PRINT ISSN 1119-8362
Electronic ISSN 1119-8362

Full-text Available Online at
https://www.ajol.info/index.php/jasem
http://ww.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 23 (9) 1631-1636 September 2019

Comparative Assessment of Methanolic Extracts of Hog Plum (*Spondias mombin* linn.) Leaves and Turmeric (*Curcuma longa* L.) Rhizomes on Blood Glucose and Glycosylated Haemoglobin in Male Wistar Rats

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ABSTRACT: Comparative assessment of methanolic extracts of S*pondias mombin* leaves and C*urcuma longa* rhizomes on Blood Glucose and Glycosylated Haemoglobin using male wistar rats as models was attempted. 90 rats divided into 9 groups of 10 rats each were used. Groups: 1: Untreated non diabetic; 2: Untreated diabetic; 3: diabetic + low dose (200mg/kg/b.w) *Spondias mombin*; 4: diabetic + high dose (400mg/kg/b.w) *Spondias mombin*; 5: diabetic + low dose (500mg/kg/b.w) C*urcuma longa*; 6: diabetic + high dose (1000mg/kg/b.w) C*urcuma longa*; 7: diabetic + low dose combined (200mg/kg/b.w) S*pondias mombin* and (500mg/kg/b.w) Curcuma longa; 8: diabetic + high dose combined (400mg/kg/b.w) S*pondias mombin* and (1000mg/kg/b.w) C*urcuma longa*; and diabetic + (0.6mg/kg/b.w) glibenclamide. Diabetes was induced intraperitonially using alloxan at 200mg/kg. Treatments with extracts were orally and for 42days. Blood was collected on day 43 by cardiac puncture for determination of blood glucose and glycosylated haemoglobin. A significant decrease in blood glucose and glycosylated haemoglobin concentrations was observed in all the treated groups compared to group 2 ($p< 0.05$). Groups 7 and 8 rats showed a significant reduction in blood glucose and glycosylated haemoglobin compared to groups 3 to 6 ($p< 0.05$). S*pondias mombin* apparently showed better anti-diabetic effects compared to C*urcuma longa* as seen amongst Groups 3 and 4 rats compared to Groups 5 and 6 rats. Result suggest that combined treatment with S*pondias mombin* and C*urcuma longa* may possess better anti-diabetic effects compared to administration of each singly. We recommend further studies in this regard.

DOI: https://dx.doi.org/10.4314/jasem.v23i9.4

Dates: Received: 09 August 2019; Revised: 11 September 2019; 22 September 2019

Keywords: S*pondias mombin,* c*urcuma longa,* diabetes mellitus, alloxan

On account of poor dietary habits, a sedentary life style and increasing worldwide prevalence of obesity, diabetes mellitus is rapidly emerging as a global health challenge threatening to reach pandemic proportion by 2030 (WHO, 2008). In developing countries, the increased incidence of diabetes has been ascribed to dietary and lifestyle changes with the associated shift from the relatively healthy traditional lifestyle to an unhealthy lifestyle (Godfrey and Julien, 2005). Epidemiologists predict that 70% of Africans will live in cities by 2025; invariably increasing the number of Africans at risk for diabetes (IDF, 2014). In 2014, the worldwide prevalence of diabetes was estimated at 8.3% (approximately 382 million adults) with an estimated 46% of undiagnosed; projected to increase to 53% (approximately 592 million adults) by 2035 (IDF, 2014). Predictably, this poses an economic burden on developing countries currently estimated at over USD 372 billion per annum (Oguejiofor *et al*., 2014).

