

Rediscovery of Apitherapy Mechanisms: A Novel Challenge in Cardiovascular Autonomic Neuropharmacology

Miran KR*

Pharmacology and Biochemistry Department, Faculty of Pharmacy, The British University in Egypt, Cairo, Egypt

***Corresponding author:** Dr. Miran KR, Pharmacology and Biochemistry Department, Faculty of Pharmacy, The British University in Egypt, El Sherouk City, Suez Desert Road, Cairo 11837, Egypt, Email: miran.rakha@bue.edu.eg; mirankhalil@hotmail.com

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Abstract

Apitherapy is the scientific term which refers to the medical use of honey, bee venom, propolis, royal jelly, bee pollen, beeswax and apilarnil. Bee venom therapy for arthritis, autoimmune and neurodegenerative diseases is the most well-known. Numerous studies supported honey for healing of wounds and burns, and even as an anticancer agent. Moreover, several studies evaluating the cardiovascular effects of honey bee products revealed very promising results, paradoxically, apitherapy is still not in focus with a cardiovascular neuropharmacological viewpoint. In an effort to provide extensive information about the cardiovascular bioactivity of natural honey, as the major honey bee product, both in terms of familiarity and profit, this review overviews, for the first time; (1) cardioactive and vasoactive effects of natural honey, (2) mechanisms underlying cardioactive and vasoactive potentials of natural honey, and (3) how improving our knowledge of the mechanisms mediating protective and ameliorative outcomes of natural honey may lead to novel therapeutic strategies for the treatment of cardiovascular diseases? Future challenge remaining will be to permit full exploitation of apitherapy potency to expand novel horizons in the cardiovascular autonomic neuropharmacology.

Keywords: Cardiovascular Autonomic Neuropharmacology; Antihypertensive Effect; Antiarrhythmic Effect; Ameliorative Effect to Cardiovascular Risk Factors; Biotherapy; Apitherapy

Introduction

Apitherapy or bee therapy is the medicinal use of the natural products made by bees such as honey, bee venom, propolis, royal jelly, bee pollen, beeswax and apilarnil to prevent or treat illness and promote healing [1]. A wide variety of conditions and diseases have been suggested as candidates for apitherapy, the most well-known being bee venom therapy for arthritis, autoimmune and neurodegenerative diseases [2-8]. The potential benefits

of honey in healing of wounds and burns are supported by numerous studies [9-12]. Recently, evidence is growing that honey have the potential to be anticancer agent [13-15].

Several studies evaluating the cardiovascular effects of honey bee products revealed very promising results, paradoxically, apitherapy is still not in focus with a cardiovascular neuropharmacological viewpoint. Despite researchers who are interested in this field of study

produced studies which are still considered scarce and there is paucity in their reports, the majorities of their emerged results are of special interest and deserve to be taken into consideration. Therefore, we should give them their due recognition. In the recent years, more attention was paid to the cardioactive and vasoactive effects of natural honey revealing its antihypertensive effect, its antiarrhythmic effect, and its ameliorative effect to cardiovascular risk factors [16-38]. In an effort to provide extensive information about the cardiovascular bioactivity of natural honey, as the major honey bee product, both in terms of familiarity and profit, and to the best of our knowledge, this review overviews, for the first time, the influence of natural honey on the cardiovascular neurophysiology, toward opening of a novel gateway to the cardiovascular autonomic neuropharmacology.

