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Review Article

A review of the anticancer properties of bee products and their molecular mechanisms: An overview on lung cancer

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Abstract

Lung cancer is one of the most common types of cancer in the world, and it represents a significant percentage of all diagnosed cancers. Despite better clinical outcomes associated with current drugs, lung cancer has a worse survival rate than any of the other commonly occurring malignancies. Evidence suggests that natural products offer promising potential for improving the current treatment approaches and/or developing novel treatment strategies. Bee products such as honey, propolis, and venom have been reported to exert anti-cancer effects on a variety of human cancer cell lines, thereby paving the way for a wide range of treatment possibilities. The current review focuses on the cytotoxic effects of bee bioactive compounds on all types of cancer, and the molecular pathways by which they might reduce tumor cell growth or trigger apoptosis of cancer cells, with particular reference to lung cancer. This strategy could potentially improve the efficacy of current remedies, reduce the doses of chemotherapy drugs, and decrease adverse effects of chemotherapy drugs. Furthermore, in vitro studies on anti-cancer properties of bee products are carefully reviewed. The results reveal that bee products have the potential to become effective treatment agents against many forms of cancer in the future.

Keywords: *Lung cancer, Natural product, Bee product, Anti-tumour*

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INTRODUCTION

Cancer is a life-threatening morbidity that arises primarily due to an abnormality in the cell cycle that induces either excessive cell proliferation, incomplete apoptosis, or both [1]. According to the World Health Organisation (WHO), cancer is the second leading cause of death globally; it caused an estimated 9.6 million deaths in 2018 alone [2]. Lung cancer is the most common kind of cancer, with high frequency and fatality equivalent to those of other malignancies [3]. There were 2 million new cancer cases diagnosed globally in 2018 [4]. Furthermore, the American Cancer Society predicted that 228,820 new cases of lung cancer would be diagnosed in the United States in the year 2020 [5]. Although smoking is regarded as a predominant cause of lung cancer, followed by genetic mutations, parameters such as co-morbid disease, environmental factors and lifestyle factors are also involved in the pathogenesis of lung cancer [6]. Among genetic mutations, the p53 gene which indues genetic instability, is the first gene

that has been implicated in lung carcinogenesis [7]. Several other causes such as retinoblastoma/p16 abnormality and the chronic lung inflammation, also contribute to development of lung cancer [7]. Studies have shown that patients with advanced stage cancer have a low 5-year survival estimate of 4.7 %, but patients with surgically removed stage I tumours have a 5-year survival of 70 % [8]. It is true that lung cancer deaths decrease, and percentage survival have seen steady increases over the past 30 years, thanks to improvements in the care approaches involved [9]. Low-dose computed tomography screening of heavy smokers enhances early diagnosis of lung cancer, leading to timely care which is considered to reduce mortality [10]. Data from the International Early Lung Cancer Action Program indicates that patients with stage I lung cancer diagnosed via screening have an estimated survival of 88 % over 10 years [11]. The current therapeutic options for cancer are surgery, chemotherapy, radiation therapy, immunotherapy, and hormone therapy. However, these treatments appear to be ineffective in advanced stages [12]. On the other hand, high risk of recurrence along with late detection, lead to poor prognosis and general mortality of about 10 percent [7]. The present treatments barely alleviate cancer. Chemotherapy is toxic to normal surrounding cells, since it could lead to gene modification, DNA methylation, and histone changes, resulting in resistance to some chemotherapeutic agents [13].

Lung cancer management and current therapy

Despite significant advances in oncology, clinical outcomes of lung cancer remain inadequate, owing mostly to late diagnosis, patient age, co-existing disorders, and relatively limited treatment options. [14]. Lung cancer therapy should be assessed on the basis of the advanced stage of cancer, clinical and functional state, co-morbidities, nutritional status, and cognitive functions [15]. It should be noted that age is not an influencing factor for care initiation. Surgery is the treatment of choice for early stage of non-small-cell lung cancer [NSCLC]. Elderly patients who are disqualified from surgery should be considered for extreme radiotherapy. Single-agent chemotherapy has been observed to be beneficial for elderly people with advanced NSCLC who have general good health, essentially due to its low toxicity and good survival estimate. Polychemotherapy is the first-line therapy for patients with small-cell lung cancer (SCLC) who require prophylactic brain radiation [15]. However, its toxicity seems to be greater than the benefits of the therapy. Increased lung cancer cases and late diagnosis, high mortality, and poor efficiency of chemotherapy and radiation contribute to the need for more efficient screening measures as well as safer and more effective treatments for elderly persons with lung cancer.

A significant number of medications used as chemotherapeutic agents may lose their effectiveness if patients develop resistance to drugs [16]. These drugs certainly have the potential to significantly improve survival of cancer patients, but they have also been found to significantly increase the probability of complications and adverse effects associated with therapy. Therefore, in order to minimize the number of lung cancer deaths, it is crucial to develop a treatment with improved efficacy and decreased adverse effects. Several studies have been conducted to achieve this in order to obtain potent sources of natural products which function as supplementary anti-cancer agents for suppressing and delaying carcinogenesis. Numerous studies have revealed the efficiency of several natural products in the treatment of lung cancer, including the use of propolis [17], honey [18], and bee venom [19].

