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REVIEW ARTICLE

Honey and Health: A Review of Recent Clinical Research

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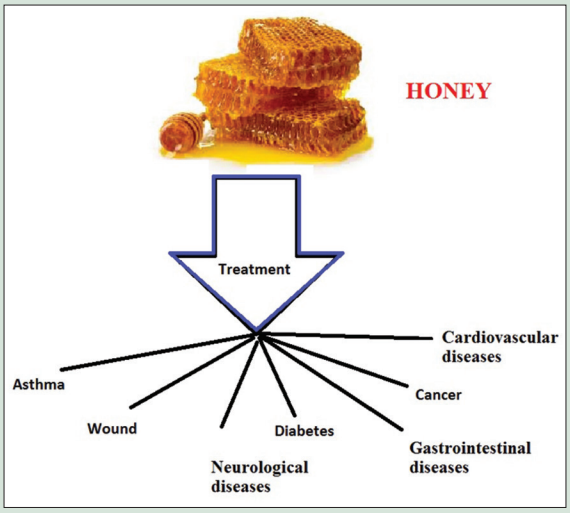
ABSTRACT

Honey is one of the most appreciated and valued natural products introduced to humankind since ancient times. Honey is used not only as a nutritional product but also in health described in traditional medicine and as an alternative treatment for clinical conditions ranging from wound healing to cancer treatment. The aim of this review is to emphasize the ability of honey and its multitude in medicinal aspects. Traditionally, honey is used in the treatment of eye diseases, bronchial asthma, throat infections, tuberculosis, thirst, hiccups, fatigue, dizziness, hepatitis, constipation, worm infestation, piles, eczema, healing of ulcers, and wounds and used as a nutritious supplement. The ingredients of honey have been reported to exert antioxidant, antimicrobial, anti-inflammatory, antiproliferative, anticancer, and antimetastatic effects. Many evidences suggest the use of honey in the control and treatment of wounds, diabetes mellitus, cancer, asthma, and also cardiovascular, neurological, and gastrointestinal diseases. Honey has a potential therapeutic role in the treatment of disease by phytochemical, anti-inflammatory, antimicrobial, and antioxidant properties. Flavonoids and polyphenols, which act as antioxidants, are two main bioactive molecules present in honey. According to modern scientific literature, honey may be useful and has protective effects for the treatment of various disease conditions such as diabetes mellitus, respiratory, gastrointestinal, cardiovascular, and nervous systems, even it is useful in cancer treatment because many types of antioxidant are present in honey. In conclusion, honey could be considered as a natural therapeutic agent for various medicinal purposes. Sufficient evidence exists recommending the use of honey in the management of disease conditions. Based on these facts, the use of honey in clinical wards is highly recommended.

Key words: Antioxidant, flavonoids, honey, polyphenols, therapeutic agent, traditional

SUMMARY

There are several evidence that suggesting the usage of honey in the management of disease. Therefore, honey in clinical wards is highly recommended.



Abbreviations Used: WA: Water activity, RDI: Recommended daily intake, Si: Silicon, RB: Rubidium, V: Vanadium, Zr: Zirconium, Li: Lithium, Sr: Strontium, Pb: Lead, Cd: Cadmium, As: Arsenic, MIC: Minimum inhibitory concentration, PARP: Poly (ADP-ribose) polymerase, ROS: Reactive oxygen species, iNOS: Inducible nitric oxide synthase, NKcells: Natural killer cells, SCFA: Short-chain fatty acid, CRP: C-reactive protein.

