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Therapeutic and Medicinal Values of Honey: An alternative therapy

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Abstract

Honey is endowed with many antibiotic agents, immune modulating, wound healing, anti- inflammatory, nutritional and antioxidants particularly phenols and flavonoids. Different diseases mainly life style disorders and metabolic syndromes such as obesity, diabetes mellitus, dyslipidemia, and hypertension are treated by natural origin medicines as compared to synthetic drugs. Honey has been used as an alternative traditional medicine from ancient times and nowadays many invitro studies are reporting the protective effects of honey against several diseases and ailments. The Glycemic index of honey is low in comparison to normal sugar, thus helps in decreasing the blood sugar levels and prevents the weight gain. Lipid metabolism and insulin sensitivity is also enhanced by stabilizing the glucose levels in blood, thus prevents the pancreas from getting over stimulated. Anti-oxidants present in honey helps in manintaining the oxidative stress. Apart from medicinal uses honey has been explored traditionally for the treatment for ulcers, caries, sore throat and skin infections. Thus honey has a strong potential in maintainence of several metabolic disorders. This review aims to highlight the therapeutic values of honey eitherutilized alone or as adjunct therapy.

Keywords: Honey, antibacterial , antioxidant, obesity, diabetes and therapeutic values.

1. Introduction

Honey is the purest and most valuable natural food product obtained from honeybees. Most popular type honey used are Eucalyptus honey, Lychee honey, Sunflower honey, Rapeseed honey, Karanja honey, Multi floral Himalayan honey, Acacia honey, Forest honey and European honey (Manuka) [1]. Morethan 150 substances are present in honey in which main component is fructose and glucose as well as fructo-oligosaccharides other sugars such as maltose, sucrose, isomaltose turanose, nigerose, meli-biose, panose and maltotriose are also present[2].Almost all types of honey contains flavonoides e.g. apigenin, pinocembrin, kaempferol, quercetin and galangin also phenolic acids such as ellagic, caffeic, p-coumaric and ferulic acids), ascorbic acid, tocopherols and catalase. Most of those compound works together to provide a antioxidant effect [3]. It is considered as the chemical combination of inorganic and organic components like proteins, sugars, vitamins, amino acids, enzymes, organic acids, minerals, pigments etc. Water is the second most important component present in honey. Acidity of honey and its characteristic taste is attributed to the presence of organic acids. The main metal present in honey is potassium followed by calcium, magnesium, phosphorus etc and re present inbeteen the range of 0.1% to 1.0 %. Enzymes such as oxidase, invertase, amylase, catalase, etc. are found in honey but mostly enzymes like invertase, distase, amylase and glucose oxidase are present [4]. These enzymes play an vital role in the production of honey, glucose oxidase produces hydrogen peroxide with gluconic acid from glucose that supports in calcium absorption. Antimicrobial property of honey is due to the production of hydrogen peroxide. Long starch chains of mylase produces dextrin and maltose while as catalase

produces oxygen and water. Honeybees *(Apis mellifera*) produce a sweet natural substance known as honey, the nectar can be collected from flowers by honeybees before converting it to a nutritious food and is added to numerous beverages and foods as flavoring as well as sweetening agent [5]. The unique properties and their different mechanism such as elevated pH and enzyme activity makes honey inimitable constituent to kill and prevent the growth of microbes. Different properties such as antioxidant, anti-cancerous and anti-inflammatory are found in honey. Apart from acting as an anti-inflammatory drug, it could find application in the protection of liver from the degenerative effects of several drugs. Its immunomodulatory property is also related to wound healing [4].From the very ancient times honey was used for both nutrional and medicinal applivcations and is believed to have very effective healing and antimicrobial property. Antibacterial activity of honey is attributed to presence of hydrogen peroxide and viscous nature that aids prevention of infection, acts as a barrier for maintenance of moist wound condition, ultimately facilitates the healing property due to spatial as well as temporal difference in the nectar source. Honey is known as conventional oldest traditional medicine that is used to treat many infectious diseases and human disorders [6-7]. It has been studies that honey can be used for curing the oral bacterial spoilages as well as pathogenic spoilage[8]. Manuka honey (*Leptospermum scoparium*) is considered as very popular type of honey produced by European honey bees having an inhibitory effect on 60 bacterial species [9] and is under study for its potential activity against E.coli and S.aureus [10]. Honey is heat stable, light and hygroscopic in nature and it dehydrates bacteria by removing out moisture from the environment. Bioactive potential of honey depends upon its origin and species of honey bees and type of feed. Several studies conducted on honey revealed that it exert many health promising effects such as antioxidant, anti-inflammatory, anti-