A large number of studies have identified the biological properties of bee products, although other articles indicate their medicinal properties and uses as nutraceutical, pharmaceutical and cosmetic agents [20]. Bee products have been studied and tested in clinical settings, but pharmacological and therapeutic standardization remain complicated because of their high chemical heterogeneity due to wide differences in honeybees and their botanical origins. While several compounds or classes of compounds have been isolated, and only a few of them were pharmacologically identified, the findings from these studies highlight the importance of bee products in the introduction of medicines from natural sources. This review was aimed at providing research information on thorough screening of the bioactive compounds present in bee pollen, venom and propolis as remedies for lung cancer or prophylactic medication, taking into account the importance of this field in the quest for new treatments for cancer.

Bee products

Since ancient times, bee products have been used as medicines. For example, bee pollen has been shown to improve energy and stamina [20]. Propolis has been shown to be beneficial in restoring good health, while royal jelly has been shown to improve the immune system and

increase energy [21]. Honey, which is primarily used as a natural sweetener, is also used as an antiseptic agent for treating wounds and sore throat. The therapeutic standardization of these drugs is hindered by variations in chemical properties because of the wide differences in the botanical origins of honeybee, although some molecules have been isolated and pharmacologically characterized [22]. Phenolics, methylglyoxal, major royal jelly proteins [MRJPs], and oligosaccharides are the chief bioactive compounds found in honey. The antimicrobial jelleins and royalisin peptides, MRJPs, and hydroxy-decanoic acid derivatives found in royal jelly, as well as 10-hydroxy-2-decenoic acid [10-HDA], have antimicrobial, anti-inflammatory, immunomodulatory, neuro-modulatory, metabolic syndrome-preventing, and anti-aging characteristics [22]. Propolis, on the other hand, contains antiviral, immunomodulatory, anti-inflammatory caffeic acid phenethyl ester and artepillin C. These compounds, and their effects on cancer, are unique to Brazilian propolis. Bee venom consists of poisonous peptides such as pain-inducing melittin, channel K-blocking apamine, and allergic phospholipase A2 [22].

Honey

Honey, one of the main bee products, consists of more than 200 components, most of which are sugars (75 % monosaccharides and 10-15% disaccharides), water, enzymes, vitamins (vitamin B6, riboflavin, niacin and thiamine); minerals, phenolic compounds (flavonoids and phenolic acids), and volatile compounds [21]. Honey has long been used as a supplementary source of food and medicine. Reactive oxygen species (ROS) and inflammation play a significant role in carcinogenesis [23]. The phenolic compounds in honey, on the other hand, have anti-inflammatory and antioxidant properties [24]. To a large extent, the phenolic compounds are responsible for the antioxidant potential of honey. However, as described earlier, the composition of phenolic compounds varies significantly as a function of floral origin. Therefore, honey can be expected to display a wide range of antioxidant intensities. Moreover, honey suppresses the growth of several microbes. The antibacterial properties displayed by specific honey samples have been evaluated with sequential neutralization, keeping in mind that the mechanisms of action are complicated and vary with the source of honey. Evidence suggests that honey has an intrinsic regulatory effect on blood glucose level [25]. Moreover, honey intrinsically possesses wound- and burn-healing capacities [26].

Propolis

Propolis is a resin-like, pliable and compact substance formed by bees by combining bee wax and saliva with materials taken from tree buds, sap flows, and other plant components [27]. Raw propolis generally contains more than 300 components, majority of which are triterpenes (50 % w/w), wax (25–30 % w/w), and volatile mono- and sesquiterpenes [8–12 % w/w). Typically, propolis has odour of resin and phenolics which constitute 5–10 % w/w [27]. Since propolis contains mostly phenolic compounds, it has been extensively researched for its antioxidant and free radical-scavenging effects. Pinocembrin, pinobanksin, and chrysin are examples of such compounds with significant antioxidant and antiradical capabilities [28]. Propolis volatile components such as β-eudesmol in Bulgarian propolis; delta-cadinene, α-pinene and trans terpineol in Greek propolis; terpineol, spatulenol, and ledol in Canary Islands; propolis insular, farnesol, dihydroeudesmol and guaiol in Democratic propolis, have shown significant anti-bacterial properties. Furthermore, propolis contains antifungal agents effective against disease-causing yeasts such as *C. albicans, C. parapsilosis, C. tropicalis,* and *C. glabrata* [29]. The antifungal properties were due mostly to volatile compounds from Brazilian propolis viz. a-pinene, b-pinene and d-cadinene, as well as volatile compounds from Turkish propolis viz. phenyl-, ethyl-, and benzyl alcohols, and decanal [30]. Propolis also possesses potential antiviral properties, sometimes better than those of regular antiviral drugs. For example, it has been demonstrated that a topical ointment containing Canadian propolis outperformed Acyclovir® or placebo in clinical trials for genital herpes simplex [31]. Propolis is also well-known for modulating immune responses, which largely accounts for its antimicrobial and antiviral properties [32]. Several studies have reported the anti-inflammatory properties of propolis, which could be due to the production of phenolic acids. Caffeic acid phenethyl ester is the second most important anti-inflammatory constituent of propolis, with potential to regulate the complex NF-kB signal pathway [33]. Moreover, it has been reported that caffeic acid phenethyl ester modulated the ERK MAPK signal pathway in T cells and mastocytes [34] and controlled the PI3K/Akt signal route in different human cells lines [35].

