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# Antidiabetic and Antioxidant Properties of N-Hexane Fraction of the Mesocarp Extract of *Hyphaene Thebaica* in Alloxan-Induced Diabetic Rats

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## ABSTRACT
Type 2 diabetes mellitus is more common and characterised by hyperglycemia, hyperlipidemia, and oxidative stress. Low efficacy, adverse side effects, and high cost limit current antidiabetics. As an alternative to current medications, traditional medicines of plant origin are becoming increasingly common in many nations to treat diabetes. *Hyphaene thebaica* is a tropical fruit used locally to treat diabetes mellitus but lacks scientific validation. This study aimed to evaluate the antidiabetic and antioxidant properties of the n-hexane fraction of the mesocarp extract of *Hyphaene thebaica* in alloxan-induced diabetic Wistar rats**.** The phytochemical analysis showed the presence of flavonoids (30%), carbohydrates (15%), alkaloids (13%), saponins (12%), glycosides (10%), cardiac glycosides (10%), and tannins (10%). Anthraquinone was not detected. Administration of 800 mg/kg body weight significantly increased ($p < 0.05$) antihyperglycemic activity and percentage weight gain in treated diabetic rats. Additionally, there was a significant increase ($p < 0.05$) in serum antioxidant enzymes: Catalase (CAT), Glutathione (GSH), and Superoxide Dismutase (SOD), with a corresponding significant decrease ($p < 0.01$) in Malonaldehyde (MDA) level in treated rats. All diabetic rats treated with n-hexane mesocarp extract showed a significant ($p < 0.05$) reduction in serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) activities. The study showed that the n-hexane fraction of the mesocarp extract of *Hyphaene thebaica* has antidiabetic and antioxidant properties and could be used to manage type 2 diabetes mellitus.

**Keywords**: Antihyperglycemic, Antioxidant enzymes, Liver enzymes, Oxidative stress, Type 2 diabetes mellitus, Wistar rats

## INTRODUCTION
Diabetes mellitus (DM) is a chronic metabolic disorder that develops due to the inability of the pancreas to make sufficient insulin, a hormone that controls blood sugar (WHO, 2016). It is undoubtedly one of the most fatal diseases in the world (WHO, 2018), characterised by abnormally elevated blood sugar levels (hyperglycemia), hyperlipidemia, and oxidative stress. It is directly responsible for sudden body weight loss (Dean and McEntyre, 2004; Oyedemi *et al.,* 2011). Blood glucose is the major type of sugar in the blood and the primary energy source. The blood transports it to all of the

body's tissues for use as energy (NIDDK, 2013). However, the condition develops from persistently high blood sugar and can affect the heart's blood vessels, eyes, kidneys and nerve cells over time (WHO, 1999). The disorder is a debilitating, multi-etiological, age-related heterogeneous metabolic illness marked by hyperglycemia, glucose intolerance, and changes in the metabolism of carbohydrates, fats, and proteins (ADA, 2014). Patients still deal with critical difficulties such as neuropathy (Shaikh and Somani, 2010), retinopathy (Schwartz and Flynn, 2007) , nephropathy (Djordjevic, 2001), hepatopathy, oxidative stress and infertility despite significant advancements in the knowledge and treatment of diabetes (Securing *et al.,* 2015; Baccetti *et al.*, 2002; Stratman and Tschoepe, 2009; Moussa, 2008; Mandel *et al.*, 2018). Epidemiologically, DM is frequently the fourth or fifth leading cause of mortality in high-income nations and the primary contributor to end-stage renal failure in many populations in both developed and developing countries (ADA, 2014; Securing *et al.,* 2015). It affects 422 million individuals worldwide and is responsible for 1.6 million deaths annually (WHO, 2023; Shaw *et al.*, 2010; Abu and Talib, 2021). In Nigeria, there are 170 million individuals living, and 3.9 million adults between the ages of 20 and 79 have been diagnosed with diabetes. By 2050, when the estimated population will have surpassed 440 million, the impact of diabetes in Nigeria will worsen. Unfortunately, a permanent cure for diabetes is not yet available. Despite significant advancements in fundamental and clinical research, it necessitates a multimodal therapeutic strategy for natural treatments (Singh *et al.,* 2012, and Chinsembu, 2019).

