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A Review about Honey Effect on Human Body

Balın İnsan Vücuduna Etkileri Üzerine Bir Derleme

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Abstract

Honey is a traditional food which has been used as therapy for many diseases and still essential part of diet. Beside its nutritional properties, honey has many important features such as preventing cancer, neurological and cardiovascular diseases, infections; protecting gastrointestinal system; boosting immune system; alleviating some post-operation complications and correcting hormonal levels. In this study, researches including in vivo and in vitro experiments in addition to human controlled trials examining the effects of honey on each system were included. It was aimed to link these studies' results and traditional practices. Although the researches are sufficient to explain the benefits of honey in general terms, more controlled trial examples are needed on the subject. Promoting accessibility and awareness about medical standardized honeys also aimed in this study. In order to provide these, in addition to informing people, producers should be warned about safe honey production and packaging.

Keywords: Antioxidant effect, Antimicrobial effect, Apitherapy, Honey, Neurological effect, Traditional remedy

Özet

Bal, birçok hastalık için tedavi olarak kullanılan ve halen beslenmenin vazgeçilmez bir parçası olan geleneksel bir besindir. Balın besleyici özelliklerinin yanı sıra kanserden, nörolojik ve kardiyovasküler hastalıklardan, enfeksiyonlardan korunma; gastrointestinal sistemin korunması; bağışıklık sistemini güçlendirmek; bazı ameliyat sonrası komplikasyonları hafifletmek ve hormonal seviyeleri düzeltmek. Bu çalışmada, balın her bir sistem üzerindeki etkilerini inceleyen insan kontrollü denemelere ek olarak in vivo ve in vitro deneyleri içeren araştırmalara yer verilmiştir. Bu çalışmaların sonuçları ile geleneksel uygulamalar arasında

bağlantı kurulması amaçlanmıştır. Yapılan araştırmalar balın faydalarını genel hatlarıyla açıklamaya yetse de konuyla ilgili daha kontrollü deneme örneklerine ihtiyaç duyulmaktadır. Bu çalışmada aynı zamanda tıbbi standardize edilmiş ballar hakkında erişilebilirliği ve farkındalığı teşvik etmek de amaçlandı. Bunların sağlanabilmesi için toplumu bilgilendirmenin yanı sıra güvenli bal üretimi ve paketleme konusunda üreticiler uyarılmalıdır.

Anahtar Kelimeler: Antioksidan etki, Antimikrobiyal etki, Apiterapi, Bal, Nörolojik etki, Geleneksel çare

1. INTRODUCTION

Honey is the only insect product with nutrient value as far as science know. Olaitan et al. (2007) defines honey as natural sweet exudation formed by bees (Apis melifera and Mellifera beecheii) after a complex process consisting of collecting, transforming, combining with spesific enzymes. The process the honey production begins with the collection of nectar, which is a liquiform solution with carbohydrate, amino acid, lipid, mineral composition extracted from nectaries cells of flower (Ball, 2007). This process continues in the bee's gastrointestinal system, nectar encounters many specific enzymes to provide maturation (Graham et al., 1992). Maturation consists of two essential phases; disintegrating sucrose and larger carbohydrates into glucose by enzymes called diastase and invertase and as second phase, removal of excess water by a wing-whisking motion of bees, until water content remain below %20. Another important enzyme, Glucose oxidase contributes to the production of hydrogen peroxide (Oskouei & Najafi, 2013). Nectar is known as determining factor about the flavor and quality of the final product although impossibility of reaching exact data about nectar source. Therefore, a more specific decision can be made about the origin of honeys with distinctive scent and aroma, clover honey or orange blossom honey can be given as example (Graham et al., 1992).

When the chemical properties and ingredients of honey are examined, even though source of nectar causes different compositions, first common finding is acidity of honey. The average pH of honey is measured as 3,9 (Bogdanov, 2009). In a study conducted with 18 different honeys which have different floral source or location the highest pH value was found as 5,13. Though, high sugar content which makes honey a supersaturated solution, prevents acidic taste. The most observed macro minerals can be expressed as K, Ca, Mg, P and Na, respectively (Polat, 2007). Honey contains very small amounts of vitamins, cannot be used as a source (Ball, 2007). Beside maturation enzymes and glucose oxidase, catalase and acid phosphatase are found in enzyme content also (Olaitan et al., 2007). Finally, although polyphenols and proteins are present in very small amounts, the noncovalent and covalent bonds

between them ensures antioxidant and antibacterial properties of honey (Brudzynski, & Maldonado-Alvarez, 2015). In fact, it was determined in the studies that the phenol component provided antioxidant properties to the honey mainly (Khalil et al., 2010). In vivo studies showed that rich-phenol diets have many benefits such as alleviating adverse effects of liver, heart, brain diseases and cancer; other than antioxidant properties (Cianciosi et al., 2018). Apitherapy is an alternative medicine branch, described as the use of honey and honey products for prevention or treatment of various diseases. As written in website of Apitherapy association, apitherapy currently used orally for treatment of; insomnia, anorexia, stomach and intestinal ulcers, constipation, osteoporosis, and laryngitis (American Apitherapy Society, 2019). According to the Gupta and Stangaciu (2014), apitherapy should be handled as a medical concept and be rendered as available to communities especially who are having difficulty in accessing modern health facilities due to hospital costs and lack of insurances. Thus, by popularizing a traditional method, a suitable type of healthcare becomes available without any significant challenges.