The Antihypertensive Effect of Natural Honey

The role of oxidative stress in hypertension is a subject of much research interest [16]. Oxidative stress is implicated in the pathology of hypertension, however some evidence also indicates that hypertension generates oxidative stress [39,40]. These lines of evidence support a role of oxidative stress as an important determinant in the imbalance between vasoconstrictor and vasodilator mechanisms [17,39,40]. The beneficial effects of antioxidants in ameliorating oxidative stress and suppressing or reducing elevated blood pressure in experimental and clinical studies further corroborate the role of oxidative stress in hypertension [41]. A recent study investigated the effect of honey on elevated systolic blood pressure (SBP) in spontaneously hypertensive rats (SHR). It also evaluated the effect of honey on the amelioration of oxidative stress in the kidney of SHR as a possible mechanism of its antihypertensive effect [17]. It was reported that honey supplementation reduced SBP and renal malondialdehyde (MDA) levels in SHR. Suppressed elevation in SBP was also accompanied by reduced activities of glutathione S-transferase (GST) and catalase (CAT) in the kidney of SHR. Findings from this study also indicated that mRNA expression of nuclear factor erythroid 2-related factor 2 (Nrf2), a potential renoprotective transcription factor, was markedly reduced or impaired in the kidney of SHR. Besides, the results of study revealed that the induction of antioxidant enzymes, perhaps as a compensatory mechanism, may occur in spite of impaired or reduced mRNA expression of Nrf2. Consequently, it was indicated that honey supplementation in SHR elicits antihypertensive effect *via* amelioration of renal oxidative stress. Moreover, honey

may ameliorate oxidative stress *via* upregulation of Nrf2 activity or expression [17,18].

A combination of diabetes mellitus and hypertension is associated with substantially increased cardiovascular risk factors [42]. Besides other factors, evidence suggests that diabetes mellitus may exacerbate hypertension *via* increased oxidative stress [43]. Induction of experimental diabetes by streptozotocin (STZ) in animal models has been used extensively to study the relationship between diabetes and autonomic cardiovascular dysfunction [44]. Recently, the effects of honey on blood pressure, antioxidant enzymes, and markers of oxidative stress in the kidneys of STZ-induced diabetic Wistar-Kyoto (WKY) and spontaneously hypertensive rats (SHR) were investigated [19]. It was indicated that STZ-induced diabetes mellitus caused reduced systolic blood pressure (SBP), total antioxidant status (TAS), activities of glutathione peroxidase (GPx) and glutathione reductase (GR) in SHR. In contrast, SBP, activities of GPx and GR were elevated while TAS was reduced in diabetic WKY. Honey treatment further reduced SBP in diabetic SHR but not in diabetic WKY. It also increased TAS, reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio, GSH, activities of GPx and GR in diabetic SHR. It was revealed that oxidative stress is implicated in the pathogenesis and/or complications of hypertension and/or diabetes mellitus. Moreover, if hyperglycemia is not a prerequisite for the development of elevated blood pressure in diabetic normotensive rats, then oxidative stress in diabetic normotensive rats may be a consequence of hypertension and/or diabetes. Furthermore, it was elucidated that oxidative stress, unlike in SHR, may not contribute considerably to elevated SBP in STZ-treated diabetic rats. The inability of honey to decrease elevated SBP of diabetic WKY further substantiates this view. The effectiveness of honey not only in ameliorating oxidative stress but also in reducing elevated SBP in diabetic SHR corroborate the prominent role of oxidative stress in elevated SBP of SHR. Therefore, it was assumed that differences in types, severity, and combinations/complications of diseases (hypertension and/or diabetes), as well as strains, may influence responses to blood pressure and antioxidant enzymes in response to changes in redox status [19,45].

The Antiarrhythmic Effect of Natural Honey

Hazards of antiarrhythmic drugs (such as lethal arrhythmias in some patients) have led to a limitation on the administration of antiarrhythmic drugs. Hence, there

is a tendency to use drugs which have less adverse effects and more efficacies [46]. On one hand, the administration of exogenous catecholamines, for example, is mandatory to support the failing circulation in acutely ill patients. In contrast to the short-term benefits, prolonged adrenergic stress is detrimental to the cardiovascular system by initiating a series of adverse effects triggering significant cardiotoxicity [47]. On the other hand, it was evident that sympathetic overactivity holds a key neurophysiological role in hypertension, heart failure, acute coronary syndromes, Takotsubo (stress) cardiomyopathy, metabolic syndrome, pheochromocytoma (an adrenaline secreting tumor), and arrhythmias [48-58].

