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Molecular Pharmacology of Honey

Afroz R[1], Tanvir EM[2], Zheng W[3] and Little PJ[4*]

[1]*Department of Biochemistry, Primeasia University, Banani, Dhaka 1213, Bangladesh*

[2]*Department of Biochemistry and Molecular Biology, Gono University, Savar, Dhaka 1344, Bangladesh*

[3]*Faculty of Health Sciences, University of Macau, Taipa, Macau, China*

[4]*School of Pharmacy, Pharmacy Australia Centre of Excellence, The University of Queensland, Woolloongabba, Queensland 4102, Australia*

[*]**Corresponding author:** Little PJ, School of Pharmacy, Pharmacy Australia Centre of Excellence, The University of Queensland, Woolloongabba, Queensland 4102, Australia, Tel: +61 33461701; E-mail: p.little@uq.edu.au

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Abstract

Honey is a natural by-product from flower nectar and the aero-digestive tract of the honey bee. Honey has a complex chemical and biochemical composition including sugars, proteins, amino acids, phenolics, vitamins and minerals. Honey is a natural medicinal agent with antioxidant, anti-bacterial, antifungal, anti-malarial and anti-tumor properties. This review describes the major active ingredients in honey and their potential pharmacological effects with a description and analysis of the underlying molecular mechanism. As an example, we describe how high fructose concentration in honey helps in lowering blood glucose levels and triggers weight loss in obese individuals by increased insulin secretion, expression of GLUT5 mRNA and activation of glucokinase activity. In this review we highlight the molecular pharmacology of the prominent chemical and biochemical constituents of natural honey along with some toxicology analysis of the constituents.

Keywords: Honey; Constituents; Pharmacological actions; Medicines

Introduction

Honey is an ancient product whose history can be traced back 8000 years in Europe and it continues to have very wide spread use as a food product with very high popularity [1]. Honey, as other such ancient products has cultural significance and also in some cultures religious significance [2] which has led to its use as a medicinal product [3,4]. Generically honey is a product derived from any bees foraging nectar for storage in hives but the product produced by honey bees, genus *Apis*, is that commonly referred to as honey [5]. Honey in the common form arises by a process of regurgitation by the host and concentration from evaporation in the bee hive. Honey develops as a primary food for bees in wax honeycombs inside beehives.

The intense sweetness of honey arises from the very high content of two monosaccharaides, glucose and fructose [6]. The natural processes through which it is derived means that honey contains many chemicals and biochemical [7]. Honey is widely used as a food in its natural state. Honey is also used in many cooking processes and products where it provides natural sweetness [8]. The physical composition of honey, mostly very low water content and high osmolality, means that microorganisms do not grow in honey however the natural origin means that it can harbor bacteria as well as spores for microorganisms including highly toxic forms such as *Clostridium botulinum*, the source of botulinum toxin, one of the most toxic chemicals known to man. The multiple chemicals and biochemical in honey has led to its use for medicinal purposes [9,10].

In this review we document the major classes of chemicals and biochemicals present in honey and we describe the molecular pharmacology and where appropriate the molecular toxicology of the most prominent of these substances. We consider the actions of these compounds within honey and also their actions more broadly as bioactive principles in their own right.

Chemical and biochemical composition of honey

The composition of honey is rather variable and primarily depends on the floral source; however, a number of external factors also play a role, including seasonal and environmental factors and processing [11,12]. Honey is a supersaturated solution of sugars, of which fructose (38%) and glucose (31%) are the main contributors [12]. Honey also contains small amounts of other constituents, such as minerals, proteins, vitamins, organic acids, flavonoids, phenolic acids, enzymes and other phytochemicals, which may contribute to its pharmacological profile. The overall composition of natural honey is summarized in Table 1 [13-17].

Sugar and water are the primary constituents of natural honey. Sugar accounts for 95-99% of the dry honey matter. The majority of these simple sugars are D-fructose (38.2%) and D-glucose (31.3%), which represents 85-95% of the total sugars [18]. These 6-carbon sugars are immediately absorbed by the small intestine. Natural honey samples are rich in both reducing and non-reducing sugars.

Honey contains a number of proteins and free amino acids [19] and the approximate percentage of proteins in natural honey is 0.5% [20]. Depending upon the species of the harvesting honey bees, different proteins of diverse molecular weights are found in natural honey [20]. Most of the enzymes found in honey are added by honey bees during the process of natural honey ripening [18]; the three main honey phytochemicals are diastase (amylase), which decomposes starch or glycogen into smaller sugar units, invertase, which decomposes sucrose into fructose and glucose, and glucose oxidase, which produces hydrogen peroxide and gluconic acid from glucose [14].

Component	Average (%)
Water	17.20
Fructose	38.19
Glucose	31.28
Disaccharides, calculated as maltose	7.31
Higher sugars	1.50
Free gluconic acid	0.57
Ash	0.17
Nitrogen	0.04
Minerals	0.20
Amino acids, proteins	0.30
pH value	3.90

Table 1: Average composition of honey (data in g/100 g) [12-17].

Amino acids account for 1% (w/w) of honey, with proline as the main contributor, as it corresponds to approximately 50% of the total free amino acids [21]. In addition to proline, there are 26 amino acids in honeys; their relative proportions depend on their origin (nectar or honeydew).

Although honey is used as a traditional medicine and in domestic needs since millennia, only recently have the antioxidant properties and constituents of honey are come to be recognized as such. The distribution of three main phenolic families (benzoic and cinnamic acids, as well as flavonoids) shows different profiles in honey from different floral origins, with flavonoids being the most common in floral honeys.

The mineral content of honey has a 50-fold range of values, the largest of any component. The minerals detected in honey are listed in Table 2 [22]. Honey contains small but detectable quantities of vitamins; however, honey should not be considered a suitable source of vitamins for therapeutic purposes as the concentrations of many are in the sub-therapeutic parts per million range [22]. The aroma and flavour of honey are attributable to the sugars, the acids and other volatile components in honey. These volatile components include a variety of C1-C5 aldehydes and alcohols. Methyl and ethyl formate have also been identified in honey. It has been noted that many phenylacetic esters have a honey-like taste and aroma [7].

