Clinical Nutrition 38 (2019) 2499–2503

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Honey and cancer: A mechanistic review

Marwa Waheed [a], Muhammad Bilal Hussain [a], Ahsan Javed [a], Zarina Mushtaq [a], Sadia Hassan [a], Mohammad Ali Shariati [b], Muhammad Usman Khan [c, d], Majid Majeed [a], Manisha Nigam [e], Abhay Prakash Mishra [f, **], Mojtaba Heydari [g, *]

[a] Institute of Home and Food Sciences, Government College University, Faisalabad, Pakistan
[b] Laboratory of Biocontrol and Antimicrobial Resistance, Orel State University Named After I.S. Turgenev, 302026, Orel, Russia
[c] Bioproducts Sciences and Engineering Laboratory (BSEL), Washington State University, Richland, 99354, WA, USA
[d] Department of Energy Systems Engineering, Faculty of Agricultural Engineering and Technology, University of Agriculture, 38000, Faisalabad, Pakistan
[e] Department of Biochemistry, H. N. B. Garhwal (A Central) University, Srinagar Garhwal, Uttarakhand, India
[f] Department of Pharmaceutical Chemistry, H. N. B. Garhwal (A Central) University, Srinagar Garhwal, Uttarakhand, India
[g] Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article history:
Received 30 July 2018
Accepted 13 December 2018

Keywords:
Honey
Cancer
Mechanism
Flavonoids
Phenolic acid
Natural

SUMMARY

Background: Globally, cancer ranks among the most common causes of death. Multiple experimental and clinical studies have investigated anticancer effects of honey with promising results. This study focused on potential background mechanisms of this effect.
Methods: The current literature was reviewed for potential anticancer pathways which are suggested for honey and its ingredients.
Results: Flavonoids (kaempferol, catechin, and quercetin) and phenolic acids (caffeic acid and gallic acid) are the most important ingredients of honey with known anti-cancer activity. The main suggested mechanisms for anti-cancer activity of honey and its ingredients are antioxidant, apoptotic, tumor necrosis factor inhibiting, antiproliferative, immunomodulatory, anti-inflammatory and estrogenic effects.
Conclusion: This review collates the current scientific understanding on the mechanism of anti-cancer activity of honey.

1. Introduction

Today, cancer represents a substantial health burden and frequent cause of death [1]. It causes roughly 8.2 million annual cancer associated expiries in the statistical data [2,3]. WHO (World Health Organization) estimates that there will be more than 15 million new cases of cancer by 2020 which exemplify that cancer is the major issue of the globe rather than Western nations.

This ubiquitous condition remained a challenge despite the significant research on its prevention and treatment. During the last few decades, conventional approaches have reported severe side effects of cancer treatment. Accordingly, scientists were attracted towards less toxic therapies and novel methods.

Nowadays, there is an increased interest toward complementary and alternative medicine use for a variety of diseases, from acute to chronic and deadly diseases [4–6]. Moreover, there has been increased interest in the search for chemopreventive and chemotherapeutic agents derived from food or natural products [7]. The relative safety of food-derived compounds [8] makes them an attractive and alternative treatment as compared to conventional cancer therapies. Honey is among the most popular natural products which are investigated for anticancer effects.

Natural honey has been consumed as medicine and food since ancient times. Indeed, review of literature revealed raw honey as the best sweetener used in early epochs and it was eminent to be used all over the world about several million years ago [9]. Natural honey has been extensively consumed owing to its healing effects and contains almost 200 constituents. Raw honey has fructo-oligosaccharides, fructose and glucose; on the other hand, it contains vitamins, minerals, enzymes and many amino acids [10]. It was reported to have antitumor [11,12], antioxidant [13], antimutagenic [14], antimicrobial [15], and wound healing properties

* Corresponding author.
** Corresponding author.
E-mail addresses: abhaypharmachemhnbgu@gmail.com (A.P. Mishra), mheydari@sums.ac.ir (M. Heydari).

https://doi.org/10.1016/j.clnu.2018.12.019

[16]. Honey has been affirmed to function as a defense mechanism because of the phenolic contents [17].

