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Honey: An overview of Skin health benefits

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ABSTRACT –
Honey has proved its medicinal and health effects as a natural food supplement. It is a potential therapeutic due to its antioxidant, antibacterial, anti-inflammatory, antifungal, antiviral, and antidiabetic activities. it also exhibits strong wound healing capacity. It is also immunomodulatory, estrogenic regulatory, antimutagenic, anticancer, and numerous other vigor effects. There are a lot of studies done on the medical uses of honey, its composition, the antibacterial properties etc. the purpose of the study is to bring all the information together and try to relate the composition and the properties of honey . as well as to look at the recent developments in using honey as a therapeutic agent.

INTRODUCTION --
Honey has become an essential commodity found in almost every house because of its nutritional and therapeutic properties. Using the nectar and honeydue from plants, bees, that belong to apiae family, make a wonder substance called "Honey". Thus honey is a natural plant product. Synthesis of honey is a complex process . it begins with the collection of floral nectar (floral or blossom honey) or secretions rich in sugar from insects (honey due honey) as raw materials, which are stored and processed in the bee hives. The collection of nectar can either be predominately monofloral (single species of plant) or multifloral (multiple species of plant) which can give rise to unique properties and distinctive tastes. Bees use the nectar, some sweet secretions present of the plant, and some excretory products by insects (hemipteran) which parasitise on plants in making honey (1). The nectar collected by bees has a lot of moisture (up to 93%) (2). Honeybees flutter their wings over the collected honey to evaporate off the water to bring it down to 20%. Then they add enzymes to break down the nectar sugars (3). All these processes modifies nectar to honey. Honey is said to be self preserving due to the high concentrations of sugar (> 70%) According to Codex Alimentarius published by the Food and AgricultureOrganization (FAO) and Directive 2001/110/EC, Honey is legally defined as "The natural sweet substance produced by Apis mellifera bees from the nectar of plants (blossom honey) or from secretions of living parts of plants or excretions of plant-sucking insects on the living parts of plants (honeydew honey), which the bees collect, transform by combining with specific substances of their own, deposit, dehydrate, store and leave in honeycombs to ripen and mature" (4)

HONEY – COMPOSITION
Honey is said to have over about 181 ingredients with numerous properties and wide use. Honey is a heterogenous mixture of several ingredients (5). Among all the constituents, glucose and fructose form a major percentage, thus honey is a supersaturated sugar solution(3). The ratio of fructose / glucose varies from 1 to 2 in several samples of honey. These percentages can differ significantly due to botanical sources, nectars, and seasons. The other predominant sugars are rhamnose, trehalose, nigerobiose,isomaltose,maltose,maltotetraose,maltotriose,maltulose,melezitose, melibiose, nigerose, palatinose, ranose, and erlose (6,7). Other than sugars honey contains water, minerals, phenolic compounds, organic acids, proteins, enzymes and a few vitamins (8,9). Honey can be characterized by products which are formed by enzyme-catalyzed reactions and non-enzymatic reactions. Glucose oxidase, amylase, catalase, peroxidase, invertase and lysozyme are important enzymes in honey. The hydrogen peroxide and gluconic acid formed by the action of glucose oxidase are important for antibacterial action of honey(10). One of the studies reported that H_2O_2 in diluted honeydew honeys is produced through an alternative non-enzymatic pathway, where plant polyphenols participate in the process of gradual H_2O_2 production (11). Hydrogen peroxide is an important component of honey to exert antimicrobial activity, and it is also first antimicrobial substance identified in honey (12). Another function of peroxide could also be to prevent the fermentation of immature honey(13). Production of hydroxymethylfurfural (HMF) from glucose or fructose is an example of non-enzymatic reactions in honey.

Honey has some acids like citric acid, succinic acid, lactic acid, tartaric acid, acetic acid, formic acid, oxalic acid, pyromucic acid and benzoic acid formed during honey formation. Mature honeys have higher amounts of these acids. The pH of honey can range between 3.4 – 6.1, average being 4.3 (14).

