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EVALUATION OF ALLIUM SATIVUM POLYSACCHARIDES AS AN ADJUNCT TO METFORMIN IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT
Background: Metformin is widely prescribed for the management of diabetes; prolonged intake of metformin at higher doses is often associated with several mild to severe side effects. In recent years, plant polysaccharides have been rigorously studied for their antidiabetic properties. In this study, the complementary effect of Allium sativum polysaccharides with metformin was investigated in STZ-induced Wistar rats. **Methodology:** The rats were divided into five groups (n=6): normal control, diabetic control, metformin-treated (100 mg/kg b.w.), and metformin + ASP (50 mg + 200, 100 mg/kg b.w.). For 28 days, FBG and body weight were monitored. After 28 days, the rats were euthanized, and liver function markers were measured. **Results and Discussion:** Compared with diabetic control, combination therapy with metformin (50 mg) and ASP (200 mg) resulted in a significant reduction in glucose levels from 324.09 ± 2.90 to 125.84 ± 3.37 mg/dL. Similarly, the combination of Met 50 mg + 100 mg ASP lowered FBG levels to 178.96 ± 3.53 mg/dL. The results of a 2-way ANOVA indicated a significant interaction between the row and column factors ($F(16, 125) = 192.6$, $p < 0.0001$). Both combination therapies led to an initial decrease in body weight by day 7, followed by a subsequent recovery by day 28. In liver function test, both the combination therapies reduced AST ($p < 0.05$) and ALP enzyme levels ($p < 0.05$). **Conclusion:** The investigated combination therapy showed antidiabetic activities by improving glucose metabolism and liver function in rats.

INTRODUCTION

Since ancient times, *Allium sativum*, commonly known as garlic, has been widely used in traditional medicine to treat various ailments, including inflammation, microbial infections, heart disease, and digestive disorders. The scientific community has studied garlic for decades due to its diverse therapeutic properties. These properties are primarily attributed to phytoconstituents found in garlic, such as allicin, allin, diallyl disulfide, and diallyl trisulfide [1,2]. Due to their rich phytoconstituent profile, garlic plant extracts exhibit diverse pharmacological activities, including antibacterial, antiviral, antioxidant, immunomodulatory, cardioprotective, anti-

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inflammatory, and anticancer effects. Recent studies have shown that garlic extract can reduce blood pressure, improve cholesterol metabolism, protect the liver and kidneys, improve glucose metabolism, and enhance immune responses. The garlic extracts also suppress the growth of pathogenic microorganisms and tumour cells [3]. In today's world, Diabetes mellitus has emerged as a significant global health threat, with estimates indicating that more than 830 million adults will be affected by 2025, which is equal to around 11.1% or one in every nine individuals aged 20 to 79 worldwide. Primarily in developed and developing countries, a considerable rise in the incidence of diabetes has been seen over the recent decades; for instance, global prevalence among adults rose from 7% in 1990 to 14% in 2022 [4,5]. This increase has been especially notable in low- and middle-income countries (LMICs), where the majority of individuals with diabetes now live. Many factors influence the rise in cases of diabetes, such as obesity, poor dietary habits, sedentary lifestyles, lack of physical activity, etc. Diabetes has a profound effect on the patient's health and wealth; if it is not properly treated or managed, it has serious life-threatening implications [6,7,8]. Oral hypoglycemic agents, which are among the most commonly prescribed for managing type 2 diabetes, are associated with a wide variety of side effects. One of the most frequent adverse effects is hypoglycemia, which can present with symptoms such as trembling, rapid heartbeat, intense hunger, irritability, sweating, dizziness, headaches, and occasionally nausea, vomiting, or abdominal discomfort. Drugs like metformin can cause gastrointestinal issues like nausea, diarrhea, stomach cramps, bloating, heartburn, constipation, and a metallic taste. In addition to gastrointestinal adverse effects, metformin and other sulfonylureas may cause weight gain, whereas other agents can cause fluid retention or swelling. In some rare cases, more severe side effects like lactic acidosis and liver dysfunction have been reported in patients who are taking metformin for a long period of time. Another category of antidiabetic drugs, thiazolidinediones, is linked with an increased risk of bladder cancer [9,10]. To overcome these issues, extensive research has been conducted to find alternative medicines/ therapies for diabetes management. This has led to increased interest in natural sources of potential antidiabetic agents to aid diabetes management. In addition to the previously mentioned phytoconstituents, *Allium sativum* contains polysaccharides. In recent years, several studies have reported that polysaccharides derived from Allium sativum exhibit diverse pharmacological activities, including antioxidant, immunomodulatory, anti-inflammatory, and liver-protective properties [11]. Polysaccharides derived from garlic exhibit antioxidant properties by scavenging reactive oxygen species and inhibiting lipid peroxidation [12]. Their immunomodulatory function is credited to the stimulation of immune cell growth and the improvement of cytokine secretion [13]. Still, the anti-hypoglycemic activity of polysaccharides derived from *Allium sativum* (ASP) has not been frequently reported. In the present study, ASP from Allium sativum was extracted, and its hypoglycemic activity, when combined with the standard drug metformin, was evaluated in streptozotocin-induced diabetic rats. Because metformin is among the most commonly used drugs for treating diabetes, it was selected to test the hypothesis proposed in the current study.

