An insight into the putative role of victuals like honey and its polyphenols in breast cancer

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Diet plays a crucial role in cancer advancement as well as prevention. Breast cancer is the second leading cause of cancer death among women. Recent research links breast cancer with diet and some evidence for the preventive effect of diet against breast cancer was also documented. The growth of cancer cells is influenced by natural sweetener honey and its multitude of phenolic phytochemical components. Honey has been used medicinally by ancient Greeks and Egyptians and also traditionally exploited in Ayurveda and Chinese medicine. In this paper, the anti-cancer properties of honey and its phytochemical's action against breast cancer have been summarized. They result in apoptosis by enhancing reactive oxygen species level, activating mitochondrial pathway, initiation of pro-apoptotic and anti-apoptotic proteins, induction of p53 pathway that finally cause DNA fragmentation. However, there is a necessity for more proteomic and genetic-based experiments to understand its molecular mechanism to promote honey and its phenolic markers as plausible candidates for breast cancer treatment. Further, there is a need for quality check of honey available in the market, which warrants significant investigation by researchers in the food industry to ensure their attributes.

Keywords: Anti-cancer, apoptosis, breast cancer, honey, phenolic.

CANCER is not just one disease, but also a large group of almost 100 diseases[1]. In 2014 alone, 585,720 deaths occurred due to cancer, corresponding to about 1600 deaths per day[2]. Skin, lung, colon, breast and prostate are the most frequent type of cancers. Among these, breast cancer is found to occur commonly in about 12% of women, i.e. 1 in 8 women are found to develop invasive breast cancer in the world. According to the American Cancer Society, about 231,840 new cases and 40,290 deaths due to invasive breast cancer were expected in 2015 in USA[3].

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A major cause for cancer is the variations that occur in the DNA sequence of a normal cell. Breast cancer in particular, develops from a mutated gene[4]. Mutation is defined as a permanent variation in the nucleotide sequence of a nucleus of an organism like virus or other genetic elements or changes in extrachromosomal DNA. It is influenced by exposure to radiation, hazardous chemicals or genetically obtained[5]. Several studies examined the dietary–gene relationship between breast cancer cells and natural food substances. These natural compounds have their benefits and some are detrimental to breast cancer cells[6].

Many studies have promoted the natural food, honey, against cancer. Honey is a sweet food created by honey bees with the help of nectar collected from various flowers. Honey, consumed by humans for a long time, is used as a sweetener and flavouring in various recipes and beverages. It is a mixture of sugars and other phytochemicals[7]. Honey was used medicinally by ancient Egyptians and Greeks. It is also used in Chinese medicine as well as in Ayurveda[8]. It was applied externally to treat wounds and burns; and to treat internal ailments like gastric disturbances and ulcers through oral intake by humans. In modern times, it is used for treating cough and rhinosinusitis[9]. Honey is said to have an anti-proliferative effect on various cancer cells which involves programmed cell death with significant changes in cell organelles. Along with honey, other phenolic compounds in honey have been examined for their effect on cancer cells[10]. These phytochemicals in honey belong to polyphenol family. This article highlights the activities stimulated by honey and its polyphenols on various breast cancer cell lines leading to cell lysis. Before venturing into this, a brief introduction about the biology of breast cancer is provided.

Biology of breast cancer

Breast cancer is a cancer that develops in the breast tissue. Breast cancers are carcinomas that start in epithelial

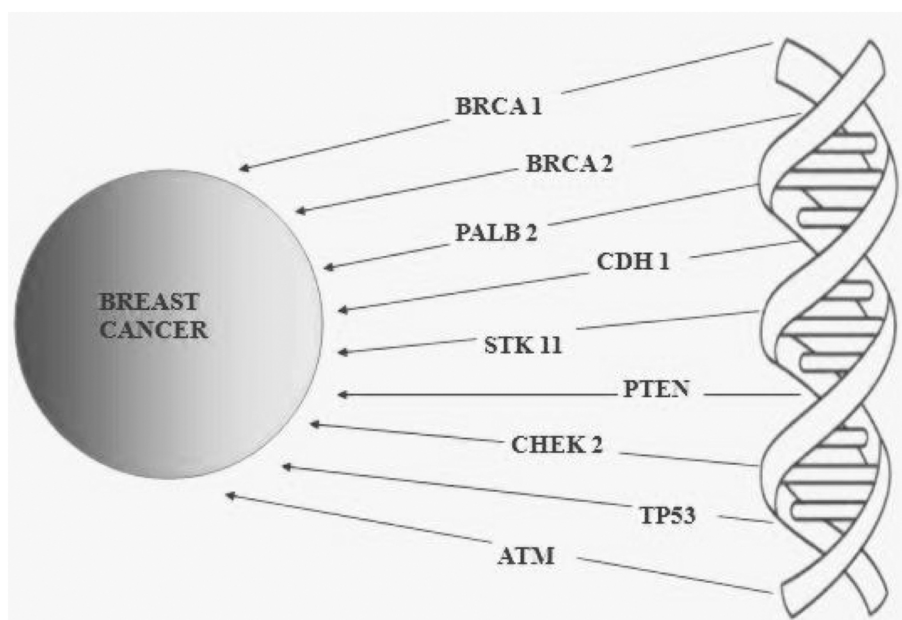

Figure 1. Genes related to breast cancer. *BRCA1* (breast cancer 1 early onset) and *BRCA2* (breast cancer 2 early onset) genes; *ATM* (ataxia telangiectasia mutated), *TP53* (tumour protein p53), *CHEK2* (checkpoint kinase 2), *PTEN* (phosphatase and tensin homolog), *CDH1* (Cadherin-1), *STK11* (serine/threonine kinase 11) and *PALB2* (Partner and localizer of *BRCA2*) genes.

cells present in the breast due to mutation[11]. About 10–15% of breast cancer cases are thought to be hereditary, which are genetically inherited from any one of the parents (acquired mutations)[12]. The most common cause of hereditary breast cancer is an inherited mutation in certain genes which are given in Figure 1. Having children after the age of 30, consumption of oral contraceptives, hormone therapy after menopause, physical inactivity and drinking alcohol are other factors that influence this cancer[13]. Studies have shown that alcohol intake does not influence breast cancer among BRCA mutation, while consumption of wine in BRCA1 mutation carriers have relationship with breast cancer[14].

Breast cancers which contain progesterone receptors (PR) are referred as PR-positive (or PR+) cancers, while those that have estrogen receptors (ER) are commonly called ER-positive (or ER+) cancers and those which have growth-promoting protein called HER2/neu (often just shortened to HER2) are known as HER2-positive[15]. The available choice of breast cancer treatment includes chemotherapy, surgery, radiation therapy, targeted therapy, bone-directed therapy and hormone therapy. Of these, chemotherapy (chemo) consists of anti-cancer drugs that may be given intravenously or orally in order to kill rapidly growing cancer cells. Chemotherapy can be employed in case of women whose cancer has spread outside breast or after initial treatments[16]. The most common chemo-preventives used for breast cancer are cyclophosphamide, methotrexate, 5-fluorouracil and doxorubicin[17]. These chemo-preventives are more potent only at the early stages of cancer detection which makes scientists to search for a novel drug. In the following section, honey and its phenolic components are introduced which serve as putative candidates in search of novel drugs for cancer.

