Journal of Natural Remedies
DOI: 10.18311/jnr/2026/53598

Research Article
eISSN: 2320-3358 | Vol 26(3), 2026 | pp. 687-697

Phytochemical Screening and Systemic Modulation of Glucose Metabolic activity by *Stephania glabra* Tuber L. and *Clerodendrum phlomidis* L. Leaves

Jetti Amos Babu, K. E. Pravallika* and Parimi Ravi

University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522 510, Andhra Pradesh, India; elvina2108@gmail.com

Abstract

Background: The tuber of *Stephania glabra* L. and the leaves of *Clerodendrum phlomidis* L. have been reported to exhibit antidiabetic, hypolipidemic, and glucose-regulating effects. **Aim:** The study evaluated the phytochemical profile and insulin secretion, lipid regulation, and glucose-linked metabolic enzymes over 28 days of ethanolic test extracts. **Methods:** Ethanolic extracts were prepared by maceration, and screened phytochemically. A 28th day chronic antidiabetic study was conducted in streptozotocin-induced male Wistar rats, with test groups receiving ethanolic extracts (100, 200, 400 mg/kg) and a standard group receiving glibenclamide (2.5 mg/kg). Blood samples were collected intravenously to determine fasting and postprandial insulin levels using Enzyme Linked Immunosorbent Assay (ELISA) while serum lipid profiles and glucose-metabolising enzymes were analysed using a semiautomatic analyser at 320 nm. **Results:** Both test extracts significantly enhanced insulin secretion in a dose-dependent manner, with the highest dose (200 and 400 mg/kg) yielding fast-acting and postprandial insulin levels of 10.1 and 34.8 µU/ml for *S. glabra* tuber and 10.3 and 35.6 µU/ml for *C. phlomidis* leaves extracts. By the 28th day, the test extracts improved lipid parameters, showing total cholesterol 90.85 mg/dl, triglycerides 41.11 mg/dl, High Density Lipoprotein (HDL) 47.70 mg/dl, Low Density Lipoprotein (LDL) 34.85 mg/dl, and Very Low-Density Lipoprotein (VLDL) 8.20 mg/dl, and 92.45, 43.93, 46.89, 36.77, and 8.78 mg/dl, respectively. Both extracts also modulated glucose-metabolising enzymes, indicating improved glycemic control. **Conclusion:** The ethanolic test extracts have bioactive compounds, respectively, which may be responsible for enhanced insulin secretions, modulate glucose metabolic enzymes and improved lipid profiles after 28 days, supporting for diabetes management.

Major Findings: Phytochemical analysis confirmed the presence of key bioactive compounds, which significantly increased insulin levels, improved lipid regulation, and modulated glucose-metabolizing enzyme activity.

Keywords: Body Weight, Diabetes, Hexokinase, Low Density Lipoprotein, Lipids and Insulin

(Article Chronicle: Article Received on: 25.11.2025; Revised on: 20.02.2026; Accepted on: 10.03.2026)

1. Introduction

Type 2 diabetes has become one of the most pressing global health challenges. In 2024, diabetes directly caused 3.4 million deaths worldwide, with nearly half occurring before the age of 25 years. The World Health Organization (WHO) projects that by 2030, diabetes could become the seventh leading cause of death globally, highlighting the urgent need for preventive measures[1]. A major factor driving this trend is insulin deficiency and lack of balanced diet, which disrupts the body's ability to regulate glucose metabolism. Enzymes involved in glucose and lipid metabolism, such as hexokinase and lipoprotein lipase, become less effective, leading to elevated blood sugar and lipid levels. Over time, these metabolic disturbances

*Author for correspondence

contribute to worsening insulin resistance. The World Health Organisation (WHO) has set a goal to halt the rise in diabetes by 2025, aiming to reduce both prevalence and associated mortality rates[2]. In addition to glucose metabolism, insulin deficiency also affects lipid regulation, leading to elevated free fatty acids. Enzymes responsible for lipid storage and breakdown, like lipoprotein lipase and hormone-sensitive lipase, become dysregulated. This imbalance contributes to increased triglycerides and cholesterol in the blood. Excess lipids can accumulate in tissues, promoting complications. The insulin deficiency and disruption of carbohydrate and lipid metabolism is a major factor in Type 2 diabetes progression. Managing these metabolic disturbances is crucial to prevent long-term endocrinal complications[3,4].

Insulin is essential for maintaining blood glucose homeostasis, facilitating cellular uptake and directing glucose toward energy production. This regulation is supported by key metabolic enzymes, hexokinase phosphorylates, glucose, to retain it within cells. glucose-6-phosphatase in the liver releases glucose during fasting states, and fructose-1,6-bisphosphatase contributes to gluconeogenesis by generating necessary intermediates[5,6]. Very-Low-Density Lipoproteins (VLDL) carry triglycerides from the liver to tissues, Low-Density Lipoproteins (LDL) supply cholesterol for structural and hormonal needs, and High-Density Lipoproteins (HDL) remove excess cholesterol and return it to the liver for elimination. Collectively, insulin, metabolic enzymes, and lipoproteins ensure the integrated control of carbohydrate and lipid metabolism required for optimal physiological balance[7].

The *S. glabra* tuber contains a rich spectrum of bioactive phytochemicals, including rutin, jatrorrhizine, palmatine, berberine, magnoflorine, cycleanine, tetrandrine, quercetin, kaempferol, apigenin, stigmasterol, β-sitosterol, lupeol, and β-amyrin, many of which exhibit significant metabolic regulatory properties. These compounds, particularly the alkaloids and flavonoids, have been associated with enhanced insulin secretion, improved peripheral insulin sensitivity, and protection of pancreatic β-cells. In addition, several constituents contribute to lipid modulation by lowering triglyceride levels, improving cholesterol handling, and supporting balanced lipoprotein metabolism. Furthermore, a number of these phytochemicals influence carbohydrate homeostasis through the regulation of key glucose-metabolizing enzymes, including hexokinase, glucose-6-phosphatase, and fructose-1,6-bisphosphatase. Collectively, this phytochemical profile suggests a multifaceted role in enhancing insulin function, regulating lipid metabolism, and maintaining glucose-linked enzymatic balance[8,9].