MATERIALS AND METHODS

Plant material

The *Allium sativum* plant was collected from a local cultivator in Chandrapur, Assam, and authenticated at the Department of Botany, Guwahati University. Reference no. Herb/GUBH/2024/059

Extraction of polysaccharides

Polysaccharide extraction was performed according to the method described by Xu et al. [14], with minor modifications. The peeled and cleaned samples of *Allium sativum* were accurately weighed and thoroughly triturated using a mortar and pestle. The mashed samples were then transferred to a beaker. They were subjected to defatting using petroleum ether under reflux conditions and subsequently dried. After drying, the samples were transferred to a beaker containing distilled water and heated at 80 °C for approximately 2 hours with occasional stirring. Subsequently, the beaker was allowed to cool to room temperature. Ethanol was added to the above beaker at a 2:1 ratio to precipitate the polysaccharides. After precipitation, the supernatant liquid was decanted. The sample was then filtered to remove excess solvent, and the filtrate was freeze-dried at -40°C to obtain the powder. The ASP extraction process is shown in Figure 1.

Animals

Wistar rats (weighing 200±10 g) of both sexes were purchased from Assam Agricultural University, Khanapara, Guwahati-22. All animals were housed in polypropylene cages under standard environmental conditions (25±2 °C, 55±10 % RH, and a 12:12 light: dark cycle). The rats were fed with a standard pellet diet

and had free access to water. All animal study protocols were approved by the institutional animal ethics committee of Assam Down Town University with reference no. ADTU/IAEC/2022/012.

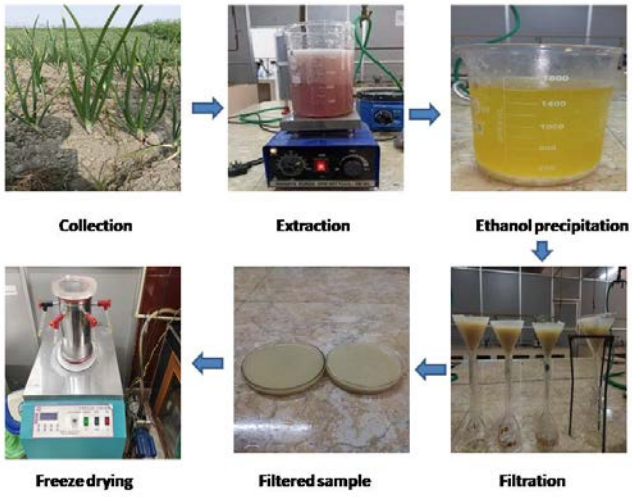

Figure 1: Extraction process of ASP

Acute oral toxicity study

Acute oral toxicity studies of the extracted products were conducted in accordance with OECD Guideline 423 [15]. The first group received distilled water, and the second group was administered 2000 mg/kg b.w. of ASP. The rats were observed for 30 minutes, 4 hours, 24 hours, and then for 14 days for any sign of toxicity, including tremors, diarrhea, convulsions, sleep, and coma.

Induction of diabetes

After an overnight fast, a single intraperitoneal injection of STZ (55 mg/kg body weight) freshly prepared in 0.1 M sodium citrate buffer (pH 4.5) was administered to induce diabetes. For 12 hours, the animals were fed a 5% glucose solution to prevent hypoglycemia. Blood glucose levels were assessed using a glucometer on the fourth day of STZ treatment. Rats with mild diabetes, defined as hyperglycemia (blood glucose>250 mg/dL), were classified as diabetic and included in the study [16].

