Chapter

Therapeutic Properties of Honey

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Abstract

Honey has been used traditionally for ages to treat infectious diseases. These amazing properties of honey are complex as a result of the involvement of various bioactive compounds. Honey is becoming sustainable as a reputable and effective therapeutic agent to practitioners of conventional medicine and to the general public. Its beneficial role has been endorsed due to its antimicrobial, antiviral, anti-inflammatory, and antioxidant activities as well as boosting of the immune system. Also, other medical conditions discussed here which can be treated with honey include but not limited to diarrhea, gastric ulcer, canine recurrent dermatitis, diabetics, tumor, and arthritis, and honey can also be used for skin disinfection and wound healing. Most of the known factors that give honey these properties include its acidity, high sugar, hydrogen peroxide, and other non-peroxide properties. Some factors may affect the therapeutic properties of honey such as exposure to heat and light.

Keywords: antimicrobial, antiviral, wound healing, immune booster, skin infection, gastric ulcer

1. Introduction

Conventional medications have been utilized to treat infectious diseases for centuries, and one of the oldest remedies for microbial infection is honey. It has not been long that researchers rediscovered natural antimicrobial properties of honey [1]. Resistance to antibiotics is on the increase every day, and few new remedies are on the horizon, which led to further increased interest in the antimicrobial potency of honey. Many reports have shown that honey has antimicrobial activity against microorganisms such as protozoa, fungi, and bacteria, including viruses ([2], other references ought to be included). Despite the fact that bee honey is produced all around the world, its therapeutic properties may vary and are basically dependent on their entomological source (the type of bee), geographical location, and botanical origin (sources of nectars). Other external factors that may play some roles include but not limited to harvesting season, processing, storage condition, and environmental factors [1, 3]. The therapeutic potential of honey is greatly complex as a result of the action of various compounds as well as due to large variations in the concentrations of these compounds among honeys. The major biological properties that make it perfect as a therapeutic agent are antimicrobial (bactericidal or fungicidal), bacteriostatic (or fungistatic), anti-inflammatory potential, wound (sunburn healing) potential, antioxidant potential, radical scavenging activity, and antiviral activity [4–6]. Apart from boosting of the immune system, it can be used to treat other medical conditions such as diarrhea, gastric ulcer, canine recurrent dermatitis, diabetics, tumor, and arthritis and can also be used for skin disinfection and wound healing.

Honey is considered among the possible alternatives, which is natural, nontoxic, and with broad spectrum of action. This could be a promising substitute or supplement to antimicrobial agents, but some factors limit its use. Clinical applicability of honey has been hindered by incomplete knowledge of the antimicrobial activity and lack of precise mechanisms for determining the type of activity of honey, variations of honey, and its cost in some countries [2, 7].

Proof from Stone Age paintings indicates that treatment of illnesses with honeybee began for over 8000 years ago. The use of honey as a medicine has been delineated by many historical records such as antiquated parchments, tablets, and books—Sumerian clay tablets (6200 BC), Veda (Hindu sacred text) 5000 years, Holy Bible, Koran, and Hippocrates (460–357 BC), and Egyptian papyri (1900–1250 BC) [7, 8]. The Qur'an clearly demonstrated the potential therapeutic value of honey. The Lord has roused the honeybees, to fabricate their hives on trees, in hills, and in man's residences; from inside their bodies comes a beverage of varying color, wherein there is recuperating for mankind, verily in this is a good signal, for the individuals who give thought [9, 10]. In spite of the fact that various articles have been published concerning honey, the vast majority of them have concentrated on the biochemical investigation, sustenance, and non-food business use. Honey was utilized for the treatment of many illnesses or disease conditions including asthma, eye diseases, tuberculosis, throat diseases, hiccups, unsteadiness, hepatitis, exhaustion, obstruction, thirst, piles, wounds, skin inflammation, worm invasion, and recuperation of ulcers (**Figure 1**) [2, 5, 8]. These properties are possible due to some of these potentials of honey to be discussed.

1.1 Antimicrobial activity

Therapeutically, the importance of antimicrobial activity of honey cannot be overemphasized, particularly in circumstance where the body's immune responses may be inadequate to clear disease or infection. In other words, honey has proven