The *C. phlomidis* leaves contain a diverse array of bioactive compounds, including gallic acid, rutin, N-methyltryptamine, luteolin, quercetin, kaempferol, apigenin, clerodin, campesterol, oleanolic acid, and ursolic acid. These phytochemicals, particularly flavonoids and triterpenoids, are recognised for their potential roles in supporting metabolic regulation[10,11]. Flavonoids such as rutin, luteolin, quercetin, kaempferol, and apigenin have been associated with improved glucose handling, modulation of insulin pathways, and regulation of key enzymes involved in carbohydrate metabolism. Triterpenoids including oleanolic acid and ursolic acid, along with sterols like campesterol, contribute to lipid balance by influencing cholesterol metabolism and supporting healthy lipid profiles. Collectively, the phytochemical composition of *S. glabra* L. tuber and *C. phlomidis* L. leaves suggests a multifaceted role in maintaining carbohydrate regulatory metabolism, lipid metabolism, and enhancement of insulin levels[12,13].

The bioactive constituents present in *S. glabra* tuber and *C. phlomidis* leaves demonstrate broad metabolic activity, collectively contributing to enhanced insulin function, improved lipid regulation, and modulation of key glucose-metabolising enzymes. Studies indicate that the alkaloids, flavonoids, sterols, and triterpenoids found in these plants can stimulate insulin release, increase peripheral insulin sensitivity, and support pancreatic β-cell function. In addition, these phytochemicals help normalise lipid profiles by reducing triglycerides, improving cholesterol handling, and stabilising lipoprotein balance, thereby supporting overall cardiovascular health. Their influence on carbohydrate-related enzymes including those involved in glycolysis, gluconeogenesis, and glucose storage further contributes to balanced glucose homeostasis[14,15]. Beyond these actions, the antioxidant and anti-inflammatory effects of the compounds help reduce metabolic stress, which aids in preventing excessive body-weight gain. Collectively,

the phytochemical synergy of both plants supports comprehensive metabolic regulation.

This study examines the antidiabetic effects of *S. glabra* tuber and *C. phlomidis* leaves extracted by ethanolic maceration process. The extracts are tested for their influence on insulin secretion, lipid profile, and key glucose-metabolising enzymes, with the hypothesis that their phytochemicals enhance insulin activity, improve lipid balance, and support glucose homeostasis in Type 2 diabetes[16].

2. Material and Methods

2.1 Materials

Insulin ELISA, lipid profile, and glucose-reciprocal enzyme detection kits were purchased from Cisco Laboratory, Chennai, India.

2.2. Phytochemical Extraction and Screening

The *S. glabra* L. tuber and *C. phlomidis* L. leaves were collected from Andhra Pradesh, authenticated, and preserved herbarium in Department of Botany, Sri Venkateswara University, Tirupati, India. The collected plant materials were thoroughly washed and subjected to maceration technique at 35 °C for seven days. The extracts were filtered, concentrated using a rotary evaporator at 45 °C, and stored in a desiccator. The ethanolic extracts were screened for alkaloids, flavonoids, terpenoids, amino acids and proteins, glycosides, volatile oils, phenolic compounds using standard procedures[17,18].

2.3 Experimental Design for *In Vivo* Chronic Studies

In the *vivo* study, animals were divided into nine experimental groups (n = 6) and labelled as Group I to IX. Group I served as the normal control and consisted of healthy Wistar albino rats receiving normal water, while all other groups were rendered diabetic using streptozotocin (55 mg/kg)[19]. Group II served as the diabetic control. Groups III-V received the ethanolic tuber extract of *S. glabra* at doses of 100, 200, and 400 mg/kg, respectively. Groups VI-VIII received the ethanolic leaves extract of *C. phlomidis* at doses of 100, 200, and 400 mg/kg (oral route), respectively. Dose selection was based on previously reported toxicity studies and published literature demonstrating safety within this range. Group IX received glibenclamide (2.5 mg/kg). All treatments were administered once daily for 28 days. At the end of the treatment period, blood samples from all experimental groups (I-IX) were collected intravenously, allowed to clot, and centrifuged at 3,000 rpm for 10 minutes to obtain serum for biochemical analysis[20,21].

2.4 Determination of Insulin Levels by Enzyme Linked Immunosorbent Assay Method

Fasting and postprandial insulin levels were determined in all experimental groups (Groups I-IX). Briefly, 100 µl of serum was added to each well, followed by the addition of biotin-conjugated antibody and streptavidin-HRP. The wells were washed with Phosphate-Buffered Saline containing Tween-20 (PBST), after which 3,3′,5,5′-Tetramethylbenzidine (TMB) substrate was added. The reaction was terminated using 50 µl of 0.1 N sulfuric acid, and absorbance was measured at 450 nm using a semi-auto analyzer[22,23].

2.5 Determination of Serum Lipid Levels in Streptozotocin-induced Diabetic Rats

To evaluate the effect of treatments on lipid metabolism, serum levels of Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoproteins (LDL), Very-Low-Density Lipoproteins (VLDL), and High-Density Lipoproteins (HDL) were estimated in all experimental groups (Groups I-IX) using standard commercial diagnostic kits. Briefly, the appropriate volume of working reagent was added to labeled test tubes, followed by the addition of serum samples or standards as per the manufacturer's instructions. The reaction mixtures were mixed thoroughly and incubated for the specified time at room temperature. Absorbance was measured using a semi-auto analyser at the wavelength recommended by the manufacturer, and lipid concentrations were calculated according to the kit protocols[24,25].

2.6 Determination of Hepatic Glucose Metabolic Enzymes Levels in Experimental Animals

For the assessment of glucose-metabolising enzymes in liver tissue, all experimental groups (Group I-IX)

were evaluated. Liver tissues were isolated from each animal, washed in ice-cold saline, and homogenised in phosphate buffer (pH 7.4). The homogenate was centrifuged at 3,000 rpm for 15 minutes at 4 °C to obtain the supernatant. The resulting liver supernatant was analysed for the activities of key glucose-metabolic enzymes hexokinase, glucose-6-phosphatase, and fructose-1,6-bisphosphatase using standard biochemical procedures and commercially available detection kits. Enzyme activity was measured using a semi-automated analyser with absorbance recorded at 340 nm[26,27].