Experimental design

For the investigation, 30 male and female Wistar rats were used. Following induction, the diabetic rats were split into five groups at random, with six rats in each group: the diabetes model group (DC), the normal control group (NC), the metformin group (Met), the metformin+ASP X dose group (MASPX), and the metformin+ASP Y dose group (MASPY). Distilled water was supplied to the rats in the DC group. Metformin was administered to rats in the Met group at 100 mg/kg body weight. Rats in MASPY and MASPX were given metformin 50 mg +200 mg ASP/kg b.w. and metformin 50 mg + 100 mg ASP/kg b.w., respectively. Except for the normal control group, all treatments were administered orally for 28 days, beginning on day 4 after STZ administration. Based on the acute toxicity study of the extracted polysaccharide, the dose levels were selected. This study aimed to assess the potential of an extracted polysaccharide to complement metformin's effect by administering a reduced (50%) dose of the drug to the MASPX and MASPY experimental groups.

Biochemical analysis

To evaluate various biochemical parameters, blood samples were collected via the retro-orbital route on days 0, 7, 14, 21, and 28 into collection tubes. The collected samples were then centrifuged at 3000 rpm for approximately 10 minutes. The resulting supernatant (serum) was carefully separated and used for biochemical analysis [17]. A glucometer was used to measure fasting blood glucose (FBG). On days 0, 7, 14, 21, and 28 at 3 p.m., body weight was recorded. The levels of alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were determined using a biochemical analyzer.

Histopathological studies

Liver tissues collected from the rats were dried in a series of 96% v/v ethanol washes. The dehydrated tissues were then embedded in paraffin wax. A Rotary microtome was used to cut thin slices of the liver tissues embedded in paraffin wax. The thin sections were then stained with hematoxylin and eosin (H&E) [18]. The sections were observed through a light microscope.

Statistical analysis

For FBG and body weight, a two-way ANOVA was performed; for AST & ALP, a one-way ANOVA was performed & Tukey's multiple comparisons test was used to compare the data. The values were considered to be significantly different when the p-value was less than 0.05. The software used was GraphPad Prism 8.0.2

RESULTS AND DISCUSSIONS

Extraction: After extraction, precipitation & drying, a white dry polysaccharide powder was obtained. The % yield was 2.15%.

Acute toxicity study: The acute oral toxicity studies on animals over 14 days resulted in no deaths. No lethal side effects were observed during the study period. Therefore, the polysaccharide extracts can be considered safe at a dose of 2000 mg/kg BW in rats.

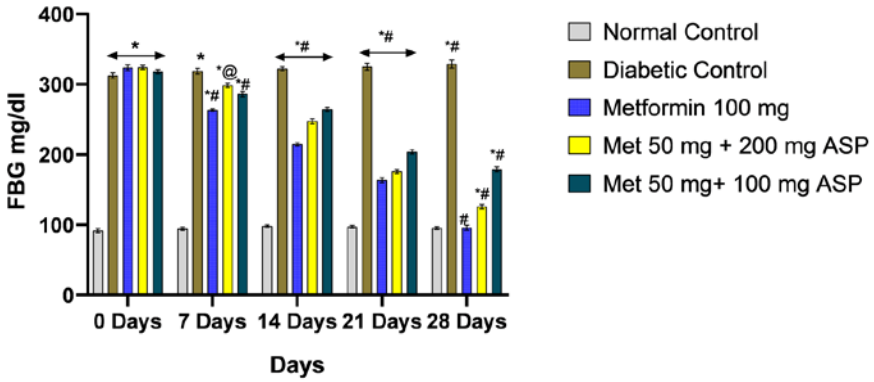

Figure 2: Effect of treatment on FBG

Two-Way ANOVA followed by Tukey's multiple comparisons test. Each value represents the mean ± SEM (n=6 for each group), * indicates p < 0.0001 significant changes compared with normal control, # indicates p <0.0001 significant changes compared with diabetic control, and @ indicates p <0.05 significant changes compared with diabetic control.

