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Pharmacological Insights and Therapeutic Potentials of Honey; An Updated Review

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ABSTRACT

A natural sweetener, honey has innumerable pharmacological properties in addition to its nutritive value. Honey has been in human use since 8000 years and has been traditionally used by almost all systems of medicine including Islamic medicine. Although chemical composition varies according to the botanical source, carbohydrates constitute a major portion of its composition. Fructose is in abundance followed by glucose. There are many other constituents present in small amounts like proteins, enzymes, amino acids, minerals, trace elements, vitamins, aromatic compounds and poly-phenols which contribute to various medicinal properties of honey. Honey has been in use traditionally for treatment of various ailments like gastritis, diarrhoea, ophthalmic conditions, skin infections, wounds etc. Enough evidence is now present supporting antimicrobial, antioxidant, wound healing and other potentials medicinal properties of honey. We systematically searched published papers on the subject in the databases of Web of Science, Scopus, PubMed, Science Direct, Crossref and Google Scholar between 1st January 2000 and July 2022 with an aim to review pharmacological and therapeutic potentials of honey. Owing to investigated pharmacological and therapeutic potentials of honey we conclude that honey can be looked upon as a safe and efficacious alternative in management and prevention of various disorders.

Keywords: Honey, Pharmacological, Therapeutic, Antimicrobial, Antioxidant.

INTRODUCTION

Honey, a sweet viscid plant bi-product, is formed when various species of honey bees (Apidae; Hymenoptera) gather nectar and sweet deposits from plants, which is afterwards stored and modified in honeycombs. Considered to be one of the natures wonder, honey is composed primarily of the glucose, fructose and water. It also contains other carbohydrates, acids, vitamins, proteins and minerals. Alkaloids, anthraquinone, glycosides, cardiac glycosides, flavonoids & reducing compounds are also present in pure honey. [1-2] Honey has been in use since time immemorial around the world, for both nutritional and therapeutic purposes. Use of honey in the treatment of several human ailments ranging from common cold to infected wounds has been documented in various ancient medical manuscripts including that of Unani Medicine. [3-4] Many medicinal properties have been attributed to honey including thoroughly investigated antimicrobial, anti-oxidant and wound healing effects. In recent times information on the applicability of honey for management of human disease is available in general magazines, journals and natural product leaflets. Many researchers around the world have reported antibacterial, antioxidant, nutritional and wound healing properties of honey and have concluded that a number of disorders respond well to the

treatment of honey and justified use of honey in these disorders.[5-6]

With an aim to review various pharmacological and therapeutic potentials of honey, databases of Web of Science, Scopus, PubMed, Science Direct, Crossref and Google Scholar was systematically searched for published papers on the subject. A combination of keywords and MeSH terms (online supplementary material, extended methods) was used. The papers were included only if they were published between January 2000 and June 2022. Only Papers published in English language were included. We also hand searched the bibliographies of included papers for relevant studies. Several combinations of the following English-language search phrases were employed to search the electronic database: honey, composition, history, pharmacological, therapeutic, antimicrobial, antibacterial, antiviral, antifungal, anti-Oxidant, ROS, anti-diabetic, cough, wounds, dressing, antidiarrheal, gastritis, gastric ulcer and infections.

ANTIMICROBIAL:

The use of honey as a traditional remedy for microbial infections dates back to ancient times. Aristotle (384-322 BC), while discussing different honeys, referred to pale honey as being "good as a salve for sore eyes and wounds".[7] Antimicrobial activity of honey can be attributed to a number of its characteristics including enzymatic glucose oxidation reaction and some of its physical properties. Other factors that contribute to its antimicrobial activity include high osmotic pressure/low water activity (Aw), low pH/acidic environment, low protein content, high carbon to nitrogen ratio, low redox potential due to the high content of reducing sugars, a viscosity that limits dissolved oxygen and other chemical agents/ phytochemicals. [8] All types of honey are not equal in antimicrobial activity owing to the differences in levels of peroxide production and non-peroxide factors, which vary according to floral source and processing. Studies on antimicrobial activity of large numbers of honey samples illustrated a wide array of activity and many with only a low level of activity. [9-12]

Antibacterial: -

Anti-bacterial activity of honey was first demonstrated by Dold et al in 1937 and they recognised 'inhibine' as the substance which inhibited bacteria. [11] It was later suggested that hydrogen peroxide could be the substance responsible for the antibacterial activity of honey. [13] A wide variety of microorganisms including bacteria, virus and fungi have been found to be sensitive to honey.