2.7 Determination of Body Weight Changes in Experimental Animals

Body weight was monitored in all experimental groups (Groups I-IX) throughout the 28-day study period. Measurements were recorded at baseline and on days 7, 14, 21, and 28 using a calibrated digital weighing balance. Animals in the test groups (Groups III-VIII) received ethanolic extracts of *S. glabra* tuber and *C. phlomidis* leaves, while the control groups received the respective control treatments. Body-weight changes were compared with normal and diabetic control groups to assess treatment-related effects[28,29].

2.8 Biostatistical Analysis

All values are expressed as mean ± SEM. Data were analysed using GraphPad Prism (version 8.1) by one-way ANOVA followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1 Phytochemical Extraction and Screening

Ethanolic extraction of *S. glabra* L. tuber and *C. phlomidis* L. leaves yielded 25% and 30%, respectively, indicating efficient recovery of soluble phytoconstituents. Preliminary phytochemical screening confirmed the presence of multiple bioactive compounds in both extracts. The broad phytochemical profile suggests diverse secondary metabolites capable of exerting complementary pharmacological effects. These constituents may contribute to antidiabetic activity by enhancing fasting state insulin (basal insulin) secretion as well as postprandial state insulin (bolus insulin) release, thereby improving glycemic control and also antihyperlipidemic effects[30]. The phytochemical screening results are in Table 1.

3.2 Effect of Ethanolic Test Extracts on Antidiabetic Activity by Chronic *In Vivo* Study

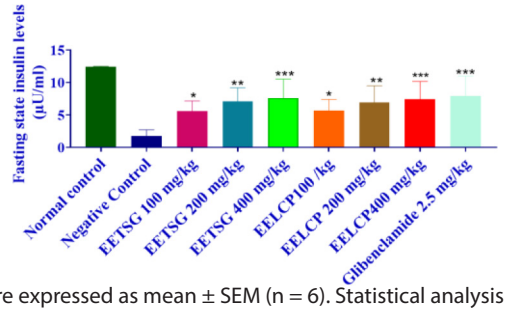
In the normal control group, Fasting Serum Insulin (FSI) and Postprandial Serum Insulin (PPSI) remained stable, while the diabetic control group showed sharp reductions of 94% and 90%. The ethanolic test extracts treated Group-III (100 mg/kg) fasting serum insulin and postprandial serum insulin increased by (60% and 61%) and (60% and 69%), respectively. Groups IV and V (200 and 400 mg/kg) produced greater increases (75% and 82%) and (70% and 87%). At 400 mg/kg, while standard glibenclamide (2.5 mg/kg) produced the highest improvement, 90% and 95% as presented in Figure 1 and 2.

3.3 Effect of Ethanolic Test Extracts on Antihyperlipidemic Activity by Chronic *In Vivo* Study

The Group-III (100 mg/kg) of ethanolic extracts showed decreases in total cholesterol, triglycerides, low-density and very-low-density lipoproteins, along with an increase in high-density lipoprotein. Group-IV and V (200 and 400 mg/kg) both extracts produced statistically significant lipid parameters[31,32]. When compared with the glibenclamide (2.5 mg/kg), the test extracts demonstrated strong lipid-modulating effects, as presented in Figure 3.

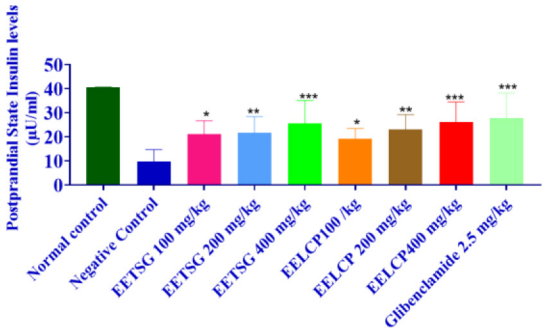
Table 1. Phytochemical screening of ethanolic test extracts

Category	*S. glabra* L. Tuber	*C. phlomidis* L. Leaves
Carbohydrates	Present	Absent
Alkaloids	Present	Present
Flavonoids	Present	Present
Proteins and amino acids	Present	Present
Terpenoids	Present	Present
Phenolic compounds	Present	Present
Tannis	Present	Absent
Phytosterols	Present	Present
Volatile oils	Present	Present



Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *S. glabra* and *C. phlomidis* leaves.

Figure 1. Effects of ethanolic test extracts on fasting state insulin levels.



Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *Stephania glabra* and *Clerodendrum phlomidis* leaves.

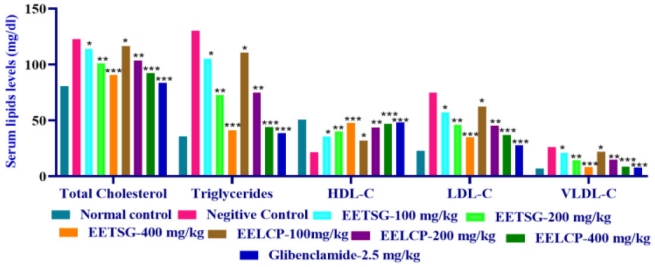
Figure 2. Effects of ethanolic test extracts on postprandial state insulin levels.

3.4 Effect of Ethanolic Test Extracts on Glucose Metabolic Enzymes by Chronic *In Vivo* Study

Normal control showed high hexokinase activity (270 IU/g protein) with low glucose-6-phosphatase (0.10 IU/g protein) and fructose-1,6-bisphosphatase (450 IU/g protein). Treatment produced dose-dependent normalization, with ethanolic tuber extract of *S. glabra* (400 mg/kg) nearly restoring control values[33,34]. Compared to standard control, glibenclamide (2.5 mg/kg) showed the greatest effect, as presented in Figure 4 and 5.

3.5 Effects of Ethanolic Test Extracts on Body Weight Chronic by Chronic *In Vivo* Study

The *S. glabra* tuber extract produced dose-dependent improvement, increasing body weight to +5.4%, +9.2% and +16.1% at 100, 200 and 400 mg/kg, respectively[35,36]. *C. phlomidis* leaves showed similar gains of +6.3%, +10.4% and +18.9%. Glibenclamide (2.5 mg/kg) produced the greatest increase in body weight, rising from 153 g to 193 g (+20.7%) as presented in Figure 6.

