Review Article

A Review on Prebiotic Importance of Stingless Bee Honey and its Ethnomedicinal and Therapeutic Potential

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ABSTRACT

Microbial drug resistance has emerged as a major problem challenging researcher to explore antimicrobial compounds which are effective, cheaper, and safe than synthetic drugs. Marketed probiotic lacks prebiotic sugars, which helps probiotic microflora in restoring or colonizing human gut keeping it healthy. It is reported that prebiotic sugars are present in honey of stingless bee, along with other therapeutic compounds. These therapeutic compounds are also reported to show effective antimicrobial activity towards drug resistant *Staphylococcus aureus* and also been used in many ethnomedicinal formulation for various health problems since ancient times. In this review we have discussed about importance and scope of stingless bee honey as potential agent for prebiotics, therapeutic and ethnomedicine providing various food and pharmaceutical application.

Keywords: Ethnomedicinal formulation, Stingless bee honey, Prebiotic, Probiotics, Therapeutic application.

INTRODUCTION

Out of entire world population 70-80% population of people depends upon natural plant and animal based product for preparation of ethnic or traditional medicines which can be easily available and harvested from the natural source.[1] From the ancient time honey plays a very important role as major component in most of the ethnomedicinal formulations.[2] Not only using honey as a delicious food, many studies have proven that honey produced by stingless bee contains certain amount of antimicrobial components like glucose oxidase, catalase, ascorbic acid, cinnamic acid, flavonoids, phenolic acids, carotenoid derivatives, organic acids, amino acids and proteins.[3] Components present in stingless bee honey shows promising wound healing, antibacterial and antinflammatory properties. Components of honey like flavonoids, oxidizing agent and cinnamic acid have shown antibacterial activity against certain pathogenic strains of bacteria and can be used for certain therapeutic applications.[4] Due to additional health benefits by nourishing gut microbial flora there is an increase in interest of research for food components such as prebiotic carbohydrates and probiotic bacteria.[5] Honey of this stingless bee contains large amount of fructose oligosaccharide which are used by probiotic bacterial strains like *Lactobacillus* and *Bifidobacter* as a prebiotic which leads to improvement in metabolic function of host gut by providing favorable metabolic substrates to the probiotic organsiam.[6] This favorable metabolic substrates are mostly those oligosaccharides or complex indigestible sugars which are utilized during saccharolytic fermentation by probiotic microorganisms usually bacteria of genus *Lactobacillus* and *Bifidobacter* leading to more growth of probiotic microflora and inhibition of pathogenic bacteria inside human gastrointestinal tract.[7]

Stingless Bee in the World

Stingless bees are those bees which naturally inhabits tropical and sub tropical regions or areas of America, Australia, Africa, and parts of Asia.[7] These bees share a common phylogenic group. Talking about classification of stingless bee these are classified into 2 different genera- *Trigona* and *Melipona*. There are about 120 species of *Trigona* which are placed under different subgenera like *Homotrigona, Heterotrigona* and *Lepidotrigona*.[8] The subgenera *Lepidotrigona* is reported to be found in tropical and subtropical region of different Asian countries like Burma, Thailand, Java, Borneo and northeastern part of India.[9] 'Putka' a local nepali word is used for one of the most popular honey produced by stingless bee species *Lepidotrigona arcifera* in northeastern part of India.[10] This stingless bee has different nesting characteristics as compared to the normal honey bee. They have unique nesting pattern in which they form brood cells which are usually for storage of pollen grains along with that some of these bee guards the entrance portion of a tube along with the queen bee which is quite larger than normal stingless bee of same nest shown in (Figure 1).

