The Effectiveness of Brown Rice Syrup (Oriza nivara) and Acacia Honey (Acacia carpa) on Uric Acid, Urea, Creatinine Levels and Kidney Histopathology imagery in Alloxan-Induced White Rats (Rattus norvegicus).

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Abstract. This study evaluated the effects of Curcuma zedoaria extract on blood glucose, Placental Growth Factor (PlGF), and kidney histopathology in diabetic nephropathy (DN) Wistar rats. DN, a severe diabetic complication, leads to progressive kidney damage. Using a post-test-only control group design, diabetes was induced in male Wistar rats with alloxan, and Curcuma zedoaria extract was administered orally at doses of 250 mg, 500 mg, and 750 mg for two weeks. Blood glucose, PlGF, and kidney histopathology were assessed. Data were analyzed using ANOVA, Kruskal-Wallis, and Bonferroni tests. Results showed significant blood glucose reduction (p ¡ 0.01), with the 750 mg dose being most effective. However, no significant differences were observed in PlGF levels (p = 0.902) or kidney histopathology (p = 0.152). These findings suggest that high-dose Curcuma zedoaria effectively reduces blood glucose in DN, but its effects on PlGF and kidney histopathology are limited.

Keywords: uric acid, urea, creatinine, and kidney histopathology.

1 Introduction

Kidney diseases significantly impact global health, with rising cases attributed to factors such as metabolic disorders, lifestyle changes, and aging populations. Impaired renal function caused by complications of microvascular in diabetic patients, characterized by elevated levels of uric acid, urea, and creatinine, leads to metabolic imbalances and organ damage. Identifying effective, natural interventions to mitigate kidney dysfunction is essential in improving health outcomes. Recent studies have highlighted the potential of natural remedies in managing renal disorders with true experimental pre-test and control group design. Brown rice syrup (Oryza nivara) and acacia honey (Acacia carpa) have shown

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promise due to their bioactive compounds with antidiabetic, antioxidant, and anti-inflammatory properties. These substances may improve biochemical markers of renal health and facilitate tissue repair, yet their therapeutic efficacy remains underexplored in systematic experimental settings. This study investigates the effects of brown rice syrup and acacia honey on kidney function and histopathology in alloxan-induced diabetic white rats (Rattus norvegicus). By analyzing changes in uric acid, urea, creatinine levels, and renal tissue morphology, this research aims to validate their role as potential nephroprotective agents. The findings could pave the way for developing natural, affordable therapies for kidney health management.

2 Literature Review

Kidney function is vital for maintaining metabolic homeostasis, with the kidneys playing a central role in filtering waste products such as urea, creatinine, and uric acid from the bloodstream. Renal impairment, characterized by the accumulation of these substances, is a significant global health concern, often linked to chronic diseases such as diabetes and hypertension [11, 16]. Research efforts have increasingly focused on natural therapeutic interventions to mitigate kidney damage and restore functionality. Brown rice syrup (*Oryza nivara*) and acacia honey (*Acacia carpa*) have emerged as promising candidates due to their rich bioactive compound profiles [3, 9].

Studies have shown that brown rice contains flavonoids, saponins, and dietary fibers, which possess antioxidative and anti-inflammatory properties [9,13]. These compounds can modulate metabolic pathways, reducing oxidative stress and inflammation, primarily contributing to kidney damage. Furthermore, brown rice has been shown to improve glucose metabolism and insulin sensitivity, making it relevant for managing diabetic complications affecting the kidneys [3]. Acacia honey, known for its high antioxidant content, has been studied for its protective effects against oxidative stress and nephrotoxicity. Thymoquinone, a key bioactive component in honey, has demonstrated the ability to prevent renal tissue damage by scavenging free radicals and reducing inflammations.

Combining these two natural substances could offer synergistic benefits for renal health. Animal models, particularly white rats (*Rattus norvegicus*), have been proven to be invaluable in studying renal pathophysiology and therapeutic interventions [8]. Alloxan-induced diabetic models replicate key features of diabetic nephropathy, allowing researchers to evaluate biochemical and histopathological changes under controlled conditions [8]. Existing studies underscore the importance of assessing uric acid, urea, and creatinine as reliable biomarkers for kidney function [11, 16].

