

Hypothesizing the role of *Embelia ribes* hydro-alcoholic extract for anti-diabetic potential

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ABSTRACT

Diabetes mellitus is a long-term metabolic disease that causes high blood sugar levels and problem with insulin action, which can lead to serious problems with small and large blood vessels. *Embelia ribes* Burm, a member of the family Myrsinaceae, also known as vidanga, is a common Ayurvedic medication with various pharmacological effects. The goal of this study to investigate the pharmacognostic effectiveness of *Embelia ribes* ethanolic extract in the treatment diabetes. The extract may be contained bioactive compounds, including alkaloids, flavonoids, tannins, glycosides, and saponins, which are reported to have antioxidant and antidiabetic properties. The pharmacological assessment will be conducted by using streptozotocin (STZ) induced diabetic Wistar rat model. After treatment with *Embelia ribes* extract, fasting blood glucose levels, oral glucose tolerance, and the liver's glycogen content will be monitored. Furthermore, the levels of blood insulin, leptin, and adiponectin, as well as the HOMA-IR index and lipase activity, will be examined, which will indicate lipid metabolism and insulin sensitivity. Above mentioned parameters may be considered and the results will be supporting the traditional claims made about *Embelia ribes* ability to treat diabetes and demonstrate its potential as a natural medicine agent. Its inclusion in upcoming medication development and the creation of safer antidiabetic treatment would be supported by a solid scientific foundation, the dual scientific pharmacognostical and pharmacological evaluation will be carried out in near future.

Keywords: *Embelia ribes*, Herbal Medicine, Phytoconstituents, *In silico* studies, Diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia, which occurs due to defects in insulin secretion, insulin action or both. It also causes long-term damage, dysfunction, and failure of several organs, including the heart, kidneys, eyes, and nerves (1). The pathophysiology of diabetes is significantly influenced by oxidative stress, which also contributes to insulin resistance, pancreatic beta cell destruction, and comorbidities such as cardiovascular disease and nephropathy (2). A little woody climber, *Embelia ribes* burm. also called vidanga in Ayurvedic medicines, has long been used in traditional medical systems of Southeast Asia to treat anthelmintic symptoms, digestive issues, and a variety of systemic illnesses. *Embelia ribes* preparations and isolated constituents exhibit a broad pharmacological profile, encompassing antioxidant, antimicrobial, anti-inflammatory, anti-obesity, and, more significantly, antidiabetic activities, as per

recent thorough reviews. This supports the ethnopharmacological claims and calls for a focused evaluation of its potential in the management of diabetes (3). While traditional antidiabetic medications such as biguanides, sulfonylureas, and DPP-4 inhibitors work well, prolonged use of these medications frequently results in adverse effects and high cost, underscoring the need for safer and less expensive alternatives (4). Phytochemical investigations have identified the bioactive compound embelin (2,5-dihydroxy-3-undecyle-1,4-benzoquinone) along with other constituents such as vilangin, quercitol, and various phenolic and flavonoid compounds present in the plant (5). Recent pharmacological research has demonstrated *Embelia ribes* ability to prevent diabetes. For instance, ethanolic extract of this plant, at 100 and 200 mg/kg for 21 days significantly decreased fasting blood glucose level, improved the oral glucose tolerance, decreased hepatic glucose-6-phosphatase activity,