Bee venom

Bee venom, also known as apitoxin, is an important chemical generated in the bee

abdomen by the venomous gland cavity. It is injected into victims through a stinger, leading to local inflammation, anticoagulation effects and stimulation of immune responses. Bee venom consists of several amphipathic polycationic peptides, among which the most commonly found are melittin and apamine enzyme (phospholipase A2), and low-molecular weight compounds including bioactive amines such as histamine and catecholamines [36]. Since ancient times, bee venom has been used for acupuncture and apitherapy in cases of chronic pain, inflammation, Parkinson's disease and immunotherapy. It has also been shown to exhibit anticancer, antimutagenic, antinociceptive, and radioprotective properties. The efficiency of bee venom in relief and management of chronic pain has been studied, with a view to assessing its beneficial potential for therapeutic use [37]. Due to its potential interaction with biological membranes and strong antimicrobial properties, studies have been done on the effect of melittin on human pathogens such as methicillin-resistant *S. aureus* [38], as well as plant pathogens [39]. Moreover, several studies have revealed anticancer properties of melittin. In addition, *in vitro* investigations have been carried out to establish the molecular mechanisms involved [40]. Although it has enormous therapeutic potential, *in vivo* injection of melittin led to some serious adverse effects such as haemolysis and injury to the liver, indicating a need to study non-toxic hybrid derivatives of the venom [40].

Bee product and cancer

Chemotherapy medications and radiotherapy surely destroy cancerous cells. However, more often than not, they also harm healthy cells in the process of killing cancer cells, leading to undesirable as well as debilitating adverse effects, which in some cases, could possibly kill the patient faster than the cancer itself. Therefore, studies on alternative anticancer drugs, especially natural products, have become an important field of cancer research. Natural products are considered weak agents, but they are much safer and stronger. A few natural products are also extremely harmful to healthy cells. However, most of them do not act directly on cells. Rather, they stimulate the immune system, relying on the natural immunological distinction between healthy and infected or transformed cells. Still, natural products with the potential to fight a variety of diseases, remain a relatively unexplored area. Therefore, only a few isolated compounds with proven clinical effectiveness are currently available. These natural compounds can be utilized as bases for developing more effective analogues via full or combination synthesis [41]. Bee products, including raw materials, crude extracts, and distilled bioactive compounds, were employed in ancient medicine for antibacterial, anti-inflammatory, and antioxidant purposes. In recent times too, bee products have been used for combating several immune-related disorders, as well as tumours. It has been observed that bee-derived peptides induce apoptotic cell death *in vitro* in several human cancer cell lines such as renal, lung, liver, prostate, thyroid, and lymphoid cancers [42]. New studies revealed that some specific natural bee compounds inhibit tumour cell growth and metastasis, and induce cancer cell apoptosis, indicating their potential benefits as alternative medical treatments for several human cancers [43].

Molecular mechanism involved in the anticancer effects of honey

The anti-cancer properties of honey have been widely hypothesized, and the underlying molecular mechanism have been investigated. Honey induces anticancer effect through cell cycle arrest, mitochondria pathway stimulation, activation mitochondrial outer membrane permeabilization [MOMP], activation of apoptosis, oxidative stress modulation, amelioration of inflammation, insulin signal modulation, and inhibition of angiogenesis [44].

Honey exerts its effect by inhibiting cancer growth at the cell cycle level. This inhibition was observed in the sub-G1 phase of bladder neoplastic cell lines [45], and at G0/G1 phase in non-small cell carcinoma cell [NCI-H460] [46]. Honey activates the mitochondrial pathway of apoptosis, leading to release of cytochrome C. Flavonoids from honey have been shown to activate the mitochondrial pathway of apoptosis [47]. Treatment of neoplastic cells with honey triggered apoptosis-induced death via activation of caspase-3, caspase-7 and caspase-9 [48]. Honey has also been shown to enhance tamoxifen-induced apoptosis by activating caspase-3, caspase-7, caspase-8 and caspase-9 [49]. The effects of honey on many apoptosis-related enzymes, genes and transcription factors have also been demonstrated. Treatment of colorectal neoplastic cell lines HCT-15 and HT-29 with honey induced down-regulation of expression of poly-ADP-ribose polymerase (PARP), a vital enzyme involved in apoptosis and repair of DNA. The honey-induced inhibition of PARP activity blocked DNA repair, and thus caused increased cytotoxicity in cancer cells [50]. In addition, the expressions of caspase-3, Bax and p53 were triggered or activated by honey,

