Honey As A Therapeutic Agent

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Abstract: The use of honey for prophylactic medicinal purpose is an ancient idea recently becoming an alternative approach to modern medicine with least possible side effects. Potent antibacterial activitiesof honey make it effective in preventing and clearing wound infections. The beneficial role of honey which attributed to its antibacterial property is due to its high osmolarity, acidity and content of hydrogen peroxide (H_2O_2) and non-peroxide components like the presence of phytochemical components. Honey may also possess properties like ant-inflammatory, deodresing and debriding of wound and stimulation of new tissue growth. Honey can be indicated in wound infection even in deep surgical wounds with infections that do not respond to the conventional therapy. Therefore, therapeutic use of honey should be a standard procedure in human and veterinary health care services.
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1. Introduction

Honey is a collection of nectar from many plants processed by honey bees. This natural product is well known for its high nutritional and prophylactic medicinal value (Ransome, 1937). It has potent antibacterial activity and is effective in preventing and clearing wound infections (Boutoille, *et al*., 2008; Stephen-Haynes *et at.,* 2014).

Honey was used to treat infected wound as longs as 2000 years before bacteria were discovered to be the cause of infections (Gunther, 1960). More recently honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, gram positive and gram negative bacteria. An antifungal action has also been observed for some yeast and species of Aspergillus and penicillium as well as all the common dermatophytes (Molan, 1992). Gencay *et al.,* (2008) indicated that supplementation of honey in presence of obstructive jaundice ameliorates bacterial translocation and improves ileal morphology. Moreover, honey combats antibiotic resistant strains of bacteria and prevents bacterial growth even in a heavily infected wound (Molan, 2006; Ahmed, *et al.,* 2003).

Therapeutic nature of honey comes from its chemical composition and properties, such as abroad-spectrum antimicrobial activity, deodorization, debriding and anti-inflammatory actions and stimulation of new tissue growth (Dunford *et al.*, 2000). Honey, for the most part, is made up of simple sugars and is an excellent source of energy. It is hypertonic and has been shown to be sterile and highly bactericidal (White *et al.,* 1993). Physiological properties of honey such as hyper tonicity, low pH and hygroscopic nature enhance wound healing when applied locally. Antibacterial effects were also attributing to these elements (Inqle *et al*., 2006).

Being non-toxic natural product and a broad-spectrum antibacterial agent effective even in resistant pathogens (Majtan, 2011), honey become interesting therapeutic agent. However, the clinical and laboratory application of honey is still underused. Therefore, the objective of this review is to illustrate properties and medicinal values of honey and hence provide scientificevidence to support the traditional use of honey in clinical cases for amelioration of different diseases.

2. Pharmacological Properties

Honey has a number of constituents and characteristics that can result in healing properties. These are studied in the following subtitles.

2.1. Chemical Composition

Honey mainly composed of sugars and water which accounts about 79.6% and 17.2% respectively. Major sugars of honey are levulose and dextrose which constitutes 38.19% and 31.28% correspondingly (Todd and Vansel,1992). However, the precise composition of honey varies according to the plant species on which the bee forages but the main constituents are the same in all honeys. Theaverage composition of honey is given in table 1 below.

The predominant acid found in honey is gluconic acid. Its presence in all honey originates largely from the activity of glucose oxidase which the bees add at ripening (White, 1993) and to a lesser extent from the bacterial action which occurs (Ruiz-Argueso, 1973).

The mineral and vitamin content of honey is very low, 0.02 %of its weight. Honey also contains a number of amino acids, proline, phenyalanine and aspartic acid with aconcentration of greater than 200 ppm (Bosi and Battal, 1978).

Table 1: Average composition of honey

Component	Average (%)
Moisture	1.7
Fructose	3.9
Glucose	31.28
Sucrose	1.31
Disaccharide calculated as maltose	7.31
Higher sugar's	1.5
Free acid as gluconic	0.43
Lactone as Glucolactone	0.14
Total acid	0.57
Ash	0.169
Nitrogen	0.041

Source: (White *et al*., 1996).