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increased liver glycogen content, normalized serum lipids, lipase, insulin, leptin, and adiponectin levels, and also alleviated oxidative stress (increase in SOD, CAT, GSH; decreased in TBARS) in a rat model of type 2 diabetes made using a high fat diet (HFD) and low dose of streptozotocin (STZ) (6). Additionally, in HFD+low dosage STZ diabetes rats, *Embelia ribes* extract demonstrated nephroprotective benefits by lowering renal oxidative stress indicators, improving kidney histology, blood total protein and albumin, and lowering creatinine, LDH, ALP, total cholesterol, and triglycerides (7). An earlier study on rats with streptozotocin-induced diabetes showed that 40 days of *Embelia ribes* aqueous extract (100 & 200 mg/kg) administration reduced blood pressure, heart rate, glycosylated haemoglobin, and blood glucose while increasing antioxidant defence (catalase, SOD, and glutathione levels) and lowering lipid peroxides in pancreatic tissue, suggesting protective effects on β cells (8). Another study, shows that the bioactive phytoconstituents found in *Embelia ribes* have a substantial anti-diabetic effect by lowering oxidative stress and increasing insulin secretion. Traditional and scientific evidence support this theory, showing that *Embelia ribes*, has a variety of pharmacological qualities, such as hypoglycemic, anti-inflammatory, and antioxidant. To confirm the purity and quality of the plant material used for preparing the extract, pharmacognostical evaluation focuses on the identification, authentication, and characterisation of the plant by macroscopic, microscopic, and physicochemical evaluation. These factors aid in the establishment of the drug standardization profile, which is necessary for pharmacological investigations (9). Pharmacological examination examines the anti-diabetic properties of *Embelia ribes* extract in experimental models of diabetes mellitus, such as diabetic rats induced with streptozotocin (STZ) or a high-fat diet. According to the theory, the main components of *Embelia ribes*, including phenolic

compounds, flavonoids, and embelin, may improve insulin sensitivity and alter the metabolism of carbohydrates (10).

1. HYPOTHESIS:

Hypothesis of the present study, the bioactive compounds found in *Embelia ribes* have a significant anti-diabetic effect by lowering oxidative stress, increasing insulin secretion and improving glucose metabolism. This theory is supported by both traditional and scientific data showing that *Embelia ribes*, has a variety of pharmacological characteristics, such as antioxidant, hypoglycemic and anti-inflammatory action reported in the previous research paper and review papers, the information collected after through systematic literature survey.

The goal of this study is to ensure the quality and purity of the plant material used to prepare extracts by identifying, authenticating, and characterising *Embelia ribes* seeds using microscopical and phytochemical screening. These factors aid in the establishment of the drug's standardized profile, which is necessary for pharmacological investigation (9). Pharmacological examination considers into the anti-diabetic properties of *Embelia ribes* extract in experimental models of diabetes mellitus, such as diabetic rats that have been produced by streptozotocin or the high-fat diet. According to the theory, *Embelia ribes* main components – embelin, flavonoids, and phenolic compounds may improve insulin sensitivity and alter the metabolism of carbohydrates (6, 10) and it is also anticipated that the antioxidant qualities of embelin will shield the pancreatic beta cells from oxidative damage, improving glycemic control (11). Pictorial representation of hypothesis is given in **Fig. 1**.





Fig. 1 Hypothesising antidiabetic effects of *Emblia ribes*

2. MATERIAL AND METHODS

2.1. Pharmacognostical and pharmacological evaluation of *Embelia ribes* extract for Anti-diabetic potential.

2.1.1. Evaluation of the hypothesis:

Numerous preclinical data provide substantial support for the idea that *Embelia ribes* seeds extract has anti-diabetic potential by boosting insulin secretion, improving glucose metabolism, and lowering oxidative stress. *Embelia ribes*, rich in bioactive substances like phenolics, flavonoids, and embelin, often contributes to its pharmacological effects. Hydro alcoholic extract of *Embelia ribes* has demonstrated to lower fasting blood glucose level significantly, increase oral glucose tolerance, and normalise serum lipid profile in an experimental model of type 2 diabetes caused by an HFD and a low dose of STZ. These results demonstrate the plant's capacity to regulate lipid and glucose metabolism efficiently (6). Understanding how embelin works to prevent diabetes, has been made possible by mechanistic research. As a partial agonist of the peroxisome proliferator-activated receptor gamma, embelin promotes GLUT4 translocation in skeletal muscle tissues, which improves glucose absorption. Additionally, the PI3K/Akt signalling pathway is activated, which is essential for cellular metabolism and insulin-mediated glucose transport (11). Together, these processes enhance insulin sensitivity,

a characteristic shortcoming of type 2 diabetes. It has been shown that the antioxidant capacity of *Embelia ribes* and embelin shields the pancreatic β cells from oxidative damage, maintaining insulin production and pancreatic integrity (12). *Embelia ribes* and embelin will be shown to have significant anti-diabetic efficacy through various pathways, including the reduction of oxidative stress and improvement of glucose homeostasis, according to a comprehensive review and meta-analysis of preclinical research (13). There are still restrictions despite these encouraging outcomes. The absence of pharmacokinetic data, inconsistent dosing, toxicological studies, and standardisation of extraction techniques restricts the translation of these findings into practical applications. Thus, even if preclinical data highly support the idea, pharmacological standardisation and carefully planned clinical trials are necessary to verify the safety and effectiveness of *Embelia ribes* extract in the human diabetic population.