Many reports have evolved supporting bactericidal and bacteriostatic activity of honey particularly against antibiotic resistant bacteria. [14] Research has been conducted on manuka (*L.scoparium*) honey, which has been demonstrated to be effective against several human pathogens, including *Escherichia coli , Enterobacter aerogenes, Salmonella typhimurium, Staphylococcus aureus*. [11-12,15-16] Laboratory studies have revealed that honey is effective against methicillin-resistant *S.aureus* (MRSA), haemolytic streptococci and vancomycin resistant enterococci (VRE).[14,17-18] A comparative study was carried out between the physico-chemical properties and antibacterial activity of honey produced by honey bees *A. mellifera* and Melliponinae (stingless bees) in Brasil.[19] For both types of honey at a concentration of 5-25%, *Bacillus stearothermophilus* was found to be the most susceptible and *E. coli* the least susceptible of the seven bacterial isolates tested (the other five being, *B. subtilis, B. subtilis Caron, Staphylococcus, Klebsiella pneumoniae* and *P. aeruginosa*). A recent study documented the sensitivity of multiresistant strains of *Burkholderia cepacia* and *P. aeruginosa* to manuka honey at concentrations ranging from 4 to 7.3 % w/v. *P. aeruginosa* and *Burkholderia spp.* are important opportunist bacteria that can cause serious and chronic respiratory

infections in vulnerable patients, especially those with underlying conditions such as cystic fibrosis or chronic granulomatous disease and are also responsible for bacteraemia, urinary tract infections and wound infections in hospitalized patients. [20]

Antiviral:

Viruses like Herpes have been shown to be susceptible to honey treatment.

A study comparing honey, royal jelly, and acyclovir against HSV-1 concluded that with no reports about their deleterious effect at least in laboratory conditions, honey can be considered alternative to acyclovir in the treatment of herpetic lesions.[21] In another study conducted to investigate, the effect of honey extract Camelyn against SARS-Cov-2 showed that Camelyn is not cytotoxic, has a stimulatory effect on cell proliferation, and has an inhibitory effect against SARS-CoV-2.[22] These results may well justify the continued use of honey in traditional systems of medicine and in some of the modern medicine.

Antifungal:

Various in vitro studies have concluded that honey has a considerable amount of antifungal activity. A study to evaluate antifungal action of three single samples of honey (wasbessie, bluegum and fynbos) against *C. albicans* and found honey to inhibit the growth of *C.albicans*.[23] The Nigerian honey has the potential to prevent the growth of a wide range of possible human pathogens which include some species of moulds and yeasts.[24] Four Algeria honeys of different botanical origin were analysed to test antifungal effect against *C. albicans*, and *Rhodotorula sp.* This study demonstrated that, *in vitro*, these natural products have clearly an antifungal activity against *Rhodotorula sp*. and *C. albicans*.[25] These studies considerably support that honey can be a potential topical antifungal agent.

ANTIOXIDANT: Metabolic processes within the human body produce highly reactive compounds derived from oxygen, called free radicals and reactive oxygen species (ROS). Although ROS have important role in pathogen resistance and cellular signalling, they are also broadly recognized as harmful reactive particles to cell as they damage intracellular proteins, lipids and nucleic acids and may result in cancer, heart disease, stroke, cataracts, Alzheimer's, arthritis and some of the old age symptoms.[26-29] Antioxidants intercept free radicals before they can do damage and employ both enzymatic (such as catalase) and non-enzymatic substances (such as tocopherols, phenolics, flavonols, catechins, ascorbic acid and carotenoids).[29]

Significant antioxidant activity has been found in honey. Its antioxidant property has been attributed largely to glucose oxidase, catalase, ascorbic acid, flavonoids, phenolic acids, carotenoid derivatives, organic acids, amino acids and proteins present in honey. [30-34] It is floral source and variety of honey that determine the amount and type of antioxidant compounds in it. Darker honeys have been shown to contain higher antioxidant content as compared to lighter honeys. [35]

Studies were carried out to know the antioxidant activity of different honey samples and it was reported that antioxidant ability of Buckwheat honey was higher as compared to Honeydew, Chestnut, Mankua and mixed varieties of honey. The antioxidant activity of buckwheat honey was also studied in vivo where it was found to increase the antioxidant capacity of human serum. [36] In a study diet added with a daily honey serving of 1.2 g/kg body weight was given to trial group. Honey improved blood concentrations of antioxidant agents: like vitamin C, carotene, uric acid and glutathione reductase.[37]

Using Oxygen Radical Absorbance Capacity (ORAC) different honey types were investigated for in vitro antioxidant capacity and total phenolic content. ORAC values for different types of honey ranged

between 3.1 to 16.3 mmol Trolox equivalent/g honey, darkest having the highest values. The results demonstrated that that honey may be used as a healthy alternative to sugar in many products and thereby serve as a source of dietary antioxidants. [38]

