Phytochemicals from Honey: Novel Weapon for the Prevention and Treatment of Cancers

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Abstract

Honey is one of the naturally available food which is well renowned for its medicinal and therapeutic properties because of its various phytochemical constituents of phenolic and flavonoid origin. These phytochemicals have been shown to contribute to its various medicinal properties like antimicrobial, antiviral, anti-inflammatory, and antioxidant activities. Numerous polyphenols present in honey are demonstrated to possess antiproliferative activities against various cancer types. This chapter focuses on the most recent reports regarding the pivotal part played by various phytochemicals present in honey during various phases of carcinogenesis, both in vivo and in vitro. Numerous epidemiological and experimental studies have demonstrated that honey is highly effective as a potential therapeutic agent that can be used as an alternative medicine for various biodiverse ailments. Although there is a huge limitation of translating the active phytochemicals in honey as drugs and to carry them from bench to bedside to be used in clinical practice, still it is well demonstrated that they can be utilized to boost the immune system of patients receiving chemotherapy.

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Keywords

Honey · Honeybee · Anticancer · Phytochemicals · Chemotherapy · Alternative medicine

Abbreviations

CAR-T	Chimeric antigen receptor T cells
CASPASES	Cysteine aspartate specific proteases
CDKs	Cyclin dependent kinases
COX	Cyclooxygenases
DISC	Death inducing signaling complex
ECM	Extracellular matrix
ER	Estrogen receptors
GBD	Global burden of disease
IARC	International Agency for Research on Cancer
IFN	Interferon
IL	Interleukin
MAPKs	Mitogen activated protein kinases
MOMP	Mitochondrial outer membrane permeabilization
NAC	*N* acetyl L cysteine
NO	Nitric oxide
O_2^-	Superoxide
OH^-	Hydroxyl
PGE	Prostaglandin E
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PR	Progesterone receptors
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TNF	Tumor necrosis factor
TP53	Tumor protein 53
VEGF	Vascular endothelial growth factor

16.1 Introduction

The malady cancer has derived its name from the Greek word "*karkinos*" (Καρκινός), or "crab" initially used by Hippocrates, the father of medicine (Skuse 2015). However, cancer is best considered as an umbrella term, and it encompasses nearly 100 different types of disease entities with marked differences in genetic, transcriptional, histological, and clinical parameters (Kapinova et al. 2018). It is regarded as one of the most dreadful diseases of the twenty-first century leading the mortality rates at the second position next to cardiovascular diseases (de Oliveira

Júnior et al. 2018). The data pertaining to the worldwide statistics of 2018 reflects that 9.6 million people succumbed to cancer and also reported that new cases of cancer increased to 18.1 million (IARC Report 2018). According to Global Burden of Disease (GBD), by 2040, the number of new cancer cases detected would reach upto 27.5 million with 16.3 million cancer deaths. This projection on cancer burden is attributed to the increasing number of the geriatric population (Bray et al. 2018).

Cancers are defined by the National Cancer Institute as a multitude of diseases wherein abnormal cells proliferate and metastasize (spread to the nearby tissue) ("What Is Cancer?" Skuse 2015). It is a complex neoplastic disease manifested by risk factors of which some are nonmodifiable (genetic factors) and some modifiable factors such as environmental factors, e.g., smoking, physical inactivity, obesity, diabetes, and infections amongst others (Aggarwal et al. 2009). Carcinogenesis (cancer development processes) mechanisms are driven by numerous genetic and epigenetic factors working in concomitance with each other. Carcinogenesis mechanisms involve three sequential steps namely: initiation, promotion, and progression. Initiation as the name suggests is the first step of carcinogenesis, wherein mutated DNA are formed due to genetic damage that is irreversible. The second step—promotion, which results due to aberrant proliferation of mutated cells outside their normal niches causing tumor formation called tumorigenesis. The last step—progression involves invasion of the tumor cells into the extracellular matrix (ECM), nonneoplastic cells and surrounding tissue reinforcing cancer metastasis (Sever and Brugge 2015). Finally, progress toward malignant tumors by altering the cell physiology through changes in tempo-spatial arrangements (Yarla et al. 2016). These steps occur because the cell escapes homeostatic control mechanisms that normally regulate cellular growth, proliferation, adhesion, invasion, survival, apoptosis, and finally death.

The plethora of cancer treatment modalities include conventional cancer chemotherapy, radiotherapy, surgical treatment, CAR-T cell therapy, stem cell therapy, and molecular targeted therapy. (Shaked 2016). Unfortunately, these conventional treatment strategies, during the last few decades, have not provided any substantial improvement due to the financial cost, availability issues of cytotoxic agents, detrimental effects to the normal cell physiology, unprecedented systemic side effects, and the development of resistance against therapies (Kydd et al. 2017). Together with this, the increase in cancer incidence and mortality rates presents significant obstacles, which mandates a closer look toward the search of novel, more tolerable treatments in order to overcome this burgeoning healthcare problem (Zeligs et al. 2016). These challenges in the field of oncology arouse the inquisitive behavior of researchers who dabble with numerous natural compounds and dietary products that may have promising effects toward cancer treatment.