Honey and its phenolic constituents

Honey remains a natural sweetener for food to humans for several centuries. It is a useful food substance which is mostly made up of sugar and water along with minute quantities of minerals as well as pigments, flavour and aroma substances and phenolic compounds[18]. For this reason it is characterized as a supersaturated sugar solution. Apart from being the only source of sweetener, it was also employed in ancient medicine to treat various ailments and complaints. It was applied externally in case of burns, wounds and acne as well as internally for cough, seasonal allergies, to boost immunity, urinary tract disorders, diarrhoea, bronchial asthma, nausea, etc.[8,9]. Besides these, scientists have found that honey has anti-inflammatory, anti-bacterial, anti-malarial and anti-cancer properties. Despite the high amount of sugar present in it, its biological properties have a strong relation to the minute quantity of phenolic compounds.

Nevertheless, phenolic content as well constituents present in honey differ, depending on its floral or botanical origin. There are different methods to find various combinations of phenolic constituents in different honey. Some types of honey and their phenolics are given in Table 1. The phenolic constituents of eucalyptus honey are chrysin, tricetin, luteolin, myricetin quercetin-3-methyl ether,

Table 1. Type of honey and the identified phenolic compounds

Type of honey	Identified phenolic compounds	Reference
Eucalyptus honey	Myricetin, tricetin, quercetin, luteolin, quercetin-3-methyl ether, kaempferol, pinocembrin, chrysin, pinobanksin, isorhamnetin, genkwanin	19
Rosemary honey	Kaempferol, ferulic acid, chrysin, pinocembrin, *p*-coumaric acid	20
Indian honey	Dihydroxy benzoic acid, caffeic acid, ferulic acid and cinnamic acid	21
Tualang honey	Benzoic acid, gallic acid, syringic acid, *p*-coumaric acid, hyacinthin, trans-cinnamic acid, caffeic acid, catechin, kaempferol and naringenin	22
Thyme honey	Caffeic acid, chlorogenic acid, *p*-coumaric acid, ferulic acid, gallic acid, gentisic acid, sinapic acid, syringic acid	23
New Zealand and Australian *Leptospermum* honey	Myricetin, tricetin, quercetin, luteolin, kaempferol, kaempferol-8-methyl ether, pinocembrin, chrysin, gallic acid, ellagic acid, chlorogenic acid, caffeic acid, *p*-coumaric acid, ferulic acid, syringic acid	24
Greek unifloral honey	Syringic acid, myricetin, quercetin, kaempferol and chrysin	25

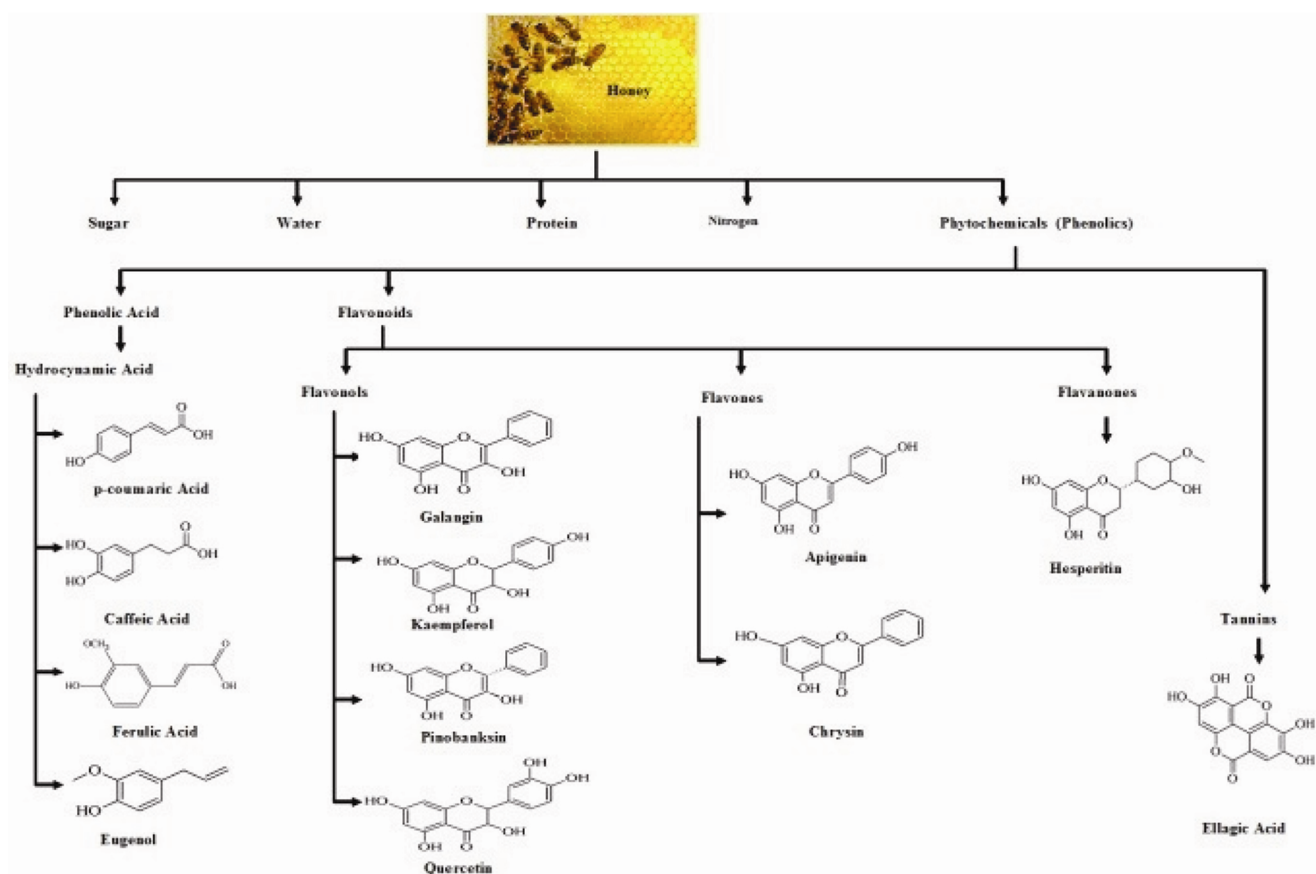

Figure 2. Phenolic markers of honey and their chemical structures.

isorhamnetin, kaempferol, pinocembrin, quercetin, genkwanin and pinobanksin[19]. Rosemary honey contains compounds like chrysin, kaempferol, *p*-coumaric acid, pinocembrin and ferulic acid[20]. Cinnamic acid, dihydroxy benzoic acid, caffeic acid and ferulic acid are the major phenolic constituents found in the Indian honey samples[21]. The phenolic constituents of tualang honey was benzoic acid, catechin, naringeningallic acid, syringic acid, *p*-coumaric acid, hyacinthin, kaempferol, trans-cinnamic acid and caffeic acid[22]. Similarly, thyme honey contained gallic acid, chlorogenic acid, syringic acid, ferulic acid, gentisic acid, caffeic acid, sinapic acid and *p*-coumaric acid[23]. The phenolic compounds of New Zealand and Australian leptospermum honey are: quercetin, luteolin, kaempferol, myricetin, kaempferol-8-methyl ether, chlorogenic acid, caffeic acid, gallic acid, *p*-coumaric acid, ferulic acid, pinocembrin, chrysin, tricetin, ellagic acid and syringic acid[24]. Phenolic profile of

