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Biochemical and Nephrotoxic Effects of Odogwu Bitters and Goko Cleanser on Wistar Rat Kidneys: A Preliminary Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author OIM managed the literature searches, managed the animals, carried out the experiment, curated the data, and carried out the kidney function test. Author ODN conceptualized the study, designed the study, analyzed the data and wrote the first draft of the manuscript. Author NEO wrote the experimental protocol, supervised the study, assisted author ODN to design the study and reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

The rising popularity of herbal remedies, perceived as safer alternatives to synthetic drugs, has led to increased consumption of various herbal mixtures, including Odogwu Bitters and Goko Cleanser in Nigeria. This study investigates the biochemical and nephrotoxic effects of these herbal products when co-administered to adult male Wistar rats. A total of 40 rats were acclimatized and divided into ten groups, receiving varying doses of Odogwu Bitters and Goko Cleanser for 42 days. Biochemical analyses were performed to measure kidney function markers—blood urea nitrogen (BUN), creatinine, and uric acid. Results indicated significant alterations in these parameters; elevated creatinine and urea levels in certain experimental groups which suggested potential nephrotoxic effects. Specifically, groups receiving higher doses of Goko Cleanser showed a marked increase in creatinine and urea levels compared to the control group (P = .001). Phytochemical analyses revealed the presence of saponins, flavonoids, and alkaloids, which may influence renal function and oxidative stress. Despite saponins being known for their nephroprotective properties, the overall findings underscore the dual nature of these herbal mixtures, where beneficial effects may coexist with risks of renal impairment. This research highlights the necessity for cautious consumption of herbal products and suggests further investigations into the long-term renal safety of these widely used herbal remedies.

Keywords: Bitters; creatinine; herbal drinks; kidney function test; urea; uric acid.

ABBREVIATIONS

ANOVA : Analysis of Variance
Co : Company
LD : Lethal Dose
Ltd : Limited
Mls : Mili Litres
RPM : Rotary per Minutes
SD : Standard Deviation
Sig : Significance
Std : Standard

1. INTRODUCTION

In recent years, the use of herbal remedies has gained popularity globally, largely due to a perception that natural products may have fewer side effects than synthetic drugs [1]. Herbal products can be a source of very potent toxins, especially when contaminated [2]. Herbal drinks are common across different societies and cultures, varying in their contents, recipes and proposed actions [3]. Herbal mixtures offer a variety of benefits, ranging from an increase in sexual performance, treatment of several diseases and even aid in weight loss [4-6]. In Nigeria, these mixtures have been widely distributed, with more brands emerging every day. Herbal bitters are alcohol-based herbal drinks, which are often used as a digestive aid and an appetite stimulant [7,8]. Among these are herbal mixtures such as Odogwu Bitters and Goko Cleanser, widely marketed for their purported health benefits, including detoxification and enhancement of bodily functions. Both products are commercially available and have become particularly popular in West African countries, where they are frequently used either alone or in combination. However, despite their widespread use, scientific research on the safety and biochemical effects of these formulations is limited.

Odogwu bitters contain various ingredients which include *Zingiber officinale* and honey [9]. These ingredients are commonly believed to have antioxidants and anti-inflammatory properties, which theoretically might provide some protection to organs such as the liver and kidneys [10]. Goko cleanser, is one of the popular herbal mixtures used by the Nigerian populace [11]. This mixture offers to aid in weight loss, prevention of the development of diabetes and hypoglycemia, detoxification and even in the treatment of several infections, including urinary tract infections. It contains active ingredients like *Vernonia amygdalina, Saccharum officinalis, Allium sativum and Cajanus cajan* [12]. The use of these products in tandem may be expected to produce combined or even synergistic effects, which, while potentially beneficial, could also pose a risk for toxicity, particularly to the kidneys, the primary organs responsible for filtering and excreting waste products from the body [13].