Substantial evidence gathered from the research of the past few decades for safer and more effective treatments diverted the focus toward the usage of numerous plant-based and dietary compounds that have demonstrated medicinal properties. These natural products serve as tremendous resources with the proven potential of promising drugs which can be utilized for preventing numerous diseases, including cancer (Rajamanickam and Agarwal 2008). However, the practical use of plants,

plant components, herbs, and spices has been in existence since ancient times. Hippocrates nearly 2500 years ago aptly quoted "*Let food be thy medicine and medicine be thy food*" (Mehta et al. 2010). Epidemiological data has shown strong evidence of the association between cancer and diet. More recently, phytochemicals have been regarded as the most promising chemopreventive treatment options for the management of tumorigenesis. "*Chemoprevention*", the term was first proposed by Sporn at the end of the 1970s (Amin et al. 2009), refers to the usage of natural, biological, or synthetic mediators to inhibit or reverse the primary phase of carcinogenesis, to prevent premalignant cells from invading other cells and to reverse the occurrence of carcinogenesis (Ranjan et al. 2019). As a consequence, a large number of health professionals are getting persuaded to use complementary and alternative medicine (CAM) for treating cancers (Yates et al. 2005). People indulging in CAM account up to 29–91% irrespective of several anticancer treatment modalities available. The reasons attributed to this shift are multifaceted, e.g., promote emotional well-being, improve immunity, usage of single CAM modality, and reduce adverse effects of conventional treatment.

16.2 Chemical and Structural Elucidation of Phytochemicals in Honey

Since time immemorial, honey was a part of diet, and well utilized due to its health promoting and healing properties across civilizations. Honey is gathered by honey bees (especially *Apis mellifera*) from flowers as nectar. *Apis mellifera* belongs to the family Apidae (Habib et al. 2014), which produces a variety of products out of nectar on which it feeds, like honey, royal jelly, pollen, and propolis that are stored in the beehive (Badolato et al. 2017). Its composition varies with variation in plant types. Natural honey is a sweet flavored syrup comprising nearly 200 distinct chemical constituents. Owing to its healing effects and unique taste, honey is extensively consumed and hence occupies an esteemed position in traditional medicine (Küçük et al. 2007). The main constituent of honey is sugar accounting for 79.6%, of which levulose is 38.19% and dextrose is 31.28%, and the rest is sucrose 1.3%, maltose 7.3%, and small amounts of fructo-oligosaccharides (Eteraf-Oskouei and Najafi 2013). Water accounts for nearly 17.2%. The other constituents of honey are proteins, vitamins (especially, niacin, riboflavin and pantothenic acid), several amino acids (mainly proline), enzymes (peroxidases, catalases, amylases, oxidases, etc.), and several minerals (like calcium, zinc, copper, potassium, and so on). Apart from these, honey also has several biologically active constituents like polyphenols which are of two main types: flavonoids and phenolic acids (Ajibola 2015). Honey's health benefits are primarily due to the presence of several phytochemical antioxidants, of which polyphenolic constituents like flavonoids, phenolic acids, and carotenoid derivatives are noteworthy (Alvarez-Suarez et al. 2013; Porcza et al. 2016). The composition of the numerous phytochemicals present in honey alongside its flavor, fragrance, and color varies markedly with the geographical regions, climate, types of flowers, and species of honey bee involved in its production.

Table 16.1 Chemical constituents of honey

Category	Compound
Flavonols	Quercetin, Kaempferol, Galangin, Fisetin, Myricetin
Flavanones	Pinocembrin, Naringin, Naringenin, Hesperidin Pinobanksin
Flavones	Apigenin, Acacetin, Chrysin, Luteolin Genkwanin, Wogonin, Tricetin
Phenolic acids	Caffeic acid, Chlorogenic acid, Cinnamic acid, *p*-Coumaric acid, Vanillic acid, Ferulic acid, *p*-Hydroxybenzoic acid, Gallic acid, Syringic acid, Rosmarinic acid and derivatives, 2-*Cis*, 4-*Trans* Abscisic acid, 2-Hydroxycinnamic acid, Ellagic acid, Protocatechuic acid, Sinapic acid

Additionally, physical conditions like weather, processing methods, handling and manipulation, packaging, and storage time also affect the composition of honey to a great extent. Also, depending upon the source/origin different types of honey exist, which are expected to have different biological activities (Missio et al. 2016). Table 16.1 depicts the classification of polyphenolic constituents of honey. The molecular structures of the polyphenolic constituents—flavonoids and phenolic acids that can be obtained from honey—are portrayed in Fig. 16.1.

16.3 Therapeutic Properties of Honey

It is apparent from the review of the literature that honey is a best sweetener, with enormous health benefits, and hence being used all over the world from the early epochs till date. Various constituents of honey have been reported to possess a wide array of therapeutic properties, of which the main include antibacterial, anti-inflammatory (Tsang et al. 2015), antioxidant (Beretta et al. 2005), antimicrobial, antiulcer (Almasaudi et al. 2016) antimutagenic, and antitumor activities (Bogdanov et al. 2008). It is also used for treatment of cough and rhinosinusitis (Lee et al. 2017), urinary diseases (Bouacha 2018), gastrointestinal diseases, eczema, psoriasis and dandruff (Samarghandian et al. 2017). Honey is also used to treat cataracts, burns and for wound healing (Al-waili 2003). Research data suggests that natural honey can be used to decrease the plasma levels of glucose, lipids and homocysteine along with c-reactive protein in healthy, diabetic and hyperlipidemic subjects (Al-waili 2004). The phenolic contents of honey also exhibit antileukemic effects in the cell lines of acute and chronic leukemia origin (Nik Man et al. 2015). Figure 16.2 summarizes various medicinal and therapeutic effects mediated by honey.