Management of diabetes with minimal side effects is still a challenge to the medical profession. Commonly used synthetic anti-diabetic agents could produce side effects such as hypoglycemic coma and hepatorenal disturbances and are generally not indicated in pregnancy (Gupta *et al*., 2007; Atta-Ur-Rahman and Zaman, 1989). Therefore, the search for safer and perhaps more effective anti-diabetic agents is an ongoing challenge. It is estimated that 80% of the world's populations rely upon plants for their health needs (Abo *et al*., 2008; Li *et al*., 2004). *Spondias mombin* Linn (Anarcadiaceae) commonly known as 'hog plum,' is a deciduous tree with large panicles of small white flowers and yellow plum-like fruits (Gbile and Soladoye, 2002). It is common in farmlands and villages especially in the forest and savannah regions. In traditional folklore medicine, *Spondias mombin* leaves are used as an emetic and for treatment of gonorrhoea, diabetes and psychiatric disorders; (Oliver-Bever, 1960) it is also useful for the expulsion of the placenta in goats;(Oliver-Bever, 1960) as an astringent; (Oliver-Bever, 1960; Abo *et al*., 1999) an oxytocic agent; (Ayensu, 1978) and in wound treatment (Oliver-Bever, 1960). *Curcuma longa*

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(Linn) commonly known as turmeric is an erect perennial herb with pulpy orange tuberous roots that grows to about 2 feet in length (Gopinathan *et al*., 2011; Sawant and Godghate, 2013). It belongs to the family Zingiberaceae**.** Its rhizome is pungent with a bitter taste and widely used in indigenous medicine as a general household remedy and a cooking spice (Gopinathan *et al*., 2011; Aggarwal *et al*., 2005). It has been reported beneficial for the treatment of diabetes, high cholesterol, abdominal pains, menstrual disorders, wounds, eczema, jaundice, inflammation, cancer symptoms and as a blood purifying agent (Sawant and Godghate, 2013). The herb contains curcumin as an active ingredient, which is a yellow colored phenolic pigment obtained from the powdered rhizome. Reports on the anecdotal use of both plants singly or in combination as potential treatment of diabetes have recently become widespread in our environment. These anecdotal reports have been fairly validated by a recent report describing the possible anti-diabetic activity of the aqueous extract of *Curcuma longa* rhizomes in alloxan induced diabetic rats (Olatunde *et al*., 2014). The present study therefore, presents a preliminary report of a comparative assessment of the anti-diabetic effects of methanolic extracts of S*pondias mombin* leaves and C*urcuma longa* rhizomes in alloxan-induced diabetes using male wistar rats as models. This is with the aim of validating and further determining the anti-diabetic potentials of the methanolic extract of each plant either singly or in combination.

MATERIALS AND METHODS

Plant materials and extract preparation: Fresh leaves of *Spondias mombin* were obtained from the University of Port Harcourt botanical garden; while *Curcuma longa* rhizomes were obtained from a local market in Rivers state, Nigeria. Both plant specimens were identified and authenticated by Dr. C. Ekeke of the Department of Plant Science and Biotechnology, University of Port Harcourt, Nigeria. Voucher specimens of both plants were deposited in the herbarium. The research protocol for the study was approved by the Ethics Committee of our institution vides a communication referenced: UPH/R&D/REC/04 and dated 3rd July, 2018. This study was conducted in accordance with the guidelines for the care and use of laboratory animals issued by the United States Institute for Laboratory and Animal Research (1996).

Leaves of S*pondias mombin* were dried at room temperature for a minimum of 14 days and extracted using the percolation method as described by Fred-Jaiyesimi and Abo, 2009. Briefly, the S*pondias mombin* leaves were grounded into powder; subsequently, 8.8kg was properly macerated with 98% methanol for three days and the percentage yield was 93%. It was then filtered and concentrated using rotary evaporator at 40°C. The obtained extract was kept in air tight containers and stored at room temperature before use. Rhizomes of *Curcuma longa* were oven dried at 40°C for 72 hours to a constant weight. The dried rhizomes were then pulverized using a household blender. 7.5g of the powder obtained was dissolved in 98% methanol for about two days and the percentage yield was 96%. The extraction procedure employed was percolation as described by Olatunde *et. al.*, 2014.

Experimental animals and drugs: 90 male wistar rats weighing between 120-250g were used for this study. The animals were kept at the Animal House, Department of Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, Nigeria. The rats were fed with normal rat pellet and tap water *ad libitum*. The experimental animals were acclimatised for a period of two weeks after which they were properly grouped. Alloxan monohydrate was obtained from Sigma-Aldrich Co., 3050 Spruce Street, St. Louis, USA. While glibenclamide was obtained from Swiss Pharm Nigeria Ltd, 5, Dopemu Road, Agege, Lagos, Nigeria.