Reports from similar studies indicate that certain herbal combinations can induce oxidative stress in the kidneys, leading to cellular damage if antioxidant defenses are insufficient [14]. Additionally, some herbal products may have

toxic components like alkaloids, tannins, or heavy metals that could contribute to renal toxicity when used over extended periods or in combination with other substances [15]. Thus, the biochemical impact of co-administering Odogwu Bitters and Goko Cleanser on kidney health is an area warranting close examination to understand potential interactions and toxicity levels, especially given their increasing popularity and the risks associated with self-medication and high-dose consumption. Examining the biochemical parameters related to kidney functions such as blood urea nitrogen (BUN), creatinine, and electrolyte levels provides insight into potential nephrotoxic effects [16]. Alterations in these parameters following exposure to herbal preparations may indicate oxidative stress or inflammation within renal tissue. Some studies have suggested that specific herbal components in products like Odogwu Bitters and Goko Cleanser might influence these parameters, either by conferring antioxidant protection or by causing damage due to the accumulation of toxic metabolites [17].

The kidneys are especially vulnerable to toxic effects from herbal products due to their role in filtering blood and excreting metabolites, which can concentrate potentially harmful compounds. In the context of herbal medicine, nephrotoxicity is a serious concern, especially when multiple herbs with unknown interactions are used simultaneously [18]. Wistar rats are commonly chosen for nephrotoxicity studies due to their physiological and biochemical similarities to humans [19]. Given the high prevalence of herbal product usage, especially in regions where access to conventional medical care is limited, assessing the safety of these products is essential. This study aims to evaluate the biochemical effects of co-administering Odogwu Bitters and Goko Cleanser on the kidneys of adult male Wistar rats, providing insight into the potential renal risks or benefits of such combined herbal use.

2. MATERIALS AND METHODS

2.1 Materials

A total of 40 adult male Wistar rats, weighing between 195 g and 230 g, were used in this study. The animals were sourced from a local farm in Nsukka, Enugu State, Nigeria. Upon arrival at the research facility, they were given a two-week acclimatization period with unrestricted access to food and water. Prior to transportation, a veterinarian confirmed the animals' health status, and they were transported under humane conditions.

The rats were housed in spacious, well-ventilated stainless-steel cages maintained at room temperature under a 12-hour light/dark cycle throughout the experimental period. Their health was carefully monitored, and they were provided with a standard diet and clean drinking water. Cage hygiene was ensured by daily cleaning and the application of sawdust bedding to minimize the risk of infection.

Materials used in the study included 200-milliliter bottles of herbal beverages - Odogwu Bitters and Goko Cleanser Herbal Mixture - purchased from distributors at Nkwo Nnewi Market in Anambra State, Nigeria. The rats were fed Top Feeds Grower's Mash Super-Deluxe, manufactured by Eastern Premier Feed Mills Limited, a subsidiary of Premier Feeds Mills Company Limited in Plateau State, Nigeria. Additionally, distilled water was provided by the Department of Anatomy at Nnamdi Azikiwe University, and all reagents used were of analytical grade, supplied by Syntron Bioresearch Inc., USA.

2.2 Methods

Duration of the study: This study was carried out over three months, structured into distinct phases. The initial two weeks focused on determining the LD_{50}, conducting a phytochemical evaluation of the herbal drinks, and acclimating the test animals to their environment. During the next six weeks, the herbal drinks were administered to the animals. This was followed by a two-week period dedicated to biochemical analyses. The study concluded with the final two weeks allocated for statistical analysis and compiling the results.

2.3 Acute Toxicity Test

This research followed the OECD Guideline 425, known as the Up-and-Down Procedure, which involves administering doses in a sequential manner, with adjustments based on the outcomes of preceding tests. This approach allows for a more accurate determination of the LD_{50} while minimizing the number of animals used [20]. The study focused on evaluating the acute oral toxicity of Odogwu Bitters and Goko Cleanser Herbal Mixture in rats and was conducted in two distinct phases.

