



Renal protective effects of natural honey on animal model of hypertension

Onwudiwe Saviour Nwachukwu ^{1,*}, Okoro Nzutechukwu Benjamin ², Nwankwo Emeka Christian ³, John Ajayi ⁴, Okonkwo Emmanuella ¹, KariKari Evelyn ¹, Mmoto Onyinyechukwu ⁵, Okoh Favour ⁶, Ugo-Olumba Olisaemeka Miracle ⁷ and Abugu Joshua Izuchukwu ⁶

¹ Department of Public Health, First Moscow State Medical University named after I.M Sechenov, Moscow, Russia.

² Department of Pharmacy, Voronezh State University, Voronezh, Russia.

³ Department of Public Health, Ahmadu Bello University, Zaria, Kaduna State, Nigeria.

⁴ Department of hospital Surgery, People's Friendship University of Russia, Moscow, Russia.

⁵ Department of Anatomy, Nnamdi Azikiwe University, Awka, Anambra State.

⁶ Department of Anatomy, Enugu State University of Science and Technology, Enugu State, Nigeria.

⁷ Department of Human Physiology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

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Abstract

Hypertension, also known as high blood pressure, is a leading cause of cardiovascular disease and premature death worldwide. Numerous investigations have established that hypertension can cause alterations in the cardiovascular system as well as renal structure and function. Fresh honey is consumed worldwide and is claimed to be highly medicinal and has therapeutic effects against a wide range of medical conditions. We investigated the renal protective effect of natural honey in an animal model of hypertension. Forty (40) male albino rats, with average weight (120 ±10 g) were administered with high salt diet, HSD (80 g NaCl + 1 kg of diet and 1% NaCl in drinking water (10 g of NaCl + 1 L distilled water) for 10 weeks to induce hypertension in the rats. Following confirmation, hypertensive male rats were randomly selected for the experiment. Twenty (20) albino rats (15 hypertensive rats and 5 normotensive rats) were divided into 4 groups, Groups A-D. Group A: (Normotensive Control) no administration was given; Groups B-D (hypertensive rats) received the following treatments. Group B was treated with natural honey (15 ml/kg), Group C treated with hydrochlorothiazide (0.15 mg/kg), daily for 21 days; while Group D received no treatment, until the end of the 21 days administrations. Blood samples were taken in the end, and renal alterations were assessed via biochemical and histopathological analyses. Results showed that salt-induced hypertension caused a marked elevation of the renal biochemical parameters. The histopathological results agree with the biochemical findings. However and interestingly, natural honey (15 ml/kg, oral) showed significant efficacy in the recovery and protection on the kidney as the standard anti-hypertensive drug, hydrochlorothiazide ($p < 0.05$ or $p < 0.01$). Natural honey has a renal protective effects and may manage renal hypertension or prevent kidney injury secondary to high blood pressure.

Keywords: Hypertension; Salt; Natural honey; Hydrochlorothiazide; Renal disease

1 Introduction

Hypertension is the major cause of death from non-communicable diseases, such as cardiovascular disease as well as kidney disease, around the world [1, 2]. The majority of people with high blood pressure have no known reason and are classed as having primary hypertension. However, 5-10% of these patients may develop secondary hypertension, indicating that there is an underlying and potentially treatable reason. Secondary hypertension affects people of all ages, however it is more common in teenagers and young adults [3]. Hypertension is a chronic high rise in blood pressure caused by blood in circulation pushing on the walls of the arteries, the body's primary blood vessels [4]. More than 90%

* Corresponding author: Onwudiwe Saviour Nwachukwu

of hypertensive patients have no known cause. It is the product of a complicated relationship between genetics, environment, and lifestyle.

The kidneys play a crucial role in regulating blood pressure. They help manage blood pressure by controlling the amount of fluid in the body and producing hormones that regulate blood pressure. However, when someone has high blood pressure, it can put extra strain on the blood vessels in the kidneys, leading to kidney damage over time [5]. Conversely, kidney disease can also cause high blood pressure. Damaged kidneys may not effectively regulate fluid and salt balance or produce hormones as they should. This can result in an increase in blood pressure, which, in turn, can further damage the kidneys, creating a cycle of worsening kidney function and increased blood pressure [6]. The connection between hypertension and kidney disease is often referred to as a two-way relationship. Managing blood pressure is crucial in preventing kidney damage, and taking steps to protect kidney health can also have a positive impact on managing high blood pressure. Regular check-ups, a balanced diet, exercise, and medication, if prescribed, are essential in managing both conditions and reducing their impact on one another [7]. Consumption of natural honey, which is claimed to be high in anti-oxidative polyphenolic compounds; which have been demonstrated to help manage blood pressure in several studies.