16.4 Honey: A Potential Cancer Chemopreventive Agent

Phytochemical and pharmacological evidence revealed the plethora of health benefits that are associated with honey and supported the ethnopharmacological use of honey in complementary medicine to cure numerous diseases, including cancer. There is a tremendous increase in research interest in honey's chemopreventive effects and its associated possible mechanisms. Evidently, the

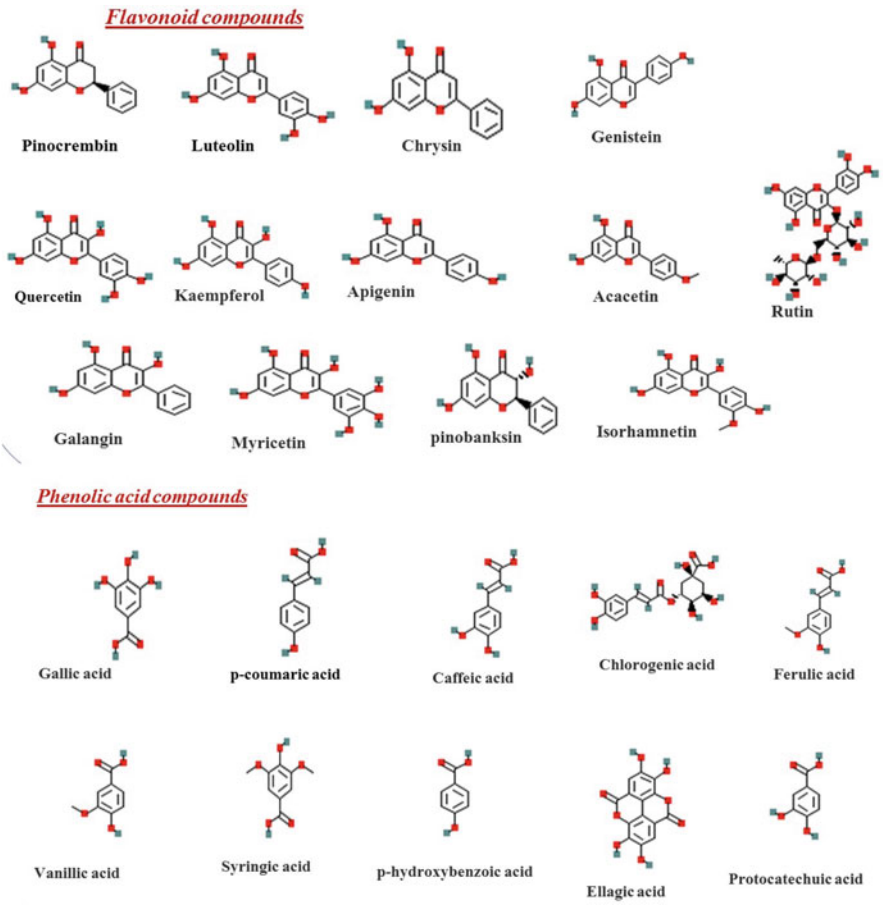

Fig. 16.1 Chemical constituents of honey and their molecular structures

chemopreventive effects of honey are mostly attributed to its polyphenol constituents (like phenolic acids and flavonoids) (Fresco et al. 2006). Chemoprevention could be achieved by blocking one of the three phases of carcinogenesis pathways, i.e., initiation, promotion, and progression (Abubakar et al. 2012). Anticancer, antiproliferative and antimetastatic effects of honey could be achieved through any one of the following probable mechanisms:

- Preventing the formation or activation of a mutagen
- Inhibiting uncontrolled cellular growth
- Arresting the cell cycle
- Inhibiting cellular proliferation
- Activation of mitochondrial apoptotic pathways
- Permeabilization of the outer mitochondrial membrane

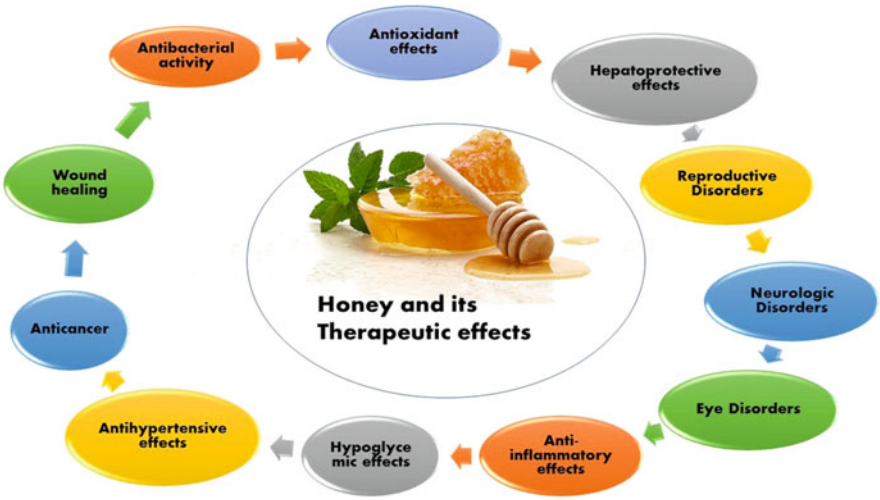

Fig. 16.2 Honey and its various therapeutic effects

- Inducing apoptosis and differentiation
- Oxidative stress modulation and quenching
- Curbing inflammation
- Modulating insulin signaling
- Inhibiting angiogenesis