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INTRODUCTION

Honey is a natural product formed from nectar of flowers by honeybees (*Apis mellifera*; Family: Apidae).[1] Honey has been used by humans since ancient times, nearly 5500 years ago.[2] Most ancient population, including the Greeks, Chinese, Egyptians, Romans, Mayans, and Babylonians, consumed honey both for nutritional aims and for its medicinal properties.[2,3] Honey is the only insect-derived natural product, and it has nutritional, cosmetic, therapeutic, and industrial values.[4,5] Honey is reviewed as a balanced diet and equally popular for male and female in all ages.[6] Honey no needs to refrigerate, it never spoils, and it can also be stored unopened at room temperature in a dry place.[7,8] The water activity (WA) of honey is between 0.56 and 0.62 and its value of pH is almost 3.9.[7,8] Honey was utilized as a natural sweetener from ancient period since it has high level of fructose (honey is 25% sweeter than tablet sugar).[8,9] Moreover, the use of honey in beverages is also increasingly popular.[8] Nowadays, information on the usage of honey for the cure of many human diseases can be found in general magazines, journals, and natural products' leaflets and suggesting a wide variety of unknown activities.[10] Evidence indicates that honey can exert several health-beneficial effects including antioxidant,[11] anti-inflammatory,[12] antibacterial,[13] antidiabetic,[14] respiratory, gastrointestinal,[15] cardiovascular, and nervous system[16] protective effects. Although many investigations were done on honey, only a few are published. This study, which is a comprehensive review of the current literature, highlights the therapeutic benefits of honey in the management of diseases.

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METHODS

A literature search was conducted to identify recent articles illustrating efficacy of honey in the cure of diseases. Several online databases were queried, including Web of Science, ScienceDirect, and PubMed. The following keywords were used individually and in combination as inclusion criteria for articles to be considered for this review: honey antioxidant, anti-inflammatory, antibacterial, antidiabetic, apoptotic, respiratory, gastrointestinal, and cardiovascular and nervous system. The present review covers a 42-year period which includes publications from 1970 to 2014. Initial searches yielded nearly 200 results. The abstracts of these papers were reviewed to confirm applicability. After considering additional exclusion criteria (non-English language, and manuscripts not available as full text), 108 papers remained.

Medicinal history of honey

Evidence from Stone Age paintings shows treatment of disease with bee product such as honey originated from 8000 years ago. Ancient scrolls, tablets and books-Sumerian clay tablets (6200 BC), Egyptian papyri (1900–1250 BC), Veda (Hindu scripture) 5000 years, Holy Koran, Bible, and Hippocrates (460–357 BC) illustrated that honey had been widely used as a drug.[17-19] Qur'an vividly indicated the activity of therapeutic value of honey.[20] The Lord has inspired the bees, to build their hives in hills, on trees, and in man's habitations, from within their bodies comes a drink of varying colors, wherein is healing for humankind, verily in this is a sign, for those who give thought. Although a number of papers have been published about honey, most of them have focused on the biochemical analysis, food, and nonfood commercial utilization. Honey was used for variety of disease conditions including eye diseases, asthma, throat infections, tuberculosis, thirst, hiccups, fatigue, dizziness, hepatitis, constipation, worm infestation, piles, eczema, healing of ulcers, and wounds in traditional medicine.[20,21]