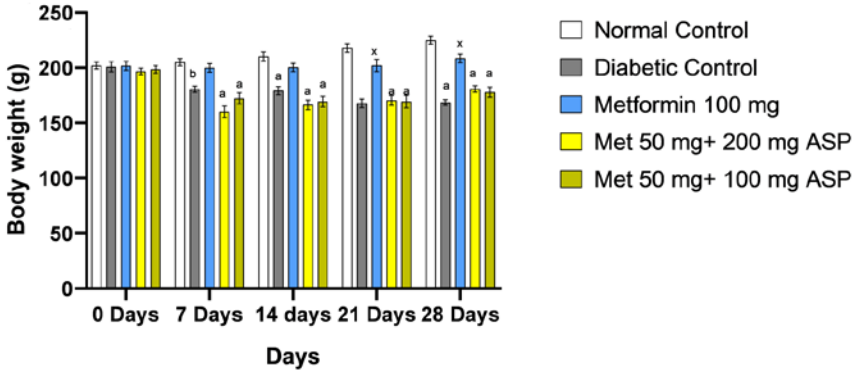

Figure 3: Effect of treatment on Body weight

Two-Way ANOVA followed by Tukey's multiple comparisons test. Effect of ASP on body weights of rats, each value represents the mean ± SEM (n=6 for each group), a indicates p < 0.0001 significant changes compared with normal control, b indicates p<0.05 significant changes compared with normal control, and x indicates p <0.05 significant changes compared with diabetic control.

Effect of the treatment ON AST and ALP levels

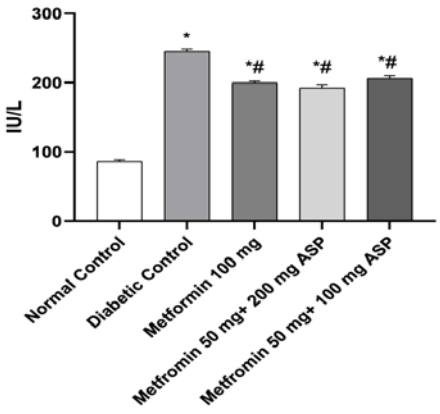

Figure 4: Effect of treatment on AST

One-Way ANOVA followed by Tukey's multiple comparisons test. Effect of ASP on AST levels; each value represents the mean ± SEM (n = 6 per group). * p < 0.05 indicates significant changes compared with the normal control; # p < 0.05 indicates significant changes compared with the diabetic control.

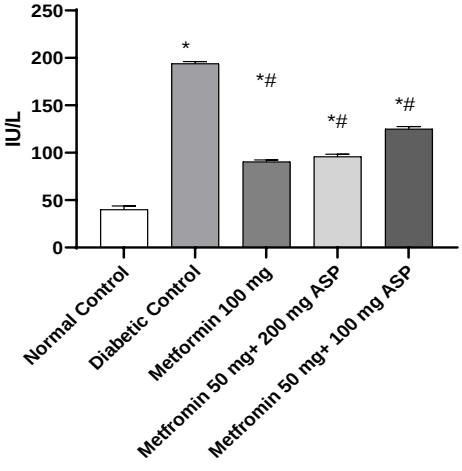

Figure 5: Effect of treatment on ALP

One-Way ANOVA followed by Tukey's multiple comparisons test. Effect of treatment on ALP levels; each value represents the mean ± SEM (n = 6 per group). * $p < 0.05$ indicates significant changes compared with normal control; # $p < 0.05$ indicates significant changes compared with diabetic control.

Histopathology study

Microscopic observation of the liver tissue section is shown in Figure 6.

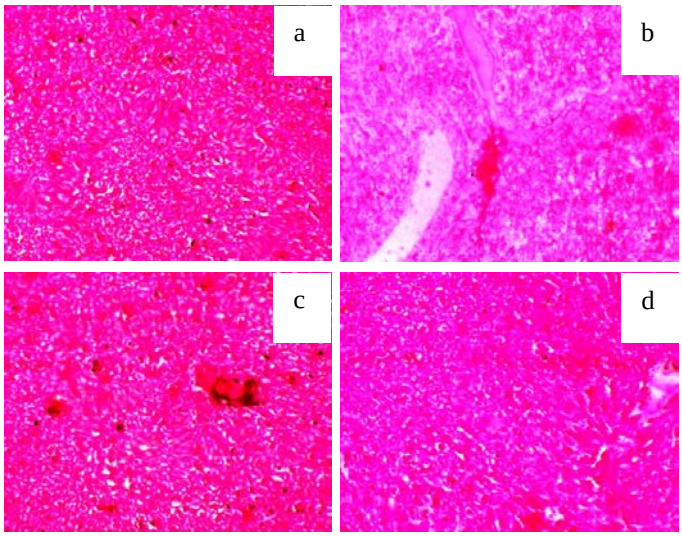

Figure 6: Histopathological examination of rat liver sections demonstrated notable differences among the experimental groups. The normal control group (a), the diabetic control group (b), the treated group ASPX (c), and ASPY (d).