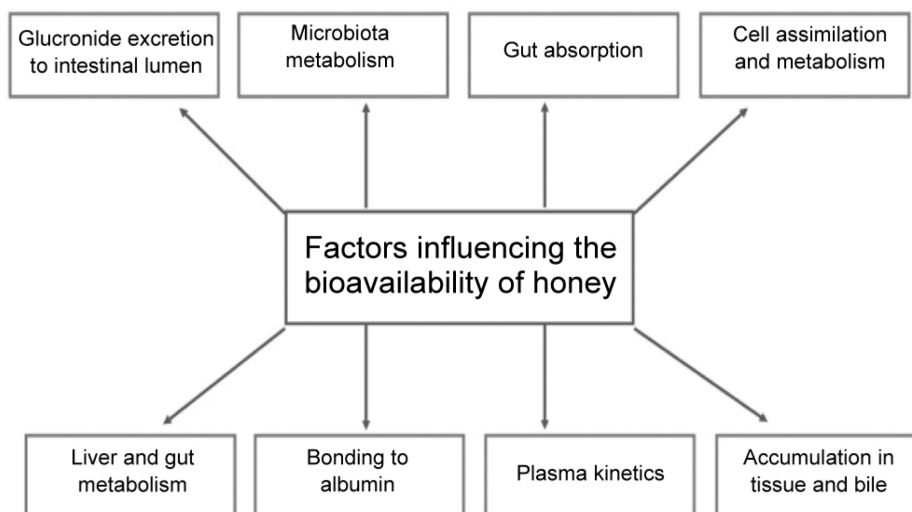

Figure 3. Factors influencing the bioavailability of phytochemicals.

the Greek unifloral honey was evaluated based on quantification of syringic acid, myricetin, quercetin, kaempferol and chrysin using high performance liquid chromatography[25]. These phenolic compounds are classified as phenolic acids, flavonoids, flavones, flavanones, flavonols, etc. This classification is based on the chemical group present in them. A schematic representation of the classification of phenolics of honey along with their chemical structure is given in Figure 2.

Similar to phenolic constituents, the phenolic concentration of honey varies depending on the type of flower and its origin. For instance, total phenolic amount was found to vary between 82.5 and 242.5 mg/kg when 40 honey samples of different floral types such as multifloral, lime, rape, raspberry, mixture and honeydew were studied[26]. While the phenolic content in coconut honey was found to be 15.6 μg/g, it was 21.4 μg/g in Gelam honey[27]. Polyphenolic phytochemicals present in honey may be classified as flavonoids and phenolic acids. The overall flavonoid content is said to be around 20 and 2400 μg/100 g (ref. 28). The total phenolic content of the North-East Nigerian honey was found to be 65.31 ± 19.50 mg gallic acid equivalent (GAE)/100 g (ref. 29). Apart from phenolics, the colour, flavour and taste of honey also differ depending on their source. The colour of honey usually varies from water white to dark amber and has a strong relation to the phenolic content present in it. Dark coloured honey is said to have a strong flavour and high phenolic content than the mild coloured honey types[30–32]. This was found to be evident in the study on 23 types of Saudi Arabia honey[33]. Regardless of all these diverse factors, polyphenols of honey are extensively studied for their biological benefits. However, it is essential to understand the bioavailability of honey and its components before explaining its anti-cancer activity.

Honey and its bioavailability

Bioavailability becomes an important factor to be studied when the medicinal property of a compound is explored. It becomes a foremost factor while deliberating a dietary substance for therapy. The bioavailability of honey polyphenols in human beings as well as their anti-oxidant capacity was experimented using 40 individuals by Schramm *et al.*[34]. Two different buckwheat honey with 0.79 ± 0.02 (Low-A) and 1.71 ± 0.21 (High-A) mg of phenolic anti-oxidants per gram were used in the study. The results showed a rise in antioxidant activity along with total-phenolic content and fall in the capacities of plasma ($P < 0.05$) after honey treatment[34]. This study supports the observation that the phenolics of honey are not only bioavailable but also exhibit excellent anti-oxidant activity.

Honey is an excellent source of flavonoids and phenolic acids. Numerous studies have shown that bioavailability of polyphenol is complex influenced by several factors (Figure 3). Besides these factors, swift elimination and limited absorption of natural polyphenols make the final plasma concentrations of flavanones and isoflavones to be at around 5 μM/l, while that of oligomeric flavonoids to be at 1 μM/l (refs 35, 36). Hence, phenolic substances can be made bioavailable by repeated consumption of food substances.

Despite these difficulties, there are a few supporting factors that make phenolics of honey easily bioavailable. It is found that the flavonoids with glycoside form encourage the Na^+-dependent transport of ATPase of monosaccharides in intestinal epithelial cells during studies on the bioavailability of natural flavonoids. Natural flavonoids are hydrolysed to aglycones which can be easily absorbed by enterocytes (intestinal absorptive cells). In case of bee honey, enzyme glycosidase present in the bee salivary

gland makes flavonoids of honey to be present in the aglycones form. Aglycones form is created when the glycosyl group of a glycoside is replaced by hydrogen. Phenolic aglycones are highly absorbed through the gut barrier in comparison to their corresponding glycosides. Therefore, it is assumed that honey flavonoids are effortlessly bioavailable than other natural flavonoids[37,38].

Phenols of honey also exhibit synergestic influence along with medicinal benefits. Synergism can be defined as the interaction between two or more substances causing an improved effect compared to the sum of their individual effects[39]. Synergy can be additive or reversal, out of which additive occurs when the interaction effect of chemicals is enhanced. Phenolic compounds are tested for their synergistic property with medically approved drugs available in the market against various cancer types. These compounds commonly increase the effect of anti-cancer drugs when used in combination rather than when used alone. In particular, phenolic compounds such as chrysin, apigenin, ferulic acid and quercetinare are found to show synergistic effect when combined with medically approved drugs such as 5-fluorouracil, tamoxifen, doxorubicin against different breast cancer cell lines[40–43]. The combination of phenolic phytochemicals and anti-cancer drugs subdued breast cancer cell growth with greater potential. Especially, the combination of phenolic constituents like quercetin and kaempferol is found to show excellent synergistic effect against breast cancer cell lines[44–46]. Their combination showed efficient suppression of cell proliferation and invasion of cancer cells. As these phenolic compounds co-exist in various concentrations, their synergistic effect is expected to promote honey as a remarkable applicant for breast cancer prevention and treatment. In the following section, the effect of crude honey against numerous breast cancer cell lines in laboratory conditions as well as animal models is highlighted before discussing the individual polyphenols anti-cancer effect.

Honey and breast cancer

Anna *et al.*[47] found that Greek honey had a bioactivity on MCF-7 breast cancer cells. The Greek honey had a weak osteogenic effect in low concentration against the MCF-7 cells. The cell viability of MCF-7 cells was reduced after treatment with honey. The cell proliferation lessened due to honey's effect on mitochondria, inducing apoptosis[47]. The effect of crude honey samples collected from Egyptian floral sources (*Ziziphus spina-Christi*, *Citrus reticulate* and *Cassia javanica*) was determined by *in vitro* study. The anti-cancer as well as antimycotic activity of the samples was observed using HTB-26 breast tumour cell line. However, crude *Ziziphus* honey had significant effect on cancer cells, compared to the other crude honey tested. The concentration of crude *Ziziphus* played a major a role in inhibiting the proliferation[48]. Jaganathan *et al.*[49] performed an *in vitro* evaluation of anti-oxidant as well as cytotoxic properties of Indian honey. The cytotoxic activity was tested against MCF-7 breast cancer cells. Indian honey retarded the cancer cell growth with increase in concentration along with increase in cells at the sub-G1 phase, showing the occurrence of apoptosis in breast cancer cells[49]. This was followed by the study of effect of honey on ehrlich ascites carcinoma[50]. Ehrlich ascites carcinoma is an impulsive murine mammary adenocarcinoma present in the ascites form and usually produced in out-bred mice via serial intraperitoneal (i/p) passages. The growth of ehrlich ascites carcinoma was significantly inhibited up to 39.98% by honey containing higher phenolic content of about 25% (volume/volume) when intraperitoneally injected.