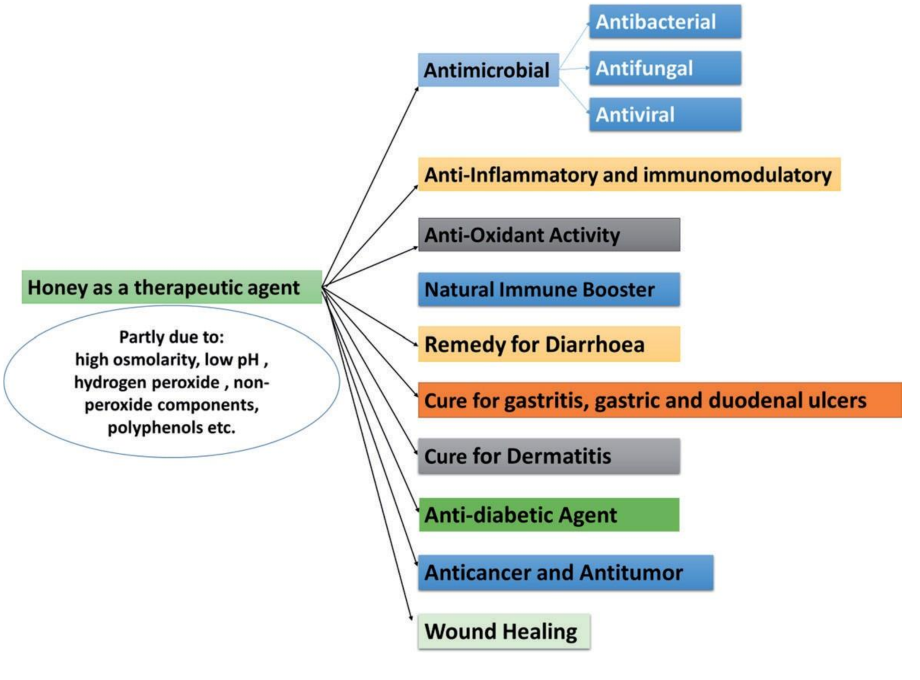

Figure 1.
Schematic representation of therapeutic potentials of bee honey.

to be an effective antimicrobial activity against both pathogenic and nonpathogenic microorganisms (such as bacteria, yeasts, and fungi), even in opposition to those microorganisms which have developed resistance to many antibiotics. The honey's antimicrobial effect could be bacteriostatic or bactericidal, relying upon the concentration used [4, 11]. Notwithstanding, its potentials have been credited to specific variables like high osmolarity (low water action), low pH (acidity), hydrogen peroxide (H_2O_2), and non-peroxide components [12, 13].

Moreover, bee honey is a solution of supersaturated sugar; these sugars prevent the thriving of microorganisms (bacteria and yeast) due to their high affinity for water molecules, thereby leaving little or no water to support their growth. As a result microbes become dehydrated and die in the end [11]. Naturally, the acidity of honey according to Fahim et al. prevents microbial growth, and usual pH of most of the pathogenic microbes ranges between 4.0 and 4.5 [14]. Be that as it may, the major antimicrobial potential has been reported to be due to hydrogen peroxide activity, a product of the glucose-oxidase enzyme oxidation of glucose, especially in diluted form of honey. The decomposition of hydrogen peroxide produces profoundly reactive free radicals, which respond and kill microbes. By and large, this honey property could easily be terminated in the presence of heat or due to catalase activity [15].

In any case, the antibacterial activity of some honeys may not always or necessarily be as a result of peroxide effect, but due to non-peroxide activity which results in a considerably more steady and stable antibacterial action. They are anyway called "non-peroxide honeys." Some examples of honey with non-peroxide activity are honeys from Australia (jelly bush—*Leptospermum polygalifolium*) and New Zealand (manuka honey—*Leptospermum scoparium*), which are hypothesized to have unidentified active component apart from the production of hydrogen peroxide. Unlike other honeys, they retain their potency to inhibit microbes even when catalase is present [2, 3].

It has been proposed that the principle part of this honeybee activity is probably of honeybee origin and partly due to plant origin. An appropriate solvent such as organic solvents (e.g., n-hexane, chloroform, ethyl acetate, and diethyl ether—by liquid-liquid or solid-phase extraction methods) could be used for extraction of the compounds exhibiting this activity. The separated mixes have been accounted for to incorporate flavonoids, unpredictable mixes (ascorbic corrosive, unbiased lipids, natural acids, carotenoid-like substances, and Maillard response items), phenolic acids, amino acids, and proteins [16, 17].

Other crucial effects of honey were related to its oligosaccharides. They have prebiotic properties, much like that of fructo-oligosaccharides. The oligosaccharides had been mentioned in reports to cause rise in population of some beneficial bacteria like bifidobacteria and lactobacilli, which are in charge of keeping up a sound intestinal microflora in human beings [18, 19]. In actuality, *Lactobacillus* spp. shield the body against some infections such as salmonellosis, and *Bifidobacterium* spp. limit the overgrowth of yeasts or bacterial pathogens in the gut wall, possibly lessening the danger of colon malignancy by out-contending putrefactive microbes equipped for freeing cancer-causing agents [18, 20].

The use of honey as a conventional remedy for microbial infections dates back to historical times [9]. There are reports on manuka (*L. scoparium)* honey, which has been proven to be effective against numerous human pathogens, inclusive of *S. aureus*, *Enterobacter aerogenes*, *Escherichia coli (E. coli)*, and *Salmonella* Typhimurium [13]. Some studies have found out that honey is very effective against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), and streptococci [2]. Be that as it may, the recently identified bee honeys may have benefits over or similitudes with manuka honey because of improved antimicrobial potential local production (in this manner—accessibility) and more noteworthy selectivity against medically important organisms [12]. In terms of susceptibility to bee honey of comparable antibacterial efficiency, coagulase-negative staphylococci are very just like *S. aureus* [13] which according to Fahim et al. were more susceptible than *Pseudomonas aeruginosa* and *Enterococcus* species [14].