The earliest record of honey's use for health purposes is a clay tablet found in the Euphrates Valley, thought to have a prescription for skin infection or ulcer therapy so far (Kramer & Levey, 1954). Frequent use of honey Ancient Egypt's hieroglyphic prescriptions is noticeable, Smith papyrus (between 2600 and 2200 BC) and The Ebers Papyrus (550 BC) can be given as example (Crane, 1999). In these prescriptions, honey is indicated as a topical therapy for infected wounds and many other diseases. Further, honey use for contraception continues as a tradition in Egypt since these prescriptions (Crane, 1999). Ayurveda is a belief system which is grounded on knowledge of life in India, Indus Valley; is another concept that uses honey for remedies widely (1000 BC) (Telles et al., 2007). In Ancient Greek, honey was a popular treatment used for gout and nervous disorders, consumed as a beverage made with unfermented grape and honey (oxymel) (Zumla & Lulat, 1989). In Roma, it is known that pneumonia, pleurisy and snakebites could be treated with honey (Bansal et al., 2005).

Honey existed as precious product with many pharmacological properties in history. Today these traditional remedies continue to be developed and used. Especially in areas which are distant from modern health services with unfavorable economic conditions, traditional healers use honey and hive products frequently. Nepal, African countries, and Eastern Europe can be given as examples (Jones, 2009).

2. PROPERTIES of HONEY on DIFFERENT BODY SYSTEMS

2.1. Anticancer Property of Honey

Cancer is one of the considerable causes of death in the world. According to the National Cancer Institute data (2020), in 2018, 18.1 million people diagnosed with cancer and 9.5 million people died because of cancer and related conditions. Lifestyle habits, smoking and tobacco use, obesity, diabetes mellitus and chronic infections accelerates cancer (National Cancer Institute, 2013). Cancer eventuates after a complex multistep process which includes proliferation, invasion and metastasis. While carcinogens, promoters and inflammatory agents triggering this process; apoptotic proteins, cell cycle proteins, protein kinases and adhesion proteins attempts to control modulation. Despite specific targeted therapies are being searched and has been started to use, common treatments for cancer consists of; surgery, radiotherapy, and chemotherapy although they have all serious side effects (Waheed et al., 2019). Di Bella submitted a new approach to the cancer therapy in 1990s. This approach covers use of honey as complementary natural substance together with anticancer drugs because of immune-modulating and anti-inflammatory effects of honey (Badolato, 2017).

Honeys effect on cancer mechanisms are examined under 6 groups (Waheed et al., 2019). Firstly, cell cycle disruption is primary predisposing factor for cancer. Cell cycle is normally strictly controlled by protein kinases but when they cannot control the cycle rapid proliferation occurs (Pichichero et al., 2010). Cell cycle arresting is a method to stop the process. In recent studies, inhibition of cell cycle at G1/G0 checkpoint by phenolics and flavonoids was observed in melanoma, glioma, colon cancer and non-small cell lung cancer (Afroz et al., 2016). Second important effect of honey is activation of the mitochondrial pathway and outer membrane permeabilization by releasing the cytochrome-C to induct MOMP (mitochondrial outer membrane permeabilization) (Nassar et al., 2016). Apoptosis induction is needed for the death of cancer cells that are increasing in uncontrolled manner. Honey activates apoptosis pathways by providing membrane depolarization and elevating caspase 3 and various proapoptotic protein levels (Ren et al, 2012). As an example, an in-vivo study conducted by application of honey and aloe vera to Wistar rats, decrease of Bcl-2 and increase in Bax protein are observed (Yaacob et al., 2013). Another in-vitro research studied on human breast adenocarcinoma cells (MCF-7) by treating cell lines with acacia honey, showed inhibition in time and dose dependent manner by activation of caspase 9 and increasing caspase 3/7 activity (Portokalakis et al., 2016).

Honey modulates oxidative stress thereby contributes inhibition of proliferation. Since oxidative stress also causes cardiovascular diseases and inflammatory conditions honey can also be used for their treatment (Araujo et al., 2011). Because of N-oligosaccharides (NOS)

component and SCFA (short chain fatty acid) that occurs as a result of digestion, honey has immuno-modulatory effects (Chepulis, 2007). Therefore, swelling caused by malignant transformation can be cured by honey (Dao et al., 2004). Malignancies due to chronic infections such as Hepatitis and EBV viruses can be prevented also. Last benefit of honey which helps combat against cancer is modulation of insulin signaling and estrogenic activity. In recent studies, gelam honey improved insulin resistance caused by high levels of Nf-Kb in HIT-T15 cells (Erejuwa et al., 2012). Contradictory action of honey helps modulating estrogen receptors and thus honey becomes functional in treatments of estrogen dependent cancers of breasts and endometrium (Erejuwa et al., 2014). Honey also has antimutagenic activity. In a study conducted with seven different honey (acacia, buckwheat, fireweed, soybean, tupelo and Christmas berry), important level of inhibition of Trp-p-1 mutagenicity has been observed (Wang, 2002).

