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REVIEW ARTICLE **OPEN ACCESS**

Honey and its Role in Medical Disorders

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ABSTRACT

Honey has been used as food and medicine by ancient and modern world, and by all traditions and civilisations. Modern medicine has accepted honey as therapeutic agent for diversity of clinical ailments. Honey is a source of important macro and micronutrients, and a rich source of calories. Honey possesses modulating effects on most of risk factors of cardiovascular diseases (CVDs). Natural honey can exert hepatoprotective effects both in term of hepatic function as well as by preserving liver structure. Natural honey proven for its anti-inflammatory, antioxidant, antimicrobial, anticancer effects, and has been tried for wound healing, eye disorders, gastrointestinal diseases, neurological disorders, and fertility disorders. This review discusses the current knowledge for the important therapeutic role of honey.

Key words: *Honey, Therapeutic, Medical disorders.*

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INTRODUCTION

Honey has been used as food and medicine by ancient and modern world, and by all traditions and civilisations [1]. Modern medicine has accepted honey as therapeutic agent for diversity of clinical ailments [2]. Honey is a nectar gathered by bees from blossoms of many flowers [3]. Following ingestion of the flower nectar, Bees convert it into honey by a process of regurgitation and evaporation, then store it in wax honeycombs inside the beehive with the clear, golden amber colour [4]. Honey is a source of important macro and micronutrients, and rich source of calories. Daily dose of 20g covers about 3% of the recommended daily intake of energy (RDI), and each 100g of honey provide 300 Kcal [5]. Honey has high nutritional value which is related to its unique composition, it has been reported to encompass more than 200 substances including: fructose, glucose, fructo-oligosaccharides, amino acids, vitamins, in addition to minerals and enzymes. Honey composition vary according to plants on which the bee feeds [2]. This variation should be considered in nutritional and pathophysiological studies conducted on honey, because it has been reported that honeys differ not only in the physicochemical properties but also differ in the biological activities [6].

COMPOSITION AND QUALITY OF HONEY

The overall composition of honey is from water and carbohydrates, the carbohydrates are the main constituent forming 95% of the overall dry honey weight [7]. Beside carbohydrates, honey contains numerous compounds such as: proteins, vitamins, minerals, phenolic acids, and flavonoids. Proteins constitute 5% of honey contents and present mainly as enzymes: amylase (digest starch or glycogen into smaller sugars), sucrase and α-glucosidase (convert sucrose into fructose and glucose), glucose oxidase (produce hydrogen peroxide and gluconic acid from glucose, gluconic acid is responsible for acidity of the honey), and antioxidant enzymes such as catalase, superoxide dismutase (SOD), and reduced glutathione [2]. Vitamins in honey include: riboflavin, niacin, pantothenic acid, pyridoxine, folate, and vitamin C [8]. Honey contains trace elements and minerals such as Potassium (major element in honey), Calcium, Magnesium, Iron, Sodium, , Zinc, sulphur and phosphorus [9]. Honey is considered a rich nutritional source for polyphenols including: phenolic acids (ellagic, caffeic, p-coumaric, and ferulic acids), and

flavonoids (apigenin, pinocembrin, kaempferol, quercetin, galangin, chrysin and hesperetin), polyphenols are the main contributor to antioxidant property of honey, their concentration average was between 56 and 500 mg/kg in various honey types [2,5]. Consistency of honey ranges from fluid, viscous to entirely crystallised, and honey's aroma depends on the botanical origin [10]. The quality of honey can be determined by many factors. Generally, they are related to its composition. Determinants and the standards of honey quality have been brought by International Honey Commission and by Codex Alimentarius Standard, they put a number of factors to be considered during honey analysis and trading among them are: moisture content, ash ,sugars content, water insoluble solids content, contaminants, free acidity, diastase activity, hydroxymethylfurfural content (HMF), electrical conductivity [10]. But the Codex Alimentarius Standard and similarly the International Honey Commission criteria are valid for honey trading worldwide and are mainly applicable for *Apis Mellifera* honey, that is why many authors suggest to make modifications applicable for each regional honey by finding quality standards for the stingless bee honey [11,12].

