Integrative analysis of Geodorum Densiflorum Bulbs in diabetes management: network pharmacology and in vivo validation

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***Abstract*—Objectives: This study aims to investigate the antidiabetic potential of Geodorum densiflorum bulbs using an integrative approach combining network pharmacology and in vivo validation. Evaluating the glucose-lowering effects and pancreatic beta-cell function of Geodorum densiflorum bulb extracts in diabetic rat models**

Method: Plant: Geodorum densiflorum

Part- Bulb

Extract- Hydroalcoholic Extract

Animal Model: - Alloxan Induced Hypoglycemic Model

1.. Preparation of extract: Collection, authentication, cleaned and dried. Extraction- dried bulb powder was subjected to maceration in a hydroalcoholic solution

2. Network Pharmacology Analysis: Identifying bioactive compounds in Geodorum densiflorum bulbs and predicting their potential targets in diabetes pathways.

3. In Vivo Validation: Using Alloxan Induced Hypoglycemic Model to evaluate the glucose-lowering effects and pancreatic beta-cell function of Geodorum densiflorum bulb extracts.

Results: The network pharmacology analysis predicted key bioactive compounds, including flavonoids and phenolic compounds, and their potential targets in diabetes pathways. In vivo validation demonstrated significant glucose-lowering effects, improved insulin sensitivity, and enhanced pancreatic beta-cell function in diabetic rats treated with Geodorum densiflorum bulb extracts.

Conclusion: This study suggests that Geodorum densiflorum bulbs may be a promising natural remedy for diabetes management, warranting further research into its therapeutic potential. The integrative approach used in this study provides a comprehensive understanding of the antidiabetic effects of Geodorum densiflorum bulbs and identifies potential therapeutic targets for diabetes treatment

***Index Terms*—Geodorum densiflorum, Diabetes management, Network pharmacology, In vivo validation, Antidiabetic effects, Insulin sensitivity, pancreatic beta-cell function, Therapeutic potential, Diabetes treatment**

I. INTRODUCTION

A. Overview of Diabetes Mellitus

Diabetes mellitus (DM) is a habitual metabolic complaint characterized by patient hyperglycaemia performing from blights in insulin stashing, insulin action, or both. The condition is associated with disturbances in carbohydrate, fat, and protein metabolism and frequently leads to long- term damage, dysfunction, and failure of colourful organs, particularly the eyes, feathers, jitters, heart, and blood vessels. The term" diabetes" is deduced from the Greek word meaning" to siphon," representing the inordinate urination seen in unbridled cases, while" mellitus" refers to the sweet taste of urine due to the presence of glucose, an individual hallmark since ancient times. Despite its literal roots, diabetes is now honoured as one of the swift- growing global health extremities of the 21st century. (Bereda, 2021; Dreyer, 2019; Katsarou et al., 2017; A. A. Yameny, 2024)

The bracket of diabetes has evolved to accommodate its complex and multifactorial nature. According to the American Diabetes Association (ADA) and the World Health Organization (WHO), diabetes is distributed into four major types

Type 1 diabetes mellitus (T1DM) is primarily autoimmune in nature, involving T- cell mediated destruction of pancreatic β- cells. It leads to absolute insulin insufficiency and generally manifests in children and adolescents, although adult- onset T1DM is decreasingly honored.(Dreyer, 2019; Katsarou et al., 2017; Rajashree et al., 2012)

Type 2 diabetes mellitus (T2DM), the most current form, is caused by a combination of insulin resistance and relative insulin insufficiency. It has a strong

inheritable predilection and is heavily told by environmental and life factors similar as rotundity, physical inactivity, and unhealthy diets. (Chatterjee et al., 2017; Olokoba et al., 2012)

Gravid diabetes mellitus (GDM) develops during gestation, generally in the alternate or third trimester, and is associated with an increased threat of perinatal complications and unborn T2DM for both mama and child. (Deshmukh and Jain, 2015; Saha et al, 2020; A. A. Yameny, 2024)

Other specific types include monogenic diabetes runs (similar as MODY — maturity- onset diabetes of the youthful), conditions of the exocrine pancreas (e.g., cystic fibrosis- related diabetes), and medicine- or chemical- convinced diabetes (e.g., from corticosteroids or antipsychotics).(Chatterjee et al., 2017; Kumar et al., 2020; Saha et al, 2020)

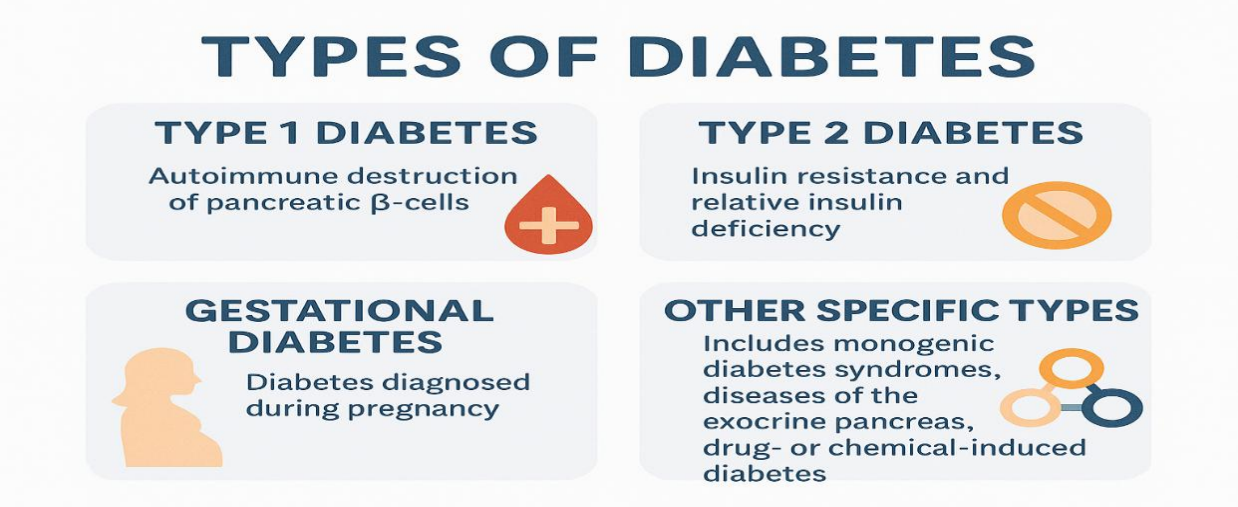


Figure 1: Types of Diabetes

Global Overview of Diabetes Mellitus (2015–2025)

Diabetes mellitus has surfaced as one of the most significantnon-communicable conditions worldwide, with its frequence steadily rising over the last decade. Encyclopaedically, the number of grown-ups progressed 20 – 79 times living with diabetes increased from roughly 415 million in 2015 to 537 million in 2021, and it's estimated to have reached 589 million by 2024, reflecting an intimidating 11.1 frequency rate among grown-ups. This swell represents a 40 rise in global diabetes cases within ten times. vaticinations by the International Diabetes Federation (IDF) suggest that this figure may surpass 640 million by 2030 and reach over 850 million by 2050. The Western Pacific and South- East Asia regions, driven by vibrant nations like China and India, contribute the loftiest number of diabetes cases encyclopedically. Still, the loftiest frequence rates are recorded in the Middle East and North Africa (MENA), where over 16 of the adult population is diabetic. China leads encyclopedically with over 140 million diabetics, followed by India and Pakistan. Despite a slightly lower frequence, Africa is anticipated to see the most rapid-fire rise due to urbanization and salutary shifts. (Abuelgasim et al., 2021; Canto et al., 2019; Irakoze, 2024; Jakhar et al., n.d.; Namazi et al., 2024; A. Yameny, 2024)

Type 2 diabetes constitutes further than 90 of all global diabetes cases and is primarily associated with life and inheritable factors. In discrepancy, Type 1 diabetes, which is autoimmune in origin, affects around 8.4 million people worldwide, and this number is projected to nearly double by 2040. Encyclopedically, diabetes was responsible for about 5 million deaths in 2015, which rose to 6.7 million by 2021. Recent estimates in 2024 report over 3.4 million deaths, making it one of the top ten causes of death worldwide. Beyond mortality, diabetes leads to severe complications including cardiovascular conditions, order failure, neuropathy, retinopathy, and lower branch amputations. These complications not only dwindle the quality of life but also put a significant fiscal burden on individualities and healthcare systems. As of 2024, the global expenditure on diabetes care has surpassed$ 1 trillion USD annually, a stunning increase from$ 232 billion in 2007. This

cost includes drug, diagnostics, hospitalizations, and long- term complication operation. (Deng et al., 2024; Liu et al., 2020; Namazi et al., 2024; Ong et al., 2023)

Indian Perspective on Diabetes Mellitus (2015 – 2025)

India holds the alternate-loftiest number of diabetes cases encyclopedically, after China. In 2015, around 69 million Indians were diagnosed with diabetes, which surged to 77 million in 2019. Still, the corner ICMR – INDIAB study published in 2023 reported a shocking rise to 101 million diabetics in India, equating to an 11.4 frequence among grown-ups. This marks a 44 increase in just four times. Also, about 136 million Indians are presently classified aspre-diabetic, posing a serious threat of unborn conversion to diabetes. Specially, over 60 ofpre-diabetics in India are likely to develop full-bloated diabetes within five times without intervention. protrusions suggest that India could witness over 134 million diabetes cases by 2045, with recent trends intimating that the factual figures may be indeed advanced. (Chauhan et al., 2025; Ding et al., 2025; Kyu et al., 2016; Tandon et al., 2018; Xu et al., 2025)

India's diabetes epidemic is driven by multiple threat factors, including inheritable predilection, urbanization, poor salutary habits, physical inactivity, and rising rotundity rates. The Asian Indian phenotype — characterized by a advanced body fat chance at lower BMI — makes Indians innately more susceptible. According to the ICMR study, nearly 29 of Indians are fat and around 40 exhibition abdominal rotundity. Comorbid conditions similar as hypertension (present in 35.5 of grown-ups) and dyslipidaemia (affecting 81.2) further amplify the threat of cardiovascular complications. Gravid diabetes is also decreasingly common among Indian women, contributing to unborn Type 2 diabetes in both mama and child. (Liu et al., 2024; Tandon et al., 2018; Xie et al., 2022; Xu et al., 2025)

B. Pathophysiology of diabetes: -

Diabetes mellitus (DM) is a habitual, progressive metabolic complaint marked by habitual hyperglycaemia and disturbances in the metabolism of carbohydrates, lipids, and proteins. The pathological hallmark of diabetes lies in the imperfect regulation of insulin, the hormone central to energy homeostasis. This dysregulation arises due to shy insulin stashing, bloodied insulin action, or a combination of both. The complaint, though unified under the term "diabetes," is largely miscellaneous in its etiology, clinical donation, and pathophysiology. An in- depth understanding of the distinct pathological mechanisms underpinning different types of diabetes is essential not only for accurate opinion and operation but also for relating new remedial targets including those from medicinal factory sources.(Bereda, 2021; Deshmukh and Jain, 2015; Kumar et al., 2020; Olokoba et al., 2012; Saha et al, 2020)

Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus is an organ-specific autoimmune complaint characterized by vulnerable-mediated destruction of the insulin- producing pancreatic β- cells located in the islands of Langerhans. The condition leads to an absolute insulin insufficiency, rendering the individual insulin-dependent for life. It generally presents in childhood or adolescence, but adult- onset forms similar as idle autoimmune diabetes in grown-ups (LADA) are decreasingly honoured. The immunopathogenesis of T1DM involves both cellular and humoral impunity. $CD4^+$ coadjutor T cells and $CD8^+$ cytotoxic T lymphocytes insinuate the pancreatic islands in a process known as insulitis, feting and attacking β- cell autoantigens similar as insulin, glutamic acid decarboxylase(GAD65), insulinoma- associated antigen- 2(IA- 2), and zinc transporter 8(ZnT8). These autoantigens also induce specific autoantibodies, which are measurable biomarkers for complaint vaticination. The presence of two or further autoantibodies predicts the progression to overt diabetes with high particularity. (Alam et al., 2014; Chatterjee et al., 2017; Katsarou et al., 2017; Korc, 2004; Nadhiya J et al., 2024; Surya et al., 2014)

Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is the predominant form of diabetes worldwide, counting for roughly 90 – 95 of all cases. The pathophysiology of T2DM is complex and involves a binary disfigurement originally, insulin resistance in supplemental apkins (muscle, liver, and adipose towel), followed by progressive β- cell failure. This binary disfigurement results in an incapability of the body to regulate blood glucose effectively, indeed in the presence of elevated insulin situations. Insulin resistance in T2DM is multifactorial. It arises from post-receptor signalling blights in insulin- responsive

apkins, frequently aggravated by intracellular lipid accumulation (lipotoxicity), pro-inflammatory cytokines, and mitochondrial dysfunction. In cadaverous muscle, glucose uptake via GLUT4 transporters is bloodied; in the liver, unbounded gluconeogenesis contributes to dieting hyperglycemia. Adipose towel contributes to metabolic dysregulation by concealing seditious adipokines similar as TNF- α, IL- 6, and resistin, while situations of insulin-sensitizing adiponectin are generally reduced.(Alam et al., 2014; Dahms, 1991; Deshmukh and Jain, 2015; Janghorbani et al., 2007; Saha et al, 2020; A. A. Yameny, 2024) Originally, pancreatic β- cells compensate by adding insulin affair (hyperinsulinemia), but over time, habitual metabolic stress induces oxidative stress, endoplasmic reticulum(ER) stress, and β- cell apoptosis, leading to relative insulin insufficiency. The decline in β- cell mass and function marks the transition from disabled glucose forbearance (IGT) to foursquare diabetes. Genetically, T2DM is associated with polymorphisms in genes similar as TCF7L2, SLC30A8, and KCNJ11, but environmental factors sedentary geste , high- fat diets, and rotundity — are the dominant threat determinants. Unlike T1DM, T2DM has an insidious onset, frequently remaining undiagnosed until complications manifest. Therefore, early intervention strategies, including life revision and pharmacotherapy, are vital to delay or help complaint progression. (Chatterjee et al., 2017; Katsarou et al., 2017; Olokoba et al., 2012)

Other Specific Types of Diabetes

allow successful operation with sulfonylureas rather of insulin. (Beltrand et al., 2020; Korc, 2004) In addition to T1DM and T2DM, several other forms of diabetes live, each with distinct etiopathological features.