Chemicals/Biochemicals	Average percentage (%)	Particular components
Monosaccharides	70.0-80.0%	Fructose, glucose
Disaccharides	7.0-8.0%	Maltose, sucrose, trehalose, isomaltose, nigerose, turanose, kojibiose, maltulose, gentiobiose, laminaribiose.
Oligosachharides (Higher sugars)	1.5-2.0%	Erlose, theanderose, panose, maltotriose, 1-ketose, isopanose, isomaltosyltetraose, theanderose, centose, isomaltosyl glucose, isomaltosyltriose, isomaltosyltaose.
Free organic acids	0.2-2.0%	Gluconic acid (70.0-80.0 % of all free acids), acetic acid, butyric acid, citric acid, formic acid, lactic acid, malic acid, oxalic acid, succinic acid, fumaric acid, α-ketoglutaric acid, pyroglutamic acid, maleic acid.
Amino acids	0.2-2.0%	Proline, lysine, histidine, arginine, aspartic acid, threonine, serine, glutamic acid, glycine, alaline, cysteine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, tryptophan.
Phenolic acids	1.5-4.2%	Gallic acid, syringic acid, p-coumaric acid, caffeic acid, trans-cinnamic acid, vanillic acid, 4-Dimethylaminobenzoic acid, Chlorogenic acid, pyrogallol
Flavonoids	1.2-2.5%	Catechin, quercetin, rutin, naringin, neringenin, luteolin, apigenin, kaempherol, galangin
Minerals	0.1-1.5%	Potassium, sodium, calcium, magnesium, iron, copper, manganese, chlorine, phosphorus, sulphur, aluminium, iodine, boron, titanium, molybdenum, cobalt, zinc, lead, tin, antimony, nickel.
Vitamins	Trace amounts	Ascorbic acid, riboflavin, pantothenic acid, niacin, thiamine, pyrodoxine, biotin, folic acid
Enzymes		Invertase (sucrase), diastase (amylase), glucose oxidase, catalase, acid phosphatase
Lipids	Trace amounts	Glyceraldehydes, sterols, phospholipids, oleic acid, lauric acid, stearic acid,
Esters	Trace amounts	Methyl formate, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, ethyl propionate, methyl butyrate, ethyl butyrate, isoamyl butyrate, methyl valerate, ethyl valerate, Methyl pyruvate, methyl benzoate, ethyl benzoate, methyl phenylacetate, ethyl phenylacetate

Aldehydes and ketones	Trace amounts	Formaldehyde, acetaldehyde, propylaldehyde, butylaldehyde, isobutylaldehyde, benzaldehyde, methylethyl ketone, isovaleraldehyde, capraldehyde
Alcohols	Trace amounts	Methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, isobutanol, 2-methyl-butan-2-ol, benzyl alcohol
Microscopic particles	Trace amounts	Pollen, fungal spores, bacterial spores, yeasts

Table 2: Chemicals and biochemical detected in honey.

High sugar content is attributed with the anti-hyperglycemic and anti-microbial effects of honey

There has been much interest in research on natural bioactive compounds in recent years, with a view by advocates that natural products are superior in terms of safety when compared to synthetic products [23,24]. Fructose and glucose, the prominent monosaccharides in honey, are the stereoisomers having the same molecular formula but different structural formula [25]. These monosaccharides do not need to be hydrolyzed by gastrointestinal tract (GIT) enzymes and thus are ready for absorption.

Previous studies documented that fructose reduces hyperglycemia or glucose levels in diabetic rodent models, healthy subjects and patients with diabetes [26-29]. Evidence suggests that gastric emptying is prolonged by fructose intake [30], which may slow the rate of intestinal absorption [31]. Besides delaying absorption, fructose consumption lowers food intake [32], which is also attributed to the delayed gastric emptying [33].The slow absorption of fructose in the intestine might prolong the duration of contact and interaction between fructose and intestinal receptors that play a key role in satiety [34,35]. This might allow more macronutrients (including carbohydrates) to be passed into the large intestine, thereby limiting their intestinal absorption. Moreover, with the evidence suggesting that fructose reduces food intake, there is a possibility for reduced weight gain (Figure 1) [36].

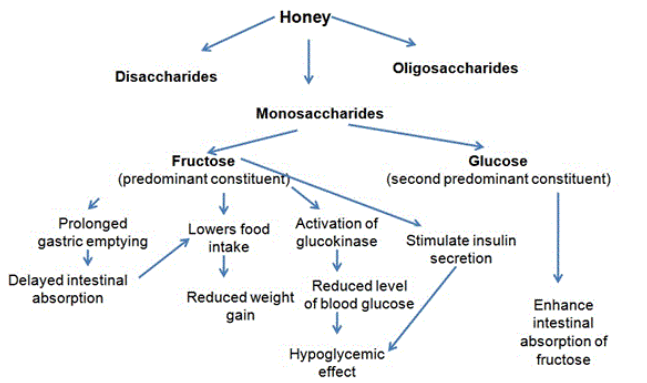

Figure 1: Action of fructose and glucose, the prominent constituents of natural honey.

However, in another interesting finding, honey might possibly exert its hypoglycemic effect through fructose [14]. Fructose neither increases plasma glucose and its metabolism does not require insulin secretion [37]. Dietary fructose is known to activate glucokinase (GKA) which is a key enzyme involved in the intracellular metabolism of glucose. GKA catalyzes the conversion of glucose to glucose-6-phosphate thereby decreasing blood glucose [38]. Fructose stimulates insulin secretion from an isolated pancreas [39]. Moreover, stronger evidence in support of role of fructose in mediating hypoglycemic effect of honey is provided by Curry and his coworkers [40]. They found that in rat pancreas preparations, there was no insulin response to fructose when very low or no concentrations of glucose were present in the medium. In contrast, it was observed that with higher glucose concentrations, insulin response to fructose was elicited (Figure 1) [40].