while Bcl-2 expression was down-regulated. A study has demonstrated that honey exerted anti-mutagenic property by inhibiting error-prone repair process in DNA [51]. In diethyl nitrosamine [DEN]-induced carcinogenic rats; honey treatment was reported to produce anti-neoplastic effects owing to restoration of p53 expression. The apoptotic effect of honey is mediated by activation of caspase-9 and, caspase-3, and down-regulation of Bcl-2 expression [52]. Honey may also prevent cancer growth by regulating oxidative stress, that is, by oxidative stress enhancement or induction. The anti-cancer effects of honey which it exerts via antioxidants or pro-oxidants, appears to be entirely dependent on the level of oxidative stress in cancer cells. If cancer cell survival is dependent on low levels of ROS and oxidative stress, honey acts as a pro-oxidant, thereby increasing ROS and oxidative stress. Inflammation is a very important element in the pathophysiology of many other cancers/malignancies [53]. Two essential components of the inflammatory pathway activated in cancers are mitogen-activated protein kinase [MAPK] and nuclear factor kappa-B [NF-kB] [54]. Activation of MAPK and/or NF-kB stimulates the synthesis of inflammatory proteins and genes such as cyclooxygenase 2 [COX 2], C-reactive protein [CRP], lipoxygenase-2 [LOX2], and pro-inflammatory mediators or cytokines such as interleukin 1 [IL-1], IL-6, and tumor necrosis alpha (TNF-α). These pathways and pro-inflammatory mediators are known to have significant roles in cancer angiogenesis and pathogenesis of inflammation [55]. Honey therapy reduced the expressions of MAPK and NF-kB in HIT-T15 cells [56]. Chrysin, a normal component of honey, has also been shown to induce apoptosis in melanoma cells of B16-F1 and A375 by modulation of MAPK [57]. In addition, chrysin enhanced apoptosis of neoplastic cell lines mediated by TNF-related apoptosis-inducing ligand [TRAIL] [58]. Study reported that high levels of serine phosphorylation in MAPK, NF-kB, and insulin receptor substrate 1 [IRS-1] were characterized by insulin resistance assembly, while Akt expression and insulin content were significantly decreased [56]. Honey therapy increased the expression of Akt, while the expressions of phosphorylated IRS-1, MAPK and NF-κB were decreased. These findings demonstrated that honey also modulates insulin signaling, which may contribute to its anti-cancer effects [56]. In cancer cells, honey prevents angiogenesis. The potential anti-angiogenic impact of honey on cancer cells (hepatoma HePG2 cell lines) was based on evidence that honey decreased the viability, metastasis, and gelatinase and protease activities of cancer cells [59]. Caffeic acid phenethyl ester, chrysin and other cytotoxic honey constituents exert anti-angiogenic and anti-cancer effects [60].

Bee products and lung cancer

Bee venom possesses unique pharmacological effect due to its complex protein composition, which includes enzymes and peptides. Melittin is the key component of bee venom, and it accounts for 50 % of the total constituents of the venom. Recent studies showed that bee venom has tremendous benefits for tumor treatment due to its synergistic antitumor effects with melittin. Mohamed *et al*, (2016) studied the effects of Egyptian and Georgian bee venoms on MCF-7 breast cancer cell line and A549 lung cancer cell line. The results showed that the Egyptian bee venom produced greater toxicity on the two cell lines than the Georgian bee venom. The study also showed crucial inhibitory effects of Egyptian bee venom and propolis on cell proliferation after 24 h of therapy, resulting in morphological changes. After 24 h of bee venom injection, the levels of expression of the pro-apoptotic gene p53 and the anti-apoptotic gene Bcl-2 were studied in both cell lines. These studies revealed possible anticancer properties of bee venom and propolis, based on the up- or down-regulation of pro-apoptotic and anti-apoptotic genes (Figure 1) [61].

Earlier, a study was conducted on the effect of propolis on the growth and apoptosis of human lung adenocarcinoma [A549 cells], and its mechanism of action [61]. The propolis cells were incubated for 72 h, and 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide and lactate dehydrogenase assays were employed for analysis of cell viability and inhibitory concentration [IC]. Findings from the study suggested that propolis produced antiproliferative and cytotoxic effects on A549 cells in dose- and time-dependent manner but failed to inhibit the growth of normal Vero cells. Compared to control A549 cells, increased apoptosis was observed in cells treated with propolis after 48 h. Propolis was shown to induce over-expressions of pro-apoptotic genes Bax and Noxa, which resulted in decreased mitochondrial membrane potential and decreased expression of anti-apoptotic gene Bcl-XL. The study also showed that the expression levels of other genes such as p53, Caspse-3, and Bax remained unaffected, except p21 which showed increased expression. Propolis induced caspase-independent apoptosis through a p53-independent mitochondrial pathway, causing arrest of the cell cycle via p21 upregulation [62].