Gravid Diabetes Mellitus (GDM) is defined as glucose dogmatism with onset or first recognition during gestation. GDM results from placental hormone-convinced insulin resistance combined with shy β- cell compensation. Hormones similar as mortal placental lactogen, estrogen, and progesterone envenom insulin action, particularly in the third trimester. Women with GDM are at high threat for preeclampsia, macrosomia, and unborn development of T2DM. Babies born to maters With GDM are fitted to rotundity and glucose dogmatism, immortalizing an intergenerational cycle of metabolic complaint. (Deshmukh and Jain, 2015; Saha et al, 2020; A. A. Yameny, 2024)

Neonatal Diabetes Mellitus (NDM) is a rare form of monogenic diabetes presenting in the first six months of life. Mutations in genes similar as KCNJ11, ABCC8, and INS vitiate insulin stashing. NDM can be flash or endless. Remarkably, some mutations

C. Insulin resistrance and β-cell dysfunction: the twin defects:

The dual pathology of insulin resistance and β-cell dysfunction lies at the heart of T2DM and is increasingly recognized in other forms such as GDM and some monogenic types. Insulin resistance occurs when normal its receptor activates the IRS-1/PI3K/Akt pathway, which promotes GLUT4 translocation and glucose uptake. In insulin-resistant states, serine phosphorylation of IRS-1 inhibits downstream signaling. Mitochondrial dysfunction, elevated free fatty acids, and inflammatory cytokines contribute to impaired insulin action. The JNK and NF-κB pathways, activated by oxidative and inflammatory stimuli, further exacerbate insulin resistance. As compensation, β-cells initially increase insulin output. However, chronic exposure to hyperglycemia (glucotoxicity), elevated lipids (lipotoxicity), and oxidative stress leads to β-cell exhaustion, ER stress, and apoptosis. Progressive loss of β-cell mass and functional impairment marks the clinical onset and deterioration of diabetes. Understanding this dual mechanism has prompted the development of therapies targeting both defects—metformin and TZDs improve insulin sensitivity, while GLP-1 analogs and DPP-4 inhibitors enhance β-cell function. (Deshmukh and Jain, 2015; Korc, 2004; Saha et al, 2020)

D. Role of oxidative stress and infaltion:-

Oxidative stress and low-grade inflammation are unifying mechanisms that contribute to both the development and progression of diabetes and its complications. In both T1DM and T2DM, excessive production of reactive oxygen species (ROS) overwhelms endogenous antioxidant defenses, leading to cellular damage. In β-cells, which are inherently low in antioxidant enzymes, ROS disrupt mitochondrial function, impair insulin gene expression, and initiate apoptotic pathways. Inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ—secreted by infiltrating

macrophages and T cells—further damage β-cells by activating NF-κB, enhancing nitric oxide production, and triggering ER stress.In peripheral tissues, oxidative stress interferes with insulin signaling via modification of proteins and lipids, leading to impaired glucose uptake. Inflammation in adipose tissue, characterized by macrophage infiltration and altered adipokine secretion, plays a pivotal role in systemic insulin resistance. Oxidative stress also contributes to vascular complications by promoting endothelial dysfunction, increasing vascular permeability, and inducing platelet aggregation. The formation of advanced glycation end-products (AGEs) and activation of the polyol pathway further link oxidative mechanisms to nephropathy, neuropathy, and retinopathy. Given their multitargeted antioxidant and anti-inflammatory properties, several medicinal plants and phytochemicals have shown promise in preclinical and clinical models. (Alam et al., 2019; Arumugam et al., 2013; Bushnak et al., 2021; Kumar et al., 2020; Sadino, 2018; Saha et al, 2020)

E. COMPLICATION OF DIABETES

Diabetes mellitus, if not properly managed, leads to a cascade of complications that compromise nearly every organ system. These complications, classified into acute and chronic, arise primarily from prolonged exposure to hyperglycemia and are amplified by oxidative stress, inflammation, dyslipidemia, endothelial dysfunction, and immune dysregulation. While acute complications demand immediate intervention to prevent mortality, chronic complications silently progress over years, culminating in disability and premature death. Both types impose an enormous burden on individuals, families, and healthcare systems globally. The World Health Organization (WHO) estimates that more than 1.6 million deaths per year are directly attributed to diabetes, with most resulting from long-term complications. Understanding these complications is critical for the justification and evaluation of plant-based therapeutic strategies. (Bereda, 2021; Deshmukh and Jain, 2015; Katsarou et al., 2017; Rajashree et al., 2012; Saha et al, 2020; A. A. Yameny, 2024)

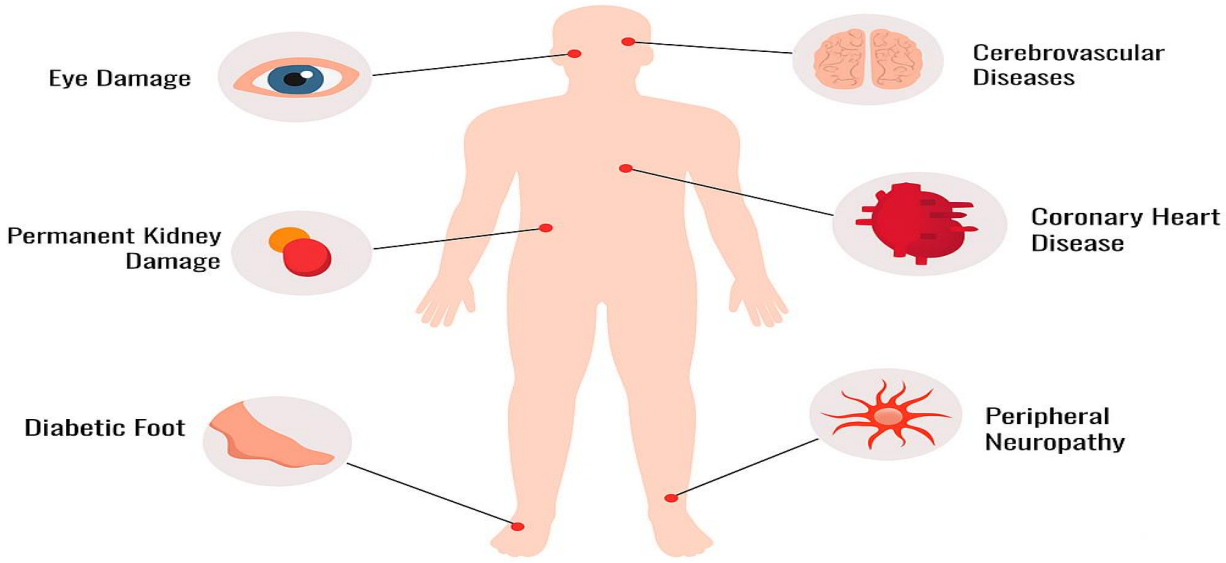


Figure 2: Complications of Diabetes

F. PLANT PROFILE:-

Biological source: It is bulbs obatined from the plant, Geodorum densiflorum.
Family: Orchidaceae

Taxonomy
Kingdom: Plantae
Phylum: Tracheophytes
Class: Monocots
Order: Asparagales

Family: Orchidaceae
Genus: Geodorum
Species: G. densiflorum

Figure 3 : Geodorum densiflorum

Common Name: Nodding Swamp Orchid; Slanting Gastrochilus; Walking-stick Orchid; Nodding Swamp Orchid

Morphology and Occurrence

Terrestrial herbs, 60-70 cm tall; pseudobulb ovoid, 5 x 2.5 cm. Leaves 30-50 x 7-10 cm, elliptic-oblong or lanceolate, acuminate. Flowers white or pinkish, raceme 50-60 cm long, from the base of the pseudobulb; flower bearing portion about 5 cm long, strongly decurved. Floral bracts 15 x 4 mm, lanceolate, acuminate, 1-3-veined; dorsal sepal 13 x 4.5 mm, oblanceolate-oblong, acute, apiculate at apex, 5-veined; lateral sepals 13 x 5.1 mm, elliptic-oblong, acute, 7-veined; petals 12.5 x 6 mm, oblanceolate, obtuse; lip cymbiform, side margins incurved, apex faintly bilobed; disc with longitudinal callus. Geodorum densiflorum is a leafy, terrestrial herb with crowded pseudobulbs 30–50 mm (1–2 in) long and 20–30 mm (0.8–1 in) wide. There are between three and five dark green to yellowish pleated leaves 250–350 mm (9.8–14 in) long and 60–80 mm (2–3 in) wide with a stalk 20–80 mm (0.8–3 in) long. Between eight and twenty resupinate, pale pink flowers 18–20 mm (0.7–0.8 in) wide are borne on a flowering stem 200–400 mm (8–20 in) long. The flowers do not usually open widely. The sepals are 10–12 mm (0.4–0.5 in) long, 3–4 mm (0.1–0.2 in) wide and the petals are a similar length but wider. The labellum is pink with dark red veins, 10–11 mm (0.39–0.43 in) long and 5–10 mm (0.2–0.4 in) wide with the sides curved upwards. Flowering occurs between December and February in Australia and between June and July in Asia.

Distribution:

Global Distribution: Peninsular India, Myanmar, China and Sri Lanka

Indian distribution: State - Kerala, District/s: Kollam, Idukki, Pathanamthitta, Malappuram, Thiruvananthapuram, Kozhikkode, Palakkad, Thrissur, Wayanad

Chemical Constituants

Geodorum densiflorum is a phytochemically rich, endangered terrestrial orchid containing a variety of bioactive compounds that contribute to its wide pharmacological profile. Phytochemical investigations have identified the presence of flavonoids, alkaloids, terpenoids, glycosides, steroids, saponins, tannins, carbohydrates, and phenolic compounds. GC-MS analyses have revealed over 20 major compounds in the ethanol extract, including hexadecanoic acid, ethyl ester, ionone, and pyran-4-one derivatives, which are associated with antioxidant, anti-inflammatory, antimicrobial, and cytotoxic activities. Elemental analysis of the plant has confirmed the presence of essential elements like phosphorus, which plays a role in DNA synthesis and energy metabolism. Different solvent extracts—particularly ethanol, methanol, and ethyl acetate—demonstrated high antibacterial, antioxidant, and cytotoxic activities. Pharmacological screenings also revealed that extracts from this orchid show thrombolytic, analgesic, sedative, anxiolytic, and neuropharmacological effects in both in vitro and in vivo models.

Traditional / Ethno medicinal Uses

Geodorum densiflorum has a long history of use in traditional medicine across regions of India, Bangladesh, and Southeast Asia. The pseudobulbs and roots are the primary parts used medicinally. The plant is traditionally applied in the treatment of diabetes, dysentery, skin infections, carbuncles, and rheumatic pain, and is used to regulate the menstrual cycle in women and improve fertility in men. Root paste mixed with honey and ghee is taken orally for menstrual regulation, while powdered tubers are consumed with milk to treat impotency. Crushed roots are also applied to cattle to repel flies. In folk veterinary practices, the plant is used as a natural insect repellent. Additional uses include treatment of wounds, joint pain, gastrointestinal infections, and as a calming sedative

for insomnia or anxiety-like symptoms. Modern studies have validated these traditional uses, revealing the plant's potent antibacterial, antifungal, analgesic, antioxidant, cytotoxic, and sedative properties.

II. MATERIAL AND METHODS

A. Collection and authentication of plant Material

Bulbs of *Geodorum densiflorum* were collected during August 2024 from the Anjeri region, of Pune District, Maharashtra. The plant was taxonomically authenticated by a botanist at Sandip University, Nashik, India. A herbarium specimen was prepared and deposited at the same institution under the voucher number SUN2024/07/04.

B. Preparation and Storage

The freshly collected plant material was first rinsed with water and subsequently treated with 95% ethanol to inhibit degradation during subsequent storage and drying. The material was then cut into smaller segments and shade-dried until complete moisture removal was achieved. The dried sample was pulverized to a fine powder and sieved through mesh no. 80 for uniformity.