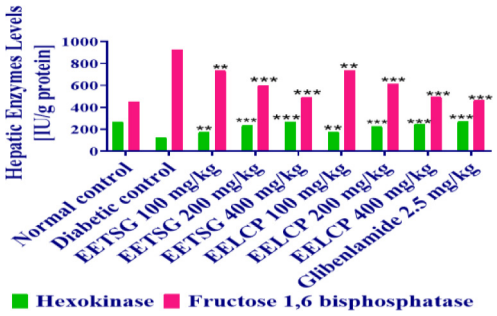


Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *S. glabra* and *C. phlomidis* leaves.

Figure 3. Effect of ethanolic test extracts on serum lipids in diabetic rats.

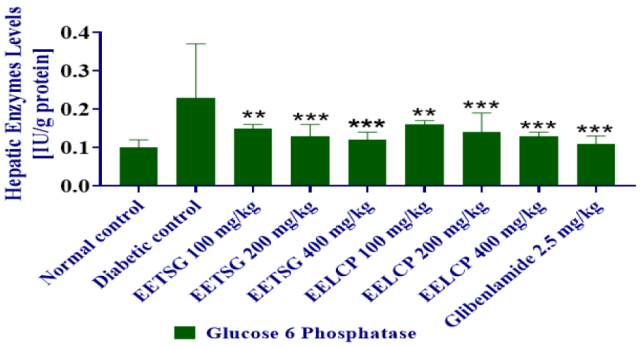
4. Discussion

Stephania glabra tuber and *C. phlomidis* leaves exert antidiabetic effects through complementary metabolic mechanisms. *S. glabra* tuber predominantly enhances insulin-mediated glucose utilisation by improving pancreatic β-cell responsiveness and peripheral glucose uptake. *C. phlomidis* leaves primarily regulate lipid metabolism by correcting insulin-dependent lipid handling. The coordinated action of these pathways improves carbohydrate-lipid integration. This dual modulation stabilises systemic energy balance[37,38]. As a result, metabolic efficiency and body weight regulation are improved. The biological activity of both extracts is supported by their phytochemical composition. Alkaloids such as berberine and palmatine protect pancreatic β-cells by limiting oxidative and inflammatory damage. Flavonoids including quercetin and kaempferol enhance insulin secretion and improve insulin sensitivity at target tissues. Phytosterols and triterpenoids contribute by reducing intestinal cholesterol absorption and hepatic lipid synthesis. These compounds act synergistically rather than independently. The phytochemical profile therefore explains the observed metabolic benefits.



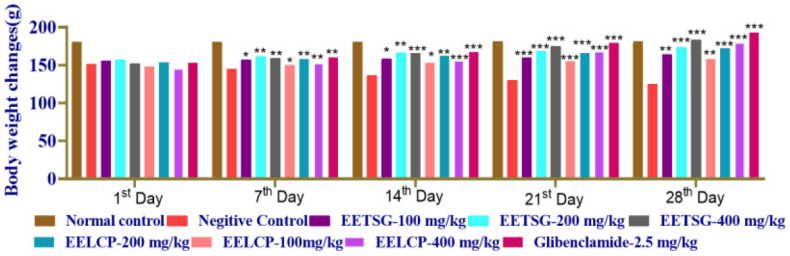
Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *S. glabra* and *C. phlomidis* leaves.

Figure 4. Effects of ethanolic test extracts on glucose metabolic enzyme levels changes of hexokinase and fructose 1,6 bisphosphatase enzyme levels.



Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *S. glabra* and *C. phlomidis* leaves.

Figure 5. Effects of ethanolic test extracts on glucose 6 phosphatase enzyme levels.



Data are expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001 vs negative control. EETSG and EELCP represent the ethanolic tuber extract of *S. glabra* and *C. phlomidis* leaves.

Figure 6. Effect of ethanolic test extracts on body weight changes in diabetic rats.

The present study demonstrates that the *S. glabra* L. tuber and *C. phlomidis* L. leaves ethanolic extracts possess a rich phytochemical composition, including alkaloids, flavonoids, phenolics, phytosterols, and triterpenoids. The presence of alkaloids such as berberine and palmatine, and flavonoids such as quercetin and kaempferol, is noteworthy, as these compounds are well documented for their ability to increases the β-cell count and followed insulin secretion, regulate lipid levels, modulate glucose-metabolising enzyme activities, and body weight. It possesses significant potential to enhance insulin levels, including both fasting and postprandial insulin levels, thereby contributing to improved glucose homeostasis. In addition, it exhibits marked antihyperlipidemic activity, indicating its ability to regulate lipid metabolism alongside its insulin-modulating effects[39,40].

According to Daniel Ejim Uti *et al.*, plant derived phytochemicals exert antidiabetic effects through direct stimulation of insulin secretion from pancreatic β-cells. These bioactive compounds enhance β-cell viability, suppress apoptosis, and improve glucose-stimulated insulin release, thereby strengthening endogenous insulin output. Alkaloids such as berberine regulate glucose sensing and insulin gene expression, while flavonoids including quercetin activate the PI3K/Akt signalling pathway, resulting in enhanced insulin secretion. Genistein further promotes insulin release by inhibiting ATP-sensitive potassium channels, leading to membrane depolarisation and subsequent calcium influx, a critical trigger for insulin granule exocytosis. In addition, polyphenols such as curcumin and resveratrol protect β-cells from oxidative stress and inflammatory damage, preserving their functional integrity. Activation of AMP-activated protein kinase and modulation of intracellular signalling cascades collectively reinforce insulin biosynthesis and secretion. Taken together, current evidence indicates that

