Anti-diabetic effect of Jobelyn® Dietary Supplement on alloxan-induced diabetic rats and molecular docking of its bioactives

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DOI: https://doi.org/10.82351/wajp.vol36no2.413

ABSTRACT

Background: Jobelyn®, containing *Sorghum bicolor* extract, is promoted as an anti-inflammatory and antioxidant supplement.

Objectives: This study explored the binding of Jobelyn's bioactive compounds to sulfonylurea receptor 1 and its in vivo anti-diabetic potential in rats.

Methods: Molecular docking of the bioactive constituents in Jobelyn® was done to evaluate potential interactions. Thirty alloxan-induced diabetic rats (110-180 g) were divided into five groups (n=6) treated with glibenclamide (0.5 mg/mL), Jobelyn® water extract, 99 % v/v ethanol extract, or 70 % v/v aqueous ethanol extract (25 mg/kg), and one diabetic control group took water. A sixth, non-diabetic group received saline. After 21 days, the blood and pancreas were histologically examined.

Results: Quercetin showed the strongest sulfonylurea receptor 1 (SUR1) binding (-9.7 kcal/mol), followed by luteolin and proanthocyanidin, surpassing glibenclamide (-8.1 kcal/mol). All Jobelyn® extracts lowered blood glucose, with 99 % ethanol showing the highest (84 %) and 70 % aqueous ethanol demonstrating the fastest effect. Biochemical and histological profiles also improved.

Conclusion: Jobelyn® showed significant antidiabetic activity at 25 mg/kg, with 70% v/v aqueous ethanol extract showing the fastest response.

Keywords: Jobelyn®, alloxan monohydrate, *in vivo, in-silico,* and anti-diabetic.

Effet antidiabétique du complément alimentaire Jobelyn® sur les rats diabétiques induits par l'alloxane et ancrage moléculaire de ses composés bioactifs

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RÉSUMÉ

Contexte: Jobelyn®, contenant de l'extrait de Sorghum bicolor, est présenté comme un complément alimentaire anti-inflammatoire et antioxydant.

Objectifs: Cette étude a exploré la liaison des composés bioactifs de Jobelyn au récepteur 1 de la sulfonylurée et à son potentiel antidiabétique in vivo chez le rat.

Méthodes: L'ancrage moléculaire des composants bioactifs de Jobelyn® a été réalisé afin d'évaluer les interactions potentielles. Trente rats diabétiques induits par l'alloxane (110-180 g) ont été répartis en cinq groupes (n = 6) traités avec du glibenclamide (0,5 mg/mL), un extrait aqueux de Jobelyn®, un extrait éthanolique à 99 % v/v ou un extrait éthanolique aqueux à 70 % v/v (25 mg/kg), et un groupe témoin diabétique a reçu de l'eau. Un sixième groupe, non diabétique, a reçu une solution saline. Après 21 jours, le sang et le pancréas ont été examinés histologiquement.

Résultats: La quercétine a montré la plus forte liaison au récepteur de sulfonylurée 1 (SUR1) (-9,7 kcal/mol), suivie de la lutéoline et de la proanthocyanidine, surpassant le glibenclamide (-8,1 kcal/mol). Tous les extraits de Jobelyn® ont abaissé la glycémie, l'éthanol à 99 % affichant l'effet le plus élevé (84 %) et l'éthanol aqueux à 70 % démontrant l'effet le plus rapide. Les profils biochimiques et histologiques se sont également améliorés.

Conclusion: Jobelyn® a montré une activité antidiabétique significative à 25 mg/kg, l'extrait d'éthanol aqueux à 70 % v/v présentant la réponse la plus rapide.

Mots-clés: Jobelyn®, monohydrate d'alloxane, in vivo, in silico et antidiabétique.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, which, left uncontrolled, can impair the eyes, kidneys, nerves, blood vessels, and heart. Over 90-95 % cases of diabetes are type 2 (T2DM), a disorder involving insulin resistance and impaired secretion by pancreatic β-cells. Dysfunction in major organs like the adipose tissue, liver, muscle, and pancreas is linked to T2DM and is influenced by gut microbiota imbalance, immune disruption, and inflammation.[1,2,3]

The global incidence of diabetes is increasing. In 2019, 4.2 million deaths occurred and 463 million adults were affected, a figure forecasted to reach 700 million by 2045. Global prevalence is anticipated to rise from 6.1 % to 9.8%, between 2021 and 2025, and may reach 1.3 billion by 2050. In 2024, diabetes cases reached 8.02 million in Nigeria. Alarmingly, one-third of global cases is undiagnosed, with low- to middle-income nations overly affected.[2,4]

Sorghum bicolor, the constituent of Jobelyn®, has polyphenols with established hypoglycemic and insulin-sensitizing potentials in rats, compared to glibenclamide.[5,6] These activities are associated with elevated adiponectin effects and decreased TNF-α expression through activation of PPAR-γ.[6] Jobelyn® is rich in anthocyanins, flavonoids, and phenolic acids, contributing to its anti-inflammatory and antioxidant potential, placing it as a promising antidiabetic agent.[7,8]

Molecular docking is a computational method used to predict the interaction of bioactive compounds with biological targets.[9] Sulfonylurea receptors (SUR) are membrane proteins targeted by sulfonylurea medications to stimulate insulin secretion from pancreatic beta cells, supporting diabetes management. This study explores the binding affinity of Jobelyn's bioactive compounds to sulfonylurea receptor 1 via molecular docking and its antidiabetic potential in alloxan-induced diabetic rats.

