

**PHARMACOLOGICAL EVALUATION OF *PANDANUS  
AUREUS* IN THE TREATMENT OF DIABETES  
MELLITUS”**

**A THESIS SUBMITTED TO**



**SHRI SHANKARACHARYA PROFESSIONAL UNIVERSITY,  
BHILAI, (C.G.)**

(Established Under Chhattisgarh Private Universities (Establishment and Operation) Act 2005)

For Partial Fulfillment for the Award of the Degree of

**Master of Pharmacy**  
**in**  
**Pharmacology**  
**BY**

**Mr. Arnav Roy**

Enrollment No.-SSPU20241067

Under the supervision of

**Dr. Arpan Ku. Tripathi**

Associate Professor  
KIPS/SSPU

**Mr. Deleshwar Ku. Sahu**

Assistant Professor  
KIPS/SSPU

---

**KAMLA INSTITUTE OF PHARMACEUTICAL SCIENCES,  
DURG-490009, CHHATTISGARH, INDIA**

**August, 2025**

©2025-SSPU, Bhilai. All right reserved

### **DECLARATION BY THE CANDIDATE**

I, the undersigned solemnly declare that the report of the thesis work entitled, **“PHARMACOLOGICAL EVALUATION OF *PANDANUS AUREUS* IN THE TREATMENT OF DIABETES MELLITUS”**, is based on my own work carried out during the course of my study under the supervision of **Dr. Arpan Ku. Tripathi** and **Mr. Deleshwar Ku. Sahu**.

I assert that the statements made and conclusions drawn are an outcome of my research work. I further certify that

- i. The work contained in the thesis is original and has been done by me under the general supervision of my supervisor(s).
- ii. The work has not been submitted to any other Institute for any other degree/diploma/certificate in this University or any other University of India or abroad.
- iii. I have followed the guidelines provided by the University in writing the thesis.
- iv. I have conformed to the norms and guidelines given in the concerned Ordinance of the University.
- v. Whenever I have used materials (data, theoretical analysis, and text) from other sources, I have given due credit to them by citing them in the text of the thesis and giving their detail in the references.
- vi. Whenever I have quoted written materials from other sources, I have put the under-quotation marks and given due credit to the sources by citing them and giving required detail in the references.

Signature  
**Mr. Arnav Roy**  
Enrollment No. :1067

**CERTIFICATE FROM THE SUPERVISOR(S)**

This is to certify that the work incorporated in the thesis entitled, **“PHARMACOLOGICAL EVALUATION OF *PANDANUS AUREUS* IN THE TREATMENT OF DIABETES MELLITUS”** is a record of research work carried out by **Mr. Arnav Roy** bearing Enrollment No. 1067 under our guidance and supervision for the award of Degree of M. Pharmacy in Pharmacology of Shri Shankaracharya Professional University Bhilai, Chhattisgarh, India.

To the best of our knowledge and belief the thesis embodies the work of the candidate himself/herself, has duly been completed, fulfils the requirement of the Ordinance relating to the degree of the University and is up to the desired standard both in respect of contents and language for being referred to the examiners.

Signature of Supervisor

**Dr. Arpan Ku. Tripathi**

Associate Professor  
KIPS

Signature of Co-Supervisor

**Mr. Deleshwar Ku. Sahu**

Assistant Professor  
KIPS

**Dr. Govind Sharma**  
KIPS

Forwarded to Shri Shankaracharya Professional University Bhilai, Chhattisgarh, India

### **CERTIFICATE BY THE EXAMINERS**

The thesis entitled “**PHARMACOLOGICAL EVALUATION OF *PANDANUS AUREUS* IN THE TREATMENT OF DIABETES MELLITUS**” submitted by **Mr. Arnav Roy** (Roll No. 232403066001, Enrollment No. 1067) has been examined by the undersigned as a part of the examination and is hereby recommended for the award of the degree of Master of Pharmacy in 2025 from the Shri Shankaracharya Professional University Bhilai, Chhattisgarh, India

Name and Signature  
of Internal Examiner  
**(Dr. Arpan Ku. Tripathi)**

Name and Signature  
of External Examiner

## **ACKNOWLEDGEMENT**

In the present of world of competition there is a race of existence in which those are having Will to come forward succeed. Project is like a bridge between theoretical working. With this Willing I joined this particular project. First of all, I would like to thank the supreme power The almighty God who is obviously the one has always guided me to work on the one has Always guided me to work on the right path of life I would like to thank Dr. Govind Sharma principal of KIPS Bhilai (C.G.) For his inspiration. I take opportunity to express my sincere gratitude and deep sense of Indebtedness toward my respected Guide **Dr. Arpan Ku. Tripathi**, Professor and **Mr. Deleshwar ku. Sahu** Associate Professor who has always inspired me and extended his full Co-operative in my project work. I also thank all teaching and non-teaching staff of Kamla Institute of Pharmaceutical Sciences, SSPU. I would like to thank my family member and all my friends whose endless motivation, co-operation and patience made me to stand to present this work.

Date: 01/09/25  
Place: Bhilai

**Mr. Arnav Roy**

## LIST OF TABLES

SN	Title	Page No.
1.	Blood Glucose Level	7
2.	Glycosylated Haemoglobin	8
3.	Group wise Diabetic table	32
4.	Identification test	39-40

## LIST OF FIGURES

SN	Title	Page No.
1.	Synthesis of Insulin	3
2.	Hyperlipidaemia	5
3.	Formation of ketone bodies	6
4.	Inhibition of progression of diabetes	21
5.	Diabetic wound healing mechanisms	21
6.	Progression of Diabetic nephropathy and renal fibrosis	22
7.	Mechanisms involved in Diabetic Osteoporosis	22
8.	Etiology of Diabetes	23
9.	Soxhlet apparatus	34
10.	Identification test- Tannins (a)	36
11.	Identification test- Glycosides (b)	36
12.	Identification test- Flavanoids (c)	36
13.	Identification test- Alkaloids(d)	36
14.	Handling of mice	42

## LIST OF ABBREVIATIONS AND SYMBOLS

1. T2DM-Type 2 diabetes mellitus
2. IDDM- Insulin dependent diabetes mellitus
3. NIDDM- Non Insulin dependent diabetes mellitus
4. IR- Insulin resistance
5. HOMA-IR- Homeostasis Insulin resistance
6. HOMA-ISI- Homoeostasis Insulin Sensitivity
7. AMPK- adenosine monophosphate protein kinase
8. m-tor - Mechanistic Target for Rapamycin
9. IRS-1 - Insulin receptor substrate 1
10. PI3K-Akt – Phosphoinosityl 3 kinase – Protein kinaseb
11. IP3 – Inosityl tri-phosphate
12. DAG- Diacyl Glycerol
13. NF-kB – Nuclear factor kappa beta
14. GLUT-4 – Glucose Transporter 4
15. cAMP – cyclic Adenosine triphosphate
16. PK-A – Protein kinase A
17. CaMKII - calmodulin-dependent protein kinase II
18. Fe- Iron
19. TCA – Tri-carboxylic acid cycle
20. TG- Triglycerides
21. FFA – Free Fatty Acids
22. ACo-A – Acetyl Coenzyme-A
23. HMG-CoA – HydroxymethylGlutaryl Co-A
24. LDL- Intermediate low density Lipoprotein
25. VLDL – Very low density lipoprotein
26. LDL- Low density lipoprotein
27. HDL- High density Lipoprotein
28. GLP-1 – Glucagon like peptide
29. Ang-II –Angiotensin II
30. ALN – Alanine
31. CREA- Creatinine
32. IL-1 – Interleukin 1 Beta
33. TC – Total Cholesterol
34. BUN – Blood Urea Nitrogen
35. FAO- Fatty acid oxidation
36. iNOS- Inducible Nitric oxide Synthesis
37. HbA1c – Glycelated Haemoglobin
38. MMP – Matrix Metalloprotease
39. HIF – Hypoxia Inducible Factor
40. ICAM – Intracellular Adhesive Molecule
41. VEGF – Vascular Endothelial Growth Factor
42. TIMP – Tissue Inhibitors Metalloproteases
43. rRNA – ribosomal Ribonucleic acid
44. FBP – Fructose 1-6 Biphosphate
45. PCK – Phosphoenol pyruvate
46. G6PC – Glucose 6 phosphate
47. GPCR – G-protein coupled receptor
48. BCAA - Broken chain Amino acids



## TABLE OF CONTENTS

<b>SN</b>	<b>Particulars</b>		<b>Page No.</b>
<b>1</b>	Declaration by the candidate		i
<b>2</b>	Declaration by the supervisor(s)		ii
<b>3</b>	Certificate by the examiners		iii
<b>4</b>	Acknowledgements		iv
<b>5</b>	List of Tables		v
<b>6</b>	List of Figures		vi
<b>7</b>	List of Abbreviation and Symbols		vii
<b>8</b>	Chapter 1.	Introduction	1-24
<b>9</b>	Chapter 2.	Literature Review	25-30
<b>10</b>	Chapter 3.	Methods and Materials	31-36
<b>11</b>	Chapter 4.	Results and Discussion	37-58
<b>12</b>	Chapter 5.	Conclusion And Summary	59
<b>13</b>	Chapter 6.	References	60-70

## **ABSTRACT**

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes is rapidly increasing, with the United States, China, and India projected to be the most affected countries by 2030. Insulin secretion is regulated through various receptors, including dopamine, serotonin, acetylcholine, ghrelin, and leptin, as well as through hypothalamic and vagal stimulation pathways. Etiology of diabetes includes stress, obesity, genetics, pregnancy, drugs, prolonged steroid therapy, hypothyroidism, and polycystic ovary syndrome. Complications of diabetes encompass cancer, polycystic ovary syndrome, Alzheimer's disease, fatty liver, delayed wound healing, retinopathy, nephropathy, and neuropathy. Recent studies have explored the potential of various natural compounds and traditional medicines in managing diabetes and its complications. These include *Strobilanthes sarcoarrhiza* root phenolic extract, boeravinone C, *Trigonella foenum-graecum* L., *Polygonum posumbu* Buch. Ham. ex D. Don, San Huang Xiao Yan recipe, *Astragali Radix - Fructus Corni*, echinacoside, and *Fernandoa adenophylla* extract. The mechanisms of action involve modulation of inflammatory pathways, oxidative stress, apoptosis, lipid metabolism, and gut microbiota. This review highlights the complex pathophysiology of diabetes and the promising therapeutic potential of natural compounds and traditional medicines in managing this chronic disorder.

# Chapter 1 - Introduction

## **INTRODUCTION**

Diabetes is a chronic disorder in which the secretion of insulin from pancreatic beta cells is decreased(Aspinwall et al., 2020) . From 51 to 72 million in industrialized nations and from 84 to 228 million in developing nations, it is predicted to change quickly, rising by approximately 42% and 170%, respectively . By 2030, the United States, China, and India will be the three nations most affected by this pandemic. (Koehn et al., 2021) .

There are mainly 3 types of diabetes mellitus: insulin-dependent diabetes mellitus (Type 1 diabetes mellitus), non-insulin-dependent diabetes mellitus (Type 2 diabetes mellitus), and gestational diabetes mellitus(Abbott, 1994) . Other types are based on etiological (cause) and genetic factors. [like primary, secondary, and monogenic]]. (Huse et al., 2021)

It is a metabolic disorder characterized by hyperglycemia (increased blood glucose levels),azotouria ,Ketonaemia.(Sugimoto et al., 1998). Overall, in 100% of diabetic patients, 90% of the patients had type 2 diabetes and 10% of the patients had type 1 diabetes. (Ikegami et al., 2022)

The abdominal cavity contains the pancreas, which is essential to digestion. The glands are classified as exocrine (releasing their secretions into the duct) and endocrine (releasing their secretions into the blood). The pancreas has essentially three different types of cells: beta cells, which aid in the production of insulin, which controls blood glucose levels; delta cells, which aid in the production of somatostatin; and alpha cells, which release glucagon and aid in the synthesis of glycogen.(Sosa-Pineda et al., 2023)

Generally, there are five receptors through which the regulation of insulin occurs (dopamine, serotonin, acetylcholine, ghrelin, and leptin). The hypothalamus, being a part of the limbic system (along with the amygdala and hippocampus), also regulates insulin secretion by ventromedial neurons. (Palkovits et al., 2021) . The different pathways through which insulin secretion occurs are described in detail below.