Odogwu Bitters: *Phase I*: Thirteen rats were divided into three groups, each consisting of three animals, and monitored over a 24-hour period for signs of morbidity and mortality. No adverse effects were observed, and all rats maintained normal health throughout the observation period, prompting progression to Phase II.

Phase II: Four additional rats were introduced, each receiving a single dose. These rats were similarly monitored for morbidity and mortality over a subsequent 24-hour period.

LD_{50} Determination for Odogwu Bitters: *Phase I*: Doses of 10 mg/kg, 100 mg/kg, and 1000 mg/kg were administered to the respective groups, with no signs of mortality or abnormal behaviour.

Phase II: At higher doses of 1200 mg/kg and 1600 mg/kg, no fatalities occurred, and animals remained calm. However, at 2900 mg/kg and 5000 mg/kg, mortality occurred within 24 and 12 hours, respectively.

The calculated LD_{50} was:

$$LD_{50} = \sqrt{AB}$$

A=Maximum dose with 0% mortality
B= Minimum dose with 100% mortality
$LD_{50} = \sqrt{1600 \times 2900} = 2154.17$mg/kg

Goko Cleanser Herbal Mixture: *Phase I*: Nine rats were divided into three groups of three male Wistar rats each. They were observed for 24 hours, with no mortality recorded, leading to the progression of Phase II.

Phase II: The rats were again monitored for 24 hours at higher doses.

LD_{50} Determination for Goko Cleanser Herbal Mixture: *Phase I*: No mortality was observed at doses of 10 mg/kg, 100 mg/kg, and 1000 mg/kg.

Phase II: At doses of 1200 mg/kg and 2600 mg/kg, no fatalities occurred, with the rats remaining calm. However, at 3900 mg/kg and 5000 mg/kg, mortality was observed within 48 and 24 hours, respectively. The LD_{50} was calculated as:

$$LD_{50} = \sqrt{A \times B}$$

A = Maximum dose with 0% mortality (2600mg/kg)
B = Minimum dosed with 100% mortality (3900mg/kg)
LD_{50} of Goko Cleanser = $\sqrt{2600 \times 3900}$ = 3184.34mg/kg

The LD_{50} values determined for both Odogwu Bitters (2154.17 mg/kg) and Goko Cleanser Herbal Mixture (3184.34 mg/kg) indicate a moderate level of acute toxicity, with higher doses resulting in mortality. Further studies are recommended to explore the safety profile of these herbal products for potential therapeutic use.

Phytochemical analysis: The study focused on analyzing bioactive compounds, including saponins, tannins, flavonoids, steroids, alkaloids, cardiac glycosides, reducing sugars, proteins, carbohydrates, and terpenoids. Both qualitative and quantitative methods were employed for the evaluation. Qualitative assessment involved specific reagent-based colorimetric and spot tests, which generated color changes or precipitates as indicators of the presence of phytochemicals. For quantitative analysis, High-Performance Liquid Chromatography (HPLC) was employed due to its precision in separating, identifying, and quantifying compounds by comparing retention times to established standards. The procedures followed standardized methodologies, consistent with protocols used in rat-based experimental studies [21].

2.4 Experimental Design

After a two-week adaptation phase, rats were weighed on a precision scale with a 5 kg limit. They were randomly divided into 10 groups (A through J), with four rats in each group. The herbal treatments were administered orally twice a day, once in the morning (6:00–8:00 am) and again in the evening (5:00–7:00 pm), corresponding to times when artisans typically consume these beverages before and after their workday. Odogwu Bitters was given in the morning, and Goko Cleanser was administered in the evening, over a 42-day period. A syringe with a cannula was used for accurate delivery into the oral cavity.

