

A Review on the Use of Honey in The Treatment of Wound Infection

ABSTRACTS

Honey is a sweet substance made by bees using nectar from flowers. Honey is of different types, but the *Apis mellifera* is the one most commonly used, consumed by people and collected by bee keepers. The flower from which bees gather nectar, determines the colour, chemical composition, flavour and aroma of the honey. The use of honey in folk medicine has been practiced since ancient times and has more recently been rediscovered by medical researchers for its use in dressing acute and chronic wounds, particularly where conventional modern therapeutic agents have failed. The wound healing property of honey is due to its antibacterial activity; the ability to maintain a moist wound condition, the high sugar content which hinders microbial growth, the high viscosity which help in providing a protective barrier to prevent infection, the immunomodulatory property which helps in wound repair, the enzymatic production of hydrogen peroxide and the high osmolarity which draws fluid out of the wound bed to enable an outflow of lymph, as occurs with negative pressure wound therapy. Different scientists reported honey, as having one of the most powerful inhibitory effect with regard to sixty species of bacteria. Although the inhibitory activity of honey has been established against wide spectrum of bacteria, it differs depending on the type of honey. Under different concentrations, honey has been reported to be active against a number of bacterial pathogens such as (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, *Salmonella*, *Shigella*, *Enterobacter* and Coagulase positive/ negative *Staphylococcus* etc.) isolated from wounds.

Keywords; Antibacterial activity, Bees, Nectar, *Apis mellifera*, Folk medicine, Enzymatic production of hydrogen peroxide, *Klebsiella*, *Escherichia coli*

1.0 INTRODUCTION

Renewed interest in honey for various therapeutic purposes including treatment of infected wounds has led to the search for the various antimicrobial activity of honey.^[1, 2] Honey is a sweet substance made by bees using nectar from flowers. The honey produced by the honey bee (The genus *Apis*) is the one most commonly referred to, as it is the type of honey collected by bee keepers and consumed by people. The *Apis mellifera* honey has been used since ancient times as a remedy in wound care. According to evidence found by anthropologist, Egyptians had used this approach about 5000 years ago.^[3] The use of honey on wounds, ranges from acute wounds, such as surgical incision wounds to hard-to-heal ulcers, such as diabetic foot ulcers (DFU). Studies have explained how the properties of honey boosts and improves the wound healing process.^[2,3]

The wide use of honey to treat different infections among Muslims and in many Islamic countries is based on the belief in the words regarding honey as stated in the Holly Quran about 1900 years ago “and your lord inspired the bee, saying: “Take your habitations in the mountains and in the trees and in what they erect, then, eat of all fruits, and follow the ways of your Lord made easy (for you).” There comes forth from their bellies, a drink of varying colour wherein is healing for men. Verily, in this is indeed a sign for people who think.^[4, 5] Evidence from animal studies and some trials has suggested that honey accelerate wound healing. The use of natural product to enhance wound healing is a common practice in many parts of the world.^[2] A survey conducted by Hermans^[6] to review the worldwide use of different treatment option for burns found that honey was used in 5.5% of instances. The composition of the nectar from which the honey originates dictates the honey composition. The natural anti-oxidants and flavonoids exhibit a wide range of biological effects including antibacterial, anti-inflammatory, anti-allergic, anti-thrombotic and vasodilatory activities^[4].

Honey has been used in folk medicine since ancient times and has more recently been rediscovered by medical researchers for its use in dressing acute and chronic wounds. Traditionally, honey has been used

to treat burns, infected and non-healing wound ulcers, boils Pilonidal sinus venous and diabetic foot ulcers. [7] A number of scientists reported honey, as having one of the most powerful inhibitory effect with regard to sixty species of bacteria. [4, 8, 9] These bacteria were found to be resistant towards antibiotics but not towards honey, this might be attributed to the fact that honey is nontoxic and produce no adverse effects. Moreover, honey is inexpensive, readily available and can be used by anyone. [8]