Nutritional and nonnutritional components of honey

Today, approximately 300 types of honey have been recognized.[22] These varieties are related to the different types of nectar that are collected by the honeybees. The main composition of honey is carbohydrates that contribute 95–97% of its dry weight. Furthermore, honey includes main compounds, such as proteins, vitamins, amino acids, minerals, and organic acids [Figure 1].[23,24] Pure honey also consists of flavonoids, polyphenols, reducing compounds, alkaloids, glycosides, cardiac glycosides, anthraquinone, and volatile compounds.[25-27] Monosaccharides (fructose and glucose) are the most important sugars of honey and may be contributed to the most of the nutritional and physical effects of honey.[28] In addition to monosaccharides, smaller quantities of disaccharides (sucrose, galactose, alpha, beta-trehalose, gentiobiose, and laminaribiose), trisaccharides (melezitose, maltotriose, 1-ketose, panose, isomaltose glucose, erlose, isomaltotriose, theanderose, centose, isopanose, and maltopentaose), and oligosaccharides are present in honey [Figure 2].[29,30] Many of these sugars are formed during the honey ripening and maturation times. Gluconic acid, a product of glucose oxidation, is the main organic acid that is present in honey; in addition, small amounts of acetic, formic, and citric have been found.[31] These organic acids are responsible for the acidic (pH between 3.2 and 4.5) property of honey.[32] Honey also consists of some important amino acids, such as all nine essential amino acids and all nonessential amino acids except for asparagine and glutamine. Proline was reported as the primary amino acid in honey, followed by other types of amino acids.[33] Enzymes (diastase, invertases, glucose oxidase, catalase, and acid phosphatase) constitute the main protein ingredients of honey.[34] The vitamin level in honey is low and does not close to the recommended daily intake [Figure 3]. All of the water-soluble vitamins exist in honey, with Vitamin C being the most frequent. Approximately 31 variable minerals have been found in honey, including all of the major minerals, such as phosphorus, sodium, calcium, potassium, sulfur, magnesium, and chlorine [Figure 4]. Many essential trace components are detected in honey, such as silicon (Si), rubidium (RB), vanadium (V), zirconium (Zr), lithium (Li), and strontium (Sr). However, some heavy metals such as lead (Pb), cadmium (Cd), and arsenic (As) are present as pollutants.[35] Previous studies have detected the approximately 600 volatile compositions in honey that contribute to its potential biomedical effects.[36] The volatile compounds of honey are generally low but include aldehydes, alcohols, hydrocarbons, ketones, acid esters, benzene and its derivatives, pyran, terpene and its derivatives, norisoprenoids, as well as

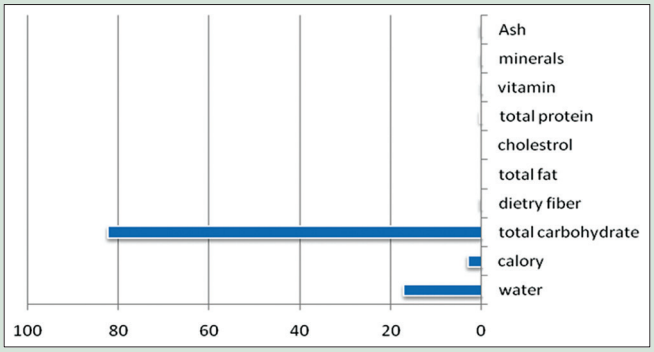

Figure 1: An overview of composition of raw honey (average amount per 100 g)

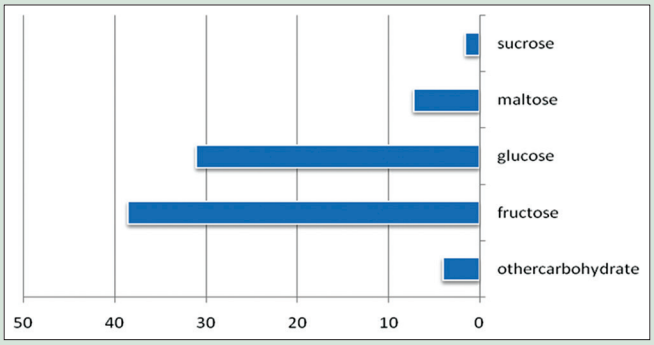

Figure 2: Carbohydrate (average amount per 100 g)

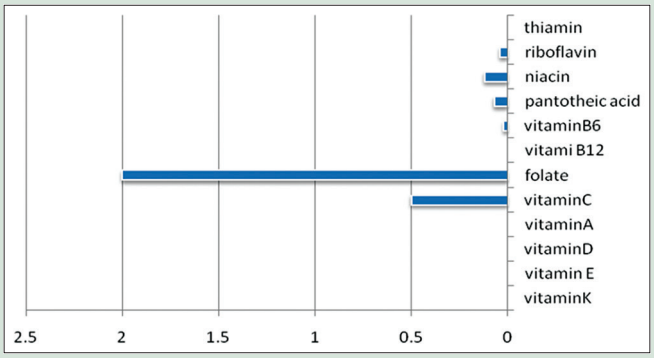

Figure 3: A comparison of the minerals found in honey (major and essential trace minerals)