HONEY CAN MODULATE CARDIOVASCULAR RISK FACTORS

Honey possesses modulating effects on most of CVDs risk factors. Based on the role of phenolic compounds in reducing risk of CVDs, honey is considered as a promising natural protective remedy against CVDs [2]. By clinical trials, daily consumption of 70g natural honey found to be able to reduce CVD risk factors in terms of mild reduction of total cholesterol (TC), low-density lipoprotein (LDL-c), triglycerides (TG), C-reactive protein (CRP), and fasting blood glucose, in addition to mild elevation of high-density lipoprotein (HCD-c), and honey present protective effect against weight gain even in obese or overweight subjects [13]. Honey given to healthy, hyperlipidaemic, and diabetic subjects found to reduce serum lipids, CRP, and homocysteine in normal and hyperlipidaemic subjects, and caused greater elevation in serum insulin in healthy individual, moreover it induced lower elevation of plasma glucose level when compared with dextrose and sucrose [14]. In patients with non-insulin dependent diabetes mellitus who consumed natural honey for six months, honey exhibited a significant reduction of TC, LDL-c, very low-density lipoprotein (VLDL-c), and TG with insignificant reduction of HDL-c [15]. Honey shown to reduce postprandial hyperglycaemia in diabetic patients more profoundly than other sweeteners did [16]. The hypoglycaemic effect of honey has been reported also in patients with impaired glucose tolerance as well as in children with insulin dependent diabetes mellitus [17,18]. Honey has been reported by animal studies to reduce blood glucose as well as serum fructosamine (indicator of glycaemic control) when given in combination with oral hypoglycaemic agents [19]. The Malaysian dorsata honey (Tualang) has been shown to exert a cardioprotective effect in animal model by causing reduction in levels of cardiac enzyme CK-MB, cardiac Troponin-I, TC, and TG, in addition to increase in activities of SOD and glutathione peroxidase (GPx) leading to inhibition of lipid peroxidation, moreover, Tualang honey showed histological protective effects on cardiac muscles [20]. The protective effects of honey against CVDs, may be attributed to the role of honey in improving coronary artery vasodilation, inhibitory effect on LDL-c peroxidation, and reducing platelets aggregation [21]. Natural wild honey may exert its cardioprotective function against the vasomotor dysfunction and epinephrine-induced cardiac disorders through its total antioxidant capacity and by its contents of antioxidant enzymes [22]. Hypertension is a major risk factor for CVDs, in animal study, honey exhibited a reducing effect on systolic hypertension through amelioration of renal oxidative stress [23].

HONEY IS A HEPATOPROTECTIVE NATURAL PRODUCT

Non-alcoholic fatty liver disease is characterised by histological as well as biochemical derangement [24]. Elevated serum levels of alanine aminotransferase (ALT), and aspartate aminotransferase (AST), in addition to other parameters of liver function test (LFT) have been used as an indicator for hepatocellular damage [25]. The Malaysian Tualang honey has been investigated in animal model for its hepatoprotective effects and exhibited reduction of serum transaminases possibly by amelioration of hepatic oxidative stress [26]. Natural wild honey has been tested for its hepatoprotective benefits against cholestasis (toxic accumulation of bile salts in the liver), honey was able to diminish the negative effects of cholestasis on hepatic ultrastructure as well as to minimis the number of apoptotic cells, possibly by antioxidant mechanisms in addition to anti-inflammatory effects [27]. Honey demonstrated hepatoprotective properties against liver toxic injury when tested against toxic effects of carbon tetrachloride (CCl_4) on liver, honey has been shown to ameliorates the biochemical as well as the haematological changes, and induced faster recovery after CCl_4 injection, this effects was attributed to the unique honey constituents [28]. In rabbit model, Gelam honey (local Malaysian honey produced by *Apis mellifera*) was given by intravenous injection showed protective functions for liver and for other organs when tested against lethal doses of lipopolysaccharide, authors reported that Gelam honey exerted potent

hepatoprotective effects by causing significant reduction in ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and neutrophilic cellular infiltration, in addition to maintaining higher survival rate in comparison to untreated animals [29]. Natural honey exhibited hepatoprotective as well as systemic protection against toxicity induced by cadmium (Cd), in comparison to vitamins B_1 B_6, B_{12}, and vitamin C, honey was the most effective in reducing serum levels of ALT, AST, ALP, and bilirubin [30].