The main enzymes found in honey which are derived from the hypopharyngeal glands of worker honeybees, are invertase (which inverts sucrose to glucose and fructose); glucose oxidase (which oxidises glucose to gluconic acid and hydrogen peroxide in the presence of water); and amylase (diastase), which breaks down starch. Other honey enzymes originate from plants as catalase (a regulator of glucose oxidase activity); acid phosphatase; and a small proportion of amylase. The enzyme glucose oxidase is of considerable interest because its activity causes the production ofhydrogen peroxide which not only stabilizes the ripening nectar against spoilage but has microbicidal action (White, 1975).

2.2. Therapeutic Properties

Honey is an ancient remedy for the treatment of infected wounds to accelerate healing, which has recently been rediscovered, particularly where conventional modern therapeutic agents fail (Vanden Berg *et al*., 2008; Simon *et al*., 2008). The healing properties of honey can be ascribed to the fact that it offers antibacterial activity, maintains a moist wound environment that promotes healing, and has a high viscosity which helps to provide a protective barrier to prevent infection. There are many reports of honey being very effective as dressing of wounds, burns, skin ulcers and inflammations; the antibacterial properties of honey speed up the growth of new tissue to heal the wound (Lusby *et al*., 2002). When honeys applied topically rapidly clears wound infection to facilitate healing of deep surgical wounds with infection (Ahmed *et al*., 2003). The application of honey can promote the healing in infected wounds that do not respond to the conventional therapy such antibiotics and antiseptics. (Ahmed *et al*., 2003), including wounds infected with MRSA (methicillin-resistant *S. aureus*) (Dunford, 2000). Moreover it can be used on skin grafts and infected skin graft donor sites successfully (Misirlioglu and Eroglu, 2000).

The beneficial role of honey which attributed to its antibacterial property is regards to its high osmolarity, acidity (low pH) and content of hydrogen peroxide (H_2O_2) and non-peroxide components, i.e., the presence of phytochemical components like methylglyoxal (MGO). The antimicrobial agents in honey are predominantly hydrogen peroxide, of which the concentration is determined by relative levels of glucose oxidase synthesized by the bee and catalase originating from flower pollen (Molan, 1992; Weston, 2000). Most types of honey generate H_2O_2 when diluted, because of the activation of the enzyme glucose oxidase that oxidizes glucose to gluconic acid and H_2O_2, which thus attributes the antimicrobial activity (Bang *et al*., 2003). But in some cases the peroxide activity in honey can be destroyed easily by heat or the presence of catalase. Besides H_2O_2, which is produced in most conventional honeys by the endogenous enzyme glucose oxidase, several other non-peroxide factors have been found to be responsible for the unique antibacterial activity of honey. Honey may retain its antimicrobial activity even in the presence of catalase (absence of glucose oxidase) and thus this type of honey is regarded as non-peroxide honey (Simon *et al*., 2008).

Honey is characteristically acidic with pH between 3.2 and 4.5, which is low enough to be inhibitory to several bacterial pathogens (Haniyeh *et al*., 2010). The antibacterial property of honey is also derived from the osmotic effect of its high sugar content and low moisture content, along with its acidic properties of gluconic acid and the antiseptic properties of its H_2O_2 (khan *et al*., 2007).

It has further been reported that physical property along with geographical distribution and different floral sources may play important role in the antimicrobial activity of honey (Taormina *et al*., 2001). Several authors reported that different honeys vary substantially in the potency of their antibacterial activity which varies with the plant source. Thus it has been shown that the antimicrobial activity of honey may range from concentrations < 3 % to 50 % and higher (Lusby *et al*.,2005; Wilkinson *et al*., 2005). Basualdo *et al*. (2007) reported the bactericidal effect of honey to be dependent on concentration of honey used and the nature of the bacteria. The concentration of honey has an impact on antibacterial activity; the higher the concentration of honey the greater its usefulness as an antibacterial agent (Badawy *et al*., 2004).