Anticancer activity of honey had been tested against diverse groups of tissues and cancer cell lines, e.g. colorectal [18], breasts, endometrial, prostate, renal [19,20], oral [21], and cervical cancer [22]. Raw honey stimulates the action of chemotherapeutic treatments such as cyclophosphamide and 5-fluorouracil. Honey comprises polyphenols that are crucial factors which account for their antioxidant and anticancer activity which have been reportedly measured by various techniques like DPPH (Diphenyl-1-picrylhydrazyl), FRAP (Ferric Reducing Antioxidant Power), ORAC (The Oxygen Radical Absorbance Capacity), ABTS [2, 2-azinobis (3ehtylbenzothiazoline-6-sulfonic acid) diammonium salt], TEAC [6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid (Trolox)-equivalent antioxidant capacity] [23]. Similarly, in recent years various enzyme-based assays, like Superoxide Dismutase and Catalase along with ascorbic acid content, have also been used for measuring the anti-oxidative content of honey. So far, research findings about anticancer responses of honey range from animal models and tissue cultures to medical practices. This review aimed to gather the information on suggested mechanisms for anticancer effects of honey in the literature.

2. Methods

Electronic databases and search engines, including Medline, PubMed, Scopus, Web of Science - Clarivate Analytics, ScienceDirect and Google Scholar were searched for cellular, animal or human studies which assessed the anticancer effects of honey. Relevant publications were collected and searched for the presented information on anticancer mechanism of honey. Then, the gathered data were classified into six subgroups including cell cycle arrest; activation of the mitochondrial pathway and outer membrane permeabilization; apoptosis induction; modulation of oxidative stress; anti-inflammatory and immunomodulatory effect; modulation of insulin signaling; and estrogenic activity, for presentation.

3. Results

3.1. Chemical constituents of honey

Carbohydrates are the chief component of honey which comprise two major sugars known as dextrose and laevulose along with 22 other sugars in minute form [24]. Natural honey consists of 75% monosaccharide sugars that are glucose and fructose, whereas 10–15% disaccharide sugars include sucrose and maltose. The remaining percentage consists of enzymes, water, minerals, vitamins, pigments, phenolic and volatile compounds [25]. Numerous different amino acids as well as minerals such as copper, magnesium, phosphorus, potassium and calcium are also the integral moieties of honey [26]. Honey is also rich in phenolic and Flavonoid constituents with potent documented anticancer effects. Flavonoids such as chrysin, kaempferolcatechin, galangin, myricetin, quercetin and some phenolic acids like caffeic acid, syringic acid, chlorogenic acid, gallic acid and ferulic acid are documented against inflammation and oxidation stress [27], as important pathways in carcinogenesis. The chemical structures of important flavonoids are shown in Fig. 1. Generally, moieties of honey confer its properties against cancer and inflammation due to variations in composition.

3.2. Anti-cancer mechanisms of honey

Few mechanisms through which natural honey could exert its anti-cancer effects are being debated in this segment. It comprises

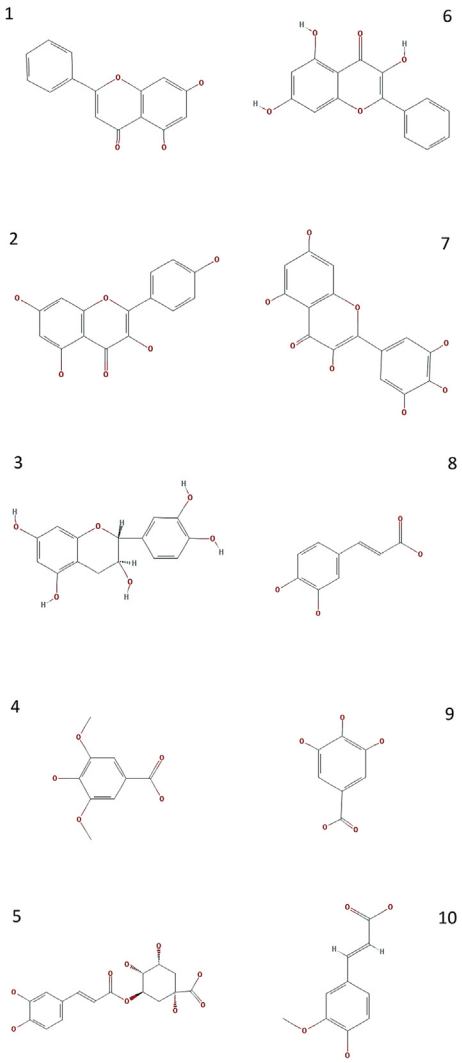

Fig. 1. 2D Molecular structure of honey flavonoids and phenolic acids: Chrysin (1), kaempferol (2), catechin (3), galangin (4), myricetin (5), caffeic acid (6), syringic acid (7), chlorogenic acid (8), gallic acid (9) and ferulic acid (10). Obtained from Open Chemistry Database, National Center for Biotechnology Information. PubChem Substance Database; https://pubchem.ncbi.nlm.nih.gov/substance.

of these processes but is not limited to, arrest of cell cycle, mitochondrial pathway activation which involves introduction of mitochondrial outer membrane permeabilization, apoptosis's induction, modulation of oxidative stress and insulin signaling, enhancement of inflammation, and estrogenic activity, as shown in Fig. 2.