From a survey study done by Assam Agricultural University, Jorhat, India and Krishi Vigyan Kendra (ICAR), Tripura, India to explore the diversity and distribution of Stingless bees in India in which they had covered different zones like North East, North West and South regions of India. Out of the 6 different species found in India only 5 species are dominant in Northeastern zone, 4 species are dominant in south zone and only 2 species are dominant in North Western zone of India. Two species of stingless bee *T. iridipennis* and *T. laeviceps* are most commonly distributed and found in almost every zones or region of India[11] (Table 1). Some of other species of stingless bee which are well known in other parts of the world are *T. praeterita*

(Srilanka), *Trigona nebulata* (Central Africa), *Cleptotrigona cubiceps* (Africa), (North East Brazil), *T. carbonaria* (Australia), *Austroplebeia australis* (Australia), *T. hockingsii* (Australia). Some of the stingless bee honey which are very popular in many countries like 'manuka honey' and due to the exotic flavor and beneficial characteristics of honey produced by varieties of stingless bee found over the world, this stingless bee honey has become product with high market demand, achieving higher importance and prices than the honey produced by normal honey bee *Apis mallifera*.

Figure 1: Stingless Bee showing their nesting behavior (a) Pollen storage pots or brood cells; (b) Bee guarding at the entrance tube of nest. (c) Consumption of honey from honey storage pots (d) Queen Bee on brood cell of hive (source: Leonhardt, Sara. (2010). Resin collection and use in stingless bees)

Table 1: Different species of stingless bee found in India

Stingless-Bee Species	Distribution into different zones within India		
Region / Zones	**South**	**North East**	**North West**
Tetragonula bengalensis	No	Yes	No
T. iridipennis	Yes	Yes	Yes
T. praeterita	Yes	No	No
T. laevicepes	Yes	Yes	Yes
T. ruficornis	No	Yes	No
Lepidotrigona arcifera	Yes	Yes	No

Components of Stingless Bee Honey

Honey is a natural product which is formed by utilization of nectar (juicy fluid) once sucked by these bees. The physical and chemical composition of this honey depends upon particular floral source from which nectar is sucked including certain different factors like climatic condition and geographical area. Mostly every honey contains similar several components like sugars, phenolic compounds, flavonoids, antioxidants. Phenolic compounds present in all types of honey are caffeic, ellagic, ferulic, P-coumaric acid apigenin, chrysin, galangin, hesperitin, kaempferol, pinocembrin, quercitin etc. It contains antioxidant such as tocopherol, ascorbic acid, superoxide dismutase, catalase and reduced glutathione.[13] All these compounds in honey are responsible for its color, quality and antioxidant activity. The phenolic composition and antioxidant activity of honey collected from different species of stingless bee have shown the presence of almost all the phenolic compounds and antioxidant compounds (Flavonoid) in stingless bee honey[14] (Table 2). Out of the total composition of stingless bee honey almost 38% of this honey is comprised of sugars like fructose, glucose, other disaccharide and oligosaccharide like sucrose, maltose, manotriose and panose. It is also a source of essential vitamins and minerals, some of the vitamins present in honey are Vitamin C (ascorbic acid), Vitamin B1(Thiamine), Vitamin B2(riboflavin), Vitamin B3(nicotinic acid),Vitamin B5 (pantothenic acid), VitaminB6 (pyridoxine), Vitamin B8(biotin), Vitamin B9 (folic acid) and Vitamin B12 (cyanocobalamin) and minerals are calcium(Ca), potassium(K), sodium(Na), magnesium(Mg), phosphorus(P), sulphur (S), iron (Fe), zinc(Zn), copper(Cu) and manganese(Mn) and enzymes like superoxide dismutase, catalase etc.[15]