sulfur, furan, and cyclic compounds.[37,38] Flavonoids and polyphenols, which act as antioxidants, are two main bioactive molecules present in honey. Recent evidence has shown the presence of nearly thirty types of polyphenols in honey.[39,40] The existence and levels of these polyphenols in honey can vary depending on the floral source, the climatic and geographical conditions. Some bioactive compounds, including galangin, quercetin, kaempferol, luteolin, and isorhamnetin, are present in all types of honey whereas naringenin and hesperetin are found only in specific varieties.[41] In general, the most phenolic and flavonoid compounds in honey consist of gallic acid, syringic acid, ellagic acid, benzoic acid, cinnamic acid, chlorogenic acid, caffeic acid, isorhamnetin, ferulic acids, myricetin, chrysin, coumaric acid, apigenin, quercetin, kaempferol, hesperetin, galangin, catechin, luteolin, and naringenin.[39,40] The ingredients of honey have been reported to exert antioxidant, antimicrobial, anti-inflammatory, antiproliferative, anticancer, and antimetastatic effects.

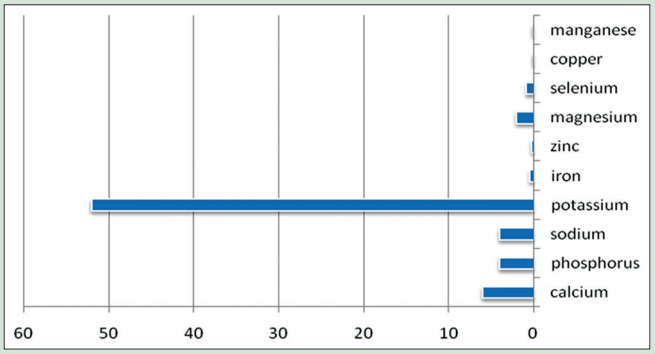

Figure 4: Vitamin (average amount mg per 100 g)

Structures of major flavonoids, organic acids, and phenolic acids in honey

Flavonoids refer to a group of active natural compounds with a 15-carbon structure, comprising two benzene rings joined by a heterocyclic pyrane ring.[42] They are generally classified as flavonols (quercetin, kaempferol, and pinobanksin), flavones (luteolin, apigenin, and chrysin), flavanones (naringenin, pinocembrin, and hesperetin), isoflavones (genistein), and anthocyanidins.[43] Some flavonoids including genistein, chrysin, luteolin, and naringenin have been reported to show estrogenic activity and are often referred to as phytoestrogens.[44] Figure 5 shows the chemical structures of the major flavonoids and phenolic acids present in honey.

Biological activities of honey

Antioxidant activity

Oxidants agents such as oxygen involve in preventing damage play as an antioxidant which is detected in foods and human body.[45] Although, the