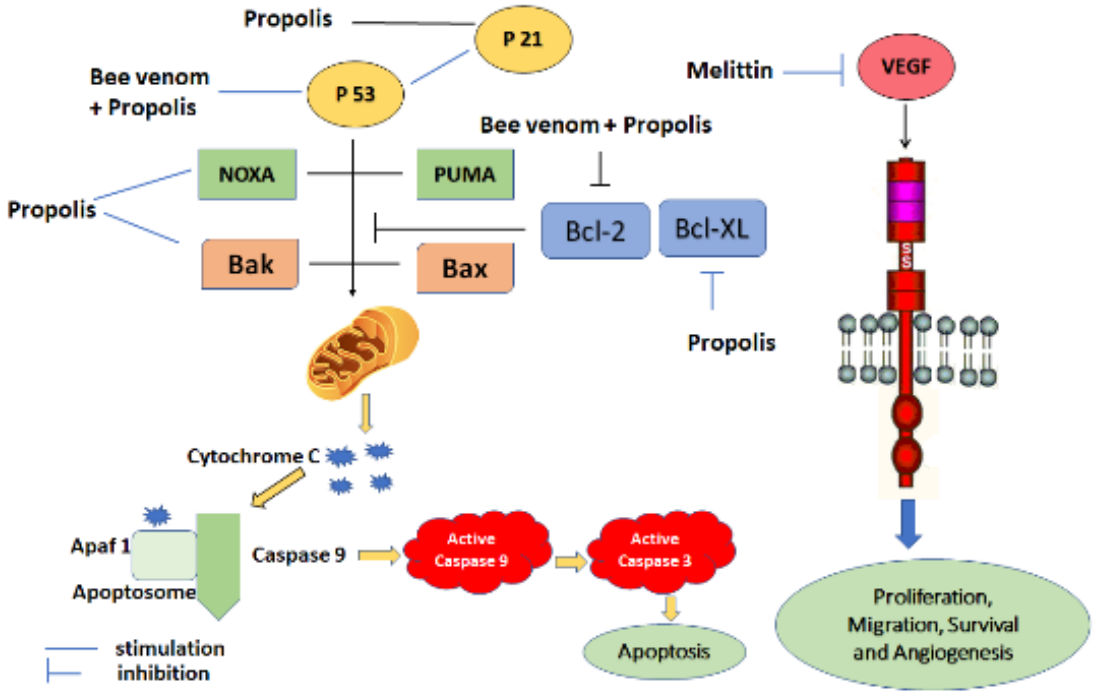

Figure 1: Molecular mechanisms of anti-cancer effects of bee products in lung cancer cell lines

Another study was conducted on the cytotoxicity of Turkish propolis ethanolic extract [EEP] on human lung cancer [A549] cells, and the mechanism involved. Results from MTT assay revealed the cytotoxicity of EEP on A549 cells [63]. The mechanism of EEP cytotoxicity on A549 cells was evaluated in relation to apoptosis, mitochondrial membrane, and the cell cycle using flow cytometry; endoplasmic reticular tension using RT-PCR, and luminometric analysis of caspase activity. It was observed that EEP produced selective toxicity on A549 cells, when compared to normal fibroblast cells. The study revealed that EEP arrested the cell cycle of A549 in the G1 stage; increased endoplasmic reticulum stress, caspase activity, and apoptosis, and decreased mitochondrial membrane potential. These results indicate the potential of Turkish propolis to halt the proliferation of cancer cells, and its likely application in the development of new anticancer drugs [63].

A study on the antiproliferative effect of an ethanolic extract of Algerian propolis [EAP] on the human lung adenocarcinoma cell line [A549] in albino Wistar rats demonstrated its chemo-preventive potential against benzo [a]pyrene-induced lung carcinogenesis. The cytotoxic effect of Algerian propolis on A549 cells was evaluated using MTT assay and cell adhesion [17]. A single intraperitoneal dose of benzo [a]pyrene [200 mg/kg] was injected into the rats, along with propolis (25 mg/kg) for 5 days before lung cancer was induced experimentally. Body weight, lung weight, lipid peroxidation, marker enzymes, and enzymatic and non-enzymatic antioxidants were measured prior to treatment. Pre-treatment evaluation revealed increases in enzymatic and non-enzymatic antioxidants and decreases in lipid peroxidation [17].

Another study was carried out to assess the antiproliferative potential of Acacia honey on NCI-H460 cells, and the associated molecular mechanism, using cell cycle, cell viability, cytokine, calcium ion, and gene expression analyses. Acacia honey dose-dependently inhibited aberrant cell division, arrested the cell cycle in G0/G1 stage, activated cytokines, released calcium ions, and reduced the expressions of p53 and Bcl-2 [64]. The antiproliferative effect of Acacia honey on the NCI-H460 cell line was attributed to cell cycle arrest, cytokine stimulation, calcium ion release, as well as downregulation of the genes Bcl-2 and p53 [64].

A study was conducted on the cytotoxic effect of Kelulut honey (*Trigona itama*), a Malaysian multiflora honey, as a probable natural anticancer agent for inducing apoptosis and cell cycle arrest on an epithelial cell line of human lung adenocarcinoma (A549) cells [65]. The cells were exposed consecutively to various concentrations of *Trigona itama* honey for 24, 48 and 72 h. Cytotoxicity and cell viability were

analysed using trypan blue exclusion assay [TBEA] and flow cytometric analysis. *Trigona itama* honey produced maximum cytotoxic effect at 72 h at a concentration of 20 %, with 100 % inhibition. The moisture content of the honey was 14.3 ± 0.8 %, which was within the international standard range. The pH was 3.17 ± 0.02, and the electrical conductivity was 0.47 - 0.55 mS/cm, while the proline contents were 19.1 and 20.2 mg/kg [65].