3.3. Cell cycle arrest

Cell growth and propagation are strongly measured in the cell cycle that is a chain of synchronized occasions which comprises of four consecutive segments G_1, G_2, M and S [28]. The G_1 and G_2 are the gap periods interlinked by M and S. Cells split into duplicate progeny cells at the M phase, while replication of DNA proceeds at the S phase [29]. At the G_1 stage, by successive mitosis or removal from the cell sequence into a dormant phase identified as G_0, the cells are reactive to extracellular signals [30]. Checkpoints and cascade of protein kinases control the regulation of events in the cell cycle. The cell cycle becomes dysregulated and also initiates hectic cancer cell proliferation [31]. Honey had been reported to

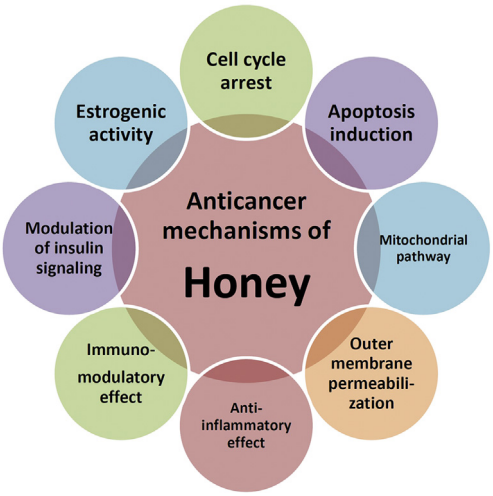

Fig. 2. Summary of potential anticancer mechanisms of honey.

affect cell proliferation. Honey with Aloe vera solution exhibited an obvious decrease in Ki67-LI expression in Wistar rat tumor cells [32].

Cell cycle arresting by honey treatment might be a possible way to lower the tumor proliferation. It was suggested that honey and its constituents, e.g. phenolics and flavonoids, are important to inhibit the cell cycle of melanoma, glioma and colon cancer cell lines in G_1/G_0 stage [33]. Various analyses, for example the trypan blue exclusion assay and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT), have confirmed that antiproliferative effect of honey is time- and dose-dependent [34]. Recently, it has been studied that the cytotoxic effect of honey against non-small cell lung cancer cell (NCI−H460) was mediated via the arrest of cell cycle at the G_0/G_1 phase [35]. Another experimental evidence showed that chrysin, an important constituent of honey, has antiproliferative effect against murine melanoma and human cells via cell cycle arrest at the G_0/G_1 phase [33].

3.4. Activation of the mitochondrial pathway and outer membrane permeabilization

Mitochondrial pathway activation is an important mechanism by which both radiotherapy and chemotherapy cause the cell death. Intrinsic mitochondrial pathway involves a series of interactions, during which various proteins, e.g. cytochrome-C located in inner membrane space (IMS) of mitochondria, are released as a result of various stimuli comprising physical stress, oxidative stress and nutrients which cause the death of the cell [36]. Therefore, honey rich in flavonoids has the ability to release the cytochrome-C during the activation of mitochondrial intrinsic pathway and it has been considered as potential cytotoxic mediators [37]. Induction of MOMP (mitochondrial outer membrane permeabilization) leaks the mitochondrial proteins in the cytosol that makes the common mechanism of inducing cell death with mediators having anticancer properties. Interestingly, it was reported that by reducing mitochondrial membrane potential, Indian honey induces MOMP in HT-29 and HCT-15 colon cancer cells. Research findings showed that quercetin, a subclass of flavonoids present in honey, causes MOMP in different cell lines. Hence, honey and its flavonoid moieties attributed cell death involve MOMP [38].