Group A acted as the control group, receiving only water and feed. Group B received 0.2 ml of Odogwu Bitters daily, while group C received 0.4 ml, and group D received 0.8 ml of Odogwu Bitters daily. Group E was given 0.2 ml of Goko Cleanser daily, group F received 0.5 ml, and

group G received 0.9 ml of Goko Cleanser daily. Group H received 0.2 ml of both Odogwu Bitters and Goko Cleanser daily. Group I was given 0.4 ml of Odogwu Bitters and 0.5 ml of Goko Cleanser daily, while group J received 0.8 ml of Odogwu Bitters and 0.9 ml of Goko Cleanser daily.

2.5 Animal Euthanasia

The euthanasia of the Wistar rats was performed in accordance with the ethical guidelines and animal welfare protocols set by Chukwuemeka Odumegwu Ojukwu University.

A CO_2 gas overdose was used to euthanize the animals. The flow rate of the gas was carefully regulated to replace 10–30% of the chamber's volume every minute, ensuring that the rats were comfortable and not distressed. The rats were closely monitored for signs of unconsciousness, and euthanasia was confirmed once there was a complete cessation of both respiratory and cardiac activity. Confirmation of death was achieved by verifying the absence of heartbeat, breathing, and reflex responses, such as the corneal reflex. The remains of the rats were disposed of following the institution's biosafety procedures.

Blood collection: Ocular puncture was used to collect blood samples from the eye, which were then transferred into sterile plastic tubes. The samples were left undisturbed for 30 minutes to allow complete clotting. After clotting, the samples were centrifuged for 10 minutes at 2500 rpm using an 800D Electric Centrifuge, which operates at 4000 rpm and has a 6 x 20 mL rotor. The resulting clear serum was carefully separated and stored in a refrigerator until required for the kidney function assay.

2.6 Kidney Function Test

The study involved performing biochemical assays to assess the serum concentrations of urea, creatinine, and uric acid in rats.

Urea Measurement: The concentration of urea was determined using an enzymatic method involving urease. This enzyme catalyzes the breakdown of urea into ammonia and carbon dioxide, with the ammonia produced being detected using a colorimetric assay.

Creatinine Determination: To measure creatinine levels, the Jaffe reaction was applied. In this reaction, creatinine reacts with picric acid in an alkaline environment, forming a colored complex. The intensity of this color, measurable via spectrophotometry, correlates directly with the concentration of creatinine in the sample.

Uric Acid Quantification: The levels of uric acid were determined using a uricase enzyme method. Uricase catalyzes the conversion of uric acid into allantoin, releasing hydrogen peroxide in the process. The amount of hydrogen peroxide formed is then measured either colorimetrically or enzymatically to estimate uric acid concentration.

For each assay, known standards and controls were used to ensure the reliability of the results. The data were recorded using a spectrophotometer, and the absorbance readings were compared to standards to determine the concentrations of urea, creatinine, and uric acid in the rat serum samples. These methods adhered to commonly used protocols for experimental studies involving rats [22].

2.7 Statistical Analysis

The data collected in this study were analyzed with IBM's Statistical Package for Social Sciences (SPSS) version 25. A 95% confidence level was used for the hypothesis testing. Both descriptive and inferential analyses were conducted. A one-way ANOVA was applied to examine the differences between the control and experimental groups.

3. RESULTS

3.1 Results of Phytochemical Analysis

Results from both the qualitative and quantitative analyses of Goko Cleanser herbal mixture showed that it contained saponin, flavonoids and tannin. However, saponin had the highest concentration (7%), followed by flavonoids (4%), and tannin (0.2) with the least concentration in the herbal drink (Table 1).

The results of the qualitative and quantitative phytochemical analyses of Odogwu Bitters showed that it contained traces of saponin (0.13%), alkaloid (0.09%), terpenoid (0.30), flavonoid (0.12), carbohydrate, cardiac glycosides, and reducing sugar (0.11) (Table 1). However, the quantitative analysis could not compute the amount of cardiac glycoside and carbohydrate in the herbal drink.