### **Hypothalamic regulation**

Specialized neurones sense changes in insulin levels and thereby activate the AMPK pathway (adenosine monophosphate protein kinase), which in turn phosphorylates and activates acetyl co-a carboxylase, thereby inhibiting gluconeogenesis and glycogen synthesis.

The other pathway is through the AMPK-Tor Pathway (Mechanistic Target for Rapamycin), which increases insulin receptor substrate 1 (IRS 1) by phosphorylation and activation of the PI3K-AKT pathway.(Destefano & Jacinto, 2021)

vagal stimulation:-

The tenth cranial nerve, which stimulates the synthesis of insulin by activating the M3 receptor, a Gq-type receptor that increases the level of the IP3 receptor (which increases Ca<sup>2+</sup> levels through the sarcoplasmic reticulum), also releases DAG, which activates PK-C. An increase in intracellular calcium levels increases calcium-calmodulin-dependent protein kinase II (CaMKII), which in turn increases calcineurin, NF-κB, and lastly increases transport of GLUT4. (Griffith et al., 2021)

Sympathetic Inhibition:-

The adrenergics bind to the Alpha-2 receptor, which is a Gs-type receptor. It inhibits the activity of adenylyase cyclase, thereby decreasing the levels of c-AMP and PK-A, resulting in a decrease in the release of insulin. (Kohn et al., 2023)

Other receptors present in pancreatic beta cells:

Stimulating the release of insulin:-

Serotonin increases insulin release by binding to 5-HT<sub>3R</sub> and activating and releasing calcium-calmodulin-dependent protein kinase II (CaMKII). NF-κB translocation by GLUT-4.

Leptin increases insulin release by binding to leptin receptors (OB-Rb), which stimulates mTOR signaling, ultimately leading to the production of IRS-1 (Insulin Receptor Substrate). (Niki et al., 2023)

Inhibiting the release of insulin

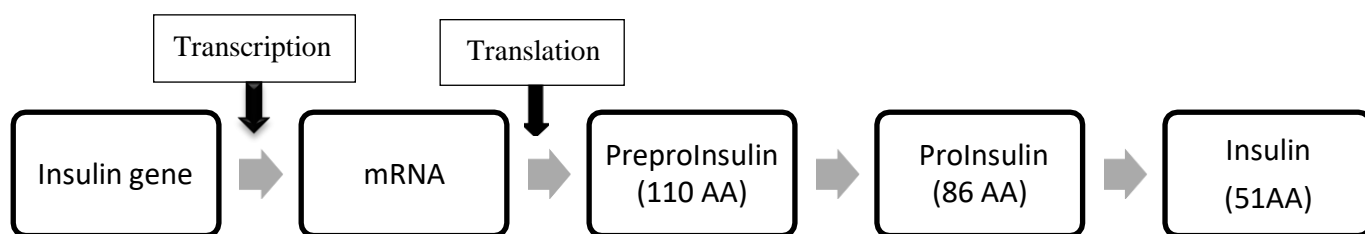
Dopamine decreases the release of insulin by binding to the D<sub>2</sub> receptor of the pancreas, which results in a decrease in the level of c-AMP.

Gherlin decreases the level of insulin by binding to the GHS-R1a, which ultimately decreases AMPK. (Fullerton et al., 2023) .

## ETIOLOGY OF DIABETES:-

1. Stress (release of gluco-corticoids eg- cortisol ) (Walter et al., 2023)
2. Overweight (Hyperlipidaemia)(Datta et al., 2024)
3. Hereditary or Genetic (Defective Insulin receptor )(Arner et al., 2023)
4. Pregnancy ( Progesterone causes Insulin desensitization ).(Eapen et al., 2020)
5. Drugs like contraceptive pills (Ireland & Allen, 2023)
6. Prolonged steroid therapy ( Glucocorticoids & Mineralocorticoids ) (Uchida et al., 2020)
7. Hypothyroidism (Hecht & Gershberg, 2025)
8. PCOS(Poly Cystic Ovarian Syndrome) /PCOD(Poly Cystic Ovarian Disorder)(Meena et al., 2025)

## SYNTHESIS OF INSULIN :-



(Bhattacharya et al., 2025)

## SIGNS & SYMPTOMS:-

- (A) **Hyperphagia** (Due to lack of glucose in skeletal muscle) (Dungan et al., 2021)
- (B) **Hyperglycaemia**

Blood Glucose (mg/dl)	Fasting	Post-Prandial
Normal	70-100	100-140
Prediabetic	101-125	140-160
Diabetes	>125	>160

Prediabetic stage can be controlled by Diet & Lifestyle Management. In Diabetic stage, Drugs are required. (Ratra et al., 2020)

**(C) Increase Glycosylated haemoglobin (Blood vessel Damage)**

Normal Range	6%
Diabetes	Above 7%

Glycosylated Haemoglobin, glucose covalently bound to Hb (is a marker or index of protein Glycosylation in the body). (Jain et al., 2024)

**(D) Glycosuria & Polyuria**

Glycosuria means the excessive amount of glucose in urine occurs due to saturation of Na-Glucose cotransporter in the nephrons. (Djeddi et al., 2020)

Polyuria means excessive amount of water loss from the body, due to excessive amount of solute content (Glucose) in the filtrate. (Oster et al., 2023)

**(E) Hyperlipidaemia :-**

The hyperlipidaemia means increase in the blood- cholesterol level in the body. (refer to fig- A)

**(F) Anaemia:-**

The increased amount of glucose in the blood causes reduced absorption of nutrients including iron (Fe). (Garzón et al., 2023)

**(G) Negative Nitrogen Balance :-**

It means the body is in catabolic condition, means the body produces excessive amount of glucose through various pathways i.e. glycogenolysis, gluconeogenesis, proteolysis. (Papachristodoulou et al., 2021)

**(H) Ketonaemia:-**

It means increase in the production of ketone bodies in that organism. (Ladd & Palmer, et al., 2023)

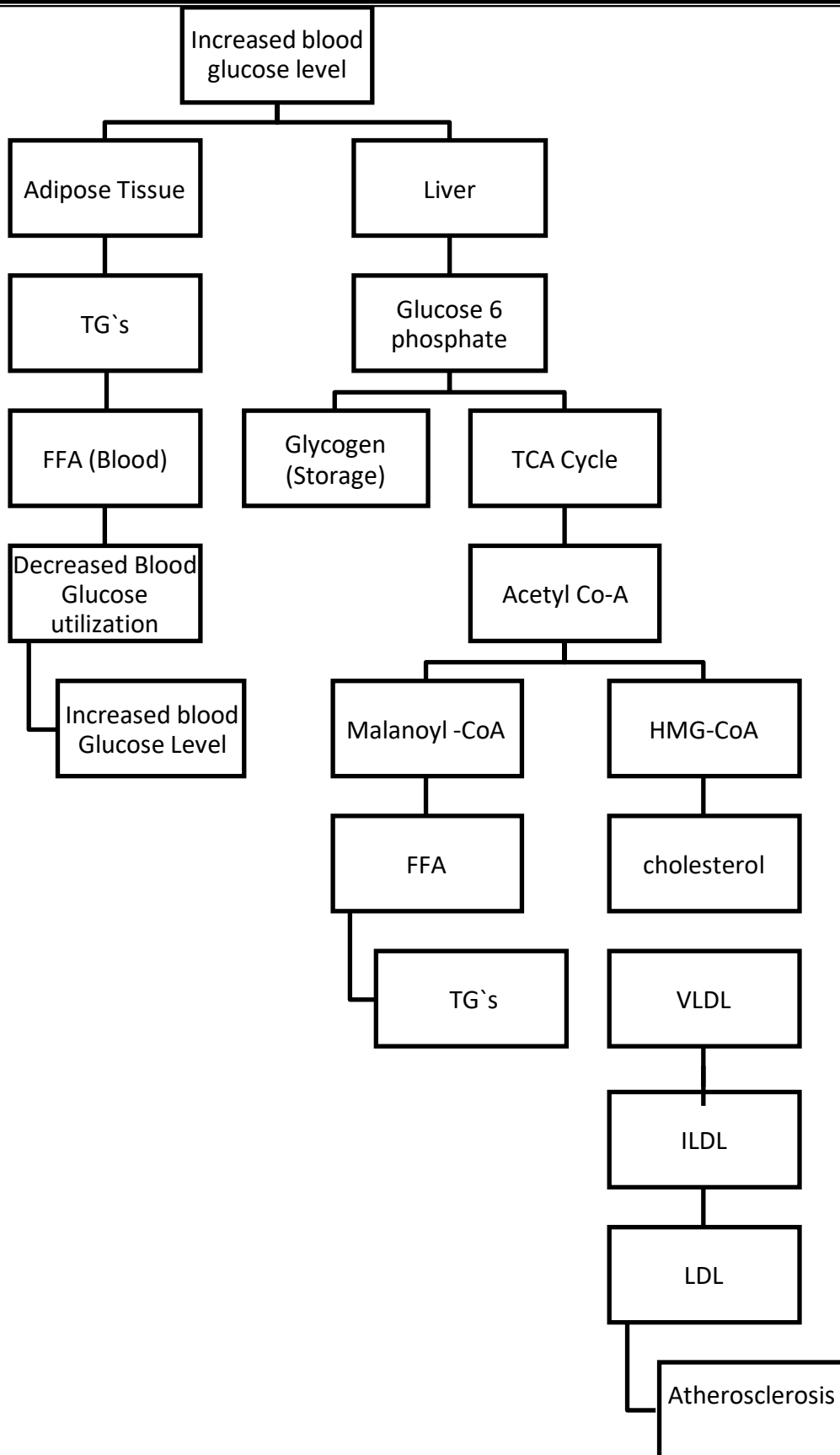
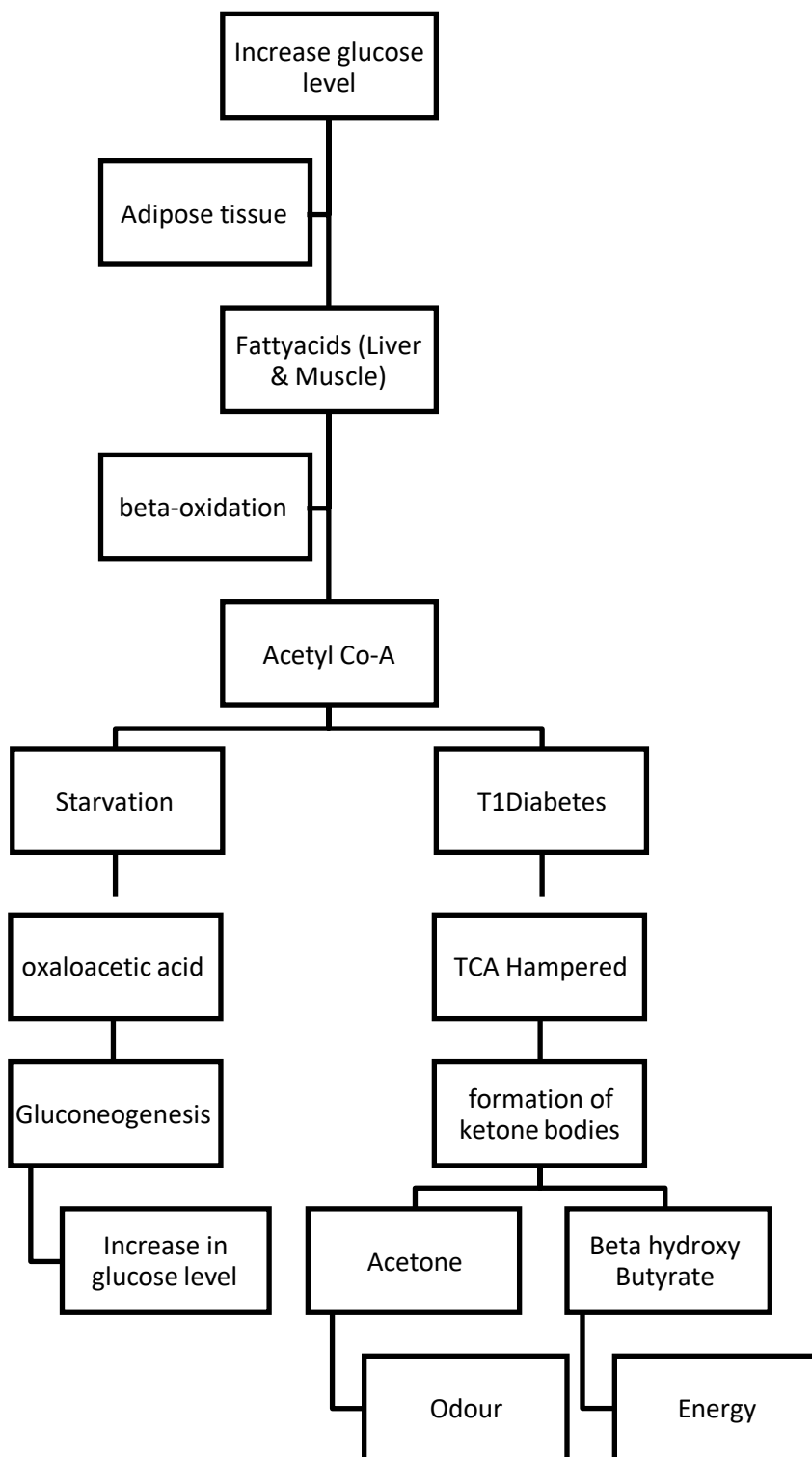