3.5. Apoptosis induction

Uncontrolled cellular propagation and irregular apoptotic turnover are two features of cancer cells. Apoptosis inducers are medications which are generally utilized for cancer cure [39]. Apoptosis or programmed cell death is classified into three stages: (a) initiation phase (b) proliferation phase, and (c) progression or deprivation stage. The initiation step encourages proapoptotic signal transduction cascade through death inducing signals. Mitochondrion, a key regulator is a way to bring cell death with the commitment to the effector stage. Nuclear and cytoplasmic events are included in the last deprivation phase. Nuclear modifications consist of nuclear and chromatin contraction, cell reduction, genetic material disintegration and blebbing of tissues [40].

A complex cascade of protein splitting enzymes named caspases is stimulated in the cytoplasm. The apoptosis generally goes through mitochondrial pathway and the death receptor or caspase 8 pathways [41]. Honey introduces apoptosis in numerous forms of tumor cells through mitochondrial membrane depolarization. Natural honey elevates the caspase 3 and various proapoptotic proteins, whereas it has been reported to downregulate the anti-apoptotic protein, Bcl-2. It has been reported that in Wistar rats, application of honey with Aloe vera decreases Bcl-2 expression and increases the appearance of proapoptotic protein Bax. The activation of executor protein caspase 3 is due to the preceding stimulation of caspase 9. Similarly another study showed that quercetin, one of the important ingredients present in honey, induces apoptosis as well as inhibition of breast and pancreatic cancer via up-regulation of Bax expression and down-regulation of Bcl-2 expressions [42]. The apoptotic activity of honey makes it a potential natural anticancer agent because it is a safer form of the cell death induced by chemotherapy [43].

3.6. Modulation of oxidative stress

The starring role of reactive oxygen species (ROS) and oxidative stress in cancer cell inhibition and development still remains controversial [44]. There is corroboration in provision of dual action of ROS in cancer, i.e. an inhibitory and stimulatory role. Small amounts of ROS increase propagation of the cells. Additionally, improved intensities of ROS that grounds oxidative damage are well recognized in numerous types of cancers like gastric cancer [45], colorectal cancer [46], lung cancer [34], and breast cancer [17]. Available researches also recommended that discriminating contact of tumor cells to lipid peroxidation products and higher intensities of ROS might be effective in cancer cell damage. Honey is well recognized as a free radical scavenger and strong antioxidant [47]. Everyday ingestion of 1.2 g/kg body weight of honey had been presented to raise the activity and amount of antioxidants such as uric acid, glutathione reductase, beta carotene, and vitamin C [48].

The antioxidant capability of honey offers inhibition from some chronic and acute ailments, for example cancer [49], cardiovascular diseases [50], inflammatory conditions [51], and diabetes. Flavonoids and phenolic acids account for the consistent antioxidant activity of honey. Consequently, the inhibitory influence of honey on tumor proliferation and progression can be arbitrated partially through oxidative stress modulation [52].

3.7. Anti-inflammatory and immunomodulatory effect

In the regulation of proteins like COX-2, iNOS, tyrosine kinase and ornithine decarboxylase, honey and its constituents have been accepted to be involved [53]. Immunoprotective and immunomodulatory property of honey is linked to its effectiveness against cancer [54]. It has been shown that honey causes the

B-cells, macrophages and T-cells to encourage anticancer effects. It is because of the fact that the digestion of honey might result in production of short chain fatty acids (SCFAs) [55,56]. Different articles have proven that SCFAs arouse immunomodulatory actions [57]. Moreover, non-sugar ingredients of honey could account for immunomodulation and immunopotentiating activity [58]. Additionally, a sugar, nigero-oligosaccharides (NOS) present in honey has been reported to induce immune potentiating effects [59].

Continued swelling is associated with malignant cell formation, and excessive inflammation can cause tissue damage and stop the healing process. Studies reviewed that honey decreases inflammation when tested in clinical trials [60], cell cultures [61], and animal models [62]. Inflammation is initiated by means of different varieties of biological and chemical agents containing cytokines and proinflammatory enzymes [59]. The enzyme cyclooxygenase-2 in the inflammatory process speeds up the metabolic rate of arachidonic acid into prostaglandin. A typical arachidonic acid breakdown is involved in swelling and carcinogenesis [63]. The mechanism for anti-inflammatory activity of phenolic compounds in honey involves the suppression of the proinflammatory events of inducible nitric oxide synthase (iNOS) and COX-2 [64]. Honey and its constituents have been reported to be involved in the regulation of COX-2, tyrosine kinase, iNOS and ornithine decarboxylase [65]. Honey and its moieties not only decrease the inflammation rate, but also inhibit or hinder the eventual carcinogenesis stage. In other words, amelioration of inflammation can help to prevent both the formation of a benign tumor and its progression to malignant cancer.