Table 1. Result of Phytochemical Analysis

Constituents	Goko Cleanser (Quantity % w/v)	Odogwu Bitters (Quantity % w/v)
Saponin	Moderately present (7.35)	Present in trace (0.13)
Flavonoid	Present in trace (4)	Present in trace (0.12)
Tannin	Present in trace (0.2)	Absent
Alkaloid	Absent	Present in trace (0.09)
Steroid	Absent	Absent
Reducing sugar	Absent	Present in trace (0.11)
Cardiac glycoside	Absent	Present in trace
Protein	Absent	Absent
Carbohydrate	Absent	Present in trace
Terpenoid	Absent	Present in trace (0.30)

Table 2. Result of creatinine, urea and uric acid analyses

GROUPS		Creatinine	Urea	Uric acid
Control Group A	Mean	.2325	51.0250	12.4825
	N	2	2	2
	Std. Deviation	.00354	.03536	.00354
Experimental Group B	Mean	.5250	47.4250	12.3425
	Std. Deviation	.03536	.03536	.00354
	Sig.	.001	.001	.006
Experimental Group C	Mean	3.0250	52.0250	12.5250
	Std. Deviation	.03536	.03536	.03536
	Sig.	.001	.001	.828
Experimental Group D	Mean	6.0250	43.0250	14.5825
	Std. Deviation	.03536	.03536	.00354
	Sig.	.001	.001	.001
Experimental Group E	Mean	1.3325	59.8250	12.5250
	Std. Deviation	.00354	.03536	.03536
	Sig.	.001	.001	.828
Experimental Group F	Mean	2.0250	68.5250	15.8925
	Std. Deviation	.03536	.03536	.00354
	Sig.	.001	.001	.001
Experimental Group G	Mean	2.0250	45.3250	12.5250
	Std. Deviation	.03536	.03536	.03536
	Sig.	.001	.001	.828
Experimental Group H	Mean	1.5250	42.0250	10.8825
	Std. Deviation	.03536	.03536	.00354
	Sig.	.001	.001	.001
Experimental Group I	Mean	2.6725	48.4250	12.3625
	Std. Deviation	.00354	.03536	.00354
	Sig.	.001	.001	.018
Experimental Group J	Mean	1.5250	54.4250	12.4225
	Std. Deviation	.03536	.03536	.00354
	Sig.	.001	.001	.471
Total	Mean	2.0912	51.2050	12.8542
	N	20	20	20
	Std. Deviation	1.58355	7.90165	1.34794
	Sig.	.001	.001	.001

3.2 Results of the Kidney Function Test

The result of the kidney function test showed a statistically significant difference (*P* = .001) between the control and experimental groups for creatinine, urea and uric acid (Table 2). The independent comparison result showed that there was a significant difference between control and experimental groups for creatinine and urea (Table 2). The independent comparison result for uric acid showed that there was a significant difference between the control group and groups B (*P* = .006), D (*P* = .001), F (*P* = .001), H (*P* = .001) and I (*P* = .018); but showed no significant difference between the control group and groups C (*P* = .828), E (*P* = .828), G (*P* = .828) and J (*P* = .471) (Table 2).

4. DISCUSSION

The results of the kidney function test indicate notable differences between the control and experimental groups in levels of creatinine, urea, and uric acid. Elevated levels of these biomarkers can signal impaired kidney function, as the kidneys are responsible for their clearance from the bloodstream. Creatinine, a waste product from muscle metabolism, is widely used to evaluate renal function. In this study, the control group displayed a significant negative mean difference in creatinine compared to group D, implying reduced clearance and suggesting potential nephrotoxicity in this group. This aligns with prior research demonstrating the role of elevated serum creatinine in indicating kidney stress or injury, especially when associated with chronic herbal or medicinal intake [23, 24].