MATERIALS AND METHODS:

Molecular docking method

Molecular modeling simulations (MDS) are extensively applied to determine potential composites, saving cost and time proficiently. In this research, Maestro 11.5 (Schrödinger) software was employed to evaluate binding affinities (Kcal/mol) and ascertain the best docked conformations of nine bioactives of Jobelyn® against the protein target, 7S5V (Protein Data Bank). The ligands were sketched and energy-minimized using Schrödinger's Maestro (LigPrep) tool, which optimized the 2D to 3D conformations employing the Optimized Potentials for Liquid Simulations (OPLS3) force field. Preparation of Protein encompassed the Protein Preparation Wizard, correction of mislaid hydrogens, incomplete rings, and disulfide bond addition, removal of water molecules above 5.00 Å from hetero groups, and generation of hetero states at pH 7.0 ± 2.0 with Epik. To support accurate docking, a receptor grid, a prototype of the protein's receptor site, was generated. Docking was assessed using binding energy, Glide scores, and interaction assessment to identify sturdy ligand-protein interactions.[10]

Sample collection

Jobelyn® dietary supplement capsules, 250 mg, were bought from a registered pharmacy in Lagos, Nigeria, having a Batch number (J2365), Manufacturing date (05/2022), and Expiry date (04/2024). The ethical clearance was obtained from the Health Research Ethics Committee of the College of Medicine (CMULHREC) of the University of Lagos (CMUL/ACUREC/04/24/1571).

Extraction of Jobelyn® sample for anti-diabetic study

Extraction of Jobelyn® powder was done according to the method highlighted by Chibuye *et al.*[11] Jobelyn® powder (7.8 g) was extracted using water, 99 % v/v ethanol, and 70 % v/v aqueous ethanol, kept for 72 hours in a dark cupboard, filtered, and concentrated. Water extract was freeze-dried “Freeze dryer”: BK-FD10P Model, Biobase Biodustry (Shandong) Co., Ltd, China); others were rotary evaporated (Rotary evaporator: Stuart™, Cole-Parmer Ltd., Stone, ST15 OSA, UK) for analysis.

Animals

Fifteen mice and seventy albino rats (110 -180 g of either sex) were procured and acclimatized for two weeks under standard conditions (12h light and dark cycle at 25^{o}C),[12] fed Ladokun™ pellets, and given water. All fasted before diabetes induction. Animal care followed Animal Care and Use Research Ethics Committee (ACUREC) guidelines.

Acute toxicity study

Acclimatized mice were divided into three groups (n=5) and given increasing Jobelyn® doses (1000, 1500, and 2000 mg/kg) to observe behavior and toxicity as highlighted by[13] with slight modifications.

Inclusion criterion
Normal and alloxan-induced diabetic rats (FBS > 120 mg/dL) were used for the study.

Exclusion criteria
Albino rats that deviated from the criteria stated above were not included in the study.

Experimental design
Thirty-six healthy rats within the inclusion criteria were utilized. Alloxan monohydrate (150 mg/kg i.p.) was used to induced diabetes in selected rats, with hyperglycemia established 48 hours post-induction (FBS >120 mg/dL). [14] Rats were divided into six groups (n=6): Group A (GBC, 0.5 mg/kg glibenclamide), Group B (JBWE, 25 mg/kg water extract), Group C (JBEE, 25 mg/kg ethanol extract), Group D (JBAEE, 25 mg/kg aqueous ethanol extract), Group E (INT, diabetic untreated), and Group F (non-diabetic control). Treatments were administered orally at 9 am daily for 20 days. Fasting blood sugar levels were observed on days 3, 7, 14, and 21 using an Accu-chek® glucometer.

Method of blood collection
Blood was withdrawn from the rat's tail with a sterile needle for measurement of FBS using an Accu-chek® glucometer.

Biochemical analysis
Blood sample was obtained through retro-orbital puncture on the 21st day after treatment, centrifuged (at 3000 rpm for about 10 mins), and plasma screened for lipids, Albumin (ALB), Protein (PRO), glucose (GLU), liver, and kidney biomarkers using a semi-autoanalyzer and Agape diagnostic kits. [15]

Lipid profile level determination
The total cholesterol (TC), high-density lipoprotein (HDL), and Triglyceride (TG) were determined using a semi analyzer (Photometer, Germany) with an Agape Kits. [15]

Kidney and liver marker estimation
Serum was evaluated for kidney and liver markers- urea, creatinine, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase SGPT-using Aspartate Aminotransferase (AST) activity assay kits. [15]

Histopathological study:
The pancreas was harvested on the 21st day after treatment, and preserved in 10 % formalin, sectioned using a microtome, stained with eosin and hematoxylin, and observed under a light microscope at 400 X magnification. [15]

Statistical analysis
Statistical analysis of the data was performed using GraphPad Prism with two-way analysis of variance (ANOVA) and Dunnett's test. Results were presented as mean ± S.E.M. and assessed using Student's t-test at a 95% confidence interval.