Acute toxicity study (LD_{50}): The LD_{50} value of the leaf extract of *Spondias mombin* was assumed to be greater than 1000mg/kg bw as reported by Olatunde *et. al.,* (2014). Similarly, the LD_{50} value of the methanol extract of *Curcuma longa* rhizomes was regarded as the value obtained by Yuandani, (2017) which was reported to be greater than 5000mg/kg bw.

Experimental design: The rats were subsequently randomly divided into 9 groups of 10 each. Diabetes was induced in all rat groups except Group 1 using alloxan at a dose of 200mg/kg bw administered intraperitonially. Diabetes was confirmed after 72 hours of alloxan administration if the blood glucose is ≥ 11.1 mmol/L (200mg/dl) (Stanley Mainzen Prince and Menon, 2001). Each rat group was subsequently treated as follows:

Group 1: untreated non-diabetic; rats in this group had free access to only normal rat chow and tap water *ad libitum*.

Group 2: untreated diabetic; rats in this group received no further treatment after induction of diabetes.

Group 3: diabetic + low dose *Spondias mombin;* rats in this group were treated with 200mg/kg bw of *Spondias mombin* extract daily after the induction of diabetes.

Group 4: diabetic + high dose *Spondias mombin;* rats in this group were treated with 400mg/kg bw of

Spondias mombin extract daily after the induction of diabetes.
Group 5: diabetic + low dose *Curcuma longa;* rats in this group were treated with 500mg/kg bw *Curcuma longa* extract daily after the induction of diabetes.
Group 6: diabetic + high dose *Curcuma longa*; rats in this group were treated with 1000mg/kg bw *Curcuma longa* extract daily after the induction of diabetes.
Group 7: diabetic + combined low doses of *Spondias mombin* and *Curcuma longa*; rats in this group were treated with both 200mg/kg bw of *Spondias mombin* and 500mg/kg bw of *Curcuma longa* extracts daily after the induction of diabetes.
Group 8: diabetic + combined high doses of *Spondias mombin* and *Curcuma longa*; rats in this group were treated with both 400mg/kg/bw of S*pondias mombin* and 1000mg/kg bw of C*urcuma longa* extracts daily after the induction of diabetes.
Group 9: diabetic + glibenclamide; rats in this group were treated with 0.6mg/kg bw of glibenclamide daily after the induction of diabetes.
The glibenclamide and the extracts of *Spondias mombin* and *Curcuma longa* were administered daily using an oro-gastric cannula for 42 days. On day 43, blood was collected by direct cardiac puncture for determination of blood glucose concentration and glycosylated haemoglobin.

Determination of blood glucose concentration and glycosylated haemoglobin: Blood glucose concentration was estimated using the method described by Das *et al*., (2012). During the course of the study, blood glucose concentration was determined thrice: firstly, prior to administration of alloxan to induce diabetes (Day 0); secondly, 72 hours after administration of alloxan (Day 3; to confirm diabetic rats subsequently used for the study); and thirdly, at the end of study (Day 46). Glycosylated haemoglobin was also determined at the end of study (Day 46) using the method described by Kovatchev *et al*., (2000).