DISCUSSION

One of the most commonly recommended oral drugs for type 2 diabetes is metformin. It's generally well tolerated and effective; however, it frequently causes moderate gastrointestinal symptoms. Symptoms like diarrhea, vomiting, nausea, bloating in the abdomen, excessive gas, and stomach pain are commonly reported by patients. These problems typically occur when therapy is initiated or after a dose increase [19]. In addition to these more frequent side effects, some individuals may experience less common reactions, such as fatigue, headaches, heartburn, or alterations in taste perception. In some rare cases, prolonged regular intake of metformin is associated with lactic acidosis, which is a potential life-threatening complication characterized by increased concentration of lactic acid in the body. This is particularly a concern in patients with underlying kidney or liver impairment, dehydration, or those who consume alcohol excessively. Severe fatigue, muscle pain, shortness of breath, and dizziness are common clinical signs of lactic acidosis. In addition, in some patients, metformin can contribute to hypoglycemia (low blood sugar), particularly when it is given in combination with other antidiabetic medications or during periods of inadequate food intake. Vitamin B12 deficiency has also been linked to long-term use of metformin, which may result in neurological symptoms such as numbness and tingling in the limbs, as well as megaloblastic anemia [19,20]. Based on available clinical data, metformin is among the most widely prescribed medications for the treatment and management of diabetes in healthcare settings. The efficacy, safety, and cost-effectiveness of metformin contribute to its widespread use.

Furthermore, metformin serves as a foundational agent in the management of type 2 diabetes and is commonly included in combination therapy regimens [21]. Several studies have suggested that, in addition to use in combination therapy with synthetic drugs, metformin can be combined with certain natural compounds to improve its glucose-lowering efficacy. Co-administration of metformin with turnip leaf extract enhances its hypoglycemic activity in a dose-dependent manner [22]. A polysaccharide derived from *Acanthopanax senticosus* roots was evaluated in rats with alloxan-induced diabetes as an adjunct to metformin for antidiabetic treatment. The study results show that co-administration of the polysaccharides with metformin improved glucose metabolism and liver and kidney function in rats, compared with metformin administered alone [23].

In the present study, the antidiabetic effects of polysaccharides from Allium sativum were assessed in Streptozotocin (STZ)-induced diabetic rats. STZ is the most widely used agent for inducing diabetes in rats; it causes DNA alkylation in beta cells and disrupts insulin synthesis, which is essential for maintaining blood glucose levels [24, 25]. In rats, administration of more than 40 mg/kg b.w. of STZ is sufficient to destroy pancreatic beta cells, leading to hyperglycemia [26]. In this study, STZ was injected at 55 mg/kg body weight, causing a marked increase in FBG on the 4th day of the experiment, which may be associated with beta-cell destruction and reduced insulin secretion. As shown in Figure 2 at the beginning of the study, both the MSPX and MSPY groups exhibited high glucose levels comparable to those of the untreated diabetic control rats. Combining Metformin with ASP produced a significant, dose-dependent reduction in blood glucose levels in diabetic rats over 28 days, compared with the diabetic control group ($p < 0.0001$). The group receiving 200 mg ASP with metformin showed a greater

decrease in glucose levels than the group receiving 100 mg ASP with metformin. By the end of the study, both ASP combination groups showed significant improvement in glycemic control, although the 200 mg ASP group achieved superior outcomes. The finding suggests that co-administration of ASP with metformin may improve beta-cell function, reduce hepatic glucose production, and enhance glucose uptake; however, further study is required to elucidate the underlying mechanisms.

Due to abnormal insulin secretion from beta cells, the rat's muscle cells are unable to use glucose as an energy source; therefore, they begin to rely on protein. This results in depletion of protein stores and a reduction in body weight [27, 28]. As shown in Figure 3, during the 28-day study period, the body weight of normal control rats increased gradually. In contrast, diabetic control rats showed a notable and long-lasting decrease in body weight, suggesting that diabetes adversely affects metabolism overall. In the Metformin (100 mg/kg) treatment group, no significant changes in body weight were observed, although there was a slight improvement over time. Interestingly, rats given ASP (200 or 100 mg) and metformin (50 mg/kg) initially lost weight, with the weight loss more pronounced in the group given the higher ASP dose. On day 28, both combination groups showed a partial recovery in body weight, indicating a steady improvement. These results are consistent with improved glucose metabolism and insulin function [29].