In addition to antibacterial effect natural honey shows antifungal and antiviral effect. Pure honey

inhibits fungal growth and diluted honey appears capable of inhibiting toxin production (Ali-Waili and Haq, 2004). An antifungal action has also been observed for some yeast and species of Aspergillus and Penicillium, as well as all the common dermatophytes (Sampath kumar, 2010). Candidiasis, caused by Candida albicans, may respond to honey. Cutaneous and superficial mycoses like ringworm and athletes foot are found to be responsive to honey. This responsiveness is partly due to the inhibition of fungal growth and partly to inhibition of bacterial infection (Bansal *et al*., 2005).

According to Al-Waili (2004) topical honey application was safe and effective in the management of the signs and symptoms of recurrent lesions from labial and genital herpes compared to acyclovir cream (Shenoy *et al*., 2009). Honey has also been reported to have inhibitory effects on rubella virus activity (Bansal *et al*., 2005).

3. Actions

Mechanisms of antimicrobial activity of honey are different from antibiotics which destroy the bacteria's cell wall or inhibit intracellular metabolic pathways. The antibacterial activity is related to four properties of honey. First, honey draws moisture out of the environment and thus dehydrates bacteria (Simone, *etal*.,2008). Second, the pH of honey is between 3.2 and 4.5, and this acidity is low enough to inhibit the growth of most microorganisms. Hydrogen peroxide produced by the glucose oxidase is the third and probably the most important antibacterial component. Lastly, several phytochemical factors for antibacterial activity have been identified in honey (Emsen, *etal.,*2007).

3.1. Osmotic effect

Honey that contains<20% water is hyperosmolar (Eddy *et al.,* 2008). By being hyperosmolar, honey creates an unfavorable environment for the growth and survival of microorganisms (Molan *etal.*, 1999). High osmolarity substrates such as honey, glucose, and sugar pastes can inhibit microbial growth because water molecules are chemically tied to the sugar molecules. Honey binds water molecules whereby water is drawn away from the microorganisms reducing water availability that will compromise the microorganism's metabolism. The high osmotic potential of honey can also lead to the breakdown of bacterial membranes, thus inhibiting microbial growth. These conditions create a non-conducive environment for organism survival, leading to death (Molan, 2006). Therefore, the hyperosmolar condition created by honey is also important for treating infections because it prevents the growth of bacteria and encourages rapid wound healing (Archer, 1990).

However only undiluted honey is sufficient for preventing microbial growth because its osmotic inhibition is lost when honey becomes diluted by wound exudates. In addition the osmotic action on bacteria is limited to the wound surface only whereas other antibacterial factors can diffuse into wound tissues (Molan, 2002).

3.2. Acidity

Honey is characteristically found at an acidic pH ranging between 3.2 and 4.5 (Crane,1975). The acidity of honey is primarily caused by the presence of gluconolactone or gluconic acidat a concentration of approximately 0.23–0.98% (1.8–7.5mmol/kg) (White,1975). It is formed through the action of a glucose oxidase enzyme produced by the bees. According to Al-Waili and Saloom (1999), honey acidity is considered to be one of the factors that contributes to its antimicrobial activity. The glucose content of honey and its acidic pH may aid in bacterial killing by macrophages (Ryan and Majno, 1977). In addition, because of its acidic nature, honey can prevent microbial biofilm formation and cross contamination (Cutting, 2007).

Moreover, the acidity of honey creates an environment that facilitates the release of oxygen from the hemoglobin that is required for newly growing cells and the stimulation of white blood cells (Vijaya and Nishteswar, 2012). It is possible to increase the oxygen release rate from hemoglobin by lowering the wound pH via honey application, thus increasing tissue granulation and improving the wound healing rate (Olaitan *et al*.,2007; Al-Waili *et al.,*2011).