WOUND HEALING:

Use of honey as a wound dressing has been in vogue since time immemorial. It was only in 1930s and 1940s, when the synthetic antibiotics took over and honey became a thing of literary attention. However, today enough evidence is available with regard to the wound healing capabilities of honey, confirming its importance as an antimicrobial agent and a promoter of healing. [39]

Wound healing activity of honey has been attributed mainly to its antimicrobial activity. Honey prevents wounds from getting infected thereby promoting healing. However, other therapeutic properties of honey including stimulation of the healing activity, clearance of infection, detergent action on wounds, promotion of tissue regeneration, anti-inflammatory effect and the comfortable dressings due to absence of adhesion to the tissues, accredit its use as a wound dressing.[40]

Comparing secondary intention healing of wounds treated daily with a topical application of hyaluronic acid (HA), Manuka honey (MH), Acemannan gel (AG), or a placebo on bilateral wounds that were surgically created on the backs of six sheep. Biopsies obtained at two- and six-weeks post-wound creation, indicated treatment with AG resulted in wound dehydration and stimulated late granulation tissue and cell proliferation while MH-treated wounds were slightly dry. However, the main effect of MH was to promote cell proliferation and neovascularization, with an overall pro-inflammatory effect thereby suggesting that MH treatment enhances the healing process.[41] Application of honey on wounds caused rapid tissue debridement, stimulated quick epithelialization, and decreased the development of oedema, resulting in quicker healing. Furthermore, the production of hydrogen peroxide stimulates VEGF and sterilizes the wound.[42] Acidity in honey increases the release of oxygen from haemoglobin thereby making the wound environment unfavourable for the activity of destructive proteases, and the high osmolarity of honey draws fluid out of the wound bed to create an outflow of lymph as occurs with negative pressure wound therapy. [43] Evaluating the potential antibacterial properties of Tualang honey dressing and to determine its effectiveness in partial thickness burn a study reported its usefulness as a wound dressing due to its bactericidal and bacteriostatic effects.[44]

ANTIDIARRHEAL:

Infections of intestinal tract leading to diarrhoea are very common throughout world and affect all age groups. Honey has been found to possess bactericidal activity against number of enteropathogenic organisms, including Salmonella and Shigella species, and enteropathogenic *E.coli*.[45] Since diarrhoea leads to compromised nutritional status along with dehydration, routine therapy is re-hydrating the body and restoring electrolytes (salts) lost in the diarrhoea, by administering fluid by mouth or intra-venously. Based on the recommendations of World Health Organisation- UNICEF, an oral rehydration supplement particularly the low osmolarity are a proven life-saving commodity for the treatment of children with diarrhoea. [46] Composed of glucose and sodium ORS promote sodium and thus water absorption via passive sodium-coupled glucose transport in intestinal villi. Glucose also serves to make ORS isotonic, thereby minimizing sodium and water secretion into the gut lumen. [47] Giving honey and ORS honey solution can reduce the frequency of diarrhoea and length of hospital stay resulting in reduced complications due to diarrhoea. Bee honey has been shown to inhibit the growth of 60 species of bacteria, fungi, and viruses and can be used as a

treatment for several gastrointestinal diseases, including diarrhoea. Honey shortened the duration of the diarrhoea in bacterial gastroenteritis due to *Salmonella*, *Shigella* and *E. coli* and was shown to be as effective as glucose in rehydration and aids in the uptake of sodium and water. Fructose being, the predominant sugar in honey, promotes potassium and additional water uptake without increasing sodium uptake.[48] Besides the antibacterial activity, honey may promote the repair of damaged intestinal mucosa, stimulate the growth of new tissues and work as an anti-inflammatory agent.[40,49-50]

GASTRITIS & GASTRIC ULCERS:

Traditional folklore as well as modern scientific evidence has supported use of honey in the treatment of peptic ulcers and gastritis. [40] In a study the treatment of indomethacin-induced gastric ulceration in albino rats with Wadi or Talh honey significantly reduced the levels of TNF-α, and CRP in gastric mucosa, which are pro-inflammatory mediators actively contributing to intestinal damage observed in gastric ulcer. The treatment with Saudi honey reversed the decrease of anti-inflammatory cytokine; IL-10, which helps in reducing the tissue damage induced by inflammation, as compared to ulcerative group. On the basis of these observation the study concluded that Wadi and Talh honey may be a beneficial therapy for patients diagnosed with gastric ulceration.[51] Sidr and Samar honey when used in ethanol-ulcerated male albino rats accelerated gastric ulcer healing and exhibited anti-inflammatory, antioxidant, gastro protective and anti- *H. pylori* properties.[52] In a study Al Masaudi SB et al., demonstrated that manuka honey has a potent antiulcer activity, which may be due to its antioxidants abilities resulting in reducing lipid peroxidation and interfering with the inflammatory process.[53]

