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Integrative Therapy with *Moringa oleifera* Leaf Extract and Sitagliptin Potentiates Antidiabetic, Antidyslipidemic, and Hepatoprotective Effects in Streptozotocin-Induced Diabetic Rats

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Abstract

Introduction: In diabetics, hyperglycemia leads to dyslipidemia and liver damage. Integrative therapy combining traditional medicine with a conventional antidiabetic drug is an innovative strategy to alleviate these issues with a lower dose and fewer adverse effects. Therefore, we investigated the antidiabetic, antidyslipidemic, and hepatoprotective effects of *Moringa oleifera* leaf extract, alone and in combination with sitagliptin, at a comparatively lower dose in streptozotocin-induced diabetic rats. **Methods:** Thirty (30) Swiss albino male rats were allocated into five groups. Except for the normal control group, diabetes was induced using a single dose of streptozotocin (STZ, 45 mg/kg, intraperitoneally). Over a 4-week experimental period, the effects of SGT (Sitagliptin, 100 mg/70 kg BW), MoLE (*Moringa oleifera* leaves extract, 200 mg/kg BW), and SGT + MoLE (integrative therapy of sitagliptin, 50 mg/70 kg BW with ethanolic *M. oleifera* leaves extract, 100 mg/kg BW) were evaluated. The study assessed blood glucose, glycosylated hemoglobin (HbA1c), serum lipid profile, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) and liver function markers such as protein level (albumin, globulin) and serum enzymes, alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). **Results and Discussion:** The SGT, MoLE, and SGT + MoLE groups showed a significant reduction ($p < 0.05$) in plasma glucose ((5.98 ± 0.44) mmol/L, (6.10 ± 0.50) mmol/L and (5.74

± 0.53) mmol/L, respectively) compared to diabetic control ((13.76 ± 0.83) mmol/L) as well as HbA1c levels (4.70% ± 0.48%, 5.24% ± 0.67% and 4.30% ± 0.23%, respectively) compared to diabetic control rats (9.38% ± 0.54%) after 4 weeks of treatment. Diabetics rats treated with SGT, MoLE, and SGT + MoLE significantly attenuated the elevation of total cholesterol ((102.9 ± 7.09) mg/dL vs (88.48 ± 6.354) mg/dL, (90.38 ± 6.419) mg/dL and (81.24 ± 5.767) mg/dL, respectively; diabetics vs SGT, MoLE, and SGT + MoLE treated group), triglycerides ((83.22 ± 7.75) mg/dL vs (72.08 ± 5.40) mg/dL, (75.24 ± 5.29) mg/dL and (70.84 ± 6.80) mg/dL, respectively), LDL cholesterol ((78.12 ± 6.98) mg/dL vs (58.90 ± 6.20) mg/dL, (61.96 ± 6.05) mg/dL and (60.26 ± 7.42) mg/dL, respectively), while attenuated reduced level of HDL cholesterol ((29.48 ± 3.59) vs (39.94 ± 4.05) mg/dL, (37.68 ± 4.54) mg/dL and (40.10 ± 5.89) mg/dL, respectively). Albumin levels decreased while globulin levels increased in diabetic rats; after treatment, both were restored to normal. Rats with diabetes had significantly higher levels of the liver enzymes ALT, AST, ALP, and GGT. The treatment of SGT, MoLE, and SGT + MoLE significantly attenuated these increased enzyme levels, but *M. oleifera* extract alone did not significantly reduce GGT levels. **Conclusion:** The study demonstrated that *Moringa oleifera* leaf extract and its combination with sitagliptin exhibited antidiabetic activity by decreasing blood glucose and HbA1c levels, antihyperlipidemic effects by stabilizing the lipid profile, and hepatoprotective effects by normalizing protein and liver enzyme levels. Furthermore, integrative therapy potentiates these effects at a comparatively lower dose.