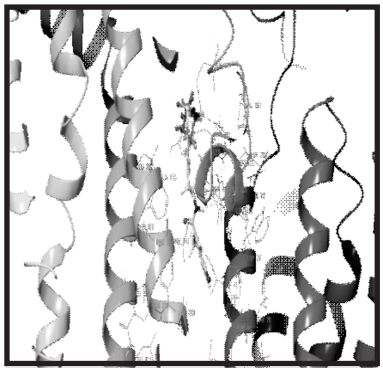
RESULTS

Molecular docking
Bioactive compounds in Jobelyn® were docked with sulfonylurea receptor 1 (7S5 V). Quercetin, Luteolin, and Proanthocyanidin presented sturdier binding affinity than glibenclamide, with overall similar binding capacities among other compounds, as illustrated in Table 1.

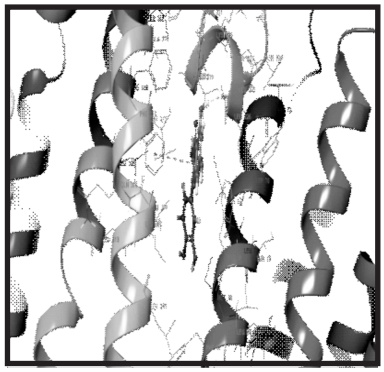
Table 1: Docking scores, binding energy, and the nature of interaction at the binding sites of sulfonylurea receptor 1 (PDB: 7S5V).

Ligand	Docking score (kcal/mol)	XP GScore (kcal/mol)	Glide GScore (kcal/mol)	Glide emodel (kcal/mol)	MMGBSA dG Bind (kcal/mol)
Quercetin	-9.724	-9.763	-9.763	-48.335	-39.24
Luteolin	-9.577	-9.625	-9.625	-48.451	-40.51
Proanthocyanidin	-9.145	-9.368	-9.368	-65.239	-38.04
Glibenclamide	-8.122	-8.148	-8.148	-75.853	-44.76
Gallic Acid	-7.841	-7.85	-7.85	-35.961	-22.69
Apigenin	-7.528	-7.576	-7.576	-45.983	-34.56
Naringenin	-7.402	-7.426	-7.426	-43.31	-30.20
Formononetin	-7.378	-7.389	-7.389	-42.899	-38.59
Apigenidin	-6.775	-6.894	-6.894	-42.516	-35.60
Caffeine	-3.821	-3.821	-3.821	-31.274	-32.57

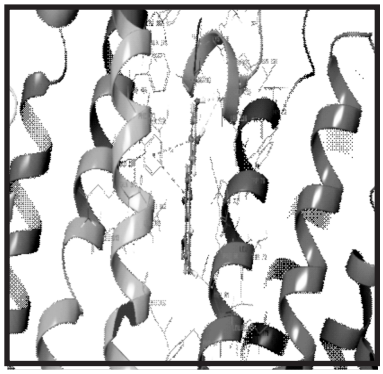
The docking study revealed interaction between Jobelyn® bioactives and sulfonylurea receptor 1 (SUR1), revealing various binding potentials and interaction modes. Glibenclamide formed hydrogen bonds with LEU225 and ARG299 and hydrophobic linkages with several residues, along with a salt bridge including ARG299 and LYS228. Quercetin and luteolin demonstrated comparable interactions, involving hydrogen bonding with LEU225 and Pi-Pi stacking with PHE373. Proanthocyanidin hydrogen bonds formed with LYS228 and ARG299 and sturdy hydrophobic and Pi-Pi contacts, with salt bridges. Gallic acid and formononetin exhibited similar hydrogen bonding through ARG299 and hydrophobic linkages. Apigenin, naringenin, and apigenidin also showed strong hydrophobic interactions and Pi-Pi stacking with basic residues like PHE373 and TYR1254. Caffeine demonstrated hydrophobic contacts and Pi-Pi stacking, mostly with PHE20 and PHE373. These residues promote ligand-receptor stability and selectivity. Remarkably, quercetin, luteolin, and proanthocyanidin exceeded glibenclamide's binding affinities, particularly through significant hydrogen bonds and hydrophobic interactions. In essence, Quercetin and luteolin bonded through LEU225; proanthocyanidin, formononetin, and gallic acid used ARG299, similar to glibenclamide's hydrogen bonding through sulfonylurea, urea, or amide groups (Figures 1A-J).