3.8. Modulation of insulin signaling and estrogenic activity

Obesity, insulin resistance and type 2 diabetes mellitus are the major risk factors for the cause of different malignancies indicated by different epidemiological studies [66]. During the past few years, research has implicated the part of insulin receptors (IR) in carcinogenesis [67], which has been recently demonstrated by some scientists; they studied that IR being targeted by the small molecules are effective against the reduction of lung cancer cell proliferation [68]. Another important component of insulin signaling is P13K/Akt which modulates several factors that regulate the cell cycle progression as well as cellular growth. Recently, the effect of gelam honey was observed on Akt activated insulin signaling pathway under glycemic conditions in HIT-T15 cells which showed that insulin resistance development involves the increased level of Nf-kB, insulin receptor substrate 1 and MAPK. Insulin content and insulin resistance are reported to be improved through pretreatment with quercetin and gelam honey extracts. Modulation of insulin signaling in the case of cancer could be done by consumption of honey [69].

Similarly, honey is also able to modulate estrogen hormone via its contradictory action [70]. It might be advantageous in estrogen dependent growths, e.g. endometrial and breasts cancers. Estrogen receptor binds to estrogen and further translocates into the nuclei. This complex then binds to the particular DNA sequences called estrogen response elements (EREs) causing translation and transcription of the estrogenic regulated genes in the targeted tissues. This signaling cascade brought by estrogens can be modified at any stage. Greek honey extracts introduce estrogen antagonistic effect at low concentrations (0.2–5 μg/mL) and agonistic action at high concentrations (20–100 lg/mL). Through the modulation of estrogen receptor activity, honey taken from different flowers are informed to facilitate estrogenic activity and this effect is credited to phenolic contents of honey [70].

4. Conclusions

Though the complete mechanism is yet to be copiously agreed, different explorations have shown that honey gives anticancer effect through its intervention with complicated cell-signaling passages, for example encouraging anti-mutagenic, apoptosis, anti-inflammatory and anti-proliferative pathway. Honey moderates the humanoid immune system. There are lots of unrequited queries on why sugar is cancer causing, while honey that is basically a sugar/carbohydrate exerts anti carcinogenic effect. Potential randomized specific experimental and clinical studies are needed to corroborate the authenticity of honey both alone and equally as adjuvant healing.

Conflicts of interest

No competing interest.