## MATERIALS AND METHODS

### Collection of plant material and extraction

The dried fruit of *Hyphaene thebaica* was obtained in February 2020. The seeds were authenticated by the herbarium curator in the department of botany, ABU Zaria, with voucher 03071 deposited at the Herbarium in the authors' institution (Ahmadu Bello University Zaria). The dry mesocarp of *Hyphaene thebaica* was processed into fine powder. Five hundred grams (500 g) of the powder was soaked in 2 litres of 70% methanol for about 72 hours using cold maceration and stirring intermittently to produce the extract. The extracts were filtered, and the filtrate was concentrated at 40°C andkept in a desicator for further studies.

### Preparation of n-hexane fraction

The crude mesocarp extract of *Hyphaene thebaica* was soaked in *n*-hexane in a separating funnel, shaken, and allowed to stand for phase separation into two fractions. The *n*-hexane fraction was carefully decanted after partitioning. More of the *n*-hexane solvent was added, and the same process was repeated until no further colour change was observed with *n*-hexane. The n-hexane insoluble *fraction* extract was dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution at 100 mg/ml concentration. The *n*-hexane soluble fraction was obtained and allowed to dry at room temperature to get the n-hexane fraction.

**Preliminary phytochemical screening and quantitative analysis**
The n-hexane extract of *Hyphaene thebaica* was screened and quantified for alkaloids, flavonoids, anthraquinone, tannins, saponin, glycosides, and carbohydrates according to standard methods (Harbone, 1993; Obdoni and Ochuko, 2001).

**Experimental rats**
Thirty (30) healthy male Wistar rats of weight between 150-200 g were used. They were acclimatised for two weeks under laboratory conditions maintained at 21- 25°C and humidity of 50-50% and 12 hours of light and dark cycle. The animals were kept on standard pellets, grower's mash, and water *ad libitum*.

**Induction of diabetes mellitus**
The rats were administered alloxan monohydrate intraperitoneally at 120 mg/kg. 120 mg of alloxan cannot induce diabetes to induce diabetes (Kannur *et al*., 2016). The alloxanised rats were allowed unlimited access to food and water. On the eighth day, the rats fasted for 12 hours, and the One Touch Glucometer was used to measure their blood glucose concentration. Rats with blood glucose levels above 120 mg/dl were considered diabetic and used for the definitive studies.

**Experiment design**
Following toxicity studies and establishing a safe lethal dose ($LD_{50}$) for n-hexane fraction, the experimental design was set up in a simple complete randomised design (CRD). Thirty (30) rats were randomized into six groups of five rats each.
Group 1: Normal control rats received normal saline.
Group 2: Negative control rats, diabetic rats received normal saline
Group 3: Positive control, diabetic rats, received glibenclamide (10 mg/kg body weight)
Group 4: Diabetic rats received orally 200 mg/kg n-hexane fraction
Group 5: Diabetic rats received orally 400 mg/kg n-hexane fraction
Group 6: Diabetic rats received orally 800 mg/kg n-hexane fraction

**Clinical observation**
The body weight changes and daily feed and water intake were monitored weekly.
Determination of blood glucose level
The blood sample was collected from the tail vein of the rats after an overnight fast at a weekly interval for four weeks. Each rat's fasting blood glucose levels were determined by a digital glucometer (One Touch Glucometer) according to the standard method. The results were expressed in the unit of mg/dl.

**Biochemical analysis**
On the 28$^{th}$ day of the study, antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD) activity, and reduced glutathione (GSH) were determined according to standard methods (Fridovich, 1989; Rajagopalan *et al*., 2004). Malondialdehyde (MDA) was determined according to the standard method (Atawodi, 2011). The live pathophysiological enzymes, Aspartate aminotransferase (AST) activity, was assayed by the method described by Sini *et al.,* 2006. The activity of alanine aminotransferase (ALT) was assayed according to the method described by Sini *et al.* (2006). The Randox test kit

was used to assay alkaline phosphatase (ALP) activity according to the manufacturer's instructions, as described by Sini *et al*. 2006.

**Data Analysis**

Data obtained were summarized and expressed as mean and standard error (SE). They were statistically analyzed using a one-way analysis of variance. Tukey's multiple comparisons post hoc tests were used to compare the test groups at a significance level of $p < 0.05$. Principal component analysis (PCA) was used to determine the correlation between treatment dosages, blood glucose level, weight changes, feed and fluid intake, MDA level, antioxidants, and liver enzymes.