diabetic, protection against nervous system as well as cardiovascular etc [2]. The main aim of this review is to highlight the therapeutic benefits of honey.

2. Physico-Chemical Composition of Honey

The honey components are plant origin and are synthesized by bees and some components are formed during maturation of honey by biochemical reactions [11]. The quality of honey depends upom the flowers consumed by honeybees as well as regional beekeeping practices and climate variances. Chemical constituents present in honey are mainly natural sugars, minerals, free amino acids, phenolic components, essential oils, sterols, pigments, hormones, vitamins etc [12]. Different chemical and physical components present in honey are studied for several important quliaties apart fron its quality in composition and taste. The viscosity of honey depends upon the several componets and their compostion as well as water content. Ability of honey to absorb moisture around its environment depends upon its hygroscopicity[13].Physical and chemical quality of honey depends upon the its components such as moisture content, sugar content, and protein content etc.

2.1 Carbohydrates

Honey is the main source of sugar and contains nearly 200 substances of which monosaccharides constitute about 75% and disaccharides about 10% to 15% and all other sugars in small quantities as shown in Figure 1. The viscosity and the energy value of honey are imparted by sugars in the honey[3].The composition of sugar in the honey varies with the origin of the nectar, climate, topographical nature, and processing storage conditions. Fructose and glucose apart from the other sugars present in less proportion like trehalose, lamina ribiose, raffinose, turanose, erlose, kojibiose, rhamnose, melibiose, maltose and others [4-14].

2.2 Amino Acid and Proteins

The Protein content in the honey varies with honey species, 0.1% to 3.3% of the protein is found in the *Apiscerana* species and 0.2% to 1.6% is found in *Apis mellifera* honeybee species[15]. Proline is one of the most dominating amino acid (50% - 85%) found in honey apart from the proline other amino acids are found in honey includes aspartic acid, glutamic acid, glutamine, lysine, cysteine, valine, methionine, leucine, and alanine with a small portion of enzyme presence like glucose oxidase, catalase, diastase, α- and β-glucosidase and invertase [11].

2.3 Moisture Content

Water activity varies with climate, season, sampling, as well as processing method, but various studies reveal that origin of the nectar have high impact on the moisture content of honey[11]. Therefore, it has been found that the honey harvested from the tropical areas has a high moisture content [16].The decrease in microbial activity and the increase in stability of honey from granulation and fermentation is attributed to its low moisture content [17].

2.4 Aroma Compounds, Phenolics and organic acids

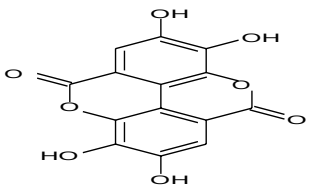
Phytochemicals such as flavonoids and phenols are present in honey including the polyphenols like ferulic acid, vanillic acid, caffeic acid and syringic acid, flavonoids like chrysin, pinocembrin, Kaempferol, quercetin and apigenin. It has been reported that antioxidant and medicinal effects of honey are due to presence of flavonoids and phenolic acid. Antioxidants like vitamin C, tocopherols, dismutase, and superoxide having distinctive medicinal and nutritional properties and the combined effect of all these components extends the vast applicability of the honey [18].Different studies had reported the presence of almost 400 - 600 different volatile compounds of different botanical origin, which produce separate flavor in honey [3]. Studies also reported that