The disk diffusion method is for the most part a subjective test for identifying the vulnerability of microorganisms to antimicrobial substances; be that as it may, the minimum inhibitory concentration (MIC) mirrors the amount required for bacterial restraint. Following the in vitro strategies, many microscopic organisms (for the most part multidrug resistant; MDR) causing human diseases were discovered to be readily susceptible to honeys [3, 14, 16].

1.2 Anti-inflammatory and immunomodulatory activities

In spite of the fact that inflammation is a critical part of the regular response to infection or damaged tissues, when it is extreme or delayed, it can forestall healing or even cause further harm. The presently existing literature has shown that inflammatory reaction has been modulated in preliminary clinical studies, animal models, and cell cultures. The most serious outcome of immoderate inflammation is the production of free radicals within the tissue. These unfastened radicals are initiated by specific leucocytes that are stimulated as major aspect of the inflammatory process, as inflammatory processes are what activate the series of cellular events which precipitate to the initiation of growth factors that influence proliferation of fibroblasts, angiogenesis, and epithelial cells [21]. Several honey types from different countries have been reported to have anti-inflammatory effect, including honeys from stingless bees [4].

The anti-inflammatory effect of bee honey is due to its substantial amounts of phenolic contents. The repression of the pro-inflammatory actions of inducible nitric oxide synthase (iNOS) and/or cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) is caused by these phenolic and flavonoid compounds [22]. Moreover, when diluted natural bee honey is ingested, it results in the decrease of the prostaglandins' concentration including prostaglandin E_2 (PGE_2), thromboxane B_2 (in plasma of normal persons), and prostaglandin $F_2\dot{\alpha}$ (PGF2á) [6]. Strangely, in a colitis inflammatory model, honey became as effective as prednisolone remedy. While many adverse side effects of corticosteroids and NSAIDS, honey has natural anti-inflammatory effect free from major side effects [23]
lso, honey and its substances have been shown to be engaged with control of proteins, inclusive of iNOS, COX-2, tyrosine kinase, and ornithine decarboxylase [23, 24]. There are reports on the induction for the production of tumor necrosis factor alpha, interleukin-6 (IL-6), and IL-1β, by different types of honey [24, 25]. As of late, some honeys such as Gelam honey have been shown to reduce ediators of inflammatory reactions, for example, TNF-α and COX-2, by means of weakening NF-κB translocation to the nucleus and in this manner hindering the initiation of the NF-κB pathway. It is well known that the NF-κB activation performs a key function within the pathogenesis of inflammation. It is believed that production of fermentation agents such as short-chain fatty acid (SCFA) is a result of the slow absorption of honey, and SCFA has immunomodulatory activities, which have been proven to be so. It means that these fermentable sugars produced from honey such as nigerooligosaccharides have the ability to induce the immune response [11, 26]. Also, nonsugar ingredients present in honey may be responsible for immunomodulation [27].

Likewise, the application of honey topically has been found and reported in some published studies to lessen the quantity of exudate and edema in wounds, the two of which are identified with the action of wounds' local inflammatory process [28, 29]. All these and other studies imply that bee honeys have true anti-inflammatory and immunomodulation properties.

1.3 Antioxidant activity

In the human body, the bee honeys' antioxidant capacity is due to its ability to decrease oxidative reactions, which is estimated by its ability to scavenge free radicals [30]. It is believed that the anti-inflammatory action of honey could at least partly be due to its antioxidant activity since what is involved in various components of inflammation is oxygen free radicals [25]. Notwithstanding, when inflammatory process is not [31] directly stifled by honeys' antioxidant contents, they can be relied upon to scavenge free radicals so as to decrease the quantity of harm that would in any other case have resulted [32]. Honey is naturally composed of various flavonoids (including chrysin, pinocembrin, hesperetin, quercetin, apigenin, galangin, and kaempferol), Maillard reaction products and peptides, ascorbic acid, phenolic acids (such as ferulic, ellagic, caffeic, and p-coumaric acids), tocopherols, catalase, superoxide dismutase, and reduced glutathione, most of which provide a synergistic antioxidant effect by working together [33, 34].

The antioxidant action of honey is exerted by repressing free radical formation and usually catalyzed by some metal ions like copper, iron, etc. These metal ions in complexes can possibly be seized by some common constituents of honey such as flavonoids and other related polyphenols, thereby keeping the development of free radicals in the first place [25]. In terms of some sources of nutritional antioxidants, there are various phytochemicals in different honey varieties (just as other substances, for example, vitamins, organic acids, and enzymes) which may serve the purpose. The quantity and kind of those antioxidants depend mainly upon the sort of the honey and its floral source. All in all, it is now well known that darker honeys possess higher antioxidant content than lighter honeys [34, 35]. It has been shown that sugar analogue of about 14 unifloral honeys (which ranges from 3.0 to 17.0 μmol TE/g) had no antioxidant activity when examined using an assessment technique called oxygen radical absorbance capacity (ORAC). Reactive oxygen species (ROS) as well as free radicals are some of the contributing factors to some of the processes of disease and aging [31, 36].

