine learning algorithms appear pragmatic in pattern recognition of various propolis. Many missing links associated with composition of propolis was unriddled with the aid of metabolome data. Chinese crude propolis makeup was analyzed by pyrolysis-GC-MS. The contents of 8 categories of flavonoids, terpenoids, acids, esters, hydrocarbons, phenols and alcohols, aldehydes and ketones in the screened propolis samples varied exceedingly. The dominant components, flavonoids and terpenoids were found in the range of 0–54.9% and 0.6–21.6%, respectively. (Yang et al., 2014). Headspace solid-phase microextraction GC-MS was employed to profile propolis volatile compounds. A large array of volatile components were obtained, the eminent of them being benzoic acid, benzyl benzoate, benzyl salicylate, benzyl cinnamate, vanillin, δ-cadinene, γ-cadinene, α-muurolene, β-eudesmol, τ-cadinol, α-cadinol etc. The findings suggest the harnessing of metabolomics in chemical fingerprint procurement of propolis (Pellati, Prencipe and Benvenuti, 2013).

CONCLUSIONS

There is no paucity of evidences to support the anticancer potentials of propolis. It has been verified effective against a broad array of cancers in brain, spine, head, neck, skin, breast, liver, pancreas, kidney, bladder, prostate, colon and blood. The key studies reflect the effective antitumor components in propolis to be caffeic acid phenethyl ester, chrysin, artepillin C, nemorosone, galangin and cardanol. While acknowledging the inevitability of conventional therapy, the key

role of alternative medicines like propolis must not be dismissed. It's anticancer effect is the cumulative result of antioxidant, anti-inflammatory, immunomodulatory, cytostatic, antineoplastic, antiproliferative and apoptotic properties. The inhibitory mechanisms of propolis are multifarious, as it acts on different targets of cancer metabolism. The crucial pathways have been unveiled to be the prevention of metastatic progression, blockade of NF-κB nuclear localization, gene expression modulation, inactivation of MMP and induction of tumour suppressors, acting as histone deacetylase inhibitor for epigenetic therapy and surmounting the TRAIL resistance of cancer cells. The genomic impact of propolis on upstream mechanistic require further probing. Augmented emphasis on the dose-response and structure-function relation is necessitated. Standardized quality control and flawless design is indispensable for clinical trials and metabolomics is strongly believed to facilitate this goal. Novel, inexpensive cancer therapeutics can be developed from propolis with optimum research undertakings. Synergistic effect of propolis with standard-of-care chemotherapeutics has been observed and it could be a promising domain of exploration. For its validated antimicrobial properties it is named 'nature's penicillin'. Escalated investigation into its anticancer competence might earn it the epithet 'nature's doxorubicin'. This review is expected to galvanize further research in this area and contribute to cancer CAM repository.

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ABOUT THE AUTHOR

Seema Patel, Address correspondence to: Dr. Seema Patel, Bioinformatics and Medical Informatics Research Center, San Diego State University, 5500 Campanile Dr San Diego, CA 92182; E-mail: seemabiotech83@gmail.com

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