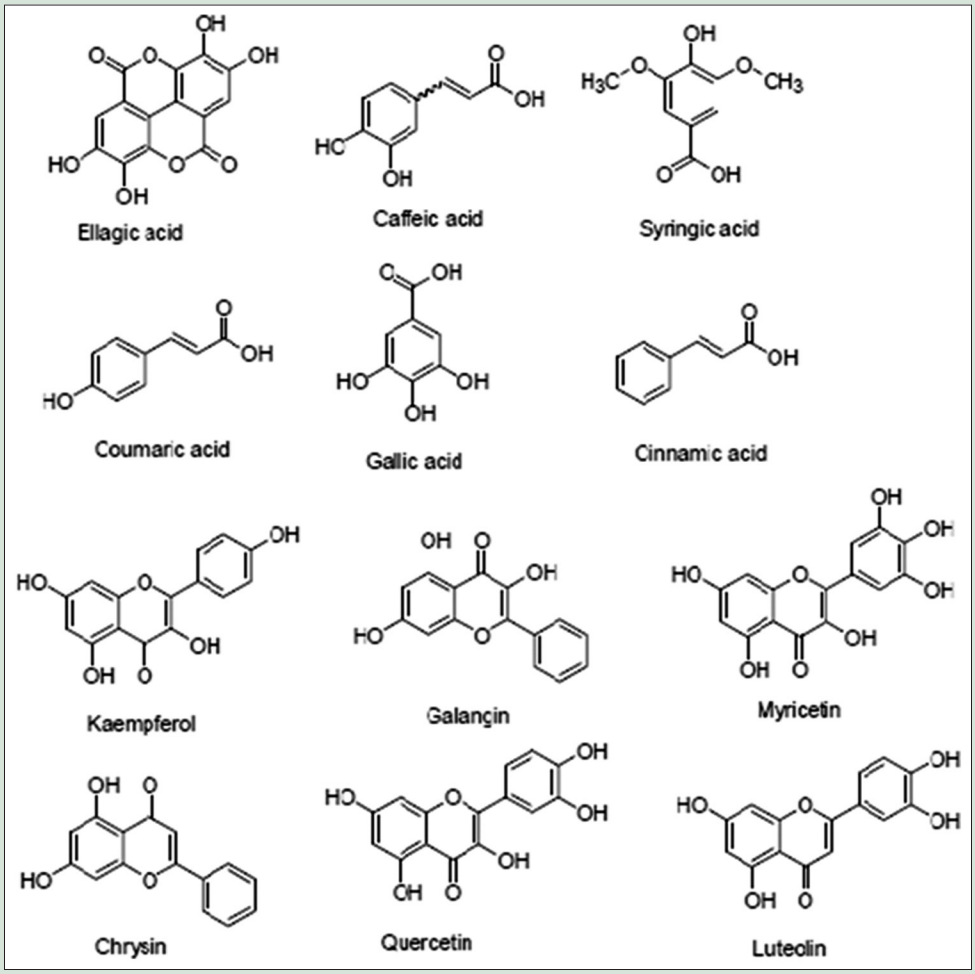

Figure 5: Chemical structures of the flavonoids, organic acids, and phenolic ingredients in honey

natural antioxidants function in human body has not fully understood, however, the investigations illustrated a function in effects of natural honey in many of aging and process highly reactive ingredient drive from oxygen which named free radicals and reactive oxygen species (ROS) are generated during metabolism. These ingredients interact with lipids and protein components in the cell membranes, enzymes as well as DNA. These damaging reactions may lead to various diseases. Fortunately, antioxidants intercept free radicals before they can do damage. Both enzymatic and nonenzymatic substances apply in protective antioxidant.[46] The ability of honey for antioxidant properties is related to the brightness of honey; therefore, the darker honey has higher value of antioxidant. It has been showed that the phenolic compounds are the major responsible factor for antioxidant activity of honey, since the phenolic level is related to radical absorbance activity values of honey.[47] The other investigations illustrated that the antioxidant activity is related to the combination of wide range of active compounds present in honey. Thus, honey has the ability to act as a dietary antioxidant. According to the scientific literature, honey applied alone or in combination with conventional therapy might be a new antioxidant in the control of commonly associated with oxidative stress.[47] In fact from the majority of these data extracted from experimental research, there is an essential need to study this antioxidant effect of honey in the different human disorders.