Keywords

Moringa oleifera, Integrative Therapy, Diabetes, Antidiabetic Effects, Antidyslipidemic Effects, Hepatoprotective Effects, Streptozotocin

1. Introduction

In traditional Chinese medicine, African medicine, and folk medicine in Oriental countries, *Moringa oleifera* Lam. has been utilized as a valuable nutritious food source since ancient times. *Moringa oleifera* is a swiftly growing, perennial tropical tree of the Moringaceae family, often recognized by a few names, including the miracle tree, mother's best friend, horseradish tree, tree of life, drumstick tree, natural gift [1]-[3]. More than 300 ailments are said to be preventable or curable by *Moringa oleifera*. In addition, *Moringa oleifera* is a vital traditional remedy utilized for treating a diversity of conditions, including inflammation, diabetes, anemia, immunodeficiency, obesity, asthma, malnutrition, blindness, stress, arthritis, depression, Alzheimer's disease, hysteria, scurvy, infection, hypertension, and various disorders related to the heart, skin, kidneys, gastrointestinal tract, and liver [2]-[5].

In 2012, the National Health Commission of PRC (previously the Ministry of Health) designated *Moringa oleifera* leaves as a novel resource food owing to their

substantial nutritional value and diverse nutrient content (including amino acids, proteins, vitamins, minerals, and others) [1]. The leaves of *M. oleifera* are edible in a variety of ways and, when preserved as a dried powder, retain their nutritional value for a long period. Therefore, in several African countries, various regional and global humanitarian organizations are focusing heavily on developing *M. oleifera* leaves as a nutritional supplement [2].

Numerous phytocompounds, including phenolic and flavonoid chemicals (Gallic acid, Ferulic acid, Isorhamnetin, Syringic acid, Kaempferol, Ellagic acid, Caffeic acid, Quercetin, O-coumaric acid, Rutin, Sinapic acid, and Myricetin [6], essential amino acids, low saturated fatty acids and polyunsaturated fatty acids [5], alkaloids, carotenoids, epicatechin, catechin, pyrocatechin, pyrogallol, glucosinolates, isothiocyanins, etc. [7] have been documented to exist in *M. oleifera* leaves. Vitamins such as vitamins A, C, D, E, and B (folic acid, pyridoxine, and nicotinic acid) and minerals such as Zn (zinc), K (potassium), Ca (calcium), Cu (copper), Mg (magnesium), and Fe (iron) are abundant in *M. oleifera* leaves [4].

Over 537 million adults worldwide have diabetes, the most common metabolic disease, and by 2045, that number is expected to reach almost 800 million. The National Diabetes Statistics Report 2023 indicated that 38.4 million individuals of all ages, or 14.7% of American adults had diabetes [8]. Patients with diabetes frequently have dyslipidemia (serum lipid abnormalities) [9]. Dyslipidemia significantly impacts major organ systems, with the liver being particularly affected due to its integral role in lipid metabolism. The liver is crucial in lipid metabolism, as it synthesizes, stores, and transports lipid metabolites. Therefore, an elevated lipid level may alter liver metabolism and cause harm to the hepatic tissue [10].

Sitagliptin (STZ) is a highly selective oral inhibitor of dipeptidyl peptidase (DPP-4) that is used to regulate blood sugar levels. Similar to other DPP-4 inhibitors, it works by raising the levels of the incretin hormones GIP (gastric inhibitory polypeptide) and GLP-1 (glucagon-like peptide-1). In both monotherapy and in conjunction with other oral antidiabetic medications, sitagliptin effectively reduces HbA1c, fasting, and postprandial glucose [11]. Additionally, sitagliptin can lower total cholesterol and LDL-c more effectively [12], and it has a hepatoprotective effect that is mediated by regulating oxidative stress, inflammation, and mTOR/NF-κB/NLRP3 signaling [13].

Nowadays, the most prevalent treatments for managing diabetes involve the use of oral medications and insulin injections to mitigate hyperglycemia. Sitagliptin is commonly utilized alongside Metformin and Ertugliflozin to enhance glycemic management through complementing modes of action. Nevertheless, the need for substitute treatments with fewer or even no side effects for diabetes patients has grown due to the progressive resistance to these medicines as well as their numerous negative consequences. Herbal remedies have become more popular in recent years as a way to treat hyperglycemia and other diabetes-related problems. The prior study evaluated the antidiabetic, hypolipidemic, and hepatoprotective properties of *Moringa oleifera* leaves. The current study sought to assess the antidia-

betic, antidyslipidemic, and hepatoprotective effects of *Moringa oleifera* leaves extracts separately and concomitant with sitagliptin comparatively at a lower dose in streptozotocin-induced diabetic rats.