C. Extraction methodology

A total of 1000 g of dried bulb powder was subjected to maceration in a hydroalcoholic solution (70:30) with intermittent stirring at 25 ± 2°C for a duration of three days. The resulting mixture was filtered through a sterilized cotton plug using a Buchner funnel. The solvent was subsequently evaporated to dryness under reduced pressure using a rotary evaporator, yielding 61.4 g of crude hydroalcoholic extract. This extract was utilized for evaluating antidiabetic activity. The percentage yield of the extract was calculated using the following formula:

Percentage yield = Weight of Extract / Weight of powdered drug ×100

D. Pharmacological Investigation

Experimental animals

Male Wistar Albino Rats

Animal identification

Animals used in the study were individually identified using tail marking, while groups and sets were distinguished with colored markers and labeled accordingly. Each label included specific details such as cage number, animal number, and set designation.

Drugs/Chemicals

Alloxan

Quarantine and Acclimatization

Quarantine involves isolating newly received animals from the existing colony to assess their health status and potential microbial load. In this study, newly acquired Wistar albino rats were quarantined for one week to reduce the risk of pathogen transmission to the established population and to ensure physiological and nutritional stabilization prior to experimental use.

Housing

The animals were maintained in a well-ventilated facility under controlled environmental conditions, with temperature and relative humidity maintained at 55–65%. They were housed in spacious polypropylene cages, with paddy husk used as bedding material.

Diet and Water

Animals were provided with a standard pellet diet and access to purified water. Both food and water were available ad libitum, except during designated fasting periods. Bedding was replaced regularly to maintain hygienic conditions.

Drug Administration

Drugs were administered orally through oral gavage. An oral feeding tube fixed to a syringe needle was used for precise dosage delivery. The drug quantity was administered as required. Wistar rats were made diabetic by a single i.p. injection of 100 mg/kg b.w. of alloxan monohydrate (Sigma Chemicals Inc. USA) in sterile normal saline.

Preparation of Dose

The hydroalcoholic extract of *Geodorum densiflorum* Bulb was evaluated at oral dose levels of 100, 250, and 500 mg/kg. Each dose was prepared by accurately weighing the extract and suspending it in 0.3% carboxymethyl cellulose (CMC) solution prepared in distilled water.

Antidiabetic Model: Alloxan Induced Hypoglycemic Model

Wistar rats were made diabetic by a single i.p. injection of 100 mg/kg b.w. of alloxan monohydrate (Sigma Chemicals Inc. USA) in sterile normal saline. The rats were maintained on 5% glucose solution for next 24h to prevent hypoglycemia, as there is massive release of insulin due to β cell damage by alloxan. After five days, rats with marked hyperglycemic condition (blood glucose > 140mg/dl) were selected and used for the study. All the animals were randomly divided into the six groups each group consists of 6 animals. Group 2, and 3 served as diabetic, and

standard drug, (Glibenclamide 5 mg/kg) respectively. Groups 4, 5 and 6 were treated with *Geodorum densiflorum* Bulb extracts at dose of 100 mg/kg, 250 mg/kg and 500 mg/kg b.w. for hydroalcoholic extract respectively. Treatment with drugs was started on the 6th day of the alloxan treatment (i.e. day 1) and was continued for 12 days. All the drugs were given orally as a single dose in the morning. All the drugs were given orally as a single dose in the morning.

Table 1 : Distribution of Experimental animals

Groups	Treatment	No of animals	Route
Group 1	Control group	6	Orally
Group 2	Diabetics induced group	6	Orally
Group 3	Standard drug (Glibenclamide 5 mg/kg)	6	Orally
Group 4	Lower dose of *Geodorum densiflorum* Bulb extracts (Low Dose; 100 mg/kg)	6	Orally
Group 5	Medium Dose of *Geodorum densiflorum* Bulb extracts (Medium Dose; 250 mg/kg)	6	Orally
Group 6	High Dose of *Geodorum densiflorum* Bulb extracts (High Dose; 500 mg/kg)	6	Orally

Description of Distribution of Experimental animals

Experimental animals: Male Wistar rats (200-250 g)

The animals were divided into six experimental groups for evaluation of the effect of extract. A total of 36 animals were used for this study. Each group consisted of 6 rats.

Control Group (Group 1):

- ✓ This group received a placebo or vehicle (no extract) to serve as the baseline or control for comparison.

Alloxan Induced Hypoglycemic Group (Group 2):

- ✓ Rats in this group were administered Alloxan to induce diabetes. They did not receive extract.

Standard -Treatment Group (Group 3):

- ✓ Rats in this group were treated with standard drug (Glibenclamide).

Low-Dose GD Group (Group 4):

- ✓ Rats in this group were received a low dose of extract for evaluation of its potential antidiabetic effects.

Moderate-Dose GD Group (Group 5):

- ✓ Rats in this group were received a moderate dose of extract to assess its impact on glucose level.

High-Dose GD Group (Group 6):

- ✓ Rats in this group received a high dose of extract to determine the potential dose-dependent effects on glucose level.

E. Evaluatıon Parameter

Collection of Biological samples: Blood and Serum

The animals were anesthetized with anesthetic ether and with the help of small capillary the retro-orbital vein was punctured and 1ml blood was collected into the Eppindrof tube. The blood collected in Eppindrof tube was allowed to clot for 30 minutes. The tubes were kept for the centrifugation (Remi Centrifuge R 24) at 2000 rpm for 10 minutes. The serum was then separated with the help of micropipette into other Eppindrof tube and stored at 2-8 ^{o}C, until it was used for the estimation of biochemical parameter.

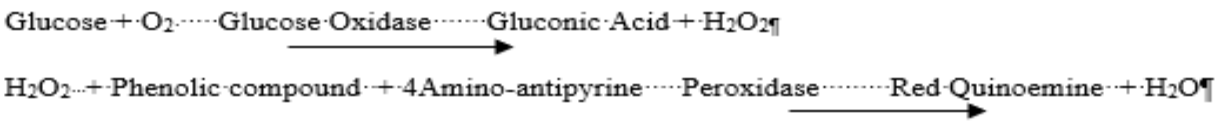
Estimation of Biochemical Parameter

GOD/POD method was used to estimate the serum glucose.

- Glucose Determination

Principle

The substrate β D- glucose is oxidized by glucose oxidase to form gluconic acid and hydrogen peroxide. The hydrogen peroxide so generated oxidizes the chromogen system consisting of 4-Amino antipyrine and phenolic compound to a red quinoeimine dye. The intensity of the color produced is proportional to the glucose concentration and is measured at 505 nm (490 – 530 nm) or with green filter.



Kit Content

Reagent 1: Glucose Reagent

- ✓ Glucose oxidase
- ✓ Horseradish peroxidase
- ✓ 4-Aminoantipyrine
- ✓ Phosphate Buffer
- ✓ P-hydroxybenzoic acid

Reagent 2: Glucose Standard

Glucose 100 mg/dl

Assay Parameters

Type of reaction : End point

Wavelength : 505 nm

Glucose Reagent Volume : 1.0 ml

Sample Volume : 10 µl

Incubation time : 10 min

Temperature : 37^0c

Standard Concentration : 100 mg/dl

Linearity : 500 mg/dl

Procedure

Pipette Out into Test Tubes	Blank	Standard	Test
Glucose Reagent	1.0 ml	1.0 ml	1.0 ml
Standard	- -	10 µl	- -
Sample	- -	- -	10 µl
Distilled Water	10 µl	- -	- -

Mixed and incubated at 37^0C for 10 min. The absorbance of the test (A_T), Standard (A_S) and reagent Blank (A_B) was read at 505 nm.

Calculation

$$\text{Glucose (mg/dl)} = \frac{A_T - A_B \times 100}{A_S - A_B}$$

- Normal Glycemic Test

Fasted rats divided into eight groups, each group contain six animals.

Groups divided as follows

Group 1 : Control group

Group 2 : Diabetics induced group

Group 3 : Standard drug (Glibenclamide 5 mg/kg)

Group 4 : Lower dose of *Geodorum densiflorum* Bulb extracts (Low Dose; 100 mg/kg)

Group 5: Medium Dose of *Geodorum densiflorum* Bulb extracts (Medium Dose; 250 mg/kg)

Group 6: High Dose of *Geodorum densiflorum* Bulb extracts (High Dose; 500 mg/kg)

After one hour of extract administration, blood sample were collected from the retro-orbital plexus at 30, 90, 120 min. after extract loading. Serum was separated and blood glucose levels were measured immediately by the glucose oxidase method.

Materials and Method

Samples

The extract was given orally. Doses selected were 100 mg/kg, 250 mg/kg and 500mg/kg b.w. for hydroalcoholic extract and suspensions were prepared with carboxymethyl cellulose (CMC) as suspending agent.

- Oral Glucose Tolerance Test (OGTT)

Principle

The oral glucose tolerance test is a widely used procedure that was originally developed to classify carbohydrate tolerance. However, because plasma glucose and insulin responses during this test reflect the ability of pancreatic β cells to secrete insulin and the sensitivity of tissues to insulin, the OGTT has also been often used to evaluate β cell function and insulin resistance. In epidemiological studies, for example, fasting plasma glucose concentrations have been used as an index of insulin resistance, and the 30 min ratio of changes in plasma insulin and glucose have been used as an index of β cell function.

Groups divided as follows

Group 1 : Control group

Group 2 : Diabetics induced group

Group 3 : Standard drug (Glibenclamide 5 mg/kg)

Group 4 : Lower dose of *Geodorum densiflorum* Bulb extracts (Low Dose; 100 mg/kg)

Group 5: Medium Dose of *Geodorum densiflorum* Bulb extracts (Medium Dose; 250 mg/kg)
Group 6: High Dose of *Geodorum densiflorum* Bulb extracts (High Dose; 500 mg/kg)
Materials and Method
Glucose Solution
Glucose (Qualigen Ltd.) 100mg/ml was prepared in pyrogen free water.
Standard Drug
Glibenclamide (Alembic Ltd., India) suspension was prepared with 1%w/v of carboxymethyl cellulose (CMC) as suspending agent.
Dose: 5 mg/kg p.o.
Sample
The extract were given orally. Doses selected were 100 mg/kg, 250 mg/kg and 500mg/kg b.w. for hydroalcoholic extract and suspensions were prepared with carboxymethyl cellulose (CMC) as suspending agent.

- Alloxan Induced Hypoglycemic Test in Rats

Principle
Alloxan (2,4,5,6-tetraoxypyrimidine; 5, 6-dioxyuracil) was first described by Brugnatelli in 1818. Wöhler and Liebig used the name "alloxan" and described its synthesis by uric acid oxidation. The diabetogenic properties of this drug were reported many years later by Dunn, Sheehan and McLethie (1943), who studied the effect of its administration in rabbits and reported a specific necrosis of pancreatic islets. Since then, alloxan diabetes has been commonly utilized as an animal model of IDDM. Alloxan exerts its diabetogenic action when it is administered intravenously, intraperitoneally or subcutaneously. The dose of alloxan required for inducing diabetes depends on the animal species, route of administration and nutritional status. Human islets are considerably more resistant to alloxan than those of the rat and mouse. The most frequently used intravenous dose of this drug to induce diabetes in rats is 65 mg/kg b.w. When alloxan is given intraperitoneally or subcutaneously its effective dose must be near about twice. The i.p. 100 mg/kg b.w. may be sufficient for inducing diabetes in the rat.
Alloxan is a hydrophilic and unstable substance. Its half-life at neutral pH and 37°C is about 1.5 min and is longer at lower temperatures. On the other hand, when a diabetogenic dose is used, the time of alloxan decomposition is sufficient to allow it to reach the pancreas in amounts that are deleterious. The action of alloxan in the pancreas is preceded by its rapid uptake by the β cells. Rapid uptake by insulinsecreting β cells has been proposed to be one of the important features determining alloxan diabetogenicity. Another aspect concerns the formation of reactive oxygen species. The formation of reactive oxygen species is preceded by alloxan reduction. In β cells of the pancreas its reduction occurs in the presence of different reducing agents. Since alloxan exhibits a high affinity to the SH-containing cellular compounds, reduced glutathione (GSH), cysteine and protein-bound sulfhydryl groups (including -SH containing enzymes) are very susceptible to its action. However, other reducing agents such as ascorbate may also participate in this reduction. Dialuric acid is formed as a result of alloxan reduction. It is then reoxidized back to alloxan establishing a redox cycle for the generation of superoxide radicals.
One of the targets of the reactive oxygen species is DNA of pancreatic islets. Its fragmentation takes place in β cells exposed to alloxan. DNA damage stimulates poly ADP-ribosylation, a process participating in DNA repair. Some inhibitors of poly ADP-ribosylation can partially restrict alloxan toxicity. This effect is, however, suggested to be due to their ability to scavenge free radicals rather than to a restriction of poly ADP ribosylation initiated by alloxan. Superoxide dismutase, catalase (EC 1.11.1.6) and non-enzymatic scavengers of hydroxyl radicals were also found to protect against alloxan toxicity. Therefore, chemicals rendering anti-oxidative properties and inhibiting poly ADP-ribosylation can attenuate alloxan toxicity.
Groups divided as follows
Group 1 : Control group
Group 2 : Diabetics induced group
Group 3 : Standard drug (Glibenclamide 5 mg/kg)
Group 4 : Lower dose of *Geodorum densiflorum* Bulb extracts (Low Dose; 100 mg/kg)
Group 5: Medium Dose of *Geodorum densiflorum* Bulb extracts (Medium Dose; 250 mg/kg)
Group 6: High Dose of *Geodorum densiflorum* Bulb extracts (High Dose; 500 mg/kg)
Materials and Method
Alloxan monohydrate Solution
Alloxan monohydrate (Sigma Chemicals) 25 mg/ml was prepared in sterile normal saline.
Standard Drug

Glibenclamide (Alembic Ltd., India) suspension was prepared with 1%w/v of carboxymethyl cellulose (CMC) as suspending agent.

