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A Review on Antimicrobial Activity of Honey

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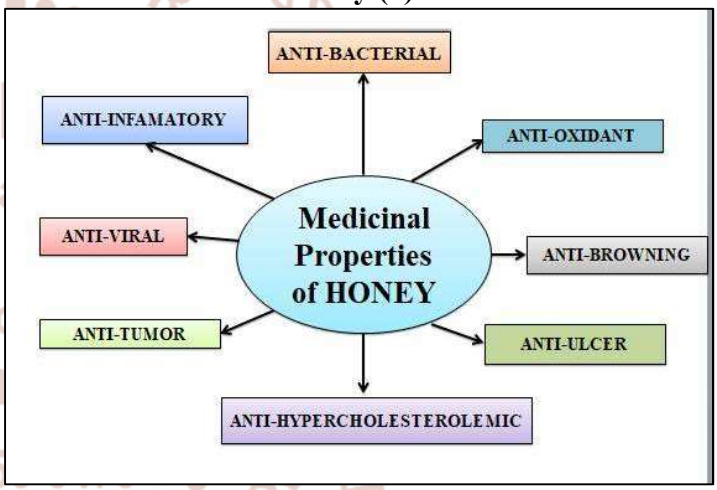
ABSTRACT
Honey is one of the natural valuable gift that has been used since ancient times to treat number of infections without any side effects. The present review has highlighted on the importance of honey and its antimicrobial properties by emphasizing the major compound that contribute to the inhibition of bacterial infection. Various mechanisms of how honey is provoking the antimicrobial activity has been describe in detail and also present scenario on honey as antimicrobial agent research reported till date has been included.

Keywords: *Honey, antimicrobial, infections, medicinal field.*

INTRODUCTION
Honey is one of the nature's wonders that have been used in therapy since ancient times. Honey has a long history of human consumption due to its nutritional as well as medicinal properties. Due to the lack of scientific proof honey is limited for using in modern medicine therapy (1). Several investigations have been going on since few decades to prove honey as a best source for treating many disorders, infections without or less side effects. One of the most remarkable discoveries was antibacterial activity of honey that has been mentioned in numerous studies (2, 3). The global production of honey is approximately 1.20 million tons per annum (4). The branch of medicine using honey bee products, including honey, pollen, propolis, royal jelly and bee venom is called *Apitherapy*.320 different varieties of honey have been reported till date (5). Bases on their origin of floral sources honey has different flavor, color, and odor of a specific type of honey are depending on the various liquid sources of the flowers and plants visited by the honey bee. Assorted types of honey are comparable in terms of temperature, rainfall and seasonal and climactic changes. Honey color ranges from light brown to dark brown depending on where the honey bees buzzed (6).

Figure:-1 Different pharmacological activity of honey (7)



Ancient reports on importance of honey:
Consumption of honey has been traced to some 8000 years ago as depicted by Stone Age paintings (8). Nutritional and medicinal qualities of honey have been documented in many books of Vedic, Greek, Roman, Christian, Islamic. Many physicians of ancient times have been using honey for so many healing properties like Aristotle (384–322 BC), Aristoxenus (320 BC) Hippocrates, Porphyry, Cornelius Celsus (early first century AD) and Dioscorides (c. 50 AD), and Arab .In the earliest Hindu Vedic texts, honey is one of the five ingredients of Panchamrit (9). In Ayurveda medicine honey was used in India for at least 4000 years and is considered to affect positively in all three primitive material imbalances of the body. Ancient Egyptian physicians used honey in medicinal compounds 5,000