**RESULTS**

**Table 1: Qualitative and Quantitative Phytochemical Constituents of n-Hexane Fractions of Mesocarp Methanol Extract of Hyphaene thebaica**

| Phytoconstituents | Qualitative analysis | Quantitative analysis (g/100g) |
|---|---|---|
| Alkaloids | + | 13.00% |
| Tannins | + | 10.00% |
| Flavonoids | + | 30.00% |
| Cardiac glycosides | + | 10.00% |
| Saponins | + | 12.00% |
| Glycosides | + | 10.00% |
| Carbohydrates | + | 15.00% |
| Anthraquinone | - | 0.00% |

**Key: + = present - = absent**

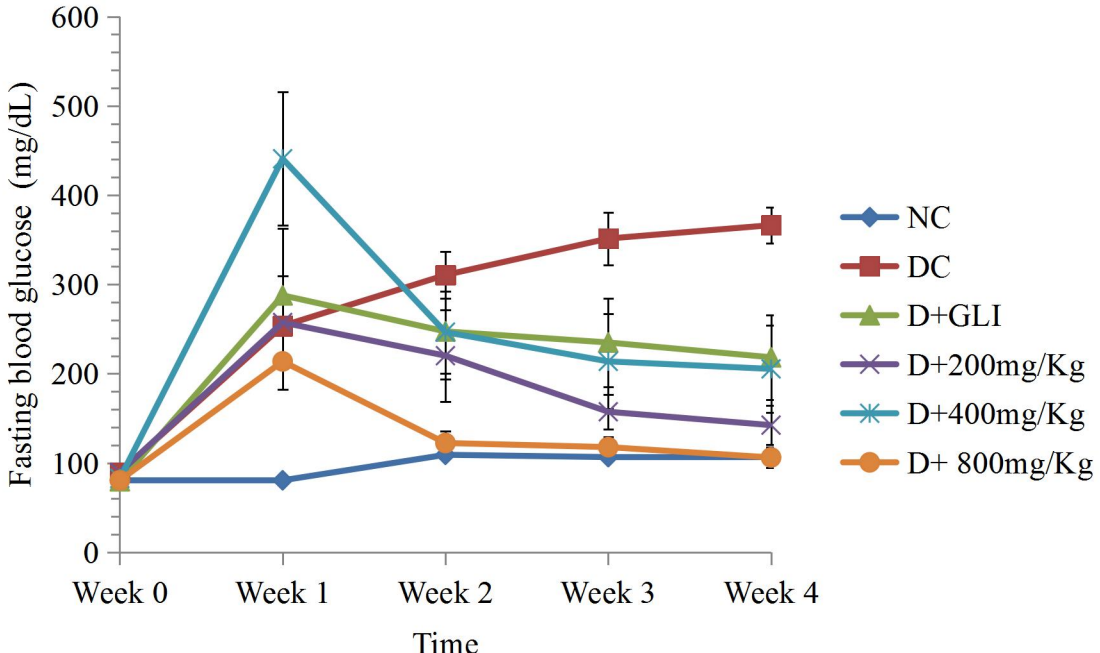

**Figure 1:** Weekly Blood Glucose Sugar Level of Control and Treated Alloxan-induced Diabetic Wistar rats.NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic GLI=Glibenclamide (standard drug) control $p < 0.05$= Significan

**Table 2: Effect of n-Hexane Fraction of Mesocarp Methanol Extract of *Hyphaene thebaica* on Weekly Body Weight of Control and Treated Alloxan-induced Diabetic Wistar Rats**