Organisms shield themselves from those unfavorable compounds, to some extent, by retaining antioxidants from antioxidant-rich foods. In healthy human adults, this also depicts the impacts of taking 1.5 g/kg body weight of buckwheat/corn syrup honey on the antioxidant, including the reducing capacities of plasma. It very well may be estimated that these honey constituents could augment defenses against oxidative stress and that they may most likely shield us from oxidative pressure. Given that the normal sugar consumption by people is assessed to be more than 70 kg for each year, honey substitution in a few nourishments for traditional sugars could result in an upgraded antioxidant defense framework in healthful adults [33, 37, 38]. An Indian volatile oil of propolis (VOP) was researched using a photochemiluminescence strategy and spectrophotometric techniques, and it was discovered (from IC50 values) that the effectiveness of scavenging ABTS radicals by the VOP was increasingly articulated when contrasted with scavenging different radicals [39]. That is why many researchers in around the world have as well pressed for the consumption of the food highly-rich in antioxidants, such as honey [32].

It is critical to note that some factors such as botanical origin greatly affect the honeys' antioxidant activity; at the same time, its antioxidant capacity is only slightly affected by handling, processing, and storage condition of the honey. A strong correlation has been reported between the antioxidant activity and its total phenolic contents, including between antioxidant activity and the color of honey. The antioxidant activity according to many researchers may be located in both the water and ether fractions, which shows that the flavonoid contents of honey might be accessible to different compartments of the human body, wherein they may exert diverse physiological impacts [19, 36, 40].

1.4 Honey as a natural immune booster

Similarly, apart from honey having a direct antibacterial action, it could get rid of infection by immune system stimulation to fight the intruders. There is currently a sizeable report that honey is a natural immune booster. Many have reported that B60 lymphocytes and T lymphocytes can be activated to increase in number in cell culture and can as well activate neutrophils [15].

Moreover, Israili et al. in their investigation revealed that in cell cultures, monocytes can be stimulated to release the cytokines IL-1, IL-6, and TNF-alpha, the cell "messengers" which can activate numerous aspects of the immune reaction to infection [11]. Carter et al. in their review concluded that the production of TNF-α in macrophages by means of Toll-like receptor could be stimulated by a component of manuka honey (5.8 kDa) [2]. Jelly bush, manuka, and pasture honey, unlike artificial and honey-treated cells ($P < 0.001$), were reported to increase significantly the immune cells released from MM6 cells (and human monocytes) [22, 31]. Also according to a report on macrophages, honey is the main source of glucose that's essential for the "respiration burst" that results in hydrogen peroxide production, the dominant aspect of their bacteria-destroying activity [26, 29]. Besides, it is the major substrates for glycolysis, the principal mechanism for energy production in the macrophages, and hence lets them to function properly in broken tissue and exudates where the oxygen supply is often bad. The action of macrophages is also aided by the low pH of honey, which helps in the destruction of bacteria, so the acidity in phagocytic vacuole is what helps in digesting killed bacteria [15, 26]. A study revealed that intake of 80 g daily of natural honey for 21 days showed that in AIDS patients, prostaglandin levels were elevated compared with normal subjects. Finally, these studies are of the opinion that consumption of honey daily really improves one's immune system [41, 42].

1.5 Clinical conditions treatable with honey

1.5.1 As remedy for diarrhea

It is not unusual to say that intestinal tract infection occurs all throughout the world, affecting people of all ages. In diverse ways, dietary deficiencies are worsened by infectious diarrhea; however, as in any infection cases, there is an increase in calorific demand. A variety of microbes (bacteria, parasites, and viruses) may be responsible for an intense inflammation of the gastrointestinal tract, which leads to acute gastroenteritis [43]. Pure or unadulterated honey has shown to possess bactericidal action against numerous enteropathogenic microbes, such as enteropathogenic *E. coli*, *Shigella*, and *Salmonella* species [44, 45]. An in vitro study has shown that the mucosal epithelial cells' attachment by *Salmonella* species was prevented by honey; attachment is taken into consideration as the initial step in the establishment of gastrointestinal tract bacterial infection [46]. Apparently, the antibacterial activity of some honey varieties and its therapeutic usefulness against infections caused by *Salmonella* Typhimurium and *E. coli* 0157:H7 have been reported [11, 16].

Samarghandian et al. in their study reported that 30 mL of honey and a bland diet when administered three times a day were observed to be an effective cure in some patients (66%) and further relief was provided to 17% of them, while in over half of anemic patients, honey proved to be effective [47]. Gastroenteritis in infants and children was reported to have been with oral rehydration solution (ORS) and honey according to an investigation by Abdulrhman et al. [48]. In this study, there was a great reduction in the frequency of both bacterial and nonbacterial diarrhea. Most likely, it is actually less demanding, to add honey to ORS, which obviously made the solution a little bit sweet and perhaps increasingly adequate. Due to the fact that honey has high sugar content, it could be utilized for the promotion of water as well as sodium absorption from the bowel. When the intestinal mucosa is damaged, honey moreover assists in its repair, performs the function of an anti-inflammatory agent, and instigates the growth of new tissues [32, 48].

1.5.2 As medicine for gastritis and gastric and duodenal ulcers

me of the health complications as a result of being infected by *Helicobacter pylori* are gastritis and gastric and duodenal ulcers. Traditional treatment for the annihilation of *H. pylori* is far from satisfactory; consequently there's search for alternative remedy. In the management of *H. pylori* infections, honey may contain a potential source of new compounds effective against the pathogen [6, 49]. Another in vitro study has shown that about 20% solution of honey was biocidal to gastritis-causing bacteria, *Helicobacter pylori*, isolated from a patient. Some of the isolates that were resistant to other antimicrobial agents were inhibited by honey solution [50, 51].