3.3. Hydrogen peroxide

The hydrogen peroxide (H_2O_2) that is found in honey is steadily produced by oxidation from the glucose oxidase enzyme which is secreted into nectar from the hypopharyngeal gland of bees. This enzyme activates when honey comes into contact with wound exudates. The H_2O_2produced is a potent antibacterial agent (Bang *et al.,* 2003). The production rate of H_2O_2 by glucose oxidase varies notably in honey and increases disproportionally depending on the degree of honey dilution (Molan, 1992). Even when honey is applied to the wound area, the rate of H_2O_2 production, destruction, and dilution by exudates in a wound varies over time (Pieper, 2009). The H_2O_2 produced by honey is not cytotoxic because its H_2O_2 concentration is approximately 1000 times lower than that of the 3% solution commonly used as an antiseptic (Dunford, 2005). The low concentration of H_2O_2 may act as a messenger in healing promotion and may stimulate both fibroblasts and epithelial cells (Lusby *et al*., 2002). Tur *et al*. (1995) reported that H_2O_2 stimulates fibroblast proliferation in vitro and angiogenesis in vivo.

Although the level of hydrogen peroxide in honey is very low it is still effective as an antimicrobial agent. It has been reported that hydrogen peroxide is more effective when supplied by continuous generation with glucose oxidase than when adding isolation (Pruitt, 1985).

3.4. Phytochemical factors

Phytochemicals are wide class of nutraceuticals found in plants which have health-promoting potential. Honey has a wide range of phytochemicals including polyphenols which act as antioxidants. Polyphenols and phenolic acids found in the honey vary according to the geographical and climatic conditions (Amiot, *et al.*,1989).

Terpenes, benzyl alcohol, 3, 5-dimethoxy-4-hydroxybenzoic acid (syringic acid), methyl 3, 5-dimethoxy-4-hydroxybenzoate (methyl syringate), 3, 4, 5-trimethoxybenzoic acid, 2- hydroxy-3-phenylpropionic acid, 2-hydroxybenzoic acid and 1, 4-dihydroxybenzene are some of the phytochemicals ascribed for the antimicrobial activity of honey (WWW, 2009).

3.5. Hygroscopicproperty

Hygroscopy is one of properties of honey and describes the ability of honey to absorb and hold moisture from environment (White,1996). In treating open wounds, honey is useful as it could help prevent scarring by keeping the skin moist, encourage the growth of new tissues, and allow easy removal of any dressing by preventing dressing from becoming stuck to the skin. Honey's hygroscopic properties also make it an ideal ingredient in a lot of cosmetics as it helps keep skin hydrated and fresh and prevents drying. Thus, some people call honey a natural "humectant" as it attracts and retains moisture.

3.6. Antioxidant property

Honeys have been shown to be one of the highest potential natural products in which phenolics, flavonoids, ascorbic acids, and some enzymes (glucose oxidase and catalase) serve as potent antioxidants (Al-Mamary *et al.*,2002; Islam *et al.*, 2012). The antioxidants found in honey work on wounds through two means. First, the antioxidants fight against microorganisms and decrease infections at the site of the wound (Estevinho *et al.*, 2008). Second, the antioxidants reduce reactive oxygen species (ROS) and inflammations caused by the wound and aid in the healing process (Phan *et al.*,2001; Estevinoho *et al.*, 2008). Honey sequesters and inactivates the free iron which catalyses the formation of oxygen free radicals.

3.7. Anti-inflammatory properties

Although inflammation is a vital sign of normal responses to infection or injury from wounding, excessive or prolonged inflammation can obstruct wound healing or even cause further damage to the wound tissues. Suppressing the inflammation and its associated pain in the wound area with honey reduces vasodilatation (Molan, 2002). This suppression results in reduced edema and exudates with positive effects on healing. The pressure created inside tissues from edema prevails through the blood flow of oxygen and nutrients through the capillaries (Chant,1999) which are required for leukocytes to combat infections and fibroblast multiplication for connective tissue synthesis (Molan, 2002; White, 2005).