Fig-2 Hyperlipidaemia





**Fig-3 formation of ketone bodies**

## Regulation of Insulin

### 1. Neural Regulation

There are two ways through which the secretion of insulin is regulated & they are

#### a. Sympathetic Nerve (Alpha-2)

The Nor-Adrenaline binds to Alpha-2 Receptor & decreases the release of Insulin.

#### b. Parasympathetic Nerve (M1/M3 Receptor)

The Acetylcholine binds to M<sub>1</sub>/M<sub>3</sub> Receptor & Increases the release of Insulin. (Wang et al., 2006)

### 2. Hormonal Regulation

The two main hormones which regulate the release of Insulin are: - Glucagon (Increases the release) & Somatostatin (Decreases the release). (Inoue et al., 2025)

### 3. Chemical Regulation

The two main chemicals through which secretion of Insulin occurs are: -

Glucose (Activates G6P-phosphate-Glucokinase-releases GLUT-4), Incretins (Present in L cells of epithelial cells) [Activates GLP-1, GIP-1-helps in secretion of Insulin]. (Koivisto et al., 2024)

## Complications: -

1. Cancer (PI3k-akt-mTor pathway)
2. PCOS/PCOD (Hyperinsulinemia)
3. Alzheimers (Due to deposition of Beta-Amyloid)
4. Fatty liver (Excessive Glycogenesis)
5. Delayed wound healing (high blood glucose, weak immunity, catabolic condition, narrow capillaries)
6. Retinopathy (Decrease in lumen size, oxidative stress, formation of sorbitol)
7. Nephropathy (Decrease in lumen size, oxidative stress, formation of sorbitol)
8. Neuropathy (Decrease in lumen size, oxidative stress, formation of sorbitol) (Murata et al., 2023)

*Strobilanthes sarcoarrhiza* root phenolic extract mitigates diabetic nephropathy in mice by modulating NF- $\kappa$ B/IL-1 $\beta$  signaling and glycerophospholipid metabolism. CTS enhanced blood glucose and lipid profiles in diabetic mice, lowered serum levels of ALT, CREA, UREA, IL-1 $\beta$ , and IL-17, minimized pathological damage and fibrosis in kidney tissue, and reduced the protein expression of VEGF, Laminin, TNF- $\alpha$ , and NF- $\kappa$ B in kidney tissue. *Strobilanthes sarcoarrhiza* potentially alleviates DN by inhibiting the NF- $\kappa$ B pathway, which results in decreased inflammation and fibrosis in renal tissue. Diabetic nephropathy (DN) is a chronic microvascular complication linked to diabetes mellitus (DM), marked by increased albumin excretion in urine and diminished kidney function. The pathogenesis of DN is primarily associated with metabolic and hemodynamic disorders, oxidative stress, inflammation, and genetic factors. Dysregulation of glucose and lipid metabolism pathways significantly contributes to the progression of kidney disease by causing renal tubular damage, apoptosis, and fibrosis. Small molecular lipids, including fatty acids, glycerophospholipids, and sphingolipids, play complex roles in both health maintenance and disease development. Polyunsaturated fatty acids (n-3 polyunsaturated fatty acids) influence inflammation by disrupting nuclear factor kappa B (NF- $\kappa$ B) activation and its translocation to the nucleus. NF- $\kappa$ B activation, a crucial element in the inflammatory process in DN, is facilitated by the Janus kinase/signal transducers and activators of transcription mechanism. In kidney cells, NF- $\kappa$ B is rapidly activated by various stimuli, such as hyperglycemia, advanced glycation end products (AGEs), reactive oxygen species (ROS), mechanical stress, angiotensin II (Ang-II), inflammatory cytokines, and albuminuria. NF- $\kappa$ B triggers the production of numerous chemokines, adhesion molecules, and proinflammatory cytokines. (Chen et al., 2025)

Boeravinone C improves lipid accumulation and inflammation in diabetic kidney disease by activating PPAR $\alpha$  signaling. Administration of boeravinone C significantly decreased creatinine (CRE), blood urea nitrogen (BUN), triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels in the serum of DKD mice. Boeravinone C notably reversed HG-induced apoptosis in HK-2 cells, as evidenced by an upregulation of the apoptosis-inhibiting protein Bcl-2 and a reduction in the expression of apoptosis-promoting proteins Bax and caspase-3. Elevated PPAR $\alpha$  expression led to the upregulation of CPT1A and ACOX1, enhancing fatty acid oxidation (FAO) to reduce lipid accumulation in HK-2 cells. The high expression of PPAR $\alpha$  mediated by boeravinone C sequestered the p65 subunit of NF- $\kappa$ B in the cytoplasm, resulting in decreased expression of proinflammatory cytokines such as iNOS, TNF- $\alpha$ , and IL-6. (Cheng et al., 2025)

*Trigonella foenum-graecum* L. ameliorates metabolism-associated fatty liver disease in type 2 diabetic mice through a multi-omics mechanism analysis. This condition manifests as a disorder of glucose, lipid, and protein metabolism, primarily due to insulin resistance (IR) and impaired insulin secretion. The liver, a key target organ for insulin action, plays a central role in the pathological progression of MAFLD in T2DM patients through IR-induced de novo lipogenesis. (Chi et al., 2025)

Metabolomic analysis of *Polygonum posumbu* Buch. Ham. Ex D. Don, focusing on its anti-

diabetic properties, was conducted using a mechanistic approach. The extract's in-vitro anti-diabetic potential was evaluated by testing its effects on  $\alpha$ -amylase and  $\alpha$ -glucosidase enzymes. Tissue and blood samples were collected to assess tissue antioxidant capacity, biochemical markers, and HbA1c levels. The group treated with the extract showed a significant decrease in blood glucose levels by the 14th day, with normalized levels of HbA1c, AST/GOT, ALP, creatinine, and urea. A metabolomic study using UHPLC-QTOF-MS, combined with network pharmacology analysis, identified EGFR, SRC, IGF1R, MET, MMP9, ESR1, KDR, MMP2, ESR2, and SMAD3 as key targets for anti-diabetic activity. The extract functions by blocking pancreatic  $\beta$ -cell potassium channels, acting as an adrenomimetic, stimulating secondary messengers, enhancing essential heavy metals in pancreatic  $\beta$ -cells, inhibiting  $\alpha$ -amylase/glucosidase and  $\beta$ -galactosidase, neutralizing free radicals, activating glycolysis and glycogenesis, and blocking gluconeogenesis and glycogenolysis, as well as inhibiting insulinase enzyme activity. (Das et al., 2025)

The San Huang Xiao Yan (SHXY) recipe aids in wound healing in diabetic ulcer mice by inhibiting Th17 cell differentiation. SHXY reduces inflammation and edema, boosts collagen synthesis, and decreases ROR $\gamma$ T and IL-17A expression without affecting Treg cells. SHXY-containing serum inhibited Th17 cell differentiation but did not impact Treg and Th1 cells. SHXY operates through inflammatory pathways, including TNF, IL-17, Th17 cell differentiation, HIF-1, and PI3K-Akt. SHXY has a positive therapeutic effect on diabetic ulcers, significantly lowering DAO, CRP, ICAM-1, and TNF- $\alpha$  levels during the acute inflammatory phase. The combination of SHXY and Huangma Tincture effectively repairs diabetic foot ulcer wounds, improving MMP-2, TIMP-1, and VEGF expression, reducing wound size, and lessening the inflammatory response. In chronic inflammation, T cells remain active and accumulate in affected tissues, producing pro-inflammatory cytokines that disrupt the local wound environment and hinder healing. CD4<sup>+</sup> T cells are closely associated with T2DM development. Th17 cells primarily secrete IL-17A, which may worsen diabetes and its complications by promoting immune-inflammatory damage to pancreatic islets. (Deng et al., 2025) A comprehensive pharmacokinetic strategy was developed to systematically evaluate the interactions of different constituents in Astragali Radix - Fructus Corni to improve diabetic kidney disease. Iridoid glycosides in FC are considered the main bioactive constituents, offering nephroprotective benefits by improving blood glucose, lipid levels, and oxidative stress, and inhibiting apoptosis. (Duan et al., 2025)

Echinacoside mitigates type 2 diabetes mellitus by inhibiting liver gluconeogenesis through the reconstruction of a gut bacterial-fungal trans-kingdom network. Fecal 16S rRNA and ITS (Internal transcribed spacer) sequencing methods were utilized to identify the gut microbiota composition, followed by an analysis of the bacterial-fungal trans-kingdom network. ECH demonstrated notable protective effects against T2DM, as shown by decreases in FBG and fasting insulin levels, enhancements in glucose and insulin tolerance, reductions in hyperlipidemia, and relief of liver, kidney, and colon damage in T2DM mice. ECH altered gut microbiota by reducing the presence of conditionally pathogenic intestinal bacteria (*Klebsiella* and *Escherichia-Shigella*) and fungi (*Debaryomyces*), while increasing beneficial bacteria (*Lactobacillus*) and fungi (*Wallemia* and *Penicillium*). ECH could restore the disrupted trans-kingdom network

between gut fungi and bacteria, thereby suppressing inflammation-mediated hepatic gluconeogenesis by downregulating FBP1 (Fructose 1-6 biphosphate), PCK1 (Phosphoenolpyruvate), and G6PC expression. Newer anti-diabetic drugs, like sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, offer cardiovascular benefits but are often inaccessible to many patients due to cost and varying responses. Dysbiosis of the gut microbiota has been linked to the development of T2DM. Our

previous studies have shown that T2DM patients experience intestinal bacterial dysbiosis and impaired intestinal permeability. Gut microbiota dysbiosis has been associated with systemic immune and metabolic responses, affecting functions such as appetite regulation, lipogenesis, gluconeogenesis, and inflammation, which contribute to T2DM progression. (Fan et al., 2025)