Honey is used in treating various ulcers, malignant wounds, and is used to ensure the cleanliness and reduction of wound size. Similarly, honey dressing quickened rates of healing in pressure wounds, and has been used to lessen foul odours emanating from wounds which cause a social barrier among patients. [10, 11] The antibacterial activity of honey is due to its acidity, hydrogen peroxide (H₂O₂), osmotic effect, nutritional and antioxidant content, stimulation of immunity and unidentified compounds. [12, 9] One important issue in evaluating laboratory and clinical evidence of the antibacterial efficacy of honey is to understand that not all honeys are alike. Blossom honeys are derived from the nectar that is collected by bees from the flowers of plants, shrubs, and trees, and they are distinct from honeydew honeys, which are produced by bees that collect secretions from injured plants, shrubs, and trees. Not only does the floral source influence honey composition, but also the species of bee, geographical location, harvesting process, subsequent storage conditions, and time impact on chemical characteristics [13]

As a result of the abuse of antibiotics, a number of pathogens evolve to become resistant and more virulent. Investigation into natural and potent antimicrobials seemed to be the right step to take. This review is set to discuss the various composition of honey, their classifications and the different activity it possesses against different types of Bacteria associated with wound infections.



(A): Honey Bees.

(B): Honey Bee on a calyx [34]

2.0 WOUND INFECTION

Wound is caused by a breach in the epidermis or dermis due to trauma or physiological change, activating the repair process. Wound is classified as either acute or chronic. [14] A broader and more general definition of wound infection, is an infection caused by physical injury of the skin as a result of penetrating traumas. Wounds break the continuity of the skin and allow microorganisms/normal floras to gain access to tissues and cause infection. Burns and chronic wound are particularly prone to infection, and the moist environment of chronic wounds creates an ideal growth medium for bacteria such as; *Escherichia coli*, *Proteus* spp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus* which in turn delayed healing. [11, 15] With the continued expansion of antibiotic-resistant bacteria, this has become an increasing problem. There is increasing interest in the use of topical antimicrobial to wound cure. Compounds such as honey, iodine and silver have been incorporated into wound dressings. [16]

2.1 Causes of Wound Infection

Wound infections are caused by the deposition and multiplication of microorganisms in the surgical site of a susceptible host. There are a number of ways microorganisms can get into wounds:

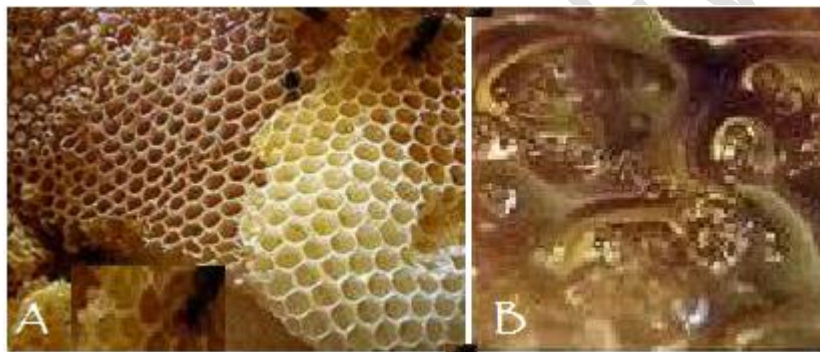
- a. **Direct contact:** transfer from surgical equipment or the hands of the surgeons or nurses.

- b. **Airborne dispersal:** Surrounding air contaminated with microorganisms that deposit unto the wound.
- c. **Self-contamination:** physical migration of the patients owns endogenous flora which are present on the skin, mucus membrane or gastrointestinal tract to the surgical site. The most common causative organisms associated with wound infections include *Staphylococcus aureus*/Methicillin Resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Enterococci* and *pseudomonas aeruginosa*.^[17]

3.0 CONCEPT OF HONEY

Honey is a sweet substance made by bees using nectar from flowers.^[18] Pure honey does not allow for the addition of any other substance such as water or other sweeteners. The flower from which bees gather nectar largely determines the colour, flavour and aroma of the honey.^[11] The chemical composition of honey depends on the flavour which it is made. Honey can be from specific types of flower nectar indeterminate origin or can be blended after collection for different taste.^[13, 19] Although the antimicrobial activity of honey has been established against wide spectrum of microorganisms, it differs depending on the type of honey.^[9]