After fructose, glucose is the second major constituent in most varieties of honey [14]. Compelling evidence indicates that the intestinal absorption of fructose is enhanced in the presence of glucose (Figure 1) [41]. Although it remains unclear how glucose enhances fructose absorption, the recruitment of GLUT2 carrier to the brush border membrane caused by increased intestinal fructose may contribute to the synergistic effect of glucose on fructose absorption [41,42]. In addition, increased expression of GLUT5 mRNA level after fructose ingestion but not glucose has also been observed [43]. There may be a disaccharide-related transport system which identifies both fructose and glucose as products of the enzymatic hydrolysis of sucrose [44]. Evidence also suggests that fructose is absorbed via a saturable carrier in the absence of glucose [45]. In contrast, in the presence of glucose, fructose is absorbed via a disaccharide-related transport system [45].

The high sugar content of honey hinders the growth of microbes, but the sugar content alone is not the sole contributor to the antibacterial properties of honey [46]. The gastrointestinal tract (GIT) contains essential and beneficial bacteria, especially *Bifidobacteria* for the maintenance of good health. One can increase the *Bifidobacteria* population in the GIT by consuming foods with rich a supply of prebiotics such as natural honey [47,48]. Prebiotics are substances that facilitate the enhanced growth and the biological activity of these beneficial bacteria. The consumption of honey has a potential effect on human digestion and this effect is produced by oligosaccharides [47-49]. Several *in vitro* and *in vivo* studies have been documented on the importance of dietary supplementation with natural honey on the growth of beneficial bacteria (*Bifidobacteria and Lactobacilli*) and their prebiotic effect in the GIT [47-51]. One comparative study on natural (honey) and artificial (sucrose) sugars showed that honey increased bacteria *Lactobacilli* in both *in vitro* and *in vivo* (within the small and large intestine of experimental rats) while artificial sugar had no effect [52]. Therefore, honey sugars not only provide sweetness to honey but are also responsible for health benefits of honey ranging from anti-hyperglycemic to anti-microbial effects.

Honey proteins and enzymes provide digestive benefits and hinder microbial growth

The presence of proteins and amino acids, as well as carbohydrates, vitamins and minerals, in natural honey has been described [18]. The enzyme content of honey is one of the characteristics that are purported to make it beneficial to human health. The main enzymes in honey are invertase (saccharase), diastase (amylase) and glucose oxidase [14]. The enzymes in honey which originate from plants are catalase, lysozyme, and acid phosphatase [53].

Invertase is a carbohydrate-digestive enzyme that splits sucrose into glucose and fructose. Its ability to hydrolyse the glycosidic bond between fructose and glucose makes it a vital part of the digestion of complex sugars into glucose which can be used as a ready fuel source by the body [53]. Invertase plays a key role not only in digestive processes, but also and perhaps more importantly in overall human disease prevention, physical rejuvenation and anti-aging processes. As invertase creates pre-digestive simple sugars, it helps to reduce stomach toxicity, because sugars do not remain in the stomach long enough to create toxic fermentation [53,54]. This enzyme also provides defence against a number of harmful microbes which might be attributed to the anti-microbial properties of honey. The ability of this enzyme to pull moisture out of the body causes bacterial infestations to subside [54].

A high content of glucose oxidase is an important property of honey [55]. In several studies, it has been shown that hydrogen peroxide is the main compound responsible for the antibacterial effect of honey [56-58]. Hydrogen peroxide is produced during glucose oxidation catalysed by bee enzyme glucose oxidase. In a honey containing a high concentration of this oxidizing compound, bacteria cannot respond normally to proliferative signals, and their growth remains arrested even when the honey is used in diluted forms [59]. Glucose oxidase present in honey is not only involved in the inhibition of pathogenic microbes but also participates in wound and burn healing. The hydrogen peroxide of honey plays important roles in inflammation, stimulation of tissue growth, epithelialization, and analgesia and wound debriding. Hydrogen peroxide also acts as a novel intracellular and intercellular messenger capable of promoting growth responses and stimulating expression of early growth genes, which are important in wound healing [18].

Pollen is the main source of honey amino acids so the amino acid profile of a honey is a characteristic of its botanical origin [13]. Proline is the prominent amino acid found in different types of honey. The main enzymes and amino acids identified in honey from different botanical and geographical origins are listed in Table 3 [14,21,60-62]. Proline is reported to mainly originate from bee salivary secretions during the conversion of nectar into honey. Proline levels are dependent on the type of bees and thus may be variable. Proline concentrations are an indicator of honey quality and of adulteration (suspected if proline levels are below 183 mg/kg) [63].

Enzymes	Free amino acids
Invertase (saccharase)	Glutamic acid (Glu)
Glucose oxidase	Aspartic acid (Asp)
Diastase (amylase)	Asparagine (Asn)
Catalase	Serine (Ser)
Lysozyme	Glutamine (Gln)
Acid phosphatase	Histidine (His)
Protease	Threonine (Thr)
Esterase	b-Alanine (b-Ala)
α-glucosidase	a-Alanine (a-Ala)
-	Tryptophan (Trp)
-	Phenylalanine (Phe)
-	Lysine (Lys)
-	Arginine (Arg)
-	Proline (Pro)
-	Tyrosine (Tyr)
-	Valine (Val)
-	Methionine (Met)
-	Cysteine (Cys)
-	Isoleucine (Ile)
-	Leucine (Leu)
-	g-Aminobutyric acid (GABA)
-	Ornithine (Orn)

Table 3: Enzymes and free amino acids reported in different honey samples.

However, proteins, enzymes and amino acids constitute only a small fraction of total honey composition, but the presence of these compounds is associated with many health benefits of honey including nutritional benefits, and the role of honey enzymes in carbohydrate digestion and most importantly the anti-microbial potential of honey.

Phenolic acids are antioxidant constituents responsible for a range of therapeutic properties of honey

Polyphenols serve as powerful antioxidants due to the hydrogen-donating ability of their hydroxyl groups as well as their ability to donate electrons to arrest the production of free radicals as a result of oxidative stress [64]. Polyphenols are important as they contribute to honey's color, taste and aroma; they also provide beneficial health effects. The antioxidant activity is primarily due to the presence of phenolic compounds and flavonoids [65]. Thus the presence of phenolic acids contributes to the functional and therapeutic properties of honey.