Chen *et al* conducted a study involving *in vivo* and *in vitro* investigations of the antitumor effect of melittin [66]. The study revealed that epidermal growth factor influenced inhibition of the invasion and migration of non-small cell lung cancer cells. In the study, subcutaneous injection of melittin at a dose of 1 mg/kg led to 27 % suppression of non-small cell lung cancer cells. However, a dose of 10 mg/kg resulted in 61% suppression. Melittin also suppressed the protein expressions of vascular endothelial growth factor [VEGF] and hypoxia-inducible factor 1 α. Therefore, it is reasonable to expect that the anticancer effect of melittin is related to its anti-angiogenic effect as demonstrated via inhibition of VEGF and hypoxia-inducible factor signaling pathways [66].

For so many decades, honey was used for nutritional purposes and topical wound care. There is no evidence of any adverse effects from most of the available varieties of honey. Gastrointestinal distress and hepatitis were reported after ingestion of Rhododendron-derived honey, colloquially known as *crazy honey* [67]. However, such incidents are uncommon and are limited to unique sources. Lately, a study performed by Fernandez-Cabezudo *et al* demonstrated the efficacy of honey as a medicinal product [68].

CONCLUSION

A plethora of evidence and data from cell culture and animal studies have proven that honey is a beneficial chemo-preventive agent and an important alternative to medications used for cancer therapy. Honey is very easily available, cheap, and easy to use. Moreover, it possesses minimal risk of detrimental side effects. The basic composition and therapeutic qualities, such as anticancer characteristics, vary according to bee species, nectar source, habitat, geographical location, extent of processing, packing, and storage. Bee products should be further studied in order to determine their prophylactic effects on invasive neoplastic lesions, and to determine the length of time that these effects last after surgery. Therefore, more research is required in order to evaluate the anticancer potential of honey before making any recommendations for its use in clinical settings.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. *Reed JC. Dysregulation of apoptosis in cancer. J Clin Oncol 1999;17[9]: 2941–53.*
2. *World Health Organisation. Cancer 2018. [updated dec 2020].*
3. *Hooshmand K, Asoodeh A, Behnam-Rassouli F. GL-9 peptide regulates gene expression of CD44 cancer marker and pro-inflammatory cytokine TNF-α in human lung epithelial adenocarcinoma cell line [A549]. Mol Cell Biochem 2016; 423[1–2]:141–9.*
4. *Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Cancer 2019; 144:1941–53.*
5. *Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70[1]:7–30.*
6. *Schwartz AG, Cote ML. Epidemiology of lung cancer. Adv Exp Med Biol 2016; 893:21–41.*