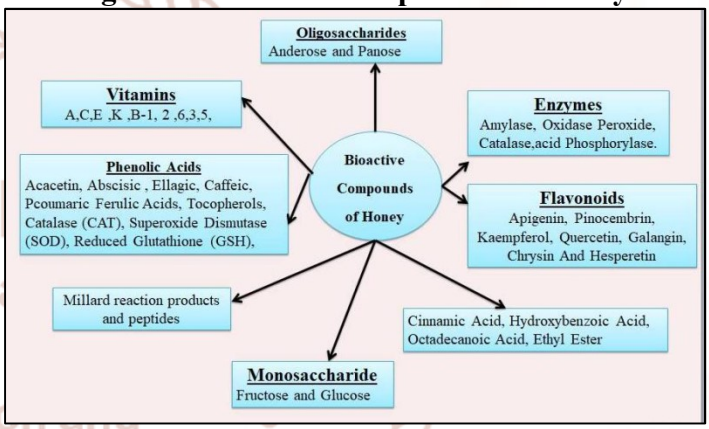
years ago and the ancient Greeks believed that honey could promote virility and longevity. Honey has been used in Traditional Chinese Medicine for thousands of years and is still important today. Ancient Russian manuscripts attributed great importance to honey as a medicine. In 1000 BC, honey was a Saxon herbal treatment for wounds, sties and amputated limbs. The use of honey as a therapeutic cure in various combinations was popularized in Medieval Europe, England, Germany, Finland, Ireland, Ghana, USA, Nepal, Nigeria, Russia, and Brazil (10). In Christendom, there are references made to the importance of bees and honey in the Bible, these include the Books of Exodus, Judges, Mathew and Proverbs. In accordance with this Christian holy book, the Bible, King Solomon was quoted thus: "Eat honey my son, because it is good". The religion of Islam recommended the use of honey as food and medicine, and even named an entire chapter in the Holy Qur'an called Surah al Nahl meaning chapter of the Honeybee. In the book of hadith, Prophet Muhammad strongly advocated the use of honey for curative and healing purposes. Likewise, the Holy Prophet of Muslims, Mohammad (PBUH) commended the usage of honey for remedying diarrhea. Prophet Mohammad himself spoke of the healing power of honey as a cure for all mental illness. In the later part of the 12th century, a Muslim physician described the healing powers of honey to disperse body fluids, soothing the bowels, curing dropsy, checking facial twitches, improving appetite, preventing the breakdown of muscles and preserving them (11).

Egyptian use honey to treat around 900 medicinal cases (12).Its prescription revealed in the Smith papyrus (an Egyptian text, dating between 2600 and 2200 B.C.) calls for a mixture of byt (honey), mrht (grease), and ftt (lint/fibre) as a typical wound lotion. Early Egyptians offered honey as a sacrifice to their goddesses. Infected injuries were healed by honey because of its antiseptic assets. Moreover, honey was operated as a contemporary ointment. People of Egypt use honey to make sweeter bakery products and other dishes in ancient times. Middle-Eastern and Egypt people also used honey for mummifying the dead. An experimental trial in Egypt indicated that continuous ingestion of honey could affect type 1diabetes. Honey oral rehydration solution promoted in Egypt for recovery from diarrhea, vomiting and rehydration (13). There is a prehistoric Greek Honey utilized occasionally as a conventional remedy for gout and few nervous disorders. A simple diet (honey) proposed by Greek scientist, preferred as hydromel (honey and water) for quenching thirst, oxymel (honey and vinegar) for pain and a combination of medicinal constituents (13). Honey had also been utilized for sore throat, laxative action, contraception, eye diseases, baldness, wound healing, cure and inhibition of scratches by him (8).

Bioactive Compounds of Honey:

200 bioactive compounds are reported till date disaccharides, monosaccharides, oligosaccharides, amino acids, vitamins, minerals, enzymes, Flavonoids, phenolic acids, Millard reaction products and peptides (4, 14-18).

Figure: 2Bioactive Compounds of Honey



Antibacterial activity of honey:

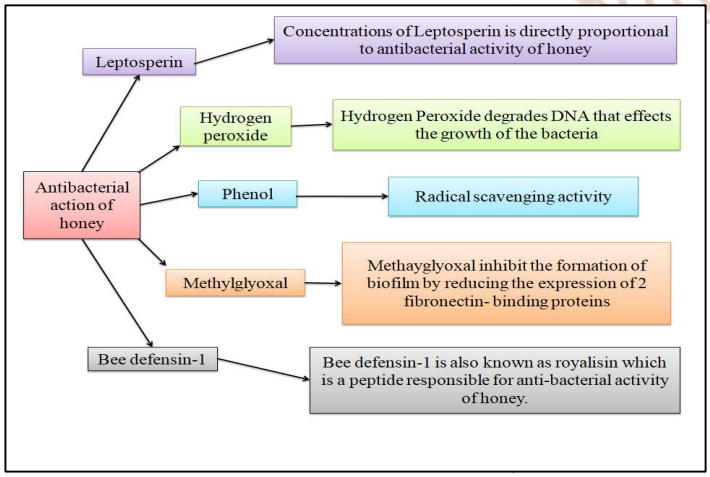
VanKetel has first time reported the antimicrobial activity of honey in 1892 (19).Multi drug resistant bacterial strains are emerging day by day due to many factors which include personal and environment factors. Although many antimicrobial agents are in use for therapy, honey has an important place in treating of microbial infections. Honey the nature gift because of no side effects compared to the drugs available now a days.Mohapatra*etal.,*2011,Irish *et al.*,2011, Alnaimat *et al.,*2012 reported antimicrobial activity of honey may be bacteriostatic or bactericidal depending on components present in the honey (20-22). There are less chances of bacterial exhibiting resistance to honey due to their variability in composition like 1) types of nectar that the bees fed, (2) the related weather conditions, (3) storage time and (4) conditions of preservation (23, 24). Bilsel*et al.,* 2002 stated that pH of honey contributes to prevent the growth of many Bacteria; example acidic pH containing honey has been reported to be a potential antimicrobial agent (25).In 2009, a study sated that honey shows antibacterial activity by inhibiting the biofilm formation by Methylglyoxal