| Treatments | Week 1 | Week 2 | Week 3 | Week 4 | Percent (% ) weight gain |
|---|---|---|---|---|---|
| NC | $130\pm8.17^{c}$ | $152\pm4.25^{c}$ | $158.8\pm7.05^{c}$ | $182.2\pm11.07^{b}$ | 40.15** |
| DC | $202\pm6.83^{a}$ | $171.8\pm6.87^{bc}$ | $165.6\pm6.77^{c}$ | $159.2\pm6.94^{b}$ | -21.19 |
| D+GLI | $179.6\pm6.33^{ab}$ | $161\pm8.34^{bc}$ | $161\pm8.34b^{c}$ | $174.4\pm10.47^{b}$ | -2.90 |
| D+200mg/Kg | $198.2\pm18.29^{a}$ | $179.4\pm5.75^{b}$ | $198\pm4.62^{ab}$ | $209\pm4.11^{a}$ | 5.45* |
| D+400mg/Kg | $194.8\pm7.01^{a}$ | $204.4\pm7.51^{a}$ | $216\pm5.14^{a}$ | $227.4\pm5.89^{a}$ | 16.74* |
| D+800mgKg | $159.6\pm6.82^{b}$ | $180\pm7.15^{b}$ | $192.6\pm8.55^{b}$ | $209.6\pm7.27^{a}$ | 31.33** |
| P-value | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

Mean with different superscripts along column are significantly different ($P < 0.05$)

**Key:** NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic, GLI=Glibenclamide (standard drug) control

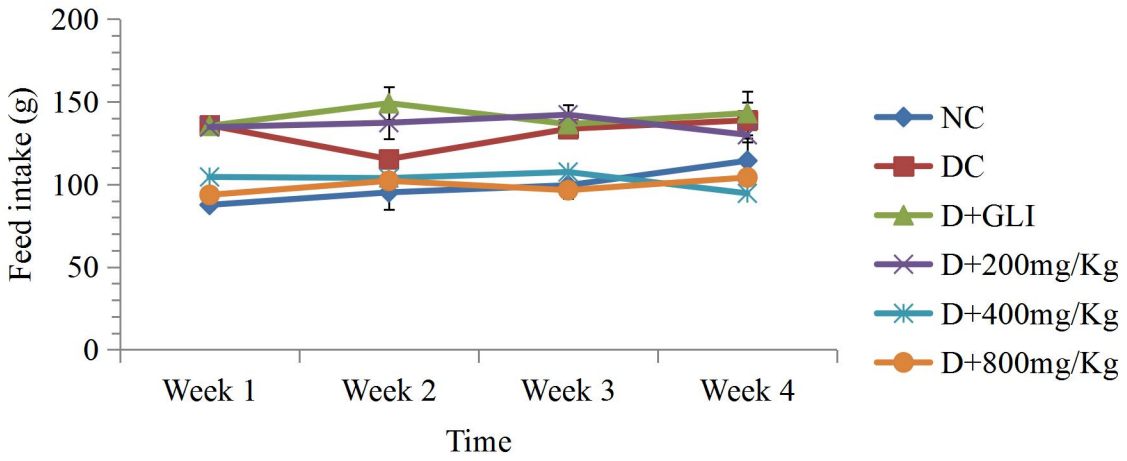


**Figure 2 (A):** Daily Feed intake among Experimental Groups**.** Key: NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic, GLI=Glibenclamide (standard drug) control

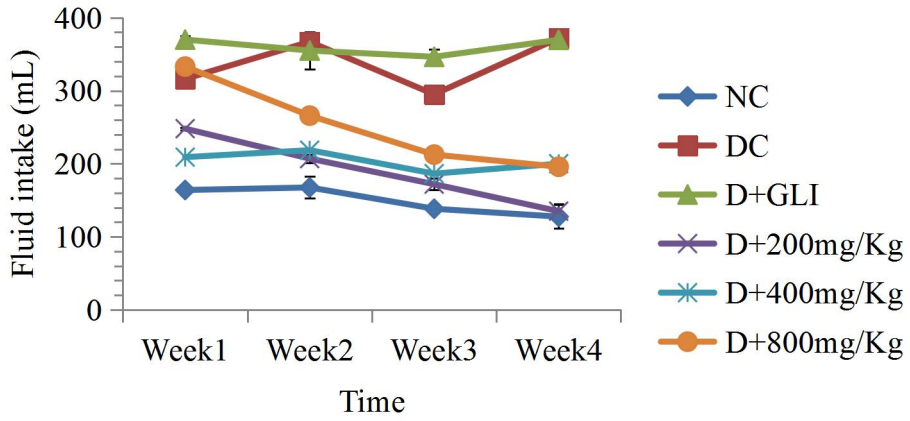


**Figure 2 (B):** Daily Fluid intake among Experimental Groups. Key: NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic, GLI=Glibenclamide (standard drug) control