Schisandra sphenanthera extract influences the sweet taste receptor pathway, IRS/PI3K, AMPK/mTOR pathway, and endogenous metabolites against T2DM. SDP has effects of lowering blood glucose, improving glycolipid metabolism, and reducing oxidative stress, and it can restore pathological damage in the liver and pancreas, activate the PI3K/AKT, AMPK/mTOR, and sweetness receptor signaling pathways, restore the sweetness receptor mRNAs, and modulate urinary compounds such as malic acid,  $\gamma$ -aminobutyric acid, leucine, N-acetylaspatic acid, and other compounds, thereby achieving the therapeutic effect of T2DM. Schisandrin B inhibited the mRNA expression of inflammatory factors like TNF- $\alpha$  and IL-6 in rat liver. Gomisin N reduced the expression of iNOS in cellular liver injury. The sweet taste receptor T1R2 and T1R3 receptor heterodimers are detected by G protein-coupled receptors (GPCRs) as the primary STRs. The binding of sugars to sweet taste receptors activates alpha-gustducin, which stimulates adenylate cyclase to produce cAMP, leading to cation inward flow through cNMP-gated channels or indirectly activating protein kinase A (PKA), resulting in K<sup>+</sup> channel closure, taste cell depolarization, voltage-dependent Ca<sup>2+</sup> inward flow, and neurotransmitter release. The GPCR-G $\alpha$ /G $\beta\gamma$ -IP3 pathway, where the sweet substance binds with the sweet receptor and the activated G $\alpha$  or released G $\beta\gamma$  activates phospholipase C $\beta$ 2, leading to the production of Inositol 1,4,5-Triphosphate (IP3) and diacylglycerol (DAG). IP3 causes Ca<sup>2+</sup> release, opening TRPM5 channels and thus promoting membrane depolarization, while DAG activates protein kinase C (PKC), leading to the closure of K<sup>+</sup> channels and causing membrane depolarization and neurotransmitter release. The IRS/PI3K/Akt pathway is a trigger for hepatic insulin resistance. The AMPK/mTOR signaling pathway affects human autophagy, with mTOR being a major negative regulator of autophagy. Hepatic insulin resistance is triggered by the IRS/PI3K/Akt pathway. Human autophagy is influenced by the AMPK/mTOR signaling system, with mTOR acting as a key autophagy negative regulator. AMPK is a crucial energy regulator that controls whole-body energy metabolism and intracellular energy balance. It can also suppress mTOR activity to trigger autophagy. T2DM is intimately associated with AMPK. mTORC1 and mTORC2, which have distinct roles in protein synthesis, autophagy, metabolism, and cell proliferation. An increased risk of type 2 diabetes has been associated with elevated levels of broken chain amino acids (BCAAs) in the blood. (Feng et al., 2025)

Guhan Yangsheng Jing alleviates oxidative stress and ferroptosis, thereby enhancing reproductive

health in diabetic male rats. It influences the expression of markers related to oxidative stress and ferroptosis, such as reactive oxygen species (ROS), superoxide dismutase (SOD), malondialdehyde (MDA), glutathione (GSH), lipid peroxidation (LPO), ferrous ion (Fe<sup>2+</sup>), nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), glutathione peroxidase 4 (GPX4), and cystine/glutamate antiporter (xCT). The GHYSJ treatment notably decreased ROS and MDA levels in the testes while boosting SOD activity, thus mitigating oxidative harm. GHYSJ also influenced the Nrf2/HO-1 signaling pathway linked to oxidative stress, thereby restoring antioxidant capacity in the testes. This is demonstrated by elevated GSH levels, increased expression of antioxidant proteins (GPX4, xCT), reduced Fe<sup>2+</sup> content, and

lower LPO levels. Retinopathy, nephropathy, and neuropathy primarily result from the buildup of advanced glycation end products (AGEs), mitochondrial dysfunction, and chronic inflammation. Diabetes affects fertility through two main pathways: hyperglycemia directly inhibits testosterone production in Leydig cells, causing hormonal imbalances, while oxidative stress damages spermatogenic epithelial cells, leading to DNA fragmentation, mitochondrial membrane potential collapse, and decreased sperm motility. Ferroptosis, a new form of iron-dependent lipid peroxidation-driven programmed cell death, serves as a key mediator connecting metabolic dysregulation and reproductive harm in diabetes. Dysregulated hepcidin levels lead to increased transferrin receptor 1 (TFR1) expression and excessive iron accumulation in testicular tissue. The inhibition of GPX4 activity weakens cellular defense against lipid ROS, disrupting the blood-testis barrier (BTB) and activating the Nrf2/HO-1 pathway, which triggers an inflammatory response. Ginsenosides, astragalus polysaccharides, and lycium polysaccharides offer protective effects through various mechanisms, including direct ROS scavenging, upregulation of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT), inhibition of the NF- $\kappa$ B/NLRP3 inflammasome, reducing pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ ) release, and modulation of the PI3K/Akt/mTOR signaling pathway, thereby improving insulin resistance. (Fu et al., 2025)

Cornuside is a promising therapeutic agent for diabetic kidney disease, targeting the regulation of Ca<sup>2+</sup> disorder-mediated apoptosis in renal tubular epithelial cells. Renal tubular epithelial cells (RTECs) play a crucial role in maintaining renal reabsorption and are essential for normal kidney function. The apoptosis of RTECs results in irreversible structural damage and functional loss in the proximal tubule, accelerating the progression of DKD. Abnormal Ca<sup>2+</sup> signal transduction in the ER and mitochondria is a key factor causing damage to RTECs. Hyperglycemia, proteinuria, AGEs accumulation, and elevated free fatty acid levels lead to endoplasmic reticulum stress (ERS), triggering the unfolded protein response (UPR). Ca<sup>2+</sup> is transferred from the ER to the mitochondria via channels composed of proteins like voltage-dependent anion channel 1 (VDAC1), directly causing Ca<sup>2+</sup> overload in mitochondria. Neural precursor cell-expressed developmentally downregulated 4 (NEDD4), an E3 ubiquitin ligase, has been identified to interact with VDAC1, facilitating its degradation through the ubiquitin–proteasome system. NEDD4 is made up of a catalytic HECT domain at the C-terminus, four WW domains positioned in the middle of the protein, and a C2 domain at the N-terminus. (G. Gao et al., 2025)

Using network pharmacology and experimental validation, modified weiling decoction reduced excessive autophagy through the AKT/mTOR/ULK1 pathway to treat type 2 diabetes. In T2DM mice, MWLD improved glucose metabolism and increased hepatic glycogen synthesis by activating the AKT/GSK3 $\beta$  pathway. In the liver of T2DM mice, MWLD reversed the rise of autophagy-associated proteins (LC3II, Beclin1, Cathepsin B, and LAMP2) and triggered the AKT/mTOR/ULK1 signaling pathway. Similar outcomes were also verified for HepG2 cells, an in vitro model for IR, produced by palmitic acid. The accumulation of cellular triglycerides, decreased fatty acid oxidation, increased endoplasmic reticulum stress, and a decline in insulin sensitivity and glucose tolerance are all consequences of dysregulated autophagy in the liver, which contributes to the development of type 2 diabetes. By inhibiting FoxO1-induced excessive autophagy, apoptosis, and fibrosis, angiotensin IV reduced diabetic cardiomyopathy. Dihydromyricetin may be involved in the pathogenesis of IR and hepatic steatosis, as evidenced

by the involvement of AMPK/PGC-1 $\alpha$  and PPAR $\alpha$ -dependent autophagy pathways. (W. Gao et al., 2025)

Deciphering *Astilbe rivularis* Buch.-Ham. ex D. Don's medicinal potential in reducing diabetic neuropathy in lab rats . To evaluate diabetic neuropathy, behavioral characteristics such as mechanical hyperalgesia and heat and cold allodynia were calculated. The sciatic nerve's levels of inflammatory markers including TGF- $\beta$  and IL-6, as well as antioxidant enzymes like SOD, GSH, and TBARS (thiobarbituric acid assay), were assessed. Inflammatory indicators such as TGF- $\beta$  and IL-6 were also discovered to be inhibited in sciatic nerves by hexadecanoic acid, heptafluorobutyric acid, and beta-sitosterol. ARHE also reduced oxidative stress and demonstrated inhibitory effect on the ALR enzyme and erythrocyte sorbitol buildup. A histopathological analysis showed that treating diabetic neuropathy rats with ARHE improved the architecture of their sciatic nerve tissue. Triterpenoids derived from the plant have demonstrated anti-hyperglycemic potential, although only in vitro, by improving glucose absorption by cells (C2C12 myotubes). (Gupta et al., 2025)

Molecular mechanisms underlying the hypoglycemic effects of *Fernandoa adenophylla* extract in diabetes induced by streptozotocin: The findings indicated an increase in G6-PDH (PPS pathway), PFKFB1 (glycolysis), GS (glycogenesis), and GLUT-4 (glucose transporter) expression, while the PEPCK (gluconeogenesis) gene was suppressed. Insulin is recognized as the primary hormone that regulates glucose metabolism in the liver, affecting glycolysis, gluconeogenesis, the pentose phosphate shunt pathway (PPS), and glycogenesis. Glucose-6-phosphatase (G6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK) are crucial rate-limiting enzymes involved in liver gluconeogenesis. Through the AKT-signaling pathway, insulin reduces the levels of G6Pase and PEPCK proteins, thereby hindering gluconeogenesis. Insulin promotes glycogenesis by activating GS (glycogen synthase) dephosphorylation and inhibiting GP (glycogen phosphorylase) dephosphorylation, a process occurring in AKT-signaling. Insulin also boosts the expression of GK via the AKT-signaling pathway, with glucokinase (GK) being the rate-limiting enzyme for glucose consumption in the liver through glucose phosphorylation. The adipokine "adiponectin," released by adipose tissue, enhances insulin sensitivity and is inversely related to the occurrence of

T2DM.(Hakeem et al., 2025)

Novel monomers derived from the Shengji-Huayu formula target the PI3K/Akt signaling pathway for diabetic wound healing, as revealed by precise network pharmacology. HPLC-MS and molecular docking showed that Calycosin (Cal) and Dehydromiltirone (DHT) strongly target Itga6 and Thbs1. Simiao Yong'an Decoction may enhance the healing of DU by affecting the Wnt/ $\beta$ -catenin pathway. Shixiang plaster was found to aid diabetic ulcer healing through the VEGF/VCAM-1/eNOS signaling pathway in vivo. The SJHY formula facilitates wound healing by modulating the Activin/follistatin Pathway, with CCN1 being a key target in the mechanisms. Network pharmacology analysis indicated that the cAMP signaling pathway glucose metabolic process, and HIF-1 pathway are involved in wound healing. (Jiang et al., 2021)