2. Materials and Methods

2.1. Collection of Leaves and Preparation of Extract

For extraction, the maceration technique was used. Fresh mature *Moringa oleifera* leaves were picked from the surrounding countryside, located at 24.2253˚N, 89.6687˚E in Bangladesh. Fresh leaves were collected, rinsed with tap water, and then distilled. For three days, the clean leaves were left to dry in the shade of the sun. An electronic grinder was used to crush the dried *Moringa oleifera* leaves. The fine powder was soaked at a 5:1 ratio in sealed glass bottles (amber) with 95% ethanol. It was subsequently left to stand at 25˚C- 30˚C for 10 - 12 days while being frequently shaken manually. After quickly passing through cotton, the extract was passed through filter papers (Whatman grade-1). The extract was then allowed to air dry at RT. The crude leaf extract was kept at 4˚C in a glass container that was tightly sealed.

2.2. Chemicals, Reagents and Drug

For extraction, 95% ethanol from Merck KGaA, Darmstadt, Germany, was used. The active pharmaceutical ingredient sitagliptin was generously provided by Square Pharmaceuticals PLC, Pabna, Bangladesh. Streptozotocin has been acquired from Sisco Research Laboratories Pvt. Ltd, Mumbai, India. Assay kits for TC, TG, LDL, HDL, SGPT (ALT), SGOT (AST), and GGT, ALP, globulin, and albumin are procured from HUMAN, Wiesbaden, Germany, and Randox assay kits from the United Kingdom, respectively. All chemicals and reagents utilized were of analytical grade.

2.3. Experimental Animal

Thirty (30) Swiss Albino male rats weighing 120.5 g (ranging from 110 g to 150 g) and aged 1.5 months were procured from a commercial laboratory rat supplier in the Rajshahi district of Bangladesh. The rats were maintained in clear polypropylene cages under a 12-hour light/dark cycle at 24˚C - 26˚C and provided with a regular mouse chow and sterile tap water ad libitum during the study. Rats were utilized for experimentation following a ten-day acclimatization period. The Khwaja Yunus Ali University ethics committee in Bangladesh examined and authorized the animal experiment, with the ethical clearance certificate number KYAU/DEAN/EGC/2024/014. Experiments followed EU guidelines (Directive 2010/63/EU) for pharmacological analysis and experimental design, as well as the WMA statement on the use of animals in biomedical research [14].

2.4. Dose Selection

A study found that the LC_{50} of ethanolic extract of leaves of *M. oleifera* in mice ex-

ceeded 6.4 g/kg [15]. According to another study, the safety threshold for Moringa leaves homogenate should not exceed 3 g/kg body weight [16]. In animal models of diabetes, the typical and efficacious amount of *Moringa oleifera* leaf extracts ranged from 100 to 300 mg/kg, administered over a treatment period of 2 to 8 weeks [17]. Thirty male Swiss Albino rats were randomly assigned to six groups (DS1-DS6) for our dose selection investigation. DS1 represents normal control, DS2 denotes diabetic control, and DS3-6 indicates diabetes treatment. In order to choose the dose, the last four groups (DS3, DS4, DS5, and DS6) were given 100 mg/70 kg sitagliptin (SGT), and 100 mg, 200 mg, and 300 mg/kg leaf extract (MoLE) respectively, for two weeks after the diabetics were introduced by streptozotocin (STZ, 45 mg/kg, i.p.). Upon evaluating blood glucose, lipid profiles, ALT, and AST in diabetic rats, we ultimately choose the dose.

2.5. Experimental Design

A total of thirty (30) Swiss Albino male rats were utilized in the experiment and separated into five groups. Diabetes was produced in rats, excluding the normal control group, using a jab of streptozotocin (STZ, 45 mg/kg, I.P.) made in 0.1 M citrate buffer at pH 4.5 [18]. The therapy duration was four weeks. At the conclusion of the testing session, rats were anesthetized and euthanized.

Group Name	Treatment Features
NC	Nondiabetic rats received a balanced diet and tap water *ad libitum*.
DC	Diabetic rats received a balanced diet and tap water *ad libitum*.
SGT	Diabetic rats received sitagliptin (100 mg/70 kg BW) orally [19].
MoLE	Diabetic rats received *M. oleifera* extract (200 mg/kg BW) orally.
SGT + MoLE	Diabetic rats received sitagliptin (50 mg/70 kg BW) + *M. oleifera* extract (100 mg/kg BW) orally.