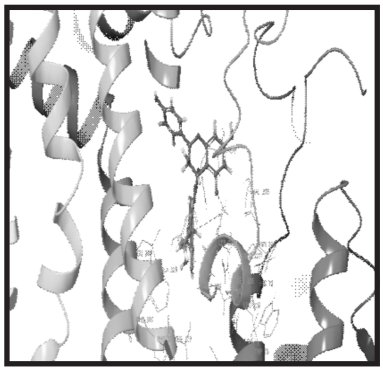
A. Glibenclamide 3D



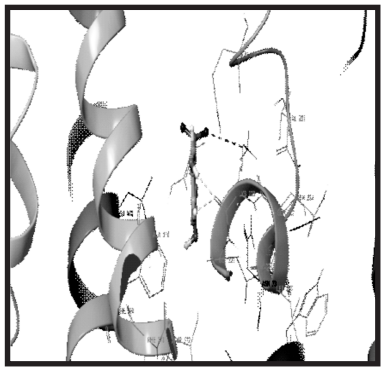
B. Quercetin 3D



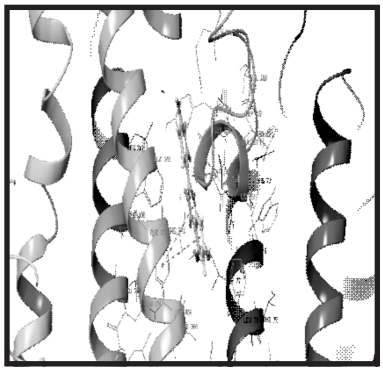
C. Luteolin 3D



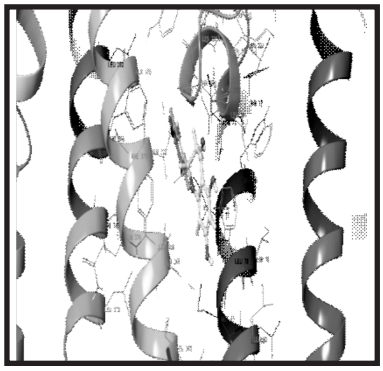
D. Proanthocyanidin 3D



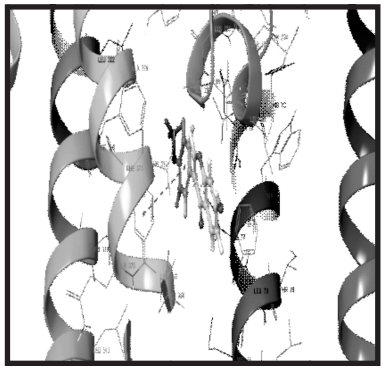
E. Gallic 3D



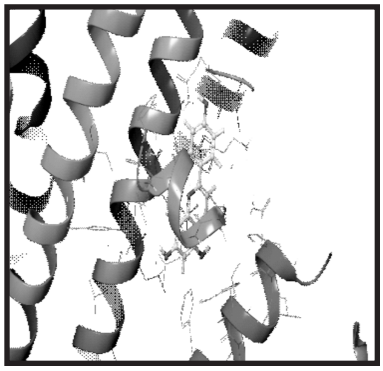
F. Apigenin 3D



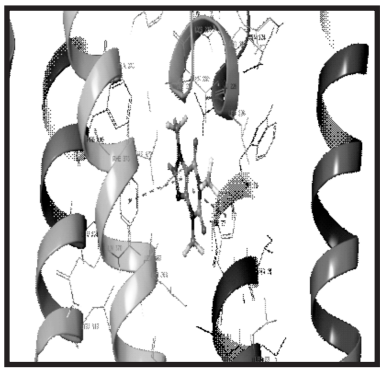
G. Naringenin 3D



H. Formononetin 3D



I. Apigenidin 3D



J. Caffeine 3D

Fig 1 (A-J): Binding conformations of glibenclamide and the bioactives of Jobelyn® at the binding site of sulfonylurea 1 (PDB: 7S5V)

Percentage yield

Jobelyn® aqueous ethanol extract (70 % v/v JBAEE) gave the highest yield (36 %), followed by water extract - JBWE (34.2%) and ethanol extract - 99% v/v JBEE (18.6 %) as represented in Figure 2 below.

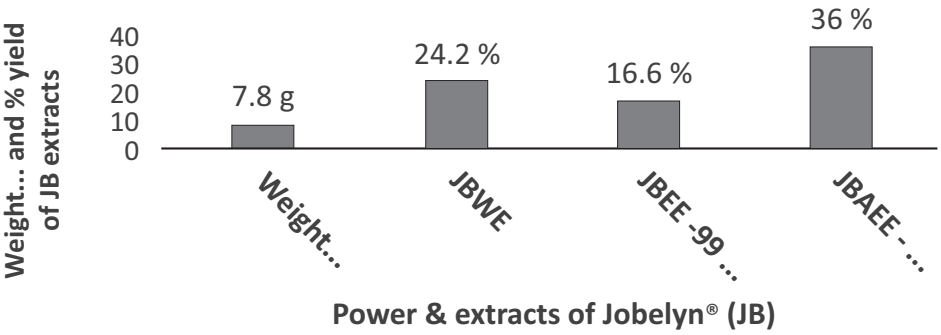


Figure 2: Percentage yield of Jobelyn® extracts

Acute toxicity

Jobelyn® presented no toxicity or mortality at 2000 mg/kg, validating safety in acute oral administration.

Anti-diabetic activity

The anti-diabetic evaluation presented a significant ($P < 0.05$) rise in fasting blood sugar (FBS) levels on day 3 in alloxan-induced diabetic rats, except the control group. A slight decrease in FBS occurred on the 7th day and was further reduced by day 14, with normalcy restored by day 21. The 70 % v/v aqueous ethanol extract of Jobelyn® (25 mg/kg), followed by glibenclamide (38.8 %) showed the highest inhibition (52.3 %) on day 7, both with significant ($P < 0.05$) percentage reductions. 70 % v/v JBAEE and glibenclamide attained FBS reductions of 76.1 % and 73.5 % respectively, by day 14, indicating no significant ($P > 0.05$) difference from the control faction. Other Jobelyn® extracts showed moderate reductions across the same period. All treated rats had FBS levels below initial and control values on day 21, with the 99% ethanol extract (JBEE) revealing the highest inhibition (94 %). Significant ($P < 0.05$) FBS differences were noted on days 3 and 7 as presented in Figures 3.