Baicalin mitigates lipid metabolism disorders in diabetic kidney disease by targeting FKBP51. FK506-binding protein 51 (FKBP51) was identified as a natural target of baicalin, with the Tyr113 residue being crucial for the binding interaction. Baicalin enhances fatty acid oxidation, reducing fibrosis in murine models of DKD and chronic kidney disease (CKD). The downregulation of the urinary FKBP51 gene in DKD patients is associated with renal interstitial

fibrosis and tubular atrophy, suggesting that FKBP51 deficiency may play a role in DKD. (M. Li et al., 2025)

A novel glycopeptide from mountain-cultivated ginseng residue protects against heart failure induced by type 2 diabetic symptoms. APMCG-1 also reduced endoplasmic reticulum stress and mitochondria-mediated apoptosis in H9c2 cells via the PI3K/AKT signaling pathway. APMCG-1 significantly lowered reactive oxygen species production and lactate dehydrogenase levels in palmitic acid (PA)-induced H9c2 cells. Glycopeptides are complex glycosylated peptides containing peptides and sugars. N-glycosites and O-glycosites differ fundamentally in chemical structures and bioactivities. In diabetic cardiomyopathy, mitochondrial dysfunction was caused by lipid droplet overload. Additionally, endoplasmic reticulum (ER) stress and reactive oxygen species (ROS) were regulated by excess lipids, leading to mitochondrial dysfunction and ultimately promoting heart failure. A comprehensive systemic study involving sixteen types of enzymes was conducted to extract MCG and evaluate their protective effect on the heart.(Z. Li et al., 2025)

Huiyang Shengji Decoction Enhances Diabetic Skin Ulcer Recovery through the NF- $\kappa$ B/STAT3/NLRP3 Signaling Pathway: A Multi-Omics Study· HYSJD modulates the NF- $\kappa$ B/STAT3/NLRP3 signaling pathway, which subsequently controls inflammatory mediators in wound tissue and serum, while also reducing cell apoptosis.· Sinapine and Arginine were identified as the main bioactive components affecting DSU lesions.(Lin et al., 2025)

Ginsenoside Ro prevents endothelial damage by promoting Epac1/AMPK-mediated mitochondrial protection in early diabetic retinopathy· Ro mitigated the progression of DR by enhancing retinal thickness and reducing pathological changes in STZ-induced diabetic mice· Ro facilitates the activation of Epac1-mediated AMPK signaling.· Despite pericyte loss and retinal neuropathy occurring in early DR, endothelial cell damage in the retina is considered a critical event in early DR.· Anti-vascular endothelial growth factor (VEGF) drugs approved by



the FDA for advanced DR treatment inhibit neovascularization and vascular permeability, thus reducing leakage due to vascular leakage.· Hyperglycemia interacts with proteins and lipids to form advanced glycation end-products (AGEs), a major factor in endothelial cell damage (promoting apoptosis).· Epac1 is a target for Celastrol in improving mitochondrial dysfunction.· Mitochondrial function can be mediated through the AMPK pathway to enhance DR. Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) is known for maintaining cellular energy status.· The expression level of endothelial marker CD31 and anti-apoptotic protein Bcl-2 was reduced in the endothelial injury model induced by AGEs, and Ro could significantly reverse the decline in its expression.· Ro could significantly lower ICAM-1, VCAM-1, PVCAM-1, IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 expression levels.· DRP1 protein significantly increased and accelerated mitochondrial fission, and the increase in fission can lead to endothelial dysfunction. Ro significantly reduced mitochondrial membrane potential and fission, thereby restoring mitochondrial function and reducing inflammation and oxidative stress.· The expression levels of mitophagy and autophagy-related proteins, and the levels of PINK1, Parkin, LC3, and P62 were increased. Renshen Zhuye decoction alleviates high-fat diet-induced obesity and insulin resistance by modulating gut microbiota and metabolic homeostasis.· RZD reduced intestinal and systemic inflammation by enhancing intestinal barrier integrity, particularly through increased expression of tight junction proteins such as

Occludin, reducing inflammation, and enhancing metabolic homeostasis.· (Liu et al., 2025)

Microbial dysbiosis can trigger inflammatory responses and compromise the mucosal barrier, subsequently leading to systemic metabolic disturbances.· Short-chain fatty acids (SCFAs), bile acids, and other microbial-derived compounds function as crucial signaling molecules, regulating energy metabolism, insulin sensitivity, and inflammatory responses.· SCFAs such as acetate, propionate, and butyrate can modulate appetite regulation and enhance glucose homeostasis. (Luo et al., 2025)

Quercetin-loaded PEGylated liposomes mitigate testicular dysfunction in alloxan-induced diabetic rats: The influence of the Kisspeptin/Neurokinin B/Dynorphin pathway.· The ALX group treated with Que-PEG-Lip showed significant improvements in glycemic index, serum reproductive hormones, testicular antioxidant status, and the immunoexpression of testicular Kiss-1, androgen receptor (AR), and proliferation marker protein (ki67) compared to the ALX group.· Administering Que-PEG-Lip to the ALX group modulated the gene expression of the Kisspeptin/Neurokinin B/Dynorphin/steroidogenesis pathway.· In diabetic patients, the decline in steroid production is linked to reduced plasma testosterone levels, which involves the downregulation of androgen-related genes, such as hydroxysteroid dehydrogenases and cytochrome P450.· Kisspeptin (Kiss) is a neuropeptide hormone that influences reproductive function in the hypothalamus. It is encoded by the Kiss1 gene in humans and interacts with the G-protein coupled receptor (GPR54 or Kiss1R).· Kiss is co-expressed with other neuropeptides like neurokinin B (NKB) and dynorphin (Dyn), encoded by the tachykinin-3 (TAC3) and prodynorphin (PDYN) genes, respectively.· Kiss plays a role in regulating GnRH release.· The study examined reproductive hormones, testicular antioxidant status, mRNA

expression of hypothalamus (PDYN, NKB, Kiss-1, Kiss-1r, and GnRH, GnIH), pituitary (GnRHr), and testicular steroidogenesis (STAR, CYP11A1, CYP17A1, HSD17B3, and CYP19A1) genes, along with the immunohistochemical protein expression of testicular Kiss-1, AR, and ki67.(Mansour et al., 2025)

Quercetin from *Parinari curatellifolia* planch.ex benth differentially regulates *Drosophila* insulin-like peptides II and V in hyperglycaemic flies. This study aims to identify the hypoglycaemic principles of *Parinari curatellifolia* (PC) and its mechanism in *Drosophila* insulin-like peptide (DILP) gene expression. The bioactive compounds of PC showed a 40% and 70% increase ( $p < 0.05$ ) in DILP2 and DILP5 gene expression, respectively. *Drosophila* insulin-like peptides (DILP) and *Drosophila* insulin receptors (DInR) are known to function similarly to their mammalian counterparts. Glibenclamide, a strong inhibitor of SUR1-TRPM4 channels, is transcriptionally upregulated in cerebral ischemia and also enhances peptide expression. (Omale et al., 2025)

Modulation of satiety, lipid metabolism, and insulin sensitivity by triphala and *Garcinia cambogia* in high-fat diet-induced obese rats. These compounds also improved satiety markers (leptin, serotonin) and glucose metabolism by reducing blood glucose, insulin levels, and HOMA-IR. Lipid profiles were enhanced, mTOR levels decreased, and adiponectin and AMPK levels were restored. Oxidative stress markers (ascorbic acid, GSH, SOD, CAT) were normalized. A high-fat diet (HFD) raises circulating TG levels, disrupting mitochondrial respiratory function by impairing adenine nucleotide translocation and generating excess reactive oxygen species (ROS), leading to oxidative stress. Short-term satiety is regulated by gut-derived peptide hormones

such as GLP-1, cholecystokinin, serotonin, and PYY, which influence digestion and food intake. The brain processes these signals along with sensory and metabolic cues to control appetite and energy balance. GA enhances glucose tolerance and lipid metabolism, while tannic acid inhibits adipocyte differentiation and supports glucose regulation. Syringic acid exhibits anti-obesity, anti-inflammatory, and anti-steatotic properties by modulating lipid metabolism and inflammatory gene expression. Epicatechin plays a crucial role in reducing obesity by activating AMPK, leading to decreased fat accumulation, particularly in epididymal white adipose tissue. HCA plays a crucial role in minimizing fat accumulation by blocking ATP-citrate lyase, which in turn reduces acetyl-CoA production and boosts energy metabolism.(Panda et al., 2025)

Optimization of extraction parameters and anti-hyperglycemic evaluation of standardized extract from *Santalum album* L. leaves · Safe oral doses of SA at 1 and 2 g/kg were identified, leading to improvements in body weight and blood glucose levels in hyperglycemic rats. · Vitexin, a natural C-glycosylated flavonoid, inhibits  $\alpha$ -glucosidase, an enzyme that breaks down polysaccharides into monosaccharides. · Vitexin has been found to mitigate pancreatic  $\beta$ -cell damage and apoptosis caused by lipopolysaccharide (LPS) by lowering levels of pro-inflammatory cytokines, TNF- $\alpha$ , and high-mobility group box 1 (HMGB1).(Phung et al., 2025)

Assessing the potential fasting and postprandial mechanisms involved in the acute hypoglycemic and anti-hyperglycemic effects of four selected plants from Iran used in traditional Persian

medicine · The potential inhibitory effect in vitro of enzymes involved in relevant pathways, such as gluconeogenesis (fructose-1,6-bisphosphatase, FBPase, and glucose-6-phosphatase, G6Pase), carbohydrate breakdown (intestinal  $\alpha$ -glucosidases), and insulin sensitivity (protein tyrosine phosphatase 1B, PTP-1B).(Safavi et al., 2025)

To establish a new quality assessment method based on the regulation of intestinal microbiota in type 2 diabetes by lignans of *Schisandra chinensis* (Turcz.) Baill · *Schisandra* lignans significantly reduce bone gamma-carboxyglutamate protein (BGP), blood lipid levels, and oxidative stress in diabetic rats, thereby providing hepatoprotective effects. · Chisandrin content (lignan) of  $\geq 3.5$  mg/g and a total lignan content of  $\geq 17$  mg/g serve as quality evaluation indicators for the improvement of T2DM by *Schisandra chinensis* Fructus. · These lignans are characterized by their high concentration and unique dibenzocyclooctadiene skeleton structure, which offer significant antioxidant, anti-inflammatory, and neuroprotective effects.(Shi et al., 2025)

The total alkaloids of *Berberidis Cortex* alleviate type 2 diabetes mellitus by regulating gut microbiota, inflammation, and liver gluconeogenesis. · TBC alleviated inflammation in T2DM rats by enhancing intestinal barrier function and inhibiting the LPS/TLR4/MyD88/NF- $\kappa$ B pathway. · TBC inhibited liver gluconeogenesis by regulating BAs/FXR/FGF15 and CREB1/PGC-1 $\alpha$  signaling pathways. · TBC significantly reduced the levels of FBG, OGTT, GSP, HOMA-IR, TC, TG, and LDL-C, and improved the histopathological changes in pancreatic and liver tissues in T2D rats. · Gut microbiome analysis through metagenomics demonstrated that TBC could improve gut microbiota dysbiosis, including an increase in beneficial bacteria (e.g., *Bifidobacterium pseudolongum* and *Lactobacillus acidophilus*) and a decrease in harmful bacteria (e.g., *Marvinbryantia* and *Parabacteroides*). · TBC significantly up-regulated the expression of three intestinal barrier-related tight junction proteins (ZO-1, occludin, and claudin-1) · Hepatic transcriptomics analysis further revealed the regulatory role of TBC on gluconeogenesis-related

genes, such as *Pgc* and *Creb1*. · Increasing TCDCA and CA levels, thereby activating several proteins in the FXR/FGF15 signaling axis (i.e., FXR, FGF15, and FGFR4), and then decreased the expression of p-CREB1 and PGC-1 $\alpha$  to inhibit liver gluconeogenesis. · BAs can regulate glucose homeostasis by acting on some key receptors, such as farnesoid X receptor (FXR).(Tao et al., 2025)

