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# Nephroprotection of Natural Honey Against Salt-Induced Hypertension in Experimental Rat

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**Abstract**

Hypertension is a major contributor to cardiovascular disease and premature death globally, with notable renal complications. This study evaluated the renoprotective effects of natural honey and hydrochlorothiazide against salt-induced hypertension. Twenty-five albino rats were divided into four groups (n=5) and treated over 21 days. Group A served as the normal control with no treatment. Groups B, C, and D were induced with hypertension using high salt doses. Group B received 15 ml/kg of natural honey, while group C (positive control) was treated with 0.15 mg/kg of hydrochlorothiazide. Group D (negative control) received only salt. Following the treatment period, blood and kidney samples were collected for biochemical and histopathological analyses. Results showed that group D had significantly ($P<0.05$) elevated blood urea nitrogen (BUN), creatinine, and potassium ($K^+$) levels compared to groups A and C. Treatment with honey (group B) or hydrochlorothiazide (group C) restored these parameters toward normal values, with group B showing better outcomes. Histopathological assessments also supported improved renal protection in the honey-treated group. Overall, both natural honey and hydrochlorothiazide provided renal protection against salt-induced hypertension, but honey demonstrated superior renoprotective effects. These findings suggest that natural honey may serve as an effective alternative or complement to conventional antihypertensive therapies in protecting kidney function.

**Keywords:** Hypertension, Renotoxicity, Salt, Natural Honey, Hydrochlorothiazide

## Introduction

Hypertension remains a major global public health challenge that has been identified as the leading risk factor for cardiovascular morbidity and mortality [1]. It increases hardening of the arteries, thus predisposing individuals to heart diseases, peripheral vascular diseases, stroke, heart failure and kidney failure. Hypertension is the commonest non-communicable disease in the world and all races are affected with variable prevalence. Castelli explained that its prevalence is on the increase in developing countries where adoption of western lifestyle and stress of urbanisation, both of which are expected to increase morbidity associated with unhealthy lifestyle, are not on the decline [2]. Andreoli *et al.* [3] were of the opinion that hypertension produces disruptions in health, disability and death in the adult population worldwide. Ejike *et al.* [4] stated that hypertension causes one in every eight deaths worldwide, making it the third leading killer disease in the world. They also estimated that about one billion adults, the world over, had hypertension in the year 2010 and the number is expected to rise to 1.56 billion in the year 2025 if a positive intervention programme is not made, also indicated that fifty million Americans have high blood pressure, approximately one in three adults.

In United States of America, approximately twenty eight (28) to thirty one per cent of adults have hypertension Of this population, 90 to 95 per cent primary hypertension (high blood pressure related to unidentified cause).The remaining five to ten per cent of this group have secondary hypertension (high blood pressure related to identified cause).In China, almost 130 million people aged 35-74 years are estimated to be hypertensive.

Similarly in Ghana, studies revealed a hypertension prevalence of forty per cent among rural dwellers and eight per cent to thirteen per cent in the urban areas. In sub-Saharan Africa, it is the most rapidly rising cardiovascular disease and affecting over 20 million people [6]. He also stated that in Nigeria, hypertension is the commonest non-communicable disease with over 4.3 million Nigerians above the age of fifteen classified as being hypertensive.

Hypertension, also known as high blood pressure is the persistent blood pressure in the arteries above ninety millimetres of mercury (mmHg) between the heart beats (diastolic) or over 140 millimetres of mercury (mmHg) at the beats (systolic). According to Hyman and Parlik, hypertension is the persistent raised levels of blood pressure in which the systolic pressure is above 140 mmHg and diastolic pressure above 90 mmHg [7]. The normal blood pressure is below 120/80 mmHg; blood pressure between 120/80 and 139/89 is called ‘Pre-hypertension, and a pressure of 140/90 or above is considered high (abnormal) blood pressure. According to the Expert Committee on Non-Communicable Diseases, blood pressure of 120/80 mmHg is considered normal for a 30 year old person, while blood pressure of 140 mmHg is considered high for such a person. Similarly, blood pressure of 150/90 mmHg is considered normal for a 60-year old person, while blood pressure of 160/100 mmHg is high for such a person. Hypertension is sometimes called “the silent killer” because people who have it are often symptom-free. In this study, hypertension is perceived as a systolic blood pressure greater than 140 mmHg and a diastolic blood pressure greater than 90 mmHg among adults [8]. The top number which is the systolic pressure corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The bottom number which is the diastolic pressure represents the pressure in the arteries as the heart relaxes after contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed. Blood pressure is normally measured at the brachial artery with a sphygmomanometer (pressure cuff) in millimetres of mercury (mmhg) and given as systolic over diastolic pressure. Hypertension is classified into two namely; primary and secondary hypertension.