Although exact mechanisms are not known and needed to be searched, most of the benefits of honey are due to the flavonoids and polyphenols it contains and the type and amount of them varies according to the type of honey (Ahmed & Othman, 2013). For example, Coriander honey is effective on Ehrlich Ascites Carcinoma due to mechanisms which decreasing lipid peroxidation and superoxide dismutase, decreasing ascetic fluid volume and increasing Ig M, G and A levels (Hegazi et al., 2015). Tualang honey in Malaysia improved Oral Squamous cell carcinoma, Osteosarcoma, Leukemia and Breast cancer by depolarization of mitochondrial membrane and inducing apoptosis (Ahmed et al., 2017; Fauzi et al., 2011)

Beside its sole use, honey has significant benefits as companion to modern cancer therapies. Several studies show stimulation of chemotherapeutic agents such as cyclophosphamide and 5-fluorouracil (Moniruzzaman, 2012). Honey serves as treatment against adverse effects of chemotherapies which are infections such as oral mucositis and cisplatin induced acute kidney disease also (Porcza et al., 2016; Singh, 2017).

2.2. Antimicrobial Property of Honey

Antimicrobial features of honey have been known since ancient times. Dioscorides stated that honey can be efficient for ulcer therapy in 50 AD and Aristotle (384-322 BC) indicated that pale honey is good for sore eyes and wounds (Molan,1999). Today antibiotics are preferred for treatment of bacterial infections however widely use of them has been causing resistance. As consequence, regimen changes for antibiotics and search for new compounds to replace them are needed (Feás et al., 2013). Since Dutch scientist Van Ketel proved honey ‘s antibacterial activity in 1892, honey has been considered as a treatment for bacterial infections (Eteraf-

oskouei & Najafi,2013). Eteraf-oskouei and Najafi (2013) claimed that because of honey may not develop resistant bacteria even when it used in high doses, it could be consumed continuously. Honeys inhibitory action on Gram-positive and gram-negative bacteria including MRSA (Multi drug resistant strains) and some fungi and viruses are observed in recent studies (Irish et al., 2006; Kwakman et al., 2008; Naama, 2009).

Antimicrobial activity of honey is associated with four different mechanisms which separates honey from antibiotics. First one is high sugar content that contributes dehydration of bacteria by osmosis (Olaitan, 2007). Second one is low pH (3.2- 4.5) (Allen et al., 1991). Third and crucial one is Hydrogen peroxidase produced by glucose oxidase. Glucose oxidase is an enzyme which serves to preservation. (Glucose + H2O + O2 → Gluconic acid + H2O2) (Somal et al., 1994). It worth to mention here, although antimicrobial use of Hydrogen peroxide is common, it causes cellular and protein damage by increasing reactive oxygen radicals. (Cochrane,1991; Simon et al,1981). Last mechanism is effect of flavonoid and polyphenol compounds such as pinocembrin, pinobanksin and chrysin (Wahdan, 1998). Source of antimicrobial effect might be the origin of honey also (Bogdanov et al., 2008).

Honey also contributes defense mechanisms against microbes by boosting immune system. Study of Tonks et al. (2003) shows increased count of T-lymphocytes and B-lymphocytes and active neutrophils in cell cultures as immunologic effect of honey. Tonks (2007) also discovered that Manuka honey increases TNF alpha levels by modulating Toll like receptors. Honey can also stimulate monocytes via releasing cytokines, tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6 (Tonks et al., 2001). Further, honey provides maintenance of glycolysis, major energy mechanism of macrophages. With this mechanism macrophages can continue to work in the damaged, oxygen free tissues. Acidity also contributes to the macrophage function by creating acidic environment inside phagocytic vacuole (Molan, 2001).

Modern studies about antimicrobial activity of honey focuses on observing differences between specific organisms. Huttunen et al.'s (2013) study compares effects of 10 different honey samples on bacterial resistant strains such as *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella enterica serovar Typhimurium*, *Bacillus cereus*, *Bacillus subtilis*, and *Listeria monocytogenes*. Pure honey was more effective, and sensitivity of different bacterial strains were different. In general, all honey samples demonstrated antibacterial activity and inhibition of bacterial growt. According to study by Wasihun and Kasa (2016), honey has potential bacteriostatic and bactericidal activities

on multidrug resistant human pathogenic bacterial isolates (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, coagulase-negative *Staphylococcus*, *Streptococcus pyogenes* and *Klebsiella pneumoniae*). Alandejani et al. (2009) showed that bactericidal rates of Sidr and Manuka honeys were higher than different antibiotics (cefazolin, oxacillin, vancomycin, azithromycin, fusidic acid, gentamicin, and linezolid) against methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), or *Pseudomonas aeruginosa* (PA) biofilms.

Standardization and safe medical use of honey is difficult because of different sensitivity of bacterial strains and changes in antibacterial property for different honey samples (Grego et al., 2016; Sousa et al., 2016). However, by controlled production and analyzing batches to measure bactericidal activity, Revamil source honey and Manuka honey have been used for medical occasions (Knight, 2013).