Gallic acid (GA) or 3,4,5-trihydroxybenzoic acid, consisting of tri-hydroxylated phenolic structure, is an intermediate of secondary plant metabolism in higher plants [66], found to be commonly present in honey [23,67,68]. GA is known to potentiate several pharmacological and biochemical pathways having strong antioxidant, anti-inflammatory, anti-mutagenic, anti-cancer and cardio protective activity. Previous studies have demonstrated a variety of biological activity of GA including anti-tumor effects. The anti-tumor activity seems to be related to the induction of apoptosis involving different signaling pathways. Apoptosis induced by GA may be associated with

oxidative stress derived from ROS, mitochondrial dysfunction and an increase in intracellular Ca^{2+} levels. Although the mechanism by which GA induces cell death seems to be distinct among various cell types, the production of ROS and the increase of intracellular Ca^{2+} concentration were required as common signals [69]. The hypothesis that the apoptotic cell death in a murine melanoma cell line is a consequence of the pro-oxidative action of GA and derivatives is supported by its ability to activate NF-ĸB, a ubiquitous transcription factor responsible for several cell processes including oxidative stress [70]. Although the NF-ĸB activation might promote the transcription of both anti- and pro-apoptotic proteins, its activation occurs in pro-oxidant conditions [71]. In this context, it is possible to infer that the NF-ĸB induction by esters of GA would be directly related to the induction of ROS generation by these compounds and conversely that GA derivatives decrease the reduced/oxidized glutathione ratio [70,72]. Changes in the GSH levels and in the redox state in mitochondria are associated with oxidative stress induced by various oxidizing agents. Additionally, at least in particular conditions, the release into the cytosol of lysosomal constituents may initiate apoptosis.

GA provides its anti-inflammatory actions by suppressing pro-inflammatory cytokines and chemokines such as COX-2 [73,74]. The acetylation of p65 regulates the biological action of NF-ĸB, including the activation of transcription and DNA binding activity. GA inhibits the activation of NF-ĸB dependent p65 acetylation and production of inflammatory markers. The low acetylation rate of p65 results in a complete loss of function of NF-ĸB indicating that its acetylation is necessary for the signaling pathway mediated by NF-ĸB. Therefore, interference in the selective acetylation of p65 with small molecules as GA might produce a new class of anti-inflammatory drugs [75].

Syringic acid is a phenolic compound abundant in many types of honey that acts pharmacologically as an antioxidant to clear free radicals and ROS [68,76]. The pathogenesis of diabetic cataracts (DC) is primarily associated with hyperglycaemia-induced osmotic pressure disorder [77]. Aldose reductase inhibitors (ARIs) are promising therapeutic agents for the prevention and treatment of DC in a number of animal model based studies [78-80]. Due to liver and gastrointestinal side effects in humans ARIs have limited clinical applicability [81]. AR is the most likely target protein for syringistic acid. Syringic acid to AR binding was explored using molecular modelling to predict the interaction between syringic acid and AR. A recent study demonstrated that Trp 111, His 110, Tyr 48, Trp 20, Trp 79, Leu 300 and Phe 122 are the preliminary amino acid residues involved in the binding process of syringic acid and AR (Figure 2) [76]. Investigation of the mechanism of syringic acid action revealed that it down-regulated the AR mRNA expression level and inhibited AR activity in a competitive and dose dependent manner. Therefore, syringic acid is capable of exerting a physiological effect on glucose metabolism and cataract formation and provides a basis for development of potential therapeutic management of DC by a naturally occurring phenolic acid, syringic acid [76].

Syringic acid interacts with seven amino acid residues of AR, among them Trp 111 and His 110 constitute the intermolecular hydrogen bond (Trp 111 and His 110 have same hydroxyl group at position 1).

Caffeic acid (CA) is a representative phenolic compound that is found in many different natural resources such as fruits, vegetables, herbs and honey [82]. CA possess numerous biological activities including antioxidative, anti-cancer, anti-diabetic effects and also inhibits human immunodeficiency virus (HIV) replication [82-84]. Chung et al. [85] demonstrated underlying mechanism of anti-cancer effect of CA. According to their study CA and its derivative caffeic acid phenethyl ester (CAPE) (1) inhibit the enzymatic action of MMP-9 (matrix metalloproteinase-9) which has a role in cancer invasion and metastasis, (2) blocks invasiveness potential through the suppression of MMP-9 gene transcription by inhibiting NF-ĸB activity in PMA (phorbol 12-myristate 13-acetate)-stimulated HepG2 cells (a human hepatocellular carcinoma cell line) and (3) suppresses the growth of HepG2 cell xenografts in nude mice. The anti-tumorigenic and anti-metastatic effects of CA and CAPE may be mediated through the suppression of MMP-9 gene expression by the activation of NF-ĸB and MMP-9 catalytic activity. Therefore, these two compounds are potential therapeutic candidates for the treatment of cancer and metastasis via dual mechanisms (i.e., dual inhibition of metastasis specific enzyme activity and gene transcription) (Figure 3).

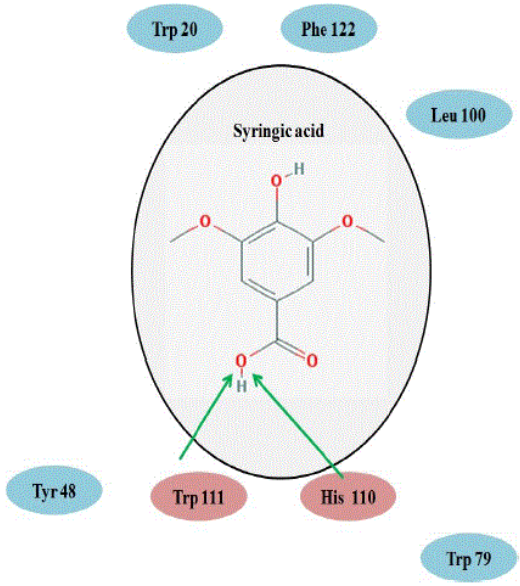

Figure 2: Interaction of syringic acid with aldose reductase (AR).