According to Stanler, hypertension is categorised into primary and secondary hypertension [9]. Primary hypertension has an unknown cause and accounts for ninety per cent to ninety five per cent of all hypertension cases. This type of hypertension is strongly associated with lifestyle. Usually, the patients do not have many signs and symptoms but may experience frequent headache, tiredness, dizziness or nose bleeds. Although the cause is not known, obesity, smoking, alcohol, diet and heredity play a role in essential or primary hypertension.

Secondary hypertension has a known cause and accounts for five per cent to ten per cent of all hypertension cases. Chris maintained that the most common cause of secondary hypertension is an abnormality in the arteries supplying blood to the kidneys [10]. Other causes include airway obstruction during sleep, stress, diseases and tumours of the adrenal glands, lifestyle, spinal cord injury, hormone abnormalities (oral contraceptive oestrogen replacement), thyroid disease, toxaemia of pregnancy, renal problems such as vascular lesion of renal arteries, diabetic neuropathy, pains as well as anxiety and hypoglycemia. There are some factors which predispose adults to hypertension.

The risk factors of hypertension are genetic factor which can be inherited from parents, age which when the body does not retain the amount of elasticity as it used to in the early years of life, obesity which is an increase in weight of over ten per cent above normal body index due to generalised deposition of fat in the body, excessive salt intake which increases blood pressure, stress which produces chemical substances that cause generalised vasoconstriction, oral contraceptive which contains oestrogen that causes salt retention that increases the volume of blood, sedentary lifestyle which has the tendency of increasing body weight and directly raises blood pressure, elevated levels of plasma lipids particularly cholesterol, excessive alcohol consumption which increases blood pressure and tobacco use (cigarette smoking) that contains nicotine which causes constriction of the blood vessels.

The signs and symptoms of hypertension include occipital headache, dizziness, restlessness, failing vision, shortness of breath, and rapid increased heartbeat. Adults should possess the knowledge of risk factors in order to prevent hypertension. This will help them recognize and prevent or treat hypertension when these signs occur.

Knowledge is used to cover such related terms as facts, information, understanding, awareness, insight, wisdom, reasons, comprehension, meaning, concept and experience. It is an organised body of knowledge shared by people. Nnachi conceptualised knowledge as the ability to understand or comprehend phenomena, the acquisition of positive information by the exercise of some capacity which humans presumably have in common [11]. Health knowledge could be said to mean putting into reality the art of mobilisation of resources by an individual, intellectually, physically and emotionally. Health knowledge and understanding of related factors have a favourable effect on quality of overall well-being. They went further to state that one’s exposure to proper health knowledge will positively influence the person’s health attitude and practice, and thus, one could rightly say that knowledge is the key to optimum well-being. Umaru pointed out that knowledge comes about as a result of learning through cognitive, affective and psychomotor domains. In this study, knowledge is referred to as all understanding and familiarity gained by learning and experience that will enable adults to recognize risk factors as well as recognizing and use of preventive measures of hypertension. Knowledge of hypertension is an important prerequisite for an individual to implement desirable behavioural practices towards its prevention. Lack of such knowledge will lead to aggravated health problems. Adults should therefore, possess adequate knowledge of risk factors of hypertension in order to prevent the disease.