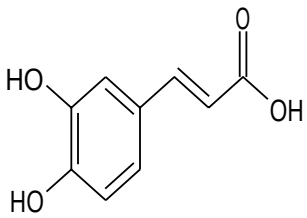
honey from arid regions produced high levels of polyphenols than the non-arid regions[19].The most significant group of compounds present in honey are known as organic acids which imparts the characteristic flavor of honey and are are derived from the sugars by enzymatic action secreted by bees during honey formation [20-21]. Honey contains many acids like butyric acid, succinic acid, formic, glutamic, glyoxylic, aspartic, malic, pyruvic, lactic, propionic etc. although predominant being the gluconic acid [22].

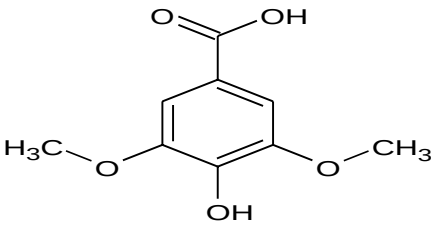
2.5 Minerals And Trace Elements

Honey is considered to possess valuable minerals like potassium, magnesium, calcium, manganese, phosphorus copper, iron, silver, barium, cadmium, lithium, zinc, sodium, and cobalt [23-24]. Many studies reported that the Malaysian based honey have appreciable percentage of potassium mineral in addition to calcium, sodium, magnesium, and iron [16]. In dark and light honeys, the content of mineral varies from 0.02% to 0.04% respectively [3]. The percentage of vitamins in the honey is very less, and the preservation of most common vitamin in honey like vitamin C in addition to the riboflavin, pantothenic acid, pyridoxine, thiamine, folic acid, biotin, and nicotinic acid is attributed to lower pH of honey [25]

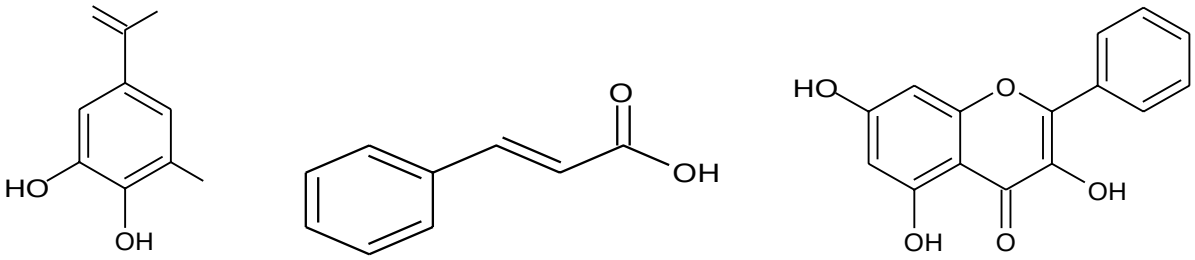
A. Ellagic Acid **B. Caffeic Acid** **C. Syringic Acid**