Dose: 5 mg/kg p.o.

Samples

The extract were given orally. Doses selected were 100 mg/kg, 250 mg/kg and 500mg/kg b.w. for hydroalcoholic extract and suspensions were prepared with carboxymethyl cellulose (CMC) as suspending agent.

Experimental Induction of Diabetes

Wistar rats were made diabetic by a single i.p. injection of 100 mg/kg b.w. of alloxan monohydrate (Sigma Chemicals Inc. USA) in sterile normal saline. The rats were maintained on 5% glucose solution for next 24h to prevent hypoglycemia, as there is massive release of insulin due to β cell damage by alloxan. After five days, rats with marked hyperglycemic condition (blood glucose > 140mg/dl) were selected and used for the study. All the animals were randomly divided into the six groups each group consists of 6 animals. Group 2, and 3 served as diabetic, and standard drug, (Glibenclamide 5 mg/kg) respectively. Groups 4, 5 and 6 were treated with *Geodorum densiflorum* Bulb extracts at dose of 100 mg/kg, 250 mg/kg and 500 mg/kg b.w. for hydroalcoholic extract respectively. Treatment with drugs was started on the 6th day of the alloxan treatment (i.e. day 1) and was continued for 12 days. All the drugs were given orally as a single dose in the morning. All the drugs were given orally as a single dose in the morning.

F. Network Pharmacology

Screening active phytoconstituents of *Moringa oleifera* leaves

The bioactive phytoconstituents of *Geodorum densiflorum* were identified through comprehensive literature review and database mining. Few phytoconstituents were retrieved, primarily using the Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) database (https://cb.imsc.res.in/imppat/), along with reported findings from sources such as Google Scholar, PubMed, and ScienceDirect.

Retrieving phytoconstituents-associated targets

The canonical SMILES of all phytoconstituents were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The compound-associated target prediction was conducted by entering the canonical SMILES in a total 6 target prediction databases, with the similarity set to 0.5. The databases used include Swiss Target Prediction (http://www.swisstargetprediction.ch/), Similarity ensemble approach (SEA) (https://sea.bkslab.org/), Binding DB (https://www.bindingdb.org/rwd/bind/chemsearch/marvin/FMCT.jsp), Pass online (https://www.way2drug.com/passtargets/), ChEMBL (https://www.ebi.ac.uk/chembl/) and Super PRED target prediction (https://prediction.charite.de/subpages/target_prediction.php).

Retrieving disease-associated targets

Disease-associated genes were identified using keywords such as "diabetes", “hyperglycemia”, etc. Gene data were retrieved from DisGeNET (https://disgenet.com/), GeneCards (https://www.genecards.org/home), and MalaCards (https://www.malacards.org/) databases. The corresponding UniProt IDs for the retrieved genes were obtained using the UniProt ID Mapping tool (https://www.uniprot.org/id-mapping).

Constructing network and analysing

The Venny tool (https://bioinfogp.cnb.csic.es/tools/venny/) was used to identify overlapping targets between phytoconstituents and disease-associated genes. Protein-compound interaction networks were then constructed using the STRING database (https://string-db.org/) to explore functional associations. Network analysis was further carried out using Cytoscape (version 3.10.3), and the CytoHubba plugin was employed to evaluate network centrality based on degree and other topological ranking algorithms.

Pathway Enrichment Analysis

Gene Ontology (GO) and KEGG pathway enrichment analyses were performed for the top 20 target nodes using the DAVID platform. GO analysis was used to explore the associated biological processes, cellular components, and molecular functions, while KEGG pathway analysis provided insights into the relevant signaling pathways (https://www.genome.jp/kegg/pathway.html).

G. Molecular docking experiment

Computational molecular docking studies were carried out using the Windows 10 operating system, Intel® Core™ i7-8700 CPU @ 3.20 GHz, and 16 GB RAM, employing the Schrödinger suite 2019-1 via Maestro

11.9 (Schrödinger, LLC, NY, 2019). The interaction pattern and potential binding affinities between the phytoconstituents and core protein were estimated through molecular docking by Mastro Suit.

a) *Ligand and protein preparation*

All ligands were constructed using the Maestro Build Panel and subsequently prepared using LigPrep (Schrödinger), which employed the MMFF94s force field to generate low-energy 3D conformers, molecular geometries, and retain specific chirality. Core protein targets were retrieved based on corresponding gene sequences from RCSB PDB (https://www.rcsb.org/) using selection criteria, including a resolution of ≤ 2.5 Å, Homosapiens origin, and X-ray crystallography and saved in PDB format. Protein is pre-processed to remove water molecules, optimise and minimize to lower energy state for docking by using the protein preparation wizard workflow in the Maestro suite.

b) *Identification of active site*

The site map tool was employed to study the prepared protein's possible binding site by recognizing active ligands. Based on the d-score (nearest to 1) the active site was selected for gride generation.

c) *Molecular docking*

The prepared ligand and protein were docked using glide ligand docking and glide extra precision (XP) mode at active sites identified by the sitemap by considering flexibility.

III. RESULTS:

A. Collection and authentication of plant Material

Bulbs of *Geodorum densiflorum* were collected during August 2024 from the Anjeri region, of Pune District, Maharashtra. The plant was taxonomically authenticated by a botanist at Sandip University, Nashik, India. A herbarium specimen was prepared and deposited at the same institution under the voucher number SUN2024/07/04.

B. Extractive Values

A total of 1000 g of dried bulb powder was subjected to maceration in a hydroalcoholic solution (70:30) with intermittent stirring at 25 ± 2°C for a duration of three days. The resulting mixture was filtered through a sterilized cotton plug using a Buchner funnel. The solvent was subsequently evaporated to dryness under reduced pressure using a rotary evaporator, yielding 61.4 g of crude hydroalcoholic extract. This extract was utilized for evaluating antidiabetic activity.

Yield of Hydroalcoholic Extract- 6.14 %

C. Pharmacological Invetigation

a) Normal Glycemic Test

The glycemic modulation potential of the hydroalcoholic extract of *Geodorum densiflorum* bulbs was evaluated through a normal glycemic test conducted across six experimental groups, including a normal control, diabetic control, and four extract-treated groups at varying doses (Groups C to F). Blood glucose levels were measured at 0, 90, and 120 minutes following oral administration. The data were subjected to two-way ANOVA, followed by Tukey's multiple comparison test to assess the statistical significance of treatment and time effects on glycemic outcomes. Two-way ANOVA revealed a significant influence of both treatment and time on blood glucose levels. Time was the most prominent factor, accounting for 66.28% of the total variation, with an F-value of 63.14 and a p-value of less than 0.0001, indicating substantial changes in glycemia over the measured intervals. The treatment groups also showed a significant effect on glycemic control, as indicated by an F-value of 15.12 and a p-value of less than 0.0001. Furthermore, a significant interaction was noted between treatment and time ($F = 4.03$, $p = 0.0001$), demonstrating that the glycemic response varied depending on the treatment group and the specific time point of observation. These results underscore a clear time-dependent and treatment-specific modulation of blood glucose levels.

Tukey's post hoc analysis further clarified the significance of the observed effects. At the baseline (0 minutes), blood glucose levels were largely comparable across most groups, although Groups E and F exhibited modest but statistically significant differences when compared to the control group, suggesting minor biological variability at the start of the experiment. At 90 minutes post-administration, the differences became more distinct. Groups C, E, and F exhibited significant reductions in blood glucose levels compared to the diabetic control group, with the greatest reduction observed in Group F. These effects continued and intensified by 120 minutes, where the extract's antihyperglycemic activity was even more pronounced. Group F demonstrated the most substantial reduction in glycemia, which was statistically significant when compared to all other

groups, including the diabetic and normal controls, confirming the high efficacy of the extract at this dose. Group E also maintained a significant reduction in glucose levels at 120 minutes, highlighting sustained efficacy at a moderately high dose.

Intra-group comparisons across time points further reinforced the extract's time-dependent activity. Groups C, E, and F showed significant glycemic reductions between 0 and 120 minutes, whereas the control and diabetic groups exhibited no significant intra-group changes, indicating a lack of spontaneous correction in glycemia. The ability of the extract, particularly at higher doses, to reduce glucose levels below those of both the diabetic and untreated normal groups confirms its potent antihyperglycemic effect. These findings demonstrate the promising role of Geodorum densiflorum in modulating blood glucose levels, with its effect becoming evident as early as 90 minutes and reaching a peak at 120 minutes post-administration. In conclusion, the combined two-way ANOVA and Tukey's multiple comparison analysis clearly establish that the hydroalcoholic extract of Geodorum densiflorum bulbs exerts a significant, dose-dependent antihyperglycemic effect in normoglycemic conditions. The extract not only prevented hyperglycemia but actively reduced glucose levels in a time-responsive manner, supporting its potential utility as a natural therapeutic agent for glycemic control.

Table 2: Comparative Effect of *Geodorum densiflorum* bulbs Extract on Blood Glucose Level in Normal Rats

Groups and Dose mg/Kg b.w.	Min.		
	0	90	120
Control group	59.92 ± 0.26	60.44 ± 0.319	59.81 ± 0.211
Diabetics induced group	60.65 ± 0.213	61.14 ± 0.485	61.22 ± 0.470
Standard drug (Glibenclamide 5 mg/kg)	60.41 ± 0.138	58.88 ± 0.135	58.66 ± 0.186
Lower Dose of GD Extract (100 mg/kg)	59.71 ± 0.277	59.43 ± 0.283	58.95 ± 0.296
Medium Dose of GD Extract (250 mg/kg)	58.71 ± 0.178	58.31 ± 0.317	57.652 ± 0.192
High Dose of GD Extract (500 mg/kg)	58.31 ± 0.169	57.94 ± 0.171	56.394 ± 0.241

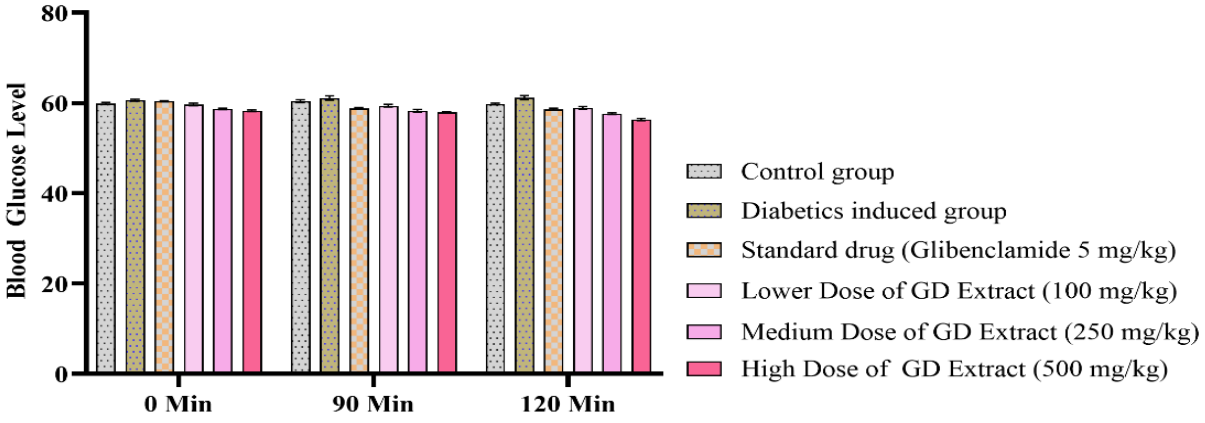


Figure 5: Effect of hydroalcoholic extract of *Geodorum densiflorum* bulbs on blood glucose levels in normoglycemic rats. Blood glucose levels were recorded at 0, 90, and 120 minutes post-administration across six groups: normal control, diabetic control, standard drug (Glibenclamide 5 mg/kg), and extract-treated groups at 100, 250, and 500 mg/kg. Data are expressed as mean ± SEM (n = 6). The extract demonstrated a dose- and time-dependent reduction in blood glucose, with the highest efficacy observed at 500 mg/kg.

b) Oral Glucose Tolerance Test in Normal Rats

The oral glucose tolerance test (OGTT) was conducted in normoglycemic rats to assess the effect of the hydroalcoholic extract of Geodorum densiflorum bulbs on postprandial glycemic regulation. Six experimental groups were evaluated, including a normal control, a diabetic control, a standard drug (glibenclamide 5 mg/kg), and three extract-treated groups receiving low, medium, and high doses. Blood glucose levels were recorded at 0, 30, 90, and 120 minutes following oral administration of glucose. The data were analyzed using two-way ANOVA followed by Tukey's multiple comparisons test to determine the significance of treatment effects, time effects, and their interactions. The two-way ANOVA results revealed a highly significant effect of both treatment groups and time points on blood glucose levels. The treatment group (row factor) accounted for 45.8% of the total variation in glucose levels, with an F-value of 1921 and a p-value less than 0.0001, indicating that the administered treatments substantially influenced glycemic control. The time factor (column factor) contributed 40.29% of the variation and was also highly significant ($F = 1014$, $p < 0.0001$), reflecting a strong temporal component to glucose regulation following glucose challenge. Furthermore, a significant interaction between treatment and time was observed, accounting for 12.95% of the total variation ($F = 108.7$, $p < 0.0001$). This interaction indicates that the pattern of glycemic response over time varied depending on the treatment group, reinforcing the biological relevance of both factors in determining postprandial glucose levels. The low residual mean square (1.017) further supports the robustness and reliability of the model used.