2.6. Monitoring Blood Glucose and Glycosylated Hemoglobin (HbA1c)

The blood glucose levels of the rats were monitored prior to and following the experiment. Blood samples were drawn from the tail vein, and a glucometer (VivaChek Biotech (Hangzhou) Co., Ltd, China) was used to measure the glucose level. HbA1c was assessed through a diagnostic kit (Agappe Diagnostic Private Limited, India) [20] by using Genius PA-50. Both analyses were conducted following the manufacturer's instructions.

2.7. Evaluation of Serum Lipids and Hepatic Function Markers

Blood samples were drawn directly from the thoracic artery following the experiment, and the serum was separated by centrifuging the whole blood for 10 minutes at 1066 g [14]. By using commercial test kits, serum total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein (HDL) levels in accordance with the manufacturer's protocol (HUMAN kits, Wiesbaden, Germany) [20] were

colorimetrically measured by using HumaLyzer 3500. Aspartate aminotransferase (AST), and alanine aminotransferase (ALT) as well as gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), globulin, and albumin, were measured in serum using HUMAN kits (Wiesbaden, Germany) and Randox assay kits (United Kingdom), respectively, in accordance with the kits' protocol.

2.8. Statistical Analysis

The data was expressed using means ± SEM. M. For statistical comparisons, p values < 0.05 were deemed significant, and the one-way ANOVA and t-test were employed. For data analysis, GraphPad Prism 9.4.1 (USA) was used.

3. Results

3.1. Preliminary Dose Selection

After 2 weeks of treatment, the plasma glucose, ALT, AST, TC, TG, HDL-c, and LDL-c in control and experimental diabetic rats were examined and presented in Table 1.

Table 1. Effect of *M. oleifera* extracts, sitagliptin on plasma glucose, ALT, AST, and lipid profile in diabetic rats for dose selection.

Parameters	DS1	DS2	DS3	DS4	DS5	DS6
Plasma glucose (mmol/L)	4.6 ± 0.33	15.2 ± 1.19	7.44 ± 0.99	9.74 ± 0.74	8.96 ± 0.72	8.34 ± 1.12
ALT (IU/L)	28.28 ± 1.02	78.1 ± 2.03	45.72 ± 1.99	63.4 ± 2.41	54.38 ± 1.76	59.96 ± 2.31
AST (IU/L)	34.32 ± 1.52	109 ± 2.43	62.82 ± 2.43	79.88 ± 2.25	71.18 ± 2.03	77.72 ± 2.45
TC (mg/dL)	82.54 ± 2.47	98.1 ± 2.44	84.26 ± 2.38	93.064 ± 2.03	88.96 ± 2.42	91.94 ± 2.49
TG (mg/dL)	68.35 ± 2.28	84.4 ± 2.83	71.4 ± 2.31	78.22 ± 2.59	74.5 ± 2.19	77.28 ± 2.90
HDL-c (mg/dL)	41.77 ± 0.87	29.14 ± 1.09	37.82 ± 2.01	31.76 ± 0.72	34.20 ± 1.48	33.24 ± 2.56
LDL-c (mg/dL)	51.66 ± 2.46	71.32 ± 2.15	58.01 ± 1.24	67.71 ± 2.04	62.42 ± 2.10	63.82 ± 2.37

DS1 = normal control, DS2 = diabetic control, DS3 = 100 mg/70 kg sitagliptin, DS4 = 100 mg extract, DS5 = 200 mg extract, and DS6 = 300 mg/kg extract.

After witnessing the dose selection investigation, *Moringa oleifera* leaves extract 200 mg (DS5) outperformed the other concentrations. The activity of the extract increased with the dose, however, the highest dose (DS6) generated nearly identical results to DS5. Furthermore, sitagliptin 100 mg/70 kg (DS3) achieved higher results. Thus, a combination of half of the concentration of DS3 and DS5 was selected for integrative therapy, and DS3 and DS5 were selected separately for study for up to 4 weeks.