Chlorogenic acids (CGA) are phenolic compounds formed by esterification of cinnamic acids and detected in many natural honey samples [86]. CGA exerts a range of biological effects including anti-bacterial, antioxidant and anti-cancer activity. Moreover, this phenolic acid also exhibits particular hypoglycemic and anti-hyperlipidemic effects [87-90]. The sortase A (Srt A) isoform plays a critical role in the pathological effects of *Staphylococcus aureus (S. aureus)* [91]. Following the discovery of Srt A, there have been many studies toward finding a potent inhibitor. Through preventing the access and binding of the sorting signal of the surface protein into the active site, CHA efficiently inhibits Srt A transpeptidation, therefore CHA is a novel Srt A inhibitor which is structurally different from other chemical inhibitors [92]. CHA can also down-regulate the expression of enterotoxins and α-toxin which are important in the pathogenesis of *S. aureus* infections [93]. Thus, through interference with both surface adhesion and endotoxins, CHA may have multifaceted anti-virulence activity [92].

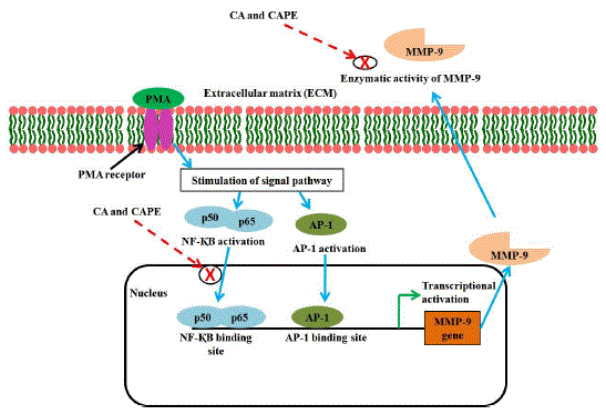

Figure 3: Illustration of dual mechanism of caffeic acid (CA) and caffeic acid phenethyl ester (CAPE) on cancer invasion and metastasis.NFKB and Ap-1 are transcription factors and p50 and p65 are the subunits of NF-KB.

Vanillic acid can exhibit antioxidant, anti-microbial and anti-malarial activities [94]. Cinnamic acid is an effective food-flavoring agent with cancer-preventing and anticancer effects [95] and in all these studies cinnamic acid was found in the form of trans-cinnamic acid. Pyrogallol is an active inhibitor of human tumor cell lines [96]. All of above mentioned phenolic acids are reported in a variety of honey types. On the whole, other honey phenolics have antioxidant properties and show promising pharmacological activity for prevention of cancer, cardiovascular diseases, inflammatory disorders, neurological degeneration and also help in wound healing, prevention of infectious diseases and aging [23].

Flavonoids are potential components that determine various pharmacological actions of honey

Flavonoids are the largest class of polyphenols with a common diphenylpropane structure (C6-C3-C6) consisting of two aromatic rings linked by three carbons. The mechanisms of action of flavonoids are exerted via scavenging or chelating processes [97]. Flavonoids are primarily responsible for the antioxidant and anti-inflammatory effects of honey.

Catechins, members of the flavone group of polyphenols are frequently reported to be present in honey samples. The therapeutic properties of this flavonoid compound have been attributed to its antioxidant and free radical scavenging ability. Catechins can scavenge both superoxide and hydroxyl radicals [98], as well as the 1,1-diphenyl 1,3-picrylhydrazyl radical [99], proxy radicals [100], nitric oxide [101], carbon center free radicals, singlet oxygen and lipid free radicals [98], and also peroxynitrite by preventing the nitration of tyrosine [102]. Catechins chelate metal ions such as copper (II) and iron (III) to form inactive complexes and prevent the generation of potentially damaging free radicals [103]. Another mechanism by which the catechins exert their antioxidant effects is through the ultra-rapid electron transfer from catechin to ROS-induced radical sites on DNA [103]. A further possible mechanism by which catechins scavenge free radicals is by forming stable semiquinonec free radicals [104]. In addition, after the oxidation of catechins, due to their reaction with free radicals, a dimerized product is formed, which has increased superoxide scavenging and iron-chelating potential [105]. In addition to their direct antioxidant effect, they can also indirectly increase the body's endogenous antioxidants to reduce oxidative damage. Furthermore, catechins can directly prevent the levels of endogenous antioxidants such as α-tocopherol and β-carotene, from being depleted by lipid oxidation through 2,2'-azobiz (2-amidinopropane) (AAPH) [106]. Epigallocatechin gallate (EGCG) modulates apoptotic pathways to protect against oxidative stress. Koh et al. [107] demonstrated that EGCG inhibited many points of the apoptotic sequence, including caspase 3, cytochrome c release, poly (ADP-ribose) polymerase cleavage, the glycogen synthase kinase-3 pathway and modulated cell signaling by activating the phosphatidyl inositol-3 kinase (PI3K)/Akt pathway (which promotes cell survival). Further studies have confirmed this by showing that after 3-HK exposure in SH-SY5Y human neuroblastoma cells, apoptosis and caspase 3 activity were inhibited by EGCG [108]. Catechins modulate apoptosis by altering the expression of anti-apoptotic and pro-apoptotic genes. EGCG prevented the expression of pro-apoptotic genes Bax, Bad and Mdm2 while inducing the anti-apoptotic genes Bcl-2, Bcl-w and Bcl-XLto protect SH-SY5Y cells from 6-hydroxydopamine (6-OHDA) induced apoptosis [109]. There is substantial evidence that the anti-inflammatory effects of catehinmay be due, in part, to their scavenging of NO and a reduction of NOS activity. However, catechins have varying effects on the three different isoforms of NOS [110]. The neuronal NOS (nNOS) isoform of NOS produces toxic effects through NO, and so catechin inhibition of nNOS may be a mechanism through which catechins are anti-inflammatory. Evidence also exists that the inhibition of iNOS may also be a mechanism behind the anti-inflammatory effects of catechins. ECGC and other catechins have inhibited the induction of iNOS mRNA and activity after treatment with lipopolysaccharides, interferon γ (IFN-γ) [111,112], IL-1, TNF-α *in vitro* [113]. Inhibition of iNOS by catechins appears not to be through a direct mechanism but by preventing inhibitor KB disappearance, which inhibits nuclear factor KB (NF-KB) from binding to the promoter of the iNOS gene thereby inactivating it [112]. High plasma lipid levels and plaque formation can lead to an increased coronary heart disease and ischemic stroke. Catechins have well-established anti-cholesterolemic properties that may in fact prevent the occurrence of cardiovascular diseases [114].