16.4.1 Effects of Honey on Cell Cycle Arrest and Antiproliferative Activity

Cell cycle is regarded as one of the highly regulated and coordinated processes which ensures cellular growth and division by controlling proper duplication of the genetic material (DNA replication). Several regulatory, molecular and biochemical signaling cascades of the cell cycle prompt cellular division. Cell cycle comprises five sequential phases—G_o (gap_o—the quiscent phase), G_1 (gap_1), S (DNA synthesis), G_2 (gap_2) and M (the mitotic phase) (Alimbetov et al. 2018). This entire process is under the direction of a cascade of protein kinases and several checkpoints. The checkpoints are significant regulatory nodes of the cell cycle (Chao et al. 2017). In cellular cycle, two pivotal checkpoints exist: one at the G_1/S phase and the other at the G_2/M phase (Dominguez-brauer et al. 2015). Generally, it has been observed that cancer cells have defective checkpoint mechanisms, which leads to uninhibited cell proliferation. Numerous studies using different honey types and cell lines were performed, which document the anticancer effect of honey by induction of cell arrest. In one of such studies, Fauzi et al. (Fauzi and Yaacob 2016) proved that honey causes growth arrest of breast cancer cells MCF-7 (ER α-positive) and MDA-MB-231 (ERα-negative) at the G_2/M and S phase of the cell cycle,

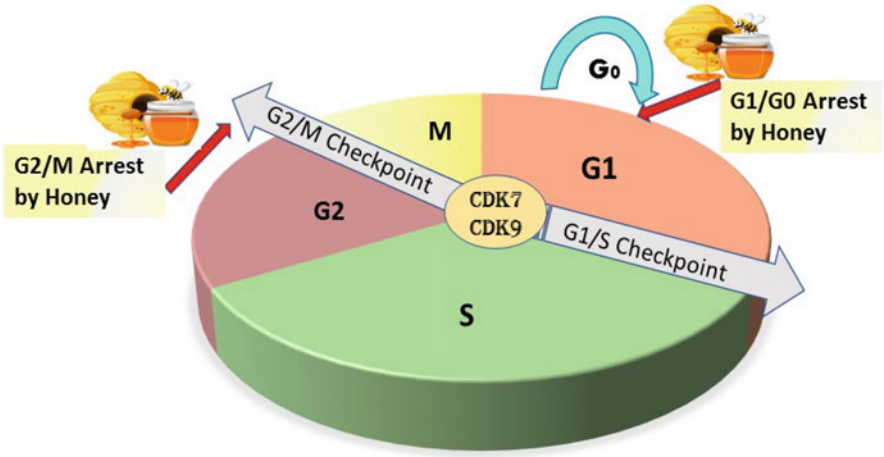

Fig. 16.3 Varied effects of honey on the cell cycle

respectively. This arresting of growth might result from the induction of DNA damage by honey. Figure 16.3 provides a pictorial description of the effects of honey on the cell cycle.

Aliyu et al. 2012 reported that the anticancer activity of honey on the PC-3 cell line is attributed to the modulation of the G_o/G_1 phase of cell cycle, expression of IL-1β and TNF-α, secretion of calcium ions, and in vitro desensitization of prostate-specific antigens. In a similar study, Afrin et al. 2018 reported that in HCT-116 cells and in LoVo cells there was induction of cell cycle arrest in the S phase and in the G_2/M phase through the modulation of cell cycle regulator genes (CDK2, CDK4, cyclin D1, cyclin and Ep21, p27 and Rb) respectively. Experimental data shows that several phenolic compounds and flavonoids (chrysin, quercetin, and kaempferol) in honey are able to cause cell cycle arrest at the G_o/G_1, G_1 and G_2/M phases as seen in human colon, glioma, cervical, esophageal, renal, hepatoma melanoma and adeno-carcinoma cell lines (Priyadarsini et al. 2010; Pinheiro et al. 2019; Pratheeshkumar et al. 2016; Zhang et al. 2008). Figure 16.4 summarizes the effects of honey as an antiproliferative, antioxidant and anticancer agent.

The hallmarks of cancer cells are high proliferative activity and aberrant genotype in comparison with the normal cells. The absence or dysfunction of one or more regulatory proteins of the cell cycle, like cyclin dependent kinase (CDK) forming complexes with cyclins, permanently turns on "molecular switch," leading to carcinogenesis or tumor development (Diehl 2002). The nuclear protein Ki67 is absent in the quiescent G_o phase of the cell cycle but its expression during other phases (G_1, G_2, S, and M) is strongly associated with cellular growth and proliferation (Li et al. 2015). Research done by Tomasin and Gomes-Marcondes (2011) proved that aloe vera on co-administration with honey causes modulation of tumor growth by decreasing the overexpressed Ki67nuclear protein in turn leading to reduction in the tumor weight and cellular proliferation (Tomasin and Gomes-Marcondes 2011).

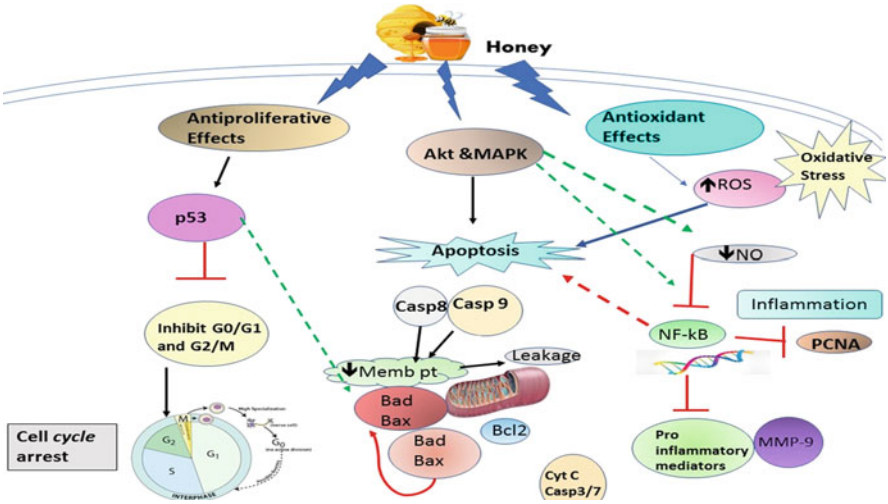

Fig. 16.4 Molecular mechanisms/targets mediating the antiproliferative, antioxidant, and anticancer effects of honey

Honey was reported to exhibit antiproliferative effects on murine (B16-F1) and human (A375) melanoma cell lines in a time- and dose-dependent manner which was proved by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay and the trypan blue test. This effect was supposed to be due to the presence of a chemical constituent in honey called chrysin (Pichichero et al. 2010). Analysis of the cell cycle demonstrated that arrest in the sub-G_1 phase of the cell cycle is responsible for the apoptotic action of honey and its constituents (Jaganathan 2009).