Antimicrobial activity

The main factors for antimicrobial activity of honey are the enzymatic glucose oxidation reaction and some of its physical aspects,[48,49] but the other factors that can show antimicrobial activity of honey include high osmotic pressure/low WA, low pH/acidic environment, low protein content, high carbon to nitrogen ratio, low redox potential due to the high level of reducing sugars, a viscosity that limits dissolved oxygen and other chemical agents/phytochemicals. Due to the properties of honey such as low WA and water acidity, glucose oxidase, and hydrogen peroxide, honey does not help in the growth of yeast and bacteria.[50] The peroxidase is not all origin of antibacterial level of honey, but many products with low antibacterial level were discovered in honey including terpenes, pinocembrin, benzyl alcohol, 3,5-dimethoxy-4-hydroxybenzoic acid (syringic acid), methyl-3,5-dimethoxy-4-hydroxybenzoate (methyl syringate), 2-hydroxy-3-phenylpropionic acid, 2-hydroxybenzoic acid, 3,4,5-trimethoxybenzoic acid, and 1,4-dihydroxybenzene.[51]

Many investigations indicated that the antibacterial activity of honey is minimum inhibitory concentration; therefore, honey has the minimum concentration necessary for complete inhibitory growth.[52] Among the many types of honey, manuka honey has the highest level of nonperoxide activity.[49,53] Investigations indicated that *Escherichia coli* and *Staphylococcus aureus* can be significantly prevented by manuka honey.[54] It has been illustrated that antibacterial activity of honey is effective on many bacterial pathogens and fungi.[55,56]

Apoptotic activity

Cancer cells are characterized by inadequate apoptotic turnover and uncontrolled cellular proliferation.[57] Chemicals which are applied for cancer treatment are apoptosis inducers.[58] Honey makes apoptosis in many types of cancer cells through depolarization of mitochondrial membrane.[58,59] Honey increases caspase 3 activation and poly (ADP-ribose) polymerase (PARP) cleavage in human colon cancer cell lines which is related to its high phenolic component.[60] Moreover, it makes apoptosis through modulating the expression of pro- and anti-apoptotic proteins in colon cancer.[60] Honey induces the expression of p53, caspase 3, and proapoptotic protein Bax and also downregulates the expression of anti-apoptotic protein Bcl2.[60] Honey produces ROS leading to the activation of p53 and p53 in turn modulates the expression of pro- and anti-apoptotic proteins such as Bcl-2 and Bax.[60] Oral administration of honey increases the expression of pro-apoptotic protein Bax and also reduces the anti-apoptotic protein Bcl-2 expression in tumor tissue of Wistar rats.[61] Intravenous injection of manuka honey acts its apoptotic effect on cancer cells lines through the involvement of the caspase 9 which in turn activates the caspase-3, the executor protein. Apoptosis was made by manuka honey which also involves in the activation of PARP, DNA fragmentation and loss of Bcl-2 expression.[62] The apoptotic properties of honey make it a possible natural substance as anti-cancer agent as many chemotherapeutics currently used are apoptosis inducer agents.

Anti-inflammatory and immunomodulatory activities

Chronic inflammation can inhibit healing by damaging tissues. According to the present literature, honey reduces inflammatory response in animal models, cell cultures,[63-65] and clinical trials.[66] Phenolic content in honey is responsible for anti-inflammatory effect.[67] These phenolic and flavonoids compounds cause the suppression of the pro-inflammatory activities of cyclooxygenase-2 (COX-2) and/or inducible nitric oxide synthase (iNOS).[68] Honey and its ingredients have been indicated to be involved in regulation of proteins including of iNOS, ornithine decarboxylase, tyrosine kinase, and COX-2. Different types of honey are discovered to induce tumor necrosis factor alpha, interleukin-1 beta (IL-1β), and IL-6 production.[69-71] Honey increases T and B lymphocytes, antibodies, eosinophils, neutrophils, monocytes, and natural killer cells generation during primary and secondary immune responses in tissue culture.[72]

It was indicated that slow absorption leads to the production of short-chain fatty acid (SCFA) fermentation agents.[73] It is a likely mechanism that the ingestion of honey may result in SCFA production.[74] The immunomodulatory actions of SCFA have been confirmed.[75] Therefore, honey may induce the immune response through these fermentable sugars.[76] A sugar, nigerooligosaccharides, present in honey has been observed to have immunopotentiating effects.[77] Nonsugar ingredients of honey are also responsible for immunomodulation.[76]

