BAJOPAS Volume 17 Number 1, June, 2024 http://dx.doi.org/10.4314/bajopas.v17i1.10

Bayero Journal of Pure and Applied Sciences, 17(1): 64 - 68
Received: 03/02/2024
Accepted: 14/04/2024
ISSN 2006 – 6996

THERAPEUTIC POTENTIAL OF *Hyphaene thebaica* METHANOL FRUIT EXTRACT IN MITIGATING GENTAMICIN-INDUCED HEPATO-RENAL TOXICITY IN WISTAR RATS

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ABSTRACT
Liver and kidney dysfunctions are closely interconnected pathologies caused by oxidative stress and inflammation, often exacerbating disease progression. The present study investigates the therapeutic potential of Hyphaene thebaica methanol fruit extract in mitigating gentamicin-induced hepato-renal toxicity in Wistar rats. Liver and kidney function markers were significantly (P<0.05) elevated in the hepato-renal toxic control group (HRTC), confirming severe liver and kidney damage after intraperitoneal administration of gentamicin injection for 14 days. Treatment with H. thebaica at 250 mg/kg (HT250) and 500 mg/kg (HT500) significantly (P<0.05) ameliorated these biochemical alterations. The extract's hepatoprotective and nephroprotective effect might be attributed to its rich polyphenolic composition. Notably, the lower dose (HT250) exhibited greater therapeutic benefits, suggesting a non-linear dose-response relationship. The results highlight H. thebaica as a promising natural candidate for managing hepato-renal toxicity, emphasizing its potential integration into therapeutic strategies for liver and kidney disorders.
Keywords: H. thebaica, Hepatotoxicity, Kidney, Liver, Nephrotoxicity

INTRODUCTION

Liver and kidney pathologies are critical complications in various diseases, which often worsen disease progression through interrelated mechanisms of inflammation and oxidative stress. These conditions disrupt the metabolic and physiological functions of the liver and kidneys, triggering systemic complications (Allameh *et al.*, 2023; Rapa *et al.*, 2019).The liver, essential for detoxification and metabolism, is particularly susceptible to damage from xenobiotics and chronic conditions such as diabetes and obesity which triggers inflammation and free radical generation (Allameh *et al.*, 2023). Similarly, the kidneys, responsible for filtration and maintaining electrolyte balance, face impairments under similar stressors, leading to fluid imbalances and toxin accumulation triggering chronic inflammation (Imenez-Silva & Mohebbi, 2022).

The interplay between liver and kidney dysfunction significantly exacerbates complications associated with various diseases, highlighting the necessity for integrated treatment approaches. The physiological and pathological interactions between these organs involve intricate mechanisms, including cytokine release, activation of inflammatory signaling pathways, oxidative stress, and altered enzymatic activities (Rui, 2014; Trefts *et al.*, 2017; Zhao *et al.,* 2023). These mechanisms underpin the phenomenon of hepato-renal crosstalk, wherein dysfunction in one organ can profoundly impact the other, creating complex clinical scenarios.

This interconnected nature of liver and kidney pathologies underscores the importance of developing therapeutic interventions that can arrest these pathological processes. Targeted treatments aimed at mitigating inflammation and oxidative stress, are essential to resolving complications in both organs and improving disease outcomes (Morelli *et al.,* 2021; Rad *et al.,* 2024; Verna & Wagener, 2013).

The doum plant (*Hyphaene thebaica*) offers promising therapeutic potential due to its potent antioxidant and anti-inflammatory properties, which may reduce liver and kidney pathology. Rich in bioactive compounds such as polyphenols, flavonoids, and tannins, doum combats oxidative stress by neutralizing reactive oxygen species (ROS), reducing lipid peroxidation, and enhancing endogenous antioxidant defenses like superoxide dismutase (SOD) and glutathione peroxidase (GPx)(Amusan *et al.,* 2024; Hossam *et al.,* 2018). Additionally, its anti-inflammatory effects

suppress key mediators such as TNF-α and IL-6, thereby reducing inflammation-driven organ damage.