For the first time, using a novel rat model for hyperadrenergic activity, the first evidence was provided that natural wild honey not only can be used to protect against the deleterious effects of epinephrine (adrenaline), as a chemical mediator and an endogenous hormone, which can be a hidden menace in cases of hyperadrenergic activity, but also can be used to treat the side adverse effects of epinephrine, as an exogenous sympathomimetic and β -agonist, thereby facilitating its safe use as an inotrope [21]. It was proven that natural wild honey exerts its cardioprotective and therapeutic effects against epinephrine-induced cardiac disorders and vasomotor dysfunction directly, *via* its very pronounced total AOC and its great wealth of both enzymatic and nonenzymatic antioxidants involved in cardiovascular defense mechanisms, besides its substantial quantities of mineral elements such as magnesium, sodium, and chlorine, and/or indirectly, *via* the enhancement of endothelium-derived relaxing factor nitric oxide (EDRF/NO) release through the influence of ascorbic acid (vitamin C) [20,21].

In isolated toad hearts, the cardiac arrhythmias induced by epinephrine, included; extrasystoles, tachyarrhythmias and bradyarrhythmias as well as abnormalities of both P-wave and ST segment [22,57]. The *in vitro* study elucidated that natural wild honey managed to suppress or attenuate the cardiotoxicity produced by epinephrine. At the same time, it potentiated the powerful inotropic effect of epinephrine [22,59]. The antiarrhythmic effect of natural wild honey against catecholamine cardiotoxicity was mainly attributed to its minerals such as magnesium, sodium and chlorine [20-22,59]. Magnesium, by inhibiting the voltage-dependent calcium channels, suppresses the delayed-after-depolarization (DAD) which is produced by catecholamines and it is considered the cause of their cardiac arrhythmias [60]. Sodium, through the process of

$\text{Na}^+/\text{Ca}^{2+}$ exchange, prevents the accumulation of Ca^{2+} ions within the cardiac cells [61], reducing the occurrence of ventricular arrhythmias such as ventricular extrasystole resulting from increased sympathetic activity under the influence of catecholamines [20-22,59]. Chlorine is essential for the process of $\text{Cl}^-/\text{HCO}_3^-$ exchange which is concerned with pH regulation in cardiac cells [60] and is activated by natural honey in response to its alkaline potentiality. Therefore, it can suppress or reduce the activity of $\text{Na}^+/\text{HCO}_3^-$ symporter which is stimulated by β -agonists leading to the cardiac arrhythmias produced by catecholamines as a result of calcium overload [20-22,59].

In this respect, the role that fructose (the major constituent in natural honey) plays in the antiarrhythmic effect of natural honey cannot be overlooked. For the first time, a recent study demonstrated an acute influence of fructose on isolated cardiomyocyte excitation-contraction coupling [62]. The findings indicated cardiomyocyte capacity to transport and functionally utilize exogenously supplied fructose. In a 'proof-of-principle' manner, the study provided functional demonstration that fructose may serve as a substrate to support cardiomyocyte excitation-contraction coupling in an acute setting. Furthermore, it was established that the fructose-specific transporter, GLUT5, is expressed in cardiomyocytes and may provide a route of cardiomyocyte fructose entry. The investigation suggested that fructose may provide ATP for this transporter thus increasing the driving force for $\text{Na}^+/\text{Ca}^{2+}$ exchange and promoting Ca^{2+} extrusion, which may prevent the accumulation of Ca^{2+} ions within the cardiac cells [61], reducing the occurrence of ventricular arrhythmias [20-22,59].