16.4.2 Effects of Honey on Apoptosis

The two most prominent features of cancer are uncontrolled cellular proliferation and decreased apoptosis. Accordingly, apoptosis is defined as the programmed cell death—a process that efficiently eliminates dysfunctional cells and regulates cell growth. Evading/escaping apoptosis is recognized as the hallmark for the development of cancer, and inhibition of apoptotic processes can lead to decreased treatment sensitivity/increased drug resistance (Hanahan and Weinberg 2011). Hence, apoptosis is regarded as a double-edged sword. Apoptosis is hallmarkedly represented by numerous morphological and biochemical changes within the cell, which include cell shrinkage, blebbing of membranes, condensation of the genetic material and collapse of the nucleus, and finally fragmentation of the cell (Lowe and Lin 2000).

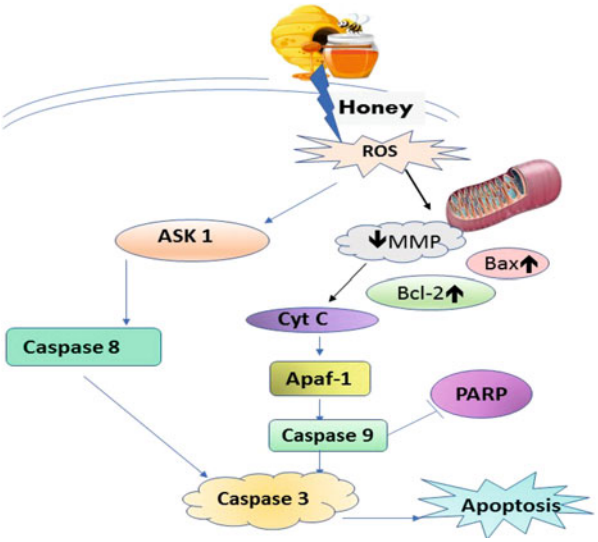

Fig. 16.5 The effect of honey on the apoptotic pathway and the antioxidant pathway. The effect of honey on the apoptotic pathway. Honey exerts apoptotic effect through up-regulation and modulation of proapoptotic proteins (p53, Bax, caspase 3, and caspase 9) and down-regulation of antiapoptotic proteins (Bcl-2). *Bcl-2* B cell lymphoma 2 protein, *Cyt. C* cytochrome C, *Apaf-1* apoptotic protease activating factor 1, *TNF* tumor necrosis factor, *TRAIL* TNF related apoptosis-inducing ligand, and *TRADD* TNFR associated death domain protein

Anticancer agents usually induce apoptosis. Three cardinal features of apoptosis include hydrolysis of the protein constituents of the cell, fragmentation of the nuclear DNA, and recognition of the dying cellular remains by phagocytic cells. Of which, protein cleavage occurs primarily due to activation specific enzymes called caspases. Caspases (cysteine aspartate-specific proteases) belong to the cysteine protease family, which plays a prominent role during apoptosis; more specifically in the phases of initiation and execution. Activation of the inactively synthesized caspases is through specific initiation mechanisms powered by three pathways (Power et al. 2002). Apoptosis proceeds either through the receptor-mediated pathway extrinsic pathway (caspase 8 or death receptor) or through the intrinsic pathway (caspase 9 or mitochondrial) centered on mitochondrial outer membrane permeabilization (Ghobrial et al. 2005). Finally, both the pathways converge to a central mechanism referred to as the endoplasmic reticulum pathway which serves as the executioner of the apoptosis process (O'Brien and Kirby 2008). Figure 16.5 summarizes the effects of honey on apoptotic and antioxidant pathways.

Apoptosis may be triggered by signals from the inside the cell or by death activators present attached to surface receptors, like TNF-alpha, lymphotoxin, and Fas Ligand (FasL) constituting death inducing signaling complex (DISC) which serves to initiate the activity of caspases, leading to the "extrinsic" pathway for apoptosis. Other mechanisms of induction are the intrinsic pathways, which are dependent upon mitochondrial outer membrane permeabilization (MOMP) and

concomitant release of intermembrane space proteins called cytochrome-c (cyt-c) into the cytosol. This released cyt-c then assembles a multiprotein caspase activating complex called "apoptosome" that promotes caspase-independent (nonapoptotic) cell death (Hassan et al. 2014). Tumor cells might suppress apoptosis through distinct molecular mechanisms. Tumor cells exhibit resistance to apoptosis due to imbalance in the antiapoptotic and proapoptotic proteins such as Bcl-2 and BAX, respectively. The presence of both Bcl-2 and BAX during apoptosis is controlled by p53 (Wong 2011). The p53 protein (or TP53) also referred to as the "guardian of genome" within the cell is the first tumor suppressor gene involved in induction of apoptosis and cell cycle regulation. The occurrence of many different kinds of human cancers is linked to downregulation or inactivation of p53.