Furthermore, different honeys obtained from different countries and regions in an in vitro study by Ndip et al. using different honey concentrations showed that there were variations in the anti-*H. pylori* activity of the honeys [52]. This may be as a result of distinctive climatic conditions which may influence the distribution of vegetative species and flowers from which honeybees acquire nectar as well as sweet plant deposits for honey production. Because of hereditary heterogeneity displayed by *H. pylori* species, in aggregate with the regional variation in the antimicrobial components within the honey, there are differences in the honey concentrations that would be biocidal to *H. pylori* in specific locations. In particular, there is a report that *H. pylori* isolates from patients in Eastern Cape of South Africa were very susceptible to honey concentration as low as $\geq$10% v/v [53]. Apparently, it has been shown that honey dilution as low as 1:2 inhibited the isolates, but undiluted honey prominently inhibited the isolates [54]. Successful treatment of gastric ulcers with honey in the form of dietary supplement has been previously documented [6, 13]. Also, before the oral administration of ethanol, the use of honey orally or subcutaneously protected against gastric damage as well as reverses changes in pH induced by ethanol [32, 47].

1.5.3 As a medicine for dermatitis

Eczema, also known as atopic dermatitis (AD), is a common chronic atopic inflammation of the skin's outer layer. It is characterized by several skin problems, such as irritating skin, inflammation, blisters, redness, etc. Recurrent dermatitis occurs mostly in children, and it could as well be a problem in adults too; it makes an individual to be unattractive. Aside the one mentioned, there are other forms of dermatitis such as diaper dermatitis, seborrheic dermatitis, etc. In the pathogenesis of dermatitis generally, various immune cells participate such as macrophages, lymphocytes, eosinophils, and mast cells. Additionally, in the epidermis during this disease pathogenesis, keratinocytes play an important part due to its interaction with different cells of the immune system as well as stimuli from the external environment [55, 56].

One of the major problems in dermatitis patients (70–90%) and normal population (5%) is the skin colonization by *S. aureus.* This may be as a result of deficient cutaneous antimicrobial peptides, skin barrier function, as well as repeated scratching. Consequently, this bacterium is the major causative agent of superinfections of dermatitis lesions [57]. Also of importance to note are the productions of highly inflammatory substances such as exotoxins (α, β, γ, and δ cytolysins) and enterotoxins (SEA to SEE), which may play the role of superantigens as well as worsen the ongoing inflammation. Due to challenges in the management of the disease, natural remedies are opted for by many patients, and the topical use of honey on the lesions showed overall improvement in their symptoms [19, 55].

A study by Alangari et al. showed that manuka honey is effective in the treatment of dermatitis, particularly, atopic dermatitis, and after 7 days irrespective of honey treatment, there was no significant changes in the skin staphylococci. Also, they observed that honey in a dose-dependent manner downregulated IL4-induced CCL26 released from HaCaT cells significantly [58]. Another study has shown the effectiveness of honey mixed with olive oil and beeswax (in a ratio of 1:1:1 v/v) for the skin fungal infections, psoriasis, as well as dermatitis [59].

It has been reported that during the 7-day trial, honey has reduced the symptoms of diaper dermatitis and eradicated *C. albicans* from 50% of culture-positive patients. Probably, anti-inflammatory effects of the mixture could be the only reason for the symptomatic improvement in patients, due to the properties of the ingredients [60]. An investigation on *Staphylococcus aureus* isolated from patients with canine dermatitis revealed that honey had bactericidal effects against the test bacteria in vitro [61].

There is a postulate that in an in vitro study, natural raw honey, such as manuka honey, helps in the healing time through a dual effect on the inflammatory pathway. At first in the disease sites, honey is believed to suppress inflammatory cells' production and migration. Again, it allows normal healing process to occur through the epithelial cells and fibroblast proliferation enhancement and the production of pro-inflammatory cytokines [62]. Natural honey from different floral varieties possesses variable moisture content, depending on the quantity of water they contain (ranges between 6 and 14%), and provides the needed moisture to the inflamed skin without causing maceration [19, 62]. Nonetheless, more investigation is still needed such as randomized controlled trials, so as to find the most effective duration, frequency, and type of honey.

1.5.4 As antidiabetic agent

Diabetes mellitus is still a serious issue which is related with poor quality of life, cardiovascular intricacies, and increased mortality and morbidity. As a result of its economic and social burdens, it is becoming a public health concern. In humans, the most common forms of diabetes are type 1 and type 2 diabetes. The former results when the insulin is destroyed by the host immune system, while the latter which is most prevalent and genetically determined may be as a result of several factors. Despite the fact that diabetes has no known cause, complex interaction of a few factors such as environmental, social, and genetic components is involved in its etiology [63]. At the moment, the obtainable antidiabetic drugs are far from being satisfactory, due to some limitations such as the cost and availability. Alternatively, some patients have resorted to the use of dietary supplements or components, herbal preparations, and other natural and apicultural products such as honey [5].