phytochemicals stimulate insulin production through coordinated molecular, cellular, and cytoprotective mechanisms targeting pancreatic β-cell function[41,42]. The active phytochemical compounds observed in both ethanolic extracts of *S. glabra* tuber and *C. phlomidis* leaves reflects a phytochemical composition commonly associated with antihyperglycemic, lipid-modulating and regulation of glucose metabolic enzyme levels providing a strong chemical basis for their potential roles in enhancing insulin activity, regulating glucose-metabolising enzymes, improving serum lipid profiles, and contributing to metabolic balance. Serum insulin estimation over the 28th day treatment period demonstrated a clear time and dose dependent restoration of insulin secretion in extract-treated diabetic rats. In the untreated diabetic group, Fasting Serum Insulin (FSI) and Postprandial Serum Insulin (PPSI) declined from day 1st to day 28th, indicating progressive β-cell destruction and impaired insulin biosynthesis. This decline is associated with hyperglycemia-induced oxidative stress, inflammatory signalling, and mitochondrial dysfunction, leading to β-cell apoptosis and reduced insulin gene expression[43]. The absence of β-cell protective mechanisms and impaired PI3K/Akt signalling further contribute to reduced insulin secretion and insulin sensitivity. According to Abu Sadat Md Sayem *et al.* activation of insulin receptor-mediated pathways, particularly the PI3K/Akt and AMPK cascades, is essential for efficient glucose uptake in skeletal muscle and adipose tissue. Experimental evidence shows that several phytochemicals enhance insulin sensitivity by promoting GLUT4 translocation and improving downstream insulin signalling. These compounds also modulate oxidative stress and inflammatory responses, thereby supporting β-cell function and insulin secretion. However, detailed *in vivo* mechanistic validation of these pathways remains limited, highlighting the need for further investigation[44]. Mechanistically, the gradual and sustained rise in both basal and postprandial insulin levels suggests protection of pancreatic β-cells against streptozotocin-induced oxidative damage, preservation of membrane integrity, and stimulation of insulin secretion from surviving β-cells, likely through enhancement of glucose-stimulated insulin release involving ATP-sensitive potassium channel modulation and calcium-dependent exocytosis. Overall, the temporal pattern supports β-cell preservation and functional recovery rather than a transient insulinotropic effect[45,46].

Serum lipid analysis demonstrated a pronounced improvement in diabetes-induced dyslipidemia in rats treated with extracts of *S. glabra* and *C. phlomidis*. In diabetic rats, elevations in Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), and Very-Low-Density Lipoprotein Cholesterol (VLDL-C) occurred alongside a reduction in High-Density Lipoprotein Cholesterol (HDL-C), indicating disrupted insulin-dependent lipid regulation and excessive hepatic lipid output. Following extract administration, these abnormalities were progressively corrected in a dose-dependent manner, with higher doses producing lipid profiles comparable to glibenclamide. This improvement is mechanistically attributed to restoration of insulin signalling, which suppresses hormone-sensitive lipase-mediated adipose lipolysis, thereby reducing free fatty acid flux to the liver and limiting hepatic triglyceride synthesis. The consequent reduction in VLDL-C production leads to decreased LDL-C formation. Concurrent activation of Lipoprotein Lipase (LPL) enhances peripheral clearance of triglyceride-rich lipoproteins, while elevated HDL-C reflects improved reverse cholesterol transport. Collectively, these coordinated molecular events account for the normalisation of lipid homeostasis observed under diabetic conditions[47,48]. Hepatic enzyme analysis demonstrated a clear improvement in glucose metabolism in diabetic rats treated with extracts of *S. glabra* tuber and *C. phlomidis* leaves. Diabetes markedly suppressed Hexokinase (HK) activity while elevating Glucose-6-Phosphatase (G6Pase) and Fructose-1,6-Bisphosphatase (F-1,6-BPase) activities, reflecting impaired hepatic glucose utilisation and excessive activation of gluconeogenesis[49,50].

Treatment with both plant extracts produced a dose-dependent normalisation of these enzymes, with the highest doses approaching the effect of glibenclamide. Notably, *S. glabra* at 200 and 400 mg/kg nearly regulates glucose metabolic enzyme levels, while *C. phlomidis* exhibited comparable efficacy[51]. Mechanistically, these changes reflect suppression of hepatic gluconeogenesis through inhibition of key rate-limiting enzymes, including Glucose-6-Phosphatase (G6Pase) and Fructose-1,6-Bisphosphatase (FBPase), coupled with enhanced

insulin-mediated activation of glycolytic pathways. Restoration of insulin signalling *via* the Phosphoinositide 3-Kinase/protein kinase B pathway (PI3K/Akt) promotes phosphorylation-dependent inactivation of Forkhead box O1 (FOXO1), thereby downregulating transcription of gluconeogenic genes and limiting hepatic glucose output. Concurrent improvement in glycolytic flux further reduces endogenous glucose production, resulting in improved glycemic control[52].

In contrast, treatment with *S. glabra* and *C. phlomidis* extracts resulted in dose-dependent recovery of body weight, with the highest doses effectively reversing diabetes-associated weight loss and closely matching the response of glibenclamide. This improvement likely arises from better glucose utilisation, reduced muscle wasting, and restoration of anabolic metabolism driven by improved insulin availability. Together, these findings demonstrate that both plant species restore hepatic metabolic balance and systemic energy homeostasis, thereby contributing to sustained glycemic control and prevention of diabetes-induced wasting[53,54].

5. Conclusion

The present studies shows that the Ethanolic Extracts of *S. glabra* tuber (EETSG) and *C. phlomidis* leaves EELCP) exert notable antidiabetic effects, improving insulin activity, lipid balance, hepatic enzyme function, and body weight. Their dose-dependent benefits support their potential as natural therapeutic candidates for diabetes, warranting further pharmacological and clinical investigation.

6. Declaration

Competing interest, the authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This study did not involve any experiments on human participants conducted by the authors.

7. Acknowledgement

The authors express their sincere gratitude to the University College of Pharmaceutical Sciences, Acharya Nagarjuna University for providing us with the support and technical facilities.

8. Statement of Ethical Approval

All animal experimental work was carried out in the Department of Pharmacology, Hindu College of Pharmacy, Guntur, after obtaining approval from the Institutional Animal Ethics Committee (IAEC Approval No. IAEC-HOCP/2022/06).

