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# Molecular targets of honey bee's products in cancer prevention and treatment

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**ABSTRACT**

Chemotherapy and radiotherapy are currently the main treatments for cancer but their toxicities on the surrounding normal cells limit their use in cancer therapy. Moreover, many cancers have developed some resistance to the available anticancer chemicals and put in failure the chemotherapy currently used in the cancer treatment. This failure of the targeted monotherapy resulting from bypass mechanisms has obligated researchers to use agents that interfere with multiple cell-signaling pathways. Recently, researches focused on the use of natural products which can target cancer promoting factors genes expression. Of these natural products, honey has been extensively studied. The pharmacological properties of honey include antioxidant, anti-inflammatory, antibacterial, immunomodulatory, estrogenic and anti-cancer effects. The honey bee's products are potent sources of nutritional components including sugar, amino-acids, water and minerals. Furthermore honey contains chemopreventive compounds such as flavonoids, phenol acids, tannins, vitamins that may interfere with multiple cell's pathways and hereby reduce the incidence of many types of cancers. However, the molecular mechanisms of honey bee's products in cancer prevention and treatment are less known. This review highlights the molecular mechanism of honey bioactive compounds in cancer prevention and treatment.

*Implication for health policy/practice/research/medical education:*
Honey bee's products are potent anticancer agents. Its anticancer mechanisms include oncogenic gene inhibition, pro-apoptotic factor activation, antioxidant and DNA repair activities. Understanding the molecular mechanism of honey bee's products can promote new strategy to develop effective anticancer drugs.

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## Introduction

Cancer is a real public health problem worldwide. The projections show that the number of new annual cases of cancer in the world will reach 15 million in 2020 (1). Cancer is a multistep process. Cell proliferation and differentiation is under the control of many regulatory proteins such as the transcription factors, pro-apoptotic proteins, anti-apoptotic proteins, onco-proteins, protein kinases, cell-adhesion molecules, cyclooxygenase-2 and other molecular targets (2). Cancer results from a malign transformation of normal cells escaping then to a cell cycle regulation system. Its genesis is characterized by the swift proliferation, differentiation, migration, invasion and metastasis (3). This dynamic process is promoted by various carcinogens including environmental mutagens and intracellular reactive species, tumor promoters and inflammatory agents (3). Chemotherapy and radiotherapy are the standard treatments for cancer but these modalities encounter many difficulties, mainly the resistance development of many cancers and the toxicity of anticancer chemicals to surrounding normal cells (4). New researches focused on natural products are capable of interfering with specific targeted molecules to promote cancer prevention and treatment (5-7). Honey bee's products are potential anticancer agents and have been screened for their anticancer mechanisms. The anticancer property of honey might be due to its antioxidant, anti-inflammatory, anti-proliferative, anti-angiogenic and apoptotic activities (8). The chemical composition of honey is varied and depends on the botanical source of

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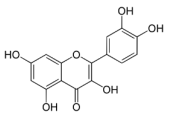
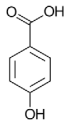
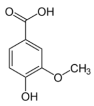
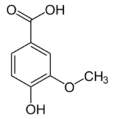
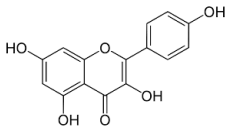
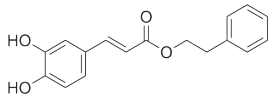
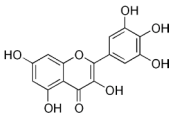
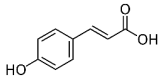
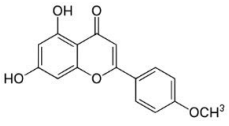
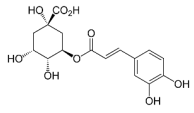
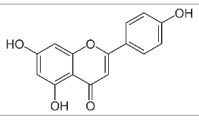
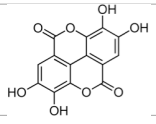
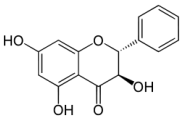
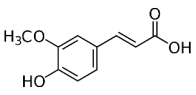
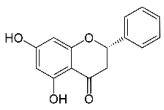
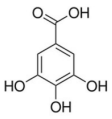
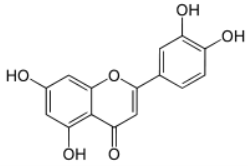
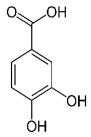
honey. The honey bee's products include various sugars, proteins, minerals, flavonoids, phenolic acids and enzymes (9). Polyphenols such as flavonoids and phenolic acids in honey are considered as the main factors responsible for the anticancer properties of honey (10). The molecular mechanisms of honey bee's products include oncogenes inhibition, pro-apoptotic factor activation, DNA repair proteins activation, tumor necrosis factors stimulation as well as other specific molecular targets. This review highlights the molecular mechanisms of honey bee's products for cancer prevention and treatment.