Honey is a sweet, flavourful liquid substance with several beneficial constituents. Extensive research has shown the therapeutic promise of the use of honey in enhancing health values and improving body systems. This manuscript documents the ancient medicinal uses of honey and provides evidence-based data demonstrating its benefits in animal models, patients, and healthy individuals. Several reports by various researchers are discussed regarding health indices and biomarkers used following apitherapy. These include physiological processes in virtually all animal and human organs. The responses of body systems after oral and systemic administration of honey are also mentioned. Honey is also evaluated for its wide acceptability as a complementary and alternative medicine for most ailments. All types of honey exhibit different biochemical activities and show greater variability in their potency as apitherapeutic agents than conventional medicines. The mechanisms of action conferring honey's protective effects, as suggested by various authors, are documented.

Besides its sugar composition, honey consists of a number of bioactive compounds such as phenolic compounds, flavonoids, carotenoid-like derivatives, organic acids, Maillard reaction products, catalase, ascorbic acid, and other compounds which function as antioxidants. Several therapeutic and medicinal effect such as antibacterial, antimutagenic, antiproliferative, hepatoprotective, hypoglycemic, and antioxidant effects have been ascribed to honey in recent years [12].

In contrast, there are limited or no available data on the effectiveness or efficacy of honey supplementation on elevated blood pressure. Recently, it was ported that STZ-induced diabetes mellitus caused reduced SBP in SHR. This hypertensive effect of diabetes on elevated blood pressure was also reported by other authors [13]. Besides, our study indicated that short-term (3 weeks) administration of Malaysian honey in STZ-induced diabetic SHR resulted in further reduction in SBP. Since honey was not administered to nondiabetic SHR in that study, it is uncertain whether the reduction in SBP after honey supplementation is due to honey or secondary effect of diabetes mellitus.

Honey is used in traditional Russian medicine to treat high blood pressure. In "The Healing Powers of Honey," author Cal Orey attributes the blood pressure-lowering ability of honey to oligosaccharides - a type of carbohydrate that has an antioxidant effect. In addition to antioxidant properties, honey also has vitamins, probiotics, minerals, amino acids and enzymes. This study was carried out to investigate Renoprotective of natural honey on animal model of hypertension.

## Materials and methods

### Plant materials

Fresh natural honey used for the study was obtained from Nsukka, a town in Enugu, Enugu state, Nigeria.

### Chemicals and reagents

Chemical: Salt was purchased from a supermarket in the neighbourhood. Reagent(s): Perlong medical analyser PL1000A electrolyte Analyser, Diacetyl monoxime, strong H2SO4, Sodium tungstate, Picric acid, all the reagents were purchased at a standard Science Store located at Ogbete main market Enugu state.

### Method of induction of hypertension

Induction of hypertension was done according to the method of Ani *et al*. (2017) in which a high salt diet and feed were mixed in the ratio of 80 g NaCl + 1 kg of diet and 1% NaCl in drinking water (10 g of NaCl + 1 L distilled water) confirmed hypertensive rats after three consecutive readings using a digital tail cuff Non-invasive blood pressure monitor (NIBP). Hypertensive male rats were selected for the experiment.

### Animals

Twenty-five (20) adult albino rats, weighing 112.17 grams, were obtained from the animal house of the College of Veterinary Medicine, University of Nigeria. The animals were housed in metallic under standard conditions of temperature (22 ± 3°C) and a 12 h light, 12 h dark cycle. The animals were kept under observation for about 14 days before the onset of the experiment for acclimatisation. Experimental protocol and handling was according to Institutional guidelines describing the use of rats and in accordance with the American Physiological Society guiding principles for research involving animals and human beings.

### Experimental design

The twenty-five (25) albino rats were grouped into grouped into (A-D) of five rats each and the received the following treatments which lasted for 21 days:

Group A: (Normal Control): Normotensive.

Group B (Test group): hypertensive rats treated with oral administration of natural honey (15 ml/kg).

Group C (Positive control): hypertensive treatment with oral administration of hydrochlorothiazide (0.15mg/kg).

Group D: (Negative control): hypertensive without treatment.

### Sacrificing of animals and sample collection

Blood samples for the determination of serum analyses of serum electrolytes (sodium and potassium), urea and creatinine were taken by cardiac puncture of the left ventricle of the heart under chloroform anaesthesia and the kidneys were harvested for histopathological analyses.