Despite promising preliminary findings, there are gaps in understanding the mechanisms through which brown rice syrup and acacia honey exert their nephroprotective effects. This study addresses these gaps by evaluating their impact on renal function and tissue morphology in alloxan-induced diabetic rats, contributing valuable insights to the field of natural therapeutics.

3 Methods

This study employs a true experimental design with a pre-test and control group approach to evaluate the effects of brown rice syrup (Oryza nivara) and acacia honey (Acacia carpa) on kidney function and histopathology in alloxan-induced diabetic white rats (Rattus norvegicus). The research was conducted in the laboratory of the Faculty of Medicine, Universitas Prima Indonesia, from March to June 2024 after had ethical clearance No. 045/KEPK/UNPRI/III/2024 from KEPK Universitas Prima Indonesia . Twenty male white rats (Rattus norvegicus) were used as subjects, weighing between 200–250 grams. They were divided into four groups:

1. Negative Control (NC): Rats received no treatment after alloxan induction.
2. Positive Control (PC): Rats were given standard diabetic treatment.
3. Treatment Group 1 (TG1): Rats received brown rice syrup at a dose of 5 mg/kgBW.
4. Treatment Group 2 (TG2): Rats received brown rice syrup at a dose of 15 mg/kgBW.

All groups were provided with standard feed and water throughout the study.

3.1 Induction of Diabetes

Diabetes was induced using alloxan monohydrate at a dose of 150 mg/kg BW via intraperitoneal injection. Diabetes was confirmed by measuring blood glucose levels after 72 hours, with rats showing glucose levels above 200 mg/dL being considered diabetic.

3.2 Administration of Treatments

Brown rice syrup and acacia honey were administered orally to the treatment groups once daily for 28 days using a feeding syringe. The control groups received equivalent volumes of distilled water.

3.3 Measurement of Biochemical Parameters

Blood samples were collected from the tail vein on days 0, 7, 14, 21, and 28. The following biochemical markers were analyzed:

- **Uric acid (mg/dL)**: Measured using standard colorimetric and electrochemical methods.
- **Urea level (Blood Urea Nitrogen - BUN)** and **Creatinine level (mg/dL)**: Measured using test kit creatinine (CREA) methods.
- **Histopathological Kidney Analysis**: At the end of the study, rats were euthanized, and kidney tissues were collected for histopathological examination. The tissues were fixed in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Kidney tissue damage was assessed based on the degree of inflammation, necrosis, and structural abnormalities.

4 Results

4.1 Phytochemical Analysis

Phytochemical analysis revealed the presence of bioactive compounds in the brown rice syrup, including flavonoids, saponins, triterpenoids, and glycosides, while tannins and alkaloids were absent. These findings suggest the therapeutic potential of the syrup in modulating biochemical parameters and kidney health.

Table 1. Phytochemical Screening Results

Phytochemistry Content	Result
Flavonoid	(+)
Saponin	(+)
Tannin	(-)
Alkaloid	(-)
Triterpenoid	(+)
Glycoside	(+)

4.2 Biochemical Parameter Measurements

The study analyzed the effects of brown rice syrup and acacia honey on uric acid, urea, and creatinine levels over a 28-day treatment period in white rats (*Rattus norvegicus*) induced with alloxan.

Uric Acid Levels Significant reductions were observed in the groups treated with 5 mg/kgBW and 15 mg/kgBW doses of brown rice syrup compared to the negative control. By Day 28, these groups exhibited levels closer to the positive control, indicating the syrup's efficacy in lowering uric acid levels ($p < 0.05$).

Urea Levels After 28 days, both treatment groups demonstrated a substantial decrease in urea levels, with results comparable to the positive control ($p < 0.001$). The reduction was dose-dependent, emphasizing the potential of brown rice syrup and acacia honey as therapeutic agents for urea management.

Creatinine Levels Both treatment groups (5 mg/kgBW and 15 mg/kgBW) exhibited significant reductions in serum creatinine levels by Day 28 ($p < 0.001$). The higher dose group achieved levels almost identical to the positive control.