Post hoc comparisons using Tukey's multiple comparison test provided more granular insights into group differences. At the baseline (0 min), all groups exhibited statistically comparable glucose levels, suggesting that the rats were normoglycemic prior to glucose administration, with the exception of a mild but significant difference in Group F compared to the control group. At 30 minutes post-glucose load, the glycemic levels peaked in all groups, with the diabetic control group displaying the highest elevation. The extract-treated groups, particularly Groups C, E, and F, showed significantly lower glucose levels compared to the diabetic group, indicating an early onset of antihyperglycemic activity. The high dose group (Group F) demonstrated the most pronounced reduction at this point, and significant intergroup differences were observed between varying extract doses, suggesting dose-dependent efficacy.

At 90 minutes, the extract's effect on glucose disposal became more prominent. All extract-treated groups showed markedly reduced glucose levels compared to both diabetic and normal controls, with statistical significance reaching $p < 0.0001$. Group F again showed the highest potency, with sustained glycemic reduction. Intragroup comparisons revealed a downward trend in glucose levels from 30 to 90 minutes in all extract-treated groups, confirming effective glycemic clearance. These trends continued through 120 minutes, where Group F maintained its superior antihyperglycemic effect. Its glucose levels were significantly lower than those of all other groups, including the diabetic and normal controls, suggesting a potent and lasting pharmacodynamic effect. The glucose levels in Groups C and E also remained significantly lower than those in the diabetic control, with moderate intergroup variation observed among the extract-treated cohorts.

Time-dependent intra-group comparisons further confirmed the extract's efficacy. In all extract-treated groups, glucose levels increased significantly at 30 minutes and progressively declined through 90 and 120 minutes. This reduction was highly significant in Groups D, E, and F, reinforcing their roles in enhancing postprandial glucose clearance. The diabetic and control groups, in contrast, demonstrated a slower and less efficient reduction in glucose levels over time. The ability of the extract to reduce glucose levels faster and more effectively indicates an enhancement of glucose uptake or utilization, which is crucial in the management of postprandial hyperglycemia. The combined ANOVA and multiple comparison analyses clearly establish that the hydroalcoholic extract of Geodorum densiflorum significantly improves glucose tolerance in normoglycemic rats. The extract acts in a time- and dose-dependent manner, with higher doses demonstrating more potent effects. These findings support the extract's role in enhancing glycemic control following glucose challenge and underscore its potential as a promising natural therapeutic agent for preventing or managing postprandial hyperglycemia.

Table 3: Effect of *Geodorum densiflorum* bulbs Extract on Blood Glucose Level (mg/dl) in Orally Glucose Fed Rats

Groups and Dose mg/Kg b.w.	Blood sugar level mg/dl at min			
	0	30	90	120
Control group	79.52 ± 0.5299	99.37 ± 0.4943	101.54 ± 0.1981	97.16 ± 0.3893
Diabetics induced group	80.64 ± 0.2201	104.66 ± 0.5979	106.98 ± 0.8029	104.74 ± 0.3337
Standard drug (Glibenclamide 5 mg/kg)	77.89 ± 0.6294	92.63 ± 0.2418	86.54 ± 0.5011	80.42 ± 0.3727
Lower Dose of GD Extract (100 mg/kg)	78.74 ± 0.3346	95.78 ± 0.3315	88.75 ± 0.3496	84.75 ± 0.3743
Medium Dose of GD Extract (250 mg/kg)	78.01 ± 0.2096	92.52 ± 0.3008	85.88 ± 0.4204	82.41 ± 0.2850
High Dose of GD Extract (500 mg/kg)	77.66 ± 0.4983	89.90 ± 0.1551	84.09 ± 0.3587	80.03 ± 0.2557

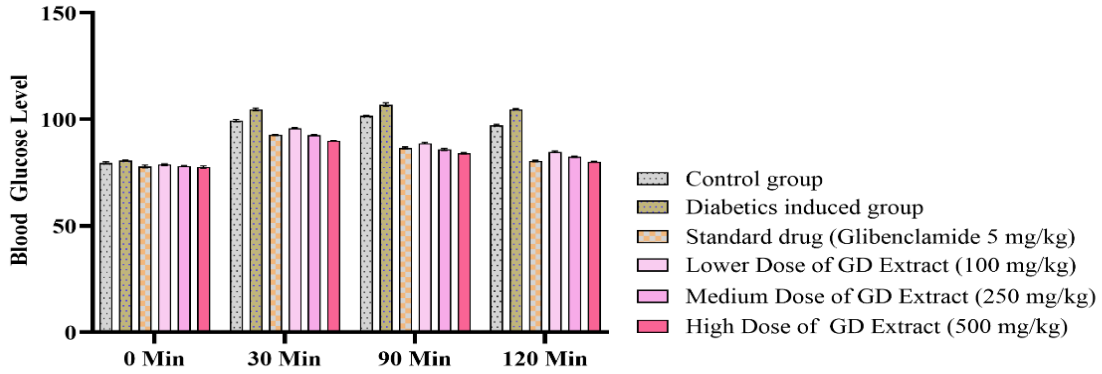


Figure 6: Effect of hydroalcoholic extract of *Geodorum densiflorum* bulbs on blood glucose levels in normoglycemic rats during the oral glucose tolerance test (OGTT). Blood glucose was measured at 0, 30, 90, and 120 minutes following oral glucose administration. Groups include control, diabetic control, standard drug (Glibenclamide 5 mg/kg), and extract-treated groups at 100, 250, and 500 mg/kg doses. The extract exhibited a dose- and time-dependent reduction in glucose levels, with the 500 mg/kg dose showing the most significant postprandial antihyperglycemic activity. Values are expressed as mean ± SEM (n = 6).

c) Alloxan Induced Diabetes in Rats

The evaluation of the antidiabetic potential of hydroalcoholic extract of Geodorum densiflorum bulbs in alloxan-induced diabetic rats was analyzed using both two-way ANOVA and Tukey's multiple comparison tests, generating a comprehensive understanding of glycemic control over the treatment period. The two-way ANOVA demonstrated highly significant effects of the treatment groups, time intervals, and their interaction on blood glucose levels. The column factor, representing time (days 1, 3, 6, 9, and 12), accounted for 44.66% of the total variation with an F-value of 545.1 and a p-value < 0.0001, indicating a strong time-dependent trend in glycemic responses. The row factor, representing different treatment groups, contributed 31.08% of the variation ($F = 474.1$, $p < 0.0001$), confirming that the administered treatments had distinct effects on blood glucose regulation. The interaction between time and treatment was also significant (21.81% of total variation, $F = 66.54$, $p < 0.0001$), suggesting that the glycemic effect of each treatment varied dynamically over the study period.

Post hoc analysis using Tukey's multiple comparison test further elucidated the progression of treatment effects. On day 1, no statistically significant

differences in blood glucose levels were observed among the groups, confirming a homogeneous baseline across all animals. However, beginning from day 3, marked differences emerged, especially between the diabetic control and extract-treated groups. Group F (500 mg/kg) exhibited a significantly lower blood glucose level compared to the diabetic control and lower dose groups, reflecting the onset of extract-induced antihyperglycemic activity. This trend intensified over time, with day 6 showing a clear separation between all extract-treated groups and the diabetic control group, most notably in Groups E and F, where glucose levels dropped significantly. By day 9 and especially day 12, the extract demonstrated potent glycemic control in a dose-dependent manner. Group F consistently exhibited the greatest reduction in blood glucose levels, significantly outperforming Groups C and D and closely approximating or exceeding the efficacy of the standard drug, glibenclamide. Intragroup comparisons across time showed that Group F experienced a consistent and statistically significant decrease in glucose levels from day 3 to day 12, with adjusted p-values < 0.0001 for each interval. Similar trends were observed in Groups D and E, though the effects were comparatively moderate in Group C. The diabetic control group, on the other hand, maintained persistently elevated blood glucose levels throughout the study, with only minor, statistically insignificant fluctuations.

No significant changes were observed within the normal control group across the entire time frame, confirming physiological glycemic stability in non-diabetic animals and supporting the validity of the diabetic model. The consistency and magnitude of glucose reduction observed in the extract-treated groups, particularly at the 500 mg/kg dose, highlight the robust antidiabetic efficacy of Geodorum densiflorum in reversing alloxan-induced hyperglycemia. These findings, supported by strong statistical evidence, demonstrate that the extract not only lowers blood glucose effectively but also sustains its therapeutic effect over time. The dose- and time-dependent pattern of glycemic improvement strongly advocates for the extract's potential use as a phytotherapeutic agent in the management of diabetes mellitus.

Table 4: Effect *Geodorum densiflorum* bulbs Extract on Blood Glucose Level (mg/dl) in Alloxan Induced Diabetes Rats

Groups and Dose mg/Kg b.w.	Blood glucose level mg/dl at days				
	1	3	6	9	12
Control group	258.38 ± 1.5071	259.79 ± 2.2745	257.01 ± 2.8620	258.15 ± 1.8164	258.25 ± 2.4691
Diabetics induced group	264.50 ± 2.8026	272.51 ± 1.237	279.17 ± 1.928	277.30 ± 3.5243	276.80 ± 3.7165
Standard drug (Glibenclamide 5 mg/kg)	260.44 ± 1.9459	235.84 ± 2.9425	204.81 ± 2.5101	191.84 ± 2.6032	142.02 ± 2.2421
Lower Dose of GD Extract (100 mg/kg)	262.75 ± 2.1871	249.96 ± 1.7526	233.11 ± 2.0701	212.87 ± 2.002	204.38 ± 3.7453
Medium Dose of GD Extract (250 mg/kg)	260.91 ± 1.6144	246.47 ± 2.2997	224.24 ± 1.1046	204.38 ± 3.4571	182.63 ± 4.0248
High Dose of GD Extract (500 mg/kg)	256.33 ± 1.2875	240.13 ± 2.3081	221.41 ± 1.8723	196.17 ± 1.1468	165.37 ± 3.2044

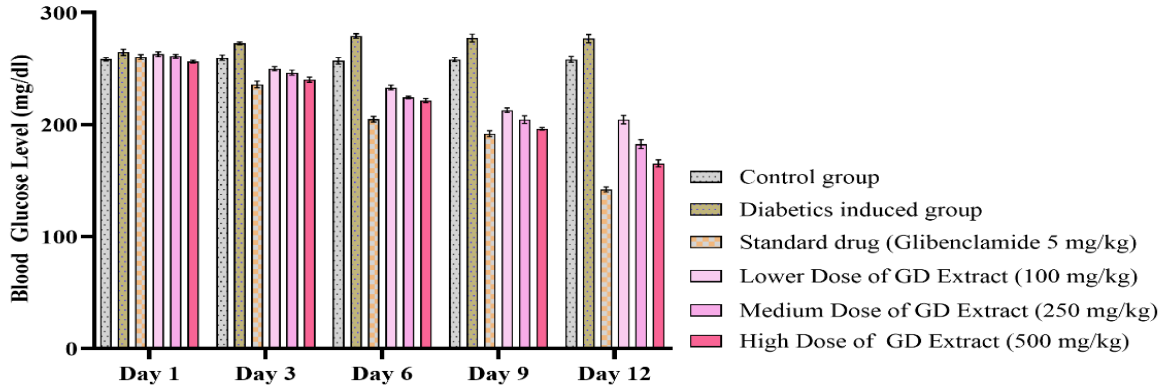


Figure 7: Effect of *Geodorum densiflorum* hydroalcoholic bulb extract on blood glucose levels in alloxan-induced diabetic rats over 12 days. Data are expressed as mean ± SEM (n = 6). A significant reduction in glucose levels was observed in the extract-treated groups, particularly at higher doses (250 and 500 mg/kg), in a time-dependent manner compared to the diabetic control group. The standard drug (Glibenclamide, 5 mg/kg) served as a positive control. Statistical significance was confirmed using two-way ANOVA followed by Tukey's multiple comparison test.

d) Body Weight on Alloxan Induced Rats

The effect of *Geodorum densiflorum* (GD) extract on body weight in alloxan-induced diabetic rats was statistically evaluated using two-way ANOVA followed by Tukey's multiple comparisons test to determine both group and time-dependent differences. The two-way ANOVA results revealed that the main effects of treatment (column factor), time (row factor), and their interaction were all statistically significant ($p < 0.0001$ for column and row factors, and $p = 0.0006$ for interaction). The interaction effect accounted for 19.8% of the total variation, indicating that treatment effects varied across the days. The treatment factor explained 10.85% of the total variation, while the time factor contributed 11.85%, confirming that both the nature of treatment and duration significantly influenced body weight dynamics in diabetic rats. The significant interaction further indicates that the trajectory of weight change over time was not uniform across all groups, reflecting different responses to the extract and standard drug.

The Tukey's multiple comparisons analysis provided more granular insights. On Day 1, significant differences were observed between the control group and both the diabetic group and Group E, suggesting an early onset of metabolic disturbance following alloxan induction. However, no significant differences were found among the treatment groups, indicating comparable baseline weights. By Day 3, significant differences emerged within groups, especially between Group C and Groups D and F, as well as between the diabetic group and Group D. This indicated early variability in how treatment influenced body mass maintenance. By Day 6, only Group D and Group F differed significantly, suggesting that weight loss was more evident in the high-dose GD group. On Day 9, all intergroup comparisons were statistically non-significant, although a general trend of weight preservation was evident in the extract-treated groups compared to the diabetic control group. On Day 12, a significant difference in body weight was noted between the control group and the diabetic group, as well as between the diabetic group and treatment Groups C, D, and E, suggesting the beneficial effects of GD extract in mitigating progressive weight loss associated with hyperglycemia.