Table 2: Composition of stingless bee honey

S. No.	Compound Present	Compound Types
1.	Flavonoids	Naringenin, chrysin, hispidulin, quercetin, aromadendrin, taxifolin, mirecetrin, isoquercitrin eriodictyol, umbelliferone syringaldehyde, carnosol vanillin, apigenin
2.	Phenolic acids	Salicylic, Mandelic P-Coumaric, Vanillic Hydroxymethyl, Sinapic Protocathechuic, Benzoic trans ferulic syringic chlorogenic
3.	Vitamins	*Vit-C,B1,B2,B3, B5,B6,B8,B9,B12*
4.	Sugars	Glucose, Sucrose, Maltose Maltotriose, Disaccharides & Oligosaccharides
5.	Minerals	Phosphorus, Zinc, Copper, Potassium, Calcium, Sodium, Iron, Sulphur, Magnesium, Manganese
6.	Enzymes	Glucoxidase, Catalase, Superoxide dismutase

Transformation of Nectar to Honey

Honey is the product formed by physical, chemical and biological changes that occur after the storage of juicy fluid or nectar which were sucked by the stingless bee from different floral sources. This honey is stored inside pots or brood cells made up cerumen a waxy material which is combination of beeswax, resin and mandibular secretion that provides sterile environment in hive.[16] Nectar in cerumen pots goes through 3 transformation process (Figure 2). In first transformation process large amount of water gets evaporated from nectar in cerumen pot or brood cells. In second transformation process fermentation by microbes takes place and in last process

of transformation where worker bee secretes enzymes which are able to chemically hydrolyzes nectar sucrose into fructose and glucose. One of the most noticeable similarity in honey of different stingless bee is their high water content which is much higher than a honey produced by normal honey bee (*Apis mallifera*).[17]

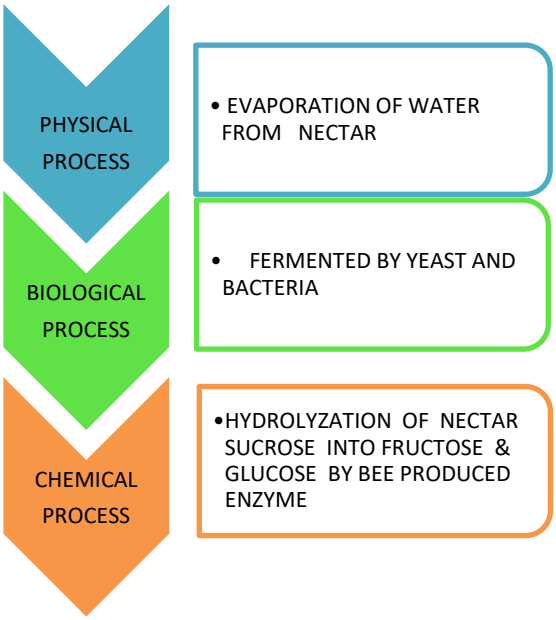

Figure 2: Process of transformation of nectar into honey: Physical process, Biological process, Chemical process

Honey as Prebiotics

Prebiotic helps the cells or strain of probiotic bacteria such as *Lactobacillus* and *Bifidobacter* by improving the balance and quality of beneficial microflora in the gastrointestinal tract by providing certain growth factors like fructose-oligosaccharides which are utilized by the probiotic microflora of gut.[18] Honey of stingless bee contains variety of sugars including fructose and glucose along with several disaccharides and several other oligosaccharides units[19] (Figure 3). The non digestible oligosaccharide in honey is fermented by *Lactobacillus* and *Bifidobacter* using saccharolytic fermentation process without involment of any proteolytic activity.[20] Due to saccharolytic fermentation process a large amount of energy is released along with end product like gases and fatty acids with short chain[21] all this have shown inhibitory properties against several pathogens and also possess potential effects on human health like anti-inflammatory, anti-diabetic, anti-cancer and helps to control the appetite[22]. The utilization of oligosaccharides present in honey is only possible by one group of microorganism called probiotic microbes in the large intestine. It is because digestive enzymes in human are not able to hydrolyze this indigestible sugar or oligosaccharides like fructose-oligosaccharide present in honey which are considered as prebiotic.[23] One of the best markers in determining prebiotic and non prebiotic sugars is the presence of β-Glycosydic linkages in prebiotic sugars. This β-Glycosydases enzymes are absent in human digestive system.[24] Potential of honey as prebiotics and its effect was reported from a recent study of using honey as encapsulant had shown improvement in survival abilities of two different strains of probiotic Bifidobacterium in gastrointestinal tract.[25] An in-vivo study on rats fed with honey is reported to increase in counts of lactic acid bacteria in rat intestine indicating the role of honey in colonization of probiotic microflora of gastrointestinal tract.[26] All this study have shown honey contains several compounds which provide essential conditions which were favorable for the growth of beneficial probiotic microflora of gut and on the same time inhibiting growth of pathogenic microorganism which shows honey as a potential prebiotics.