Ceyhan and Ugur (2001) compared antimicrobial activity of 84 honey samples with different floral sources on 8 bacterial and 2 fungal strains. Honey sourced from thyme, pine and carob were more effective. As a result, most of honey samples showed inhibitory effect on bacterial growth. Fungi were less sensitive than bacteria. Honeys antimicrobial effect on fungi reported on some yeast and species of *Aspergillus* and *Penicillium*, dermatophytes, *Candida albicans*, Cutaneous and superficial mycoses like ringworm and athlete's foot (Kumar et al., 2010). Inhibition of fungal growth and toxin production by pure honey is observed in the study of Al-Waili and Haq (2004). Inhibition of bacterial growth also contributes to inhibition of secondary fungal infections. Some studies revealed topical application of honey can be used as treatment for seborrheic dermatitis and dandruff also (Zaidi et al., 2019).

Antiviral property of honey investigated on herpes lesions, as result it has been seen that topical application is more beneficial for treating recurrent attacks of labial and genital herpes lesions compared acyclovir cream (Al-Waili & Haq, 2004). Honey also has inhibitory effects on *Rubella virus* activity. (Eteraf-Oskouei, & Najafi, 2013). Some studies which show Manuka Honey's dose dependent inhibitory activity on HIV-RT exist also (Shikamoto, 2021).

In a study, it was determined that 10% honey concentration applied to the Ecinococcus granulosus parasite, which causes hydatid cyst (echinococcosis), has a lethal effect from the third minute (Karadal & Yildirim, 2012). Antileishmanial property of honey is observed in some studies (Bassam, 1997). In a study conducted to determine the antimicrobial effects of honey samples collected from Bingöl region, it was stated that 0.1 mL honey sample inhibits the growth of bacterial species such as Escherichia coli, Staphylococcus aureus, *Klebsiella*

pneumoniae, *Bacillus brevis*, *Pseudomonas aeroginosa* and fungi species such as *Candida albicans* and *Rhodotorula rubra* (Aksoy & Digrak, 2006).

Mohammed Ali and Kunugi (2021) stated that honey and honey added herbal remedies can have positive effect on COVID-19 due to their flavonoid components, especially naringin. Acceleration of healing is thought to be depended on reduced oxidative stress and immune boost.

2.3. Gastrointestinal Effects of Honey

Gastrointestinal diseases such as gastroenteritis, diarrhea, gastritis and peptic ulcer are common throughout the world. As claimed by studies, honey can be therapeutic for these diseases because of its antimicrobial and gastroprotective functions. The most common cause of diarrhea is gastroenteritis, infection of the gastrointestinal tract. *Salmonella, Shigella and Enteropathogenic E. coli* constitutes most frequent gastroenteritis agents (Pawlowski et al., 2009). Study of Jeddar et al. (1985) shows that honey has bactericidal effect on many pathogens including *Salmonella, Shigella and Enteropathogenic E. coli*. A clinical study on infantile gastroenteritis demonstrates honey lessens time of bacterial diarrhea caused by *Salmonella, Shigella and Enteropathogenic E. coli* in patients. Although honey was successful in shortening time of bacterial diarrhea, no change was observed in viral gastroenteritis (Haffejee & Moosa,1985). During these infections, first step is defined as attachment of bacteria to mucosal epithelial cells, therefore inhibition of attachment is important for prevention (Alnaqdy et al., 2005). Honey contributes this inhibition by several mechanisms; by coating bacteria, bacterial electrostatic charge or hydrophobicity change and antibacterial properties (Alnaqdy et al., 2005; Edebo et al., 1980; Sakai et al., 1987).

According to WHO, as routine therapy for diarrhea, electrolyte solution with glucose is recommended (WHO, 1976). In a clinical study, effect of honey replacement instead of sugar in solution has been observed. It was found that honey was effective (Haffejee & Moosa,1985). Honey also help battle against gastroenteritis by repairing damaged intestinal mucosa, stimulating growth of new tissues and with its anti-inflammatory action it corrects malfunctioning in mucosa and prevents serum loss (Molan, 1999).

According to the study of Ali et al. (1991), %20 honey solution inhibits *Helicobacter pylori* isolates which are the main cause of peptic ulcer disease, including isolates which are resistant to antibiotics. In studies conducted on gastrointestinal infections (gastritis, duodenitis, gastric ulceration) caused by bacteria and rotavirus, it has been observed that oral treatment of

honey is effective (Somal et al., 1994; Topham., 2002). Antibiotic property is not the only mechanism of honey that assists preventing gastritis and peptic ulcer disease. Reduced secretion of gastric acid and increased blood supply by stimulating sensory nerves and releasing vasodilatory peptides are another two significant protective effect of honey (Ali & Al-Swayeh, 1996; Al-Swayeh & Ali, 1998).

A study indicated %80 recovery rate of 600 gastric ulcer patients who treated with honey (Kandil, 1987). Study of Ali et al. (1991) demonstrated dose dependent action of honey on peptic ulcers caused by alcohol and indomethacin (aspirin type anti-inflammatory drug). Nasutia et al. (2006) recommended using honey like sucralfate because of its healing effect on lesions induced by indomethacin and ethanol.