Medicinal properties

Honey and wound

Honey is the oldest wound-healing agent known to mankind when some modern chemicals have failed in this regard.[53] Experimental research illustrated more documents supporting its usage in wound healing because of its bioactivities including antibacterial, antiviral, anti-inflammatory, and antioxidant activities.[78] Honey induces leukocytes to release cytokines, which is what begins the tissue repair cascades. Furthermore, it actives immune response to infection.[79] The stimulation of other properties of the immune response by honey is also reported (Proliferation of B- and T-lymphocytes and the phagocytes activity). Honey induces the generation of antibodies. Many evidence suggest the use of honey in the control and treatment of acute wounds and for mild to moderate superficial and partial thickness burns.[80] Although some studies indicated the efficacy of honey in relation to wound treatment and leg ulcers, more studies are needed to strengthen the current evidence.

Honey and diabetes

There are strong evidences which indicate the beneficial effects of honey in the treatment of diabetes mellitus.[81] These results point out the therapeutic prospects of using honey or other potent antioxidants as an adjunct to standard antidiabetic drugs in the control of diabetes mellitus. Regarding the restrictions associated with using of antioxidants, other

interventions targeted at decreasing ROS generation may also be used as an adjunct to conventional diabetes therapy. In one of the clinical trials of Type 1 and Type 2 diabetes mellitus, the application of honey was associated with dramatically lower glycemic index than with sucrose or glucose in type 1 diabetes and normal.[82] Type 2 diabetes has values similar for honey, glucose, and sucrose. In the diabetic patients, honey can induce significantly a reduction in plasma glucose level versus dextran.[83] In normal and hyperlipidemic patients, it also reduces blood lipids, homocysteine and C-reactive protein contents. However, several questions have been remained, especially as it relates to the prospect of controlling diabetes mellitus by interventions that target both oxidative stress and hyperglycemia. Furthermore, the therapeutic effects of honey in the management of diabe tes may not only be restricted to controlling glycemia but also may be extended to ameliorating the associated metabolic complication diseases.[81]

Honey and cancer

Current studies show that honey may exert anticancer effects through several mechanisms.[84] Investigations have indicated that honey has anticancer property through its interference with multiple cell-signaling pathways, including inducing apoptosis, antimutagenic, antiproliferative, and anti-inflammatory pathways. Honey modifies the immune responses.[84] Honey has been indicated to prevent cell proliferation, induce apoptosis, modify cell cycle progression, and cause mitochondrial membrane depolarization in several types of cancer such as skin cancer cells (melanoma),[85] adenocarcinoma epithelial cells, cervical cancer cells,[86] endometrial cancer cells,[87,88] liver cancer cells, colorectal cancer cells, prostate cancer cells,[89-91] renal cell carcinoma,[92] bladder cancer cells, human nonsmall cell lung cancer,[93] bone cancer cells (osteosarcoma), and leukemia and mouth cancer cells (oral squamous cell carcinoma).[94] In addition, honey could be able to inhibit several forms of tumor in animal modeling including breast cancer, carcinoma, melanoma, colon carcinoma, hepatic cancer, and bladder cancer. However, more studies are needed to improve our understanding of the positive effect of honey and cancer.

Honey and asthma

Honey is commonly used in folk medicine to treat inflammation, cough, and fever.[95] The ability of honey to act in reducing asthma-related symptoms or as a preventive agent to preclude the induction of asthma was showed. Chronic bronchitis and bronchial asthma were treated by oral honey consumption in animal modeling.[95] Furthermore, a study conducted by Kamaruzaman *et al*. showed that treatment with honey effectively inhibited ovalbumin-induced airway inflammation by reducing asthma-related histopathological changes in the airway and also inhibited the induction of asthma.[96] Inhalation of honey was also discovered to effectively remove mucus-secreting goblet cell hyperplasia. However, future studies are needed to investigate these effects of honey to better understand the mechanisms by which honey reduces asthma symptoms.