Several investigations were carried out to prove the effect of honey on apoptosis and its use as an anticancer agent. The anticancer effects of honey are attributed to its effective ability of inducing apoptosis via increased expression of numerous pro-apoptotic proteins such as Bax, caspase 3, caspase 9, BAX, and p53 coupled with the decreased expression of Bcl-2 (antiapoptotic) protein in addition to the prevention of the proliferation of cancerous cells. In human renal adenocarcinoma cell lines (ACHN), where apoptosis serves as the pivotal mechanism for the induced cell death, honey has been demonstrated to increase its effectiveness several fold (Samarghandian et al. 2011). Research has demonstrated that honey induces apoptosis by many mechanisms like induction of DNA damage, increased expression of p53, and finally activation of numerous caspases, which brings about the death of HepG2 cell lines (Cheng et al. 2019). Swellam et al. showed that honey could be used to induce apoptosis in three (T24, 253 J and RT4) human bladder cancer cell lines and one (MBT-2) murine bladder cancer cell line. They showed that 1–25% honey significantly decreased the proliferation of T24 and MBT-2 cell lines and 6–25% honey decreased the proliferation of RT4 and 253 J cell lines. Further, in vivo studies showed that intralesional injection with 6% and 12% honey, as well as oral ingestion of honey significantly suppressed tumor growth (Swellam et al. 2003). Research shows that honey exhibits apoptosis via the death receptor pathway (Fauzi and Yaacob 2016). Furthermore, overexpression of p53, activation of intrinsic (caspase-9) and extrinsic (caspase-8) pathways along with caspase 3 and cleaved-PARP treated two genetically well recognized human colon adenocarcinoma cell lines, HCT-116 and LoVo, which confirms the apoptotic action of honey (Afrin et al. 2018).

Honey is known to induce apoptosis in different cancer cell lines and types through induction of MOMP causing reduction in mitochondrial membrane potential. Cancers caused due to defective DNA damage repair can be treated by the flavonoids in honey which is effective in inhibiting the activity of PARP. Honey has the potential to cause the upregulation of Bax, downregulation of Bcl-2, activation of caspases 3 and 9 and induction of p53, thereby inhibiting cancer (Pasupuleti et al. 2017). Honey exhibited significant anticancer activity against human breast and cervical cancer cell lines. This was possible through a decrease in mitochondrial membrane potential ($\Delta\Psi m$), activation of caspase-3/7 and -9 in all honey treated cancer cells lines signifying the involvement of mitochondrial apoptotic pathway

(Fauzi et al. 2011). Honey helped in modulating the anticancer activities of tamoxifen via depolarization of the mitochondrial membrane and induction of caspase-dependent apoptosis in ERα-dependent MCF-7 and ERα-independent MDA-MB-231 breast cancer cell lines (Yaacob et al. 2013). Quercetin a constituent of cancer may induce caspase-dependent apoptosis in HepG2 cell lines by direct activation of the mitochondrial pathway and inhibition of survival signaling. Apoptotic activity of honey can be attributed to flavonoids such as Quercetin causing MOMP (Chien et al. 2009).

16.4.3 Effects of Honey on Inflammation

Chronic inflammation has proven harmful and is found to be associated with a wide variety of cancers (Wang and Karin 2015). Chronic inflammation is linked to several endogenous mediators like chemokines, pro-inflammatory cytokines, inflammatory enzymes, and adhesion molecules (Aggarwal et al. 2006). Cancer-related inflammation is generally of two types: tumor-extrinsic inflammation and cancer-intrinsic or cancer-elicited inflammation. Several factors that can trigger tumor-extrinsic inflammation are autoimmune diseases, smoking and obesity; bacterial and viral infections (e.g., bladder cancer by schistosomes) (Zaghloul 2012); oral infections by human papilloma virus (HPV) (Shaw and Robinson 2011); and tobacco, alcohol, and asbestos exposure, which are responsible for stimulating malignant progression and thereby increasing the cancer risk. Similarly, cancer-initiating mutations by the recruitment and activation of inflammatory cells lead to malignant progression and thus cancer-elicited inflammation (Allavena et al. 2008). These two interrelated inflammatory processes can result in immunosuppression. The expansion of inflammatory-induced cancers is restricted within the locale of the neoplastic cells or tissues. Chronic inflammations due to inflammatory bowel diseases (IBDs) and ulcerative colitis are significant contributors to the risk of induction, development and advancement of colorectal cancer (CRC) (Aggarwal et al. 2009). In various types of cancers, numerous key inflammatory molecules have been identified that have been shown to induce and sustain tumorigenesis, at the intersection of the intrinsic and extrinsic pathways. Chronic inflammation and cascades of tumorigenesis have been demonstrated to be elicited by a series of cross-talk amid multiple signaling pathways that include the nuclear factor kappa-B (NF-κB) pathway, the stress-responsive mitogen-activated protein kinase (MAPK), and STAT3 signaling pathways (Aggarwal et al. 2009).

Key chemical or inflammatory mediators/pathways that promote proliferation and malignant cell survival and angiogenesis and metastasis include cytokines such as NFκB, tumor necrosis factor (TNF-α), and interleukins (IL-1, IL-6, IL-11, IL-17, IL-21, IL-22, and IL-23). Also several other mediators such as chemokines CCL2 and CXCL8, matrix metalloproteinase 9 (MMP9), cyclo-oxygenase 2 (COX-2), interferon (INF-γ), inducible nitric oxide synthase (iNOS), vascular endothelial growth factor (VEGF), and PGE 2 are identified. Furthermore, cancer development can be ablated by TGFβ and IL-10 (Del Prete et al. 2011; Nikolaou et al.