3.2. Antidiabetic Activity

The plasma glucose and HbA1c (glycated hemoglobin) values in control and ex-

perimental diabetic rats are presented in Table 2. The plasma glucose levels considerably were increased in all groups following the induction of diabetes with streptozotocin (STZ, 45 mg/kg, i.p.), with the exception of the NC group. After treatment, the results demonstrated a significant reduction ($p < 0.05$) in plasma glucose levels and HbA1c in the SGT, MoLE, and SGT + MoLE groups compared to the diabetic control rats (DC group). Nevertheless, the altered levels of plasma glucose and HbA1c were considerably ($p < 0.05$) normalized when SGT + MoLE was administered orally to diabetic rats.

Table 2. Effect of *M. oleifera* extracts, Sitagliptin, and their combination therapy on plasma glucose and HbA1c in diabetic rats.

Groups	Plasma glucose (mmol/L)		HbA1c (% Hb)
	Before 4 weeks	After 4 weeks	
NC	4.42 ± 0.25[a]	4.80 ± 0.30[a]	3.58 ± 0.15[a]
DC	14.20 ± 1.05[b]	13.76 ± 0.83[b]	9.38 ± 0.24[b]
SGT	14.30 ± 0.48[b]	5.98 ± 0.44[a]	4.70 ± 0.22[c,d]
MoLE	13.64 ± 1.43[b]	6.10 ± 0.50[a]	5.24 ± 0.30[d]
SGT + MoLE	14.56 ± 2.00[b]	5.74 ± 0.53[a]	4.30 ± 0.11[a,c]

Here, NC stands for Normal Control (NC), DC for Diabetic Control, SGT for Sitagliptin treated, MoLE for *Moringa oleifera* Leaves extract treated, and SGT + MoLE for Sitagliptin + *Moringa oleifera* Leaves Extract treated groups. The results obtained were examined using one-way ANOVA. Tukey's multiple comparison test indicates significant differences ($p < 0.05$) with superscript letters; identical letters signify no significant differences.

3.3. Effect on Lipid Profile

After a 4-week investigation period, the effects of administering *M. oleifera* extracts (MoLE), Sitagliptin (SGT), and a combination of sitagliptin (50 mg/70 kg BW) and the ethanolic leaves extract of *M. oleifera* (100 mg/kg BW) (SGT + MoLE) on the serum lipid profile, specifically TC, TG, HDL-c, and LDL-c were examined. The findings are displayed in Figure 1. In diabetic rats, blood total cholesterol, LDL cholesterol, and triglycerides significantly increased, while HDL cholesterol markedly decreased compared to normal control animals; however, these alterations were mitigated by SGT, MoLE, and SGT + MoLE treatment. SGT, MoLE, and SGT + MoLE all markedly decreased LDL and total cholesterol levels. However, the combination of sitagliptin (50 mg/70 kg body weight) with ethanolic leaf extract of *M. oleifera* (100 mg/kg body weight) significantly decreased serum triglyceride levels. Furthermore, HDL cholesterol levels in the treated groups were considerably reduced compared to those in the diabetic control rats. The lipid profiles showed that the combination of SGT + MoLE outperformed others in restoring the lipid profile of experimental animals, demonstrating potential antidyslipidemic effects.