Honey is a natural sweetener obtained from the plant nectar, pollen and resin [8]. It has been known to be effective in traditional medicine for decades. Since pre-historical times, honey is well known for its nutritional and therapeutic values. Honey is mainly made up of carbohydrates (most especially fructose and glucose). The sweet taste of honey is as a result of supersaturated solution of monosaccharides like fructose (about 38%) and glucose (about 31%). Honey also contains a number of minor constituents, most of them are naturally occurring antioxidant. They are phenolic acids, flavonoids, certain enzymes (glucose oxidase and catalase), ascorbic acid, carotenoid-like substances, organic acids, Maillard reaction products, amino acids and proteins [9].

Based on the studied relationship between oxidative stress and high blood pressure, using an agent that can have both antioxidant and antihypertensive properties can go a long way in the prevention, management and treatment of hypertension. In addition to the fact that natural honey can be easily gotten from our local markets around the country, honey is rich in phenolic acids, amino acids (such as arginine and glutamate), flavonoids and ascorbic acid, these are widely known for their antioxidant properties which have been seen to have antihypertensive effects [10].

The effect of natural honey on hypertension is quite objectionable, but due to its anti-oxidant properties, study on its hypertensive effect is becoming relevant. Only few studies have shown that hypertension could be affected by the intake of natural honey, and most of these research were done in America. There is also a rise in the incidence of hypertension, due to the unhealthy lifestyle of individuals and in addition the little to no progress seen in the use of treatment drugs, coupled with the side effects of these drugs. Therefore, we hypothesize that honey and its antioxidant properties could improve the treatment and management of hypertension. The aim of this study is to assess the cardioprotective effects of natural honey on salt-induced hypertension in rats.

2 Materials and methods

2.1 Laboratory animal

Twenty (20) albino adult rats, weighing (110 ± 10 g), were procured from the University of Nigeria's College of Veterinary Medicine's animal home. The rats were housed in a metallic cage with a regular temperature of 22 ± 3 °C and a 12-hour light-dark cycle. The animals were monitored for 14 days earlier than the experiment date, in order to allow them to acclimatize to the environment. The experimental design and management complied with institutional regulations detailing the use of rats and the guidelines for the care and use of vertebrates in study published by the American Physiological Society [11].

2.2 Experimental design

A total of forty (40) male albino rats, with average weight (120 ± 10 g) were administered with high salt diet, HSD (80 g NaCl + 1 kg of diet and 1% NaCl in drinking water (10 g of NaCl + 1 L distilled water) for 10 weeks to induce hypertension in the rats. We confirmed hypertensive rats after three consecutive readings using a digital tail cuff using a Non-invasive blood pressure monitor (NIBP). Hypertensive male rats were randomly selected for the experiment. Twenty (20) albino rats (15 hypertensive rats and 5 normotensive rats) were divided into 4 groups, Groups A-D. Group A: (Normotensive Control) no administration was given; Groups B-D (hypertensive rats) received the following treatments. Group B hypertensive rats treated with natural honey (15 ml/kg), Group C hypertensive rats treated with hydrochlorothiazide (0.15 mg/kg), daily for 21 days; while Group D hypertensive rats received no treatment, until the end of the 21 days

administrations. Blood samples were taken in the end, and renal injuries and alterations were assessed via various biochemical analyses.

2.3 Animals sacrifice and sample collection

Under chloroform anesthesia, blood samples for biochemical analysis were taken from the left ventricle of the heart. The kidneys were excised for histopathological analyses.

2.4 Biochemical analyses

2.4.1 Measurement of renal function test biochemical markers

Electrolyte, urea, and creatinine levels in the blood were measured to assess renal function: using a Perlong Medical PL1000A Electrolyte Analyzer, serum K⁺ and Na⁺ levels were measured. Urea level was estimated using diacetylmoxime technique involving protein precipitation [12], while creatinine level was estimated using Jaffe's method [13].

2.5 Histopathological analysis

The paraffin wax embedding method was employed to prepare the removed kidney tissues. Sections of kidney were made at a thickness of 5 microns, and Hematoxylin and Eosin staining technique was used for better general examination of the tissues [14]. An Olympus™ light microscope was used to examine the tissue sections.