A variety of polyphenolic compounds are present in honey.They can scavange free radicals and inhibit oxidation, and have antimicrobial activity. The important phenolic group compounds are Hydrocinnamic acid (and its derivatives p-comaric acid, ferulic acid, caeic acid and sinapic acid) and Hydroxyl benzoic acid (and its derivatives vanillic acid, salicylic, syringic and gallic acid)(15). The flavonoids are constituted by pinocembrin, quercetin, chrysin, hespiratin, kaempferol and naringenin. Some of these are heat labile. (16).

Bisabolol. Thymol, cineol and farnesol are some essential oils in honey. Among the amino acids present in honey proline takes a major composition of 50-80%. Small quatities of vitamins are seen in honey , like the pyridoxine, thiamine, p-amino benzoic acid, riboflavin, vitamin C, A and E , pantothenic acid and folic acid. Manganese, Iron, zinc, magnesium, copper, sulfur, calcium, potassium, and phosphorus constitute the minerals in honey. Although the quantity of these minerals was less, they are very valuable because of their bioavailability. Some of these minerals have a bioavailability of 80 – 90%(17). It was reported in a study that H_2O_2 in aqueous solution could not oxidize nucleic acids, proteins or lipids in absence of transition metal ions such as Cu(I) or Fe(II) (18).

Bee defensin-1 is an antimicrobial peptide (AMP) found in bee hemolymph and is produced in their salivary glands, and it is incorporated into honey during the primary processing
Every honey is specific because of some volatile compounds present in small quantities(19). Some of these compounds have antimicrobial properties. The volatile compounds in Hungarian honeys are around 0.12 – 0.26% (20), which show antimicrobial activity. Ulmo honey volatiles also have similar properties(21).

The proportion of chemical components of honey , the way it tastes , the color, are dependant on the botanical origin, species of bees, and geographical location. Nevertheless it is also influenced by weather conditions. The procedures followed for processing and packing also effect the composition. The age of the honey also determines the composition of certain componants in honey.

HONEY -- AGAINST MICROBES

Honey is being used worldwide for its nutritional and therapeutic benefits. Its use can be traced to very ancient vedic period. Furthermore, references are there to prove honey consumption in the Bible (The Bible, Proverbs 24:13) and in the Quran (16:68–69). The potential of honey to be used as a therapeutic agent is because of its antioxidant and antimicrobial function.

Inside the cells oxidation reactions occur naturally producing free radicals. These free radicals in turn undergo chain reactions during which they cause damage to cells, tissues and eventually the physiological functioning of the cell. Antioxidants are compounds that can donate an electron to the free radicals, neutralizing, reducing, or removing their ability of damaging cells and protect the essential biomolecules such as nucleic acids, lipids, and proteins from getting oxidized . The antioxidant and antimicrobial properties of honey are mostly attributed to the presence of polyphenols and flavonoids (22- 26). There are some non phenolic compounds in honey which also have antioxidant properties (27). The high concentration of sugars combined with the low moisture content are responsible for the low water activity values of honey, which range from 0.562 and 0.62 (28,29), and cause osmotic stress in microorganisms (30,31).The sugars glucose and fructose comprise the highest percentage in honey. The sugars present in honey have shown to interfere in bacterial quorum sensing (32,33), making survival of bacteria very difficult.

The high sugars cause osmotic pressure which interferes with the formation of biofilm by bacteria (34).
The essential oils of honey though not studied in great detail are said to have antioxidant properties(35). The bactericidal efficacy of honey was reported more than a century ago by Van Ketel (36), and those findings prompted extensive research on honey over the next decades . There are in vitro and in vivo studies which have demonstrated the antimicrobial, antifungal, and antiviral activities of honey (37 -39) . The antimicrobial activity of the various types of honeys can be due to the generation of hydrogen peroxide (H_2O_2) (40 -42). The action of glucose oxidase on the glucose of honey results in the formation of hydrogen peroxide and gluconic acid (43,44) . A study by azhar sindi etal showed that the western Australian honey solutions showed antibacterial and antibiofilm activity which was proportional to the amount of hydrogen peroxide that they contained. They also showed there is a decrease in bactericidal activity after adding catalase to honey solutions (48).