The use of medicinal plants in treating multi-organ pathologies presents significant challenges, particularly when targeting interconnected organs like the liver and kidneys. Both organs are crucial for metabolism, detoxification, and maintaining homeostasis, and they often share common pathways of damage, such as oxidative stress and inflammation (Phaniendra *et al.,* 2015). However, these shared mechanisms can complicate treatment, as the bioactive compounds from medicinal plants may not adequately meet the therapeutic needs of both organs simultaneously (Galicia-Garcia *et al., 2*020). Issues such as uneven distribution of active compounds, metabolic competition between the liver and kidneys, and compensatory mechanisms in one organ potentially worsening dysfunction in the other further complicate their treatment (Klaassen & Aleksunes, 2010; Palipoch & Punsawad, 2013). While *H. thebaica* has shown notable hepatoprotective and nephroprotective effects individually (Hassan, 2020; Kaka *et al*., 2019; Shehata & El-Ghffar, 2017), its effectiveness in addressing simultaneous liver and kidney damage remains poorly understood. This study aims to evaluate the effect of *H. thebaica* fruit extract in mitigating gentamicin-induced hepato-renal toxicity in rats.

MATERIALS AND METHODS

Chemicals and Reagents

The following chemicals and reagents were used during the analysis; Gentamicin, silymarin, methanol, aspartate transaminase (AST) and alanine transaminase (ALT) kits (Randox), alkaline phosphatase (ALP), urea and creatinine kits (Randox), bilirubin and electrolytes (Randox).

Plant Collection and Identification

Hyphaene thebaica dried fruits were purchased from Kawo market, Kaduna State, Nigeria. The plant was identified and authenticated by a specialist in the Department of Biological Sciences, Kaduna State University and assigned a voucher specimen no. 2220. The fruit was crushed into fine powder using mortar and pestle.

Plant Preparation

Approximately 100 g of *Hyphaene thebaica* fruit powder was placed into the thimble of a Soxhlet extractor. Methanol was added to a round-bottom flask positioned on a heating mantle. The Soxhlet extractor was connected above the flask, and a reflux condenser was attached to the extractor with cold water circulating to maintain optimal conditions. Heating was applied to reflux the methanol, and extraction continued for an appropriate duration until complete extraction of the fruit powder was achieved. The extract was placed in a rotary evaporator to separate the extract from the solvent.

Experimental Animals

Thirty albino wister rats weighing 150–290g were procured from the National Institute of Trypanosomiasis Research (NITR), Kaduna and housed in the animal facility of the College of Medicine, Kaduna State University. The rats were housed in aluminum cages (6 animals per cage) with wood shavings as bedding, changed weekly. They were acclimatized for seven days under standard laboratory conditions with unrestricted access to rat pellets and water. Their weights were recorded for accurate dosing. After one week acclimatization, rats from group two to five were induced with Hepatorenal toxicity by administering gentamicin injection intraperitoneally at a dose of 80 mg/kg body weight daily for 14 days followed by treatment with varying doses of the extract for three weeks.

Animal grouping and induction of Hepato-renal toxicity

The rats were randomly divided into five groups (n=6 per group):

Group 1: Normal control.

Group 2: Hepatorenal control.

Group 3: Hepatorenal toxicity group treated with methanol extract of *Hyphaene thebaica* (250 mg/kg).

Group 4: Hepatorenal toxicity group treated with methanol extract of *Hyphaene thebaica* (500 mg/kg).

Group 5: Hepatorenal toxicity group treated with standard Silymarin (100 mg/kg).

Blood Sample Collection

After three weeks of treatment, blood samples were collected via cardiac puncture under sterile conditions. The samples were analyzed for liver and kidney function parameters, including ALT, AST, ALP, serum creatinine, urea, bilirubin and electrolytes, using standard methodology in their respective kits as described by the manufacturer (Randox).