Danggui Buxue decoction enhances autophagy to mitigate renal fibrosis in diabetes via the miR-27a/PI3K/AKT pathway. It improves the urine albumin-to-creatinine ratio and blood urea nitrogen levels. DBD can enhance renal function and lessen renal fibrosis in diabetic nephropathy (DN) mice, increase mRNA expression of Beclin-1 and ULK1, and reduce mRNA expression of Vimentin and  $\alpha$ -SMA. Serum containing DBD enhances the viability of human renal podocytes in high glucose conditions, safeguarding cells and adjusting mRNA levels of Beclin-1, ULK1, P62, and PI3K, with miR-27a-mimic reversing these changes. Autophagy removes damaged organelles and protein aggregates to maintain cellular balance and interacts with signaling pathways that influence the progression of diabetic nephropathy. miR-27a, an endogenous non-coding RNA, is crucial in regulating cell proliferation, apoptosis, and metabolism, impacting renal processes by targeting various genes. Danggui Buxue Decoction (DBD) reduces renal fibrosis in DN rats by

modulating the miR-27a/TGF- $\beta$ 1/Smad pathway. In the pathological context of renal fibrosis, DBD may also indirectly influence cell survival and proliferation by inhibiting the PI3K/AKT/mTOR pathway, facilitating the transition between fibrogenesis and growth inhibition. Components within DBD, such as astragaloside and angelica polysaccharide, downregulate TGF- $\beta$  expression, thereby reducing Smad3 phosphorylation, inhibiting fibroblast activation, and collagen deposition—key actions in halting fibrosis progression. (N. Wang, Feng, et al., 2025)

$\alpha$ -Linolenic acid from Mori Folltfm, identified as a Cholesterylglycine hydrolase inhibitor by a developed fluorescent probe, alleviates type 2 diabetes.  $\alpha$ -Linolenic acid, as a natural CH inhibitor, significantly regulates glucose metabolism in a type 2 diabetes mellitus (T2DM) mouse model via the FXR signaling pathway. Bile salt hydrolase plays a crucial role in bile acid-mediated signaling pathways, which regulate lipid absorption, glucose metabolism, and energy homeostasis. Metformin and theabrownin can increase the amount of conjugate bile acids in the intestinal tract by inhibiting BSH activity, thereby inhibiting intestinal FXR, and subsequently alleviating obesity, high cholesterol, diabetes, and non-alcoholic fatty liver diseases. Bile salt hydrolase plays a crucial role in bile acid-mediated signaling pathways, which regulate lipid absorption, glucose metabolism, and energy homeostasis. (X. Wang, Zhao, et al., 2025)

Integrating metabolomics and network pharmacology to investigate Da-Chai-Hu Decoction prevents kidney injury in diabetic mice. DCHD ameliorates DN by regulating the AGEs/RAGE pathway and metabolic profiling. In clinical practice, the use of hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs, and renal protection drugs, either alone or in combination, is common for treating and slowing the progression of DN, including sodium-glucose cotransporter-2, glucagon-like peptide-1 receptor, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists. (X. Wang, Zhong, et al., 2025)

Qing'e Pill addresses the imbalance in bone homeostasis associated with diabetic osteoporosis through the AGE/RAGE pathway: A network pharmacology analysis and multi-omics validation. Diabetic osteoporosis (DOP), a metabolic condition linked to diabetes mellitus, leads to elevated blood sugar levels that damage bone microstructure, strength, and quality, heightening fracture

risk and complicating treatment and recovery. Its potential to promote angiogenesis was assessed using scratch, migration, and tube formation assays. The advanced glycosylation end product-receptor (AGE/RAGE) signaling pathway and oxidative stress in a high-glucose environment are identified as crucial elements in the onset and progression of DOP. QEP influences the Wnt/ $\beta$ -catenin signaling pathway, encouraging bone formation and reducing osteoclast activity in postmenopausal osteoporosis patients, thus preserving bone metabolism and calcium absorption balance. QEP can prevent iron-induced cell death and boost cell survival by modulating the PI3K/AKT pathway and ataxia telangiectasia mutated signaling pathway, showcasing significant anti-osteoporosis properties. (Y. Wang, Yang, et al., 2025)

Exploring the molecular mechanisms of Jiangu Decoction in managing type 2 diabetic osteoporosis, JGD enhanced alkaline phosphatase (ALP) activity, supported bone mineralization, and increased the expression of osteogenic marker genes like runt-related transcription factor 2 (Runx2), osteocalcin (Ocn), and collagen type 1 alpha (Col1a1). JGD lowered oxidative stress

levels and reduced reactive oxygen species accumulation by adjusting the Keap1/Nrf2/HO-1 axis both in vivo and in vitro. Nuclear factor erythroid-derived 2-like 2 (Nrf2) is a transcription factor that coordinates cellular defense against oxidative and toxic damage by promoting the expression of genes involved in the oxidative stress response. Under oxidative stress, Nrf2 separates from Keap1 (kelch-like ECH-associated protein 1) and moves to the nucleus, where it stimulates the expression of antioxidant genes like HO-1. Considerable evidence suggests that high glucose exposure disrupts the Keap1/Nrf2/HO-1 signaling pathway, leading to oxidative stress and subsequently hindering bone remodeling processes. Activating the Keap1/Nrf2/HO-1 signaling pathway may counteract high glucose-induced osteoblast toxicity, presenting a potential therapeutic target for T2DOP. (Wei et al., 2025)

The Kouqiangjie formula mitigates diabetic periodontitis by regulating alveolar bone homeostasis through the miR-29a-3p-mediated Dkk-1/Wnt/ $\beta$ -catenin signaling pathway. KQJF maintains alveolar bone structure and reduces osteoclast activity. KQJF influences the miR-29a-3p-Dkk-1/Wnt/ $\beta$ -catenin signaling pathway, affecting osteoblastic activity and inflammatory responses. KQJF activates miR-29a-3p and suppresses Dkk-1 in bone preservation. Diabetic periodontitis (DP) is a frequent complication in diabetes patients, marked by severe gum disease and bone loss. Dkk-1 serves as an antagonist to the Wnt/ $\beta$ -catenin pathway, blocking its signaling by binding to and inhibiting the activation of the Wnt receptor alongside LRP5/6. TNF- $\alpha$ , a major inflammatory factor, influences the cellular functions of the Wnt/ $\beta$ -catenin pathway by activating the ERK pathway to regulate cellular physiological functions. The Wnt/ $\beta$ -catenin pathway interacts with the OPG/RANKL system to affect the balance between osteogenesis and osteoblastogenesis within the skeletal framework. miR-29a encourages osteoblast proliferation by down-regulating DKK-1 expression and activating the Wnt/ $\beta$ -catenin signaling pathway. (Wu et al., 2025)

· miR-29a enhances osteoblast proliferation by suppressing DKK-1 expression and activating the Wnt/ $\beta$ -catenin signaling pathway. Pae/exo@PF-127 facilitates diabetic wound healing through miR-424-5p. · Paeonol (Pae), with its anti-inflammatory and vascular-enhancing properties, serves as a therapeutic herbal extract for diabetic wound treatment in stem cell-derived exosomes (exo). · The effects of Pae/exo on human skin fibroblasts (HSF) and human umbilical vein endothelial cells (HUVEC) were evaluated using CCK-8, migration, and transwell assays. · Western blotting, qPCR, and immunofluorescence experiments were conducted to analyze the regulation of

associated genes and proteins. · This study confirmed that Pae/exo increased the proliferation and migration of HSF and HUVEC by promoting epithelial-mesenchymal transition (EMT) and angiogenesis. · The expression of miR-424-5p was significantly upregulated upon treatment with Pae/exo, which correlated with the induction of EMT and angiogenesis. · Pae exerts protective effects against atherosclerotic cardiovascular disease via various mechanisms, including modulating inflammation, inhibiting platelet aggregation, adjusting lipid metabolism, preventing mitochondrial injury, reducing endoplasmic reticulum stress, regulating autophagy processes, and altering noncoding RNA expression. · Pae can activate the c-myc/VEGFR2 signaling pathway to repair vascular damage and regulate vascular reendothelialization. · Pae up-regulated miR-1 expression through the PI3K/AKT pathway to inhibit cardiac muscle cell apoptosis. · EMT

facilitated the conversion of fibroblasts into myofibroblasts, thereby augmenting their migratory and contractile capabilities. The myofibroblasts exhibited  $\alpha$ -SMA expression, while E-cadherin and Vimentin played pivotal roles during the proliferative phase of wound healing. · VEGFA, a crucial angiogenic factor, synergistically stimulated the formation of new immature capillary rings and branches with other pro-angiogenic factors to guide blood vessel growth from the periphery of the wound to the hypoxic region in the wound bed.(Xia et al., 2025)

Serum metabolomics and 16S rRNA amplicon sequencing reveal the role of puerarin in alleviating bone loss aggravated by the antidiabetic agent pioglitazone in type 2 diabetic mice. · Hematoxylin and eosin (H&E) staining and tartrate-resistant acid phosphatase (TRAcP) staining were performed to observe the difference in skeletal phenotype. · PUE promoted alpha-linolenic acid metabolism and glycerophospholipid metabolism, and affected the alpha diversity of the gut microbiome by regulating the genera of *Alloprevotella*, *Fusobacterium*, and *Rodentibacter*. · PIO treatment for six months significantly increased bone marrow fat in the lumbar spine and proximal femur. · PUE acted on the pancreas to lower blood glucose, enhancing the GLP-1R signaling pathway and improving the PI3K/Akt pathway. · PUE increased GLUT4 levels on the plasma membrane in skeletal muscle and adipocyte membrane to reduce insulin resistance and enhance glucose absorption from blood circulation. · PUE promoted angiogenesis and suppressed bone marrow fat accumulation. · Puerarin alleviates atherosclerosis via the inhibition of *Prevotella copri* and its trimethylamine production.(Yang et al., 2025)

Through network pharmacology analysis, the mechanism and active components of jiao tai wan (JTW) in managing type 2 diabetes mellitus have been elucidated, focusing on the SRC/PI3K/AKT signaling pathway. JTW has been shown to lower blood glucose and lipid levels, decrease HOMA-IR, and increase HOMA-ISI in T2DM mice, while also reducing ALT, AST, and MDA levels and boosting SOD levels. JTW effectively addresses upstream dysregulation by reducing SRC phosphorylation and enhancing the phosphorylation of PI3K and AKT. SRC activation plays a role in modulating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. The regulation of glucose uptake involves facilitating the insulin-driven translocation of the SLC2A4/GLUT4 glucose transporter to the cell surface. Berberine from HL can counteract metabolic dysfunction and restore redox balance by activating Clock/Bmal1 in diabetic fatty liver. The primary targets of JTW in T2DM treatment are closely associated with genes in pathways such as SRC, PIK3A1, STAT3, HSP90, and GRB2. GRB2 can mitigate lipid accumulation and inflammatory infiltration in rats with atherosclerosis (AS) by activating the PI3K/AKT/NF- $\kappa$ B pathway. The AGE-RAGE signaling pathway, with HSP90, is

involved in modulating cellular stress and inflammatory responses, thereby reducing chronic inflammation linked to AGEs, which affects diabetes progression. In the tyrosine kinase inhibitor EGFR pathway, SRC is a key player in EGFR signaling, promoting cell proliferation and migration, with GRB2 also being significant. STAT3 and GRB2 are crucial for endocrine regulation, impacting pancreatic  $\beta$ -cell function and insulin responsiveness. Epiberberine (EPI) may be a significant active compound in JTW, playing a vital role in diabetes management due to its diverse mechanisms and favorable safety profile. d-Pinitol and Catalpol significantly reduce

liver gluconeogenesis and promote glycogen synthesis by activating the PI3K/AKT signaling pathway, effectively lowering blood glucose levels. (Ye et al., 2025)