A recent study observed that the peroxide content in a >10 year old honey may fall to 50%, yet retained sufficient therapeutic function. This is referred to as nonperoxide activity (NPA).This gave a conclusion that the antibacterial activity of honey is because of hydrogen peroxide and also other components in honey which act synergistically (45). 1,2

dicarbonyls are NPA substances, which are highly reactive and are formed from Maillard reactions. 1,2 dicarbonyl breakdown product, the methylglyoxyl has antimicrobial activity. The Manuka honey has methylglyoxyl as main antibacterial compound (46), with concentrations ranging from 38 to 1541 mg/kg) (47).

Fenton reaction is important as it forms hydroxyl radical from the hydrogen peroxide of honey. The hydroxyl radicals in turn cause oxidative stress in bacteria. Another chain of reactions that trigger formation of hydroxyl radical is the hydrolysis of hydrogen peroxide, which forms oxygen, this oxygen in turn helps in auto oxidation of polyphenols in the honey. The polyphenols will get triggered to form hydrogen peroxide and this gives rise to more hydroxyl radicals. Presence of trasition metals is required for these reactions (49)

It has been observed that the H_2O_2 can react with benzoic acid present in honey to form peroxy-acids. The peroxy acids are very stable and strong antimicrobial agents than H_2O_2, and they are resistant to catalase activity (50,51).

Manuka ,avocado, chestnut, and a polyfloral honey have induced membrane depolarization to a significant degree in p. aeruginosa, S. aureus, and E. coli (52- 54), which led to collapse in membrane potential. This makes the bacteria very difficult to survive due to inability of bacteria to generate the energy required for several processes (52).

Iron is an important mineral for bacterial metabolism. Manuka honey is shown to chelate the iron in *E. coli* (55,56) as well as on P.aeruginosa (56,57) and S. aureus (55),and tampering its survival.

There is a study by Bouza etal, which hypothesized that the decrease in membrane potential, and an increase in permeabilisation, together cause an increase in the drug uptake by the bacteria , thus enhancing the drug potency(52). This can be correlated with the activity of Manuka honey, where it was able to restore the tetracycline antibiotic activity against bacterial strains that were otherwise resistant (52,58).

Bacterial biofilms are complex surface attached communities of bacteria held together by self produced polymer matrixes mainly composed of polysaccharides, secreted proteins, and extracellular DNAs. It is now understood that about 40 80% of bacteria cells on earth can form biofilms (59). The formation of biofilms is detrimental in several situations (60-62) . Bacteria due to the Biofilms get an extraordinary microbial drug-resistance, which makes them extremely difficult to destroy (63,64).Honey because of its osmotic properties, coupled with the low pH and the presence of H_2O_2 is able to inhibit bacterial growth, along with reducing or preventing the formation of biofilms, from both Gram-negative and Gram-positive bacterial species (65 - 71).Honey can inhibit biofilm when it is forming and also it reduces the number viable cells of bacteria (66- 68,71,72). Studies on the gene expression analysis also confirmed the role of honey on the expression of different genes related to the formation and the development of biofilms (73)

Plants in order to protect from oxidative damage and biotic and abiotic stress produce some metabolites which are phenolic compounds, which are transferred to honey through the nectar. Phenolic acids and flavonoids are the main families of phenolic compounds(74,75) A set of 10 types of honey (knotweed, linden, wild cherry, acacia, honeydew, oilseed rape, sunflower, phacelia, plain polyflora and hill polyflora) from Banat region were studied and their flavonoid content ranged from 9.29 mg QE/100 g for wild cherry honey to 263.83 mg QE /100 g for linden honey. Polyphenols were measured and found to be between 177.6 mg GAE/100g for acacia honey to 1159.3 mg GAE/100g for honeydue. They found linden honey to have the highest antioxidant properties (76). About 144 honey samples from northern poland were analysed for their antibacterial activity. Their total antioxidant activity was analysed by measuring the total phenolic content and the hydrogen peroxide generated. Some of the honeys showed very high antimicrobial activity, especially towards the staphylococcus with Minimal Inhibitory Concentration (MIC) values of only 1.56% (v/v). The authors contributed the antimicrobial activity towards the hydrogen peroxide and polyphenols (77).