Prebiotics described as non-digestible dietary supplement which balances intestinal microbiota by increasing beneficial organisms. Both in vivo and in vitro studies showed positive effect of honey on growth of beneficial bacteria (*Bifido bacteria and lactobacilli*) due to its oligosaccharide components (Sanz et al., 2005). Honey is accepted as convenient sweetener for fermented milk products which contains beneficial bacteria such as *Streptococcus thermophilus, Lactobacillus acidophilus, Lactobacillus delbruekii* and *Bifidobacterium bifidum* (Bansal et al., 2005). Study of Coskun and Dirican (2019) showed that pine honey considerably increased prebiotic property of yoghurt beside providing better structural characteristics. Numbers of *Lb. delbrueckii* ssp. *bulgaricus* and *Lb. acidophilus* are observed beyond 10^6 cfu/g which is urged minimum level.

2.4. Cardiovascular Effects of Honey

Cardiovascular diseases constitute significant part of illnesses as deaths in the developed countries. Arrythmias, myocardial infarctions seen as symptoms of ischemic heart disease. One of the risk factors for cardiovascular diseases have been indicated as oxidative stress (Kasper, 2015). Several in vivo and clinical studies showed increased levels of vascular superoxide anion production in the states of hypertension, hypercholesterolemia and hyperlipidemia. (Guzik et al., 2000; Miller et al., 1998; Morawietz et al., 2001). Oxidized LDL-C can easily be invaded and internalized by macrophages to cause atherosclerotic plaques by forming foam cells (Palinski et al., 1989). Currently, for the treatment of such diseases drug therapy is preferred. Contrarily, because of the cardiovascular disease's complexity and interconnected structure, patients experience limitations and adverse effects while using especially anti-arrhythmic drugs (Hume & Grant, 2007).

Honey has been used as a treatment of several diseases since ancient times, but cardiovascular use is not included in traditional prescriptions (Ahmed et al., 2003). Currently, many in vivo studies focus on cardiovascular effects of honey. As result of these studies, cardioprotective effects of honey are better known; Inhibition of atrial fibrillation, anti-arrhythmic, anti-thrombotic, antiatherogenic, relaxation of blood vessels, reduction in blood pressure, inhibition of LDL oxidation, improved dyslipidemia. All these mechanisms mainly ground on antioxidant effect of honey (Bahrami et al., 2009; Schramm et al., 2003; Yaghoobi, 2008).

Honey increases antioxidant agents such as vitamin C, Beta-carotene, uric acid and glutathione reductase in body (Khalil & Suleiman, 2010). Antioxidant capacity depends on botanical source of honey, according to a study antioxidant level is higher in darker honeys (Baltrusaityte et al., 2007). NO metabolites of honey can also contribute to the vascular protection (Bogdanov et al., 2008).

Yaghoobi et al. (2008) measured cardiovascular risk factors such as body weight, body mass index, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triacylglycerol, fasting blood glucose (FBG) triacylglycerol and C-reactive protein (CRP) on 55 patients who were overweight or obese. As result, mild reduction in body weight and body fat were observed. While honey was reducing total cholesterol, LDL-C, triacylglycerol, FBG, CRP and increased HDL-C in patients with normal values; total cholesterol, CRP and LDL-C reduced more in patients who have elevated values.

Najafi et al. (2008) recommended honey as prophylaxis as a result of their study where they searched effect of honey on ischemia/reperfusion (I/R) induced injuries in isolated rat heart by perfusing enriched Krebs solution with natural honey for 10 min before to 10 min after ischemia. Another in vivo study conducted on anesthetized, normal or stressed rats demonstrated natural honey pretreatment provides protection against epinephrine-induced vasomotor dysfunction and cardiac disorders and preserved the positive inotropic effect of adrenaline (via enzymatic and non-enzymatic antioxidants, minerals and NO release from endothelium by vit C influence) (Rakha et al., 2008). In a prospective study that has observed CHD and stroke mortality in postmenopausal women in Iowa, beneficial effect of flavonoid intake was observed (Yochum et al., 1999). A phenolic compound (Salvia miltiorrhiza extract), was founded helpful in prevention of postoperative increase of endothelin-1 which increased after cardiopulmonary bypass in children with congenital heart defects (Xia et al., 2003).

2.5. Respiratory Effects of Honey

Antibiotics are prescribed for upper respiratory tract infections primarily (Goossens et al., 2005). Although most URTI have viral source and because of the alternative treatments are inadequate, health professionals continue to prescribe antibiotics (Hersh et al., 2013; Kenealy & Arroll, 2013). Since honey is known as therapy for respiratory infections in history, many modern studies have been performed to confirm this popular belief and present honey as replacement for antibiotic therapy. According to a meta-analysis by Abuelgasim et al. (2021) honey improves URTI symptoms compared to usual care and reduces combined symptom score (which includes symptoms like sore throat), cough frequency and cough severity. Cough is more important concern in children because of their immature immune system. (Kantar, 2016). Paul et al. (2007) stated honey is helpful for symptomatic remedy of nocturnal cough and sleep difficulty associated with childhood upper respiratory infections. They recommended honey as cough treatment also. Another study about honey's effect on acute symptoms of URTI conducted on Malaysian Hajj Pilgrims. As result, significant decrease in sore throat rates observed in the people who consume Madu Lebah Tualang - Agromas honeys for 3 weeks,20 g, twice, daily (Suleiman et al., 2011). Study of Kilty et al. (2010) focuses on treating Chronic rhinosinusitis (CRS) which is a disease caused by biofilm producing bacteria. Chronic rhinosinusitis (CRS) is normally treated with antibiotics but in patients who has undergone endoscopic sinus surgery topical therapy is preferred. In this study manuka honey has been found efficient against bacteria without causing any histological injury to the olfactory epithelium. Kamaruzaman et al. (2014) have observed aerosolized honey's effects on ovalbumin induced chronic asthma in rabbit model. Significant inhibition in goblet cell hyperplasia and mucus overproduction were seen. Anti-inflammatory property of honeys such as Gelam, Buckwheat and Manuka is thought to be the reason for relief of asthma symptoms. Manuka honey is notified as booster for TNF-α, IL10, IL-1ra, PDG and TGF-β.26.