2013). Inflammatory cells involved in the progression of carcinogenesis secrete TNF, which because of its pro or antitumorigenic effects acts as a double-edged sword (Aggarwal 2003). In human gastrointestinal cancers, IL-11 is the dominant inducing factor, which exhibits a significant association with STAT3 activation in comparison to IL-6 in promoting tumorigenesis (Singh et al. 2019; Coussens and Werb 2002).

The recent in vivo studies conducted showed that honey has anti-inflammatory properties. Honey is helpful in reducing the promotion as well as the progression of cancers by decreasing MAPK and NF-κB expression in neoplastic cell lines. The induction of apoptosis in cancer cells and consequent halting of the release of various inflammatory molecules like COX-2, iNOS, IL-1β, IL-6, and TNF-α have been shown to be because of flavonoids in honey. In HT-29 cells, treatment with different varieties of honey down-regulated the expression of NF-κB and up-regulated that of IκBα, and the action was comparable to common anti-inflammatory drugs (Tahir et al. 2015; Wen et al. 2012). Several research studies proved that Manuka, Pature, Nigerian Jungle, and Royal Jelly honey varieties increased IL-1β, IL-6, and TNF-α expression (Ahmed and Othman 2013; Tonks et al. 2001). Gelam honey also exhibits anti-inflammatory effects by significantly decreasing the production of pro-inflammatory cytokines such as NO, PGE2, TNF-α, and IL-6 in the plasma, which tallies with the reduction in the expression of the corresponding genes and proteins in carrageenan-induced acute paw edema in rat. The possible mechanism for this anti-inflammatory effect might be the inhibition of COX-2 and iNOS mediators of inflammation (Hussein et al. 2012). These anti-inflammatory mechanisms of honey make it a promiscuous therapeutic agent that can be used to modulate disease.

16.4.4 Effects of Honey on Modulation of Oxidative Stress

Oxidative stress is referred to as the "*imbalance between oxidants and antioxidants.*" It is due to excessive production of oxidants or free radicals like superoxide anions (O_2•) and hydroxyl (•OH), peroxyl (ROO•), and alkoxyl radicals (RO•) and failure to remove oxidants by protective mechanisms called antioxidants, which ultimately leads to potential damage to the cell. The agents that quench reactive oxygen species (ROS) and reactive nitrogen species (RNS) are called antioxidants (Orrenius et al. 2007). Balance between oxidation and reduction states is pivotal for normal cell growth and proliferation. The relationship between ROS and tumor progression or carcinogenesis is well documented in the literature. ROS may lead to carcinogenesis due to persistent DNA damage and mutations in p53 (Saeidnia and Abdollahi 2013). Various types of cancers might occur due to exhaustive cell proliferation because of the decreased levels of ROS, in contrast higher levels of ROS would result in oxidative damage. The participation of ROS and hence their production especially of hydrogen peroxide (H_2O_2) in promoting tumor initiation and progression is supported by both in vivo and in vitro studies (Lee and Lee 2006). The "hypocritical" character of ROS is substantiated by evidence that ROS not only induces and maintains the oncogenic phenotype of cancer cells, but can also induce apoptosis and

cellular senescence, hence acts as antitumorigenic species (Valko et al. 2006). Honey is a potent antioxidant associated with good radical scavenging properties (Ahmed et al. 2018). Among the various constituents of honey, vitamin C and E, phenolic compounds, flavonoids, peroxides, catalase, glucose oxidase enzymes and carotenoids have been found to possess a high level of antioxidant activity (Lewoyehu and Amare 2019). Although the precise mechanism by which honey exerts its antioxidant activity is unclear, many proposed ones include flavonoid substrate action for hydroxyl free radical sequestration, chelation of metallic ion, donation of hydrogen, and superoxide radical action. Manuka honey was reported to be cytotoxic to MCF-7 breast cancer cells in vitro correlating that the effects are due to the presence of the total phenol content and antioxidant power (Portokalakis et al. 2016). Antitumor activity of Jungle honey fragments was proved to be due to chemotactic induction for neutrophils and reactive oxygen species (ROS) (Fukuda et al. 2011).

Modulation of oxidative stress is one of the main reasons for the anticancer effect of honey. It has been reported that treatment of colon tumor cells (HCT-15 and HT-29) with honey leads to the depletion of nonprotein thiol, thereby decreasing their free radical scavenging capacities. Furthermore, honey also leads to the increased production of ROS which gives it an effective antiproliferative activity. In addition, treatment with honey leads to cell death because of the fragmentation of DNA. The activity is inhibited by treating the cells with antioxidant, *N*-acetyl-L-cysteine (NAC) (Jaganathan and Mandal 2010).

16.4.5 Effects of Honey on the Insulin Signaling Pathway

The binding of insulin to the insulin receptor on the cellular surface is responsible for its diverse actions. The insulin mediated signaling pathway is responsible for the mitogenic, pro-migratory and the metabolic effects of insulin (Vella et al. 2018). Deregulation of the insulin signaling pathway directly leads to insulin resistance, which further causes hyperinsulinemia. Hyperinsulinemia and other obesity-related factors have been strongly linked to both clinically and epidemiologically as the major risk factors responsible for the initiation and progression of a variety of malignancies (Poloz and Stambolic 2015). Studies also implicated that cancer development and progression may be due to an aberrant insulin level and insulin-mediated signaling pathways, including cancers of breast, colon, esophagus, endometrium, kidney, liver, and pancreas (Ray et al. 2014). Recent investigations revealed the concept that the insulin receptor is involved in carcinogenesis. The PI3K/Akt signaling pathway is another key component of insulin signaling responsible for the metabolic actions of insulin along with insulin receptor-mediated cell proliferation and survival. However, insulin exhibits mitogenic effects through the activation of the MAPKs cascade. Moreover the two cascades—PI3K/Akt and MAPKs—are interrelated and do converge to the common mTOR/p70S6K pathway, which is responsible mainly for regulating cell growth, survival, and metabolism (Cheng et al. 2010). Another important component responsible for various effects in