Acknowledgement

There is no grant supporting the study.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. 2016 CA A Cancer J Clin 2016;66:7–30.
[2] Bansal VK, Rajan K, Sharma A, Paliwal P, Chaubal G, Jindal V, et al. Prospective case–control study to evaluate the role of glutathione s transferases (GSTT1 and GSTM1) gene deletion in breast carcinoma and its prognostic significance. Indian J Surg 2015;77:1067–72.
[3] Lin R, Zhao L. Mechanistic basis and clinical relevance of the role of transforming growth factor-β in cancer. Cancer Biol Med 2015;12:385–93.
[4] Shakeri A, Hashempur MH, Mojibian M, Aliasl F, Bioos S, Nejatbakhsh F. A comparative study of ranitidine and quince (Cydonia oblonga mill) sauce on gastroesophageal reflux disease (GERD) in pregnancy: a randomised, open-label, active-controlled clinical trial. J Obstet Gynaecol 2018:1–7.
[5] Hashempur MH, Sadrneshin S, Mosavat SH, Ashraf A. Green tea (Camellia sinensis) for patients with knee osteoarthritis: a randomized open-label active-controlled clinical trial. Clin Nutr (Edinb) 2018;37:85–90.
[6] Khiveh A, Hashempur MH, Shakiba M, Lotfi MH, Shakeri A, Kazemeini S, et al. Effects of rhubarb (Rheum ribes L.) syrup on dysenteric diarrhea in children: a randomized, double-blind, placebo-controlled trial. J Integrative Medicine 2017;15:365–72.
[7] Dorai T, Aggarwal BB. Role of chemopreventive agents in cancer therapy. Cancer Lett 2004;215:129–40.
[8] Hashempur MH, Khademi F, Rahmanifard M, Zarshenas MM. An evidence-based study on medicinal plants for hemorrhoids in medieval Persia. J evidence-based complementary & alternative medicine 2017;22:969–81.
[9] Chari RV. Targeted cancer therapy: conferring specificity to cytotoxic drugs. Acc Chem Res 2008;41:98–107.
[10] da Silva PM, Gauche C, Gonzaga LV, Costa ACO, Fett R. Honey: chemical composition, stability and authenticity. Food Chem 2016;196:309–23.
[11] Ahmed S, Othman NH. Honey as a potential natural anticancer agent: a review of its mechanisms. Evid Based Complement Altern Med 2013. 2013.
[12] Can Z, Yildiz O, Sahin H, Turumtay EA, Silici S, Kolayli S. An investigation of Turkish honeys: their physico-chemical properties, antioxidant capacities and phenolic profiles. Food Chem 2015;180:133–41.
[13] Almasaudi SB, El-Shitany NA, Abbas AT, Abdel-dayem UA, Ali SS, Al Jaouni SK, et al. Antioxidant, anti-inflammatory, and antiulcer potential of manuka honey against gastric ulcer in rats. Oxid Med Cell Longev 2016;2016:3643824.
[14] Saxena S, Gautam S, Maru G, Kawle D, Sharma A. Suppression of error prone pathway is responsible for antimutagenic activity of honey. Food Chem Toxicol 2012;50:625–33.
[15] Wasihun A, Kasa B. Evaluation of antibacterial activity of honey against multidrug resistant bacteria in Ayder Referral and Teaching Hospital, Northern Ethiopia. SpringerPlus 2016;5.
[16] Molan P, Rhodes T. Honey: a biologic wound dressing. Wounds 2015;27:141–51.
[17] Erejuwa OO, Sulaiman SA, Wahab MSA. Effects of honey and its mechanisms of action on the development and progression of cancer. Molecules 2014;19:2497–522.
[18] Afrin S, Forbes-Hernandez TY, Gasparrini M, Bompadre S, Quiles JL, Sanna G, et al. Strawberry-tree honey induces growth inhibition of human colon cancer cells and increases ROS generation: a comparison with manuka honey. Int J Mol Sci 2017;18:613.