7. MacKinnon AC, Kopatz J, Sethi T. The molecular and cellular biology of lung cancer: identifying novel therapeutic strategies. Br Med Bull 2010; 95[1]:47–61.
8. Dominioni L, Imperatori A, Rovera F, Ochetti A, Torrigiotti G, Paolucci M. Stage I non-small cell lung carcinoma: analysis of survival and implications for screening. Cancer 2000; 89[1]:2334–44.
9. American Cancer Society. Cancer Treatment & Survivorship Facts & Figures 2019-2021. Atlanta: American Cancer Society; 2019 [updated Dec 2020].
10. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365(5):395-409.
11. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of Patients with Stage I Lung Cancer Detected on CT Screening. N Engl J Med 2006; 355[17]:1763–71.
12. Krishnakumar N, Sulfikkarali N, RajendraPrasad N, Karthikeyan S. Enhanced anticancer activity of naringenin-loaded nanoparticles in human cervical [HeLa] cancer cells. Biomed Prev Nutr 2011;1[4]:223–31.
13. Moorthi C, Manavalan R, Kathiresan K. Nanotherapeutics to overcome conventional cancer chemotherapy limitations. J Pharm Pharm 2011; 14: 67–77.
14. Chabowski M, Polanski J, Jankowska-Polańska B, Rosińczuk J, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther 2016; 9:1023.
15. Venuta F, Diso D, Onorati I, Anile M, Mantovani S, Rendina EA. Lung cancer in elderly patients. Journal of Thoracic Disease 2016;8: S908–14.
16. Fauzi AN, Norazmi MN, Yaacob NS. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. Food Chem Toxicol 2011;49[4]:871–8.
17. Brihoum H, Maiza M, Sahali H, Boulmeltout M, Barratt G, Benguedouar L, et al. Dual effect of Algerian propolis on lung cancer: Antitumor and chemopreventive effects involving antioxidant activity. Brazilian J Pharm Sci 2018;54[1].
18. Porcza L, Simms C, Chopra M. Honey and Cancer: Current Status and Future Directions. Diseases 2016;4[4]:30.
19. Mohamed AF, El-Fiky AA, Hassan OS, Nada A. El-Megharbel. Controlled Study of Application of Bee Products as New Medicine Against Breast and Lung Cancer. Int J Adv Res 2016; 4[6]:392–402.
20. Burlando B, Cornara L. Honey in dermatology and skin care: A review. J Cosmet Dermatol 2013;12[4]:306–13.
21. Da Silva PM, Gauche C, Gonzaga LV, Costa ACO, Fett R. Honey: Chemical composition, stability and authenticity. Food Chemistry 2016; 196:309–23.
22. Cornara L, Biagi M, Xiao J, Burlando B. Therapeutic properties of bioactive compounds from different honeybee products. Frontiers in Pharmacology 2017; 8: 412.
23. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860–7.
24. Vallianou NG, Gounari P, Skourtis A, Panagos J, Kazazis C. Honey and its Anti-Inflammatory, Anti-Bacterial and Anti-Oxidant Properties. Gen Med 2014;2[2].
25. Erejuwa OO, Sulaiman SA, Ab Wahab MS. Honey - A novel antidiabetic agent. International Journal of Biological Sciences 2012; 8: 913–34.
26. Vandamme L, Heyneman A, Hoeksema H, Verbelen J, Monstrey S. Honey in modern wound care: A systematic review. Burns 2013; 39:1514–25.
27. Huang S, Zhang CP, Wang K, Li GQ, Hu FL. Recent advances in the chemical composition of propolis. Molecules 2014; 19:19610–32.
28. Sun C, Wu Z, Wang Z, Zhang H. Effect of ethanol/water solvents on phenolic profiles and antioxidant properties of Beijing propolis extracts. Evidence-based Complement Altern Med 2015; 595393.
29. Mutlu Sariguzel F, Berk E, Koc AN, Sav H, Demir G. Antifungal Activity of Propolis Against Yeasts Isolated from Blood Culture: In Vitro Evaluation. J Clin Lab Anal 2016; 30[5]:513–6.
30. Ioshida MDM, Young MCM, Lago JHG. Chemical composition and antifungal activity of essential oil from Brazilian propolis. J Essent Oil-Bearing Plants 2010;13[5]:633–7.
31. Vynograd N, Vynograd I, Sosnowski Z. A comparative multi-centre study of the efficacy of propolis, acyclovir and placebo in the treatment of genital herpes [HSV]. Phytomedicine 2000;7[1]:1–6.
32. Orsi RO, Funari SRC, Soares AMVC, Calvi SA, Oliveira SI, Sforcin JM, et al. Immunomodulatory action of propolis on macrophage activation. J Venom Anim Toxins. 2000;6 [2]:205–19.
33. Armutcu F, Akyol S, Ustunsoy S, Turan FF. Therapeutic potential of caffeic acid phenethyl ester and its anti-inflammatory and immunomodulatory effects. Exp Ther Med 2015; 9[5]:1582–8.
34. Cho MS, Park WS, Jung WK, Qian ZJ, Lee DS, Choi JS, et al. Caffeic acid phenethyl ester promotes anti-inflammatory effects by inhibiting MAPK and NF-κB signaling in activated HMC-1 human mast cells. Pharm Biol 2014;52[7]:926–32.
35. Li L, Sun W, Wu T, Lu R, Shi B. Caffeic acid phenethyl ester attenuates lipopolysaccharide-stimulated proinflammatory responses in human gingival fibroblasts via NF-κB and PI3K/Akt signaling pathway. Eur J Pharmacol 2017; 794:61–8.
36. Lee G, Bae H. Anti-inflammatory applications of melittin, a major component of bee venom: Detailed mechanism of action and adverse effects. Molecules 2016; 21
37. Sobral F, Sampaio A, Falcão S, Queiroz MJRP, Calhelha RC, Vilas-Boas M, et al. Chemical characterization, antioxidant, anti-inflammatory and cytotoxic properties of bee venom collected in Northeast Portugal. Food Chem Toxicol 2016; 94:172–7.