Honey and cardiovascular diseases

Antioxidants present in honey such as flavonoids, polyphenolics, Vitamin C, and monophenolics may be associated with a reduced risk of cardiovascular failures. In the coronary heart disease, the protective effects of flavonoids such as antioxidant, antithrombotic, anti-ischemic, and vasorelaxant and flavonoids reduce the risk of coronary heart disorders through three mechanisms: (a) improving coronary vasodilatation, (b) reducing the ability of platelets in the blood to clot, and (c) inhibiting low-density lipoproteins from oxidizing. Although there is a wide spectrum of antioxidant types, caffeic acid, quercetin, phenethyl ester, kaempferol, galangin, and acacetin predominate in different types of honeys. Several investigations showed that certain honey polyphenols have a promising pharmacological function in reducing cardiovascular disorders. However, *in vitro* and *in vivo* research and clinical trials should be initiated to further validate these compounds in medical applications.[97]

Honey and neurological diseases

There is important scientific literature for the illustration of nutraceutical agents as novel neuroprotective therapies, and honey is one such promising nutraceutical antioxidant.[16] Honey exerts anxiolytic, antidepressant, anticonvulsant, and antinociceptive effects and ameliorates the oxidative content of the central nervous system. Several studies on honey propose that honey polyphenols have nootropic and neuroprotective properties.[98] Polyphenol ingredients of honey quench biological ROS that lead to neurotoxicity, aging, and the pathological deposition of misfolded proteins, including amyloid beta.[99] Polyphenol ingredients of honey counter oxidative stress through excitotoxins, including quinolinic acid and kainic acid, and neurotoxins, including 5-S-cysteinyl-dopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.[99] Furthermore, honey polyphenols constituents counter direct apoptotic challenges through amyloid beta, methyl mercury induced and retinoid.[100] Raw honey and honey polyphenol reduce the microglia-induced neuroinflammation that is induced through immunogenic neurotoxins or ischemia damage.[101] Most significantly, honey polyphenols counter neuroinflammation in the hippocampus, a brain structure that is involved in memory.[102] Honey polyphenols prevent memory disorders and induce memory production at the molecular level.[102] Several researches propose that the modifications of specific neural circuitry underlies the memory improving and neuropharmacological effects of honey.[16] However, more studies are needed to determine the ultimate biochemical impact of honey on mitochondrial dysfunction, apoptosis, necrosis, excitotoxicity, and neuroinflammation and anxiolytic, antinociceptive, anticonvulsant, and antidepressant activities should be examined in further detail.

Honey and gastrointestinal diseases

Honey has been suggested as potentially useful for various conditions of the gastrointestinal tract, such as periodontal and other oral disorders,[51] dyspepsia, and as part of oral rehydration therapy. *In vitro* studies propose that honey exerts bactericidal activity against *Helicobacter pylori*[103] although a clinical trial of manuka honey therapy to induce *Helicobacter* eradication failed to indicate a beneficial treatment.[104] In addition, honey may be effective as a part of oral rehydration therapy, and as a clinical trial, honey shows therapeutic effects in the treatment of infants and children admitted into hospital with gastroenteritis indicated remarkable reduced duration of diarrhea in the honey-treated patients.[105,106]

CONCLUSION

Sufficient evidence exists recommending the use of honey in the management of disease conditions. Evidence confirming the use of honey in all areas of clinical practice is needed. Studies revealed that the medicinal effect of honey may be due to of its antibacterial, anti-inflammatory, apoptotic, and antioxidant properties. This review should provide practitioner with remarkable evidence supporting the use of honey in the medical field. Although some studies exist having tested the efficacy of honey in relation to medical purposes, more studies are needed to cover all medicinal aspects of honey.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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