### Biochemical analysis

The levels of serum electrolyte, urea and Creatinine were estimated.

### Measurement of Serum Electrolyte

Serum Electrolytes were determined using the Perlong Medical PL1000A Electrolyte Analyser.

The Electrolyte analyser applies the principle of ion-selective electrode, which gives the instrument a stable and reliable measurement. It measures the ion concentration of K+, Na+, Cl-, HCO3 and pH values in whole blood, serum and urine samples.

### Measurement of Blood Urea Nitrogen

Blood Urea Nitrogen was determined according to Diacetyl Monoxime (DAM) method.

### Measurement of Serum Creatinine
Serum Creatinine was determined using the spectrophotometric method according to Jaffe-slot Method [14].

### Histopathological analysis
The excised kidney was/were processed using the paraffin wax embedding technique, sectioned at 5 microns and stained using the Haematoxylin and Eosin [H and E] staining procedure. The histological sections were examined using an Olympus TM light microscope.

### Statistical analysis
Data analysis was done using GraphPad prism version 7.0 (GraphPad, San Diego, CA, USA). The results of the biochemical assays were reported as mean±SEM (standard error of mean). The level of significance was tested using one-way analysis of variance (ANOVA), followed by the Tukey post hoc analysis. Probability levels less than 0.05 ($p<0.05$) was considered significant.

### 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).

**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.

### Histopathological results.
In Fig 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 (Fig 4). However, the glomeruli of test group rats (natural honey) appeared constricted while some tubules (arrows) appear to have moderately degenerated epithelia (Fig 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 (Fig 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.

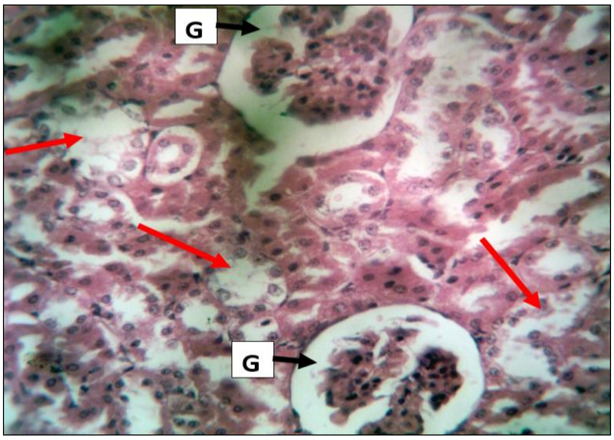


**Fig 2**: Representative micrograph of kidney of animals in group B. The glomeruli (G) appear constricted while some tubules (arrows) appear to have degenerated epithelia. **Stain**: Haematoxylin and Eosin. **Magnification**: X400

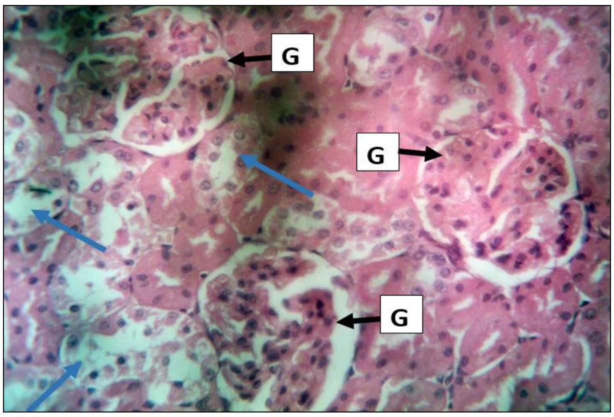


**Fig 1**: Representative micrograph of kidney of animals in group A. The glomeruli (G) appear normal while some tubules (arrows) appear to have degenerated epithelia. **Stain**: Haematoxylin and Eosin. **Magnification**: X400