Fauzi *et al.*[51] examined the effect of Tualang honey (TH) on two breast cancer cell lines, MCF-7 and MDA-MB-231. Apoptosis was shown to occur in both the cells. There were fluctuations in the mitochondrial membrane potential ($\Delta\psi(m)$), with the activation of caspase-3/7 and -9 after TH treatment. TH promoted mitochondrial dependent apoptosis induced by tamoxifen in both MCF-7 and MDA-MB-231 breast cancer cell lines[51]. TH promoted caspase oriented apoptosis in MDA-MB-231 cells. It reduced mitochondrion membrane potential in both cell lines along with tamoxifen compared to tamoxifen treatment alone[52]. This was followed by a comparative study of cytotoxicity and genotoxicity of TH in combination with 4-hydroxytamoxifen on the breast cancer cells. Both the cancer cells were affected after 4-hydroxytamoxifen treatment, while TH treatment affected MCF-7 cells alone. During the combination treatment of TH and 4-hydroxytamoxifen, TH encouraged genotoxicity of 4-hydroxytamoxifen in cancer cells, while non-cancerous cells were unaffected. The selectivity of TH was evident from the increased expression of damaged DNA proteins in MCF-10A cells[53]. Honey's radiation hygienization property in relation to anti-cancer, DNA protective and antimutagenicity effect was recorded by Saxena *et al.*[54] Honey displayed strong anti-proliferative property against breast cancer cell lines devoid of normal cell line (Int-407, intestinal epithelial cell) indicating its differential and selective cytotoxicity. The study demonstrated that honey provides safety during radiation treatment as well as maintaining its nutraceutical value[54].

Kadir *et al.*[55] performed *in vivo* experiments to evaluate the effect of Malaysian jungle TH on the growth of breast cancer in rats. About 80 mg/kg of 7,12-dimethylbenz(α) anthracene (DMBA) was used for developing breast cancer in rats. The growth of cancer cells was degraded by TH treatment at *in vivo* conditions. Results of the histological evaluation indicated the presence of grade 1 and 2 tumours in the TH treated rats whereas grade 3 tumour was present in untreated rats. Pre-clinical study concludes that, differed action on DMBA-induced breast cancers

was exerted by TH in pre-clinical study[55]. Orsolić *et al.*[56] explored the transplantable murine mammary tumours when treated with honey bee products. The tumour growth, metastasizing ability, initiation of programmed cell death and necrosis in murine tumour models by honey bee venom royal jelly and propolis were studied. It was found that honey significantly subdued the tumour growth when orally administered (2 g/kg). They also suggested that the oral or intravenous administration of honey bee products exerted control over metastasis[56].

Honey and its polyphenols

Polyphenols of honey have been investigated against breast cancer. Phenolic phytochemicals such as apigenin, caffeic acid, quercetin, *p*-coumaric acid, eugenol, chrysin, kaempferol, ferulic acid, ellagic acid, hisparetin, pinobanksin and galangin were tested against breast cancer cell lines. The notable effects of each phytochemical are discussed below.

Apigenin

The influence of apigenin on MCF-7 and MDA-MB-468 breast carcinoma cells was studied by Yin *et al.*[57] Apigenin retarded the growth of both cancer cell lines through cell cycle regulatory molecules. G_2/M cell cycle phase arrest includes reduction of cyclin B1, D1, A and CDK1 proteins, whereas there was no change in CDK6, CDK2 and cyclin E protein expression. Rb phosphorylation was degraded in MCF-7 cells by apigenin in time- and dose-dependent manner[57]. Apigenin caused degradation of HER2/neu protein and induced apoptosis in breast cancer cells. Furthermore cytochrome *c* was released leading to initiation of caspase-3 thereby causing cleavage of DFF-45. Additionally, apigenin up-regulated the level of *p*27 protein while decreasing cyclin D1, D3 and CDK4 in breast cancer cells[58].

Influence over the VEGF expression by apigenin on MDA-MB-231 human breast cancer cells was described by Jin *et al.*[59]. The secretion and mRNA levels of VEGF as well as its transcription activity was decreased by apigenin. Moreover apigenin treatment also initiated the expression of p53 while declining HIF-1alpha and *p*-AKT expressions in MDA-MB 231 cells. Hepatocyte growth factor (HGF) stimulated metastasis and the invasive growth was averted by apigenin in MDA-MB-231 cells[60]. Along with this, there was also a reduction in HGF-stimulated cell-matrix adhesion and cell-endothelial cells adhesion in breast cancer cells after apigenin treatment. The anti-metastatic property also involved the blocking of PI3K/AKT pathway of the cancer cells.

Choi *et al.*[61] combined apigenin with 5-fluorouracil and tested it with MDA-MB-453 breast cancer cells. The cellular proliferation was notably expressed by 5-fluorouracil and apigenin combination when compared with the effect of 5-fluorouracil alone. The induction of apoptosis was due to the activation of caspase-3, ErbB2 expression and inhibition of AKT expression[40]. This was followed by experimentation of apigenin alone with MDA-MB-453 cells. Apigenin induced mitochondria-mediated apoptosis with the release of cytochrome *c* causing the activation of caspase-3 and -9 in MDA-MB-453 cells[61]. Similarly, apigenin caused apoptosis of SK-BR-3 human breast cancer cells with cell cycle arrest at G_2/M phase along with changes in p21 (Cip1) and CDC2. The higher concentration of apigenin induced changes in Bax and cytochrome *c* expressions of p53 downstream[62]. Following this, apigenin was tested with MCF-7 breast cancer cells. Here, apigenin induced apoptosis by an extrinsic pathway. This involved the up-regulation of caspase-8 and increase in G_0/G_1 phase cells. Apigenin induced p53 and inhibited STAT3 and nuclear factor-kappa B (NF-κB) signalling in HER2 over-expressing MCF-7 breast cancer cells[63].

In another study, apigenin blocked the activity of vascular endothelial growth factor mRNA and protein in T47D human breast cancer cells treated with progestin. Apigenin was found to have no effect on the mRNA levels of progesterone and estrogen receptor-α while obstructed the MPA-dependent secretion of VEGF[64]. It caused programmed cell death in HER2/neu-over-expressing breast cancer cells. This was found to have a relationship with proteasomal degradation of HER2/neu via phosphatidylinositol 3-kinase/AKT-dependent pathway. The PI3K activity was directly affected by apigenin while AKT kinase activity was ambiguously affected. All these results were apigenin-dose dependent[65,66].

p53-dependent apoptosis was induced by apigenin in T47D and MDA-MB-231 breast cancer cell lines. Exposure to apigenin-treated cells augmented G_2/M phase, cleaved PARP, caspase-3 and increased p-CDC2, p21, Bax and p53 expression. These changes depended on dosage of apigenin[67,68]. Harrison *et al.*[69] recorded various reactions induced by sub cytotoxic dose of apigenin in three breast cancer cell lines (MDA-MB-231, MBA-MB-468, MCF-7 and SK-BR-3). Apigenin inhibited the proliferation of MDA-MB-468 cells with production of excessive reactive oxygen species (ROS) and accumulation of cells at G_2/M phase. There was also reduction of phosphorylation of AKT (protein kinase B) which caused apoptosis of breast cancer cells[69].

Caffeic acid

Caffeic acid phenethyl ester (CAPE), one of the derivatives of caffeic acid, was tested with three breast cancer cell lines namely MDA-MB-231, MCF-7 and SK-BR-3 (ref. 70). The viability of CAPE treated breast cancer cells was affected in a dose- and time-dependent fashion.