Statistical Analysis

Data were expressed as mean ± standard error of the mean (SEM). Groups comparison were performed using one-way analysis of variance (ANOVA), followed by post-hoc tests. Statistical analysis was conducted using SPSS version 17.0,

with significance set at $p < 0.05$ at 95% confidence interval.

RESULTS

The hepatoprotective and nephroprotective effects of the methanol fruit extract of *Hyphaene thebaica* were evaluated. In the liver function analysis (Table 1), the hepato-renal toxic control group (HRTC) exhibited significantly ($P<0.05$) elevated AST, ALT, ALP, total bilirubin, and conjugated bilirubin levels, compared to the normal control (NC), indicating severe liver damage. Treatment with *Hyphaene thebaica* at 250 mg/kg (HT250) and 500 mg/kg body weight (HT500) significantly ($P<0.05$) reduced these parameters, with HT250 showing a greater effect. Silymarin at 100 mg/kg (SL100) demonstrated the most pronounced protective effect, normalizing these parameters to near-control levels. Similarly, in kidney function analysis (Table 2), HRTC showed elevated urea, creatinine, and sodium levels, along with electrolyte imbalances, signifying renal dysfunction. Treatment with HT250 and HT500 improved renal parameters, with HT250 providing better restoration than HT500.

Table 1: Effect of methanolic fruit extract of *Hyphaene thebaica* on liver function parameters

	NC	HRTC	HT250	HT500	SL100
AST (IU/L)	50.67 ± 9.45^{a}	212.67 ± 18.15^{b}	114.00 ± 5.00^{c}	81.67 ± 7.64^{d}	44.67 ± 4.51^{a}
ALT(IU/L)	14.00 ± 3.46^{a}	89.67 ± 5.51^{b}	27.67 ± 1.53^{c}	33.00 ± 7.21^{c}	29.33 ± 3.51^{ac}
ALK-PHOS (IU/L)	38.67 ± 8.50^{a}	164.00 ± 11.53^{b}	83.67 ± 7.77^{c}	103.00 ± 5.57^{d}	58.00 ± 6.25^{a}
T-BILIRUBIN (µmol/L)	9.00 ± 1.00^{a}	80.00 ± 5.57^{b}	16.00 ± 2.65^{a}	36.67 ± 9.02^{c}	13.33 ± 5.13^{a}
C-BILIRUBIN (µmol/L)	4.37 ± 1.48^{a}	$48.00\pm9.542.52^{b}$	8.13 ± 0.32^{a}	28.10 ± 0.92^{c}	6.33 ± 1.53^{a}

T-Bilirubin= Total Bilirubin, C-Bilirubin= Conjugated Bilirubin, NC=Normal Control, HRTC= Hepatorenal toxicity Control, HT250= Hepatorenal toxicity group treated with methanolic extract of *Hyphaene thabaica* 250 mg/kg; HT500= Hepatorenal toxicity group treated with methanolic extract of *Hyphaene thabaica* 500 mg/kg; Hepatorenal toxicity group treated with Silymarine 100mg/kg. The results are expressed as the mean ± SEM. Different superscripts across rows indicate significant difference (Tukey's-HSD multiple range test, $P<0.05$).

Table 2: Effect of methanolic fruit extract of *Hyphaene thebaica* on Kidney function parameters