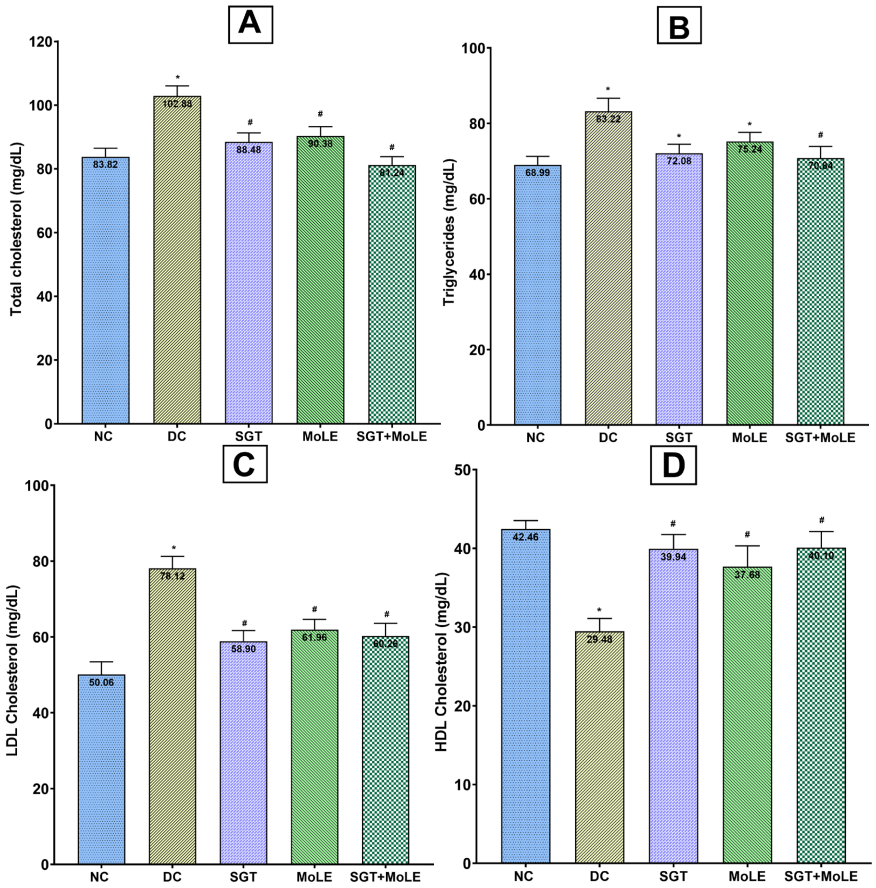

Figure 1. Effect of *M. oleifera* extracts, Sitagliptin, and their combination therapy on (A) TC, (B) TG, (C) LDL-c, and (D) HDL-c in experimental rats.

3.4. Effect on Liver Function

The effects of administering *M. oleifera* extracts (MoLE), Sitagliptin (SGT), and a combination of sitagliptin (50 mg/70 kg BW) and the ethanolic leaves extract of *M. oleifera* (100 mg/kg BW) (SGT + MoLE) on the serum liver profile, which includes the protein level (albumin, globulin) and the serum liver enzyme activities (ALT, AST, ALP, and GGT), in experimental rats after a 4-week period were examined and the results are displayed in **Figure 2** and **Figure 3**, respectively. In diabetic rats, albumin concentrations are generally reduced relative to treated diabetic rats. Moreover, the globulin level was markedly elevated in diabetic rats; however, following four weeks of treatment, the globulin concentration was significantly reduced.

The levels of liver enzymes ALT, AST, ALP, and GGT were significantly raised in the streptozotocin-induced diabetic rats. The rats administered *M. oleifera* extracts (MoLE), sitagliptin (SGT), and a combination of sitagliptin (50 mg/70 kg BW) with the ethanolic leaves extract of *M. oleifera* (100 mg/kg BW) (SGT + MoLE) were exhibited a significant decrease of elevated liver enzyme levels. However, *M. oleifera* extract was unable to appreciably decrease high levels of the GGT enzyme. These findings showed the hepato-protective effects of sitagliptin, *M. oleifera* ex-

tracts, and the combination of Sitagliptin and *M. oleifera* ethanolic extract of leaves.

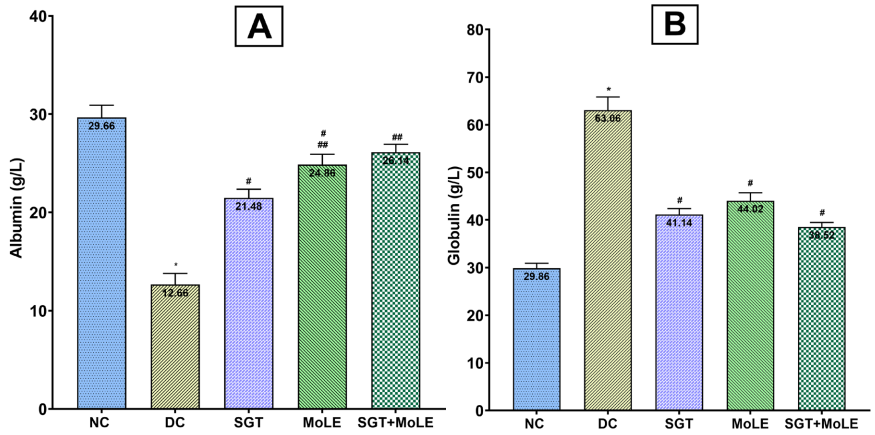

Figure 2. Effect of *M. oleifera* extracts, sitagliptin, and their combination therapy on (A) albumin and (B) globulin level in experimental rats.