Ischemic heart disease (IHD) causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. Cardiac arrhythmias and myocardial infarction are serious manifestations of IHD. In the course of cardiac surgery and myocardial infarction, ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation are the most important causes of mortality [63]. A group of evidence supported potential cardioprotective effects of natural honey against ischemia/reperfusion (I/R)-induced injuries, and consequently against cardiac arrhythmias and myocardial infarction [23-31]. It was articulated that short-term perfusion of isolated rat heart with natural honey as a pharmacologic preconditioning agent has prophylactic effects on I/R-induced cardiac arrhythmias and myocardial infarction [31]. Besides, it could reduce left ventricle perfusion pressure [27]. Also, prolonged (long-term) preconditioning of isolated rat heart with

natural honey has antiarrhythmic and anti-infarct activities against I/R-induced injuries [24]. In addition, chronic administration of natural honey produced antiarrhythmic effects against I/R-induced cardiac arrhythmias in isolated rat heart [29]. Moreover, acute administration of natural honey in normothermic ischemic conditions could protect the isolated rat heart as the reduction of cardiac arrhythmias and myocardial infarction size [25]. On the other hand, preischemic administration of natural honey before zero flow global ischemia showed protective effects against I/R-induced cardiac arrhythmias and myocardial infarction in isolated rat heart [28]. Furthermore, postischemic administration of natural honey in global ischemia protected isolated rat heart against I/R-induced injuries [26]. Antioxidant and free radical scavenging activity, reduction of necrotized tissue, existence of rich energy sources such as glucose and fructose, and improvement of some hemodynamic functions were supposed to be responsible for these cardioprotective effects of natural honey [24-26,28,29,31].

The Ameliorative Effect of Natural Honey to Cardiovascular Risk Factors

Currently, there is much evidence linking cardiovascular autonomic functions and the most well-established major cardiovascular risk factors including dyslipidemia, hypertension, diabetes mellitus, and obesity [64-67]. Various clinical and preclinical studies focused on potential influence of natural honey on cardiovascular risk factors [33]. Emerging results of these studies should be taken into consideration as indicators of the indirect effect of natural honey on the cardiovascular autonomic functions. Especially, it is now substantiated that natural honey ameliorates cardiovascular risk factors in healthy individuals and in patients with elevated cardiovascular risk factors [36-38], as well as in experimental animals [32,34,35]. It was indicated that consumption of honey, particularly in hyperlipidemic, hypertensive, diabetic and overweight or obese individuals, reduces the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), C-reactive protein (CRP), fasting blood glucose (FBG), homocysteine (HC) and blood pressure (BP) in hypertensive patients. Moreover, it increases the levels of high-density lipoprotein cholesterol (HDL-C) and plasma insulin (PI). Furthermore, it does not increase body weight in overweight or obese subjects.

The ameliorative effect of natural honey to CRP level, as a marker of inflammation, was explained by its anti-

inflammatory and antioxidant properties [36]. On one hand, consumption of natural honey could lower concentrations of inflammatory mediators such as plasma and urinary prostaglandin E2 (PGE2), prostaglandin F2 alpha (PGF2 alpha) and thromboxane B2 (TXB2) of healthy individuals [68,69]. On the other hand, many reports have demonstrated lowering effects of antioxidants on CRP levels [70,71]. Supporting this is that a wide range of phenolic constituents, which act as natural antioxidants, is present in honey like quercetin, caffeic acid, acacetin, kaempferol, galangin and have a promising pharmacological role in preventing cardiovascular diseases [72]. Many epidemiological studies have shown that regular flavonoid intake is associated with a reduced risk of cardiovascular diseases. In coronary heart disease, the protective effects of phenolic compounds include mainly antithrombotic, anti-ischemic, antioxidant, and vasorelaxant. It was suggested that flavonoids decrease the risk of coronary heart disease by three major actions: improving coronary vasodilatation, decreasing the ability of platelets in the blood to clot, and preventing low-density lipoproteins (LDLs) from oxidizing. Additionally, it was elucidated that CRP, at concentrations known to predict adverse vascular events, directly quenches the production of nitric oxide (NO), in part, through the posttranscriptional effect on the endothelial NO synthase (eNOS) mRNA stability. Diminished NO bioactivity, in turn, inhibits angiogenesis, an important compensatory mechanism in chronic ischemia. Through decreasing NO synthesis, CRP may facilitate the development of diverse cardiovascular diseases. Thereby, risk reduction strategies designed to lower plasma CRP may be effective by improving NO bioavailability [73]. In this regard, it was reported that natural honey increased the contents of plasma and urinary nitrite/nitrate, the stable NO metabolites or end products, in healthy individuals as well as experimental animals [68,74]. Therefore, natural honey may partly affect the CRP levels through NO production [36].