Statistically significant = ($P < 0.05$)

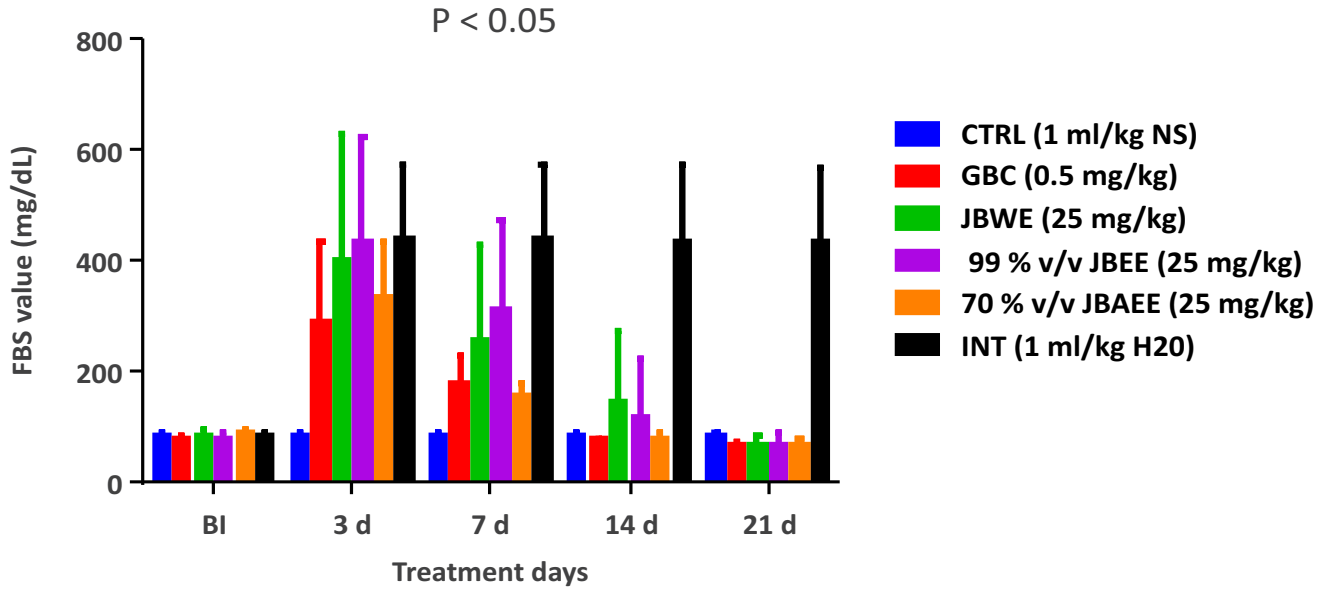


Figure 3: Effect of Jobelyn® extract on alloxan-induced diabetic rats

Lipid profile

JBWE-treated rats showed increased HDL and reduced LDL, while 99 % v/v JBAEE decreased triglycerides. JBEE, JBAEE, and glibenclamide lowered total cholesterol; however, only triglycerides and cholesterol were statistically significant ($P < 0.05$) compared to control (Figure 4).

* = Statistically significant ($P < 0.05$)