The results of a research which was done on the honeys produced in apiaries located in Pomeranian Voivodeship (Northern Poland), confirmed presence of bacteria producing metabolites with growth inhibition potential against important human and animal pathogens (78)

Eucalyptus globulus is a plant known to humans for ages for its medicinal values. A mixture of essential oils and honey of eucalyptus is found to be good for skin as they have good antioxidant properties (79).

A study by katrina etal observed that there is macromolecular crowding in the ripened honey . They hypothesized that only under high concentrations of molecular crowding conditions, the hydrogen peroxide is produced and antibacterial activity is seen in honey (80)

Among the various factors contributing to antibacterial activities of honey, the low pH, osmotic pressure, bee defensin , methyl glyoxyl, low protein content and a high osmolality of honey are important. Most bacteria grow around neutral pH

ranging from 6.5 to 7.5. honey has a low pH range between of 3.5 and 5.5, which is acidic and unfavourable for the bacteria to grow(81). Bacterial cells shrink, dehydrate and cannot grow in the presence of honey because of high osmotic pressure exerted due to its high sugar content (82). A very high phytochemical diversity with various phenolic and flavonoid contents, which have a high carbon to nitrogen ratio, also contribute to antimicrobial property of honey (83).

One study observed that the peroxide present in honey could pass through plasma membrane through aquaporins, and in cytosol it mediates an increase in Ca^{+2} through melastatin. This in turn results in the healing of the wound. This is very similar to tissue regeneration by Ca^{+2} signalling. (84).

A study was conducted by Asma etal to investigate the mechanism of bactericidal action of two honeys, the yeminisidr honey (SH) and manuka honey (MH) against Escherichia Coli . They found that the SH honey acted by disrupting the bacterial wall permeability and increased the potassium and protein leakage. The MH on otherside inhibited bacterial protein synthesis. Both had an negative impact on the DNA function . Thus they concluded that honey can be used for bacterial wound infections(85).

A Chinese group worked on the antimicrobial and antioxidant activities of nine kinds of Chinese monofloral honeys and concluded that the fennel, agastache and pomegranate honey were best and had highest anti microbial properties, and thus these can be developed into medical grade honey. They also observed a positive correlation between the amount of total phenol content and its total antioxidant properties (86).

The tineas, most common fungal ailments are increasing with time (87). It is said every person will suffer with this infection at sometime of life (88). Athletes foot or tinea pedis has rosen to 25% in adults (89) , These long duration dermatophytes infections lead to significant morbidity burden (90). Honey has given positive results for a variety of fungal infections (91). A study showed agastache honey has antifungal property (92). Recently a study on the jarrah honeys antifungal activity was tested and found that it inhibited the dermatophytes with a minimum inhibitory concentrations(MIC) of 1.5 – 3.5%. It was also observed that the MIC rose to >- 25% in the presence of catalase (93).

A recent study conducted by Theun etal confirmed that medical honey irrespective of its origin has strong anti microbial activity reducing the growth of *C. auris* and other *Candida* species in patients of intensive care unit with high mortality rates. Another important conclusion was that the raw local honey was superior to the medical honey and was more efficient and inhibited the growth of almost all Candida species (94).

For the past several decades there has been the use of Honey in cosmetics and medicines as an antimicrobial, emollient, and humectant . With recent advent of licensing of sterilized honey for clinical use, there has been extensive usage of honey in a variety of modern cosmetics, (95). The antimicrobial effects of honey have been reported for a wide range of fungi (96), and bacteria (97 -99).

The antifungal properties of honey are due to its supersaturated concentrations of glucose and fructose sugars, and because of a diverse range of proteins of bee and plant origin, as well as pigmented and antioxidant compounds including polyphenols, flavonoids, and Maillard reaction products (100 -103).