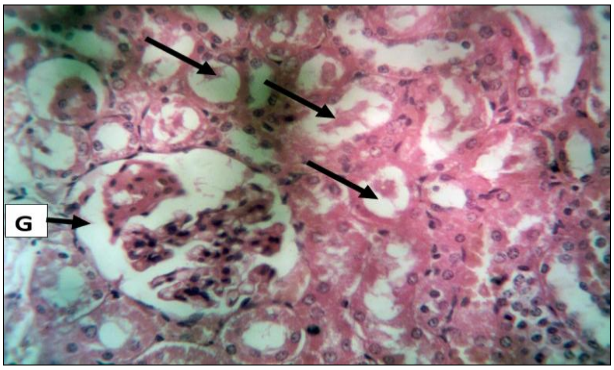


**Fig 3**: Representative micrograph of the kidney of animals in group C. Some of the glomeruli (G) appear mildly eroded while the tubules (arrows) appear normal with some tubules having intraluminal eosinophilic casts. **Stain**: Haematoxylin and Eosin. **Magnification**: X400

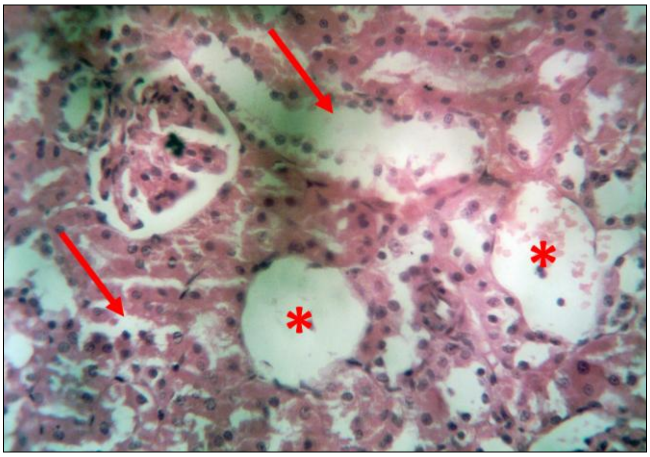

**Fig 4**: Representative micrograph of kidney of animals in group D. Some glomeruli are eroded (*) while some of the tubules (arrows) have eroded epithelia. **Stain**: Haematoxylin and Eosin. **Magnification**: X400

## Discussion

The kidney is a vital organ of the body that performs a variety of functions, including filtration of blood, maintenance of a healthy balance of salts, water and minerals such as sodium and chlorine and excretion of waste products [15]. High sodium consumption above 2 grams/day, equivalent to 5 g salt/day and insufficient potassium intake (less than 3.5 grams/day) contribute to high blood pressure and increase the risk of heart disease and stroke [16]. Most people consume too much salt on average 9 to 12 grams per day, or around twice the recommended maximum level of intake [17]. This study focused on the renoprotective effect of natural honey and hydrochlorothiazide on salt induced hypertension. Honey is a nutritional food low in glycemic index and has been used due to its protective effect against hypertension, diabetes and cardiovascular diseases and its high antioxidant potency. Hydrochlorothiazide is a diuretic agent and has also been used in therapeutic hypertension because of its effect in lowering blood pressure.

From Table 1, the results from this study showed that salt was able to induce hypertension and this was shown from the elevated levels of blood urea nitrogen (BUN), creatinine and potassium ($K^+$) seen in the salt-treated group when compared with normal control and positive control. Although Fig 4 which represents the group treated with salt alone showed normal myocardial fibres, 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. This further proves that salt is a potent hypertensive agent. 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. This shows that natural honey and hydrochlorothiazide individually protects against hypertension. This is in agreement with previous studies carried out to demonstrate the protective effect of honey and hydrochlorothiazide separately. However, the glomeruli of test group rats treated with natural honey appeared constricted while some tubules appeared to have moderately degenerated epithelia. Also in the hydrochlorothiazide group, some of the glomeruli appeared mildly eroded while the tubules appeared normal with some tubules having intraluminal eosinophilic casts. This is in tandem with the biochemical results and suggests that natural honey showed better renoprotection than hydrochlorothiazide against high doses of salt and a synergistic effect would seem to have a more reno-protective effect.

## Conclusion

Results of this investigation showed that natural honey and hydrochlorothiazide provided protection to the kidneys against salt induced hypertension. Although natural honey proved to have more reno-protective effect than hydrochlorothiazide.

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