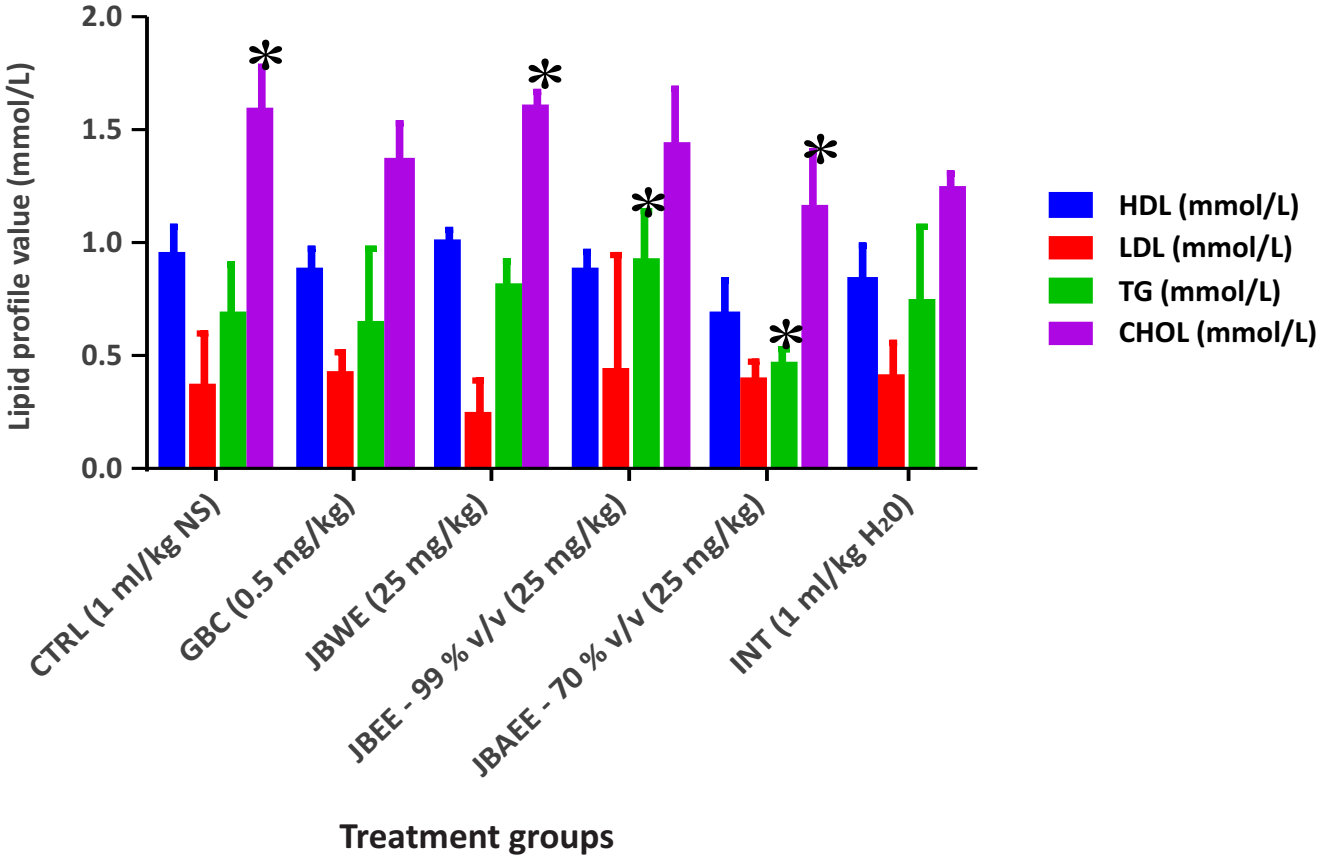


Figure 4: Effect of Jobelyn® extracts on the lipid profile of alloxan-induced diabetic treated rats.

Biochemical profile

Untreated diabetic (or Induced Not Treated - INT) rats showed elevated SGOT, SGPT, urea, creatinine, protein, and glucose levels. All Jobelyn® extracts (25 mg/kg) and glibenclamide reduced SGPT; JBAEE, JBEE, and glibenclamide lowered SGOT, while JBWE increased it. All extracts decreased urea, creatinine, and glucose, and increased albumin, though still below control levels. SGOT reduction in JBEE-treated rats was statistically significant ($P < 0.05$) compared to INT and control rats. Results are illustrated in Figure 5.

* = Statistically Significant

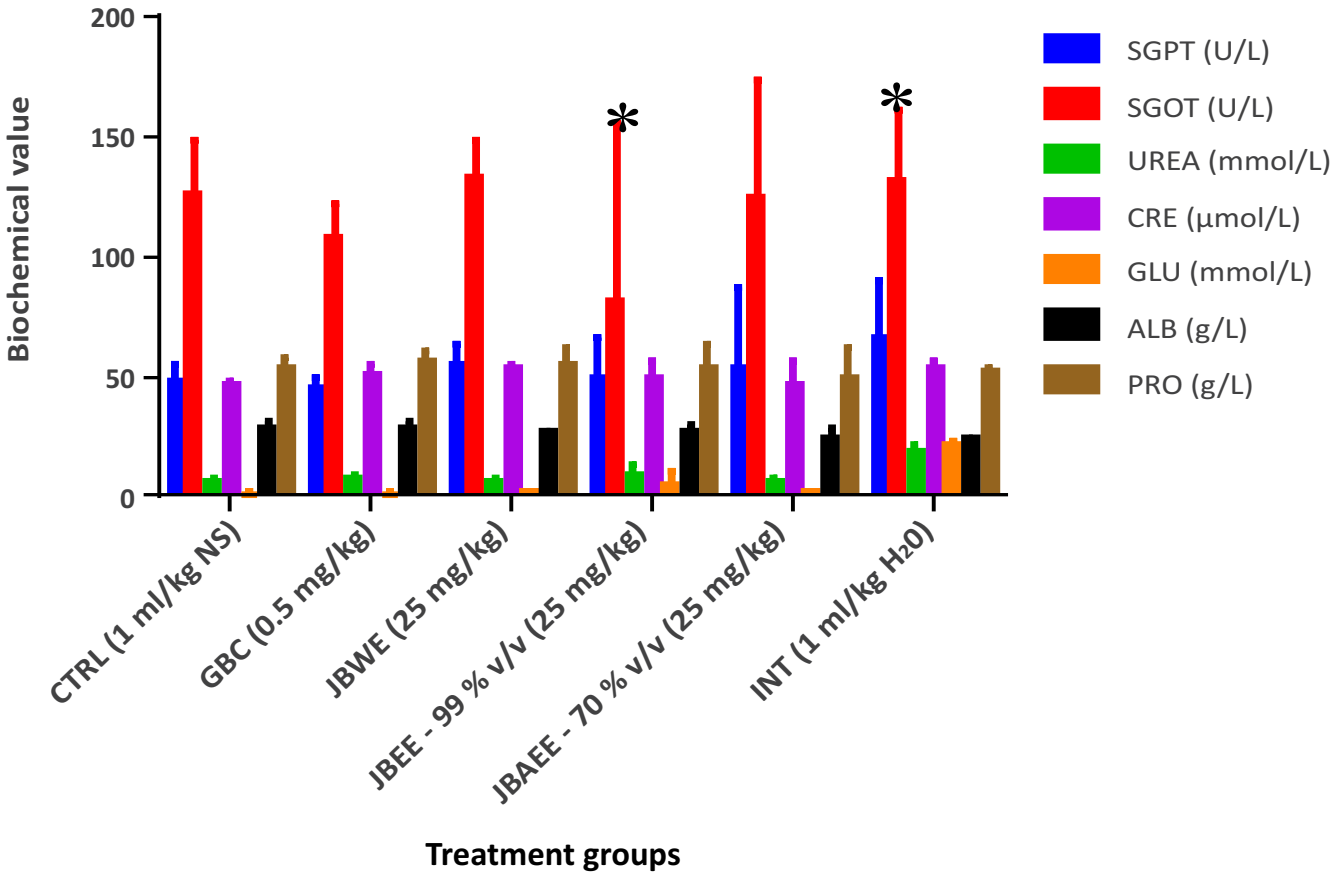


Figure 5: Effect of Jobelyn® extracts on the biochemical profile of alloxan-induced diabetic treated rats.