Reshaping the gut microbiota: Tangliping decoction and its core blood-absorbed component quercetin improve diabetic cognitive impairment. Tangliping decoction and Quercetin enhance cognitive function in diabetes and regulate gut microbiota, with Quercetin being the main component. TLP and QR can improve learning and memory in DCI mice, reduce homeostasis model assessment insulin resistance (HOMA-IR), and restore homeostasis model assessment- $\beta$  function (HOMA- $\beta$ ), leading to increased fasting insulin (FIN) levels and decreased fasting blood glucose (FBG) levels. Administering FMT from donor mice to pseudo-sterile DCI mice has been shown to alter the composition and abundance of gut microbiota, leading to improvements in pathological damage in the colon and hippocampal tissues. Gut microbiota contributes to the pathogenesis of DCI through pathways such as the gut-brain axis, endocrine, and immune systems. Occludin and zonula occludens-1 (ZO-1) are crucial for maintaining the integrity of both the gut barrier and the blood-brain barrier (BBB). TLP, including QR berberine, mangiferin, and chlorogenic acid, demonstrates the ability to enhance HOMA- $\beta$ , reduce food intake and FBG levels, repair the BBB, and protect hippocampal synaptic function. (W. Zhang et al., 2025)

Efficacy and mechanism of Schisandra chinensis active component Gomisins A on diabetic skin wound healing: network pharmacology and in vivo experimental validation. Gomisins A enhanced the healing process of diabetic skin wounds by blocking the TLR4-p38 MAPK-IL6 inflammation signaling pathway. Alongside Gomisins A, compounds such as Longikaurin A, Deoxyharringtonine, Wuweizisu C, and Interiotherin B play a role in modulating biological activities linked to diabetic skin wounds, including the positive regulation of phosphorus metabolism, facilitation of cell migration, and response to injury. Gomisins A improved skin wound recovery by enhancing insulin sensitivity and mitigating the toll-like receptor 4 (TLR4)-p38 MAPK-IL6 inflammation signaling pathway influenced by advanced glycation end-products. Cytokines, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), stimulate angiogenesis, while the short peptide RL-QN15 supports the regeneration of epidermal nerve fibers and keratinocyte migration, contributing to skin wound healing. Compounds like curcumin, gallic acid, epigallocatechin-3-gallate, and quercetin have been shown to decrease reactive oxygen species (ROS) production, reduce oxidative stress, and maintain oxygen balance in wounds, thereby aiding skin wound healing. Gomisins N inhibits adipocyte formation and counters obesity induced by a high-fat diet. Gomisins J reduces liver fat synthesis triggered by oleic acid by activating the AMPK pathway and suppressing the hepatokine fetuin A in HepG2 cells. Schisandrol A decreases obesity and lipid accumulation in mice on a high-fat diet and protects against neuronal cell death caused by advanced glycation end-products (AGEs) by allosterically targeting the ATP6V0d1 subunit of V-ATPase. The ethanol extract of Caragana

jubata alleviates symptoms in mice with STZ-HFD-induced type 2 diabetes mellitus through the PKC/GLUT4 pathway. CJEE predominantly activates the PKC pathway, with minimal involvement of the Akt pathway, emphasizing the critical role of  $\text{Ca}^{2+}$  release in GLUT4 regulation. The impact of CJEE on intracellular  $\text{Ca}^{2+}$  levels was measured using Fluo-4 dye, and

the modulation of GLUT4 by Akt, AMPK, and PKC signaling pathways was examined using specific inhibitors. (Z. Zhang et al., 2025)