9. References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi JA. Epidemiology of Type 2 diabetes - global burden of disease and forecasted trends. J Epidemiol Glob Health. 2023; 10(1):107-111. https://doi.org/10.2991/jegh.k.191028.001 PMid: 32175717. PMCid: PMC7310804.
2. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Sci Rep. 2024; 7(3):e2004. https://doi.org/10.1002/hsr2.2004 PMid: 38524769. PMCid: PMC10958528.
3. Gupta R, Misra A. Hyperlipidaemia management in diabetes: First line or supportive therapy. Diabetes Metab Syndr. 2023; 16(4):102470. https://doi.org/10.1016/j.dsx.2022.102470 PMid: 35378385.
4. Kim S, Subramanian S. Approach to lipid management in the patient with diabetes. J Clin Endocrinol Metab. 2025; 110(6):1740-1755. https://doi.org/10.1210/clinem/dgaf018 PMid: 39797609.
5. Rabbani N, Xue M, Thornalley PJ. Hexokinase 2 linked glycolytic overload and unscheduled glycolysis-driver of insulin resistance and development of vascular complications of diabetes. Int J Mol Sci. 2022; 23(4):2165. https://doi.org/10.3390/ijms23042165 PMid: 35216280. PMCid: PMC8877341.
6. Poelje PD, Potter SC, Erion MD. Fructose 1,6 bisphosphatase reduces excessive endogenous glucose production in Type 2 diabetes. Diabetes - Perspectives in Drug Therapy. Handbook of Experimental Pharmacology. 2011; (203):279-301. https://doi.org/10.1007/978-3-642-17214-4_12 PMid: 21484576.
7. Tian W, Cao S, Guan Y, Zhang Z, Liu Q, Ju J, Xi R, Bai R. The effects of low-carbohydrate diet on glucose and lipid metabolism in overweight or obese patients with T2DM: A meta-analysis of randomized controlled trials. Front Nutr. 2025; 11:1516086. https://doi.org/10.3389/fnut.2024.1516086 PMid: 39834467. PMCid: PMC11743357.
8. Akomolafe SF, Ajayi OO, Agboola OE, Adewale OO. Comparative evaluation of the antidiabetic potential of

three varieties of *Ipomoea batatas* L. Toxicol Rep. 2025; 14:102015. https://doi.org/10.1016/j.toxrep.2025.102015 PMid: 40230512. PMCid: PMC11995110.
9. Adam SY, Eltahir HA, Ismaeel FAM, Abdallah RH, Abaker AO, Musa HH, Husien HM, Mohammed LA, Cai D, Ahmed AA. Gum arabic regulates glucose metabolic enzymes through modification of hepatic phosphoenolpyruvate carboxykinase expression in diabetic rats. Bioact Carb Diet Fib. 2025; 34:100490. https://doi.org/10.1016/j.bcdf.2025.100490
10. Marimuthu S, Gurav AM, Prasad GP. Phytochemical identification of *Clerodendrum phlomidis* L. by GC-MS analysis and its acetylcholinesterase inhibitory activity. Pharma Res. 2022; 14(2):166-171. https://doi.org/10.5530/pres.14.2.24
11. Krishnaveni R, Rajan S. *In-vitro* antioxidant and anti-inflammatory activity of the aqueous and ethanol leaf extracts of *Clerodendrum phlomidis* Linn. F. Res J Pharma Technol. 2021; 14(10):5217-5223. https://doi.org/10.52711/0974-360X.2021.00908
12. Keith D, Apte K, Chintamaneni A, Chintamaneni A, Chintamaneni M, Sharma U, *et al*. Phytochemical interventions of medicinal plants in the management of diabetes and obesity: A recent therapeutic overview. J Appl Pharm Sci. 2025; 16(1):46-69. https://doi.org/10.7324/japs.2025.217666
13. Hussain A, Ali AA, Ishaq S, Ahmad S, Zainab W, Qasim M. Medicinal plants and their active phytoconstituents used in the management of diabetes mellitus: A comprehensive review. JHWCR. 2025; 3(13):e774. https://doi.org/10.61919/ectdsm05
14. Abdelazim AM, Afifi M, Abu-Alghayth MH, Alkadri DH. *Moringa oleifera*: Recent insights for its biochemical and therapeutic potentials. J Food Biochem. 2024. https://doi.org/10.1155/2024/1270903
15. Li L, Ma L, Wen Y, Xie J, Yan L, *et al*. Crude polysaccharide extracted from *Moringa oleifera* Leaves Prevents Obesity in Association With Modulating Gut Microbiota in High-Fat Diet-Fed Mice. Fronti Nutri. 2022; 9:861588. https://doi.org/10.3389/fnut.2022.861588 PMid: 35548566. PMCid: PMC9083904.
16. Phimarn W, Sungthong B, Wichaiyo K. Efficacy and safety of *Moringa oleifera* on blood glucose and lipid profile: A meta-analysis. Pharma Mag. 2021; 17:373-378. https://doi.org/10.4103/pm.pm_49_20
17. Abraham SM, Varkey IC. Phytochemical analysis, antioxidant, antibacterial and wound healing efficiency of *Peperomia pellucids*, leaf extracts. J Nat Rem. 2025; 25(10):2363-2379. https://doi.org/10.18311/jnr/2025/50933
18. Elango A, Radhakrishnan A, Chittrarasan S. Anti-inflammatory and organ-protective effects of *Kabasura Kudineer*, a *Siddha* polyherbal formulation in Lipopolysaccharide (LPS) induced Systemic Inflammatory Response Syndrome (SIRS) in Wistar albino rats. J Nat Rem. 2025; 25(10):2433-2446. https://doi.org/10.18311/jnr/2025/51131
19. Wongsa P, Phatikulrungsun P, Prathumthong S. FT-IR characteristics, phenolic profiles and inhibitory potential against digestive enzymes of 25 herbal infusions. Sci Rep. 2022; 12:6631. https://doi.org/10.1038/s41598-022-10669-z PMid: 35459897. PMCid: PMC9033800.
20. Feenna OP, Estella OU, Obodike EC. Phytochemical analysis and anti-diabetic activity of leaf extract of *Psydrax horizontalis* Schum and Thonn (*Rubiaceae*). Pharmacogn J. 2020; 12(1):95-102. https://doi.org/10.5530/pj.2020.12.15
21. Alam S, Sarker MMR, Sultana TN, Chowdhury NR, Rashid MA, Chaity NI, *et al*. Antidiabetic phytochemicals from medicinal plants: Prospective candidates for new drug discovery and development. Front Endocrinol. 2022; 13:800714. https://doi.org/10.3389/fendo.2022.800714 PMid: 35282429. PMCid: PMC8907382.
22. Ismail S, Chandel TI, Ramakrishnan J, Khan RH, Poomani K, Devarajan N. Phytochemical profiling, human insulin stability and α-glucosidase inhibition of *Gymnema latifolium* leaves aqueous extract: Exploring through experimental and *in silico* approach. Comput Biol Chem. 2023; 107:107964. https://doi.org/10.1016/j.compbiolchem.2023.107964 PMid: 37820470.
23. Ansari P, Khan JT, Chowdhury S, Reberio AD, Kumar S, Seidel V, *et al*. Plant-based diets and phytochemicals in the management of diabetes mellitus and prevention of its complications: A review. Nutrients, 2024; 16(21):3709. https://doi.org/10.3390/nu16213709 PMid: 39519546. PMCid: PMC11547802.
24. Althaher AR, Alwahsh M, Hasan A, Al-Majali D, Awadallah MW, Al-Qirim T. Anti hyperlipidemic effect of *Ruta chalepensis* ethanolic extract in triton WR 1339 induced hyperlipidemia in rats. Appl Sci. 2024; 14(19):9017. https://doi.org/10.3390/app14199017
25. Bencheikh N, Bouhrim M, Merrouni IA, Boutahiri S, *et al*. Anti hyperlipidemic and antioxidant activities of flavonoid rich aqueous extract of *Ziziphus lotus* fruits. Appli Sci. 2021; 11(17):7788. https://doi.org/10.3390/app11177788
26. Tchamgoue AD, Dzeufiet PDD, Kuiata JR, *et al*. *Costus afer* modulates the activities of glycolytic and gluconeogenic enzymes in streptozotocin induced diabetic rats. J Drug Delivery Ther. 2020; 10(4-s):63-70. https://doi.org/10.22270/jddt.v10i4-s.4270
27. Sureka C, Elango V, Al-Ghamdi S, Aldossari K K, Alsaidan M, *et al*. Ameliorative property of *Sesbania grandiflora* on carbohydrate metabolic enzymes in the liver and kidney of streptozotocin induced diabetic rats. Saudi J Biol Sci. 2021; 28(7):3669-3677. https://doi.org/10.1016/j.sjbs.2021.05.002 PMid: 34220217. PMCid: PMC8241611.
28. Satyanarayana N, Chinni SV, Sunitha P, Sankar AU, Muthuvenkatachalam BS. Antidiabetic activity of *Solanum torvum* fruit extract in streptozotocin-induced diabetic