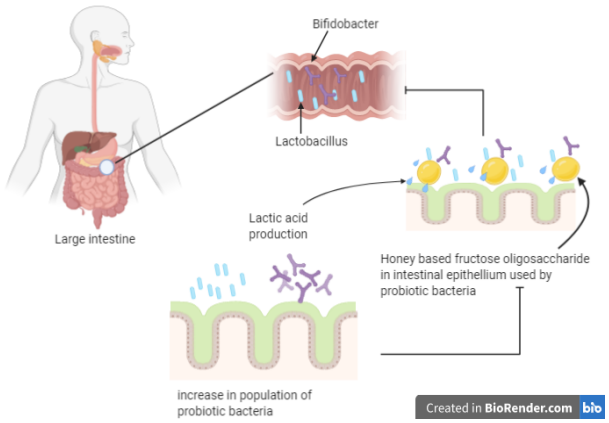

Figure 3: Honey based fructose-oligosaccharide showing prebiotic and probiotic effect

Therapeutic Application of Stingless Bee Honey

Honey is used as a functional food and is also a good source of several beneficial components essential for our body. Stingless bee honey contains about 200 or more beneficial compounds in it and are believed to have numerous therapeutic properties, antioxidant, anti-inflammatory, anti microbial, anti diabetic, anticancer, effect on fertility, moisturizing and wound healing activity.[27]

Anti-microbial properties

Many microbial sensitivity studies has reported that drug now a days are becoming less sensitive for microorganism further leading to emergence of problem like multi drug resistant microorganism.[28] Plants also act as promising alternative for presence of certain antifungal and antibacterial compounds towards many bacterial and fungal infections without causing any side effect.[29] Like the same way plant and nectar sucked by stingless bee contains certain phenolic compounds which are able to treat infections caused by pathogenic microorganism like multidrug resistant *Staphylococcus aureus* (MRSA), *Escherichia coli* (0157:H7), *Proteus vulgaris*, *Shigella sonnei* and *Klebsiella* sp etc.[30] The antibacterial activity of stingless bee honey against N315 strain of MRSA when treated with 1.25% of stingless bee honey can be easily observed through image scanned through scanning electron microscopy[31] (Figure 4). Honey are also reported to contain more than 200 beneficial compounds which includes many phenolic acids, sugars, flavonoids, antioxidant and many

enzymes like glucose oxidase, catalase and hydrogen peroxide (H_2O_2) etc.[32] The anti bacterial activity of honey depends upon the water content, acidity (low pH) and content of hydrogen peroxide (H_2O_2) and other phytochemicals sucked in form of nectar by stingless bee species.[33] Hydrogen peroxide when used in more concentration ranging from 0.8M to 8M it has shown bactericidal effectiveness against many microorganisms like *Staphylococcus*, *Streptococcus*, *Pseudomonas* sp. and *Bacillus* spores.[34] Many studies indicates that hydrogen peroxide is responsible for causing cell death of many yeast and bacterial cells by causing chromosomal DNA degradation.[35] From recent study it is found that some phenolic compounds such as pinocembrin, syringic acid, and some other compounds are also responsible for antimicrobial activity and the presence of non peroxide component metylglyoxal in honey which is responsible for antibacterial activity of honey against several pathogenic bacteria.[36]