IN DIABETES:

The role of honey has remained controversial in diabetes and has no effect as a hypoglycaemic agent in diabetic patients of either type. Earlier the people with diabetes were advised to avoid simple sugars including honey as they were thought to cause a sharp and rapid elevation in blood glucose levels and an overwhelming insulin demand. However, the absence of a sweetener in the diet of diabetics reduced overall dietary compliance among them. With the introduction of Glycemic Index (GI) and Glycemic Load (GL) of carbohydrates the view has changed. Both GI and GL are used to indicate the dietary significance of carbohydrates in respect to their effect on the plasma glucose levels. Carbohydrates having high GI and GL produce high blood glucose while those having lower GI induce a low blood glucose levels. American Diabetic Association in 2002 recommended that it is total amount of carbohydrate in meals and snacks, not mere the type of carbohydrate that is important in producing the glycaemia response. Honey types with low GI and GL if consumed may have beneficial physiological effects and could be consumed by type-2 diabetics.[54-55] In view of the lower GI common sugars like sucrose, fructose and other natural sweeteners including honey may be allowed as part of individual's diet,[56] which may improve overall dietary compliance in diabetics.

Studies have shown that in gastrointestinal tract absorption of fructose is slow as compared to glucose and fructose is taken up by liver rapidly resulting in low plasma glucose level rise after ingestion of fructose.[57] There was no added acute hyperglycemic effect of honey in diabetic patients when compared to bread and sucrose or bread alone.[58-59] In comparison to dextrose, in diabetic patients, honey caused a lower rise in plasma glucose levels and also reduced blood lipids, homocysteine levels and CRP (C reactive protein) levels in normal and hyperlipidemic subjects.[60]

Honey due to its antioxidant properties has also been considered significant in

prevention of diabetic complications including renal damage which are thought to be caused by increased oxidative stress in diabetes. Studies have shown potential of antioxidants in prevention of oxidative damage of kidney.[61] Significant increase in total antioxidant status (TAS) , activities of glutathione S-transferase, glutathione reductase, catalase, and glutathione peroxidise, was observed when honey was administered to diabetic rats. There was significant improvement in renal morphology in honey treated diabetic rats owing to its antioxidant activity and the same was evidenced by reduced mesangial matrix expansion and thickening of glomerular basement membrane.[62] A recent study however, demonstrated that 8 weeks consumption of 50 g/day honey increased HbA1c of patients with type 2 diabetes suggesting that, the increment of HbA1c may result in exacerbation of diabetes complications, therefore, honey need to be consumed with caution by patients with type 2 diabetes. [63]

COUGH AND COMMON COLD:

Use of honey in the relief of cough and common cold has been practised since ancient times. Based on folk claims and traditional knowledge various cough formulas containing honey are available commercially. Polysaccharide-resin-honey is well tolerated by children and rapidly improves all measured clinical cough symptoms, beginning from the first night of therapy. Both nocturnal and daytime cough improved, as did the sleep quality for children.[64] Administration of small doses of honey have proven to influence cough favourably and increase sleep in children.[65-67] Honey is superior to diphenhydramine in relieving cough in children and improving the quality of sleep of children and of their parents.[68] Honey based cough syrup reduced acute non-productive cough and throat irritation without causing drowsiness as compared to a cough syrup containing diphenhydramine, ammonium chloride and sodium citrate. [69] In relieving the symptoms of upper respiratory tract infections honey was superior to usual care and provides a widely available and cheap alternative to antibiotics.[66]

CONCLUSION

Honey has been in use as medicine from ancient times and over time evidence has evolved supporting its role as a medicine in various ailments. It has been proven beyond doubt that honey has antibacterial, antiviral, antifungal and antioxidant properties. And these properties of honey depend on its floral source. Excellent wound healing properties have been found in honey and has been found effective in difficult to treat wounds. The GI/GL of different varieties of honey have been found to be low and hence can be used in diabetic diet as a sweetener. Gastritis, gastric ulcers, diarrhoea, cough and cold have all been treated successfully with honey. Honey is relevant as a medicine in current scientific era and can be looked upon as a safe and efficacious alternative in management and prevention of various disorders. However, there is a need of sustained studies to exploit honey as a potent pharmacological agent with multiple actions.

Declaration by Authors

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