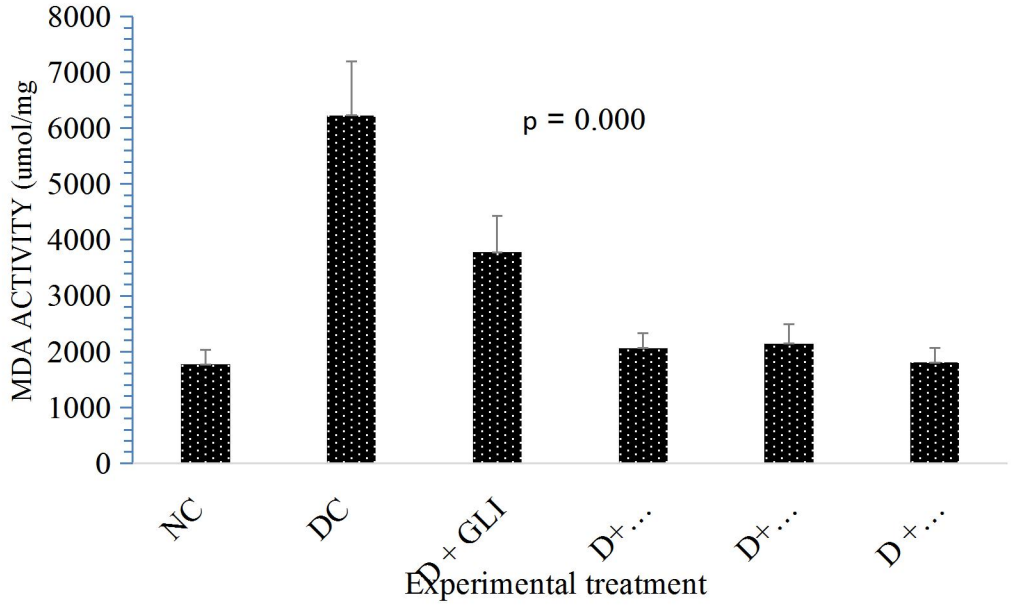


**Figure 3:** Level of Malondialdehyde Activity among the Experiment Groups

Key: MDA = Malonaldehyde (index for measuring Lipid peroxidation)

NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic

GLI=Glibenclamide (standard drug) control $p < 0.05$ =Significant

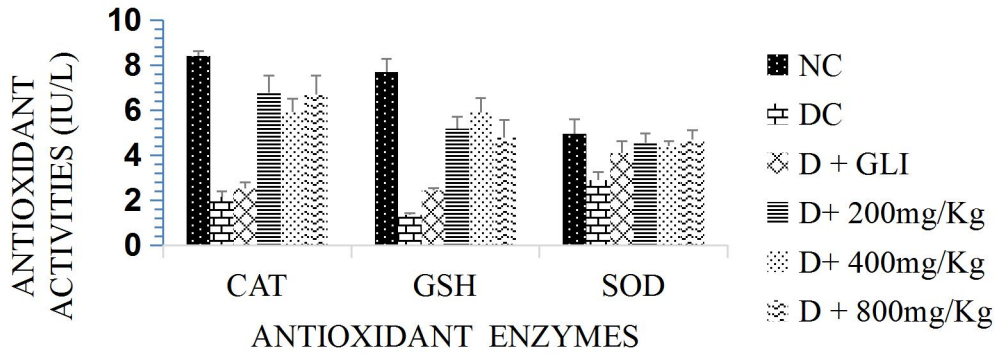


**Figure 4: Level of Antioxidant Enzymes Activities among the Experimental Groups**

**Key:** CAT = Catalase, GSH = Glutathione, SOD = Superoxide Dismutase, NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic GLI=Glibenclamide (standard drug) control P< 0.05 =Significant