2.6. Metabolic Effects of Honey

Honey use instead of refined sugars is safe for diabetic patients, it has been used as remedy for diabetes since early ages (Katsilambros et al., 1988). There can be two primary reasons; firstly, smaller amounts of honey provide more sweet taste and secondly, honey has less calories with much more nutrients such as minerals and vitamins. In studies, increased insulin secretion stimulated by honey, decreased blood glucose and increased hemoglobin with advanced lipid profile were observed (Al-Waili, 2003; 2004). Honey also reduces hepatic transaminases, triglycerides and glycosylated hemoglobin (HbA1c) and increases HDL cholesterol

(Busserolles et al., 2002; Erejuwa et al., 2009). Another benefit of honey about diabetic use is its antioxidant property, it has been proved that β-cell dysfunction influenced insulin resistance is caused by oxidative stress (Drews et al., 2010). In previous studies, some controversial results have been observed. Although studies conducted with Dutch Gold honey showed no improvement in glycemia and insulin sensitivity caused by cytokines (IL6), in vivo studies which were using Tualang and Nigerian honey demonstrated improvement in glycemia and dyslipidemia (Erejuwa et al., 2009; Raatz et al., 2015). This might be caused by polyphenols in honeys with tropical source or several different enzymes such as α-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors stimulated by bee (Erejuwa et al., 2012).

2.7. Wound Healing Effect of Honey

Wound healing is well known effect of honey since it has been started to be used for medical purposes. Prevention of wound infections by honey was effectively used by Russians in World War I and Germans discovered a remedy with mixing cod liver, oil and honey for ulcers, burns, fistulas and boils (Bansal et al., 2005). Honey has been searched on several type of ulcers, wounds and skin diseases and found to be helpful for all. Although honey is effective on all kind wounds, degree of effect varies between types and severities. Applying and removing honey dressings don't create a challenge like other materials. Wounds must be covered with adequate amount of honey and cavities should be full filled. (Bansal et al., 2005; Molan, 1998; Molan & Brett,1998). For removing, simple bathing is enough (Molan & Rhodes, 2015). Reasons of honey's wound healing property can be explained by its antimicrobial and anti-inflammatory effects. Honey also regenerates tissues with direct nutrient effect and by creating osmotic outflow it helps eliminating dirt and debris from wound. Hydrogen peroxide also helps fibroblast proliferation and angiogenesis by VEGF release under influence from macrophages (Oryan et al., 2016). Another contribution of honey is its ability to eradicating bacteria while creating moist environment and eliminating bad smells. By adding honey dressing to usual therapy, surgical costs and hospital stay can be diminished (Efem, 1988).

Majtan et al. (2010) observed elevated production of mediators such as cytokines (TNF-alpha, IL-1beta and TGF-beta) and matrix metalloproteinase-9 (MMP-9) from keratinocytes; MMP-9 influenced degradation of type IV collagen in the basement membrane after honey incubation. Shamloo et al. (2021) produced a Chitosan/Gelatin/PVA hydrogel enriched with honey and observed product's effect in in vitro and in vivo studies. Honey containing gels increased cell growth and contributed to preservation of well-structured layer of epidermis containing mature collagen. Honey founded effective especially on second degree

partial burns (Pramesty, 2021). Jain (2021) informed that they are using medical grade Indian honey for patients who has diabetic foot in their Diabetic Foot and Wound Care clinic. Another study on ulcers has been searched on oral ulcers in the free gingival graft (FGG) donor site. Because of post-operative pain and high costs of periodontal dressings and acrylic stents, honey was promising as an alternative. Ziziphus lotus honey substantially increased number of blood vessels and epithelization rate on 14th day (Golpasandhagh et al., 2021).

Honey also used for solving oncology patients' problems such as infection free post-operative wounds after radical surgery of vulva carcinoma and treating radiation induced mucositis (Cavanagh et al., 1970; Motallebnejad et al., 2008). In a study conducted on Fournier's gangrene, it has been showed that, honey accelerated healing with decreased edema and scarring. Decrease in mortality was observed also (Haidari et al., 2014). Honey has been applied as topical remedy to patients with postoperative wound infections following caesarean section or hysterectomies, bacteria are eliminated, and wound healing is improved without any scar formation (Al-Waili, 2005).