rats. Fronti Nut. 2022; 9:987552. https://doi.org/10.3389/fnut.2022.987552 PMid: 36386935. PMCid: PMC9650639.
29. Huang YC, Chen BH. A comparative study on improving streptozotocin-induced diabetic rats using cinnamon extract and cinnamon nanoemulsion. Antioxidants. 2023; 12(1):29. https://doi.org/10.3390/antiox12010029 PMid: 36670891. PMCid: PMC9855112.
30. Adil M, Filimban FZ, Ambrin, *et al.* Phytochemical screening, HPLC analysis, antimicrobial and antioxidant effect of *Euphorbia parviflora* L. (*Euphorbiaceae* Juss.). Sci Rep. 2024; 14:5627. https://doi.org/10.1038/s41598-024-55905-w PMid: 38454096. PMCid: PMC10920658.
31. Lad SS, Kolhe SU. Evaluation of antihyperlipidemic potential of aqueous corm extract of *Colocasia esculenta* in experimental model of rats. Pharmacol Res Mod Chin Med. 2023; 9:100307. https://doi.org/10.1016/j.prmcm.2023.100307
32. Kubi SA, Amponsah IK, Turkson BK, *et al*. *Invivo* toxicity, anti-hyperlipidaemic, antioxidant and safety assessment of a herbal formulation "LIPO A" A traditional herbal product in rodents. Heliyon. 2024; 10(2):e24352. https://doi.org/10.1016/j.heliyon.2024.e24352 PMid: 38293377. PMCid: PMC10826722.
33. Husna F, Suyatna FD, Arozal W, Purwaningsih EH, Hanafi M, Razali R, Asrizal CW. *Murraya koenigii* extract improving rate-limiting enzymes on carbohydrate metabolism and GLUT-4 expression of hyperglycaemic rats. J Appl Pharm Sci. 2022; 12(12):143-149. https://doi.org/10.7324/JAPS.2022.121215
34. Mohamed FA, Sayed RH, Khalil MNA, Salem MA, El Senousy AS, El-Halawany AM. Ameliorative activity of standardized ethanolic leaves extract of *Coccoloba uvifera* against streptozotocin-induced diabetic rats. Future J Pharm Sci. 2024; 10:132. https://doi.org/10.1186/s43094-024-00707-0
35. El-Newary SA, Afifi SM, Aly MS, Ahmed RF, *et al.* Chemical profile of *Launaea nudicaulis* ethanolic extract and its antidiabetic effect in streptozotocin-induced rats. Molecules. 2021; 26(4):1000. https://doi.org/10.3390/molecules26041000 PMid: 33668635. PMCid: PMC7918448.
36. Pratiwi RY, Elya B, Setiawan H, Forestrania RC, Dewi RT. Antidiabetic properties and toxicological assessment of *Antidesma celebicum* Miq: Ethanolic leaves extract in sprague-dawley rats. Adv Pharmacol Pharm Sci. 2022: 05, 24, 2022:2584698. https://doi.org/10.1155/2022/2584698. PMid: 35656164. PMCid: PMC9155931.
37. Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, Zhao C, Xiao J, Hafez EE, Khan SA, Mohamed IN. Antidiabetic phytochemicals from medicinal plants: Prospective candidates for new drug discovery and development. Front Endocrinol. 2022; 13:800714. https://doi.org/10.3389/fendo.2022.800714 PMid: 35282429. PMCid: PMC8907382.
38. Sani UM. Phytochemical screening and antidiabetic effect of extracts of the seeds of *Citrullus lanatus* in alloxan-induced diabetic albino mice. J Appl Pharm Sci. 2015; 5(3):051-054. https://doi.org/10.7324/japs.2015.50309
39. Sknepnek A, Miletic D, Stupar A, Salevic-Jelic A, Nedovic V, Kljakic AC. Natural solutions for diabetes: The therapeutic potential of plants and mushrooms. Front Nutr. 2025; 12:1511049. https://doi.org/10.3389/fnut.2025.1511049 PMid: 40686811. PMCid: PMC12273588.
40. Ansari P, Reberio AD, Ansari NJ, Kumar S, Khan JT, Chowdhury S, *et al.* Therapeutic potential of medicinal plants and their phytoconstituents in diabetes, cancer, infections, cardiovascular diseases, inflammation and gastrointestinal disorders. Biomedicines. 2025; 13(2):454. https://doi.org/10.3390/biomedicines13020454 PMid: 40002867. PMCid: PMC11853317.
41. Uti D E, Atangwho I J, Alum E U, Egba S I, Ugwu O P, and Ikechukwu G C. Natural antidiabetic agents: Current evidence and development pathways from medicinal plants to clinical use. Nat Pro Commun. 2025; 20(3). https://doi.org/10.1177/1934578x251323393
42. Sknepnek A, Miletic D, Stupar A, Salevic-Jelic A, Nedovic V, Kljakic AC. Natural solution for diabetes: The therapeutic potential of plants and mushrooms. Front Nutri. 2025; 12:1511049. https://doi.org/10.3389/fnut.2025.1511049 PMid: 40686811. PMCid: PMC12273588.
43. Kumar A, Nirmal P, Kumar M, Jose A, Tomer V, *et al*. Major phytochemicals: Recent advances in health benefits and extraction methods. Molecules. 2023; 28(2):887. https://doi.org/10.3390/molecules28020887 PMid: 36677944. PMCid: PMC9862941.
44. Sayem AS, Arya A, Karimian H, Krishnasamy N, Hasamnis AA, Hossain CF. Action of phytochemicals on insulin signaling pathways accelerating glucose transporter (GLUT4) protein translocation. Molecules. 2018; 23(2):258. https://doi.org/10.3390/molecules23020258 PMid: 29382104. PMCid: PMC6017132.
45. Lee D, Lee JS, Sezirahiga J, Kwon HC, Jang DS, Kang KS. Bioactive phytochemicals isolated from *Akebia quinata* enhances glucose-stimulated insulin secretion by inducing PDX-1. Plants. 2020; 9(9):1087. https://doi.org/10.3390/plants9091087 PMid: 32847055. PMCid: PMC7570369.
46. Bas KU, Kopuz TNY. Therapeutic prospects of phytochemicals in diabetes: Insights from recent clinical evidence. Endokrynol Pols. 2025; 76(6):586-593. https://doi.org/10.5603/ep.107193 PMid: 41340339.
47. Wickramasinghe ASD, Kalansuriya P, Attanayake AP. Herbal medicines targeting the improved β-cell functions and regeneration for the management of diabetes mellitus. Evidence-Based Complementary and Alternative Medicine. Willey. 2021. https://doi.org/10.1155/2021/2920530 PMid: 34335803. PMCid: PMC8298154.