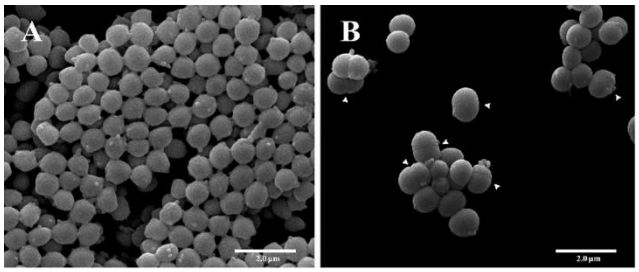

Figure 4: SEM images of the antibacterial effect of Stingless bee honey against the MRSA N315 strain after 3 h of incubation. (A) Negative control (without honey); (B) cells treated with Stingless bee honey (1.25%) (Source: https://doi.org/10.1038/srep21641)

Anticancer properties

Polyphenols are involved in various mechanisms which prevent cancer and all these cancer preventive mechanism includes inhibition of uncontrolled cancer cell proliferation, modulation of cancer signal pathway, and inhibition of apoptosis due to tumor cells. If this uncontrolled cell proliferation can be inhibited then cancer can be reduced or treated.[37] Many in-vitro studies have revealed that not only honey but the product like propolis formed by stingless bee exhibit high cytotoxicity towards all cancer cell line of human cell.[38] One of the best biomarker in identifying colon cancer development is Aberrant crypt foci. Stingless bee honey is neither harmful nor toxic to animal. Whenever stingless bee honey is administered orally it has proved to reduce total number of aberrant crypt and its multiplicity.[39]

Anti-diabetic properties

α-amylase and α-glucosidase are 2 enzymes which helps in conversion of complex sugar (polysaccharide, oligosaccharide and disaccharides) into simple sugar like glucose. We know that diabetes occurs due to increase in blood glucose level. From in vitro studies on α-amylase and α-glucosidase it is found that stingless bee honey have potential to inhibit these 2 enzymes leading to anti-diabetic properties of stingless bee honey. Blood glucose level increases with faster rate whenever these 2 enzymes are active.[40] From many scientific studies it is found that polyphenols in dietary source are used to treat diabetes. Different types of polyphenols are also found in stingless bee honey which are detected and found to have anti diabetic properties by decreasing amount of blood glucose level by inhibiting mechanism of α-amylase and α-glucosidase. Some of these polyphenols like quercetin successfully inhibits α-glucosidase enzyme leading to decrease in maltose level in hypoglycemic patient.[41] Polyphenol luteolin which helps in inhibition of both α-amylase and α- glucosidase leads to anti-diabetic effect. β cells of pancreas regulates the level of glucose in blood so pancreas must be protected in order to maintain level of glucose in blood for this a polyphenol quercetin helps to protect pancreatic β- cells.[42]

Wound healing properties

During wound healing process stress is created to cells or tissues by the factors like ultraviolet radiation, pollution, smoke, drug etc producing a free reactive molecule produced often termed as free radical like singlet oxygen, superoxide, peroxyl and hydroxyl radicals. These are reactive oxygen species which leads to deterioration of membranes, lipids, amino acids and DNA.[43] This damage to DNA leads to breakdown of muscle protein called collagen invading the proliferation stage during wound healing process. All these wound recovering tissues are saved by antioxidant molecule preventing the harmful effect of reactive oxygen species or free radical towards recovering tissue or cells of wound.[44] Antioxidant works into enzymatic and non-enzymatic way to help wounded cells or tissue to recover safely. Honey of this stingless bee contains both of this antioxidant enzymes and non enzymatic compounds, where antioxidant enzyme like superoxide dismutase neutralize the free radical or reactive oxygen species into a molecule which is less harmful to a body and non enzymatic compounds like ascorbic acid, tocopherol and phenolic compounds neutralize reactive oxygen species by blocking and cutting damaging chain reaction caused by free radical.[45]