In terms of urea, a byproduct of protein metabolism excreted by the kidneys, similar patterns emerged. Groups E and F showed a high negative mean difference from the control, indicating elevated urea levels and pointing to potential renal impairment. Conversely, groups D, G, and H exhibited a positive mean difference, suggesting improved urea clearance or metabolic response. Studies have shown that various factors, such as the specific type of herbal supplements or their components, can influence urea metabolism, either enhancing or diminishing renal function [25, 26].

Uric acid results further underscore the variability in response among the experimental groups. High levels of uric acid, typically associated with conditions like gout, may also indicate kidney stress due to reduced filtration capacity. The observed positive mean difference in uric acid in groups D and H relative to the control group suggests a possible strain on renal excretory function in these groups, while the negative mean differences seen in groups D and F could indicate either a protective effect or differences in metabolic response. These findings align with studies linking certain phytochemicals with both uric acid reduction and excretory modulation in the kidneys [27].

The result showed statistically significant differences (*P* = 0.001) between the control and experimental groups across all tested markers (creatinine, urea, and uric acid). This outcome underscores a distinct overall response to the interventions across the groups. Interestingly, the results for uric acid demonstrated group-specific variations, with significant differences found between the control and groups B, D, F, H, and I, while no significant differences were noted with groups C, E, G, and J. This variability may suggest differential metabolic or renal responses to the herbal compounds tested, potentially linked to individual phytochemical profiles and their interactions with kidney function [28, 29].

The phytochemical analysis results for the Goko Cleanser and Odogwu Bitters provide additional context. Goko Cleanser contained saponins, flavonoids, and tannins, with saponins in the highest concentration (7%). Saponins are known for their nephroprotective properties, as well as for anti-inflammatory and diuretic effects, which may influence renal function markers like creatinine and urea [30]. Flavonoids, present at 4% in Goko Cleanser, are also associated with antioxidant and nephroprotective effects, which could mitigate oxidative stress on the kidneys and influence biomarker levels [31]. The low tannin content (0.2%) suggests minimal impact on kidney function, as tannins have been linked to both protective and adverse renal effects depending on dosage and duration of intake [32].

The phytochemical profile of Odogwu Bitters, though different, included traces of saponins (0.13%), alkaloids (0.09%), terpenoids (0.30%), flavonoids (0.12%), carbohydrates, cardiac glycosides, and reducing sugars. Saponins, even in low concentrations, may have contributed to renal modulation in certain experimental groups. Alkaloids, although known for diverse biological activities, have been associated with nephrotoxicity in some cases, particularly when present in herbal supplements consumed regularly [33]. Terpenoids, known for their anti-

inflammatory properties, could play a role in reducing renal inflammation, thus influencing markers like urea and uric acid [34]. However, the precise effect of Odogwu Bitters on kidney function remains complex, as the phytochemical diversity likely leads to multiple overlapping effects on renal physiology, both protective and adverse.

5. CONCLUSIONS

The study results highlight significant differences in kidney function markers - creatinine, urea, and uric acid between the control and experimental groups, indicating varied renal responses to herbal supplements tested. Elevated creatinine and urea levels in some experimental groups suggest potential nephrotoxic effects, aligning with established knowledge of these markers as indicators of kidney stress. The variations in uric acid levels further point to differential responses in renal excretory function, potentially due to the distinct phytochemical compositions in the tested herbal mixtures. Overall, the study emphasizes the potential renal impacts of chronic intake of herbal supplements and supports further investigation into the safe dosage and long-term effects of specific phytochemicals to better understand their implications for kidney health.

DECLARATIONS

This research article is an original article. It has not been submitted for review to another journal and has not been published in any journal or conference proceedings.

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and / or analyzed during the current study are available within the text.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that generative AI technology such as Large Language Models has been used during the editing of the manuscript to improve language and readability. ChatGPT (GPT-4o mini) was used.

CONSENT

It is not applicable.

ETHICS APPROVAL

The Ethical Approval was obtained from the Ethics Committee of the Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli Campus, Anambra state. The approval number is COOU/BMS/008.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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