48. Ansari P, Islam SS, Akther S, Khan JT, Shihab JA, Abdel-Wahab YHA. Insulin secretory actions of ethanolic extract of *Acacia arabica* bark in high fat-fed diet-induced obese Type 2 diabetic rats. Biosci Rep. 2023; 43(5). https://doi.org/10.1042/BSR20230329 PMid: 37133312. PMCid: PMC10214104.
49. Tehrani SD, Shojaei M, Bagherniya M, Pirro M, Sahebkar A. The effects of phytochemicals on serum triglycerides in subjects with hypertriglyceridemia: A systematic review of randomized controlled trials. Phytother Res. 2023; 37(4):1640-1662. https://doi.org/10.1002/ptr.7763 PMid: 36756995.
50. Eilam Y, Pintel N, Khattib H, Shagug N, *et al*. Regulation of cholesterol metabolism by phytochemicals derived from algae and edible mushrooms. Int J Mol Sci. 2023; 23(22):13667. https://doi.org/10.3390/ijms232213667 PMid: 36430146. PMCid: PMC9697193.
51. Thopireddy L, Yarrappagaari S, Benne L N, Seethamma G, Tenkayala SR, Saddala RR. Protective role of methanolic extract of *Cleome viscosa* L. and *Cleome gynandra* L. on carbohydrate metabolic enzymes in STZ - induced diabetic rats. Int J Ayurvedic Med. 2025; 16(3):670-679. https://doi.org/10.47552/ijam.v16i3.5888
52. Anis S, Singh RK. Evaluation of hypoglycemic activity of bark extracts of *Clerodendrum phlomidis*. Int J Pharm Res Appl. 2023; 8(5):1159-1172.
53. Govindarajan S, Babu SN, Vijayalakshmi MA, Manohar P, Noor A. *Aloe vera* carbohydrates regulate glucose metabolism through improved glycogen synthesis and downregulation of hepatic gluconeogenesis in diabetic rats. J Ethnopharmacol. 2021; 281:114556. https://doi.org/10.1016/j.jep.2021.114556 PMid: 34438036.
54. Rebollo-Hernanz M, Aguilera Y, Martin-Cabrejas MA, Mejia EG. Regulation of lipid and glucose metabolism in hepatocytes by phytochemicals from coffee by-products and prevention of non-alcoholic fatty liver disease *in vitro*. Proceedings. 2020; 61(1):20. https://doi.org/10.3390/IECN2020-06996

Author Contribution

Conceptualization: Parimi Ravi; Methodology: K.E. Pravallika, Parimi Ravi and Amos Babu. Jetti; Validation: K.E. Pravallika, Parimi Ravi and Amos Babu. jetti; Writing and editing: K.E. Pravallika, Parimi Ravi Amos Babu. jetti. All authors have read and agreed to the published version of the manuscript.