Predominantly, honey is made up of monosaccharaides (fructose and glucose) and water as well as other components (more than 200). For quite a while, some people have the notion that diabetic patients cannot consume honey due to its high sugar content. This has given rise to a number of questions, such as "Can honey replace sugar in diabetic diet? Is sugar in honey essential in the prevention and treatment diabetes mellitus?." But many researchers around the globe have been working on honey characterization from different sources and the determination of its biological properties for a long period. Different studies have acknowledged the effectiveness of honey and its use in diabetes mellitus patients, including animal model studies, preclinical and clinical studies, and human studies [64].

In a natural honey, fructose content and the fructose/glucose ratio range from 21 to 43% and 0.4–1.6 (or even higher), respectively. The glycemic index of fructose, glucose, and sucrose (refined sugar) are, respectively, 19, 100, and 60, even though the naturally occurring sweetener and the sweetest is fructose. Although the mechanism of hypoglycemic effect of honey is still unknown, various studies have proven it to be so [8, 65]. In animal model experiments, reduction in blood glucose due to fructose has been reported, and it is believed that it may be as a result of reduced food intake, reduced rate of intestinal absorption, and prolongation of gastric emptying time. In hepatocytes, fructose activates glucokinase, which is needed in the assimilation as well as storage of glucose as glycogen by the liver. Glucose unlike fructose boosts the fructose absorption and aids in its hepatic actions through strengthening its delivery to the liver. The pancreas is an essentialorgan in diabetes, in that it produces insulin and glucagon; the antioxidant mol- ecules in honey help in its protection against oxidative stress and damage, which may be another likely mechanism of hypoglycemic effect of honey. The insulin response and glucose homeostasis in normal rats are ameliorated due to intake of only fructose or in combination with sucrose molecule, compared to rats which received glucose. The hypoglycemic effect of honey has been demonstrated using various animal models, such as type 1 and type 2 diabetes induction in alloxan andstreptozotocin using appropriate doses [64, 66, 67].

In another investigation, honey and fructose were used to feed diabetic (alloxan-induced) and healthy rats, respectively, and it was reported that the former had significant reduction in glucose level while it was not significant in the latter [68]. Honey proved its potency compared with sucrose and dextrose when included in the diet of diabetic (or hypertriglyceridemia) and healthy patients. There was a decrease in the elevated and normal C-reactive protein, homocysteine value, and triacylglycerol (in hypertriglyceridemia patients), and lipid profile was improved. The rise in plasma glucose level in diabetic patients was significantly reduced with bee honey compared with dextrose. Honey unlike sucrose made the insulin level to rise; in normal subjects, there was reduction in C-reactive protein, blood lipids, and homocysteine, after consumption of honey at different time [47, 69]. In summary, honey may be very effective in the management of patients with diabetes mellitus based on the evidence from experimental studies. Although very few reports have contrary view on the use of honey, most researchers believe that it is very useful in reducing metabolic disorders, managing hyperglycemic state, and reducing diabetic complications on different organs.

1.5.5 Anticancer and antitumor activity

The potential to induce genetic mutation is called mutagenicity, which is interlinked with carcinogenicity. The heterocyclic amines such as Trp-p-1 (3-amino-1, 4-dimethyl-5H-pyridol [4,3-b] indole) are formed especially during food frying and roasting processes. Many studies around the world have demonstrated the anticancer potential of honey in tissue cultures [70, 71], in animal models, and in clinical trials. One of the main active constituent of honey responsible for its anticancer activity is believed to be the polyphenols. Some of the anticancer properties of honey apart from its anti-inflammatory, antioxidant, and immunomodulatory activities are due to its antiapoptotic, antiproliferative, antitumor, antimutagenic, and estrogenic modulatory activities.

Programmed cell death and cellular proliferation (uncontrolled) are the main features of cancer cells. Fauzi et al. reported that through mitochondrial membrane depolarization, honey is able to induce apoptosis (programmed cell death) in various types of cancer cells [71]. In human colon cancer cell lines, the high tryptophan and phenolic content of honey induces programmed cell death by upregulating the expression of proapoptotic proteins (caspase 3, p53, and Bax) and modulating the expression of antiapoptotic proteins (Bcl-2) [72]. Manuka honey-induced programmed cell death involves activation of PARP, loss of Bcl-2 expression, and induction of DNA fragmentation [73].

Throughout human and animal life, there is division of epithelial cell, and in this cell cycle, G_1/S phase transition regulates cell growth. The loss of this regulation leads to tumor/cancer. Honey is very promising in arresting the cell cycle. A study has reported that honey supplemented with *Aloe vera* solution significantly reduced the expression of tumor cell proliferation (nuclear protein—Ki67-LI) in rat by arresting the cell cycle [74]. The antiproliferative activity of honey and its components (like flavonoids and phenolics) in G_0/G_1 phase cell cycle has been reported in colon [75], melanoma [76], and glioma [77] cancer cell lines. This potential of honey has been confirmed to be dose- and time-dependent [76].