HONEY – AGAINST ANTIBIOTIC RESISTANT MICROBES

Antibiotics are very commonly used as prophylactic or therapeutic agents to treat several infections in human being. Recently there has been indiscriminate use of antibiotics which led to emergence of drug-resistant bacteria. (104). Under selective drug pressure, susceptible to antibiotics, bacteria are killed or inhibited. While resistant bacteria or bacteria having acquired antibiotic-resistant characteristics have more chances to survive (104,105).The World Economic Forum reports the antibiotic resistance as a global risk and one of the greatest threats to human health. (106,107). On another side we have Anthropogenic climate change. Both the global climate variations and the increasing antimicrobial resistance (AMR) together are being a threat to human health for the past 5 decades. Today, antimicrobial resistance has become a challenging situation, not only for human health, but also for human-connected animals, farms, food, water, and natural ecosystems worldwide (108-113). The overuse and misuse of antibiotics accelerates this situation. Now we are facing a situation where we have bacteria which are able to resist almost all approved antimicrobial agents for their treatment. Consequently, even simple and common health problems have become very difficult, or even impossible, to treat (114,115).

Looking at the various health problems around the world, antimicrobial resistance(AMR) seems to be a serious one. It is a serious threat to human life around the world. There is an increase in the multi drug resistant bacteria, and limited or non availability of affective drugs. In order to combat this problem scientists are looking at alternate medicine. In this context a lot of attention is given to natural biologically active substances. One of the most important substance is the

honey. Moreover due to its various mechanisms of action (116,117), no side effects is honey became center of focus. No resistance development is recorded till today.

The pioneer work on ability of honey against antibiotic-resistant microorganisms was carried out in vivo, to heal a hydroxyurea-induced leg ulcer colonised by, MRSA (methicillin-resistant Staphylococcus aureus) using Manuka honey. The work concluded that Manuka honey with its rich content of MGO(methyl glyoxyl) not only had antibacterial properties against resistant bacteria but also helps in healing of the wound (118). Later several studies were done to to confirm the effects of Manuka honey on MRSA in vitro (119 -124), and in vivo (125), vancomycin-resistant *S.* aureus (126), and vancomycin-resistant enterococci (VRE) (127). Linezolid is an an oxazolidinone antibiotic used in the treatment of infections caused by a range of Gram-positive pathogens. It was demonstrated that Manuka honey increases the sensitivity of S. aureans to linezolid(139).

Ureaplasma parvum and Ureaplasma urealyticum, are pathogens without a cell wall with high levels of intrinsic and acquired antibiotic resistance. Manuka honey had anti bacterial effect on both these pathogens (128)

Honey has shown excellent results on antibiotic resistant bacteria. Buckwheat and multifloral honey from kazakhstan have shown beneficial and curing effects on methicillin resistant staphylococcus aureus and enterococcus faecalis. The study showed both these honeys had high content of phenols and excellent for use in wounds and skin infections (129)

Candida auris is a pathogenic yeast causing threats in intensive care units with very high mortality rates. To treat the of C.auris infection is challenging due to high resistance rates. A potential alternative antifungal treatment is medical-grade honey (130)

The Pseudomonas aeruginosa (MDR & XDR strains) causes an increased resistance to infection in burn patients creating an issue of infection control. A research study used honey successfully in a ZOUSH herbal ointment for gene silencing of Pseudomonas aeruginosa. They showed a decrease in the expression of genes exoS, lasS and lasB which improved wound healing. (131)

Ulmo90 honey from chile has been demonstrated to have antibacterial activity against all MRSA (Methicillin-resistant Staphylococcus aureus) isolates. It has been shown that ulmo honey showed lower MIC(minimum inhibitory concentration) (3,1 % - 6.3% v/v) compared to Manuka honey (12.5% v/v). ulmo honeys activity is because of the hydrogen peroxide (132).

A study aimed to evaluate the in vitro antibacterial potential of ten different rare Greek honeys in 5 consecutive dilutions against Verona integron-encoded metallo-β-lactamase (VIM)- or Klebsiella pneumoniae carbapenemase-producing multidrug-resistant Gram-negative pathogens. A lot of Physicochemical parameters such as hydrogen peroxide, free acidity, pH, total phenols, lactonic acid, total flavonoids, free radical scavenging activities, tyrosinase enzyme inhibitory activity and kojic acid were analysed, and their concentrations varied among different honeys. Even though the honeys were different varieties the damaging effect to the bacterial cells was the same regardless of the bacterial species or strain. (133)

Revamil, a medical grade honey, was shown to have antibacterial activity against several antibiotic resistant wound pathogens (134 -136). They also looked for any skin infections in the healthy volunteers, and found none.