Ethnomedicinal Application of Stingless Bee Honey

Honey is produced by stingless bee honey while storing a juicy fluid into a cerumen pots. This juicy fluid or nectar is comprised of more than 200 such components which are very beneficial for our body. Not only it is used in 21st century but there are many evidences from ancient civilization about the usage of honey in ailments of various problems of human body.[46] In ancient Indian Vedic civilization or Indian Ayurveda this honey is said to be one of the precious gift of nature to mankind. Many experts of Ayurveda believe that honey is able to treat teeth and gum problems. Along with that it is also recommended for problems of digestive system and problem of throat like cough. From the evidence of ancient civilization like ancient Egypt, ancient Greek, Romans and Chinese all of them have used honey against problems of digestive

system and problem of wounds and burn.[47] From the ancient time till now in northeastern Himalayan region of Darjeeling, Indian people are using this stingless bee honey in traditional or ethno medicine for treatment of various problems related to skin, eye, joints, digestive or intestinal problems, throat or respiratory problems by formulating or mixing honey with other parts of plant, milk or any other naturally available product.[48] The oral problems of infant can be cured by applying stingless bee honey on that particular area for few days and also used for treatment of gastrointestinal diarrhea.[49] For the problem like burn and cured wounds in both the cases, a fresh honey is applied directly to burn portion.[50] Out of all the problems of digestive system, commonly occurring problem includes bacterial infection like stomach or gastric, diarrhea, and gastroenteritis. This stingless bee honey if taken one table spoon every morning with empty stomach or before taking breakfast can be able to cure ulcer of stomach.[51] 15 ml of honey if consumed orally can cure stress or fatigue. When this 15 ml honey consumed daily when mixed with the fruit like pomegranate is able to cure the weakness.[52] For the problem of conjunctivitis a few drops of this stingless bee honey is applied to affected area of eye till it is cured.[53]

Bronchial asthma, common cough, nasal and sinus problem are some of the respiratory tract infection or problems. Natural remedy for all these kinds of problem are possible and are prepared using stingless bee honey as main component. For the Bronchial asthma a mixture of few drops of honey and ginger juice along with a pinch of black pepper powder if consumed three times a day can cure symptoms of bronchial asthma.[54] Few drops of ginger juice along with honey consumed for few days can cure common cough.[55]

CONCLUSION

At present microorganisms are becoming less sensitive towards drugs which make them more resistant for variety of drugs, leading to one of the major emerging problem called multidrug resistance and only some of the antimicrobial drugs are available against them which are mostly expensive and can leads to various side effect to the body. Many studies on stingless bee honey have proven effective against many pathogenic microorganism including resistant pathogen bacteria like MRSA (Methicillin resistant *staphylococcus aureus*) without causing any side effects. On the other hand stingless bee honey are also a good source of indigestible prebiotic sugar molecules like fructo oligosaccharides which act as major substrate for probiotic microflora of human gut. Due to presence of 200 or more compounds, it is used in various ethno-medicinal formulation and contains different potential properties like anti microbial, anti diabetic, anti cancerous, wound healing which makes honey of stingless bee a better and natural alternative source for preparation of many therapeutic agent and also provides opportunities for researchers to understand the potential uses of those bioactive ingredient or compound present in stingless bee honey. Although having so many potential benefits only few of the stingless bee species have been explored. Many species of stingless bee honey are unexplored which can provide opportunities for researchers in finding those new species of stingless bee along with possibility of discovering new bioactive compounds hidden in honey produced by them. Therefore, there is further need to explore these benefits provided by honey of Stingless bee and at the same time innovative strategies must be followed for converting and formulating honey based compound into beneficial product like wound healing hydrogel, creams, prebiotic capsules, prebiotic beverages.

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