## Anticancer mechanisms of honey polyphenols

Honey bee's products include sugars, proteins, amino acids, minerals, polyphenols as well as other compounds (11). The anticancer properties of honey are mainly attributed to its polyphenols contents such as flavonoids and phenol acids (Table 1).

Many researchers have identified the molecular targets of honey polyphenols for cancer prevention and treatment.

**Table 1.** Chemical structure of anticancer polyphenols from honey

| Flavonoid compounds | | Phenol acids and derivate compounds | |
|---|---|---|---|
| Quercetin |  | p-hydroxybenzoic |  |
| Chrysin |  | Vanillic acid |  |
| Kaempferol |  | Caffeic acid phenethyl ester |  |
| Myricetin |  | P-coumaric acid |  |
| Acacetin |  | Chlorogenic acid |  |
| Apigenin |  | Ellagic acid |  |
| Pinobanksin |  | Ferulic acid |  |
| Pinocembrin |  | Gallic acid |  |
| Luteolin |  | Protocatechic acid |  |

Honey flavonoids include quercetin, kaempferol, apigenin, luteolin, chrysin, acacetin, pinobanksin, pinoccembrin and myricetin. Quercetin induces mitochondria-mediated apoptosis and enhances G2/M phase cell cycle arrest in human cervical cancer (HeLa) cells. This anticancer action of quercetin is due to various mechanisms: the induction of cell cycle regulatory proteins (p21, p53, cyclin D1), the upregulation of proapoptotic proteins (Bad, p-Bad, Bcl-xL, Mcl1, Bax), cytochrome C, Apaf-1 and caspases as well as downregulation of the antiapoptototic Bcl-2 protein (12). Quercetin exercises an inhibition of mitogen-activated protein kinase and Raf1 kinase activities and subsequently attenuates TPA-induced phosphorylation of ERK/p90 ribosomal S6 kinase in JB6 promotion-sensitive mouse skin epidermal (JB6 P+) cells (13). Moreover, the application of quercetin on prostate cancer cell enhances cancer cell apoptosis through the down-regulation of the levels of heat shock protein (Hsp) 90 and the activation of caspase activity (14). Some cytokines including TNF-related apoptosis inducing ligand (TRAIL) ate able to set off to apoptosis in colon cancer cells by engaging death receptors. Quercetin can induce the accumulation of death receptors in colon cancer cells and thereby enhance TRAIL-mediated apoptosis (15). Chrysin is a major flavonoid of honey. Its anticancer mechanisms include the down-regulation of Bcl-2 and the up-regulation of Caspase-3 and -9 genes expression (16), the stimulation of TNF-alpha (tumor necrosis factor-alpha) release (17), the induction of p38 mitogen-activated protein kinase gene expression (18) and the increase of p-PERK, p-eIF2α and ATF4 levels (19). In addition, chrysin inhibits the breast cancer resistance protein (BCRP), the multidrug resistance-associated protein-2 (MRP-2) and the phosphoglycoprotein-170 (P-gp) in Caco-2 colon carcinoma cells (20). Recent researches have demonstrated that the flavonoid myricetin exercises some anticancer activity by modifying aberrant cell proliferation, migration and invasion. It inactivates oncoproteins such as protein kinase B (PKB), Fyn, MEK1, and JAK1– STAT3 and targets the overexpression of cyclin-dependent kinase 1 (CDK1) reducing considerably the mitotic index of liver cancer cells (21). Pinobanksin and pinocembrin are the abundant flavonoids of *Leptospermum scoparium* tree's honey. The dietary intake of *Leptospermum scoparium* honey by patients with chronic hepatitis C showed that honey could prevent hepato-carcinogenesis through the activation of the immune system, decrease of PCR and T-regulatory cell (CD4, CD25) levels, and the Fox P3 gene expression (22). The anticancer property of the flavone acacetin (5,7-dihydroxy-4'-methoxyflavone) in prostate cancer cell is due to the suppression of NF-κB/Akt signalling pathway through the inhibition of the phosphorylation of IκBα and NF-κB (23). Many researches screened the molecular targets of apigenin for the cancer treatment and prevention. It has been demonstrated that apigenin increases the expression of cell cycle regulatory proteins INK4a/p16, INK4c/p18, WAF1/p21 and KIP1/p27 but down-modulates the expression of various cyclins such as D1, D2 and E as well as cyclin-dependent kinases (cdk), cdk2, cdk4, and cdk6 in prostate cancer cell xenograft (24,25). Moreover, apigenin enhances the proteasome degradation of breast cancer cell by inhibiting PI3K and Akt kinase activities, and also decreases the HER2/neu autophosphorylation and transphosphorylation (26). The flavonol kaempferol decreases the expression of Bcl-2 and set off to the alteration of the mitochondrial membrane potential followed by the elevation of active caspase-3 expression in human glioblastoma cells (27). Its enhances the sensitization of U251 and U87 glioma cells to tumor necrosis factor–related apoptosis-inducing ligand (TRAIL/Apo2L) leading to cells proteasome degradation (27). Luteolin, 3',4',5,7-tetrahydroxyflavone has been reported to have a strong anticancer effect on many cancer models through the apoptosis induction (28). The apoptotic effect of luteolin is due to the increase of the expression of the pro-apoptotic protein Bax and the decrease of the expression of the anti-apoptotic protein Bcl-2, with a simultaneous enhancement in caspase-3 (29,30). Furthermore, luteolin promotes cancer cells death via the phosphorylation and the stabilization of the cell cycle regulatory protein p53 (31).