Of great importance is that honey contains a number of mineral elements such as potassium, calcium, sodium, magnesium, phosphorus, zinc, copper, iron, manganese, chromium, and selenium [75]. Some of these minerals such as chromium are recognized for their role in lowering plasma total cholesterol, reduction of elevated blood glucose, maintenance of normal glucose tolerance and insulin secretion from the pancreatic beta-cells [76,77]. Other studies have also demonstrated that zinc and copper can improve insulin sensitivity thereby decreasing blood glucose levels [78,79]. Even though the amounts of these minerals in honey may be low, it is

suggested that the daily ingestion of honey may achieve adequate concentrations of these minerals and thus exert pharmacological responses [80]. Coupled with the evidence which proved that the daily consumption of honey increased serum concentrations of zinc and copper in healthy subjects, these ions may contribute to the antidiabetic effect of honey [78,79,81]. Surprisingly, it was reported that fructose feeding in mice was associated with lower blood glucose levels [82]. Increased C-peptide and insulin secretion and modulation of appetite-regulating hormones such as leptin, ghrelin and peptide YY may also contribute to improved glycemic control as a result of honey supplementation. In addition, honey could reduce prostaglandin levels and elevate NO [74,68,69,80,83-86]. It was proven that PGE2 is one of the major physiological inhibitors of insulin, acting *via* specific receptors [87]. Interleukin-1beta (IL-1beta) and PGE2 are two well-recognized inhibitors of glucose-induced insulin secretion and endogenous PGE2 mediates the inhibitory effects of exogenous IL-1beta on beta-cell function [88]. Moreover, different NO donors stimulated a marked increase in insulin secretion [89]. Therefore, honey might partly affect glucose levels through its effects on prostaglandin and NO production [36].

Although the mechanisms by which honey decreases weight gain are still not fully understood, findings from some recent studies suggest that honey may also reduce weight gain *via* modulation of appetite-regulating hormones such as leptin, ghrelin and peptide YY [84,85]. Furthermore, based on findings which showed lack of significant difference in food efficiency ratio (FER) in sucrose- and honey-fed rats, reduced food intake might contribute considerably to reduce weight gain in honey-fed rats [84]. Fructose and oligosaccharides which are present in honey may also contribute to reduced body weight and food intake in honey-fed rats [90-93]. Also, it was evident that body weight gain in fructose-fed mice was reduced [82]. Besides, available evidence which indicates that honey may reduce body weight through reduced digestion and absorption of protein and increased fecal nitrogen output [94]. Considering the overwhelming evidence which elucidates that honey increases plasma antioxidants and ameliorates oxidative stress in tissues [16,19,81,95-98], antioxidant effect of honey may also contribute to reduced weight gain [99].

Conclusion

A closer look at the presented data obtained by a cascade of integrated scientific studies characterizing the cardiovascular bioactivity of natural honey, supported by

several studies, reveals that natural honey has very promising protective and ameliorative outcomes which cannot be ignored. Consequently, more in-depth *in vitro* and *in vivo* studies jointly with clinical trials should be initiated to objectively substantiate efficacy of natural honey as an important complementary and/or alternative apitherapy, its rationale, evidence supporting its use, its possible interaction with conventional medicines, and where possible, what is known about its safety and efficacy to further validate natural honey in medical applications as a promising biotherapy.

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