Honey bees transform nectar into honey via regurgitation and store it as a primary food source in wax honey comb inside the beehive. The sweetness of honey is obtained from the monosaccharide fructose and glucose, which have approximately the same relative sweetness as that of granulated sugar.^[12, 19] Honey is often taken as an energy food and yield about 64 calories of energy which is high compared to other sweeteners. Its sugar is absorbed into the blood stream with complete digestion. The optimum storage temperature for honey is below (11°C) or (21-27°C) in air tight container.^[11, 18, 20]



(A): a Honeycomb. (B): a Raw honey^[34]

3.1 Classification of honey

- a. **Crystallized honey:**-Is honey in which some of the glucose content has spontaneously crystallized from solution as the mono-hydration. This is otherwise referred to as granulated honey. Honey that has crystallized can be returned to a liquid state by warming.^[12, 21]
- b. **Pasteurized honey:** - Is honey that has been heated in a pasteurized process (71.7°C) or higher. Pasteurization destroys yeast cells and liquefies any microcrystals which delays the onset of visible crystallization. Exposing honey to excessive high temperatures denatures the constituents and increases the level of hydroxymethyl furfural and reduces diastase enzyme activity.^[6]
- c. **Raw honey:** - Is honey as it exists in the beehive or as obtain by extraction, settling or straining without adding heat.^[18] Raw honey contains some pollen and may contain small particles of wax. local raw honey is sought after by allergy sufferers as the pollen impurities are thought to lessen the sensitivity to fever.
- d. **Ultra-sonicated Honey:** - Is honey that has been processed by ultra-sonication (a non-thermal processing). Ultra-sonication destroys most yeast cells, while those that survive generally lose their ability to grow, and this reduces the rate of honey fermentation substantially.^[18]

3.2 Local test for real honey

Honey can be altered by adding sugar cane syrup and other ingredient which can be processed to give the colour and near texture of honey. The aroma of adulterated honey varies with pure one. When diluted, pure honey does not leave sediments unless if not properly filtered. The originality of honey can be tested using honey stained match stick. When a match stick is stained with honey, Original honey brings light immediately, whereas adulterated honey does not.

Table 1. **Composition of honey**

The various Composition of honey			
Parameter	Average	Range	Standard deviation
Fructose (glucose)	1.23	0.76-1.86	0.126
Fructose (%)	38.38	30.91-44.26	1.77
Glucose (%)	30.31	22.89-40.75	3.04
Minerals (Ash) (%)	0.169	0.020-1.028	0.15
Moisture (%)	17.2	13.4-22.9	1.46
Reducing sugar (%)	76.75	61.39-38.72	2.76
Sucrose (%)	1.31	0.25-7.57	0.8700
pH	3.91	3.42-6.10	---
Total acidity	29.12	8.61-56.40	10.33
Protein (meg/100g)	16857	5-67.5	70.9

Adapted from Carina et al.^[19] and National Honey Board.^[20]

4.0 ANTIBACTERIAL ACTIVITY OF HONEY

Honey has been principally used for its antibacterial effects since ancient times.^[22] The first antibacterial activity of honey was recorded in 1892, but its use was limited due to the absence of scientific evidence. Ayurveda (Indian medicine) refer honey as the nectar of life and recommends its use in various ailments.^[29] Due to its antibacterial and wound healing activity, it is believed that honey could be used in the topical treatment of wounds and burns.^[23] but only recently have the antiseptic and antibacterial properties been chemically explained.^[4, 24]

Different factors contribute to the antibacterial effects of honey. The first antibacterial factor discovered in honey was H₂S which is not detectable in undiluted honeys. However, most honeys generate H₂S on dilution by the activation of glucose oxidase (an enzyme secreted by worker bees). This enzyme oxidizes glucose to gluconic acid with the release of hydrogen peroxide. The levels of hydrogen peroxide generated by honeys are influenced by the floral source, processing, and storage.^[12, 24] Low concentrations of hydrogen peroxide are normally generated over 24 hours, with maximal yields obtained from honey diluted to concentrations between 50% and 30%.^[25] reported some significant levels of antibacterial activity generated from honey dressings in heavily exuding wounds.^[26] Honeys that have been processed to delay the onset of crystallization, usually have low levels of antibacterial potency.^[13, 24] The inhibitory effects of honey against bacterial pathogens may be due to its high sugar content (80% to 85% sugar and 15% to 20% water) which hinders microbial growth. This is believed to be as a result of its osmotic effect, which prevents the growth of bacteria and promotes healing.^[24, 27] To remove contaminants, honey needs to be sterilized by gamma-irradiation, and its reported to have no effects on the antibacterial activity of the honey.^[28] An in-vitro experiment to determine the antibacterial effect of Omani and Africa honey against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* using standard antibacterial assay showed that both honey samples were active against these organisms. Omani honey was reported to have anti-*S. aureus* and *E. coli* activity against *Pseudomonas* which previously was reported not to be susceptible to honey.^[29] For the optimal inhibitory activity of honey at the deepest sites of infection, there need to be high concentration of honey on the surface of the wound.^[8]