Within-group comparisons across days further confirmed these effects. The diabetic group exhibited a significant and consistent decrease in body weight from Day 1 to Day 12, with notable drops observed by Days 9 and 12. In contrast, the extract-treated groups maintained relatively stable body weights, with only occasional minor reductions that did not consistently reach statistical significance. For instance, Group E showed statistically significant weight reductions between Day 1 and Day 3 and between Day 1 and Day 12. Group F showed a significant drop from Day 1 to Day 6, but subsequent time points reflected

stabilization. The control group maintained consistent body weight throughout the study duration, underscoring the deleterious effect of alloxan on body mass and the ability of GD extract to counteract this effect. Collectively, these findings confirm that treatment with Geodorum densiflorum extract, particularly at medium and high doses, demonstrated a protective effect on body weight in alloxan-induced diabetic rats. The results provide robust statistical evidence supporting the metabolic stabilizing potential of the GD extract in diabetic conditions, with effectiveness approaching that of the standard antidiabetic drug Glibenclamide over the 12-day experimental period.

Table 5: Effect *Geodorum densiflorum* bulbs Extract on Body Weight on Alloxan Induced Rats

Groups and Dose mg/Kg b.w.	Effect on Body Weight (gm) At Days				
	1	3	6	9	12
Control group	213.97 ± 3.0287	218.62 ± 3.9099	217.94 ± 1.2369	212.17 ± 4.5671	218.30 ± 3.2949
Diabetics induced group	230.16 ± 4.7308	224.49 ± 3.8433	217.12 ± 6.1529	214.65 ± 4.008	198.58 ± 1.7267
Standard drug (Glibenclamide 5 mg/kg)	226.80 ± 4.6829	227.04 ± 4.4275	221.35 ± 3.2547	223.89 ± 3.6721	225.22 ± 4.7720
Lower Dose of GD Extract (100 mg/kg)	227.50 ± 1.9571	210.04 ± 3.7413	225.05 ± 3.9164	220.64 ± 2.6117	215.09 ± 2.1343
Medium Dose of GD Extract (250 mg/kg)	230.07 ± 1.9842	214.45 ± 2.0763	216.56 ± 3.7016	217.73 ± 4.5092	215.45 ± 3.0248
High Dose of GD Extract (500 mg/kg)	223.65 ± 2.1150	211.71 ± 5.6726	207.04 ± 5.2466	211.75 ± 3.0306	210.95 ± 3.1912

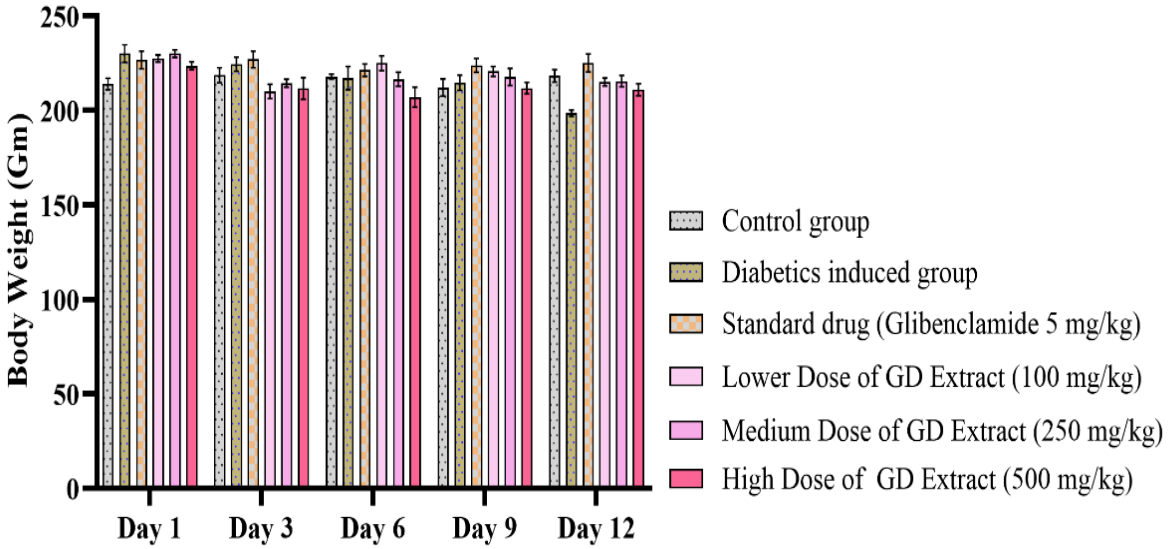


Figure 8: Effect of *Geodorum densiflorum* (GD) extract on body weight in alloxan-induced diabetic rats over 12 days. Rats were divided into six groups: normal control, diabetic control, standard drug-treated (Glibenclamide 5 mg/kg), and three GD extract-treated groups (100, 250, and 500 mg/kg). Body weights were recorded on Days 1, 3, 6, 9, and 12. The diabetic group exhibited progressive weight loss, whereas GD extract-treated groups showed dose-dependent attenuation of weight reduction, with the high-dose group demonstrating near-stabilization, comparable to the standard drug group.

D. Network Pharmacology

a) Target Identification and Overlap Analysis

The hydroalcoholic extract of Geodorum densiflorum bulbs was analyzed for its potential antidiabetic effect. Based on GC-MS and literature reports, the primary identified bioactive constituents included Hexadecanoic acid, Ionone, 3-Deoxy-D-mannoic lactone, 2,3-Butanediol, and 2-Piperidinone, N-[4-bromo-n-butyl]. These compounds were subjected to SwissTargetPrediction and BindingDB to retrieve potential protein targets, yielding a total of 337 drug-related targets. Simultaneously, a disease gene set for diabetes mellitus, with a focus on mechanisms relevant to Alloxan-induced pancreatic beta-cell damage and insulin resistance, was obtained using GeneCards, CTD, and DisGeNET, resulting in 2603 diabetes-associated targets.

The Venn diagram (Figure 9) revealed 109 overlapping targets, representing key proteins influenced by both the phytoconstituents and diabetic pathophysiology. This intersection supports the hypothesis that the bulb extract may exert its antidiabetic effect by acting on critical regulatory proteins involved in insulin sensitivity, glucose metabolism, beta-cell apoptosis, and inflammatory response.

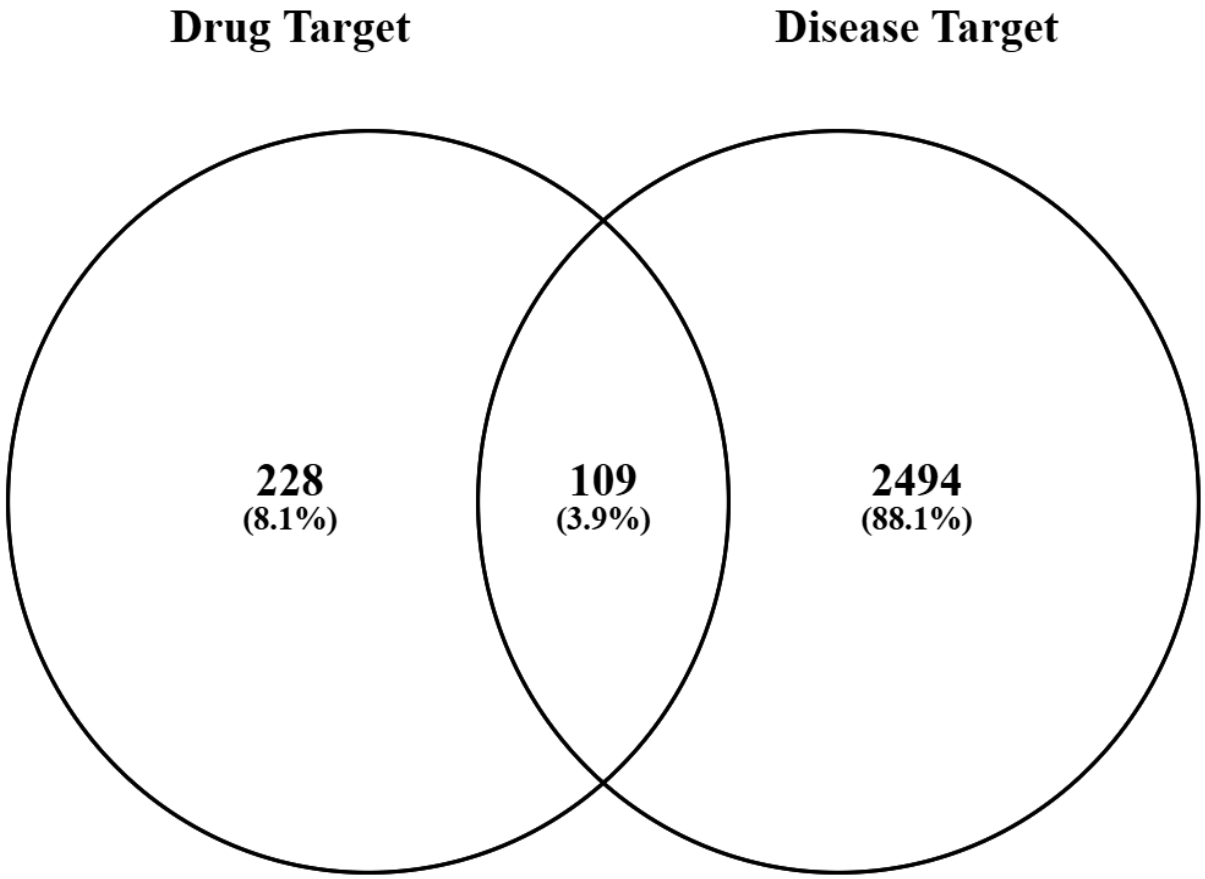


Figure 9: Venn diagram showing the intersection between drug targets (from Geodorum densiflorum compounds) and disease targets (Alloxan-induced diabetes). A total of 109 overlapping genes were identified.

b) Protein–Protein Interaction Network

The 109 intersected genes were mapped into a protein–protein interaction (PPI) network using STRING (Figure 10). The resulting network displayed significant interconnectivity with a dense cluster of highly connected proteins, reflecting the tight biological association between glucose homeostasis, insulin signaling, and inflammation. This connectivity indicates that the targets are not functioning in isolation but are part of tightly coordinated networks that regulate insulin receptor function, cytokine signaling, glucose uptake, and pancreatic beta-cell integrity—all key elements in diabetes management.

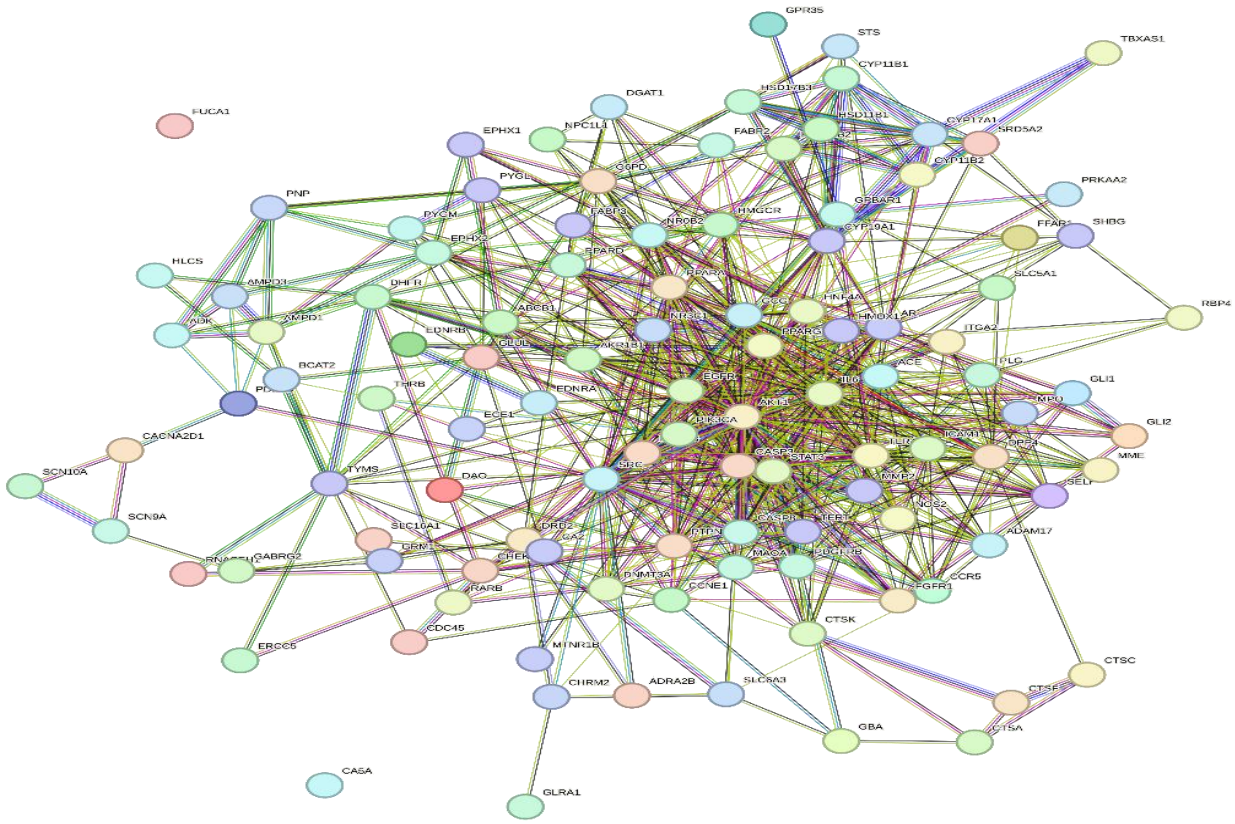


Figure 10: Protein–Protein Interaction (PPI) network of the 109 common targets visualized using STRING. Dense interconnectivity reflects their coordinated role in diabetic signaling.

c) Hub Gene Analysis

From the protein–protein interaction network of 109 common targets, hub gene analysis was performed using Cytoscape with the cytoHubba plugin based on degree centrality. The top-ranked hub genes included AKT1, PPARG, IL6, STAT3, TLR4, PPARA, EGFR, SRC, CASP3, and ACE. These genes are critical in the regulation of multiple biological processes central to diabetes mellitus, especially those induced by Alloxan, such as insulin resistance, inflammation, beta-cell apoptosis, and oxidative stress.