Acetylation of histone proteins with reduction of ER-α and PR expressions was observed in MDA-231 and MCF-7 cell lines while *p*-HER2 expression decreased in SK-BR-3 cells. Alkyl esters of caffeic acid exhibited strong growth inhibition on MCF-7 (ref. 71). The viability of breast cancer cells was reduced by 80%. There was also inhibition of lipid peroxidation, which was concentration-dependent.

Boudreau *et al.*[72] studied the anti-cancer effect of caffeic acid on cancerous (MCF-7 cells) and normal (MCF-10A cells) human mammary epithelial cell lines. Growth induction of MCF-7 cells decreased after caffeic acid treatment. This confirmed the selectivity of acid as the MCF-10A cells were unaffected. Effects of caffeoyl pyrrolidine derivative LY52 on MB-231 human breast cancer MDA-cells were reported by Qu *et al.*[73] LY52 suppressed MMP-2 activity with succinylated gelatin degradation. It also inhibited the invasion of MDA-MB-231 cancer cells in mice during oral administration with no prominent side effects[73]. The compounds formed after oxidative dimerization of methyl caffeate affected the viability of MCF-7 as well as MDA-MB-231 cells. It induced apoptosis, which involved DNA fragmentation, which is one of the notable changes observed during apoptosis, which was again dose- and time-dependent[74].

CAPE dose-dependent inhibited the growth of breast cancer stem cells by progenitor formation. Colony formation was reduced after CAPE treatment in *in vitro* condition. There was an upsurge in S-phase cells combined with reduction in G_0/G_1 phase cells due to caffeic acid treatment[75]. Ahn *et al.*[76] found that the multidrug-resistant MCF-7/Dox human breast carcinoma cells were affected by caffeic acid. The results obtained suggest that caffeic acid is potentially a chemosensitizing agent with greater selectivity to drug-resistant MCF-7/Dox cells mediated by the induction of TGF beta isotypes. Both TGF beta 1 and TGF beta 2 expressions were high in MCF-7/Dox cells after caffeic acid treatment[76].

Quercetin

Choi *et al.*[77] examined quercetin-induced programmed cell death and cell cycle arrest in human breast cancer cells. Quercetin treatment led to G_2/M phase cell cycle arrest and decreased antisense p21CIP1/WAF1 expression in MCF-7 cells[77]. This was followed by a study on the antiproliferative effects of quercetin in human breast cancer MDA-MB-453 cells. Similar to MCF-7 cells, there was cell cycle arrest and induction of apoptosis in MDA-MB-453 cells. While the expressions of Bax and PARP were boosted, there was degeneration of Bcl-2 expression and caspase-3 in cancer cells ultimately leading to cell death[78].

Another study investigated effects of quercetin on cell viability in MDA-MB-231 cells. Quercetin affected the number of viable cells in a dose- and time-dependent manner, along with cell cycle arrest causing apoptosis. There was a decline in mitochondrial membrane potential and increase of cytosolic Ca(2+) levels. Apart from this, quercetin activated caspase-3, -8 and -9, along with fluctuations of Bax and Bcl-2 protein levels and release of apoptosis-inducing factor (AIF), stimulating the translocation of nucleus[79]. Quercetin mediated apoptosis of MCF-7 cells through mitochondrial pathway. The treatment increased the number of S phase and sub-G_1 phase cells in a dose- and time-dependent manner. There was a decrease of protein expression of CDK2, cyclins A, Bcl-2 and B, while increasing the p53 and p57 proteins and activations of caspase-6, -8 and -9 in quercetin treated cancer cells[80].

Soyocak *et al.*[81] studied the effect of quercetin in relation to induction of antiproliferation and apoptosis in breast cancer cell lines, on Bak protein. After the treatment, levels of Bak protein increased in MCF-7 cell line. Quercetin treatment had a dose-dependent effect on MCF-7 cells[81]. Lee and Park[82] studied the anti-cancer activity of quercetin against MCF-7 cells. Treatment of quercetin caused changes in mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK) and hypoxia inducible factor-1α (HIF-1α), thereby controlling the signalling pathways and inducing apoptosis[82].

The combined effect of quercetin and tamoxifen in MCF-7 cell lines was reported. All doses of quercetin and tamoxifen induced apoptosis via telomerase enzyme activity in MCF-7 cell lines. Their synergistic effect was greater when compared to their individual effect[41]. Zhang *et al.*[83] explored combinational activities of quercetin and quercetin-5′,8-disulphonate on breast cancer cell lines. MCF-7 cells were found to undergo apoptosis after quercetin treatment. Furthermore, quercetin's strong antitumour activity was in relation to ROS-dependent apoptosis pathway[83].

Co-treatment with quercetin and 1,2,3,4,6-penta-O-galloyl-β-D-glucose (5GG) motivated apoptosis in human breast cancer MDA-MB-231 and AU565 cells. This treatment reduced S-phase kinase protein 2 expression leading to S-phase arrest in MDA-BM-231 cells and reduced HER2 expression causing G_2/M phase arrest in AU565 cells. It was concluded that quercetin enhanced the anti-cancer activity of 5GG in MDA-MB-231 cells[42]. Deng *et al.*[84] described the effects of quercetin against MCF-7 cells in laboratory conditions. Quercetin treatment led to variations in survivin mRNA expressions and G_0/G_1 phase cell cycle arrest in MCF-7 cells. All these effects depended on concentration and exposure time[84].

An *in vivo* experiment on the synergistic effect of quercetin with doxorubicin injected in mice with breast cancer was carried out. The combination of quercetin and doxorubicin reduced the growth of 4T1 breast cancer leading to survival of mice. However, individual quercetin or doxorubicin treatment was not effective. Treatment

with quercetin also promoted lymphocyte proliferation and regulated Th1/Th2 cytokine imbalance[85]. Zhong *et al.*[86] examined the effects of quercetin on proliferation and apoptosis in transplantation tumour of breast cancer in nude mice. Tumour weight in mice after quercetin treatment was drastically reduced. The antiproliferative action was due to apoptosis, which was indicated by the decrease in Bcl-2 protein level in the tumour cells[86].

p-coumaric acid

Chang *et al.*[87] studied the cytotoxic effect of *p*-coumaric acid using T-47D breast cancer cells[87]. There was subdual in the growth of cancer cells. *p*-coumaric acid treatment led to apoptosis of T-47D cells with significant accumulation of cells in sub-G_1 phase cells leading to G_1 phase of cell cycle arrest. *p*-coumaric acid was tested on breast adenocarcinoma cell line. It exhibited toxicity against MCF-7 breast cancer cells[88]. This toxicity was in a dose-dependent manner. The studies also showed that there were changes in calcium signal transduction and gene expression in cancer cells due to *p*-coumaric acid treatment.

Eugenol

The time- and dose-dependent effects of eugenol in human MCF-7 breast cancer cells were noted by Vidya and Niranjali[89]. There was a rise in the percentage of breast cancer cell apoptosis along with DNA fragmentation apart from depletion of intercellular glutathione level. The profusion of thiobarbituric acid reactive substances (TBARS) formation inferred increase in lipid peroxidation level[89]. Eugenol triggered apoptosis in MCF-7, T-47D and MDA-MB-231 breast cancer cells with down-regulation of E2F1/surviving[90]. Eugenol treatment induced different effects in different cancer cells at low dose. The treatment caused changes in NF-κB and cyclin D1 genes with down regulation of E2F1 and upregulation of cyclin-dependent kinase inhibitor p21 WAF1 protein. Similar results were seen in xenograft of human breast tumours during *in vivo* condition.