Quercetin is a naturally occurring flavonoid that exerts multiple pharmacological effects. Yoshizumi et al. [115] proposed that daily intake of bioflavonoids reduces the incidence of ischemic heart disease (IHD). It was hypothesized that bioflavonoids may affect angiotensin-II (Ang-II)-induced MAP (mitogen activated protein) kinase activation in cultured rat aortic smooth muscle cells (RASMC). Ang-II stimulated rapid activation of extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), and p38 in RASMC. Ang-II induced JNK activation was inhibited by quercetin, whereas ERK1/2 and p38 activation by Ang-II were not affected by quercetin. Ang-II caused a rapid tyrosine phosphorylation of Src, which was inhibited by quercetin. This flavonoid compound also activated PI3K/Akt pathway in RASMC. Moreover, a PI3K inhibitor and quercetin derivative inhibited Ang-II-induced JNK activation as well as Akt phosphorylation. These findings suggested that the inhibitory effect of quercetin on Ang-II-induced vascular smooth muscle cell (VSMC) hypertrophy are attributable, in part, to its inhibitory effect on PI3K-dependent JNK activation in VSMC. Therefore, inhibition of JNK by quercetin may imply its usefulness for the treatment of cardiovascular diseases (CVDs) [115,116]. Quercetin is able to reduce the release of

TNF α and IL 1β, thereby alleviating inflammatory responses [117]. Quercetin down-regulates the LPS-induced inflammatory responses. NF-ĶB plays an essential role in regulation of inflammatory processes in macrophages [118]. Both TNF α and IL 1β are NF ĶB target genes and the expression of these two target genes are increased in LPS stimulated macrophages [119]. Quercetin down-regulates NF ĶB activation as well as TNF α and IL 1β expression in LPS challenged macrophage. Quercetin also suppresses the phosphorylation of IKK (inhibitors of κB kinase) and IκBα (inhibitors of κBα) as well as the subsequent nuclear translocation of NF-ĶB subunits p65 and p50. Therefore, quercetin is able to inhibit the NF ĶB signaling pathway and this is accompanied by an alleviation of LPS-stimulated TNF α and IL 1β expressions in macrophages, which provides a possible mechanism by which quercetin prevents LPS-induced lethality in mice *in vivo*. Thus, quercetin seems to have therapeutic potential for protection of systemic inflammatory diseases such as sepsis [120]. Rutin can interact with free radicals and various protein systems to exhibit antioxidant, anti-inflammatory, anti-allergy and anti-tumor activity. Rutin is considered to be a very good antioxidant because of its ability to bind free radicals and metal ions [121]. This flavonoid compound is capable of chelating iron (II) and iron (III) ions, which can initiate oxygen free radical formation [122]. The agyclone (aglycone is the form of flavonoid glycosides) of rutin is capable of reducing iNOS activity, thereby reducing the risk of the development of ischemic and reperfusion injury. iNOS causes the active formation of NO and superoxide anions. By reacting with free radicals, NO forms peroxy-nitrites with a high damage potential [123]. They are capable of targeting oxidation of LDLs, which results in irreversible damage to cell membranes [124]. The aglycone of rutin can disrupt this reaction chain by binding NO, which reduces the risk of lipid membrane injury. Xanthine oxidase, involved in reactions leading to oxidative injury is also inhibited by rutin [125]. On the other hand, the anti-inflammatory effect of rutin is attributed to its ability to bind free radicals that prevents the induction of inflammatory cytokine transcription factors [126]. Rutin is an antagonist of calmodulin, which mediates the Ca^{2+} transfer through cell membranes and initiates multiple intracellular processes. Rutin can inhibit calmodulin-dependent cellular enzymes (ATPase and phospholipase), thereby influencing the permeability of cell membrane [127]. Arachidonic acid is the principal substrate for producing thromboxane and inflammatory mediators (prostaglandin, leukotriene's). Inhibition of phospholipase by rutin leading to the inhibition of conversion of arachidonic acid from cell membrane phospholipids, therefore it inhibits the thromboxane and inflammatory mediator formation [128]. Mutations in gene p53 (involved in cell cycle regulation) are encountered in 50 percent of cancerous tumors. Rutin reduces the expression of p53 gene, and cell division is interrupted in the G2 phase [129,130]. Rutin inhibits the release of histamine from basophils and fat cells and thereby exerts an anti-allergic action [131].

Naringin is a flavanone glycoside, isolated from citrus fruits [132] is also an important flavonoid compound in different honey samples from different botanical origins in a considerable amount [23,67]. Naringin suppresses high glucose induced NF-ĶB expression [133]. Nuclear factor-erythroid 2-related factor 2 (Nrf 2) mediated regulation of cellular antioxidant production and the anti-inflammatory mechanism plays an important role against various degenerative diseases. Naringin up-regulates NAD(P)H: quinine oxidoreductase and γ-glutamylcysteine ligase mRNA expression followed by activation of Nrf 2 and decreased expression of pro-inflammatory mediators such as TNF-α, COX-2 and iNOS, which can be considered as a probable mechanism of the anti-inflammatory actions of the bioflavonoid, naringin [134].