The anti-inflammatory effects of honey can reduce ROS formation and prevent tissue destruction (Flohe, *et al.*,1985). Honey was reported to control both acute and chronic inflammation (Dunford, 2005). the anti-inflammatory effects of honey are supported by decreased amounts of inflammatory cells in histological studies of honey-treated biopsy specimens (Molan, 2002) and the ability of honey to alter the activity of immunocompetent cells in low pH (Lusby *et al.*, 2002).

3.8. Stimulation of new tissue growth

Wounds dressed with honey often have a rapid rate of healing. Honey is also able to start the healing process in dormant wounds. Honey has been reported to promote the formation of granulation tissue and to stimulate the growth of epithelium over wounds. It has also been reported that honey is a reliable alternative to conventional dressing for the management of skin excoriation around stomas (ileostomy and colostomy), giving a more rapid epithelialization of the raw surface (Aminu *et al.*, 2000). These clinical observations of the stimulatory effect of honey on tissue growth in wounds have been confirmed by measurements and histological observations in studies of experimental wounds in animals (Postmes *et al.*, 1997) where honey treatment has been shown to give improvements. In these experimental wounds honey has also been shown to stimulate the synthesis of collagen (Suguna *et al.*, 1992) and other connective tissue components (Suguna *et al.*, 1993), and to stimulate angiogenesis (development of new blood vessels) (Kumar *et al.*, 1993).

The stimulation of angiogenesis by honey could be via its production of hydrogen peroxide, as topical application of hydrogen peroxide has been found to enhance cutaneous blood recruitment in ischaemic ulcers (Tur *et al.*, 1995). In vascular, smooth muscle cells, hydrogen peroxide is endogenously produced as part of the process of response to stimulation by platelet-derived growth factor, and exogenous hydrogen peroxide in the concentration range of 0.1 to 1.0 mmol/l will also function in the response (Rao and Berk, 1992). The promotion of formation of granulation tissue by honey may also be via the stimulation of growth of fibroblasts by the hydrogen

peroxide produced in honey as hydrogen peroxide has been found to stimulate the proliferation of fibroblasts (Chung *et al.*, 1993). There is a large amount of evidence that hydrogen peroxide is involved in many cell types in the body as a stimulus for cell multiplication by acting at various points in the mechanisms of the cells that control the cycle of cell growth and division (Burdon, 1995). It has been proposed that low concentrations of hydrogen peroxide might be used to stimulate wound healing in place of the expensive cell growth factors used for this purpose (Burdon, 1995; Postmes and Vandeputte, 1999). However, this is feasible only if the concentration could be carefully controlled to avoid tissue damage (Chung *et al*, 1993).

3.9. Deodorising

Malodor is a common feature of chronic wounds and is attributed to the presence of anaerobic bacterial species that produce malodorous compounds from decomposed serum and tissue proteins. Honey rapidly deodorises wounds (Alcaraz and Kelly, 2002; Ahmed *etal.*, 2003). And it has the potential ability to minimize offensive-smelling wounds through its strong osmotic action, which draws exudates and lymph fluid from the wound out towards the surface to add the moisture needed for autolytic debridement (Pieper, 2009).

The rapid deodorising of wounds from honey dressings is probably due to more than just antibacterial action. The malodorous substances that bacteria produce in wounds, such as, ammonia, amines and sulphur compounds are formed from the metabolism of amino acids derived from decomposed serum and tissue proteins. Honey deodorizes wounds by providing a rich source of glucose that bacteria metabolise in preference to amino acids resulting in the production of a non-odorous metabolite lactic acid. Hence, malodorous compounds are not formed (Nychas *et al*., 1988).

3.10. Debriding

Debridement is a very crucial process that facilitates wound healing process. During debridement old dead cells or tissues are removed by mechanical, chemical, surgical, or autolytic means. There are several mechanisms through which honey facilitates the rapid debridement of wounds and aids in healing. Honey contains protease enzyme that induces wound tissues to start autolytic debridement (self-digestion) (Molan, 2002). Honey employs its intense osmolytic power to draw out lymph fluid from the wound tissue, thus creating the moist environment necessary for autolytically removing dead, damaged, or infected wound tissues. This mechanism ensures a continuous supply of proteases at the edge of the wound area and the overlying necrotic tissue. With this combined action, honey removes debris and effortlessly removes slough and necrotic tissue without any feeling of pain (White, 2005).