2.6 Statistical analysis

Version 7.0 of Graph Pad Prism (San Diego, CA, USA) was used to analyze the data. The results of the biochemical experiments were presented as mean ± SEM (standard error of mean). One-way analysis of variance (ANOVA) was used to determine the degree of significance. Probability levels below 0.05 (p<0.05) were taken as being significant.

3 Results

3.1 Biochemical results

The function of the kidneys was assessed by evaluating the biochemical markers at different levels in the blood, such as creatinine, blood urea nitrogen (BUN), potassium (K⁺), and sodium (Na⁺) (Table 1). From the results, a statistically significant (P<0.05) elevated levels of blood urea nitrogen (BUN), creatinine and potassium (K⁺) were seen in salt-treated group D (negative control) when compared with group A (normal control) and group C (positive control). The co-administration of salt and natural honey or hydrochlorothiazide separately, restored the level of these parameters to near normal when compared with the salt-treated group (negative control). Furthermore, we observed that natural honey showed better renoprotection than hydrochlorothiazide (positive control) against high doses of salt (Table 1).

3.2 Histopathological results

Table 1 Statistical Comparison of biochemical concentrations of the kidneys of treated groups with negative controls Groups

GROUP	BUN (mg/dl)	Creatinine (mg/dl)	K ⁺ (mmol/l)	Na ⁺ (mmol/l)
A: Normal Control	20.56 ± 1.38*	0.88 ± 0.21*	5.67 ± 0.08*	144.42 ± 1.33*
B: Salt + Honey (15 ml/kg)	21.73 ± 1.04*	0.91 ± 0.29*	6.14 ± 0.84*	142.99 ± 0.26*
C: Salt + HCTZ (0.15mg/kg)	21.86 ± 3.67*	1.01 ± 0.13*	6.75 ± 0.22	140.07 ± 3.03
D: Salt Alone	38.63 ± 3.98	1.51 ± 0.08	8.94 ± 0.04	138.29 ± 0.32

Values given as Mean ± SEM. *p<0.05 is significant when salt alone (negative control) is compared with all other groups.

In Figure 1, The glomeruli appear normal while some tubules appear to have slightly degenerated epithelia. The kidney section salt-treated group (negative control) showed normal myocardial fibres but abnormal changes were observed. In the salt-treated group, it was observed that some glomeruli were eroded while some of the tubules had eroded epithelia (Figure 4). However, the glomeruli of test group rats (natural honey) appeared constricted while some tubules (arrows) appear to have moderately degenerated epithelia (Figure 2). Also in hydrochlorothiazide group (positive control), some of the glomeruli appeared mildly eroded while the tubules appeared normal with some tubules having

intraluminal eosinophilic casts (Figure 3). The histopathological findings were in tandem with the biochemical results as we observed that natural honey showed better renoprotection than hydrochlorothiazide (positive control) against high doses of salt.