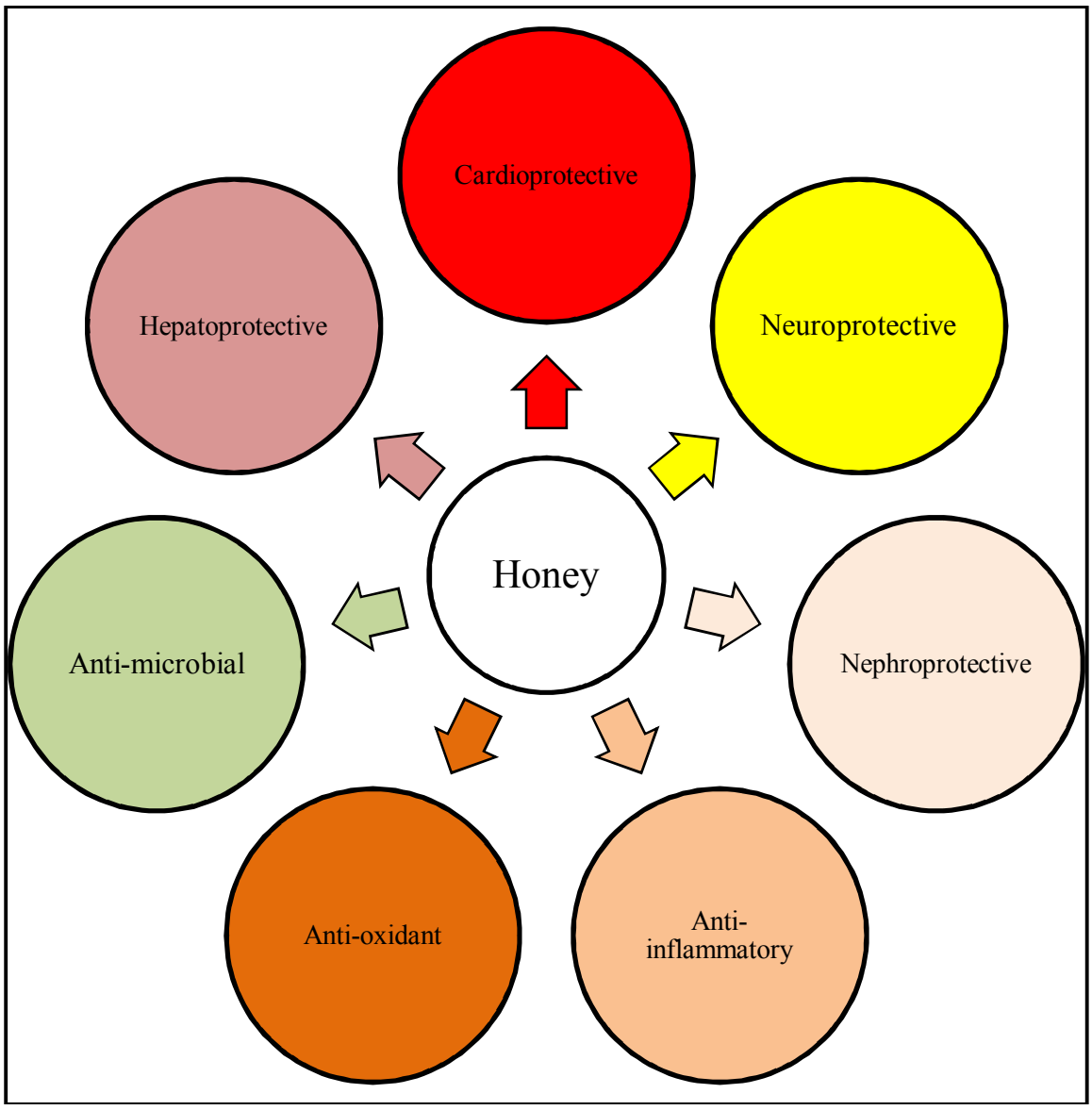

Figure 1: Health benefits of natural honey

HONEY IS A NATURAL ANTIOXIDANT

Antioxidant capacity of honey can be defined as the ability of honey to reduce the oxidative reactions with the human body and in the food systems [31]. The antioxidant function of honey is the result of its collective contents of phenolic compounds, ascorbic acid, tocopherols, and antioxidant enzymes namely: catalase, SOD, and reduced glutathione, which work synergistically together to produce this property [32]. Regular intake of dietary antioxidants has been found to augment the endogenous antioxidant defence mechanisms and thereby suppress the harmful effects of reactive oxygen species (ROS) on human physiology. Honey has been found to inhibit oxidative stress which is partly responsible for its hepatoprotective [26], cardioprotective [22], neuroprotective [33], nephroprotective [34] functions. Tualang honey specifically has been investigated for its protective effect on pancreas against oxidative stress, the results were strongly suggestive for its hypoglycaemic effect and restoring activities of CAT and SOD, and reducing levels of malondialdehyde (MDA) in the pancreas of diabetic rats [35].

THERAPEUTIC BENEFITS OF HONEY

Natural honey whether produced by stingless bee or sting bee has many reported medicinal applications (Figure 1). Beside its hepatoprotective and cardioprotective effects, natural honey proven for its anti-inflammatory, antioxidant, antimicrobial ,anticancer effects, and has been tried for wound healing, eye disorders, gastrointestinal diseases, neurological disorders, and fertility disorders [4,36–38].

Honey as an anti-inflammatory