Honey contains diversify phenolic acids and derivate such as caffeic acid phenethyl ester, p-hydroxybenzoic, vanillic, caffeic, coumaric, ellagic, gallic, ferulic, protocatechuic and chlorogenic acids. Phenol acids of honey can interfere with multiples cellular signaling pathways and thereby inhibit cancer initiation, migration, metastasis and invasion. Caffeic acid phenethyl ester possesses an apoptotic property on C6 glioma cells through the activation of the tumor suppressor proteins p53 and p38/ MAPK. Furthermore it induces the release of cytochrome c from mitochondria into cytosol and activates the protein CPP32 accentuating the p53-dependent apoptosis (32). Caffeic acid phenethyl ester suppresses vascular endothelial growth factor (VEGF)-induced angiogenesis in human umbilical vein endothelial cells suggesting the potentiality of this compound as preventive and therapeutic agents against angiogenesis-related human diseases (33). The following phenol acids, p-hydroxybenzoic acid, vanillic acid, caffeic acid from conifer tree, thyme and citrus honeys respectively, down-regulate the TNF- α-induced adhesion molecule and VCAM-1 expression in endothelial cells (HAEC), prostate cancer (PC-3) and breast cancer respectively (34). Gallic acid and caffeic acid from *Thymus vulgaris* and *Leptospermum scoparium* honey in combination with quercetin, kaempferol and chrysin down-modulate the expression of both MMP-2 and -9 in prostate cancer (PC-3) cells and thereby suppress migration, invasion and adhesion (35). Ellagic, gallic, ferulic, chlorogenic and caffeic acids, the major phenolic acids of *Apis mellifera*