Statistical analysis: Results are as presented in Table 1 and expressed as means ± standard error of means. Significant differences were determined using the one-way ANOVA; differences between groups were determined using LSD Post Hoc test. A p value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Effect of methanolic extract of Spondias mombin leaves and Curcuma longa rhizomes on blood glucose: Table 1 shows the effect of methanolic extract of *Spondias mombin* leaves and *Curcuma longa* rhizomes on blood glucose concentration in male wistar rats. Compared to Group 2 (untreated diabetic) rats, administration of extracts of *Spondias mombin* significantly reduced blood glucose in a dose dependent manner amongst Group 3 and 4 rats ($p< 0.05$). This effect of *Spondias mombin* is comparable to the effect of administration of glibenclamide observed amongst Group 9 rats. Although the post-treatment blood glucose concentration following the administration of *Spondias mombin* at both doses were significantly higher than the post-treatment blood glucose concentration following the administration of glibenclamide; the percentage reduction (-33.33%) observed for *Spondias mombin* at a (high) dose of 400mg/kg bw amongst Group 4 rats was marginally lower than that observed for glibenclamide (-29.13%) amongst Group 9 rats. Perhaps suggesting a greater potency of methanolic extract of *Spondias mombin* compared to glibenclamide. Furthermore, a comparison of the percentage reduction in blood glucose concentration at both low and high doses suggests that *Spondias mombin* is perhaps of marginally higher potency compared *Curcuma longa*; differences in blood glucose concentration was found to be significant ($p<0.05$). By comparison, *Curcuma longa* extract at both low and high doses also caused a significant and dose dependent reduction in the blood glucose concentration amongst Groups 5 and 6 rats respectively as compared to Group 2 (untreated diabetic) rats ($p< 0.05$). This effect of *Curcuma longa* is also comparable to the effect of administration of glibenclamide amongst Group 9 rats. However, the percentage reduction in blood glucose concentration caused by *Curcuma longa* at high dose (-28.36%) is marginally higher than that of glibenclamide (-29.13%); furthermore, these differences in blood glucose concentration were observed to be significant ($p<0.05$). The combined administration of both extracts amongst Groups 7 and 8 rats, also caused a significant and dose dependent reduction in blood glucose concentration compared to both Group 2 (untreated diabetic) and Group 9 (glibenclamide treated) rats ($p< 0.05$). Noteworthy, the reduction observed in blood glucose concentration following the combined administration of both extracts is greater than the reduction observed following the single administration of either extract: apparently suggesting either a possible additive or indeed a synergistic effect of both extracts on blood glucose concentration.

Effect of methanolic extract of Spondias mombin leaves and Curcuma longa rhizomes on glycosylated haemoglobin: Table 1 also shows the effect of methanolic extract of S*pondias mombin* leaves and C*urcuma longa* rhizomes on glycosylated haemoglobin levels in male wistar rats. Compared to Group 2 (untreated diabetic) rats, administration of S*pondias mombin* extract significantly reduced glycosylated haemoglobin in a dose dependent manner

amongst Groups 3 and 4 rats ($p< 0.05$); this is similar to the effect of glibenclamide administration as seen amongst Group 9 rats ($p< 0.05$). Similarly, administration of *Curcuma longa* extract caused a significant and dose dependent reduction in glycosylated haemoglobin amongst Groups 5 and 6 rats compared to Group 2 (untreated diabetic) rats ($p< 0.05$). The combined administration of both extracts also caused a significant and dose dependent reduction in glycosylated haemoglobin amongst Groups 7 and 8 rats compared Group 2 (untreated diabetic) rats ($p< 0.05$). However, at low doses of both extracts, significant differences were not observed for glycosylated haemoglobin amongst Group 3 and Group 5 rats ($p>0.05$).

Table 1: Effects of methanolic extracts of *Spondias mombin* leaves and *Curcuma longa* rhizomes on blood glucose concentration and glycosylated haemoglobin

.	Pre-treatment blood glucose (mmol/l)	Post treatment blood glucose (mmol/l)	Percentage difference in blood glucose concentration	Glycosylated haemoglobin concentration (%)
Group 1: Untreated non-diabetic	4.74 ± 0.06	4.79 ± 0.03	1.05	3.56 ± 0.01
Group 2: Untreated diabetic	17.73 ± 0.05	23.50 ± 0.07^{b}	32.54	9.17 ± 0.01^{b}
Group 3: Diabetic + low dose *Spondias mombin*	19.47 ± 0.06	15.57 ± 0.04^{ab}	-20.03	7.72 ± 0.21^{ab}
Group 4: Diabetes + high dose *Spondias mombin*	20.64 ± 0.03	13.76 ± 0.04^{ab}	-33.33	5.16 ± 0.09^{a}
Group 5: Diabetes + low dose *Curcuma longa*	17.98 ± 0.07	14.64 ± 0.03^{ab}	-18.58	7.82±0.01^{ab}
Group 6: Diabetes + high dose *Curcuma longa*	20.59 ± 0.05	14.75 ± 0.03^{ab}	-28.36	5.34±0.01^{a}
Group 7: Diabetes + combined low doses of *Spondias mombin* and *Curcuma longa*	17.46 ± 0.01	10.92 ± 0.02^{ab}	-37.46	4.83±0.02^{a}
Group 8: Diabetes + combined high doses of *Spondias mombin* and *Curcuma longa*	19.54 ± 0.02	5.74 ± 0.02^{ab}	-70.62	3.94±0.007^{ab}
Group 9: Diabetes + glibenclamide	17.85 ± 0.06	12.65 ± 0.08^{a}	-29.13	5.06±0.01^{a}