Although honey does not allow vegetative bacteria to survive, it does contain viable spores, including *Clostridia*. Honey processing kills *Clostridia* spores without loss of any of the antibacterial activity.^[4, 24]

Under different concentrations, honey has been reported to be active against a number of bacterial pathogens isolated from wounds. This is reported in table 2.

Table 2: Antibacterial activity of honey against different bacteria under different honey concentrations

Isolate	Percentage of honey				
	10%	15%	20%	25%	30%
<i>Proteus vulgaris</i>	---	---	+	+	+
<i>Salmonella</i>	---	+	+	+	+
<i>Shigella</i>	---	+	+	+	+
<i>Streptococci</i>	---	+	+	+	+
<i>Citrobacter freundii</i>	---	+	+	+	+
<i>Citrobacter diversus</i>	---	---	+	+	+

<i>Escherichia coli</i>	---	---	+	+	+
<i>Enterobacter cloacae</i>	*	*	*	+	+
<i>Proteus mirabilis</i>	---	---	+	+	+
<i>Klebsiella pneumoniae</i>	---	---	+	+	+
Coagulase positive <i>Staphylococcus</i>	---	---	+	+	+
<i>Bacillus anthracis</i>	*	*	*	+	+
<i>Pseudomonas aeruginosa</i>	+	+	+	+	+
Coagulase negative <i>Staphylococcus</i>	+	+	+	+	+
<i>Haemophilus influenza</i>	*	*	*	+	+
<i>Listeria monocytogenes</i>	*	*	*	+	+
<i>Mycobacterium tuberculosis</i>	*	*	*	+	+
<i>Salmonella choleraesuis</i>	*	*	*	+	+
<i>Streptococcus pyogenes</i>	*	*	*	+	+
<i>Staphylococcus epidermis</i>	*	*	*	+	+
<i>Pasteurella multocida</i>	*	*	*	+	+
<i>Serratia marcescens</i>	*	*	*	+	+
<i>Staphylococcus aureus</i>	*	*	*	+	+
<i>Streptococcus pneumoniae</i>	*	*	*	+	+
<i>Streptococcus mutans</i>	*	*	*	+	+
<i>Alcaligenes faecalis</i>	*	*	*	+	+
<i>Vibrio cholerae</i>	*	*	*	+	+
<i>Mycobacterium phki,</i>	*	*	*	+	+
<i>Enterobacter aerogenes</i>	*	*	*	+	+

Keys: (---) = Active. (+) = active. (*) = No data is available on the concentrations. Adapted from Subrahmanyam et al. [2] Ahmadi et al. [4] Ramalivhana et al. [9] and Wasihun and Kasa. [13]

5.0 CLINICAL CONDITIONS THAT RESPOND TO TREATMENT WITH HONEY

Honey is one of the most widely used topical agent for wound care. Its used can be traced back to Egypt's ancient times. Its application ranges from acute wounds, such as surgical incision wounds to hard-to-heal ulcers, such as diabetic foot ulcers (DFU). [35] Effective wound treatment with honey depends on the appropriate management of the main disease(s), which a patient is suffering from, as well as any systemic infection and wound bed preparation. However, in some patients like diabetic patients, where circulation may be impaired antibiotic delivery to the wound tissue (to treat systemic infections) can be compromised. [36]

In diabetic wounds, the important factors that impaired wound healing, are the hydroxyl radicals and hypochlorite anions, formed from the superoxide anions produced by activated polymorph nuclear neutrophils (PMNs) at the wound site. The superoxide anion usually reacts with the nitric oxide produced by macrophages to form peroxynitrite, a third strong oxidant that damages the surrounding tissues. [37] In a study conducted by Astrada et al. on the successful treatment of a diabetic foot ulcer using Trigona honey, this honey variety seemed promising as it prevents the critical colonisation advancement in wound infection, as demonstrated by the decline in wound bed temperature after one month of treatment [38]