D. Gallic Acid **E. Cinnamic Acid** **F. Kaempferol**



G. Quercetin **H. Luteolin**

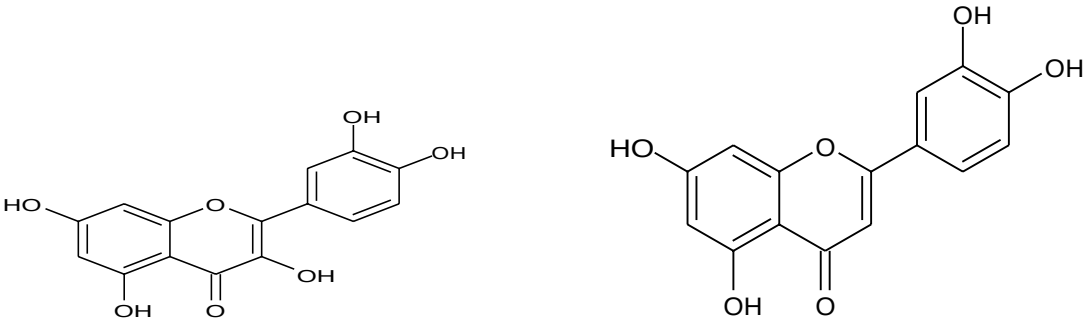


Figure A-H representing the structure of phenolic compounds in honey

3. Nutritional and non-nutritional compounds of honey

Approximately 300 varieties of honey have been identified till date [26] and are characterized on the basis of variation in nectar source collected by the honeybees. The honey is composed of vitamins, amino acids, organic acids, proteins, and minerals apart from the presence of reducing components, glycosides, anthraquinone, alkaloids, cardiac glycosides etc. in the pure honey [27]. The honey possesses the key essential sugars (monosaccharides) which impart the desirable nutritional and physical property to it [28]. Honey is currently processed in two varieties across

the globe, traditional Apis mellifera honey as well as stingless bee honey. Honey includes macro and micronutrients that are dependent on a number of factors: A) species of bee , B) floral source, and C) processing and environmental aspects. Honey contains around 200 compounds, including sugar, protein, enzymes, minerals, vitamins, amino acids, and a variety of other substances. Each honey has a varied colour, flavour, viscosity, and therapeutic activity due to the various ratio of these chemicals. As a result, the mixture of all these chemicals works synergistically in many applications. The physical features and chemical content of most honeys around the world are nearly identical [29]. The presence of laminaribiose, galactose, sucrose, gentiobiose, beta-trehalose, trisaccharides (panose, maltotriose, isomaltose glucose, melezitose,1-ketosetheanderose, isomaltotriose, maltopentaose, centose and isopanose) and oligosaccharides in honey is reported in trace quantities [30]. These sugars are formed during maturation and ripening of honey. Gluconic acid is the major organic acid present in honey including trace amount of formic, citric, and acetic acid. For the acidity (pH between 3.2 and 4.5) of honey, some organic acids are responsible[31]. Honey is the reservoir of amino acids excluding asparagine and glutamine. The presence of enzymes like acid phosphatase, catalase, invertases and glucose oxidase is mainly found in honey as major constituents [32].

The presence of heavy metals like arsenic, cadmium, and lead are also reported in honey [33]. Near about 600 volatile components have been reported to be present contributing to its biomedical effects [34] Components that are volatile in nature are present in very low quantity but hydrocarbons, aldehydes, acid esters ketones, terpene and its derivatives, alcohols, benzene, and cyclic components are also present in high quantity[35]. The flavonoid and phenolic components in honey contains syringic acid, gallic acid, ellagic acid, cinnamic acid, chrysin, chlorogenic acid, caffeic acid, ferulic acids, coumaric acid, naringin, apigenin, Kaempferol, quercetin, catechins,

and luteolin [36]. Aroma is one of the most distinctive attributes of a food, both for its organoleptic and authentic quality. Its origin is determined due to the large number of volatile compounds, a ‘‘fingerprint’’ of the product is represented by the aroma profile [37].Flavour of honey is one of the significant attributes of honey making it suitable for the application in food industries and for the consumer’s choice it is also a selection criterion.

4. Functional properties of honey

4.1. Antibacterial effect of honey

According to the different clinical trials and in vitro study reports broad-spectrum antimicrobial properties of honey were observed. It was found that the growth of infecting strains e.g. *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumonia* in were declined in rats with burn wound[38].The presence of inert antibiotic factors such as acidic pH, osmotic effects of sugars, presence of hydrogen peroxide by peroxidase influence the antibacterial effect of honey.Substances such as flavonoids, phenols also support antibacterial activity. High sugar congtent in honey also eliminates the bacteria growth by process known as osmosis [39]. Reports have revealed thar there are two mechanisms behind the antimicrobial acitivity of honey: inhibition of bacterial quorum sensing (QS) system to retard the expression of *las, MvfR,* and *rhl* regulons and its associated virulence factors as well as bactericidal components which actively kill bacterial cells [40].Methylglyoxal present in honey and its precursor dihydroxyacetone are reported as inhibitors of bacterial growth by inhibition of urease. Urease enzyme facilitates bacteria to acclimate and grow rapidly by producing ammonia in acidic environment[41].Antimicrobial activities of different types of honey were tested against human pathogenic microbes, like *Enterobacter cloacae, Escherichia coli, Klebsiella spp, Pseudomonas aeruginosa* and *Shigella*

dysenteriae. Suitable and systemic antibiotics (oflaxocin) and honey applied on wounds four times a day were studied with comparing to control values. The growth of isolates was inhibited by 30–100% honey concentrations [42].