[19] Othman N. Honey and cancer: sustainable inverse relationship particularly for developing nations-A review. Evid Based Complement Alter Med 2012:1–10. 2012.
[20] Samarghandian S, Afshari J, Davoodi S. Honey induces apoptosis in renal cell carcinoma. Phcog Mag 2011;7:46–52.
[21] Porcza L, Simms C, Chopra M. Honey and cancer: current status and future directions. Diseases 2016;4:1–26.
[22] Fauzi AN, Norazmi MN, Yaacob NS. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. Food Chem Toxicol 2011;49:871–8.
[23] Moniruzzaman M, Khalil M, Sulaiman S, Gan S. Advances in the analytical methods for determining the antioxidant properties of honey: a review. Afr J Tradit, Complementary Altern Med 2012;9:36–42.
[24] Buba F, Gidado A, Shugaba A. Analysis of biochemical composition of honey samples from North-East Nigeria. Biochem Anal Biochem 2013;2:1–7.
[25] Khalil MI, Moniruzzaman M, Boukraâ L, Benhanifia M, Islam MA, Islam MN, et al. Physicochemical and antioxidant properties of Algerian honey. Molecules 2012;17:11199–215.
[26] Liberato MdCTC, Morais SMd, Magalhães CEdC, Magalhães IL, Cavalcanti DB, Silva MMdO. Physicochemical properties and mineral and protein content of honey samples from Ceará State, Northeastern Brazil. Food Sci Technol 2013;33:38–46.
[27] Ahmed S, Othman NH. Review of the medicinal effects of tualang honey and a comparison with manuka honey. Malays J Med Sci: MJMS 2013;20:6.
[28] Williams G, Stoeber K. The cell cycle and cancer. 2012 J Pathol 2012:352–64.
[29] Boonstra J. Progression through the G1-phase of the on-going cell cycle. J Cell Biochem 2003;90:244–52.
[30] Kosaka N, Iguchi H, Yoshioka Y, Hagiwara K, Takeshita F, Ochiya T. Competitive interactions of cancer cells and normal cells via secretory microRNAs. J Biol Chem 2012;287:1397–405.
[31] Pichichero E, Cicconi R, Mattei M, Muzi M, Canini A. Acacia honey and chrysin reduce proliferation of melanoma cells through alterations in cell cycle progression. Int J Oncol 2010;37:973–81.
[32] Samarghandian S, Farkhondeh T, Samini F. Honey and health: a review of recent clinical research. Pharmacogn Res 2017;9:121–7.
[33] Afroz R, Tanvir E, Zheng W, Little P. Molecular pharmacology of honey. Clin Exp Pharmacol 2016;6:1–13.
[34] Yang Y, Karakhanova S, Werner J, Bazhin A. Reactive oxygen species in cancer biology and anticancer therapy. Curr Med Chem 2013;20:3677–92.
[35] Gogvadze V, Orrenius S, Zhivotovsky B. Multiple pathways of cytochrome c release from mitochondria in apoptosis. 1757 Biochim Biophys Acta Bioenerg 2006:639–47.
[36] Ren J, Cheng H, Xin W, Chen X, Hu K. Induction of apoptosis by 7-piperazinethylchrysin in HCT-116 human colon cancer cells. Oncol Rep 2012;28:1719–26.
[37] Jaganathan SK, Mandal M. Involvement of non-protein thiols, mitochondrial dysfunction, reactive oxygen species and p53 in honey-induced apoptosis. Invest N Drugs 2010;28:624–33.
[38] Nassar D, Blanpain C. Cancer stem cells: basic concepts and therapeutic implications. 2016 Annu Rev Pathol 2016:47–76.
[39] Safarzadeh E, Shotorbani S, Baradaran B. Herbal medicine as inducers of apoptosis in cancer treatment. Adv Pharmaceut Bull 2014;4:421–7.
[40] Andersen MH, Becker JC, thor Straten P. Regulators of apoptosis: suitable targets for immune therapy of cancer. Nat Rev Drug Discov 2005;4:399.
[41] Angst E, Park JL, Moro A, Lu Q-Y, Lu X, Li G, et al. The flavonoid quercetin inhibits pancreatic cancer growth in vitro and in vivo. Pancreas 2013;42:223.
[42] Yaacob N, Nengsih A, Norazmi M. Tualang honey promotes apoptotic cell death induced by tamoxifen in breast cancer cell lines. 2013 Evid Based Complement Alternat Med 2013:1–10.
[43] Bhagat SS, Ghone RA, Suryakar AN, Hundekar PS. Lipid peroxidation and antioxidant vitamin status in colorectal cancer patients. Indian J Physiol Pharmacol 2011;55:72–6.
[44] Balestrieri ML, Dicitore A, Benevento R, Di Maio M, Santoriello A, Canonico S, et al. Interplay between membrane lipid peroxidation, transglutaminase activity, and Cyclooxygenase 2 expression in the tissue adjoining to breast cancer. J Cell Physiol 2012;227:1577–82.
[45] Peddireddy V, Siva Prasad B, Gundimeda S, Penagaluru P, Mundluru H. Assessment of 8-oxo-7, 8-dihydro-2'-deoxyguanosine and malondialdehyde levels as oxidative stress markers and antioxidant status in non-small cell lung cancer. Biomarkers 2012;17:261–8.
[46] Epplein M, Franke AA, Cooney RV, Morris JS, Wilkens LR, Goodman MT, et al. Association of plasma micronutrient levels and urinary isoprostane with risk of lung cancer: the multiethnic cohort study. Cancer Epidemiology and Prevention Biomarkers 2009;18:1962–70.