38. Choi JH, Jang AY, Lin S, Lim S, Kim D, Park K, et al. Melittin, a honeybee venom-derived antimicrobial peptide, may target methicillin-resistant Staphylococcus aureus. Mol Med Rep 2015;12[5]:6483–90.
39. McManus PS, Stockwell VO, Sundin GW, Jones AL. Antibiotic use in plant agriculture. Annu Rev Phytopathol 2002:40:443–65.
40. Gajski G, Garaj-Vrhovac V. Melittin: A lytic peptide with anticancer properties. Environ Toxicol Pharmacol 2013;36: 697–705.
41. Cragg GM, Newman DJ. Nature: A vital source of leads for anticancer drug development. Phytochem Rev 2009; 8[2]:313–31.
42. Premratanachai P, Chanchao C. Review of the anticancer activities of bee products. Asian Pac J Trop Biomed 2014;4[5]:337–44.
43. Yusuf N, Irby C, Katiyar SK, Elmets CA. Photoprotective effects of green tea polyphenols. Photoimmunol Photomed 2007; 23:48–56.
44. Erejuwa OO, Sulaiman SA, Wahab MS. Effects of honey and its mechanisms of action on the development and progression of cancer. Molecules 2014 :19[2]:2497-522.
45. Swellam T, Miyanaga N, Onozawa M, Hattori K, Kawai K, Shimazui T, Akaza, H. Antineoplastic activity of honey in an experimental bladder cancer implantation model: In vivo and in vitro studies. Int. J. Urol 2003; 10:213–219.
46. Aliyu M, Odunola OA, Farooq AD, Mesaik AM, Choudhary MI, Fatima B, Qureshi TA, Erukainure OL. Acacia honey modulates cell cycle progression, pro-inflammatory cytokines and calcium ions secretion in PC-3 cell line. J. Cancer Sci. Ther 2012;4: 401–407.
47. Ren J, Cheng H, Xin WQ, Chen X, Hu K. Induction of apoptosis by 7-piperazinethylchrysin in HCT-116 human colon cancer cells. Oncol. Rep 2012; 28:1719–1726.
48. Fauzi AN, Norazmi MN, Yaacob NS. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. Food Chem. Toxicol 2011; 49:871–878.
49. Yaacob NS, Nengsih A, Norazmi MN. Tualang honey promotes apoptotic cell death induced by tamoxifen in breast cancer cell lines. Evid. Based Complement. Altern. Med 2013: doi:10.1155/2013/989841.
50. Wang Y, Kim NS, Haince JF, Kang HC, David KK, Andrabi SA, Poirier GG, Dawson VL, Dawson TM. Poly(ADP-ribose) (PAR) binding to apoptosis-inducing factor is critical for PAR polymerase-1-dependent cell death (parthanatos). Sci Signal 2011;4(167):ra20.
51. Saxena S, Gautam S, Maru G, Kawle, D, Sharma A. Suppression of error prone pathway is responsible for antimutagenic activity of honey. Food Chem. Toxicol 2012; 50:625–633.
52. Fernandez-Cabezudo MJ, El-Kharrag R, Torab F, Bashir G, George JA, El-Taji H, Al-Ramadi BK. Intravenous administration of manuka honey inhibits tumor growth and improves host survival when used in combination with chemotherapy in a melanoma mouse model. PLoS One 2013, 8, e55993.
53. Jiang X, Shapiro DJ. The immune system and inflammation in breast cancer. Mol. Cell. Endocrinol 2014; 382:673–682.
54. Wang H, Cho CH. Effect of NF-kappaB signaling on apoptosis in chronic inflammation-associated carcinogenesis. Curr. Cancer Drug Targets 2010; 10:593–599.
55. Goldberg JE, Schwertfeger KL. Proinflammatory cytokines in breast cancer: Mechanisms of action and potential targets for therapeutics. Curr. Drug Targets 2010; 11:1133–1146.
56. Batumalaie K, Zaman Safi S, Mohd Yusof K, Shah Ismail I, Devi Sekaran S, Qvist, R. Effect of gelam honey on the oxidative stress-induced signaling pathways in pancreatic hamster cells. Int. J. Endocrinol. 2013, doi:10.1155/2013/367312.
57. Pichichero E, Cicconi R, Mattei M, Canini A. Chrysin-induced apoptosis is mediated through p38 and Bax activation in B16-F1 and A375 melanoma cells. Int. J. Oncol. 2011; 38: 473–483.
58. Li X, Wang JN, Huang JM, Xiong XK, Chen MF, Ong CN, Shen HM, Yang XF. Chrysin promotes tumor necrosis factor [TNF]-related apoptosis-inducing ligand [TRAIL] induced apoptosis in human cancer cell lines. Toxicol. In Vitro 2011; 25:630–635.
59. Abdel Aziz A, Rady H, Amer M, Kiwan H. Effect of some honey bee extracts on the proliferation, proteolytic and gelatinolytic activities of the hepatocellular carcinoma Hepg2 cell line. Aust. J. Basic Appl. Sci. 2009; 3: 2754–2769.
60. Abubakar MB, Abdullah WZ, Sulaiman SA, Suen AB. A review of molecular mechanisms of the anti-leukemic effects of phenolic compounds in honey. Int. J. Mol. Sci. 2012; 13:15054–15073.
61. Mohamed A, El-Fiky A, Hassan O, El-Megharbel N. Controlled Study of Application of Bee Products as New Medicine Against Breast and Lung Cancer. Int J Adv Res 2016 4[6]:392–402.
62. Friõn-Herrera Y, Díaz-García A, Ruiz-Fuentes J, Rodríguez-Sánchez H, Sforcin JM. Brazilian green propolis induced apoptosis in human lung cancer A549 cells through mitochondrial-mediated pathway. J Pharm Pharmacol 2015; 67[10]:1448–56.
63. Demir S, Aliyazicioglu Y, Turan I, Misir S, Mentese A, Yaman SO, et al. Antiproliferative and proapoptotic activity of Turkish propolis on human lung cancer cell line. Nutr Cancer 2016; 68[1]:165–72.
64. Aliyu M, Odunola OA, Farooq AD, Rasheed H, Mesaik AM, Choudhary MI, et al. Molecular mechanism of antiproliferation potential of Acacia honey on NCI-H460 cell line. Nutr Cancer 2013; 65[2]:296–304.
65. Salim SNM, Ramakreshnan L, Fong CS, Wahab RA, Rasad MSBA. In-vitro cytotoxicity of Trigona itama honey against human lung adenocarcinoma epithelial cell line [A549]. Eur J Integr Med 2019; 30:100955.
66. Zhang SF, Chen Z. Melittin exerts an antitumor effect on non-small celllung cancer cells. Mol Med Rep. 2017; 16 [3]:3581–6.

67. Sari Dogan F, Ozaydin V, Incealtin O, Guneysel O, Demireller M. A case of acute hepatitis following mad honey ingestion. Turkish J Emerg Med. 2015; 15[4]:185–6.
68. Fernandez-Cabezudo MJ, El-Kharrag R, Torab F, Bashir G, George JA, El-Taji H, et al. Intravenous Administration of Manuka Honey Inhibits Tumor Growth and Improves Host Survival When Used in Combination with Chemotherapy in a Melanoma Mouse Model. PLoS One 2013; 8(2): e55993