Epoxypseudoisoeugenol-2-methyl butyrate (EPB), a eugenol derivative, was experimented with MCF-7 (estrogen-dependent) and BT-549 (estrogen-independent) breast cancer cells. There was a dose- and time-dependent suppression of propagation and cell cycle arrest in both the cell lines after EPB treatment. However, NF-κB mediated transcription activity was seen in MCF-7 cells due to phorbolmyristate acetate (PMA) and tumour necrosis factor-7 (TNF-7). It also caused cell cycle arrest at G_1/G_0 phase in both MCF-7 and BT-549 cells. Hence, the anti-cancer property of EPB against both hormone-dependent and hormone-independent breast cancer cells was found[91]. Apoptotic effect of paclitaxel in MCF-7 cells produced by 1′S-1′-acetoxyeugenol acetate (AEA) was reported by In *et al.*[92] which was found to be related to NF-κB inactivation. The apoptosis induced depended on the dysregulation of NF-κB. Phosphorylation of inhibitor of κB-kinase complex was reduced by AEA treatment which led to the removal of apoptotic resistance. Apart from this, the combined treatment of AEA and paclitaxel had a chemosensitizing role against MCF-7 cells.

Chrysin

Potential effects of chrysin in MDA-MB-231 breast cancer cells were studied by Hong *et al.*[93] Cell viability of the cells was affected depending on the dose after treatment, which was accompanied by DNA fragmentation and mitochondrial dysfunction. Chrysin treatment increased expression of PPAR alpha mRNA, one of the early events of cell regulation, in breast cancer cells[93]. Yang *et al.*[94] assessed the anti-metastatic activity of chrysin with the help of TNBC breast cancer cell lines that are metastatic triple-negative. Chrysin induced changes in E-cadherin and vimentin expression in TNBC cells. Moreover, AKT signal pathway played a dominant role in chrysin-induced anti-metastatic activity by regulating matrixmetalloproteinase-10 (MMP-10) and epithelial-mesenchymal transition, suggesting chrysin as a potential therapeutic candidate[94].

Both *in vivo* and *in vitro* activities of chrysin on breast cancer cells were recorded[95]. Inhibition of HDAC8 enzymatic activity showed that chrysin was a histone deacetylase inhibitor (HDACi) after enzymatic evaluation. The dose-dependent anti-cancer effect of chrysin against MDA-MB-231 cells was evident in the *in vitro* experimentation. The xenograft model containing MDA-MB-231 cells was orally injected with chrysin. The tumour size significantly decreased after 6 weeks of treatment. Overall, *in vitro* and *in vivo* data indicated that chrysin might be a standardized candidate against breast cancer. It suppressed the hypoxic survival and metastatic growth of 4T1 mouse breast cancer cells[96]. Growth of 4T1 cells in Balb/c mice was reduced by oral administration of chrysin. Along with this, chrysin improved the antimetastatic effect of DR5 mAb. It selectively repressed hypoxia-induced STAT3 phosphorylation avoiding HIF-1α protein along with abrogating hypoxia-induced VEGF gene expression. The synergistic effect (in combination with DR5 mAb) and individual effect of chrysin on the mouse model of breast cancer was also studied.

The activity of synthetic chrysin analogue, 5,7-dihydroxy-8-nitrochrysin (NOC), was studied using human cancer cells[97]. The NOC treatment was not very effective in HBL-100 cells (ER-positive) while highly affecting MDA-MB-453 cells (ER-negative) and modestly affecting the MCF-7 cell line (ER-positive). This showed the selective toxicity of NOC. Moreover, NOC-induced

apoptosis involved a rise in reactive oxygen species (ROS) level and AKT dephosphorylation. Xiao *et al.*[98] found that NOC activated FOXO3a/Bim signalling in MDA-MB-453 cancer cells. Release of cytochrome *c* into cytoplasm showed that the cell death induced by NOC was mitochondrial pathway-dependent. Additionally, AKT and FOXO3a phosphorylation was suppressed by NOC in MDA-MB-453 cells causing apoptosis[98].

Kaempferol

Kaempferol had effects on MCF-7 cells. The treatment of ER-positive breast cancer cells with kaempferol resulted in a time- and dose-dependent decrease in cell number. Kaempferol treatment reduced insulin receptor substrate 1 (IRS-1), cyclin D1 and progesterone receptor (PR) expressions and aggregation in the nuclei. The degradation of ER-α was also induced by kaempferol along with anti-estrogen and estradiol[99]. Oh *et al.*[100] studied kaempferol effect against estrogen-related diseases. Change in E2 concentration showed the activity of kaempferol on ER-mediated pathway in MCF-7 cell. Kaempferol treatment stopped the focus formation induced by E2 (ref. 100).

Kaempferol-3-*O*-rhamnoside, the bioflavonoid, also inhibited MCF-7 cell growth by initiation of various caspase cascade pathways[101]. This antiproliferation happened in a dose-dependent pathway. Kaempferol-3-*O*-rhamnoside treatment upregulated caspase-9, -3 depending on the duration of treatment, and variation of poly (ADP-ribose) polymerase (PARP) level contributing to programmed cell death of the cancer cells. In another study, kaempferol was found to be the strongest inhibitor of breast cancer growth[102]. It had a concentration-oriented effect on MDA-MB-231 human breast carcinoma lines in *in vitro* experiment. Further, it was found to bind to the DNA and led to cleavage causing lysis of the cell.

An in-depth analysis on MCF-7 cell death was reported along with mechanisms[103]. The occurrence of apoptosis was specified by an increase in G_1 phase cells. In addition, there was also cleavage of PARP, Bax and caspase-7,-9 signifying the intracellular pathway of apoptosis. Kaempferol also down-regulated polo-like kinase 1 (PLK-1) controlling the mitotic progression of cancer cells. The combined effect of quercetin and kaempferol was studied in MCF-7 cells. The treatment influenced the transcription of CYP1A1 and AhR function in a dose-dependent manner[44]. CYP1A1 mRNA and CYP1A1 enzyme activities were boosted by quercetin treatment. However, kaempferol treatment subdued CYP1A1 transcription.

Kaempferol also abolished TCDD-induced XRE binding and caused cytotoxicity to the breast cancer cells. The flavonols quercetin and kaempferol, synergistically avoided invasion of MDA-MB-231 cells under *in vitro* condition[45]. They reduced matrix metallopeptidase (MMP-3) activity with respect to concentration changes along with anti-metastatic behaviour in the cancer cells. Margaret *et al.*[46] reported the combined antiproliferative effect of quercetin and kaempferol on PMC42 human breast cell line. The flovonols diminished expression of nuclear proliferation antigen Ki67 and total protein levels after treatment. Thus the phenolic compounds showed enhanced anti-cancer activity when combined than when treated individually[46].

Ferulic acid

Ferulic acid, a naturally occurring aromatic compound, was experimented for its phytoestrogenic effects on ER-positive T-47D and ER-negative MDA-MB-231 cells in culture. The co-treatment of ferulic acid along with Fulvestrant had significant effect on breast cancer cells than ferulic acid treatment alone. Ferulic acid up-regulated pS2 mRNA expressions, potential marker for hormone-dependent breast cancer and overexpression of ER-alpha protein in treated cancer cells[104]. Ferulic acid was found to produce synergistic effect with *d*-tocotrienol. There was high increase in G_1 phase due to p21 (waf-1/cip-1) variation. Additionally cyclin/cyclin-dependent kinases (Cdks) were also affected[43]. Conclusively, the synergistic effect of *d*-tocotrienol and ferulic acid was predominantly found in cancer cells.