which is an important property for the bacteria like *S. aureus* and *P. aeruginosa* to cause infection by adhering to the wound (26, 27). Halawani and Shohayeb (2011) has also stated that there was no relationship between color and antibacterial activity of honey because some honeys of light coloration like orange blossom and clover, were potential antibacterial against *Salmonella enteritidis* than dark honeys (28).

Mechanism of antimicrobial activity of honey:

Previous reports of experiments have stated that antimicrobial property of honey may be due to reducing sugars, high viscosity, high osmotic pressure, low water activity, low protein and pH, phenolic content , Methylglyoxal and hydrogen peroxide (29-33).Few mechanisms like degrade DNA, radical scavenging activity, inhibition of biofilm formation by reducing the expression of 2 fibronectin-binding proteins by Methylglyoxal, Quorum sensing inhibitory activity of hydrogen peroxide or by down regulated 2 specific proteins that are necessary for growth and up regulated a stress-related protein (cold-shock protein C) were reported in previous literature (33-44).Cooper *et al*., 2011b stated that biofilms formation can prevented by down regulating of two genes coding for surface-binding proteins which were found to contribute to the prevention of biofilm formation (45).honey inhibits cell division and involves in multiple changes of cellular proteins that effect infection (46)whereas gene expression (47)and causing changes in the bacterial cell wall that led to instabilities, resulting in cell lysis (46,48,49).

Some of the compounds that contribute to the antimicrobial activity of honey are presented in Figure:-2 (33-43, 50, 51)



Sensitive bacteria towards honey:

Honey has been reported to have an inhibitory effect to around 60 species of bacteria including aerobes and anaerobes, gram-positives and gram-negatives (52). Ram meena , rajgopalacharya reported manuka honey and pasture honey shows antibacterial effect on *E.coli, P.aeruginosa, S.aureus, V.chlorelae, Serratiamarceseens, proteus spp.* (53). Several reports have proved the broad spectrum activity of honey on diverse species of bacteria such as *Acinetobacterbaumannii, Alcaligenes faecalis, Aeromonashydrophila, Bacillus cereus , B. subtilis ,Burkholderiacepacia, Campylobacter spp., Citrobacter freundii, Erwiniacarotovora, Enterobacter aerogenes, Enterobacter cloacae, vancomycin-resistant Enterococcus faecium, Escherichia coli, Haemophilus influenza, Helicobacter pylori, Klebsiella oxytoca, K. pneumonia, Listeria monocytogenes, Micrococcus luteus, Mycobacterium phlei, Proteus sp* (*P. mirabilis and P. vulgaris*), *Pseudomonas aeruginosa, Salmonella (S. california, S.enteritidis, S.typhimurium), Serratiamarcescens, Shigella dysenteriae, Shigella sonnei, Staphylococcus aureus,MRSA, S. epidermidis, Stenotrophomonasmaltophilia, Streptococcus hemolyticus group B, Streptococcus pyogenes, Yersiniaenterocolitica* and several multidrug-resistant bacterial isolates (54-85).

National and international Reports on Antimicrobial activity of honey:

Research on evaluating honey's antimicrobial property has been in progress and available reports are mention in this review.