[47] Alzahrani HA, Boukraâ L, Yuva Bellik FA, Bakhotmah BA, Kolayli S, Sahin H. Evaluation of the antioxidant activity of three varieties of honey from different botanical and geographical origins. Global J Health Sci 2012;4:191.
[48] Akkol E, Orhan D, Gurubuz I, Yesilada E. In vivo activity assessment of a "honey-bee pollen mix" formulation. Pharm Biol 2010;48:253–9.
[49] Rakha M, Nabil Z, Hussein A. Cardioactive and vasoactive effects of natural wild honey against cardiac malperformance induced by hyperadrenergic activity. J Med Food 2008;11:91–8.
[50] Hassan MI, Mabrouk GM, Shehata HH, Aboelhussein MM. Antineoplastic effects of bee honey and Nigella sativa on hepatocellular carcinoma cells. Integr Canc Ther 2012;11:354–63.
[51] Kadirvelu A, Gurtu S. Potential benefits of honey in type 2 diabetes mellitus: a review. Int J Collab Res Intern Med Public Health (IJCRIMPH) 2013;5:199.
[52] Araújo JR, Gonçalves P, Martel F. Chemopreventive effect of dietary polyphenols in colorectal cancer cell lines. Nutr Res 2011;31:77–87.
[53] Attia W, Gabry M, El-Shaikh K, Othman G. The anti-tumor effect of bee honey in Ehrlich ascite tumor model of mice is coincided with stimulation of the immune cells. Egypt J Immunol 2008;15:169–83.
[54] Honey Majtan J. An immunomodulator in wound healing. Int J Tissue Repair Regen 2014;22:187–92.
[55] Chepulis L. The effect of honey compared to sucrose, mixed sugars, and a sugar-free diet on weight gain in young rats. J Food Sci 2007;72:S224–9.
[56] Mesaik M, Dastagir N, Uddin N, Rehman K, Azim M. Characterization of immunomodulatory activities of honey glycoproteins and glycopeptides. J Agric Food Chem 2015;63:177–84.
[57] Leong AG, Herst PM, Harper JL. Indigenous New Zealand honeys exhibit multiple anti-inflammatory activities. Innate Immun 2012;18:459–66.
[58] Alam F, Islam M, Gan SH, Khalil M. Honey: a potential therapeutic agent for managing diabetic wounds. Evid Based Complement Altern Med 2014. 2014.
[59] Hussein SZ, Mohd Yusoff K, Makpol S, Mohd Yusof YA. Gelam honey inhibits the production of proinflammatory, mediators NO, PGE2, TNF-α, and IL-6 in carrageenan-induced acute paw edema in rats. Evid Based Complement Altern Med 2012;2012:109636.
[60] Dao TT, Chi YS, Kim J, Kim HP, Kim S, Park H. Synthesis and inhibitory activity against COX-2 catalyzed prostaglandin production of chrysin derivatives. Bioorg Med Chem Lett 2004 Mar 8;14(5):1165–7.
[61] Ricciotti E, FitzGerald G. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31:986–1000.
[62] Hyde C, Missailidis S. Inhibition of arachidonic acid metabolism and its implication on cell proliferation and tumour-angiogenesis. Int Immunopharm 2009;9:701–15.
[63] Dayem A, Hossain M, Lee S, Kim K, Saha S, Yang G, et al. The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. Int J Mol Sci 2017;120:1–21.
[64] Fair AM, Dai Q, Shu X-O, Matthews CE, Yu H, Jin F, et al. Energy balance, insulin resistance biomarkers, and breast cancer risk. Cancer Detect Prev 2007;31:214–9.
[65] Belfiore A, Malaguarnera R. Insulin receptor and cancer. Endocr Relat Canc 2011;18:R125–47.
[66] Vincent E, Elder D, Curwen J, Kilgour E, Hers I, Tavare J. Targeting non-small cell lung cancer cells by dual inhibition of the insulin receptor and the insulin-like growth factor-1 receptor. PLoS One 2013;8, e66963.
[67] Zaid S, Sulaiman S, Sirajudeen K, Othman N. The effects of tualang honey on female reproductive organs, tibia bone and hormonal profile in ovariectomised rats-animal model for menopause. BMC Complement Altern Med 2010;10:82.
[68] Tandara A, Mustoe T. Oxygen in wound healing-more than a nutrient. World J Surg 2004;28:294–300.
[69] Erejuwa OO, Sulaiman SA, Ab Wahab MS. Honey-a novel antidiabetic agent. Int J Biol Sci 2012;8:913.
[70] Sibbald R, Woo K. The biology of chronic foot ulcers in persons with diabetes. Diabetes Metab Res Rev 2008;24:S25–30.

Acronyms and Abbreviations

DPPH: Diphenyl-1-picrylhydrazyl
FRAP: Ferric Reducing Antioxidant Power
ORAC: The Oxygen Radical Absorbance Capacity
ABTS: 2, 2-azinobis (3-ehtylbenzothiazoline-6-sulfonic acid) diammonium salt
TEAC: 6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid (Trolox)-equivalent antioxidant capacity
SOD: Superoxide Dismutase
CAT: Catalase
COX-2: Cyclooxygenase-2
ROS: Reactive Oxygen Species
MTT: 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide
MOMP: Mitochondrial Outer Membrane Permeabilization
INOS: Inducible Nitric Oxide Synthase
EREs: Estrogen Response Elements
PMNs: Polymorph Nuclear Neutrophils
GIT: Gastrointestinal Tract
CVD: Cardiovascular Diseases