Another bioflavonoid namely naringenin is present in many honey types [23]. Naringenin inhibits the TNF-α induced VSMC proliferation and migration, which is a critical event in the pathogenesis of atherosclerosis and hypertension [135]. Naringenin also blocks the increased ROS generation induced by TNF-α. Oxidative stress and TNF-α may also trigger the activation of MAP kinases, which are the key regulatory factors for VSMC proliferation. Naringenin prevents ERK/MAP kinase and Akt phosphorylation, whereas p38 MAP kinase and JNKs remained unchanged [135]. This overall effect is probably mediated via the induction of heme oxygenase 1 (HO-1) and reduction in oxidative stress [136].

The flavonoids present in different types of honeys, namely chrysin and kaempferol [116], are very active in inhibiting the replication of several herpes viruses, adenoviruses and rotaviruses [137]. However, other studies showed that quercetin and rutin exerted antiviral activity against HSV, syncytial virus, poliovirus and Sindbis virus [138,139]. These compounds exert their action by inhibiting the viral polymerase and binding to the viral nucleic acids or viral capsid proteins [139]. Cushine et al. [140] and Amoros et al. [141] described the synergistic effects of kaempferol and apigenin on HSV, which may explain why honey per se, exhibits greater antiviral activity than its individual components. Honey flavonoids chrysin, acacetin and apigenin, inhibit the activation of human immunodeficiency virus-1 (HIV-1) in latent models of infection through a mechanism that likely includes the inhibition of viral transcription [142]. Galangin, another honey flavonoid [116], inhibits COX and lipo-oxygenase enzyme activity, limiting the action of polygalacturonase, and reducing the expression of the inducible isoform of COX-2 [143,144] and thereby exerting an anti-inflammatory effect.

Honey flavonoids (collectively rather than any single flavonoid compounds) have been studied for their cardioprotective and anti-diabetic potentials. It is suggested that flavonoids decrease the risk of CVDs by improving coronary vasodilatation, decreasing the ability of platelets to clot and preventing LDLs from oxidizing [116] (Figure 4a). On the other hand, Solayman et al. [145] proposed possible treatment strategies of honey flavonoids along with other polyphenols. According to their study, honey flavonoids such as quercetin and luteolin inhibit α-amylase and α-glucosidase restricting the conversion of complex carbohydrates to a simple sugar, glucose, thus exhibiting a hypoglycaemic effect. Catechin, quercetin and EGCG inhibit sodium dependent glucose transporter (SGLT 1), therefore limiting the entry of free glucose to the circulation. Glucogenic enzymes are also inhibited by rutin, EGCG to decrease the rate of gluconeogenesis pathway, that involves the biosynthesis of glucose from non-carbohydrate sources. Flavonoids namely EGCG, rutin, epicatechin and quercetin protect pancreatic cells from oxidative damage and also increase the rate of insulin secretion by pancreatic β cells. Quercetin, EGCG, rutin also enhance glucose uptake by cells using GLUT4 and thereby contribute to reduce free glucose in the circulation (Figure 4b).

Honey toxicity and corresponding health hazards

There is a wealth of information about the nutritional and medicinal properties of honey. However, honey contains compounds that may lead to toxicity. To ensure high quality of honey, to maintain its freshness and to increase its shelf life, it is usually processed by heating or sterilization. Heating leads to the formation of compounds not naturally present in honey and dangerous to human health, such as

heterocyclic amines, nitrosamines and polycyclic hydrocarbons [146,147].

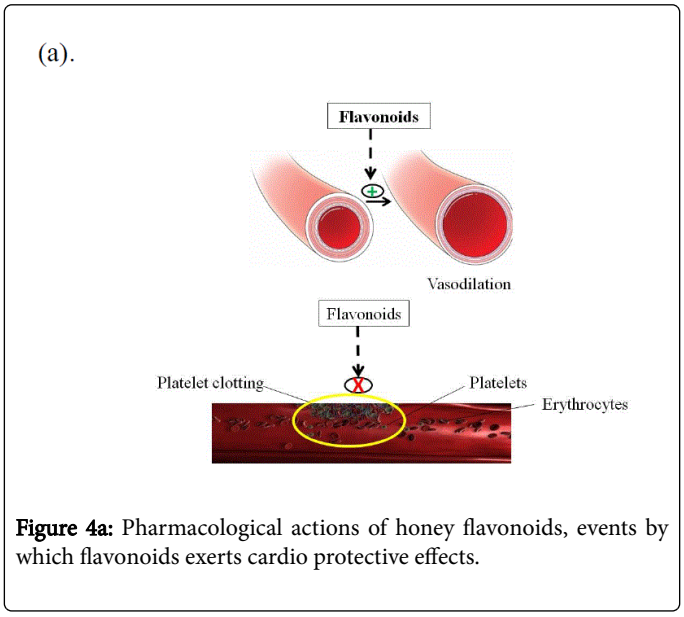

Figure 4a: Pharmacological actions of honey flavonoids, events by which flavonoids exerts cardio protective effects.

One such compound that is a major concern is 5-hydroxymethylfurfural (HMF), which is a cyclic aldehyde formed from sugar [148]. HMF has gained much interest, as it is commonly detected in honey samples, especially samples that have been stored for a long time. HMF is a compound that may be mutagenic, carcinogenic and cytotoxic [149]. High concentrations (more than 75 mg/kg) of HMF are not only cytotoxic but also irritating to the eyes, upper respiratory tract, skin and mucous membranes [150]. The carcinogenic activity of HMF has been investigated in studies on rodents. HMF induces and promotes aberrant crypt foci, which are pre-neoplastic lesions, in the rat colon [151]. A previous study described the induction of skin papillomas after the topical administration of 10-25 mmol of HMF to mice [152]. The development of lipomatous tumors in rat kidneys occurs after the subcutaneous administration of HMF [153]. The major concern regarding HMF is related to its conversion to 5-sulfoxymethylfurfural (SMF). SMF is strongly nephrotoxic in mice [154]. The effect of a human SULT polymorphism on the conversion of HMF to SMF was investigated by Glatt and Sommer [155]. The researchers analyzed all thirteen SULT forms that can convert HMF to SMF. Based on the kinetics parameters, SULT1A1 expressed in many tissues, including the colon and can be regarded as the most critical enzyme for the bioactivation of HMF to the genotoxic metabolite SMF [156]. HMF can also be metabolized via allylic chlorination yielding 5-chloromethylfurfural, which is much more mutagenic than SMF in *S. typhimurium* [152]. In addition to the temperature, the rate of HMF formation in honey is dependent on the pH of honey samples [157,158], as well as the water content [157,159]. Thus, low moisture content in honey samples should be maintained to inhibit HMF formation.