honey enhance the TNF-alpha (tumor necrosis factor-alpha) release suggesting their apoptotic properties on common cancer cells (36). Di-hydroxy benzoic acid, caffeic acid, ferulic acid and cinnamic acid from *Koompassia excels* honey disrupt the mitochondrial membrane potential and activate the caspase-3/7 and -9 activities in human breast and cervical cancer cell lines and set off to the apoptosis process (37). Moreover, previous researches demonstrate that ferulic acid can target the fibroblast growth factor receptor 1-mediated PI3K-Akt signaling pathway, and conduct to the depletion of melanoma growth and angiogenesis (38). *P*-coumaric acid downregulates the mRNA transcriptional levels of the vascular endothelial growth factor and the basic fibroblast growth factor, and thereby supress tumour maturation and migration in rat model. Furthermore, *p*-coumaric acid inhibits both the AKT and ERK signaling pathways, which are known to be the main promote angiogenesis pathways (39). Protocatechuic acid has been reported to possess an apoptotic effect on human breast, lung, liver, cervix, and prostate cancers (40). Its apoptotic mechanisms include caspase-3 activation, lactate dehydrogenase leakage increasing, mitochondrial membrane potential reduction and Na+-K+-ATPase activity inhibition. Protocatechuic acid targets RhoB activation and down-regulates the Ras/Akt/NF-kB pathway, the MMP-2 production and thereby inhibits the cancer cells metastasis and migration in mice melanoma cells in *vivo* (41). Table 2 presents anti-cancer properties of honey along with its molecular mechanisms.

## Anticancer mechanisms of other active compounds of honey

Honey contains other anticancer molecules such as glyoxal and its derivate, methylglyoxal. Methylglyoxal is structured as a simple carbonyl compound of honey containing a reactive aldehyde and a ketonic group which can suppress the growth of cancer cells without affecting the integrity of the normal surrounded cells (48). Cancer cells need large amount of energy to multiply which must be provided by ATP. Methylglyoxal inactivates the enzyme Glyceraldehyde-3-phosphate Dehydrogenase (GA3PD) needed for the ATP production in cancer cells and thereby sets off to the cancer cells death (48). Glyoxal induces apoptosis in human embryonic lung epithelial cell line L 132 through the upregulation of pro-apoptotic proteins Bax and caspase-3, and the downregulation of antiapoptotic proteins Bcl-2 and galectin-3 (49). Furthermore glyoxal and methylglyoxal from *Leptospermum scoparium* honey can enhance the depolarization of the mitochondrial membrane and the activation of caspase-3 and -9 genes expression causing cancer cells apoptosis (50).

## Conclusion

This review demonstrated that honey bee's products can promote new strategies for the development of effective anti-cancer compounds. These compounds which interfere with multiple signaling pathways can be alternative candidates for combating cancer resistance to the conventional cancer therapy.

## Authors' contributions

AR reviewed the literature and prepared the first draft of manuscript; MC and MK reviewed the literature, helped in preparing first draft of manuscript, checked and corrected the grammar. All authors read and approved the final report.

## Conflict of interests

All authors declare that no conflict of interest exist.

## Ethical considerations

Ethical issues including text plagiarism, manipulation or appropriation, data fabrication, falsification, redundant publication as well as duplicate submissions have been carefully observed by authors. The Authors warrant that the article contains no libelous or unlawful statements, contains no instructions that may cause harm or injury and does not violate the copyright or trademark, or infringes on the rights or the privacy of others; and that all statements in the article asserted as facts are either true or are based upon reasonable research

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**Table 2.** Anti-cancer properties of honey and its molecular mechanisms