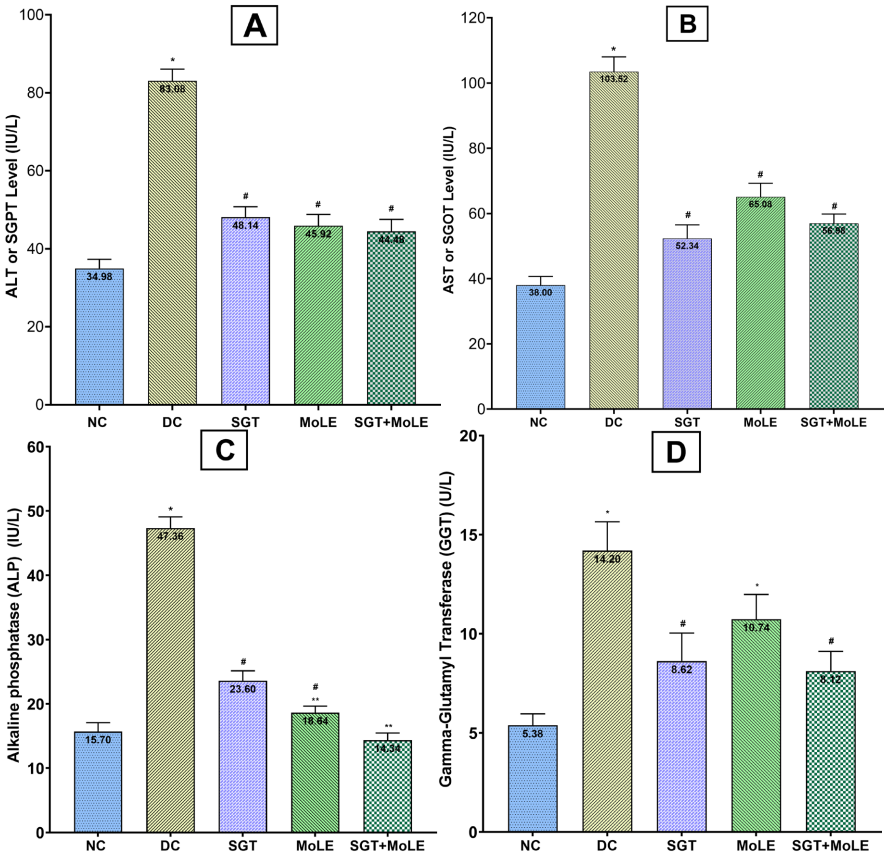

Figure 3. Effect of *M. oleifera* extracts, Sitagliptin, and their combination therapy on serum liver enzyme activities (A) ALT, (B) AST, (C) ALP, and (D) GGT in experimental rats.

4. Discussion

Diabetes mellitus (DM) is a common metabolic disorder primarily characterized by hyperglycemia resulting from impaired insulin production or action [13]. Fur-

thermore, regardless of insulin resistance or insufficiency, diabetics commonly exhibit serum lipid abnormalities (dyslipidemia) [21]. Hyperglycemia-induced oxidative stress and the resultant disruption of carbohydrate, protein, and lipid metabolism are the primary contributors to liver damage in diabetes patients [22]-[24]. However, the integrative therapy of herbal medicine and synthetic drugs is significant because it can lessen adverse effects while providing comparable therapeutic advantages at lower doses. Therefore, this study aims to assess the antidiabetic, antidyslipidemic, and hepatoprotective effects of *Moringa oleifera* leaves extracts alone and in conjunction with sitagliptin, in streptozotocin-induced diabetic rats.