Plant toxins may be transferred to the honey that is produced from their nectar. Plants containing secondary metabolites such as pyrrolizidine alkaloids, grayanotoxins (GTXs), hyoscyamine, hyoscine, saponin, strychnine, gelsemine, tutin, hyenanchin, oleandrin and oleandringenin have been shown to have toxic properties and can be easily transferred to honey by honeybees [160]. GTXs, a family of lipid-soluble toxins responsible for the clinical manifestations of mad-honey intoxication syndrome. GTXs are classified as toxins that bind two sites in the Na^{2+} channels, resulting in a shift of Na^{2+} channel activation producing hyperpolarization of trans membrane potentials.

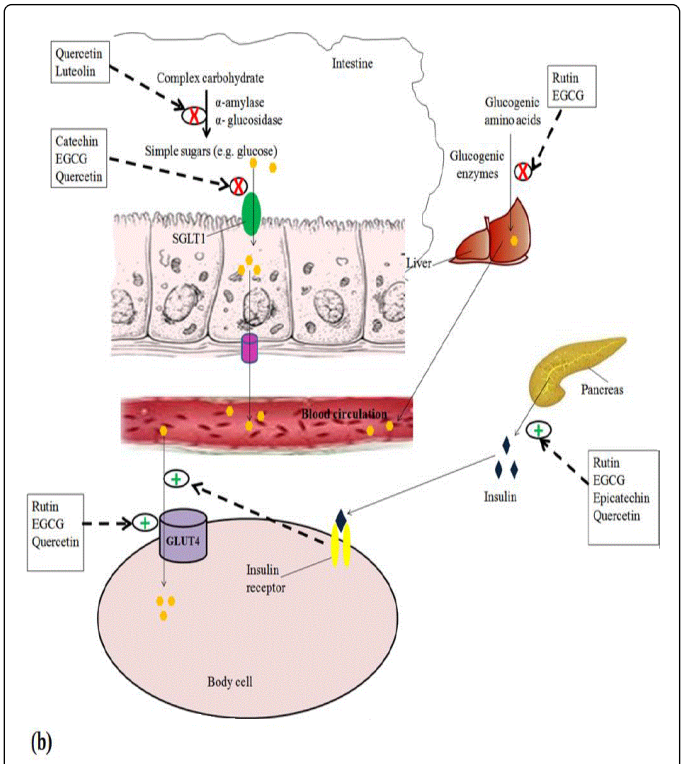

Figure 4b: Pharmacological actions of honey flavonoids, possible mechanisms of anti-hyperglycemic actions of particular flavonoids.

The resulting effect is deactivation of Na^{2+} channels because the Na^{2+} channel remains in its open state. These toxins require repetitive rather than single, long-lasting, depolarizing stimuli to adjust the Na^{2+} channels in excitable cells. Another possible mechanism of GTX toxicity occurs via muscarinic receptors, which can be explained by the usefulness of atropine in cases of honey intoxication. GTX I may affect both sinus node and atrioventricular (AV) conduction [161]. On the other hand, GTX II is capable of suppressing the spontaneous beating of the sinoatrial node because of the depolarization caused by GTX II. Using feline cardiac Purkinje fibers, it has been demonstrated that the possible mechanism underlying GTX-III–induced arrhythmias is the production of triggered activities in the form of oscillatory after potentials [162]. Additionally, the effects of GTXs via muscarinic receptors may be responsible for the presence of supra-His conduction abnormalities during AV block and may explain the effectiveness of atropine in patients with mad honey intoxication [161].

Honeybees fly up to a 4 km radius of their apiary, thus accessing an area of 50 km^2 [163]. The bees come into contact with air, soil and water and therefore, the heavy metal levels in honey may reflect the actual amount found in the surroundings [164]. Honey can easily be contaminated with heavy metals, especially during processing due to the location of hives. To date, 54 chemical elements in various honey types have been identified and can be divided in three groups such as major or macroelements (e.g. Na, K, Ca, Mg, P, S, Cl etc.), minor or trace elements (e.g. Al, Cu, Pb, Zn, Mn, Co, Ni, Fe, Pt, As, B, Br, Cd, Hg, Se etc.) and heavy metals (trace elements that have a specific

gravity at least 5 times higher than that of water and inorganic sources). Although minerals and heavy metals are minor constituents of honey, they play a vital role in determining its quality [165]. Honey contains potentially toxic heavy metals (such as Co, Cr, As, Cd, Hg and Pb), all of which have detrimental health effects. One of the most hazardous heavy metals found commonly in honey is as which is both toxic and carcinogenic. The long term intake of as may give rise to skin lesions. As exposure regardless of the source can cause cancer of the skin, lung, bladder and other internal organs together with numerous other non-cancerous diseases [166-173]. Therefore, it is important to set the locations for honey production hives, where the environment is not polluted and thus in areas which are distant from highways and railways and general industrial activities.

Conclusion

Studies have demonstrated that honey could be a potential agent against oxidative stress disorders including cardiovascular disease, cancer, diabetes, hepatic and renal failure and aging processes. This review focused on the pharmacological potential of sugars, enzymes and some selective phenolic compounds of honey and their molecular mechanisms of action. These molecular pathways might be helpful to the health professionals for utilization of honey as dietary supplementation and alternative medicine for the management of diverse oxidative stresses and future drug development. Extensive *in vitro* and *in vivo* studies are therefore required and justified to explore the pharmacological potential of honey as a natural product and of the properties and therapeutic potential of its multiple individual chemical and biochemical components.

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