AKT1 acts as a central node in insulin signal transduction. It is downstream of insulin receptor activation and is required for the translocation of GLUT4, promoting glucose uptake. In the diabetic state, impaired AKT1 function leads to reduced glucose metabolism, making it a primary therapeutic target. PPARG, a nuclear receptor, plays a vital role in lipid metabolism, adipocyte differentiation, and insulin sensitivity. It is targeted by thiazolidinediones and also modulated by natural compounds, including those found in G. densiflorum. Its central placement in the hub network suggests that the extract may restore insulin action through PPARG agonism. IL6 and TLR4 are pro-inflammatory markers. Their presence among the top hubs reflects the inflammatory nature of Alloxan-induced diabetes and supports the hypothesis that the extract possesses anti-inflammatory properties. CASP3, a pivotal executor of apoptosis, is responsible for the destruction of pancreatic β-cells in Alloxan-treated models. Modulating CASP3 can preserve insulin-producing cells. STAT3, another major transcriptional regulator, interacts with cytokines and hormones and controls genes involved in metabolism and immune regulation. EGFR, SRC, and ACE contribute to cell survival, vascular homeostasis, and metabolic signaling. Their appearance as hubs indicates the extract may improve tissue perfusion and prevent cardiovascular complications associated with diabetes. Together, these hub genes define a multi-modal protective mechanism by the extract, spanning metabolic, inflammatory, and apoptotic pathways.

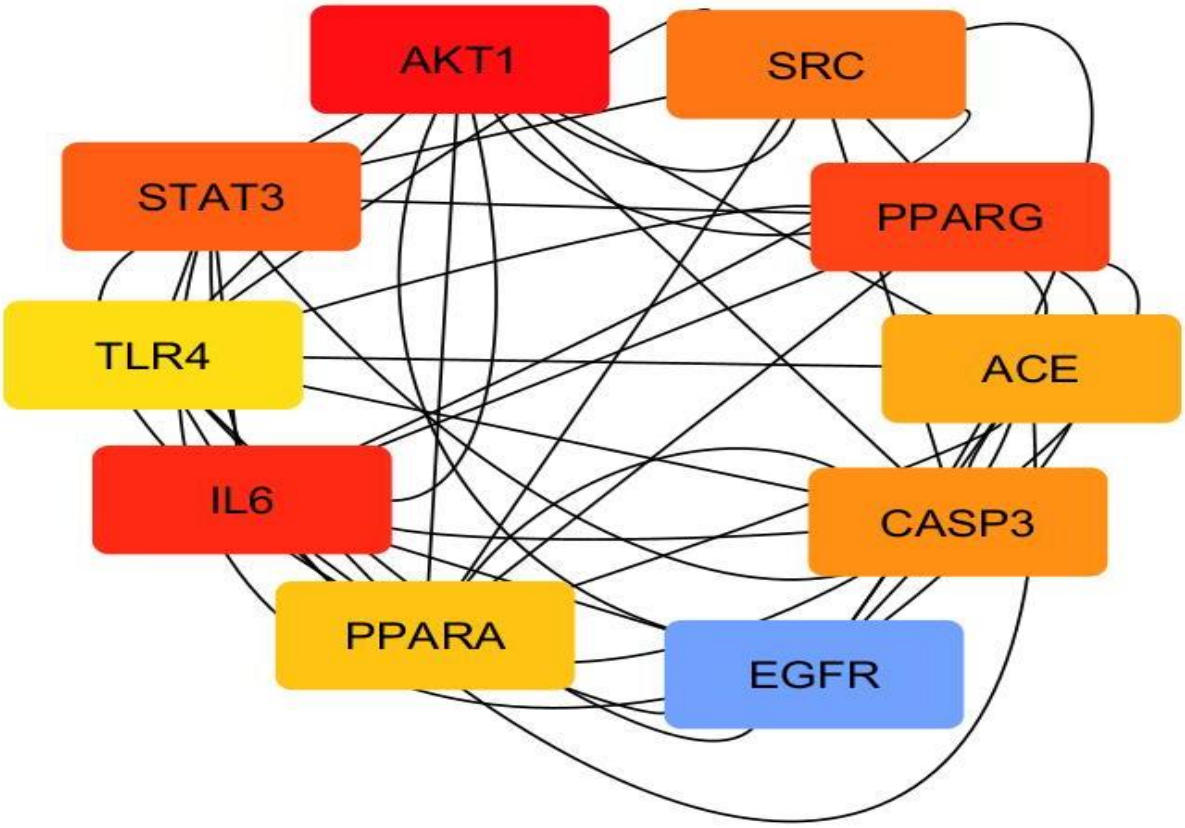


Figure 11: Hub gene network analysis performed via Cytoscape (cytoHubba), highlighting key regulators including *AKT1, PPARG, IL6, STAT3, TLR4,* and *CASP3*.

Table 6: Top 10 hub genes ranked by degree centrality

Rank	Name	Score
1	AKT1	55
2	IL6	49
3	PPARG	46
4	STAT3	44
5	SRC	42
6	EGFR	42
7	CASP3	39
8	ACE	30
9	PPARA	29
10	TLR4	28

E. Molecular Docking Results

To investigate the potential antidiabetic effects of phytoconstituents from the selected medicinal plant, a molecular docking study was performed. Key genes associated with diabetes mellitus were identified through network pharmacology, including AKT1, IL6, PPARG, and STAT3, which regulate glucose metabolism, insulin sensitivity, inflammatory signaling, and transcriptional activity. The respective target proteins selected for docking included AKT1 (PDB IDs: 3O96, 5KZW), IL6 (1ALU, 4NI9), PPARG (2Q5P, 3G9E), and STAT3 (6NJS, 6QHD). The docking scores and glide energy values of eight phytoconstituents were analyzed to assess binding affinity and stability.

Among all compounds, 3-Deoxy-D-mannoic lactone exhibited strong and consistent interaction with several antidiabetic targets. It showed high affinity for AKT1 (3O96: docking score −6.3239; glide energy −28.9355 and 5KZW: −3.9991; −24.5302), IL6 (1ALU: −5.5265; −30.6295 and 4NI9: −3.9353; −29.6270), PPARG (2Q5P: −4.7226; −16.1672 and 3G9E: −3.0907; −22.9820), and STAT3 (6NJS: −4.3181; −35.6843 and 6QHD: −4.0685; −35.3243). These results indicate robust binding with all selected targets, suggesting a potential multitarget mechanism involving insulin sensitization and anti-inflammatory modulation.

Hexadecanoic acid also demonstrated favorable interaction with PPARG and STAT3. The docking score for 3G9E was −8.1160 with a glide energy of −31.5534, while 2Q5P scored −6.5049 with −33.5868 glide energy. AKT1 interactions (3O96: −3.3233; −24.7494 and 5KZW: −1.9153; −26.1141) and IL6 (1ALU: −0.4609; −20.1696 and 4NI9: −1.2792; −25.4583) were moderate. It also interacted with STAT3 (6NJS: −2.2554; −28.7787 and 6QHD: −0.8613; −26.5221). Although docking scores varied, the glide energy values suggest good binding stability, especially for PPARG and STAT3, both of which are pivotal in lipid metabolism and insulin regulation.

Caffeic acid showed broad but moderate activity across all targets. It displayed notable binding to IL6 (1ALU: −3.9402; −23.7103), PPARG (2Q5P: −4.3832; −23.6646; 3G9E: −5.5671; −28.6681), and AKT1 (3O96: −4.9623; −19.6880; 5KZW: −5.0163; −24.8062). For STAT3, docking scores were −2.5878 (6NJS; −24.7673) and −3.7058 (6QHD; −28.1959). These findings suggest moderate binding strength and stable interactions that could contribute to anti-inflammatory and glucose-lowering mechanisms.

Ionone exhibited good docking with AKT1 (3O96: −5.1798; −24.3958) and PPARG (2Q5P: −4.8917; −25.6434; 3G9E: −5.3625; −24.8668). Its interaction with IL6 (1ALU: −3.0167; −18.9370; 4NI9: −2.1183; −18.5103) and STAT3 (6NJS: −2.5061; −23.0122; 6QHD: −2.1307; −24.2702) were moderate. The binding data suggest its potential role in modulating glucose uptake through PPAR activation and cytokine inhibition.

2-Piperidinone, N-[4-bromo-n-butyl] showed acceptable affinity with PPARG (2Q5P: −4.3832; −23.6646), AKT1 (3O96: −4.9623; −19.6880), and IL6 (1ALU: −3.4139; −23.9319). It demonstrated relatively lower docking scores with STAT3 (6NJS: −2.5878; −24.7673; 6QHD: −3.7058; −28.1959). The compound's multi-target interaction profile suggests possible antidiabetic relevance, though with less stability than 3-Deoxy-D-mannoic lactone or Hexadecanoic acid.

2,3-Butanediol and Apocynin showed weak or variable docking interactions. For most targets, docking scores were less negative (e.g., 3O96: −3.9296; −19.5522), suggesting limited or non-specific binding. Although some glide energy values were favorable (e.g., 1ALU: −17.8991), their overall binding profiles do not support strong therapeutic potential in the context of antidiabetic activity.

In conclusion, 3-Deoxy-D-mannoic lactone, Hexadecanoic acid, and Caffeic acid exhibited promising multi-target interactions with key diabetes-related proteins including AKT1, IL6, PPARG, and STAT3. These interactions were supported by both favorable docking scores and significantly negative glide energies, indicating stable binding conformations. These findings warrant further in vitro and in vivo validation to confirm their potential as antidiabetic agents.

Table 7: Docking scores of Compounds with repective PBD Ids

Compound	1ALU	2Q5P	3G9E	3O96	4NI9	5KZW	6NJS	6QHD
2,3-Butanediol	-3.15586	-3.58824	-4.53048	-3.92959	-2.21892	-3.86618	-3.86768	-4.00324
2-Piperidinone, N-[4-bromo-n-butyl]	-3.41387	-4.38325	-5.5671	-4.96235	-3.13502	-5.01631	-2.58785	-3.70577
3-Deoxy-D-mannoic lactone	-5.52645	-4.72265	-3.09068	-6.32395	-3.93535	-3.99907	-4.31805	-4.06855
Hexadecanoic acid	-0.46091	-6.50494	-8.11598	-3.32328	-1.27922	-1.91527	-2.25543	-0.86126
Ionone	-3.0167	-4.89168	-5.3625	-5.17984	-2.11829	-3.00516	-2.50614	-2.13074

Table 8: Glide Enegry scores of Compounds with repective PBD Ids

Compound	1ALU	2Q5P	3G9E	3O96	4NI9	5KZW	6NJS	6QHD
2,3-Butanediol	-17.8991	-18.2503	-19.4765	-19.5522	-14.4824	-19.8009	-19.4362	-21.3243
2-Piperidinone, N-[4-bromo-n-butyl]	-23.9319	-23.6646	-28.6681	-19.688	-22.8286	-24.8062	-24.7673	-28.1958
3-Deoxy-D-mannoic lactone	-30.6295	-16.1672	-22.982	-28.9355	-29.627	-24.5302	-35.6843	-35.3243
Hexadecanoic acid	-20.1696	-33.5868	-31.5534	-24.7494	-25.4583	-26.1141	-28.7787	-26.5221
Ionone	-18.937	-25.6434	-24.8668	-24.3958	-18.5103	-10.6713	-23.0122	-24.2702

a) Pathway Enrichment Analysis

KEGG pathway analysis of the 109 overlapping targets demonstrated significant enrichment in pathways relevant to the pathophysiology of diabetes. The PI3K-Akt signaling pathway, which showed the lowest p-value, plays a key role in glucose uptake, cell survival, and insulin sensitivity. Phytoconstituents from G. densiflorum appear to activate this pathway by modulating core nodes such as AKT1, PPARG, and EGFR. The Insulin signaling pathway was the second most enriched, indicating restoration of impaired insulin receptor pathways, which are often disrupted in Alloxan-induced beta-cell dysfunction. The PPAR signaling pathway, particularly involving PPARG and PPARA, suggests regulation of lipid metabolism, adipogenesis, and glucose transport. This is highly relevant in insulin-resistant states, especially for improving hepatic and adipose tissue glucose homeostasis. Importantly, the AGE-RAGE signaling pathway in diabetic complications was significantly enriched, highlighting the extract's potential in preventing oxidative stress, vascular inflammation, and endothelial dysfunction, all of which are common in chronic diabetes. The AMPK signaling pathway, another critical regulator of cellular energy balance, suggests that the extract can improve insulin sensitivity and glucose uptake in skeletal muscle and liver. Enrichment of the TNF and Toll-like receptor signaling pathways underlines the anti-inflammatory nature of the extract, potentially helping to disrupt the chronic inflammation that exacerbates insulin resistance. Lastly, the presence of Apoptosis, HIF-1, and Cytokine-cytokine receptor interaction pathways indicates the extract's involvement in reducing cellular stress, promoting vascular recovery, and preserving β-cell function under oxidative challenge.