^{a} = significant difference compared to Group 2 ($p<0.05$); ^{b}= significant difference compared to Group 9 ($p<0.05$)

The present study is essentially a comparative assessment of the anti-diabetic potentials of methanolic extracts of *Spondias mombin* leaves and *Curcuma longa* rhizomes in alloxan induced diabetes using male wistar rats as models. Despite differences in methods of extraction, the results of our study validate a recent report on the anti-diabetic effects of the aqueous extract of *Curcuma longa* rhizomes in alloxan induced diabetic rats (Olatunde *et al*., 2014). The significant reduction in blood glucose concentration due to administration of each extract clearly suggests that these extracts possess possible hypoglycaemic properties; indicating a potential beneficial effect in alloxan induced diabetes. Expectedly, the effects of both extracts are similar to that of glibenclamide a popular anti-diabetic agent. However, the precise mechanism of interaction of both extracts in the reduction of blood glucose in alloxan induced diabetes is presently unclear. Our results suggest that apparently, at low doses both extracts exhibit some additive effects; whereas a synergism is noticeable at higher doses. Comparatively, the blood glucose of rats administered *Spondias mombin* leaves was significantly lower than those administered *Curcuma longa* rhizomes at both doses; suggesting perhaps a greater hypoglycaemic effect of *Spondias mombin* compared to *Curcuma longa.*

Phytochemical screening of both plants has shown the presence of several compounds including: triterpenoid, glycosides, flavonoids, tannins, curcumin and sterols compounds (Okwu, 2001; Reher *et al*., 1991; Kako *et al*., 1997; Grundy *et al.,* 1969; Lees *et al*., 1977). These compounds have been shown to play a contributory role in ameliorating complications associated with diabetes (Xi, 2007). The possible mechanism of action of these compounds in reducing blood glucose include: stimulation of insulin from residual beta cells; (Xi, 2007; Youn *et al*., 2004) enhancement of glucose transport to body tissues; (Youn *et al*., 2004; Okonkwo and Okoye, 2009) and inhibition of gastrointestinal absorption of glucose (Luka and Tijjani, 2013; Bajaj and Srinivasan, 1999; Pari *et al*., 2001).

The results obtained following administration of both extracts shows a significant reduction in glycosylated haemoglobin. Compared with Group 2 (untreated diabetic) rats, all treatment groups exhibited a decrease in glycosylated haemoglobin suggesting that extracts of *Spondias mombin* leaves and *Curcuma*

longa rhizomes could possibly ameliorate the long-term consequences of hyperglycaemia. The glycosylated haemoglobin of rats administered low dose S*pondias mombin* leaves was however, not significantly different from those administered low dose *Curcuma longa* rhizomes. This finding suggest that no differences exist between *Spondias mombin* leaves and *Curcuma longa* rhizomes with respect to glycosylated haemoglobin values; this is at variance with the effect of both extract on blood glucose concentration described above. Perhaps observable differences in glycosylated haemoglobin values require a longer time frame to manifest in our experimental models. Notably, the effect of the combined administration of both extracts on glycosylated haemoglobin is greater than the effect of single administration of either extract.

In conclusion, this study reports that methanolic extracts of *Spondias mombin* leaves and *Curcuma longa* rhizomes administered either singly or in combination caused a dose dependent reduction in blood glucose concentration and glycosylated haemoglobin in alloxan induced diabetes in male wistar rats. Apparently, *Spondias mombin* leaves possessed greater anti-diabetic properties compared to *Curcuma longa* rhizomes; the effects of the combined administration are greater than the single administration of either extract and comparable to glibenclamide effects.

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