The presence of H_2O_2 in honey also plays an important but indirect role by activating proteases during debridement. There are two processes through which protease can be activated during wound healing. First, H_2O_2activates the inactive matrix metalloproteases in connective tissue into active protease (Peppin and Weiss, 1986). Second, it blocks an inhibitor molecule that is present in wound tissue (which is responsible for inactivating neutrophil serine protease) and makes protease active (Molan, 2002).

4. Indication

Honey has been used to treat infections in a wide range of wound types. These include burns (Efem, 1988), venous leg ulcers, leg ulcers of mixed etiology, diabetic foot ulcers, pressure ulcers, unhealed graft donor sites, abscesses, boils, pilonidal sinuses, infected wounds from lower limb surgery (Betts and Molan, 2001), and neonatal postoperative wound infection (Vardi *etal*.,1998). Honeyis used successfully for treating ulcerations following radical surgery for carcinoma of the breast and varicose veins. It is also used following radical surgery for carcinoma of vulva resulting in infection free wound (Cavanagh *et al*.,1970). It is also indicated in patients with postoperative wound infections following caesarean section or hysterectomies (Ali-Waili, 2005).

Honey is used for the treatment of various ophthalmological conditions like blepharitis, keratitis, conjunctivitis, corneal injuries, chemical and thermal burns to eyes (Shenoy *et al*.,2009). Biswal *et al*. (2003) investigated the use of honey in cancer patients suffer from mucositis, a side effect of chemotherapy that attacks the entire gastrointestinal tract from the mouth to the anus. There was significant reduction in the symptomatic grade mucositis among patients consumed honey post-treatment.

5. Contraindication

Honey is not completely free from adverse effects. For example, there has been a report on peppery sensation when honey is applied to ulcers in a patient (Oluwatosin *et al*., 2000). It is plausible that the low pH and high organic compounds in honey may contribute to the stinging sensation especially in some patients with more sensitized nerve endings. Sometimes honey contain dormant endospore of bacterium *Clostridium botulinum* which can be dangerous to infant as the endospore can be transform in to toxin producing bacteria in infant immature intestinal tract leading to illness and even death (Shapiro *et al*., 1998).

Honey may have undesirable effects on humans health such as intoxication events, including cardiac

dysrtythmias, hypotension, respiratory depression, and altered mental status caused by grayanotoxin present in nectar of Rhododendron and other plants (Choo *et al.*, 2008; Gunduz *et al.*, 2008).

However many studies reported honey as a nontoxic, non-allergenic, nonirritating healing agent with no cytotoxic effects (Toit and Page, 2009). It is a safe, cheap, and effective healing agent (Jull and walker, 2008; Gethin and cowman, 2005).

6. Conclusion And Recomendetion

Honey is an alternative medicine considered to be suitable therapy with an antimicrobial actionas well as other activities that are beneficial to the wound healing process like rapid autolytic debridement, deodorizing of wounds, stimulation of tissue growth, enhanced epithelialization and minimized scar formation. These effects are ascribed to various factors working either independently or synergistically the most salient of which are honey's acidity, hydrogen peroxide content, phenolic compounds, osmotic effect, nutritional and antioxidant contents, stimulation of immunity, and to unidentified compounds. Topical application of honey has been effectively used on mucocutaneous injuries, superficial skin burns and post operation wounds. In addition, honey has been used in some gastrointestinal, cardiovascular, inflammatory and neoplastic states. Therefore, Additional successful clinical evidence is required with valuable laboratory finding to establish honey as one of most effective topical medicine for treating wounds and the clinical usage of honey should be given emphasis.

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7/5/2017