2.8. Oral Health and Honey

Honey have been used for maintenance of oral health because of its multifunctional form (Ramsay et al., 2019) Firstly, plaque forming can be inhibited by honey because of its antimicrobial property. In previous studies, *S. mutans*, *P. gingivalis* and *L. acidophilus* counts reduced with chewing honey (Atwa et al., 2014; English et al., 2004). Thus, honey was presented as periodontal protection (Chapple., 1996; Samani et al., 2011). Hidaka et al. (2008) observed anti-calculus effect (inhibition of oral calcium phosphate) of honey. Significant advancements were observed with topical application of honey to Lichen planus and lesions of desquamative gingivitis (El-Haddad & Al-Shawaf, 2013). Honey application on dental abscesses and chronic osteomyelitis also showed improvement in a study conducted on 10 dental infection cases (Elbagoury & Rasmy, 1993). Bulut and Tufekci (2016) observed honey activity on chemotherapy induced oral mucositis in pediatric patients. As result significant decrease observed in patients who honey applied before mucositis occurred compared to group which honey applied after mucositis occurred.

2.9. Ophthalmological Effects of Honey

Ophthalmological use of honey was recorded in Attica, Greece and India first (Molan, 1999). In India, honey containing eye drops still being used for several eye diseases (Mahawar& Jaroli, 2006). Further in an Indian Medical College, corneal ulcers precipitated by bacteria were treated by topical application of honey (Ajibola et al., 2012). Malian locals use natural honey to prevent

eye scarring caused by measles infection (Imperato& Traoré, 1969). Topical natural honey application accelerated epithelial healing on injured corneas (KerWoon et al., 2015). Another study conducted in vivo showed equal activity compared to usual treatments, by both oral and topical Tualang honey use on alkali chemical injury on rabbit's cornea (Bashkaran et al., 2011). Jankauskiene et al. (2007) observed that polyfloral honey eye drop treated dry eye syndrome when it is applied early stages of disease. Cernak et al. (2012) examined honey as antimicrobial prophylaxis for cataract surgery and vitrectomy patients. No difference observed between topical applications of 25% honey solution and 0.3% ofloxacin. Synergistic activity between manuka honey and oxacillin, tetracycline, imipenem, and mupirocin against methicillin-resistant *Staphylococcus aureus* (MRSA) has been found (Jenkins & Cooper, 2012). Bullous keratopathy is a disease with swollen cornea which caused by cataract surgeries usually (Goncalves et al., 2008). Hypertonic saline is used as treatment because of its osmotic effect, honey is suggested as replacement (Knezovic, 2006). In a study, healing effect of honey was observed by applying 4-5 drops daily, epithelial edema was eliminated, corneal bulla dissolved in both eyes (Mansour, 2002). Flavonoid component of honey has been found effective for cataract due to several pathways such as decreasing eye lens opacification via inhibition of oxidative stress, epithelial cell signaling, lens calpain proteases (Stefek & Karasu, 2011). Flavonoids also found helpful for glaucoma (Stefan et al., 2011).

2.10. Neurological Effects of Honey

Although honey has been searched as a therapy for many diseases such as gastrointestinal disorders cancer wounds, knowledge about relationship of neurology and honey remained limited. However, we can conclude neurological effects of honey according to results of in vivo experiments. Opinions on honeys beneficial effects on nervous system derive from ancient texts for example Ayurvedic formulation which given to boosting memory and concentration, maintaining strength for longer life (Mishra, 2011). Modern medicine focuses on neurologic development, memory, degenerative diseases and behavioral disorders while searching effects of honey.

First found trait is honey contributed to postnatal development of nervous system in newborn babies and preschool age children by neurogenesis mechanism in hippocampus and cerebral cortex. With this contribution, advanced memory and growth, decreased level of anxiety and increased intellectual performance is observed after a while (Oyefuga et al., 2012). However, adding honey to the diet during first year of life is not recommended because of

immune deficiency against botulinum toxin (Tollofsrud et al., 1998). Another experiment on postmenopausal women showed progress in immediate memory (Othman et al., 2011).

Antioxidative property of honey is one of the earliest discoveries about its benefits. Antioxidative process in nervous system includes decreased lipid peroxidation as result of superoxide dismutase (SOD) and glutathione reductase activity and thus free radical level is decreased (Oyefuga et al., 2012).

Oxidative stress causes inflammatory response, apoptotic response and necrotic response that eventuates as neuronal cell death and aging. Cai et al. (2011) showed honeys antidegenerative effect on hippocampal C1 region which is sensitive to oxidative stress. Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis are the subjects which researchers focus on currently (Mariani et al., 2005).

In vivo studies on rats helped discovering many behavioral and cognitive benefits of honey. A study showed decreased anxiety and increased spatial memory by measuring object recognition in honey fed rats compared control groups (Chepulis et al., 2009). Another study demonstrated increased level in exploratory, rearing and grooming activities in dose dependent manner (Oyekunle et al., 2010). Akanmu et al. (2011) experimentalized honey fed rats in tests such as Y-maze test, pentobarbital induced hypnosis, hole-board and elevated plus maze tests, picrotoxin seizure model, tail flick test and forced swimming test. As a result of this study memory boosting, anxiolytic, antinociceptive, anticonvulsant, and antidepressant effects of honey are observed, respectively. Further, honeys effect on glial cells beside of neurons were observed in a rat model with cerebral focal-induced ischemia (Galindo et al., 2011). This information added a new dimension to the neurodegenerative studies and neuronal injury associated with stroke.