Hematological profile

Some hematological parameters were elevated in untreated diabetic (INT) rats and reduced in treated groups. Significant changes ($P < 0.05$) occurred in MID#, LYMPH#, RDW-SD, RBC, and PLT; other parameters were not statistically significant - $P > 0.05$ (see Figures 6a - 6c).

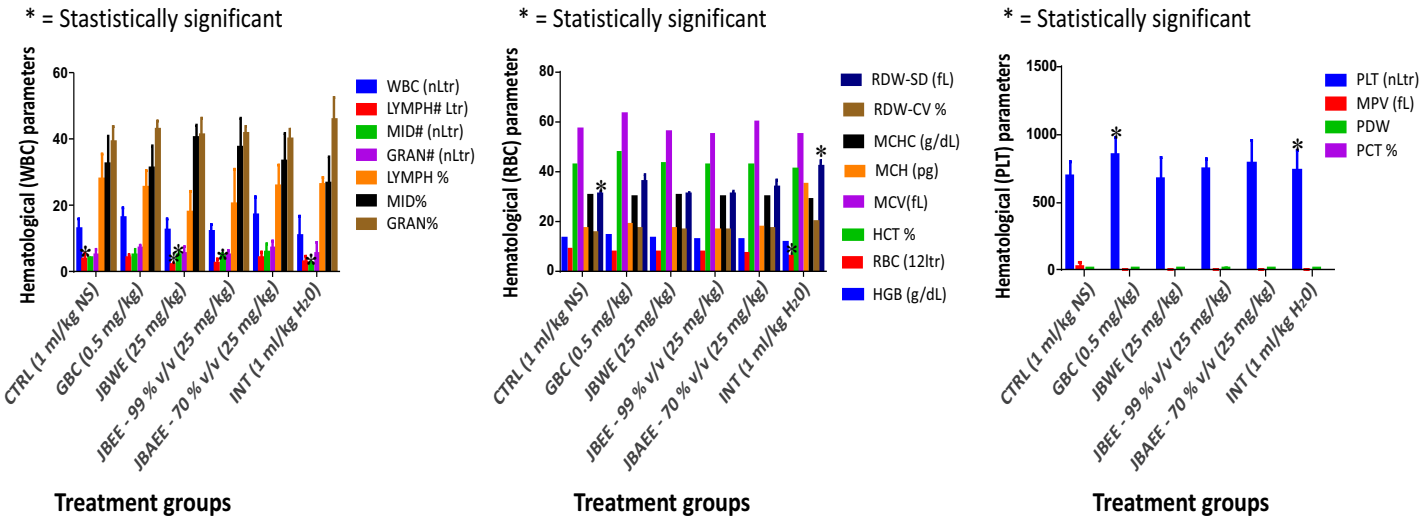
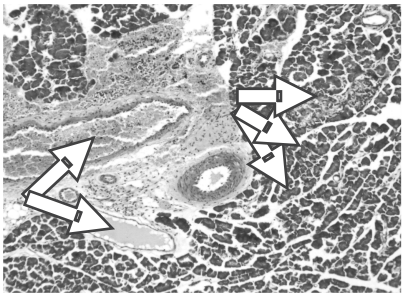


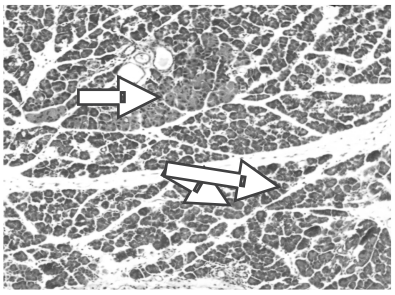
Figure 6a - 6c: Effect of Jobelyn® extracts on the hematological profile of alloxan-induced diabetic treated rats.

Histopathological profile

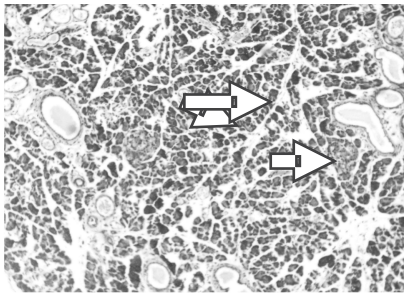
Histopathological data showed an improvement in the pancreatic islets' size in Jobelyn®-treated groups compared to diabetic untreated rats, as shown in Figure 7a - f.