IR signaling is c-Abl tyrosine kinase. Insulin has been demonstrated to stimulate c-Abl phosphorylation and FAK dephosphorylation in normal cells. However, in tumor cells with dysfunctional c-Abl, insulin induces FAK phosphorylation and cell proliferation, survival, and migration (Belfiore and Malaguarnera 2011). Lori et al., proved that the treatment of HepG2 cells with honey extracts increases the expression of insulin receptors, and stimulates glucose uptake (Lori et al. 2019). Pretreatment of subjects with quercetin and Gelam honey extract improved insulin resistance and insulin action by increasing the expression of Akt, while reducing the expression of IRS-1 serine phosphorylation (ser307), MAPK, and NF-κB. The anticancer properties of honey are due to its modulatory action on the insulin signaling cascade (Batumalaie et al. 2013).

16.4.6 Effects of Honey on Angiogenesis

Angiogenesis is one of the complex physiological processes involving the interdependent interactions of numerous kinds of cells and their mediators, which in turn results in the development of new blood vessels from preexisting vessels (Oskouei et al. 2014). In the repair processes, apoptosis occupies an important aspect especially during the restoration of blood vessels. For proper functioning and viable growth of the reparative cells, the restoration process plays an essential role in providing ample oxygen and nutrients to the damaged tissue. Additionally, cancer development and progression to advanced stages, angiogenesis, has been found to play an essential part in driving the processes (Toshiro et al. 2014). In numerous morbid diseases, neovascularization has been shown to be the sentinel characteristic of the affected tissue. (Al-Husein et al. 2012). Neovascularization is one of the highly regulated processes which involves a number of complex phases like sprouting, splitting, and remodeling, resulting in a change of the existing blood vessels to meet the demands of the disease burden, and hence when angiogenesis becomes unregulated and uncontrolled, it almost always is shown to promote tumorigenesis. In contrast, inadequate angiogenesis is reported to be involved in coronary artery disease pathogenesis (Polverini 2002).

The process of tumorigenesis involves disturbance in the balance between pro-angiogenic and antiangiogenic factors, for the conversion and development of normal cells to the tumor masses and then further advance them to metastasis. Thus a loss of tight control of the angiogenesis called as “angiogenic switching” is pivotal for the carcinogenesis process to be established and then further driven to metastatic end by secondary growth factors and cytokines (Naik et al. 2015). Several proangiogenic molecules such as fibroblast growth factors (FGFs), vascular endothelial cell growth factors (VEGFs), and angiopoietins and their counterparts, i.e., inhibitors of angiogenesis such as endostatin, platelet factor-4, vasostatin, and angiostatin exist to drive the process (Pandya et al. 2006). Angiogenesis process in tumor development has been demonstrated to be highly effective target for preventing and treating cancers effectively. Basic mechanism for the antiangiogenic effects of honey is unclear; however it can be credited to the existence of various

phytochemicals and Vitamin E in natural honey, both of which contribute to decrease VEGF concentration. Eteraf-Oskouei T et al. have reported a potent antiangiogenic effect of honey in his in vivo models, when they were treated with honey for chronic inflammation. Furthermore, honey has been demonstrated to inhibit COX and VEGF in pouch fluid leading cessation of production of PGE 2. This effect is in turn reflected in the reduction of angiogenesis (Oskouei et al. 2014).

16.5 Conclusion

Honey, a natural food supplement, has several phytochemicals with medicinal and health benefits. Several epidemiological and experimental studies have proven the efficacy of honey as a potential therapeutic agent that can be used as an alternative medicine for various biodiverse ailments. Investigational data from several studies consolidated that honey can be effectively used as an antibacterial, antifungal, antiviral, anti-inflammatory and antidiabetic alternative drug. It also exhibits strong wound healing and immunomodulatory action, retains estrogenic regulatory action, and anticancer, antimutagenic, and abundant other vital effects. Evidence-based research suggests that honey exhibits all the abovementioned potential therapeutic effects via modulation of numerous signal transduction pathways and multiple molecular targets.

With the development of varied resistances to drugs coupled with the numerous side effects of conventional therapies, researchers have shifted their focus to chemopreventive agents. Honey in this regard is considered to be a good anticancer and chemopreventive agent. Though there is lack of exploratory data revealing the full mechanism of honey as an anticancer agent, the existing data suggests that it exerts antiproliferative, anticancer, antitumor, and antimutagenic effects all of which are facilitated by various mechanisms, some of which include activation of the mitochondrial pathway; cell cycle arrest; permeabilization of the mitochondrial outer membrane; caspase activation in apoptosis; inflection of oxidative stress; enhancement of inflammation; intonation of insulin signaling; angiogenesis inhibition in cancer cells; stimulation of IL-1β, TNF-α, IFN-γ, IFNGR1 and p53; inhibition of IL-1, IL-10, COX-2, and LOXs in inflammation; and modulation of numerous other miscellaneous targets. However, there are many more open apertures regarding the therapeutic benefits and the associated mechanisms of honey that need to be explored in depth. Further clinical and experimental research is warranted to corroborate the pharmaceutical benefits of using honey either alone or as an adjuvant treatment. Moreover, there is an urgent need to disseminate the acquired knowledge about honey to the medical community to facilitate its use as a chemopreventive agent.

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