Ellagic acid

The changes in expression of human telomerase reverse transcriptase (hTERT) $\alpha+\beta+$ transcript after ellagic acid treatment were studied by Strati *et al.*[105] using MCF-7 (ER-positive) cancer cells. Ellagic acid increased hTERT $\alpha+\beta+$ mRNA expression. Meanwhile its coexistence with 17β-estradiol significantly reduced 17β-estradiol-induced increase in hTERT $\alpha+\beta+$ mRNA. It was concluded that ellagic acid exerted a chemopreventive effects in breast cancer by down-regulating 17β-estradiol-induced hTERT $\alpha+\beta+$ mRNA expression. It was found to have antiproliferative activity on the MCF-7 breast cancer cells[106]. This antiproliferative activity was via regulation of the TGF-β/Smad3 signalling pathway, which was due to decreased phosphorylation of RB proteins. Ellagic acid induced G_0/G_1 cell cycle arrest in MCF-7 cells after the treatment.

The phenolic compound also exerted anti-angiogenesis effects via VEGFR-2 signalling pathway in breast cancer cells[107]. The structure-based interaction between ellagic acid and VEGFR-2 was studied. Ellagic acid treatment suppressed VEGF thereby affecting angiogenesis, by affecting VEGFR-2 tyrosine kinase activity. Besides this, mitogen-activated protein kinase (MAPK) and PI3K/AKT pathways were also inhibited by ellagic acid. This was also seen in MDA-MB-231 cancer growth in the xenograft

observation. Ellagic acid showed diverse effects in MDA-MB-231 and MCF-7 human breast cancer cell lines[108]. In MDA-MB-231 cells ellagic acid had a dose-dependent activity along with decrease of Bcl-xL expression and cytochrome *c* release, while it had antiproliferative effect against MCF-7 cells. Yet, there was cell cycle arrest in both cell lines and decreased the expression of survivin. However, at high doses of ellagic acid, upregulation of c-fos and pS2 protein in MCF-7 cells was noted.

The activity of ellagic acid on MCF-7 cancer cells and Hs 578T lung fibroblast cells was documented under *in vitro*[109]. While it reduced the proliferation of MCF-7 cells, it did not affect normal Hs 578T cells. Apoptosis induction was accompanied by a decrease in the levels of pro-matrix metalloproteinase-2 (pro-MMP-2 or gelatinase A), pro-matrix metalloproteinase-9 (pro-MMP-9 or gelatinase B) and vascular endothelial growth factor (VEGF165) after the treatment. Results show the selective toxicity of ellagic acid on cancer cells. Ellagic acid was found to have cytotoxicity in MCF-7 cancer cells when a zinc layered interrelation compound (EAN) was formed[110]. Cytotoxicity of EAN was determined in MCF-7 cells and other normal cell lines. EAN displayed toxic effect against MCF-7 cells while reduced effect on normal cells. It was found that caspase-3 and -9 were activated, inferring the occurrence of apoptosis via mitochondrial pathway. In addition, EAN also increased DNA fragmentation, which was in a time- and concentration-dependent manner.

Hesperetin

Choi recorded that hesperetin affected MCF-7 cell growth dose-dependently along with G_1-phase cell cycle arrest[111]. Hesperetin treatment up-regulated p21Cip1 and p27Kip and down-regulated cyclin-dependent kinases (CDKs) and cyclinsin cells. In addition, the binding of CDK4 with p21Cip1 was boosted by hesperetin, showing their involvement in anti-cancer activity in MCF-7 cells. Hesperetin impaired the uptake of insulin-generated glucose and inhibited proliferation in MDA-MB-231 cancer cells[112]. This was followed by inhibition of insulin-related redistribution of GLUT4, phosphorylation of insulin receptor and AKT, finally causing antiproliferation of breast cancer cells.

Lan *et al.*[113] demonstrated hesperetin anti-proliferative activity in aromatase-expressing MCF-7 tumour in ovariectomized athymic mice[113]. Dietary administration of hesperetin significantly deterred the xenograft growth. There was also reduction of CDK4, Bcl-x(L), cyclin D1 and *pS2* (estrogen-responsive gene). This was followed by the study of prevention of letrozole-induced bone loss in a mouse model of breast cancer. Aromatase-over expressing MCF-7 cells were transplanted in postmenopausal mice model. Hesperetin not only decreased the plasma estrogen level and tumour size but also reversed the bone volume fraction induced by letrozole[114].

Pinobanksin

Xuan *et al.*[115] found that pinobanksin affected MCF-7 (ER-positive) and MDA-MB-231 (ER-negative) breast cancer cells in a dose- and time-dependent pattern. The main changes observed in the breast cancer cells were – increase in ANXA7 expression, excessive ROS generation and reduction of mitochondrial membrane potential. Apart from these, there were changes in NF-κB p65 level and p53 level. Further, apoptosis of MCF-7 and MDA-MB-231 cells was caused by pinobanksin treatment.

Galangin

Tessa *et al.*[116] reported the activity of galangin against the growth of human breast cancer Hs578T cell line. Galangin treatment induced dose-dependent apoptosis combined with the suppression of AhR-dependent transcriptional activity in Hs578T cells. Apart from this, there was also G_0/G_1 cell cycle phase arrest and degradation of cyclins D3, E and A after galangin treatment leading to cell lysis[116]. Galangin affected the proliferation of human MCF-7 breast cancer cell line (an ER-positive). It blocked the cell proliferation of cancer cells. Cell death included binding of galangin to the estrogen receptor inhibition of DMBA-induced pre-B-cell apoptosis. Moreover galangin was observed to be more effective among the flavonoids tested[117].

Discussion and conclusion

Cancer is a killer disease of which breast cancer is a major threat to women around the globe claiming a second place. With the increase in the number of breast cancer patients, investigations for novel and effective anti-cancer agent for its prevention as well as cure are underway. However, there is no single drug which can cure cancer at all stages. In such a scenario, some scientists concentrate on natural diet for averting and treating this disease. One of the useful food substance with anti-cancer property is honey. Along with the crude honey, its phenolic components are also being explored. This review summarized the anti-cancer activity of honey and its phenolic markers on breast cancer and promoted it as a promising candidate.

It is evident that both crude honey and its phenolic compounds are able to induce apoptosis in breast cancer cells. Conclusively, when the cancer cells are treated with honey, a range of changes like activation of caspase-3, caspase-8, caspase-9, boost in ROS level activating

Table 2. Effect of phenolic phytochemicals of honey against breast cancer

Phytochemical tested	Notable findings	Reference
Apigenin	G2/M cell cycle phase arrest Decrease in cyclin B1, D1, A and CDK1 protein levels Induction of caspase-3 activity Inhibited the hepatocyte growth factor (HGF) Activation of ERBB2 expression Release of cytochrome *c* Inhibited STAT3 and NF-κB signalling PARP cleavage Production of reactive oxygen species (ROS)	50–63
Caffeic acid phenethyl ester (CAPE)	Reduction of cell viability Decrease in the expression of ER-α (estrogen receptor) ,PR (progesterone receptors) and p-Her2 (phosphorylated-HER 2) Inhibition of lipid peroxidation Inhibition of MMP-2 expression Decrease in G0/G1 phase cells an increase in S phase cells Induction of TGF beta isotypes	64–70
Quercetin	Accumulation of cells at G2/M phase Increase of Bax expression Decrease Bcl-2 expression Activation of caspase-3, -8 and -9 Increase of cytosolic Ca(2+) levels Promotion of apoptosis-inducing factor (AIF) release from mitochondria Decrease of CDK2, cyclins A protein expression Increase in the levels of Bak protein Reduced survivin protein levels Down-regulation of S-phase kinase protein 2 expression	71–82
p-coumaric acid	Suppression of cell growth Cell cycle arrest at sub-G1 phase Dose-dependent toxicity	83, 84
Eugenol	Dose- and time-dependent effect Induction of apoptosis E2f1/survivin down-regulation Up-regulation of cyclin-dependent kinase inhibitor p21waf1 protein Nf-b transcriptional activity Inhibited phosphorylation levels Enhancement of proapoptotic activity	86–88
Chrysin	DNA fragmentation Mitochondrial dysfunction Increased expression of PPAR alpha mRNA Increase of E-cadherin expression Decrease of vimentin expression Inhibition of hypoxia-induced STAT3 phosphorylation Akt dephosphorylation	89–94
Kaempferol	Time- and dose-dependent decrease in cancer cell number Up-regulation of caspase-9 and caspase-3 Cleavage of poly (adpribose) polymerase (PARP) Down-regulation of polo-like kinase 1 (plk-1)	95–99
Quercetin and kaempferol	Reduced CYP1A1 transcription Decrease of Matrix metallopeptidase (MMP-3) activity Concentration-dependent changes Decreased expression of nuclear proliferation antigen Ki67	100–102
Ferulic acid	Up-regulated ps2 mRNA expressions Increased level of ER alpha protein expression G_1 phase cell cycle phase arrest Reaction with p21 (waf-1/cip-1)	103, 104