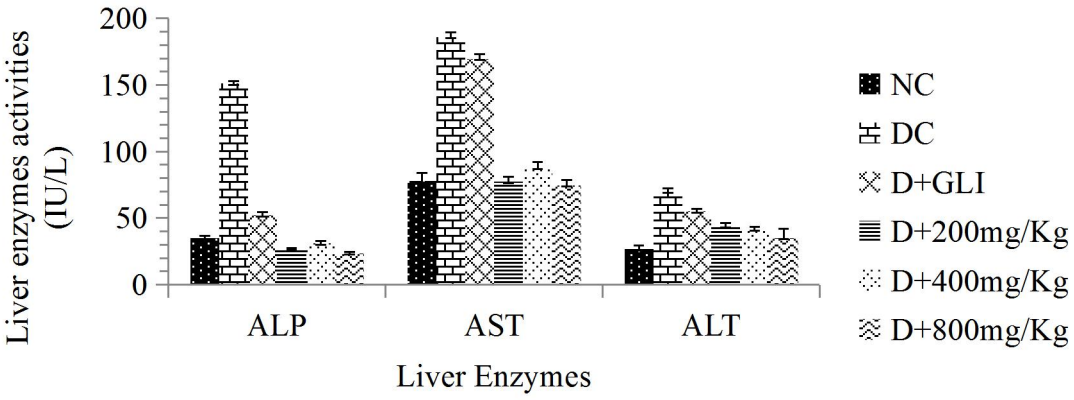


**Figure 5:** Level of Liver Pathophysiological Enzymes Indices among the Experimental Groups

**Key:** ALP = Alkaline phosphatase, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase NC= Normal non-diabetic control, DC= Diabetic non-treated control, D= Diabetic GLI=Glibenclamide (standard drug) control

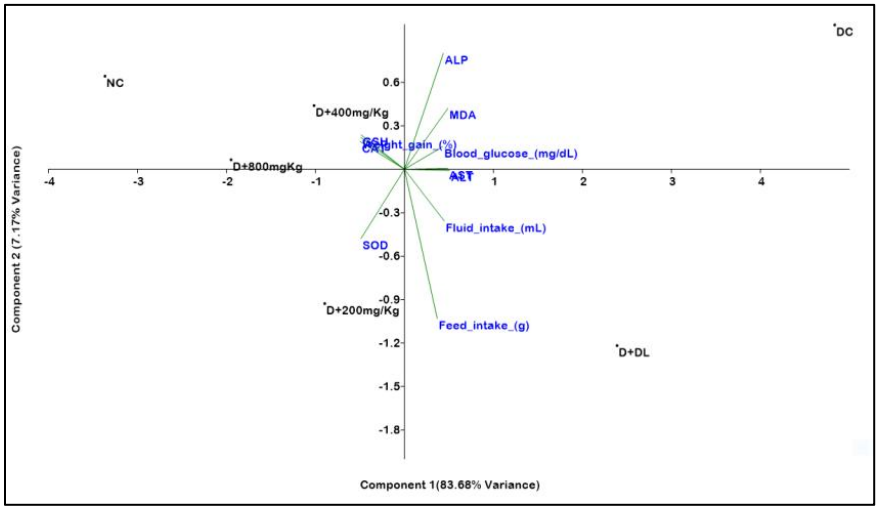


**Figure 6:** Multivariate Based PCA Correlation Biplots of Administration dosages of n-hexane mesocarp extract of *Hyphaene thebaica*, blood glucose level, percent weight gain, feed intake, fluid intake, MDA activity, antioxidant enzymes activities (CAT, SOD, GSH), liver enzyme activities (ALP, AST, ALT)