Even in the absence of infection, honey reduces inflammation, oedema, as well as exudation, and promote healing and stimulate tissue regeneration [39]. In many inflammatory processes the nuclear factor kappa B (NF-$_k$B) has been implicated as a key factor, Gelam honey has been reported to inhibit the nuclear translocation and activation of NF-$_k$B and subsequently caused reduction in expression of proinflammatory mediators tumour necrosis factor-alpha (TNF-α) and cyclooxygenase-2 (COX-2), thereby reducing the inflammation [40]. Regular consumption of natural honey by normal individuals has been shown to reduce serum levels of prostaglandins (PGE_2, $PGF_{2\alpha}$, and thromboxane B_2), and this inhibitory effect found to increase with time, the site of action may involve COX-2, COX-1, or both [41]. C-reactive protein, is an acute phase reactant has been implicated in pathogenesis of inflammatory diseases, shown to be lowered by daily ingestion of natural honey for a period of 15 days [14].

Honey for wound healing

Long time ago 2100-2000 BC, honey was prescribed by Sumerians for wound treatment. In 384-322 BC, Aristotle in his writings referred to a pale honey as being "good as a salve for sore eyes and wounds" [42]. Owing to extensive researches done on benefits of honey in wound healing, honey has been widely accepted as a medicine for treatment of surgical incisions, pressure ulcers, burns ,and catheter exit sites [43,44]. Clinical observation of wounds treated with honey showed: rapid clearance of infection, reduction in the inflammation, oedema, and pain, sloughing of necrotic tissues, and tissue regeneration, in addition to healing with minimum wound scarring, moreover, honey does not cause any tissue damage [44,45]. Study conducted on full-thickness cutaneous wounds had come out with evidence that honey has the potential to hasten cellular regeneration, reduce scarring, increase the epithelialisation, and angiogenesis in early phase of healing [46]. Due to its dual effect as antimicrobial and immune modulator, honey has the ability to sterilise wounds, suppress inflammation, and promote healing, this ability most likely because of honey's physicochemical characteristics [47].