Streptozotocin is the most common diabetogenic, cytotoxic glucose analogue, antimicrobial, and chemotherapeutic alkylating agent, and causes the destruction of pancreatic islet β-cells, which can result in insulin deficiency (T1DM), impaired oxidative stress, dyslipidemia, and hyperglycemia [25]. Oxidative stress significantly contributes to the pathophysiology of T2DM [26], alongside notable elevations in hepatic oxidative stress, inflammation, and hepatocyte damage [13]. In our investigation, diabetes was produced in rats using streptozotocin (STZ, 45 mg/kg, i.p. injection). Our findings demonstrate that the treatment of STZ-induced diabetic rats with *Moringa oleifera* leaves extract (MoLE) alone and integrative therapy with sitagliptin (SGT + MoLE) significantly reduced blood glucose levels and HbA1c (%) compared to untreated diabetic rats as shown in **Table 2**, demonstrating a definite antidiabetic effect. Yassa and Tohamy (2014) observed a substantial reduction in blood glucose levels in diabetic rats induced by STZ after administering *Moringa oleifera* leaves [27]. Also, the antidiabetic activities of *Moringa oleifera* leaves have also been reported by many studies [17]. The antihyperglycemic effect of *Moringa oleifera* leaves may be caused by improving insulin resistance, stimulating β-cells to secrete insulin, or regenerating β-cells [17].

Diabetic dyslipidemia, which was seen in STZ-induced diabetic rats, is characterized by higher levels of TC, TG, and LDL-c and HDL-c [28]. The results showed that *M. oleifera* extract alone (MoLE) and integrative therapy with sitagliptin (SGT + MoLE) have a beneficial effect on controlling dyslipidemia linked to diabetes by improving aberrant lipid levels in diabetic rats. According to the lipid profiles, the combination effect of SGT + MoLE performed better than the experimental animal's control lipid profile, suggesting a possible better antidyslipidemic effect.

The significant decline in albumin levels and the increased globulin levels in serum due to STZ exposure result in substantial liver damage. The administration of MoLE, SGT, and SGT + MoLE stabilized serum albumin and globulin concentrations. The stabilization of proteins may indicate increased protein synthesis in hepatic cells due to the prevention of lipid peroxidation and the scavenging of free radicals [29]. The liver enzymes AST, ALT, ALP, and GGT are commonly utilized as reliable indicators for evaluating liver health [10]. In this investigation, levels of ALT, AST, ALP, and GGT were markedly increased in the streptozotocin-induced diabetic rats. The rats administered MoLE, SGT, and SGT + MoLE exhibited a

significant decrease in elevated liver enzyme levels. However, *M. oleifera* extracts alone failed to appreciably diminish high levels of the GGT enzyme. The potent antioxidant properties of Moringa leaf [2] primarily mitigate oxidative stress and inflammation in the liver, potentially alleviating damage from STZ-induced diabetes, resulting in reduced levels of liver enzymes (such as AST, ALT, GGT, ALP), indicating improved liver function. The results indicated the hepatoprotective effects of *M. oleifera* extracts, sitagliptin, and the combination of sitagliptin with the ethanolic leaf extract of *M. oleifera*. However, this study showed that the combined effect of SGT + MoLE was superior in protecting the liver of the experimental rat.

The overall results of this study indicated that the treatment with MoLE alone and the integrative therapy of SGT + MoLE exhibited antidiabetic activity by effectively reducing blood glucose and HbA1c, as well as antihyperlipidemic effects by stabilizing the lipid profile. Additionally, the treatment protected against liver damage by normalizing abnormalities in liver proteins and enzymes. Integrative therapy of *Moringa oleifera* and sitagliptin may provide synergistic advantages in diabetes treatment by addressing complementary processes. While sitagliptin improves glycemic control, *Moringa oleifera*'s extensive phytochemical profile provides additional antidiabetic, antidyslipidemic, and hepatoprotective benefits. This combination can potentially enhance pharmacological benefits and reduce the need for sitagliptin, resulting in a more effective and safer therapeutic strategy.

5. Limitations

This study has some limitations. The precise active ingredients that might be responsible for the hepatoprotective, antidiabetic, and antidyslipidemic effects are hard to predict. Only a basic mechanism was proposed in this study despite the fact that the exact mechanisms of action were not fully investigated. The effect of combination therapy outperformed that of a single extract; however, additional, comprehensive studies are needed to elucidate the precise mechanism behind its supra-additive effects. While our work shows *Moringa oleifera* has promise antidiabetic, antidyslipidemic, and hepatoprotective effects in mice, the applicability of these findings to humans is dubious. Therefore, clinical trials in humans are required to evaluate this therapeutic potential.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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