4.2. Antioxidant activity

It has been reprted that honey inacreses the level and amount of antioxidant agents in healthy human being in the form of beta-carotene, vitamin C and glutathione reductase.The basic mechanism of antioxidants are not known but it is may be sequestration of free radica,oxide radical actions, metallic ion chelation or hydrogen donation[43].Oxygen plays an important key role as antioxidant, prevents damage inside the human body and prevents the oxidative reactions in foods [44]. Although, in human body the function of natural antioxidants has not been authenticated but the studies showed that a natural honey functions in various ageing and process ingredient derived from O_2 called as reactive oxygen species (ROS) and free radicals generated during different metabolic activities.Antioxidants has significant role in scavenging of free radicals prior to their risk of causing undesirable reactions. Both non-enzymatic and enzymatic constituents serve as protective antioxidants [45]. The antioxidant property of honey is associated to its brightness; thus, honey is having hazier color is considered to be the potential antioxidant. Antioxidant property of honey is due to phenolic compound since the phenolic content is associated with free radical scavenging activity of honey The other study reveals that the antioxidant property is associated with the combination of various bioactive components present in honey. Therefore, honey is considered to be strong dietary antioxidant. As per the scientific reports, honey is used in traditional therapy that controls different disorders related to oxidative stress [46].

4.3. Apoptotic activity

Cancer cells have been characterized by uncontrolled cellular proliferation and inappropriate apoptotic turnover [47]for cancer treatment chemicals that are applied are apoptosis inducers depolarization of mitochondrial membrane occurs in various kinds of cancer cells due to apoptosis by honey[48].Honey enhances poly (ADP-ribose) polymerase (PARP) cleavage and caspase 3 activation in colon cancer cell lines that is associated to its higher phenolic compound. Furthermore, apoptosis occurs by modulating the expression of anti- and pro-apoptotic proteins in colon cancer.Honey encourages caspase and proapoptotic protein Bax expression and downregulates anti-apoptotic protein expression [49].

4.4 Immunomodulatory and anti-inflammatory activities

In the current literature it has been reported that honey decreases inflammatory response in animal models, cell cultures, and clinical trials [50].Chronic inflammation could prevent healing by destroying tissues. These components cause inhibition of the pro-inflammatory activity of cyclooxygenase-2 (COX-2) and/or inducible nitric oxide synthase (iNOS) (Viuda-Martoset al., 2008). Honey and its ingredients are considered to regulate proteins like ornithine decarboxylase, COX-2, iNOS, and tyrosine kinase. Several types of honey have been used to induce tumor necrosis factor alpha, IL-6 productioninterleukin-1 beta (IL-1β) etc.[51]. Honey augments the production of B and T lymphocytes, eosinophils, antibodies, monocytes, neutrophils, and natural killer cells generation while secondary and primary immune responses in cell culture[52].

4.6. Antifungal activities

Honey has strong anti-fungal activities that can be used at a minimal cost and with no risk. Several causative agents, including yeasts and filamentous fungi are increasing the occurrence of fungal infections in both the community and hospital environment. Because the enzyme glucose oxidase,

oxidases glucose to gluconic acid and hydrogen peroxide, is activated when most varieties of honey are diluted, they produce hydrogen peroxide. Honey's antibacterial activity is mostly due to hydrogen peroxide, and variable amounts of this molecule in different honeys result in diverse antibacterial effects.Honey's antifungal efficacy in vitro has been demonstrated to inhibit the growth of Candida albicans, Candida krusei, and Cryptococcus neoformans. The antifungal activity of honey distillate with some antimycotic treatments against *C. albians* and discovered that the active part of honey distillate inhibits all strains resistant to standard antimycotic drugs [53]. Jujube honey has great potential to fight against honey such as *C. albicans* and is also potential to prevent the growth of *C. albicans* biofilms [54]. It has been shown recently that various extracts obtained from plants along with honey synergize the antifungal characteristics of honey [55].