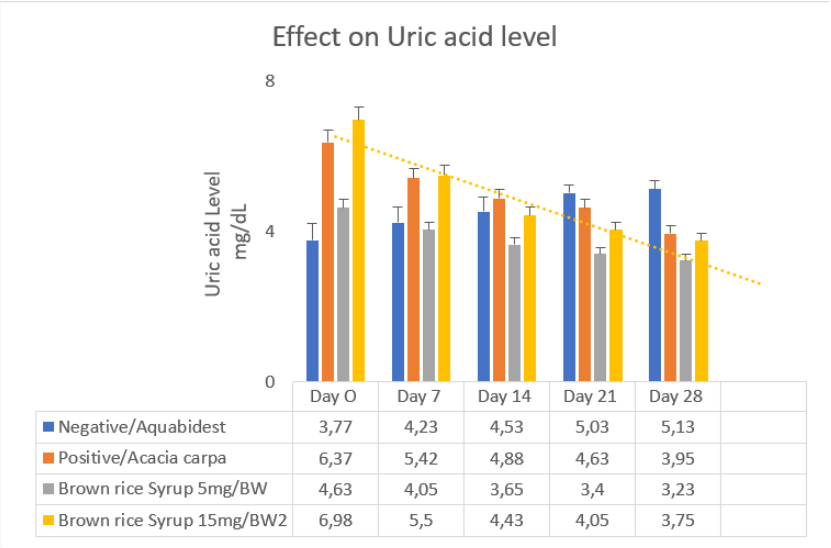

Fig. 1. Effect on Uric Acid Level

Table 2. Serum Levels of Ureum and Creatinine (mg/dL)

Level	Group	H-0	H-28
Ureum	Control Negative (*Aquabidest*)	108,33 ± 12,88	115,83 ± 11,65
	Control Positive (*Acacia carpa*)	99,33 ± 5,92	71,17 ± 8,93
	Perlakuan 5 mg/BW	98,17 ± 5,85	83,33 ± 6,06
	Perlakuan 15 mg/BW	99,17 ± 6,43	75,83 ± 5,98
Creatinine	Control Negative (*Aquabidest*)	108,33 ± 12,88	115,83 ± 11,65
	Control Positive (*Acacia carpa*)	99,33 ± 5,92	71,17 ± 8,93
	Perlakuan 5 mg/BW	98,17 ± 5,85	83,33 ± 6,06
	Perlakuan 15 mg/BW	99,17 ± 6,43	75,83 ± 5,98

4.3 Histopathological Analysis

Histopathological examination of kidney tissues showed noticeable improvements in the treated groups. Before treatment, severe damage, including necrosis and tubular swelling, was prevalent in the negative control group. After 28 days, the positive control group and both treatment groups displayed restored glomerular and tubular architecture, with a marked reduction in inflammatory cell infiltration.

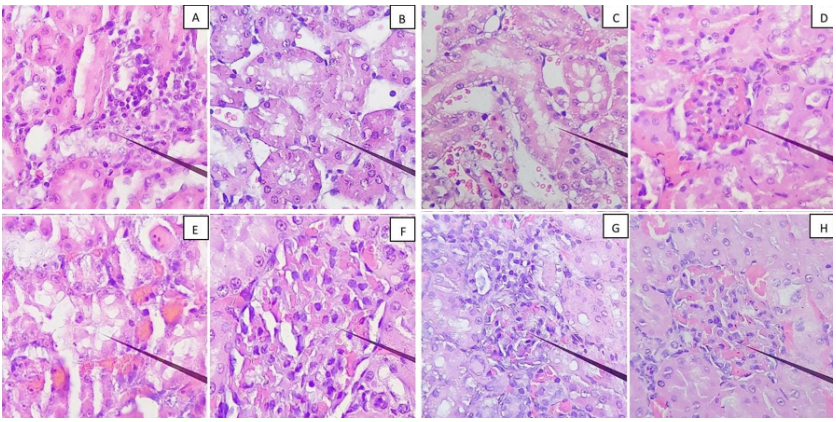

Fig. 2. Histopathological Analysis of Kidney Tissue

Table 3. Index Score of Kidney Damage

Score	Description
0	Normal
0,5	Partially normal
1	Infiltration of cells inflammation
2	Edema spatinum bowman
3	Necrosis
4	Tubulus swelling

Table 4. Kidney Damage Score

Group	H-0	H-28
Negative group	3	4
Positive group	4	0.5
Dose 5 mg/kgBW	4	0.5
Dose 15 mg/kgBW	3	0.5