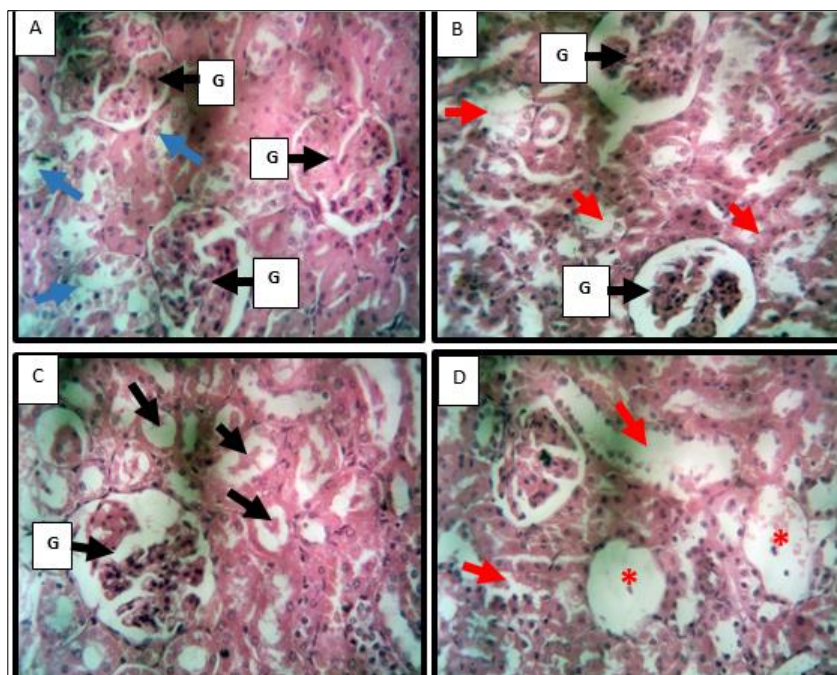


Figure 1 Plate A) Representative micrograph of kidney of animals in group A. The glomeruli (G) appear normal while some tubules (arrows) appear to have degenerated epithelia. Plate B) Representative micrograph of kidney of animals in group B. The glomeruli (G) appear constricted while some tubules (arrows) appear to have degenerated epithelia. Plate C) Representative micrograph of the kidney of animals in group C. Some of the glomeruli (G) appear mildly eroded while the tubules (arrows) appear normal with some tubules having intraluminal eosinophilic casts. Plate D) Representative micrograph of kidney of animals in group D. Some glomeruli are eroded (*) while some of the tubules (arrows) have eroded epithelia. Stain: Haematoxylin and Eosin. Magnification: X400

4 Discussion

Numerous investigations have shown the well-established link between high blood pressure and dietary salt intake. In addition to lowering blood pressure and the prevalence of hypertension, dietary sodium reduction is also linked to a decline in cardiovascular disease morbidity and mortality [15]. For all types of hypertension, non-pharmacological therapies are advised, such as limiting alcohol intake, reducing sodium intake, adopting a heart-healthy diet, quitting smoking, increasing physical activity, and managing weight [16]. Eating plant foods with a high antioxidant chemical content is advantageous since it will reduce the prevalence of several chronic diseases, such as diabetes, cancer, and cardiorenal diseases, by managing oxidative stress [17]. An example is honey. Honey is a naturally occurring chemical that has a wide range of medical benefits, including antibacterial, hepatoprotective, hypoglycemic, reproductive, antihypertensive, and antioxidant characteristics [18]. The aim of this study was to evaluate the effects of honey on renal biochemical parameters, on salt-induced hypertension in rats.

The renal biochemical parameters, which include Creatinine, Urea and K^+ , were more elevated in the group administered with salt alone (affected group), in this study. From the results, it was shown that the Creatinine, Urea and K^+ levels were significantly increased compared to the normal control group. It has been demonstrated that excessive sodium intake, which the World Health Organization defines as greater than 5g sodium per day, causes a significant rise in blood pressure and is associated to the development of hypertension and its cardiovascular and renal consequences [15].

The Creatinine, Urea and K^+ levels were seen to be significantly decreased in group that was administered with salt and the standard antihypertensive drug; hydrochlorothiazide (positive control group), when compared to that of the affected group (salt alone). The first line of treatment for essential hypertension is still frequently thiazide diuretics since they are more effective at preventing one or more of the major forms of the condition from cardiovascular disease

[17]. Thiazide use rapidly increases fluid loss to urine by reducing sodium reabsorption, which causes a decrease in extracellular fluid (ECF) and plasma volume. A decrease in venous return, an increase in renin release, a decrease in cardiac output, and a drop in blood pressure are all caused by this volume loss. Certain thiazide diuretics appear to have antioxidant effects that may help in the treatment of hypertension.

The mechanism of action of the anti-oxidative properties of honey has been established in several studies, this can be compared to the anti-oxidative effect exhibited by the hydrochlorothiazide drug. Based on the result, it was also observed that the group that received salt diet and subsequently oral administration of honey have a significant reduction in their Creatinine, Urea and K⁺ levels, when compared to the group that received salt diet alone. This result shows a renal protective effect of honey, which correlates with a study carried out similar studies [19-22], where it was stated that honey exerts renalprotective effect by limiting the increase in kidney damage indicators (Creatinine, Urea and K⁺) , amidst other renal protective mechanism of honey. These results also correlates with a study carried out by Erejuwa *et al.* [23]. where it was observed that the systolic blood pressure was significantly lower in the honey-treated spontaneously hypertensive rats than in the spontaneously hypertensive rats control.

5 Conclusion

The present study showed salt induced hypertension, as shown by an increase in cardiac biomarkers. However, the administration of natural honey subdued the adverse effects. Thus, this study suggests that natural honey is of health benefits to patients suffering from salt-induced hypertension. Further suggestion would advised a reduced dietary sodium intake.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The author(s) declared no potential conflicts of interest.

Statement of ethical approval

Ethical approval was issued by the Ethics Committee of the Department of Veterinary Medicine, University of Nigeria (Approval number: UNN/eTC/14/67485).

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