The wound healing properties of honey in general results from its antimicrobial and antioxidant properties, although the chemical constituents vary depending on the honey type, the types of bee and the nectar, geographical and climate conditions. The low water concentration possesses by honey causes wound pain, especially after few minutes of application (about 30 minutes). The use of honey with low water content should be avoided as it results in a cascade of cellular responses, especially in sensory neurons, which can result in pain in the wound. This is linked to the higher viscosity of water-based ointments in comparison with normal saline which may cause the cellular membrane within the wound bed to shrink during wound dressings. [24, 30, 35]

Some among the factors limiting the use of honey for clinical use includes; honey contamination by Microbes, pesticides and antibiotics among others. Honeys meant for medical use should ideally be produced hygienically in unpolluted areas. Unlike honeys produced for human ingestion, those selected for use in medical devices are usually chosen on the basis of their antibacterial potency. Several medical grade honeys are being used clinically in licensed wound care products. [39]

Some of the clinical conditions that respond to treatment with honey include the following:

- The use of honey as regards to wounds:** - in these, honey act as highly viscous barrier preventing bacteria penetration and colonization of wound surface. [2]

- b. **The use of honey to treat severe acute post-operative wound infection:** Topical application of crude undiluted honey have been used in the treatment of severe acute post-operative wound infection caused by Gram positive and Gram negative bacteria following caesarean sections and hysterectomies. This prevents bacterial infections, reduced period of antibiotic use and hospital stay, accelerated wound healing, prevent dehiscence and used for restructuring and results in minimal scar formation.^[31, 24]

6.0 HOW TO USE HONEY

In minor burns, it is recommended to pour some clean water immediately, as this reduces the temperature. Afterwards, honey can be applied directly or soaked in gauze before its applications onto burns, and wound. Occlusive or absorbent secondary dressings are applied to prevent honey from oozing out, and the frequency of dressing changes depending on how rapidly the honey is diluted by the exudates which decline as treatment progresses.

7.0 RELIGIOUS SIGNIFICANCE OF HONEY

In Islam, there is a chapter (surah) in the Holy Qur'an called an-Nahl (the bee).^[5] According to his teachings (Hadith), Muhammad (Peace be Upon Him) strongly recommended honey for healing purposes (Sahih Bukhari Vol. 7).^[33] The Qur'an promotes honey as a nutritious and healthy food^[5]. In Christian New Testament, (Mathew 3:4).^[32] John the Baptist is said to have live for a long period of time in the wilderness on a diet consisting locust and wild animal.

8.0 CONCLUSION

The medical grade honeys have potent in-vitro bactericidal activity against antibiotic resistant bacteria, that cause several life threatening infections among humans. There is a large variation in the antimicrobial activity of some natural honeys, which is due to spatial and temporal variation in sources of nectar. There is also some evidence to suggest that honey may actively promote wound healing. In laboratory studies, it has been shown to have an antimicrobial action against a broad Spectrum of bacteria causing wound infections. The antimicrobial activity in honey is due to enzymatic production of hydrogen peroxide, low pH level, low water activity of honey and its high sugar content, (high osmolarity) which is enough to hinder the growth of microbes. However, further research is needed to optimize the effective use of this agent in clinical practice. Present evidence supports the finding that honey, due to its various modes of action is useful in the treatment of superficial and partial-thickness burns and chronic wound infection.

9.0 RECOMMENDATION

Efforts should be made by relevant stakeholders, communities, health care providers and the Government towards the following;

- i. The use of honey in wound dressings should be adopted, as substitute for antibiotic because of its effect on bacterial pathogens.
- ii. The intake of honey frequently is recommended in order to reduce the incidence of common bacterial infections.
- iii. Precaution against loss of antibacterial activity should be taken and honey with high activity should not be blended with honey of low activity because a honey with low activity could as well have components present that destroy antibacterial activity.
- iv. Topical use of honey on wounds is advised to prevent bacterial infection thus accelerate wound healing.
- v. Honey for transaction should be well packaged in brown glass containers like other medical products to prevent loss of antibacterial activity on exposure to light.

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