The multifunctional signaling protein, tumor necrosis factor, plays vital beneficial and deleterious roles in diverse cellular events including initiation, promotion, and progression of tumor cell. In vitro and in vivo in mice, the antitumor effect of honey has shown that it is effective in inhibiting the growth of different bladder cancer cell lines (T24, RT4, 253 J, and MBT-2), and when administered orally or intralesionally in the bladder cancer (MBT-2) implantation mice models, a good result was obtained. Royal jelly honey proteins (apalbumin-1 and apalbumin-2) according to Šimúth et al. [78] stimulate macrophages to release cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), as well as TNF-α. Different honeys at very low concentration (1% w/v) such as manuka, jelly bush, and pasture honey initiate release of the TNF-α and interleukin- (IL-) 1β and IL-6 [79, 80].

Researchers have shown that honey has a strong antimutagenic property and hence has anticarcinogenic potential [81, 82]. The cells of *E. coli* exposed to UV or γ radiation showed that honey elicited SOS response (SOS is an error-prone repair pathway contributing to mutagenicity). This study on genes involved in SOS-mediated mutagenesis including *umuC*, *recA*, and *umuD* demonstrated that honey inhibited the changes significantly, thus confirming the strong antimutagenic effect of honey [82]. Another study that used Ames assay to investigate the antimutagenic activity of honeys (acacia, buckwheat, Christmas berry, soybean, tupelo, and fireweed) against Trp-p-1 in comparison with sugar analogues reported that they exhibited a significant inhibition of Trp-p-1 mutagenicity [83]. The antitumor properties of honey and its possible mode antimetastatic action were investigated using anaplastic colon adenocarcinoma of Y59 rats and spontaneous mammary carcinoma in methylcholanthrene-induced fibrosarcoma of CBA mice. This study showed that oral administration of honey produced statistically significant antimetastatic effect. Their findings showed that apart from the immune cells' activation, ingestion of honey may be more beneficial with respect to cancer and metastasis prevention [84, 85]. Aside from all of these, more research such as randomized controlled clinical trials is still required to validate the uses of honey either alone or as adjuvant therapy for cancer and its associates.

1.5.6 The action of honey in wound healing

A wound is said to result when there is an interruption of the progression of a tissue structure. Wound healing, a continuous as well as complex process, has three stages, viz., inflammation, a proliferative phase, and tissue remodeling. It is essentially the aftereffect of interactions among blood, growth factors, cellular elements, cytokines, and the extracellular matrix [15, 86].

The healing properties of honey have long been recognized and documented [24]. Both endogenous (pathophysiology) and exogenous (microorganisms) factors ffect the healing of wounds. Due to the local conditions of the wound environ- ment, there is increased risk of infection of the wound by pathogens. Many bacte- rial species have been recouped from infected wounds; however, *Staphylococcus aureus* is the most as often as possible isolated. *Pseudomonas aeruginosa* is addition- ally an essential pathogen in chronic wounds and burns; this has been reported in various investigations and has been found in one third of chronic leg ulcers [5, 47]. The use of honey for treatment of infected wounds and normal wounds has been reported in many articles [5, 6]. Honey with demonstrated antibacterial action can possibly be a compelling treatment choice for wounds infected or at risk of infection with different human pathogens.

The use of honey in the treatment of wounds as a result of skin ulcers resulting from various etiologies has been documented in literatures [6]. A review by Jull et al. showed that out of over 470 cases observed in which honey was used as a therapeutic agent, successful healing was not achieved only in five cases [87]. Honey exerted both deodorizing effect and anti-inflammatory actions on the wound and thus reduced the level of pain. A study carried out in the UK which tried to determine the effect of medical honey on three patients suffering from chronic leg ulceration proved the honey treatment to be effective. Even though they all had some years of disease reoccurrence, there was significant healing in all cases with a decrease in occurrence rate, pain, and discomfort [88]. In another study by Dunford and Hanano, Medihoney dressings were used on the leg ulcers of 40 patients for a 12-week study period. These ulcers had previously been subjected to 40 patients whose leg ulcers had not responded to 12 weeks of compression therapy with no recorded improvement. However, after treatment with Medihoney, there was a remarkable decrease in the ulcer pain and size, and the odorous wounds were promptly deodorized [89]. Another study in Ireland done to qualitatively determine the bacteriological changes that occurred in a 4-week treatment period with either a hydrogel dressing or manuka honey enrolled 108 study subjects. Methicillin-resistant *S. aureus* was identified in 16 of the patients, 10 in the honey group and 6 in the hydrogel group. The authors reported that at the end of the 4-week period, manuka honey showed its potency in eradicating MRSA from 70% of patients with chronic venous ulcers [90].

Burn injuries are typically connected with a high occurrence of death and disability. Advances in biology of cells and knowledge in wound healing as well as growth factors have aided in the burn injuries' management. Split-thickness skin grafting with autografts is a well-known standard of care for burn wounds.

Researches that investigated the use of honey in the treatment of burns have been documented [6, 87]. A review by Zbuchea made mention of a study carried out in France, in which there was rapid healing for first- and second-degree burns, and in Netherlands, honey-treated burns were found to show less inflammation than thosetreated with sugar and silver sulfadiazine [91]. In a randomized study in Pakistan, the efficacy of honey for the treatment of superficial and partial-thickness burns covering <40% of human body surface area was determined in 150 patients, and the results compared with those of silver sulfadiazine. The re-epithelialization rate and healing of both superficial and partial-thickness burns were remarkably faster in the sites treated with honey than in the sites treated with silver sulfadiazine. *P. aeruginosa* was isolated from 6 patients in the honey-treated site, while 27 patients had positive culture in the silver sulfadiazine-treated site [92].