4.7. Bioburden

A considerable antimicrobial activity against wound pathogens has been reported by honey and against biofilm created on wounds by bacteria[56].A biofilm is defined as a bacterial colony existing within a self-produced extracellular polysaccharide matrix which prevents them from phagocytic and antimicrobial onslaught. Moreover, recalcitrant wounds are treated by honey and is effective against numerous resistant microbes like methicillin resistant *Staphylococcus aureus,* multi-resistant *Pseudomonas aeruginosa* and vancomycin-resistant *Enterococci* [57]. The above discussed biological activities of honey is also shown in Figure 2.

4.8 Immunity and hematology

Honey has been proven to be effective against the anemia. Californian study showed that population consuming honey have excellent blood proliferation as well as haemato protection

[58].Some researchers have also proposed that honey can preserve the aqueous component of the blood. This may be because maximum antioxidant compounds are water soluble. Therefore, it is concluded that honey is supposed to be one of the acceptable immuno-nutrients, As a result, honey is thought to be one of the approved immuno-nutrients; some researchers even believe that honey eating may contribute to increased antibody synthesis[59].

4.9 Hypertension and dyslipidemia

Dyslipidemia constantly increases the risk of atherosclerotic cardiovascular disease. Honey intake was shown to reduce cardiovascular risk factors. In addition, several investigations studies have found honey has an anti-lipedema effect that is aided by HMG-CoA reductase inhibition [60]. In comparison to the control group of rats, animals administered honey showed a reduction in blood cholesterol and triglycerides [61].Honey has been shown to have favorable or prospective effects in the gastrointestinal tract (GIT), gut microbiota, liver, and pancreas, and these benefits may help with glycemic control and metabolic disorders. Honey's anti-diabetic or hypoglycemic properties may be due to fructose that has been demonstrated to promote hepatic glucose phosphorylation via glucokinase activation while inhibiting glycogenolysis via phosphorylase suppression. In diabetic and non-diabetic people, fructose treatment increased hepatic glycogen production through activating glycogen synthase[62].Obese people may show hypertension due to distinctive variables: expanded actuation of the thoughtful apprehensive framework with resulting vasoconstriction and expanded cardiac output because of elevated leptin-levels the thoughtful apprehensive framework with resulting vasoconstriction and expanded cardiac output because of elevated leptin-levels and higher sodium retention by renal tubules[63-64] endothelial dysfunction and renal oxidative stress[65].It was studied that the decrease in cardiovascular risk

postmenopausal women by honey supplement for 12-months. Honey supplementation over 12 months reduced cardiovascular risk in postmenopausal women, according to research. In another study, lower chances of prehypertension in women by the slight regular intake of honey was observed in the Chinese populations [66]. Honey polyphenols might represent an appropriate constituent for the cardiovascular health due to ameliorate cardiovascular disease [67].The characteristics attributed to flavonoids and its derivatives are largely incontestable in animal models or cell cultures, results could facilitate to reports of mechanisms by honey exhibits its useful effect against CVD. Kaempferol and quercetin can induce protective effect on CVD by:

(1) Activation of Ca^{2+}-activated K^{+} channels will stimulate relaxation of arteries [68].

(2) Regulation of eNOS with stimulation of the NO/cGMP pathway[69].

(3) Vessels protection against hypochlorous acid–induced endothelial by activation of adenosine monophosphate protein kinase and subsequent enhance in NO production[70].

(4) Activation of NF-κB and decreased TNF-α production, with the consequent inhibitory action on cell adhesion and migration to endothelial [71].