2.2. Computational study:

Computational analysis of *Embelia ribes* for its anti-diabetic potential is a vital supplement to pharmacognostical and pharmacological assessment. *In silico* computational study for *Embelia ribes* will be conducted to determine and confirm the expected pharmacological activity of the plant. Drug likeness study, along with molecular docking, ADMET prediction, and network pharmacology study, will be conducted to detect and characterise bioactive compounds present in this plant. The binding affinity of the phytoconstituents with important diabetes

receptor targets like TNF α , IL1 β , α -glucosidase, dipeptidyl peptidase-IV, peroxisome proliferator-activated receptor gamma, and insulin receptor will be evaluated by docking studies. These interactions help in the prediction of potential mechanisms, such as the improvement of insulin sensitivity, the hydrolysis of carbohydrates and the modification of glucose metabolic pathways. Furthermore, the conformational behaviour and stability of ligand-protein complexes in a physiological setting would be determined with the help of molecular dynamics simulations. Additionally, pharmacokinetic properties would be assessed using ADMET and drug-likeness analysis to make sure that the bioactive substances satisfy the safety and efficacy standards. This combination of computational methods would help in providing predictive evidence that would validate and enhance experimental pharmacological results, and hasten the discovery of prospective lead compounds from *Embelia ribes* for the development of antidiabetic medications.

2.3. Experimental design:

A standardised hydroalcoholic extract of *Embelia ribes* seeds will be prepared using the cold maceration method, and the extract, percentage yield will be determined. To quantify the marker compound embelin, and to ensure batch-to-batch consistency, pharmacognostical characterization such as microscopy, seed powder microscopy, organoleptic tests (total ash, water-soluble ash, loss on drying), will be performed, and preliminary phytochemical screening (flavonoids, alkaloids, phenolics, saponins), and chromatographic fingerprinting (HPTLC, HPLC) will be carried out (14). In pharmacology, establish a safe dose range by first performing an acute oral toxicity study (OECD 423) will be carried out. After receiving institutional animal ethics clearance, male wistar rats will be used (n=6-8 per group). A validated model for insulin resistance + β -cell damage, type-2-like diabetes will be induced by a 4-week HFD followed by a low dose of streptozotocin (STZ, 35mg/kg i.p.). The animal will be randomly divided into the following groups: vehicle, diabetic control, normal control, extract low and high dose and positive control metformin will be decided after the acute oral toxicity results. The medication will be administered orally for 21 days while adhering to the

HFD. The primary outcome measures, including the Oral glucose Tolerance Test (OGTT), fasting insulin (compute HOMA-IR), and fasting blood glucose levels will be determined. Secondary objectives include the liver/kidney function, lipid profile, and glycosylated haemoglobin (HbA1c), antioxidant indicators (SOD, CAT, MDA), inflammatory markers (TNF- α , IL-6), and pancreatic histology (H&E, Insulin immunostaining). The following mechanistic experiment *in vitro*: insulin secretion in INS-1 cells, glucose absorption in L6 myotubes or 3T3-L1 adipocytes, and α -glucosidase inhibition. Analysis of the data will be conducted: ANOVA with post-hoc test, mean $\pm$ SEM; $p < 0.05$ significant. To support n, use the sample size calculation (power 0.8) (7). Pharmacological efficacy and safety are linked to the pharmacognostical fingerprint (embelin content) in outcome interpretation of the present study. After getting the significant results, the study will be carried forward on to formulation bioavailability, and ultimately, preclinical toxicology studies (13).