The infection of the wound is a critical factor that delays or hinders wound healing. Honey has many properties, both antibacterial and otherwise, that enhance its beneficial effects on wound healing [6]. The properties of honey that give it its wound healing power have been previously discussed, such as hydrogen peroxide which is an important antiseptic and stimulant of wound healing process.

ther property is due to its high osmolarity which inhibits microbial growth in light of the fact that the sugar molecules tie up water molecules such that there is insufficient water for the microbes to grow. Research has shown that the application of antioxidants to burns reduces inflammation [38]. Honey inactivates the free iron, which is believed to catalyze the oxygen free radical formation produced as a result of H_2O_2, and its antioxidant components aid in the removal of oxygen free radicals [93]. Apart from various immune system cells' stimulations and nitric oxide end product in honey, honey provides a protective barrier and, by osmosis, set up a soggy wound recuperating condition that does not adhere to the underlying wound tissues.

Factors that may affect the therapeutic potentials of honey

The destruction of therapeutic properties of honey by exposure to light and heat was first reported by Dold and Witzenhausen, who found that inhibine in honey was not stable [94]. Other numerous reports have confirmed this finding, but variations in the properties of honey as a result of heat and light presently reported vary. On exposure of honey samples heated at 56°C for 30 min, 80°C for 10 min, and 100°C for 5 min, 17% of the samples partly lost their inhibitory activity against the test organisms [95]. Also, a complete loss of activity has been reported. The antimicrobial activity of honey, both new and stored, reduced after heating at 80°C for 1 h. Also, long storage of honey (5 years) reduced this activity [96]. In some instances, when honey is subjected to lesser degrees of heating, the activity is retained which may be due to partial destruction of the heat-sensitive factor [97]. Similarly, exposure of honey to heat at 46°C for 8 h, 52°C for 8 h, and 55°C for 8 h resulted in the increase in the MIC from 4 to 8%, to 12%, and to 16%, respectively [98]. Another investigation showed that when honeys are held at 40°C for 96 h and 37°C for 24 h, there was no reduction in its antibacterial activity, as in the cases previously mentioned. This is possible since the temperature in the beehive where honey can spend quite a long time is around 34°C. At the same condition, diluted honey may not be stable, since the hydrogen peroxide production rate drops off with time [96]. The variations in antimicrobial action of honey due to heat is believed to depend mainly on pH of the honey, and at low pH, activity can rapidly be lost [98].

The effect of light on honey therapeutic potentials has been reported long ago. This observation has been confirmed by many researchers [99, 100]. The non-osmotic activity of honey has been reportedly lost after its exposure in a layer 1–2 mm thick to sunlight for 15 min [100]. Honey stored on a window sill for 8 months in 2.5 L transparent polystyrene jars completely lost its activity, but when stored in white polyethylene jars for the same period, its activity remained the same [101]. This shows that protecting honey from sunlight or UV light above 400 nm will prolong its activity [94]. But Molen reported that there was no reduction of activity when a thin film of honey solution was exposed for 1 h to an ultraviolet (UV) lamp (254 nm) [102]. Unlike light-colored honey, the light stability of dark-colored honey has been reported, and it is believed to be as a result of reduction in light wave reaching the bulk of the honey [102].

2. Conclusions

For ages, honey has been traditionally used to treat human diseases. Recently, it is becoming acceptable to everybody as a therapeutic agent that is cost-effective and lacks side effects. The therapeutic and beneficial properties of honey have been endorsed due to:

- Its antibacterial, antifungal, antiviral, and antiparasitic activities against a wide range of organisms.

- Its anti-inflammatory effect and immunomodulatory activities due to its substantial amounts of phenolic contents

- Its antioxidant capacity, which is estimated by its ability to scavenge free radicals.

- Diarrhea caused by enteropathogenic *E. coli*, *Shigella*, and *Salmonella* species.

- Gastritis and gastric and duodenal ulcers which may be as a result of *H. pylori* infections.

- Canine recurrent dermatitis, diaper dermatitis, and seborrheic dermatitis.

- Diabetics, where honey has been shown to be very effective in the management of patients with diabetes mellitus based on the evidence from animal model studies, preclinical and clinical studies, and human studies.

- Cancer and tumor—which may be due to its antiapoptotic, antiproliferative, antitumor, antimutagenic, and estrogenic modulatory activities.

- Wounds—its action on wound healing has been medically accepted especially in diabetic patients.

Most of the known factors that give honey these properties include its acidity, high sugar, hydrogen peroxide, and other non-peroxide properties. But some other factors may affect the therapeutic properties of honey such as:

- Its exposure to heat or higher temperature

- Its exposure to light, sunlight, or UV light

In all, honey has an interesting potential as a therapeutic agent which might in the near future complement/replace conventional drugs such as antibiotics. Therefore, more research is still needed to finally establish the basis for classifying honey as medical grade.