Blossom, heather, highland, and Portobello orchard honeys from Scotland had antimicrobial acivity on clinical isolates of penicillin resistant Acinetobacter calcoaceticus, S. aureus, P. aeruginosa and E. coli (137).

The honey samples of several botanical origins from spain (avocado, chestnut, eucalyptus, rosemary, thyme, polyfloral) have also showed in vitro efficacy against MRSA and other pathogenic bacteria (Streptococcus pyogenes, E. coli, and P. aeruginosa) with different degrees of antibiotic-resistance. The effective concentrations were variable, ranging between 0.05 and 0.40 g/mL, depending on the honey variety and the microorganism tested (138).

HONEY -- SKIN CARE

Honey is not only used for treatment but has turned out to be a good skin care product. The components of honey inhibit the development of bacteria and fungi on the skin surface. It is suitable to be used for dressing of wounds and burns. Ayurvedic masters Characa and Sushruta included honey in their dressing aids to purify sores and promote the healing. Honey, a bee product, offers a broad-spectrum of biological properties including antimicrobial and wound healing activity. Importantly, antibacterial and anti-biofilm potentials of honey have been considered as an exclusive criterion for its wound healing properties .

The three layers of skin (epidermis, dermis, and hypodermis), are supposed to function as physical barrier against any external infectious agents. Wounds are defined as the disruption in the continuity of the skin, induced by mechanical, chemical, or thermal harms, and resulting in the loss of the defensive functions of this tissue (140). In The process of wound-healing the skin has to recover the integrity of the damaged tissue and has to regenerate the epithelium lost, and it is a very dynamic as well as very complex process which universally occurs in four overlapping steps: Hemostasis, Inflammation, Tissue proliferation, and Regeneration (141). These 4 overlapping phases help in healing of acute wounds in an efficient way (142 -144)

For the past several decades Honey was used as medicine . Honey due to its composition, like low water content (osmotic effect), , low pH (acidic environment), and presence of phenolic compounds, flavonoids, methyl glyoxal (MGO), lysozyme and defensin-1 (DEF-1) contributes to the antimicrobial activity. It inhibits growth of bacteria and fungi by reducing their development on the skin surface. All these properties make honey the best medicine for skin care and wound management.

Prolonged chronicity of wounds is normally related to a bacterial injured-tissue colonization, which can progress into a bacterial resistance to topical and systemic antimicrobial agents, or into biofilm development, which complicates, in both cases, their treatment(145). It may end up causing sepsis and inflammation in organs and lead to increased morbidity and mortality. The management of wound healing has become the primary field of therapeutic application of this natural product honey (146, 147).

Honey has been used for wound healing since ancient times, mainly due to its antimicrobial activity. In addition to the broad spectrum of antibacterial activity against common wound-infecting microorganisms, honey has been demonstrated to be effective against antibiotic-resistant bacteria and was able to restore the efficacy of some antibiotics against bacteria with previously acquired resistance (147-149). Furthermore, due to its several antimicrobial components and its different antibacterial action mechanisms, the development of bacterial resistance to honey is very unlikely (147,150,151). Moreover, the wound-healing ability of honey is also related to its anti-inflammatory and antioxidant activity, as well as its capacity to promote re-epithelialization and angiogenesis and stimulate skin and immune cells (152,153). All these mechanisms act together favoring the regeneration process of the damaged tissue with the help of honey.

The most common honey medical use is topical wound healing activity, as it preserves wound moistness due to its viscosity that acts as a barrier to infection (154)

HONEY -- TOPICAL OINTMENTS

Honey due to its excellent skin care activities can be used as dressing material. It can serve the purpose at a lesser cost compared to conventional dressing material. For people living in remote places honey can work as a first aid dressing material.

Honey is filtered and sterilized by gamma irradiation and is available in market as a medical product. Manuka honey (new zealend) , Tualang honey (Malaysia) Medi honey (Manuka based honey), Revamil (blossom based honey), honevo (kanuka based honey) are already in market.