In patients with type 2 diabetes mellitus (T2DM), liver enzymes such as AST (Aspartate Aminotransferase) and ALP (Alkaline Phosphatase) are typically elevated compared with those without diabetes, suggesting liver involvement and metabolic disruption [25]. Research indicates that patients with T2DM tend to exhibit increased levels of these enzymes, with one study reporting average AST levels of approximately 49.7 IU/L and ALP levels of approximately 115.9 IU/L, both significantly higher than in non-diabetic controls [27]. Among the liver enzyme abnormalities, elevated AST appears to be the most prevalent, affecting more than half of the diabetic participants in certain studies. This increase in liver enzyme levels may be associated with changes in glucose metabolism, enhanced hepatic gluconeogenesis, hepatic fat accumulation, and impaired bile flow. The elevated enzyme levels may point to underlying liver conditions such as non-alcoholic fatty liver disease (NAFLD), which is commonly observed in diabetic patients. Regular monitoring of AST and ALP, along with other liver function parameters, can help assess liver status and detect potential complications. Moreover, elevated liver enzymes have been associated with poor blood sugar control and increased cardiovascular risk, emphasizing their relevance in managing diabetes [30]. As shown in Figures 4 and 5, the extracted polysaccharide, when combined with low-dose metformin, significantly improved liver enzyme profiles compared with diabetic controls by reducing both AST and ALP levels ($p < 0.05$). Histopathological examination of liver tissue from the normal control group (Figure 6a) revealed almost normal hepatic histology with preserved architecture, minimal sinusoidal dilatation, and intact hepatocyte nuclei, reflecting effective hepatoprotection. In contrast, the diabetic control group (Figure 6(b) exhibited marked pathological alterations, including cytoplasmic vacuolation, necrosis, inflammatory cell infiltration, and central vein congestion, indicative of severe hepatocellular injury due to persistent hyperglycaemia [31]. Both the plant-treated groups, ASPX and ASPY, in Figure 6(c) & (d), showed significant improvement compared with the negative control, with reduced necrosis and vacuolation, improved sinusoidal architecture, and predominantly intact hepatocytes, although occasional fatty changes remained. The improvement may be attributed to the antioxidant and hepatoprotective activity of *Allium sativum* polysaccharides [32,33].

The findings of the present study indicate that ASP may exert a synergistic effect when combined with metformin, especially at higher dosages. This combined therapy appears to enhance glycemic control more effectively than either agent alone, suggesting that ASP could be a valuable adjunct in the management of diabetes. Beyond its antihyperglycemic action, ASP also shows potential in mitigating diabetes-induced hepatic damage. Its hepatoprotective properties may help preserve liver function, which is often compromised in diabetic conditions. When used alongside metformin, ASP may confer dual benefits, improving metabolic outcomes while protecting vital organs, underscoring its potential as a complementary therapeutic agent in comprehensive diabetes care.

CONCLUSION

The present study highlights the beneficial effects of administering *Allium sativum* polysaccharide (ASP) in combination with metformin as a complementary medicine in

the management of type 2 diabetes. Although metformin is still a mainstay in the treatment of diabetes because of its effectiveness and affordability, gastrointestinal side effects and other issues may restrict its use. With the 200 mg ASP combination exhibiting the most noticeable effects, our results reveal that co-administration of ASP with a lower dose of metformin improves glycemic control in a dose-dependent manner. In addition, this complementary therapy significantly improved liver function markers, particularly AST and ALP levels, in diabetic rats, along with an improvement in body weight. Based on these findings, it can be suggested that administering ASP as a complementary medicine with metformin may provide antidiabetic effects similar to those of metformin administered alone, potentially reducing dose-dependent side effects of metformin. However, additional studies are needed to confirm these results and to investigate the full potential of ASP in diabetic populations.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
H Deka performed the literature survey and experimental work. A Choudhury contributed to the conceptualization of the original draft. D. Ganguly, JM. Jimenez and J. Sarmah contributed to data analysis.

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