5 Discussion

Based on the research results, it was found that brown rice syrup can lower the levels of uric acid, urea, and creatinine after 28 days of treatment. The phytochemical test results showed that brown rice syrup contains bioactive compounds such as flavonoids, saponins, terpenoids, and glycosides. Flavonoids can reduce uric acid levels by inhibiting the formation of free radicals [10]. Uric acid can bind with flavonoids, forming a complex that damages the structure of uric acid and reduces its activity. Xanthine oxidase (XO) plays a role as a catalyst in purine metabolism, converting hypoxanthine into xanthine and then xanthine into uric acid, using oxygen as an electron acceptor. This process generates superoxide anion and hydrogen peroxide, indicating that increased XO activity contributes to increased uric acid production and reactive oxygen species (ROS) synthesis.

Excess uric acid stimulates ROS synthesis, which decreases the bioavailability of nitric oxide (NO). This disruption in insulin signaling can cause endothelial dysfunction, increasing the risk of cardiovascular complications such as hypertension, atherosclerosis, and stroke. By inhibiting XO formation, the ROS formation process will also be inhibited [4]. Flavonoids have the potential to act as inhibitors of xanthine oxidase (XO) and adenosine deaminase (ADA), leading to a decrease in uric acid levels. Furthermore, flavonoids act as antioxidants capable of neutralizing reactive oxygen species (ROS) through lipid metabolism, free short-chain fatty acids, and cholesterol esters.

The decrease in urea and creatinine levels in the group consuming brown rice syrup is suspected to be caused by bioactive compounds such as fiber, saponins, and flavonoids, which function as antioxidants. Flavonoids inhibit hydrolytic and oxidative enzymes and provide electrons to free radicals, preventing damage to glomerular cells [2]. According to research, flavonoids are known to improve β pancreatic cells by activating the cAMP signaling pathway, which enhances insulin secretion affected by glucose. This mechanism contributes to the improvement of kidney tissue, thereby reducing urea and creatinine levels.

In cases of diabetes mellitus, angiopathy causes narrowing and blockage of blood vessels, including those leading to the kidneys. The high blood plasma viscosity in diabetic patients results in slower blood flow, reducing the supply of oxygen and nutrients to the tissue, which leads to cell necrosis, including in the kidneys [18]. Long-term hyperglycemic conditions can lead to significant changes in kidney tissue, potentially causing kidney failure. This damage can result in various abnormalities in the histological structure of kidney tissue, including extracellular matrix accumulation, glomerular basement membrane thickening, and glomerulosclerosis. The improvement in kidney structure in the group treated with brown rice syrup is suspected to be caused by the antioxidant compounds it contains, including flavonoids.

Flavonoids have effective antioxidant properties to address vascular diseases and function as anti-inflammatory agents. These compounds can directly prevent reactive oxygen species (ROS) by binding to free radicals and stabilizing or neutralizing them [13]. Flavonoids and other phytochemicals can reduce free radical production caused by long-term hyperglycemia in diabetic patients, thus

preventing the formation of new free radicals. Overall, this effect enhances kidney protection from damage caused by prolonged hyperglycemic conditions [6].

6 Conclusion

This study demonstrates the potential therapeutic effects of brown rice syrup (*Oryza nivara*) and acacia honey (*Acacia carpa*) in improving kidney health and biochemical parameters in alloxan-induced diabetic white rats (*Rattus norvegicus*). The findings are summarized as follows:

1. **Reduction in Biochemical Markers:** Administration of brown rice syrup at doses of 5 mg/kgBW and 15 mg/kgBW significantly reduced levels of uric acid, ureum, and creatinine. The reductions observed in the treatment groups were comparable to those in the positive control group.
2. **Histopathological Improvement:** Histopathological analysis revealed substantial kidney tissue recovery in the treated groups, with reduced inflammation, necrosis, and tubular swelling, demonstrating the protective effects of the interventions.
3. **Phytochemical Contributions:** The bioactive compounds in brown rice syrup, such as flavonoids and saponins, are likely responsible for its antioxidative and anti-inflammatory effects, which contribute to the observed improvements.

The results suggest that brown rice syrup and acacia honey have the potential to serve as natural therapeutic agents for managing kidney health, particularly in conditions characterized by biochemical dysfunction and tissue damage. Further studies with larger sample sizes and higher doses are recommended to validate these findings and explore their clinical applications.

7 Acknowledgement

None declared

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