Most chronic wound infections are caused by the bacterial biofilms which are highly resistant to antibiotic treatments. New Zealand honeys were examined for combating the polymicrobial biofilms in chronic wounds and found that honey-based wound dressings not only inhibited *P. aeruginosa* biofilm formation but also greatly reduced established biofilms. All these activities were found to be because of sugar component. Honey when used at clinically obtainable concentrations completely eradicated established *P. aeruginosa* biofilms. Thus Manuka honey from new zealand has a great future in treatment of infected chronic wounds. (155).

The physical properties of honey (viscous and inherently sticky) makes it difficult for direct application on an affected area, as it may liquefy at skin temperature. It becomes more fluid at higher temperatures; this restricts the body location on which it can be used. The liquefaction and leakage of honey leads to difficulties in maintaining the required therapeutic concentration for enough time. All these limitations can be solved by impregnating honey with other materials, such as collagen, gelatine, starch, cellulose, alginate, and agarose(154, 174 -177), and to develop wound care products which, compared to neat honey, are more convenient to use and, therefore, more appealing to patients and health care professionals.

The biomaterials, the cross linked polymers used in hydrogels have high biocompatibility, they have minimal inflammatory responses, tissue damage or thrombosis . They help cell proliferation and migration. They do not cause any irritation to the wound. They help in promotion of wound repair by transferring moisture between the wound and the dressing and also provide a means for loading growth factors and antibacterial agents (156), which would create a cool

and calm effect and also would relieve the pain associated with dressing changes.(157, 158). Epithealisation is another important aspect of hydrogel dressing. Cellulose, chitosan and alginate are some natural polymers that are used in hydrogels which possess high biocompatibility, immunogenicity and low toxicity and resistant to enzymatic breakdown.(159,160) . When compared with standard gauge dressings, the hydrogels have higher healing capacity. (161,162)

Honey has a small amount of protein originating from bee pollen . This protein could cause some allergy and hypersensitivity reactions. Fortunately honey used for dermatosesis goes through thorough filtration eliminating all the pollen particles. Consequently honey allergy is very rare (163). A study was conducted on bee keepers and not even one of them was found to be hypersensitive (164).

There are a lot of commercial wound dressings available in the market (165). Some of them may contain antimicrobial agents which may have cytotoxic effects, especially after prolonged use, leading to a delay in wound healing (165,166). Most of the time the dressings stick to the wound surface and then damage the newly formed epithelium. Some of these problems associated with conventional dressings can be overcome by incorporating natural products like honey to the formulations (166) . Honey is not a new product and is known to us for ages thus can be used by preference(167) . There is also evidence that honey can contribute to the four stages of wound healing—Haemostasis, Inflammation, Proliferation, and Remodelling—and it has a positive impact on the natural physiology of wound healing by reducing oedema and wound exudation (168). Furthermore, there are studies where honey has been shown to activate collagen synthesis, angiogenesis, autolytic debridement, deodorizing of malodorous wounds, and growth of fibroblasts and epithelial cells in wounds while also preventing scar tissue and keloid formation (169). As we have already mentioned, the wound healing effects of honey can be related to its high osmolarity and acidity, its ability to generate hydrogen peroxide and nitric oxide upon contact with water, as well as the presence non-peroxide factors, which collectively, all together exert antioxidant, anti-inflammatory, and antimicrobial activities. A lot of research studies have reported the successful use of honey to treat mild to moderate superficial and partial thickness burns (170-173), including a randomized clinical trial involving 105 patients that showed medical grade honey to confer significant clinical benefits in wound care . It is, however, challenging to apply neat honey as a wound healing agent. The US Food and Drug Administration (FDA) has approved several honey-loaded wound care products formulated as hydrogels, dressings, ointments, and pastes . Manuka products from genus Leptospermum are popularly seen in the market.. The other honeys with various phytochemical activities also have good wound healing properties. The Western Australian endemic flora produce unique honeys with anti oxidant and antimicrobial properties ,which are good for wound healing (178- 181) . Aside from honey type, other limiting factors provide further impetus for developing improved honey-based wound care products.