2.4. Implication:

There are several significant rectifications for basic science, drug discovery, and validation of traditional medicine for the hypothesis that a pharmacognostical (botanical, macroscopic, microscopic, and physicochemical) and pharmacological (*in vitro*, *in vivo*, and mechanistic) assessment of *Embelia ribes* extract will reveal anti-diabetic potential. Before conducting repeated pharmacological testing or creating a botanical formulation, pharmacognostical profiling, determines the *Embelia ribes* identity the quality control markers, and standardization criteria. Standardised raw material increases the translational validity of preclinical outcomes and decreases the batch variability (14). To determine whether the antihyperglycemic effects observed in several animal studies are due to insulin sensitization, insulin secretion, inhibition of carbohydrate-digesting enzymes, antioxidant protection of pancreatic β -cells, or a combination of these mechanisms, will go through pharmacological evaluation such as acute/chronic toxicity, oral efficacy in validated diabetic models, dose-response, and mechanism studies. The biological plausibility required to support clinical investigation is strengthened by the demonstration of one or more tenable processes (7).



Emblica ribes or its phytochemical lead, embelin and derivatives, are more likely to be worth moving forward with formulation development and early-phase human trials when independent preclinical research (including meta-analytic synthesis) consistently yields promising results. However, before clinical translation, systematic reviews highlight heterogeneity and demand standardized extract, GLP, toxicology and pharmacokinetics (13). Beyond medication development, pharmacognostic confirmation of anti-diabetic effectiveness encourages sustainable production practice for this medicinal species, enabling evidence-based integration of *Embelia ribes* into complementary treatment, and suggest safe dosing and regulatory quality requirements. However, contradictory or ambiguous results may redirect efforts toward

isolating the active ingredients or developing alternatives to effective traditional claims which may be having a significant scientific value in the present study (15).

2.5. Biological pathway:

2.5.1. Insulin Signalling pathway:

This picture depicts the insulin signalling pathway, in which IRS (Insulin Receptor Substrate), PI3K (Phosphoinositide 3-kinase), AKT (Protein Kinase B) are activated when insulin attaches to its cell membrane receptor. As a result, cells absorb glucose, and FOXO (Forkhead Box O) regulates gene expression, which helps keep blood glucose levels within acceptable ranges. Shown in **Fig. 2**

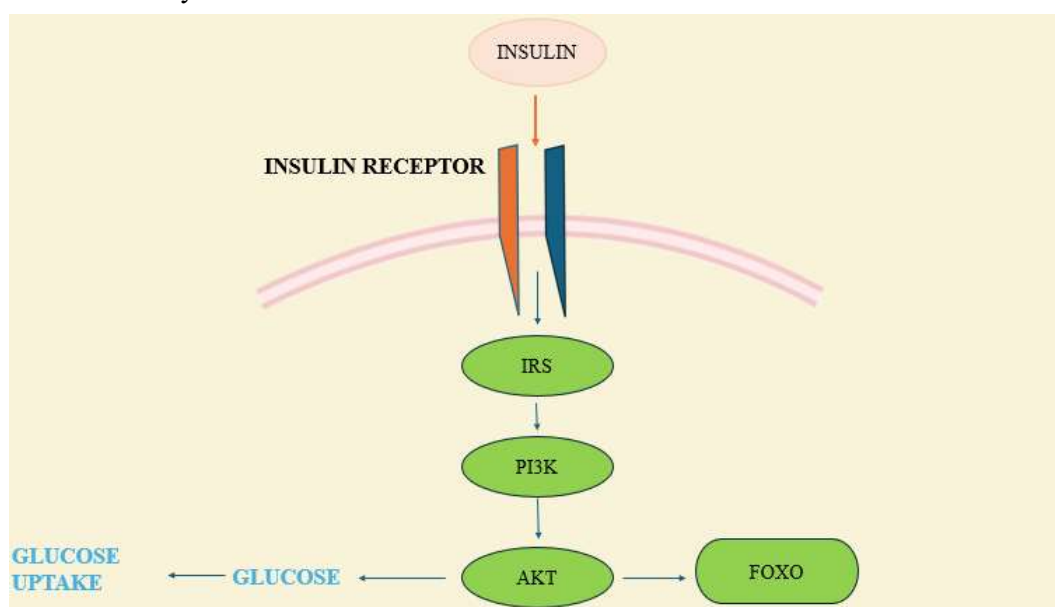


Fig. 2 Insulin signalling pathway

Diabetes mellitus is caused by a biological process that disrupts normal insulin signalling and glucose balance. When blood level rises in healthy humans, the pancreatic β -cells release the hormone insulin, and when it binds to the insulin receptor on the target cells (muscle, adipose tissue, liver), the receptor's β -subunits are autophosphorylated. This leads to the recruitment and phosphorylation of the adaptor proteins, like the insulin receptor substrate-1 (IRS-1). The phosphoinositide 3-kinase (PI3K) regulatory subunit is subsequently bound and activated by the activated IRS, which results in the conversion of PIP_2 to PIP_3 , as well as the recruitment of AKT (protein kinase B), and its activation via PDK1/mTORC2. The