| Honey types | Anti-cancer compounds | Molecular target | Ref. |
|---|---|---|---|
| Conifer tree honey, thyme and citrus honey | Protocatechic acid, p-hydroxybenzoic acid, vanillic acid, caffeic acid and p-coumaric acid | Down-regulation of TNF- α-induced adhesion molecule expression in endothelial cells (HAEC) | (34) |
| *Melaleuca cajuputi* and *Acacia mangium* honey | Quercetin, naringenin, Kaempferol, rutin, hesperetin, apigenin, *P*-coumaric acid, ferulic acid, ellagic acid and penta-*O*-galloyl-β-D-glucose | Inhibition of VEGF expression in ovarian cell | (42) |
| *Cistus ladanifer* L. and *Cistus albidus* L. honey | Caffeic acid phenethyl ester | Prevent VEGF-induced angiogenesis in human umbilical vein endothelial cells | (33) |
| Gelam honey | Polyphenolic compounds | Down-regulation of Akt, mTOR, Raptor, Rictor, β-catenin, Gsk3β, Tcf4 and cyclin D1 gene expression and upregulation of cytochrome C and caspase 3 genes expression in colon cancer cells | (43) |
| Acacia honey | P-hydroxybenzoic, ferullic, t-cinnamic acid, abscisic acid, pinobanksin, apigenin, pinocembrin, chrysin and acacetin | Modulation of G0/ G1 phase of cell cycle, TNF-α, IL-1β, calcium ions secretion and down regulation of prostate specific antigen in NCI-H460 cell line | (44) |
| *Thymus vulgaris* and *Leptospermum scoparium* honey | Gallic acid and caffeic acid | Down-regulation of the expression of both MMP-2 and -9 in PC3 cells | (35) |
| Honey bee venom | Chrysin | Down-regulation of Bcl-2 and up-regulation of Caspase-3 and -9 genes expression in human ovarian cancer cells | (16) |
| *Apis mellifera* honey | Ellagic, gallic, ferulic, chlorogenic, caffeic acids and myricetin. | Enhancing TNF-alpha (tumor necrosis factor-alpha) release | (36) |
| *Koompassia excels* honey | Di-hydroxy benzoic acid, caffeic acid, ferulic acid and cinnamic acid | Activation of caspase-3/7 and -9 in human breast and cervical cancer cell lines | (37) |
| | | Set off the actuation of caspase-9 followed by caspase-3 protein expression in hepatocellular carcinoma | (45) |

**Table 2.** Continued

| Honey types | Anti-cancer compounds | Molecular target | Ref. |
|---|---|---|---|
| Various honey | Acacetin(5,7-dihydroxy-4'-methoxyflavone) | Suppression of NF-κB/Akt signaling in prostate cancer cells by inhibiting the phosphorylation of IκBα and NF-κB | (23) |
| | Caffeic acid phenethyl ester | Activation of extracellular signal-regulated kinase (ERKs) and p38 mitogen-activated protein kinase (p38 MAPK) in C6 glioma cells | (32) |
| | Pinobanksin, pinoccembrin | Activation of immune system and decreasing the level of PCR, T-regulatory cell (CD4, CD25) and Fox P3 gene expression | (22) |
| | Myricetin | Inactivation of oncoproteins such as protein kinase B (PKB) (Akt), Fyn, MEK1, and JAK1– STAT3 (Janus kinase–signal transducer and activator of transcription 3) | (21) |
| | Chrysin | Stimulation of TNF-alpha (tumor necrosis factor-alpha) release | (17) |
| | | Induction of p38 mitogen-activated protein kinase gene expression in C6 glioma cells | (18) |
| | | Increase levels of p-PERK, p-eIF2α and ATF4 in bladder cancer cells | (19) |
| | | Inhibition of phosphoglycoprotein-170 (P-gp), multidrug resistance-associated protein-2 (MRP-2), and breast cancer resistance protein (BCRP) in Caco-2 colon carcinoma cells | (20) |
| | Quercetin | Induction of cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells through p53 induction and NF-κB inhibition | (46) |
| | | Inhibition of mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK) 1 and Raf1 kinase activities and attenuation of TPA-induced phosphorylation of ERK/p90 ribosomal S6 kinase | (13) |
| | | Increase cancer cell apoptosis by down-regulation of the levels of heat shock protein (Hsp) 90 in prostate cancer cells | (14) |
| | Kaempferol | Decrease of the expression of Bcl-2 and alteration of the mitochondrial membrane potential with elevation of active caspase-3 expression in human glioblastoma cells | (27) |
| | | Sensitization of U251 and U87 glioma cells to tumor necrosis factor–related apoptosis-inducing ligand (TRAIL/Apo2L) | (47) |
| | Apigenin | Increase of the protein expression of WAF1/p21, KIP1/p27, INK4a/p16 and INK4c/p18, the down-modulation of the protein expression of cyclins D1, D2 and E and cyclin-dependent kinases (cdk), cdk2, cdk4, and cdk6 | (24) |
| | | Decrease of cyclin D1 and E expression, and inactivation of CDK1 | (25) |
| | | Inhibition of PI3K and Akt kinase activities, and HER2/neu autophosphorylation and transphosphorylation | (26) |

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