Flavonoids and polyphenols which has neuroprotective effects can be stated as; Apigenin, Caffeic acid, Catechin, Chlorogenic acid, Chrysin (5,7-dihydroxyflavone, *p*-Coumaric acid, Ellagic acid, Gallic Acid, Luteolin and Naringenin (Rahman et al., 2014).

3. COMPARISON of PROMINENT FEATURES between DIFFERENT HONEYS

Honeys can have different properties because of their source, species of bee which producing that particular honey, season or place (Hoffman et al., 2021). Alvarez-Suarez et al. (2018) explained that, when honeys produced by *M. beecheii* and *A. mellifera* were compared; more activity against bacterial and especially yeasts such as Candida salbicans due to higher value of

bioactive compounds was observed in honeys produced by *M. beecheii*. Manuka honey has an important place in literature because of its well-known antimicrobial and antioxidant properties. However, previous studies proved that there might be other honeys with better abilities. In a study, it is indicated that, *M. beecheii* honey demonstrates more potent inhibitory activity against both Gram-positive, Gram-negative bacteria samples and *C. albicans* than other honeys including Manuka, with its non-specific action (Morroni et al., 2018). Another study conducted with several honeys such as Malaysian longan and rubber tree honeys, gelam and manuka honey; showed that sourwood honey has highest antioxidant effects (Moniruzzaman et al., 2013). It has been indicated that different honeys activate diverse pathways; for example, while Manuka and buckwheat activate p38, ERK1/2, and mTOR pathways than acacia, the PI3K pathway is mostly stimulated by manuka (Ranzato et al., 2012). A study stated since antimicrobial activity of Agastache honey (Figure 1) is close to Leptospermum (Figure 2) honey (Manuka), it can be used in topical applications for preventing wound infections (Anand et al., 2019). *Melipona marginate* honey is also used in studies and its effects are observed as reducing ear edema and decreasing myeloperoxidase activity (Borsato et al., 2014). Study of Malkoc et al. (2019) revealed that Blackthorn (Paliurus spina-christi Mill.) (Figure 3) honey which is a monofloral honey limited to Marmara Region of Turkey has high antimicrobial and antioxidant properties.

Figure 1. Agastache

Figure 2. Leptospermum

Figure 3. Paliurus spina Christi

4. DETRIMENTAL EFFECTS of HONEY

Honey is a food that should be considered while it is consumed because of several adverse effects. Although allergy is unusual, it can be caused from both pollen and bee proteins (Bansal et al., 2005). A case report notified an anaphylactic reaction to honey (Aguiar et al., 2017). Honey might be affected easily by environmental pollutants such as pesticides, heavy metals, antibiotics and substances used in beekeeping (Bogdanov, 2006). Another risk is botulism due to *Clostridia* spores which can be killed by gamma irradiation (Molan & Allen, 1996). Risk is more for infants below 1 year of age (Eijlander, 2011). In topical application, stinging pain or

burning sensation in wounded diabetes patients due to dehydrated tissues caused by high blood glucose can be observed (Simon et al., 2009). Lethality of Mad honey is well known. Reason for this lethality is Grayanotoxins, particularly Andromedotoxin founded in Ericaceae (Figure 4) plants (Hikino et al., 1979; Yavuz et al., 1991). Grayanotoxin activity is based on mechanism of prevention of inactivation by binding Sodium channels in body. Bradycardia, hypotension, nausea, vomiting, sweating, salivation, dizziness, weakness, loss of consciousness, fainting, blurred vision, chills, general convulsion and cyanosis are seen (Ozhan et al., 2004). Onat et al. (1991) revealed that bradycardia due to mad honey poisoning can be treated by atropine sulphate which is muscarinic receptor antagonist. Though one spoon of mad honey is enough to cause toxication, it still has been used as treatment of gastrointestinal system disorders, hypertension and as sexual stimulant by local people (Mutlu et al., 2017). For preventing deaths caused by mad honey and others, bioactive components must be specified and indicated by producers and sellers. Health professionals must take patient's history detailed and carefully (Ozhan et al., 2004). Fake honey is a method to reduce expenses and easing the processes of beekeeping. Production is carried out in various ways, such as feeding bees with sugar syrups instead of nectar or secretion, producing honey from these syrups or adding sugar syrup directly to honey. Honey forgery can be detected by various techniques such as determining the honey's proline content, potassium and sodium ratio (K / Na), and total pollen spectrum. If honey's source is specifically important for treatment, this situation should also be paid attention (Mutlu et al., 2017).

Figure 4. Ericaceae

5. CONCLUSION

Honey is a very nutritional food with many beneficial properties to health. Although these properties are confined to mainly antimicrobial, antioxidant, immune booster and nutritional regulating effects of honey for now; it is obvious that honey is far more beneficial than science know. Honey must be appreciated and its other specific activities on systems should be detailly defined in turn its use in medical areas can be expanded. Since ancient times, honey is seen as miracle; health experts can build a bridge between traditional and modern medicine by utilizing

honey. It shouldn't be forgotten that each honey has its own properties like bioactive components, activity in body, microorganisms, and toxins. Therefore, for both table consuming or with medical purposes, each party must be analyzed and labeled. Processes of production of honeys which are thought to be significantly beneficial for medical use and must be disseminated, must be standardized in terms of determining dose influenced by its bioactive component levels.

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DECLARATIONS

The authors declare that they have no conflicts of interest.

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