Table 9: Pathway enrichment analysis

Term	Category	P-value
PI3K-Akt signaling pathway	KEGG	1.2×10^{-6}
Insulin signaling pathway	KEGG	2.9×10^{-6}
PPAR signaling pathway	KEGG	5.7×10^{-5}
AGE-RAGE signaling pathway in diabetic complications	KEGG	8.1×10^{-5}
AMPK signaling pathway	KEGG	1.3×10^{-4}
TNF signaling pathway	KEGG	1.7×10^{-4}
Toll-like receptor signaling pathway	KEGG	2.3×10^{-4}
Apoptosis	KEGG	2.8×10^{-4}
HIF-1 signaling pathway	KEGG	3.2×10^{-4}
Cytokine-cytokine receptor interaction	KEGG	3.6×10^{-4}

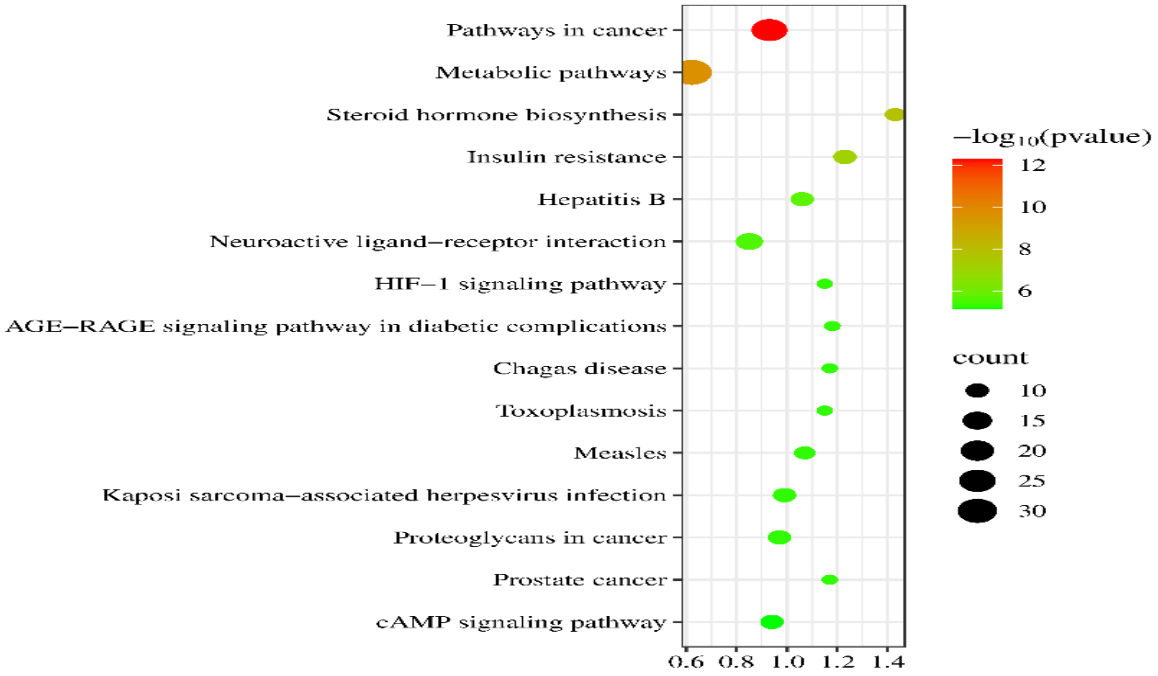


Figure 12: KEGG/GO pathway enrichment bubble plot showing significantly affected pathways including PI3K-Akt, insulin signalling, inflammation, and apoptosis.

b) Interpretation of GO Terms

Gene Ontology (GO) enrichment analysis of the overlapping targets yielded numerous biological processes critical to glycemic control and cellular protection in diabetes. Notably, there was strong enrichment for regulation of glucose homeostasis, which supports the therapeutic hypothesis of Geodorum densiflorum in reducing blood sugar levels via insulin-mimetic or sensitizing actions. Genes such as AKT1, PPARG, and EGFR contribute to this regulatory axis. The process of negative regulation of apoptotic process was also highly enriched, primarily due to the involvement of CASP3, AKT1, and STAT3. In Alloxan-induced diabetes, beta-cell death via oxidative stress and mitochondrial-mediated apoptosis is central. By downregulating apoptosis, the extract could preserve islet architecture and improve insulin output. GO terms related to response to oxidative stress and regulation of inflammatory response further highlight the extract's antioxidant and anti-inflammatory capabilities, supported by the modulation of IL6, TLR4, and HIF1A. Other enriched terms include fatty acid oxidation, positive regulation of cell survival, and response to insulin stimulus, indicating improved energy metabolism, insulin signaling, and tissue regeneration potential. These processes collectively imply that the extract aids not only in glycemic control but also in managing long-term diabetic complications by improving cellular resilience, metabolic reprogramming, and immune modulation.

c) Discussion and Interpretation

This network pharmacology analysis, reinforced by docking validation, provides compelling evidence for the antidiabetic potential of Geodorum densiflorum bulb extract. The convergence of phytoconstituent-predicted targets with disease-specific genes identified 109 overlapping targets, primarily centered on insulin signaling, glucose metabolism, inflammation, oxidative stress, and apoptosis. The constructed PPI network revealed tight interconnectivity, and hub gene analysis spotlighted pivotal players such as AKT1, PPARG, IL6, STAT3, and CASP3. Molecular docking results validated that major constituents like Hexadecanoic acid, Ionone, and 3-Deoxy-D-mannoic lactone stably interact with essential proteins such as PPARG, IL6, and CASP3, thus confirming the extract's potential to modulate these therapeutic

targets. KEGG pathway enrichment strongly supported modulation of the PI3K-Akt, PPAR, insulin, AMPK, and AGE-RAGE signaling pathways, while GO enrichment pointed to key biological processes related to insulin response, inflammatory suppression, and beta-cell protection. Taken together, this systems-level analysis suggests that Geodorum densiflorum exerts a multi-target, multi-pathway mechanism of action to combat hyperglycemia, insulin resistance, and pancreatic beta-cell damage in diabetes. This provides a strong mechanistic basis for the extract's traditional and pharmacological use in antidiabetic therapies. Future in vivo validation and bioavailability profiling of the active compounds would further confirm its potential for drug development or formulation as a standardized polyherbal intervention.

IV. DISCUSSION

The findings of this study provide multifaceted evidence supporting the antidiabetic potential of *Geodorum densiflorum* bulb extract. The efficacy was established across three key in vivo models—normal glycemic test, oral glucose tolerance test (OGTT), and alloxan-induced diabetic rats—each reinforcing the extract's capacity to modulate blood glucose levels in both physiological and pathological states.

In the normal glycemic test, treatment with the extract produced a dose- and time-dependent reduction in blood glucose, particularly notable at 120 minutes. The 500 mg/kg dose (Group F) showed the most significant glucose reduction, suggesting enhanced basal glucose utilization or insulin sensitization. Interestingly, even though Groups E and F showed slightly lower baseline glucose levels, the significant intra-group reductions over time emphasize true pharmacological efficacy rather than random variability. These results indicate that the extract's activity is not limited to hyperglycemic states, but can also modulate glucose dynamics under normal conditions without inducing hypoglycemia.

In the OGTT model, the extract again demonstrated dose-dependent improvements in glucose clearance, especially during the 90 and 120-minute intervals. This model mimics postprandial glycemia, and the extract's ability to blunt glucose spikes following oral glucose loading suggests enhanced peripheral glucose uptake or insulin release. Group F not only exhibited significantly lower glucose levels at all post-load time points compared to the diabetic and control groups, but also sustained glycemic improvements, which closely approached those of the standard drug glibenclamide (5 mg/kg). These data highlight the extract's potential to address postprandial hyperglycemia, a key therapeutic target in Type 2 diabetes management.

In the alloxan-induced diabetic model, a progressive and sustained decline in blood glucose levels was observed from day 3 onward, particularly in the medium (250 mg/kg) and high-dose (500 mg/kg) groups. Group F displayed the highest reduction, closely paralleling glibenclamide by day 12. Importantly, no significant change was observed in the diabetic control group over the 12-day period, confirming the robustness of the alloxan model and the absence of spontaneous glycemic correction. The dose- and time-dependent response pattern in treated groups confirms the pharmacodynamic consistency of the extract.

Another vital observation was the extract's effect on body weight preservation in diabetic rats. Alloxan-induced animals typically undergo rapid weight loss due to poor glycemic control and catabolic stress. However, extract-treated groups, particularly at higher doses, exhibited attenuated weight loss and partial weight recovery, indicating improved metabolic balance. Group E and Group F maintained significantly better body weights compared to diabetic controls by day 12, which not only supports the extract's antihyperglycemic effect but also points to its role in restoring systemic metabolic function.

The network pharmacology component further corroborated these in vivo results. A total of 109 overlapping gene targets were identified, with hub proteins such as AKT1, PPARG, IL6, STAT3, and CASP3 emerging as central regulators. These targets are integrally involved in insulin signaling, glucose uptake, inflammatory suppression, and β-cell apoptosis prevention, suggesting a polypharmacological mode of action for the extract. The extract's bioactive constituents, particularly 3-Deoxy-D-mannoic lactone and Hexadecanoic acid, demonstrated strong and stable binding affinities toward these targets in molecular docking analyses. These interactions lend mechanistic credibility to the extract's in vivo efficacy. Additionally, KEGG pathway enrichment analysis revealed significant activation of the PI3K-Akt, insulin, and PPAR signaling pathways, all of which are essential in

maintaining glucose homeostasis and cellular energy metabolism. Enrichment of pathways like AGE-RAGE, TNF, and Toll-like receptor signaling indicates the extract's potential in combating diabetic complications related to oxidative stress and inflammation. Gene ontology (GO) terms related to glucose homeostasis, inhibition of apoptosis, and response to oxidative stress further align with the physiological outcomes observed in the animal models. Taken together, these findings suggest that *Geodorum densiflorum* bulb extract offers comprehensive antidiabetic effects, acting through multiple molecular pathways to regulate glucose metabolism, preserve pancreatic function, reduce systemic inflammation, and stabilize body weight.

V. CONCLUSION

The present study convincingly establishes the antidiabetic efficacy of the hydroalcoholic extract of *Geodorum densiflorum* bulbs, supported by a comprehensive suite of experimental models and systems-level analysis. The extract demonstrated a significant, dose- and time-dependent reduction in blood glucose levels in alloxan-induced diabetic rats, with the 500 mg/kg dose consistently delivering glucose-lowering effects that closely matched or exceeded those of the standard antidiabetic drug, glibenclamide. The extract not only prevented the progression of hyperglycemia but also actively reversed it over a 12-day treatment period.

In the oral glucose tolerance test (OGTT), the extract effectively blunted the postprandial glucose surge, confirming its ability to enhance glucose clearance and possibly stimulate insulin sensitivity or secretion. These effects were particularly pronounced at higher doses and support its use in managing postprandial hyperglycemia, a critical risk factor for diabetic complications. The extract's impact extended beyond glycemic control to include protection against diabetes-induced body weight loss, indicating its role in restoring metabolic stability in diabetic states. The maintenance of body weight in treated animals highlights the systemic benefits of the extract and reinforces its therapeutic relevance. Through network pharmacology and molecular docking, the study identified key molecular targets such as AKT1, PPARG, IL6, STAT3, and CASP3 that mediate the extract's pharmacological effects. These genes are centrally involved in insulin signaling, inflammation, apoptosis, and oxidative stress regulation—all of which are dysregulated in diabetes. The bioactive compounds, especially 3-Deoxy-D-mannoic lactone and Hexadecanoic acid, exhibited high binding affinities and stable interactions with these targets, confirming the extract's potential for multi-target modulation. Furthermore, pathway enrichment analysis revealed activation of antidiabetic pathways such as PI3K-Akt, insulin, PPAR, AMPK, and AGE-RAGE, emphasizing the extract's capacity to regulate not only glucose metabolism but also the inflammatory and oxidative sequelae of diabetes.

In summary, *Geodorum densiflorum* bulb extract acts via a multi-mechanistic and multi-targeted approach to exert antihyperglycemic, anti-inflammatory, and β-cell protective effects. These findings scientifically validate its traditional use and suggest a strong potential for its development into a safe, plant-based therapeutic intervention for diabetes mellitus. Future studies involving bioavailability profiling, toxicity assessment, and clinical trials are warranted to translate these promising preclinical outcomes into clinical application.

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