5.3.Neurodegeneration

A risk factor that has been identified for Alzheimer Disease (AD) is Midlife obesity. Diet rich in cholesterol, reduction in physical activity and the dullness in lifestyle gives rise to Alzheimer disease. The rapid increase in the neuro inflammation and memory dysfunction due to the diabetes type II as consequences of obesity has been reported. Some studies suggest the escalated chances of Alzheimer Disease AD by chronic presence of pro inflammatory cytokines due to obesity. Neurotoxins and inflammatory components come out from activated astrocytes, neurons,

microglia, and T-cells resulting in neurodegeneration. Also, the oxidative stresses have direct effect on neuro

inflammation. Huge levels of reactive oxygen species ROS related with enhanced inflammation levels and Alzheimer Disease AD biomarkers have been observed in brain of high fat diet induced mice. It has been observed that after obesity, cognitive dysfunction could lead to oxidative stress. 1g/kg honey was fed orally within 12 hours with five frequency cycles showed reduced neuronal degeneration in rat which resulted in attenuated hyperactivity and the increment of KA-induced thiobarbituric acid reactive compounds, inflammatory markers (glial fibrillary acidic, IL-1β, allograft inflammatory factor 1, cyclooxygenase 2and protein) and caspase-3 activity[72].The oxidative stress was inhibited by the consumption of 1–1.5 ml/kg body weight for 28 days and neurobehavioral deficit in the lead-induced neurotoxicity rat model due to an increased anti-oxidative activity. In another investigation it was observed that the acetylcholinesterase activity and oxidative stress levels got decreased and brain-derived neurotrophic factor concentration got increased due to honey intake[73].The improvement in cognitive drop linked aging and memory loss was seen in animal studies by honey intake. The existence of flavonoids such as naringin, catechins, apigenin and luteolin and phenolic acids like benzoic, Gallic, p-coumaric and syringic in the honey increases its antioxidant activity and beneficial properties. It has been revealed that consumption of honey increased power of memory and learning ability due improvement of cholinergic system also prevention of neuro inflammatory and microglial activation.

4.10 Cardiovascular diseases

Antioxidants in honey like polyphenolics, mono phenolics and ascorbic acid may be related to a decreased risk of cardiovascular disease. Flavonoids and antioxidant compounds present in honey decrease the threat of coronary heart diseases. These heart disease risks are reduced by following

mechanisms (a) by improvement in coronary vasodilatation (b) by declining the capacity of blood platelets from clotting, and (c) by preventing oxidation of lipoproteins with low density. Several different kinds of antioxidant such as quercetin, caffeic acid, galangin, phenethyl ester are present in honey. Various research exhibited that several honey have potential pharmacological function in declining the cardiovascular diseases. Moreover, different research including clinical trials are required to be carried out to authenticate these components for curative purposes[74].

4.11 Asthma prevention

The most common uses for honey are to treat inflammation, fever, as well as cough. Honey has also been proven to be effective in reducing asthma-related symptoms and acting as a protective agent against asthma induction. In animal models, honey is used to treat bronchial asthma and chronic bronchitis.Honey can also help to reduce asthma symptoms by reducing inflammation caused by ovalbumin induction. Honey inhalation was also found to effectively remove goblet cell hyperplasia that secretes mucus. While future research will continue to look into the impact of honey on the mechanism of action by which honey suppresses asthma symptoms[75].

4.12 **Anti-obesity**

Obesity is regarded as the one of the central occurrence among the metabolic syndromes with the accumulation of fat known by increased waist diameter. Excess consumption of sugars and carbohydrates and harmonal imbalance are the main reasons for obesity as well as unused energy that gets stored in th body will lead to deposition of fat. Several invitro studies have proven their protective effects against obesity. Rats were fed honey for short period of time which resulted in less weight gain as compared to those who were fed with sucrose and sugar diet mixture with no difference in the total energy gain. Similarly admintration of honey for more than 6 months

decresed weight gain and prevented overall gain [76].Further demonstration about anti-obesity effect of honey was given by[it was reported that 20% carbohydrate diet from honey decaresed the weight gain as well as fat pad weight gain was reduced in comparision to rats fed with liquid sucrose[77].