Honey as an anti-microbial

Antimicrobial effect of honey has been confirmed by in vitro as well as by clinical trials, such studies brought the evidence of broad-spectrum antimicrobial activity of honey as antibacterial, antifungal, antimycobacterial, and antiviral [48]. Studies showed that the antimicrobial activity of honey is dependent largely on the floral source of honey that contributes to the honey composition [31]. Honey has been tested for its antibacterial effect against many bacterial species such as: *Escherichia coli* [49], *Helicobacter pylori* and *Pseudomonas aeruginosa* [50], *Staphylococcus aureus* [51], *Streptococcus pyogenes* [52], methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* [53]. Malaysian Tualang honey has been investigated for its antibacterial properties and exhibited good inhibitory effect against Gram-positive bacteria such as *Streptococcus pyogenes*, coagulase-negative Staphylococci, MRSA, *Staphylococcus aureus*, and against Gram-negative bacteria such as *Acinetobacter baumannii*, *Proteus mirabilis*, *Shigella flexneri*, and many others [54]. Manuka honey is known to has antibacterial function, it has been investigated by in vitro study against multidrug resistance tuberculosis (MDR TB), it showed good efficacy at high concentration [55]. Because of its antimycobacterial effect, honey has been recommended as a dietary supplement for prevention and management of tuberculosis [48]. The broad-spectrum antibacterial effects of honey have been attributed to the antioxidant polyphenols and the radical scavenging ability of honey [56,57], in addition to hydrogen peroxide level in honey [58]. Hydrogen peroxide, phenolic compounds, and radical scavenging ability of honey collectively lead to bacterial DNA degradation and contribute to the bactericidal activity of honey [59]. Honey found to exerts its antibacterial effect by prevention of bacterial division and separation [60], in addition to other mechanisms such as: bacterial disruption, lysis, and blocking bacterial attachment to tissues [61]. Beside its antibacterial effect honey has antifungal as well as antiviral activities. Honey reported to has antifungal effect and has been applied for treatment of some fungal infections such as: erythema, desquamation and pruritus in *Tinea. mycosis* [62], *C. albicans* infections including resistant strains [63], and many other fungal and yeast infections [48]. Honey demonstrated antiviral activity in clinical trials and in vitro studies. Topical application of honey on recurrent herpes lesions has been shown to reduce recurrence, and pain. Viruses such as: type 1 herpes simplex virus [64], varicella zoster [65], and respiratory syncytial virus [48] have been shown to be significantly inhibited by honey.

Honey for diseases of gastrointestinal tract (GIT)

Honey has been used as a therapeutic natural remedy for treatment of gastritis, duodenitis, and for rota virus GIT infection [2]. Some beneficial effects of honey have been reported in treatment of periodontal diseases and dyspepsia [38].

Other medical applications of honey

Natural honey has been investigated as medicinal therapy for neurological, ophthalmological, reproductive, and oncological disorders. Malaysian Tualang honey has been shown to improve cerebral hypoperfusion status which is impacted in pathogenesis of some chronic neurodegenerative disorders such as Alzheimer's disease [66]. On long term administration, honey reported to improve memory and cognitive functions [67]. Tualang honey antioxidant function has been suggested as the mechanism operating behind its effect against memory decline and neural oxidative stress [68]. Honey has been used for treatment of some eye diseases such as cataract and glaucoma [38], keratoconjunctivitis [69]. Honey has significant positive effects on fertility by amelioration of altered levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone indicating its healthy effects on the reproductive system organs [70]. Honey may play an important role in the management of cancer, this is based on the promising findings of in vitro, as well as of in vivo researches. More than one study from Malaysia indicated the anticancer potential of honey, for example; against human cervical and breast cancer [71]. Malaysian Tualang honey showed in vitro antiproliferative effect against human osteosarcoma and against oral squamous cell carcinomas most likely by inducing cancer cells apoptosis [72].

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