	NC	HRTC	HT250	HT500	SL100
UREA (mmol/L)	2.69 ± 0.27^{a}	17.63 ± 1.94^{b}	4.70 ± 0.44^{ac}	7.30 ± 0.56^{dc}	3.70 ± 0.62^{a}
CREATININE(µmol/L)	44.00 ± 9.84^{a}	121.00 ± 7.21^{b}	60.67 ± 3.79^{a}	89.33 ± 11.02^{c}	75.33 ± 8.50^{a}
SODIUM(mmol/L)	71.33 ± 2.08^{a}	152.00 ± 2.65^{b}	138.67 ± 7.57^{c}	138.33 ± 2.08^{c}	139.33 ± 4.51^{c}
POTTASIUM(mmol/L)	2.27 ± 0.21^{a}	10.67 ± 0.58^{b}	2.80 ± 0.35^{ac}	4.73 ± 0.47^{d}	3.80 ± 0.26^{cd}
CHLORIDE(mmol/L)	50.33 ± 5.03^{a}	125.33 ± 16.65^{b}	93.67 ± 4.04^{c}	102.67 ± 7.09^{bc}	101.33 ± 7.77^{bc}
BICARBONATE(mmol/L)	15.33 ± 1.53^{a}	39.67 ± 2.52^{b}	25.00 ± 3.00^{c}	27.00 ± 2.65^{c}	26.00 ± 3.61^{c}

NC=Normal Control, HRTC= Hepatorenal toxicity Control, HT250= Hepatorenal toxicity group treated with methanolic extract of *Hyphaene thabaica* 250 mg/kg; HT500= Hepatorenal toxicity group treated with methanolic extract of *Hyphaene thabaica* 500 mg/kg; Hepatorenal toxicity group treated with Silymarine 100mg/kg. The results are expressed as the mean ± SEM. Different superscripts across rows indicate significant difference (Tukey's-HSD multiple range test, $P<0.05$).

DISCUSSION

The present study evaluated the hepatoprotective and nephroprotective effects of methanol fruit extract of *Hyphaene thebaica* against gentamicin-induced hepato-renal toxicity in wistar rats. The study findings indicate that treatment with *H. thebaica* extract, particularly at a dose of 250 mg/kg (HT250), significantly ameliorated liver and kidney dysfunction markers, suggesting its potential therapeutic efficacy.

Gentamicin is known to induce oxidative stress and inflammation, leading to hepatic and renal damage (Yarigani *et al.,* 2019). This is evidenced by elevated levels of liver enzymes (AST, ALT, ALP) and bilirubin, as well as increased urea and creatinine levels, as observed in the hepato-renal toxic control group. The administration of *H. thebaica* extract at both 250 mg/kg and 500 mg/kg doses resulted in a significant reduction of these parameters, with the HT250 group showing a more pronounced effect.

The hepatoprotective effect of *H. thebaica* has been previously documented. Shehata and El-Ghffar (2017) demonstrated that *H. thebaica* extract improved liver function by enhancing antioxidant defenses and reducing pro-inflammatory cytokines in mercuric chloride-induced hepatotoxicity in rats. Similarly, Hassan (2015) reported the ameliorative potential of *H. thebaica* on streptozotocin-induced diabetic nephropathy, highlighting its role in reducing oxidative stress and apoptosis in renal tissues (Wu *et al.,* 2023).

Interestingly, the present study found that the lower dose of *H. thebaica* extract (250 mg/kg) was more effective in improving liver and kidney function parameters than the higher dose (500 mg/kg). This non-dose-dependent response suggests that a lower concentration of the extract may be optimal for therapeutic efficacy, possibly due to the complex interplay of its bioactive compounds. Zanna *et al.* (2008) observed that while *H. thebaica* root extract exhibited some beneficial effects, higher doses could lead to hepato- and nephrotoxicity, indicating the importance of dose optimization.

The curative effects observed in this study can be attributed to the rich phytochemical composition of *H. thebaica*, which includes polyphenols, flavonoids, and tannins. These compounds are known for their antioxidant properties, scavenging free radicals, and enhancing endogenous antioxidant defenses, thereby mitigating oxidative stress-induced cellular damage.

CONCLUSION

In conclusion, the methanol fruit extract of *Hyphaene thebaica* exhibits significant hepatoprotective and nephroprotective effects against gentamicin-induced toxicity in rats, with the 250 mg/kg extract dose being more effective. These findings support the potential therapeutic application of *H. thebaica* in managing liver and kidney disorders associated with oxidative stress and inflammation.

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