5. Mechanism of action of honey in treatment of diseases

Different studies on honey have demonstrated its widespread antimicrobial activity [10]. Many studies showed that application of honey has led to inhibition of fatal microorganisms *Streptococcus typhi, Streptococcus pyogenes, Staphylococcus aureus, Streptococcus and E.coli.* Significant healing of burns in rats with fewer growth of infectious bacteria such as *Acetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumonia* can because of antibiotic factors such as osmotic effect of sugars, pH, and release of H_2O_2.Phenolic acids, flavonoids and lysozyme also expand the antibacterial activity of honey[78]. High sugar content in honey acts as a key factor in the eradication of bacterial load by osmosis [79].In urease inhibition the dihydroxyacetone (DHA) precursor of Methylglyoxal (MGO) in honey contributes to the inhibition of bacterial growth. The enzyme urease is responsible for the promotion of bacterial growth by production of ammonia[80]. Antibacterial action of honey depends upon two basic mechanisms comprising killing of bacterial cells and honey quorum sensing (QS) system both decreases the expression of *MvfR, las* and *rhl* regulons [81].Biofilm is commonly known as main factor that is responsible for resistance of antibiotics. Usually microbes have been protected by biofilms from most of the infections. Honey functions as a bactericidal negotiator, eradicates colonies, cures aggressive infection, and penetrates in biofilms [82]. It is used to treat wounds, inhibits biofilm colonization, interrupts outbreak, prevents invasive infections, and hence helps to preserve current antibiotic stocks[83].The linkage of tissue fibronectin and bacterial strains at the infection spot helps

prevention of biofilm growth and also reduces the fibronectin binding surface proteins that are vital for bacteria to bind with fibronectin [84].The repression of biofilm formation is attributed to the sugar levels (fructose and glucose) of honey. The honey has the wide application in the treatment of some serious health problems including wound and burns[78].

Interventions in the application of honey in wound healing for the inhibition of bacterial growth and removal of necrotic tissue has been reported [79].The studies suggested the rapid rise in the formation of TNF-α and IL-6 by honey near the wound spots in the method of healing in IL-6-deficient mice. It is believed that the high sugar content of honey and its osmolality further provides impetus in the wound healing by draining out water from the wound [85].One of the investigations suggested that oxidative stress is boosted by triggering antioxidant enzymes and AMPK in honey resulting in wound healing property through the mechanism of antioxidant reaction. There are two types micronutrients present in the antioxidants system of honey i.e. exogenous contains few micronutrientswhile as endogenous antioxidants containenzymatic antioxidants likeglutathione peroxidase and non-enzymatic antioxidants and catalase like glutathione,vitamins C and E. Such antioxidants also facilitate human dermal fibroblast proliferation, migration, and mitochondrial activity to assist healing[67].

8. Conclusion and Future prospects

Honey is known as one of the most important natural products with multiple medicinal and food uses from very ancient period across the world.Nowdays more attention is paid to the medicines obtained from natural sources as compared to the synthetic drugs. Honey has got its imporatance in traditional system of medicine also and has been accepted as an effective therapy for different ailments due to its high nutritional and therapeutic potential. Among all antibacterial activity is well known effect followed by inhibitory effect on yeast, fungi, leishmania and some viruses.

Superficial administration of honey has shown its effect on several skin and mucous membrane including skin burns and post perative wounds.Apart from this honey is also used in gastrointestinal, cardiovascular, inflammatory and neoplastic states and these effects depends upon the botanical origin of honey bee and bio availability of the constituents present in honey. Thus honey can be consider as strong potrential agent that can be explored in the management of several diseases including life style disorders with adjunct therapeutic agent..Moreover, the incorporation honey in different food products particularly in beverages can play an essential role to develop functional beverages and other value added products.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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