(*Contd*)

Table 1. (*Contd*)

Phytochemical tested	Notable findings	Reference
Ellagic acid	Down-regulation of the 17β-estradiol-induced hTERT $\alpha + \beta +$ mRNA expression Regulation of the TGF-β/Smad3 signaling pathway Decrease of RB protein phosphorylation G_0/G_1 phase cell cycle arrest Directly inhibited VEGFR-2 tyrosine kinase activity, MAPK and PI3K/Akt pathway Decrease of Bcl-xl expression Increase in the expression of cytochrome *c* in the cytosol Decrease in the levels of pro-matrix metalloproteinase-2,9 DNA fragmentation	105–110
Hesperetin	Down-regulation of cyclin-dependent kinases (cdks) and cyclins Up-regulation of p21Cip1 and p27Kip1 Inhibition of insulin-induced redistribution of GLUT4 Decrease in the expression of the estrogen-responsive gene ps2 Reduction in the plasma estrogen level	111–114
Pinobanksin	Dose- and time-dependent cytotoxic effect Drastic increase of ANXA7 expression and ROS level and NF-κB p65 level Change in p53 level	115
Galangin	Suppression of Ahr-dependent transcriptional activity Cell cycle block at G0/G1 phase Down-regulation of cyclins D3, E and A Inhibits DMBA-induced pre-B-cell apoptosis	116, 117

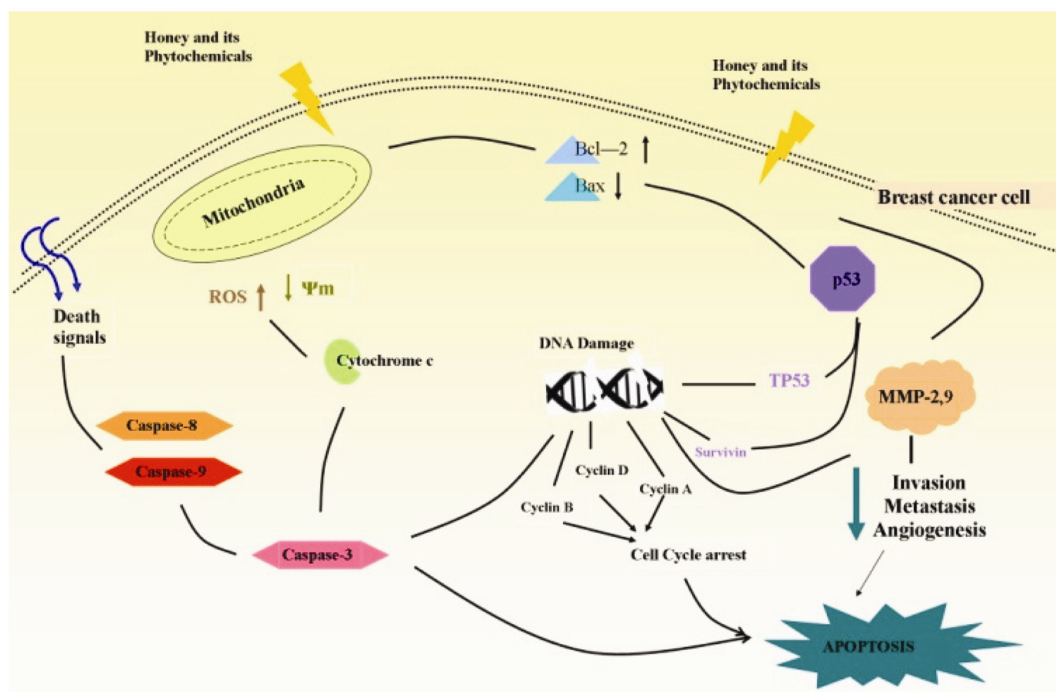

Figure 4. Targets of honey and its phenolic markers against breast cancer cells.

mitochondrial pathway, lipid layer breakage, increase of $G_1/G_2/M$ phase cells, up-regulation of Bax regulators, down-regulation of Bcl-2 proteins and p53 pathway which cause the DNA fragmentation and down-regulation of apoptosis dependent genes like CDK 1 and TP53, may occur (Figure 4). Table 2 shows the major observations against breast cancer by phenolic phytochemicals.

Polyphenols like caffeic acid[64–70], chrysin[87–91], quercetin, kaempferol[98–102] and ellagic acid[106] are found to down-regulate the matrix metallopeptidase in diverse breast cancer cells like MCF-7 and MDA-MB-231. Matrix metallopeptidases (MMP) is an enzyme that belong to zinc-metalloproteinases family and tangled in the degradation of extracellular matrix during physiological

procedures, such as, development of the embryo, wound healing, cell migration, angiogenesis, etc. MMPs expressions are high in cancer cells and they have an alleged role in extracellular matrix remodelling and angiogenesis and are also considered as possible mediators of invasion and metastasis[115]. MMP is said to be one of the important biomarkers of breast cancer since MMPs 1, 2, 7-11, 13, 14 and 16 expressions were predominantly found in MDA-MB-231, T47D and MCF-7 cancer cell lines[116]. In another study, MMP-9 was concluded to be the gene expression signature of different grades (G1, G2 and G3) of invasive ductal carcinoma of breast cancer. Higher expression of MMPs was associated with higher grades of tumour invasion and metastasis in breast cancer. Hence, from the above studies, it may be suggested that honey and its phytochemicals are able to inhibit MMPs, one of the recognized biomarkers of breast cancer, suppressing its invasion and metastasis.

Thus honey and its phenolics can be used to prevent as well as treat breast cancer. However, there are some limitations associated with this. Phenolic composition of honey around the world is different depending on the nectar source, geographical origin and processing conditions. Nevertheless, success of honey against cancer depends on its bioactive components, which in turn offer diverse challenges for honey producers. Apart from this, there are some other gaps that needed to be fulfilled. From this review, it is evident that there have been lot of investigations done on the anti-cancer property of honey as well as phenolics in some breast cancer cell lines and animal models. However, more information regarding the genetic response would be helpful. This may be illustrated by *in vivo* studies on knock-out mouse model. In addition, human clinical trials regarding effect of honey and its phenolic components should be performed. For this, both healthy volunteers and participants with increased risk for breast cancer are to be recruited in large groups which demands more investments. Hence it is high time for researchers and other key-players to develop a sound clinical knowledge about honey and its components in order to spearhead the campaign against breast cancer.

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