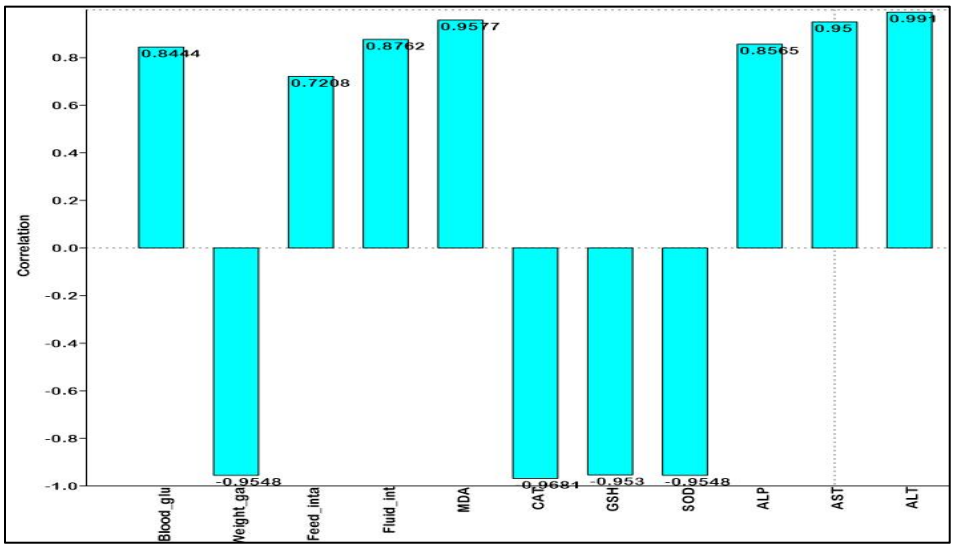


**Figure 7:** PCA Correlation Loadings of Administration dosages of n-hexane mesocarp extract of *Hyphaene thebaica*, Blood Glucose Level, Percent Weight Gain, Feed intake, Fluid intake, MDA activity, Antioxidant Enzymes Activities (CAT, SOD, GSH), Liver Enzyme Activities (ALP, AST, ALT).

## DISCUSSION

The doum plant, *Hyphaene thebaica,* is a tropical fruit traditionally used to treat diabetes mellitus but lacks scientific validation. This study was carried out to assess the antidiabetic and antioxidant properties of the n-hexane fraction of the mesocarp extract of *Hyphaene thebaica* in alloxan-induced diabetic Wistar rats**.** In the current study, bioactive constituents that give insights into the biologically active nature of the plant

were analyzed. Results confirmed the existence of essential phytoconstituents, including alkaloids, tannins, flavonoids, saponins, cardiac glycosides, glycosides, and carbohydrates. However, anthraquinone was absent. The presence of alkaloids, tannins, flavonoids, saponins, cardiac glycosides, glycosides, and carbohydrates has antioxidant and antidiabetic properties (Warjeet, 2011, Dias *et al*., 2005, and Lukacinova, 2008). Alkaloids and flavonoids have been isolated to treat endocrine system diseases, especially diabetes (Abu- odeh and Talib, 2021, and Abulazeez *et al.,* 2019). The preliminary oral toxicity study of the extract had an LD50 higher than 5000 mg/kg body weight, indicating that the extract is non-toxic and has a high safety margin when administered in Wistar rats. Shehu *et al*., (2017) reported the fruit pulp of *Hyphaene thebaica* to be non-toxic even at a higher oral dose of 5000 mg/kg body weight in Wistar rats.

The higher reduction in blood glucose in all treated diabetic rats implies that the mesocarp extract of *Hyphaene thebaica* has antihyperglycemic properties and can reverse type 2 diabetes within four weeks of administration. This antihyperglycemic property can be attributed to alkaloids and flavonoids, as studies have shown that flavonoids have antihyperglycemic effects and prevent renal glucose uptake by inhibiting sodium-glucose symporters in the proximal renal convoluted tubule (Lukacinova, 2008; Hungo *et al.,* 1998; and Mahler, 1995). This result is in tandem with findings by Bayad (2016), who reported that giving *Hyphaene thebaica* extract orally significantly decreases blood glucose. Similarly, observations were made in related studies in alloxan-induced diabetic rodents (Loew and Kaszkin, 2002, Dias et al., 2005 and Mard *et al.,* 2010). On the other hand, alkaloids' antidiabetic and antioxidant activities in blood glucose pathogenesis are mediated through various pathways, including inhibiting the β-glucosidase enzyme, improving insulin sensitivity, and moderating oxidative stress (Mahler *et al*., 1995 andAjebli *et al.,* 2021).

The weight loss in diabetic rats was reversed to a considerable extent following four weeks of oral administration of n-hexane mesocarp extract of *Hyphaene thebaica*. This finding is suggestive that mesocarp extract of *Hyphaene thebaica* can regulate glucose levels and diabetes-related muscular atrophy and adipogenesis (Shenoy and Ramesh, 2002). This finding conformance with a similar study by Oyedemi *et al.* (2011). Even though substantial increases were seen in feed and fluid intakes for the diabetic non-treated rats, these increases did not result in weight gain. Instead, a substantial weight loss was detected in this group.