Alginate dressings are used because they can form gels when in contact with wound exudates. This results in excellent absorbency, and helps alginate dressings to maintain a physiologically moist environment while minimizing bacterial infections at the wound site (182). Commercially available alginate dressings include AlgicellTM and AlgiSite MTM, which are used to treat diabetic foot ulcers, leg ulcers, pressure ulcers, and traumatic and surgical wounds (183). In a study four types of honeys from western Australia, comprising a Jarrah honey, two types of Manuka honeys, and a Coastal Peppermint honey, and one, Manuka honey from new Zealand were formulated into alginate-based topical formulations. They made three formulations, a pre-gel solution consisting of 2–3% (w/v) sodium alginate solution with 70% (w/v) honey, as well as a wet sheet and a dry sheet. The formulated samples were appropriately packaged and stored over 6 months at 5, 30, and 40 C. it was shown that all samples retained all physical characteristics with no loss of integrity of the monitored honey constituents. Therefore it was concluded that the developed methodology is suitable to manufacture different honey-based formulations in a consistent and reproducible manner(186).

A team by Samiyah tasleem etal formulated an ointment which contained active honey upto 20% . This ointment was used in a clinical trial consisting of 27 patients(23 skin wound infection and 4 diabetic foot ulcer)the honey ointment was applied on a guaze, 2 to 3 times per day until the wound was completely healed. They found 99.16% and 95% healing on skin wounds and diabetic foot respectively. Thus the formula is very effective and is affordable due to low cost. (184)

It's a great challenge to deal with the outbreak of a highly resistant candida auris (pathologic yeast), in intensive care units . L-Mesitran Soft, a honey based formulation was investigated and found to have strong anti fungal activity. It was also observed that unprocessed local honey reduced the growth of nearly all *Candida* species more strongly than medical-grade honey(185)

Topical honey hydrogel formulations were prepared using three honey concentrations (25%, 50%, 75%) with gelling agents; chitosan and carbopol 934. The pH and spreadability were in the range of 4.3–6.8 and 5.7–8.6 cm, respectively. In-*vitro* antimicrobial activity using Disc Diffusion antibiotic sensitivity test against common burn infections bacteria*;* Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumonia *and* Streptococcus pyogenes.,*and* in-

vivo burn healing using burn-induced wounds in mice were assessed using honey hydrogel. Highest antimicrobial activity was shown by 75%honey chitosan. The formula was compared to commercial product and study concludes that 75% honey-chitosan hydrogel possesses greater wound healing activity compared to commercial preparation and could be safely used as an effective natural topical wound healing treatment (187).

Honeys from Kazakhstan have demonstrated a good microbial activity against microorganism of wounds and skin infections(129). Kumari etal (188) conducted a pilot study to understand the morphological and physical effects of honey on cutaneous and traumatic wounds and found excellent positive results without any adverse effects . similar results were reported by Al-Waili etal in surgical wounds (189).

Any type of wound is challenging in neonates due to the fragile and vulnerable skin structure. The injury is susceptible to various infections because the skin injury is open and is left to environmental conditions. A 23 week gestation neonate had a difficult wound, and was successfully treated using honey hydrogel. The outcome of this case was quick healing, very little scaring, and no functional problem to the affected extremities.(190).

HONEY --- COSMETICS

Honey in cosmetics is named "Honey" or "Mel" according to the International Nomenclature of Cosmetic Ingredient (INCI), it is an emollient or humectant, and exhibits moisturizing properties. Some cosmetics contain derivatives of honey, defined in the INCI as "Mel Extract" with moisturizing properties, "Hydrogenated Honey" which is humectant, and antistatic "Hydroxypropyltrimonium Honey". Hydroxypropyltrimonium honey is used in shampoos and hair conditioners. More often the concentration of honey in cosmetics is up to 10%. Higher concentrations (up to 70%) are obtained by dispersing in oils, gels or polymer entrapment (191).

CONCLUSION

Today pollution is a grave situation everywhere in the world. Most of the pollutants are man made. Not enough is done in this direction. Its not just humans but even animals are badly effected. Plants are no exception to this, rather plants are first effected by pollution. Due to the good effects of honey and no side effects noted, people have started using it a lot. Honey being a plant product could contain some pollutants which could be harmful for the users. There should be more studies done on the common pollutants of plants and also we should search for ways by which we can make honey free of pollutants.

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