Allen *et al*.,1991 reported variation in antibacterial activity of 345 unpasteurized honey samples collected from New Zealand which are mostly unifloral of 26 different floral sources like Kanuka (*Kunzeaericoides*), manuka (*Leptospermum scoparium*), ling heather (*Calluna vulgaris*) and kamahi (*Weinmanniaracemosa*) (69). Willix*et al*., 1992 compared the non-peroxide activity of manuka honey with that of a peroxide-producing honey against several pathogenic wound bacteria and reported that there was no significant difference between the two types of activity overall but there was marked differences existed in the ranking order of sensitivity because 1.8% (v/v) of manuka honey was enough to completely inhibit the growth of *S. aureus* after 8 h of incubation whereas the other one was 11%

(v/v) (86). Lusby *et al.,* 2005 reported that low concentration of Tualang honey was showing antimicrobial activity against gastric infection causing bacteria S. *typhi*, *S. flexneri* and *E. coli* (62). Hegazi and Fyrouz, 2011 reported 40 to 80% concentration of honey sample collected from Sidr and Mountain region of Saudi were inhibiting E. *coli*.(87) Roslan*et al.,*2015 has reported 40% honey dilution showed higher inhibitory effect on *E. coli* (88) Strate*vest al*.2015 reported various concentrations of royal jelly [10, 20, and 30%] possess inhibitory effect against *A. hydrophila* ATCC 7965 (89). Taormina *et al*.,2001 reported against 5 pathogens *E .coli ,S. typhimurium , Shigella sonnei, Listeria monocytogenes , S. aureus* .(71)Manyi-Loh CE reported against *Helicobacter pylori* (90). Minimum inhibitory concentration of Commercial Agmark honey purchased from Khadikraft, India was reported as 11% against *Pseudomonas aeruginosa* isolated from diabetic foot ulcers and burn wound infections (91). Wilkinson and Cavanagh (2005) reported that MIC of different honey samples were showing variation and in general 50% and 20% of honey showed antimicrobial effect on *P. aeruginosa* (76). Hegazi (2011) reported antimicrobial activity of honey from various sources like *Acacia honey, Citrus honey, Clover honey, Coriander honey, Cotton honey, Palm honey, Sesame honey* and Saudi Seder honey against *Klebsiella, pneumonia*, *P. aeruginosa* and *Escherichia coli* have their significant property of inhibiting the bacterial pathogens (92). Mohapatra *et al*., 2011; Irish *et al.,*2011; Alnaimat *et al*., 2012 reported the antimicrobial activity of honey against 5 Gram positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Enterococcus faecalis*, and *Micrococcus luteus*) and 3 Gram negative bacteria (*E. coli*, *P. aeruginosa*, and *Salmonella typhi*) (20-22). Mamatha Ballal*et al* 2012 has reported that all strains of *P. aeruginosa* including both resistant phenotypes and sensitive strains were inhibited at 20% antibacterial honey concentrations *in vitro* (93). Abd-El Aal*et al.* 2007 showed that honey had a more pronounced inhibitory effect (85.7%) on Gram negative bacteria (*Pseudomonas aeruginosa*, Enterobacter spp., *Klebsiella*) in comparison to commonly used antimicrobial agents. 100% inhibition was observed in the case of Gram positive methicillin-resistant *Staphylococcus aureus* in comparison to the use of antibiotics alone (94). Cooper *et al.,* 2002 reported that concentration less than 10%, Manuka Honey was inhibiting the 58 strains of Gram-positive MSSA and 18 strains of MRSA isolated from wounds (95, 96).

Elin Juliant*iet al.,* 2017 reported MICs of honey against *Propionibacterium acnes* and *Staphylococcus epidermidis* and stated that combination of extract of cinnamon bark and honey against showed an additive activity with a FracICI value of 0.625 suggesting that the extract of cinnamon bark and honey have good potential activity against acne-causing bacteria (97). The lowest concentration of sugar that prevents the growth of S. aureus has a water activity of 0.86, equivalent to a concentration of 29% (v/v). This is equivalent to a concentration of honey of 22%. In the present study, both of the honeys inhibited S. aureus completely at much greater dilution. This is because their mode of action is not exclusively through their osmolarity (98). The lack of significant variance in the sensitivity of a large number of clinical isolates collected from a wide range of wounds indicates that there is no mechanism of resistance to either of the additional types of antibacterial activity in honey (phytochemical or hydrogen peroxide). This contrasts with the variations seen in staphylococcal sensitivity to antibiotics (99). Thus, either of these two honeys might be an effective treatment for a wound infected with any strain of S. aureus. However, although their MIC values differed little in vitro, in vivo the hydrogen peroxide produced in mixed pasture honey would be partly inactivated by the catalase in tissues and blood and manuka honey with its non-peroxide antibacterial activity is likely to be more effective. Their relative merits need to be tested in clinical trials (82).

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