In contrast, the non-treated diabetic rats had significant and progressive weight loss. This could be attributed to the mechanism of action of alloxan, which causes autoimmune destruction of pancreatic beta-cells and has been related to the breakdown of structural proteins, muscle wasting, and decreased body weight (Thulesen *et al.,* 1997 and Rajkumar et al., 2005). Increased feed and fluid intake in non-treated diabetic rats is associated with type 2 DM and is a direct consequence of inadequate insulin (Leow and Kaszkin, 2002 and Swantson *et al.,* 1990). Higher blood sugar level in diabetic rats leads to a rise in osmotic diuresis, which results in large amounts of urine output, which could explain the increased water consumption of diabetic rats. Hunger and thirst are coping mechanisms for losing fluid and being unable to use nutrition (Lawrence, 1998).

After administering *Hyphaene thebaica* extract, the feed and fluid intake decreased considerably.

Elevated Malondialdehyde (MDA) levels in all diabetic rats indicate oxidative stress, a characteristic feature of diabetes mellitus. MDA level measures lipid peroxidation (Rajaskaran *et al.,* 2005 and Haggard, 1968) and is frequently used to predict increased oxidative stress and subsequent oxidative damage (Hauggard, 1968). Like many chronic diseases, the metabolic problems of diabetes cause the mitochondria to make too much superoxide in several tissues, including the endocrine pancreas. This activates pathways involved in the emergence of the issues and increases the production of reactive oxygen species (ROS) within cells (Giacco and Brownlee, 2012). ROS appear to be causative agents in the pathogenesis of diabetes due to their cell-damaging effects. However, excessive ROS elimination may result in metabolic dysfunction and susceptibility to diabetes (Abu- odeh and Talib, 2021). Interestingly, the level of MDA in diabetic rats was reversed after administration of an n-hexane fraction of the mesocarp extract of Hyphaene *thebaica*.

Another fascinating property of the *Hyphaene thebaica* mesocarp extract established in this study is its antioxidant capability. Decreased activities of antioxidant enzymes have been well documented during diabetic mellitus (Rajaskaran 2005, Sugiura, 2006). Interestingly, there were a significant increase in catalase (CAT) and superoxide dismutase (SOD) activities after administration of the n-hexane *Hyphaene thebaica* mesocarp extract. The antioxidant properties of *Hyphaene thebaica* is attributed to the high amount of flavonoid, which is reported to possess scavenging ability of free radicals via inhibition of enzymatic pathways responsible for free radical generation. It is known that phenolic compounds act as antioxidants and inhibit lipid oxidation by scavenging radicals (Huyut *et al.,* 2017). These results conform to other similar studies (Abdulazeez et al*.,* 2019). Glutathione (GSH) is a tripeptide essential in detoxifying and metabolising many xenobiotics and endobiotic compounds,The significant decrease in GSH in the diabetic non-treated rats compared with the standard control was reversed after administering the *Hyphaene thebaica* for four weeks. The effect was dose-dependent and in line with the reports of previous studies. The results of these antioxidants may help delay the complications of associated with type 2 DM**.**

The liver is the major organ in the body and plays a significant role in controlling glucose homeostasis. Liver enzymes, including serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST), are critical indicators for detecting liver dysfunction and have been demonstrated as good indicators for monitoring the liver's health and to be related with hepatic insulin resistance and the risk of type 2 diabetes. High levels of serum liver enzymes such as ALT and AST in non-treated diabetic rats indicate necrosis or damage to the liver cells. However, the group treated with the *Hyphaene thebaica* mesocarp extracts showed significantly reduced serum ALT, ALP and AST levels. The reduction in levels of these enzymes following the administration of the extracts was statistically equal to that of the standard drug (Glibenclamide) administered group, and this implies that the extract of *Hyphaene thebaica* is very effective in treating liver pathology associated with type 2 DM, and this agrees with the findings of Bayad  and Al-Masri and Riyadh.

## CONCLUSION

The study showed that the active compounds in the n-hexane fraction of the mesocarp extract of *Hyphaene thebaica* have antidiabetic and antioxidant prospects for managing type 2 diabetes mellitus and can be utilised as an antihyperglycemic, anti-weight loss, and antihyperlipidemic agent at an optimum dosage 800 mg/Kg body weight. However, further studies should be carried out for clinical evaluation.

## CONFLICTS OF INTREST

The authors declare no conflicts of interest

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