translocation of the glucose transporter GLUT4 to the plasma membrane in muscle and adipose tissue (improving glucose uptake), inhibition of Glycogen Synthase Kinase-3 (GSK-3), a glycogen synthesis promoter, suppression of gluconeogenic gene expression (via FOXO1 inhibition) in the liver, and stimulation of lipogenesis are all subsequent metabolic effects of activated AKT (16). Despite normal or high insulin levels, target tissues in the context of insulin resistance a defining feature of Type 2 diabetes mellitus fail to respond appropriately to insulin. Some examples of defects include a reduction in insulin receptor (IR) autophosphorylation, abnormal phosphorylation of IRS-1/2 serine instead

of tyrosine residues, increased activity of negative regulators such as PTP1B, PTEN, and disruption in downstream signalling pathways, particularly the PI3K/AKT pathway. Reducing GLUT4 translocation, thereby decreasing muscle/adipose glucose adsorption, and increasing hepatic glucose production (via unchecked gluconeogenesis) leads to raised glucose levels in circulation and subsequent chronic hyperglycemia. As β -cells deteriorate over time, insulin insufficiency and diabetes may develop (17). Therefore, it can be understood as a failure of the insulin-receptor signalling cascade, particularly the PI3K/AKT branch, which typically decreases blood glucose by encouraging uptake, storage, and inhibition of glucose synthesis. Maintaining glucose homeostasis depends on the pathway upstream of it (IRS/PI3K/AKT) and the downstream metabolic processes (GLUT4 translocation, glycogen synthesis, and gluconeogenesis suppression). The any kind of disruption at any stage leads to hyperglycemia and metabolic dysfunction, typical of diabetes (18).

3. RESULT AND CONCLUSION:

The anti-diabetic potential of *Embelia ribes* extract has been studied through pharmacognostic and pharmacological evaluation, and the findings indicate that it may have promising therapeutic benefits for managing diabetes mellitus based on traditinal claim. Pharmacognostical studies may ensure the dependability of the extract used for pharmacological testing by verifying the authenticity and purity of the plant material using in-depth physicochemical, microscopic and macroscopic analysis. Bioactive substances with antioxidant and hypoglycemic properties may be present due to phytoconstituents such as embelin, flavonoids, alkaloids, and tannins, will be investigated by phytochemical screening of *Embelia ribes* extract. The experimental model of diabetes, pharmacological research shows that *Embelia ribes* extract dramatically lowers fasting blood glucose levels, enhances glucose tolerance and recovers biochemical parameters such as serum insulin, lipid profile, and hepatic enzyme levels. The strong antioxidant activity in this plant extracts may also helps in lowering the oxidative stress and damage to pancreatic β -cells, two major causes of problems associated with diabetes. According to these results, *Embelia ribes* has an antihyperglycemic impact

through increased insulin production, better peripheral glucose utilization and suppression of intestinal glucose absorption. As a plant-based, natural treatment for diabetes, *Embelia ribes* will be having a lot of promising effects for the treatment of DM. To confirm its effectiveness and safety in human subjects, further research is necessary, including the identification of active ingredients, elucidation of molecular mechanisms, and clinical assessment. A solid base for the development of *Embelia ribes* will be a promising candidate in the creation of innovative anti-diabetic phytomedicines by using pharmacognostical and pharmacological approach a combined approach.

4. Consent Statement/ethical approval:

There are no relevant ethical issues to declare. There are no patient data and no experiments that were performed for this publication.

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6. Competing theories and counterarguments:

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

7. Credit authorship contribution statement:

Mr. Subhadip Dinda produces and written a conceptual idea about the manuscript and Dr. Ved Pal reviewed the study and approved for the final submission.

8. Declaration of 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.



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