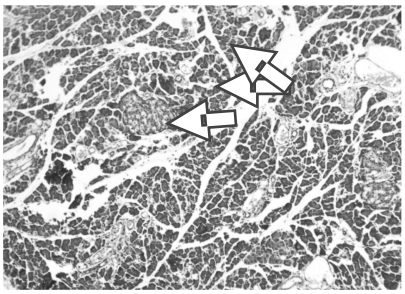
A. Diabetic untreated group



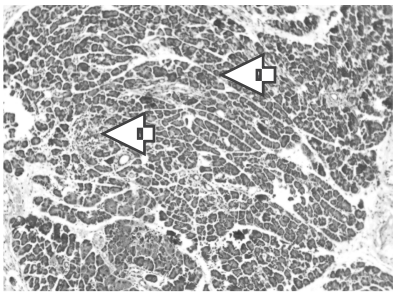
B. GBC Treated Group



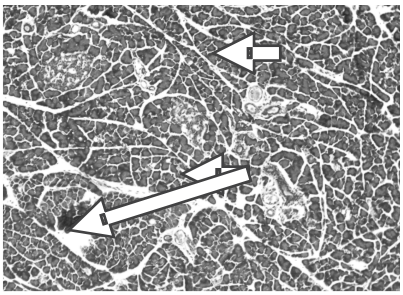
C. Water extract-treated group



D. Ethanol extract group



E. Aqueous ethanol extract group



F. Control group

Figure 7 (A-F): Pancreatic islets of treated and untreated groups of Rats: Figures 7b-f showed Pancreatic islets and acini cells are normal (X100 H & E stain), while 7a revealed impaired islets with edema and vascular congestion-black arrow - Islets of Langerhans; Red arrow - Acini cells.

DISCUSSION

Sorghum bicolor, whose leaf extract is the constituent of Jobelyn®, contains phenolic compounds known to aid glucose metabolism in rats.[5,6,17] Despite its anti-inflammatory and antioxidant potential, Jobelyn® is yet to be officially acknowledged as an antidiabetic agent. Thus, this study seeks to investigate the binding affinity of Jobelyn's bioactive compounds to sulfonylurea receptor 1 via molecular docking and its antidiabetic potential in alloxan-induced diabetic rats.

A previous phytochemical evaluation unveiled quercetin, formononetin, luteolin, and gallic acid in Jobelyn®,[17] emphasizing both dietary and therapeutic benefits.[17] Molecular docking showed sturdy interactions between Jobelyn® compounds and sulfonylurea receptor 1, a target for diabetes management.[18] Quercetin presented the highest binding score (-9.7 kcal/mol), outperforming glibenclamide (-8.1 kcal/mol), with other bioactives like luteolin and proanthocyanidin also performing better. These interactions may be directly implicated in the antidiabetic potential of Jobelyn® through the modulation of insulin secretion pathways.[18]

Toxicological analyses revealed Jobelyn's safety, since heavy metal content is within WHO limits.[16,17] Acute oral toxicity (2,000 mg/kg) presented no harmful effects, signifying a high safety margin. A dose of 25 mg/kg was selected based on established human-to-animal dose conversion.[19] One capsule of Jobelyn® contains 250 mg of *Sorghum bicolor* leaf sheath extract. Based on the standard dose conversion principle, the animal dose is typically one-tenth of the human dose, hence the selected dose of 25 mg/kg.[19]

Diabetes was induced using alloxan, a compound known to selectively destroy pancreatic β-cells.[20] Alloxan was chosen over streptozotocin because it is more cost-effective, readily available, and induces diabetes through a distinct mechanism that does not alter calcium levels or membrane potential in nociceptive neurons. This property makes it particularly suitable for studies on

painful diabetic neuropathy, where direct neuronal effects, commonly associated with streptozotocin, are undesirable.[20,21] Amid the extracts analyzed, the 70 % aqueous ethanol extract (JBAEE) at 25 mg/kg significantly decreased blood glucose between days 7 and 14, comparable to glibenclamide, demonstrating a fast onset of action. While no previous report has connected Jobelyn® directly to antidiabetic management, its bioactive constituents and traditional application of *Sorghum bicolor* support this potential.[6,16,17,22,23,24]

Jobelyn® congruently improved lipid profiles in hyperglycemic rats, reducing LDL, total cholesterol, and triglycerides, whereas increasing HDL. This supports earlier investigations performed with fermented *Sorghum bicolor.*[25] Remarkably, JBAEE-treated rats demonstrated healthier lipid profiles than controls and untreated rats. The hypolipidemic potential is possibly due to the specific phytochemicals present.[17,22,23,24]

Biomarkers of liver and kidney (SGPT, SGOT, urea, and creatinine) were increased in untreated diabetic rats but reduced after treatment with Jobelyn® extracts, mainly JBEE-indicating hepatoprotective and nephroprotective potentials. Histological evaluation of the pancreas, which presented improvements across treatment groups, supported these findings. This also aligns with a previous study on *Sorghum bicolor.*[26]

Polyphenols in Jobelyn® (Quercetin, Luteolin, Proanthocyanidin, Gallic acid, Apigenin, Naringenin, Formononetin, and Apigenidin)[8,17] may aid glucose levels regulation through β-cell function enhancement and inhibition of carbohydrate digestion and absorption.[27,28] Plant sterols also likely impact to their observed antidiabetic activity.

Overall, Jobelyn® compounds showed strong binding affinity to the surfonylurea receptor 1, and its extracts exerted significant antidiabetic activity at 25 mg/kg, with JBAEE showing the fastest response. However, additional studies are required to isolate and characterize the specific bioactive constituents responsible and to evaluate the potential dose-dependent impact employing advanced analytical and simulation techniques.

CONCLUSION

This study unveiled Jobelyn®'s antidiabetic and lipid-lowering effects in diabetic rats, indicating its potential for diabetes and dyslipidemia management. However, a major limitation of the present study is the lack of dose-response evaluation and the absence of long-term toxicity studies, which should be addressed in future research to better establish the safety and efficacy profile of Jobelyn®.

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