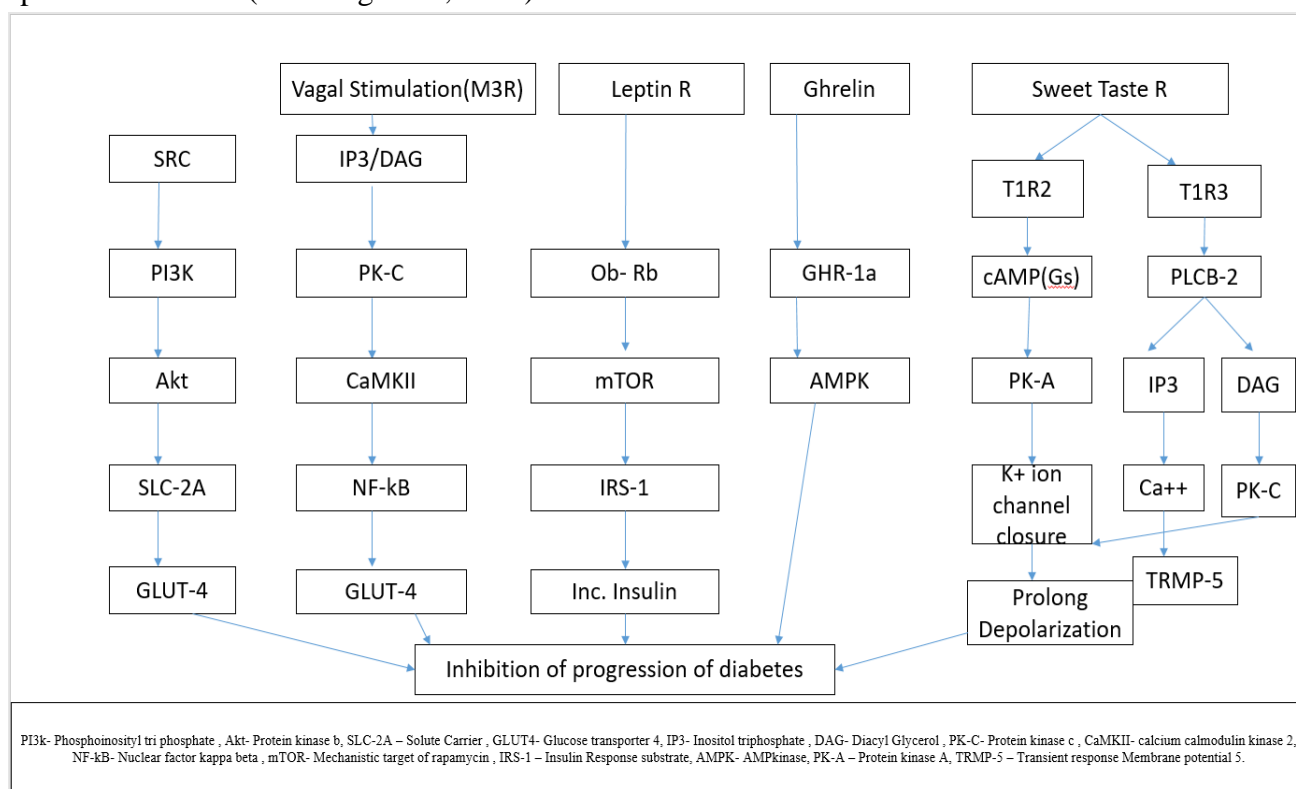


Fig – 3 Inhibition of progression of diabetes

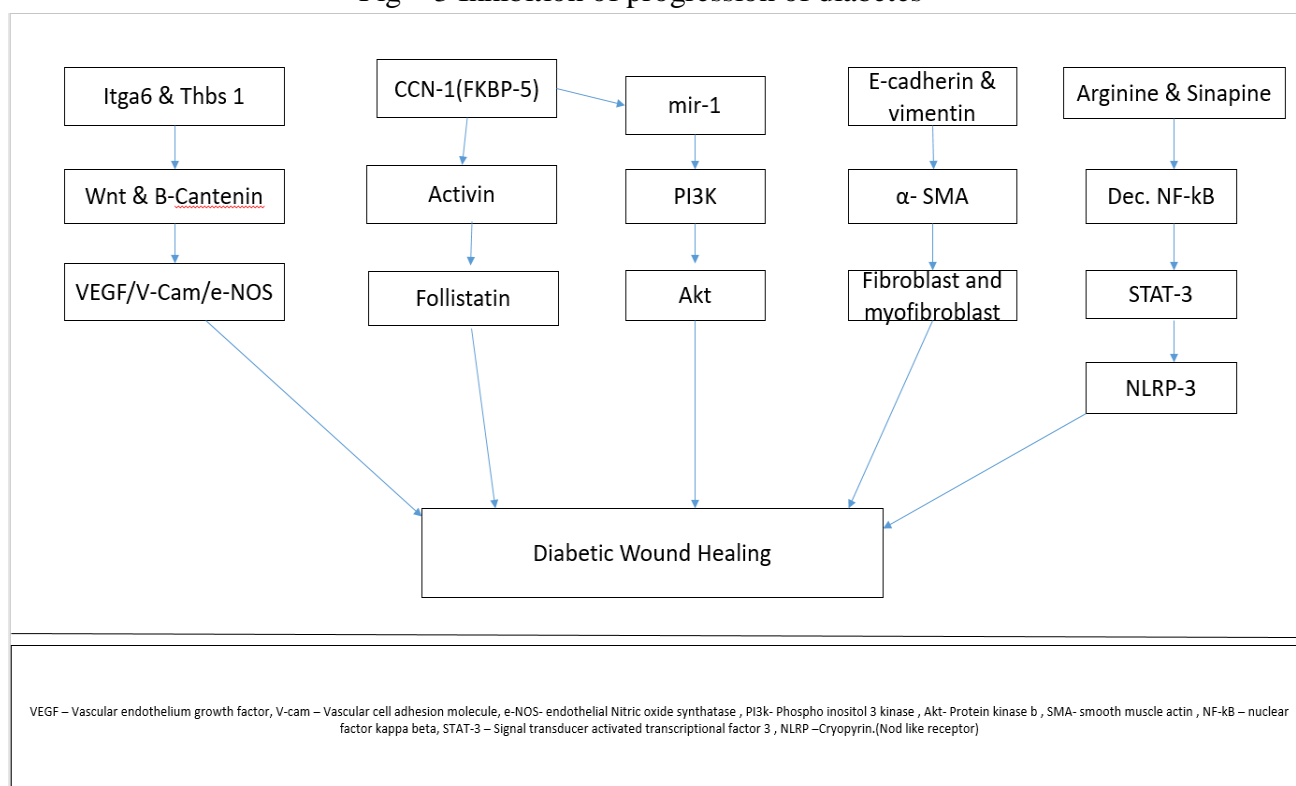


Fig -4 Diabetic wound healing mechanisms



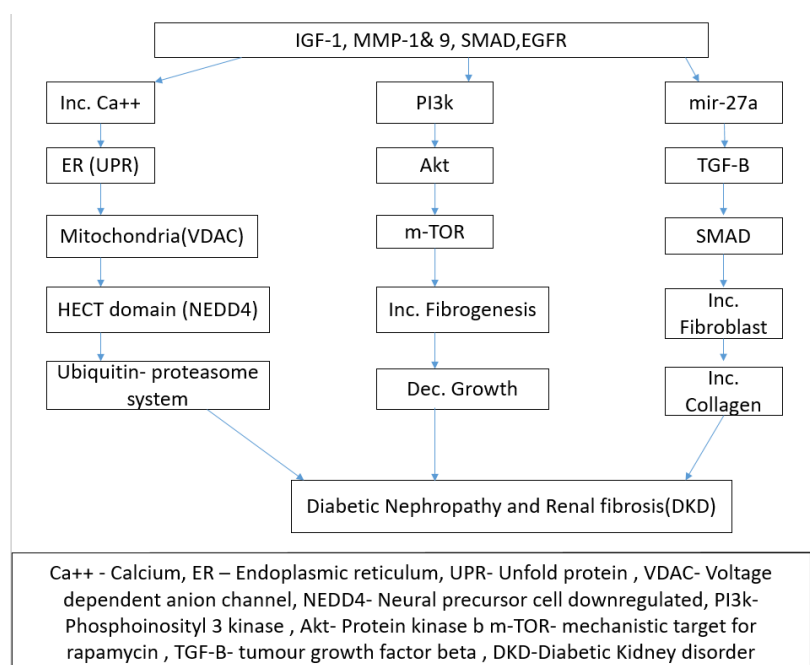


Fig- 5 Progression of Diabetic nephropathy and renal fibrosis

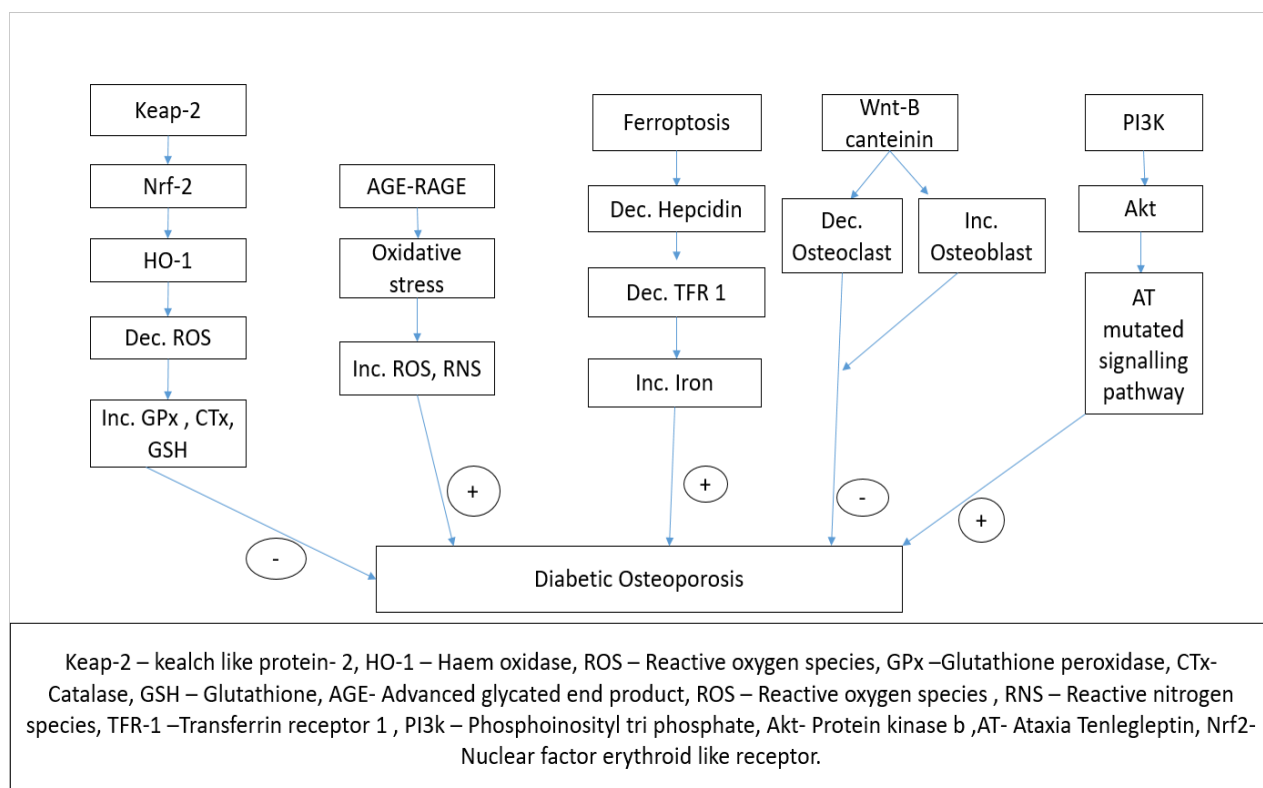


Fig-6 Mechanisms involved in Diabetic Osteoporosis

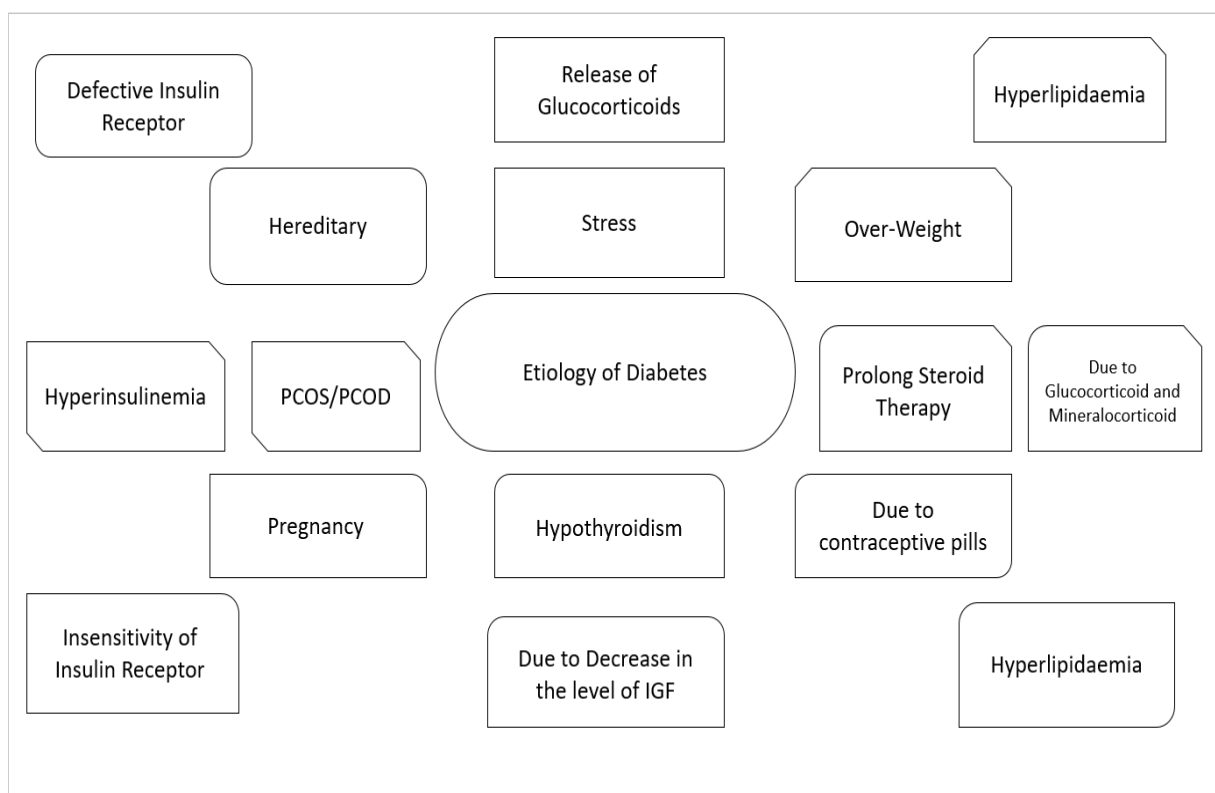


Fig-7 Etiology of Diabetes

## Plant Profile



Name- *Pandanus aureus*

Synonym- Basmati Screw Pine plant/ Spyder

Family- Pandanaceae

Genus- *Pandanus*

Geographical source:- It is present mostly in Indian subcontinent, apart from that it is also available in certain parts of Bangladesh, Bhutan, Nepal, & other Indo-Pacific countries like Malaysia & Thailand.

Chemical Constituents:- The different types of chemical constituents present are alkaloids, phenolics, organic acids, terpenoids, and chlorophyll derivatives. Apart from that other chemicals like 4 hydroxy benzoic acid, Beta-4-glucan, ( $\pm$ )- pandamarine, pandamarilactonine-A etc.

Uses- Antidiabetic, Antioxidant, Antipyretic.

## Chapter 2 – Review of literature

**Review of literature**

1. **Gebert *et al.*, 2025** – The Scottish Computed Tomography of the HEART (SCOT-HEART) trial assessed the impact of diabetes mellitus on quantitative plaque and long-term outcomes in patients with and without diabetes mellitus. Results showed that patients with diabetes mellitus had higher quantitatively assessed calcified, non-calcified, low attenuation, and total plaque burdens. Diabetes mellitus was an independent predictor of calcified plaque burden, but not other plaque types. During 8.7 years follow-up, diabetes mellitus was associated with an increased risk of fatal or non-fatal myocardial infarction.
2. **Jayaseelan *et al.*, 2025** - Diabetes Mellitus is a common comorbidity in patients with SARS-CoV-2. A study in Puducherry, India, found a higher relative risk of developing the condition in moderate to severe COVID-19 cases. Factors such as age, smoking, and comorbidities were key in the development of the condition. The study highlights the need for closer monitoring of severe COVID-19 patients for new-onset diabetes in the post-COVID period, emphasizing the importance of early detection and management.
3. **Vasudevan *et al.*, 2025** - This study used Mendelian randomization analysis to study the causal association of iron levels with type 2 diabetes mellitus and glycaemic traits. The researchers used organ iron levels (liver, spleen, and pancreas) as direct markers of iron status. They used summary data from genome-wide association studies to analyze the effect of organ iron levels on type 2 diabetes and glycaemic traits. The results showed no causal association between liver and pancreas iron levels with type 2 diabetes, except for a negative effect on HbA1c. Spleen iron levels also had a negative effect on type 2 diabetes. The study concluded that organ iron levels, which are more direct indicators of iron status, showed no causal association with type 2 diabetes in the European population.
4. **Liepert *et al.*, 2025** - The study presents a case series of patients who had a change in diagnosis from type 2 diabetes mellitus (T2DM) to autoimmune diabetes mellitus (DM) supported by positive anti-GAD antibodies. The patients were identified through a retrospective chart review of anti-GAD antibodies tests. The main reasons for ordering antibodies were diabetic ketoacidosis, insulin insufficiency, inadequate effect of oral medications, young age, and a family history of autoimmune conditions.
5. **Narayanan *et al.*, 2025** - This study explores the underutilization of the National Diabetes Prevention Program among women with a history of gestational diabetes mellitus. A qualitative study with 18 women aged 29-43 years revealed four key themes: challenges in navigating health information, perceived facilitators for participation, perceived barriers, and insights into patient perspectives on gestational diabetes mellitus care. The study emphasizes the need for improved communication, personalized support, and accommodating unique challenges faced by women with gestational diabetes mellitus to enhance participation in the program. A patient-centric approach could significantly impact Type 2 diabetes mellitus prevention in this high-risk population.

6. **Raghuveer *et al.*, 2025** - A cross-sectional study of 108 individuals with Type 2 Diabetes Mellitus (T2DM) in two tertiary care teaching hospitals found that 45.70% had cognitive impairment, with higher rates among those aged  $\geq 60$  years and those with diabetes for over 7 years. The study also found that cognitive impairment was significantly higher among participants with hypertension. The prevalence of cognitive impairment in T2DM was 58.30%, with the duration of diabetes  $\geq 7$  years being the significant factor associated with cognitive impairment.
7. **Lei *et al.*, 2025** - The study investigates the link between arsenic exposure and type 1 diabetes mellitus in mice. Streptozocin (STZ) was used as an inducer to initiate pathological changes. The study found that arsenic exposure combined with low-dose STZ led to increased fasting blood glucose, impaired glucose tolerance, decreased insulin sensitivity, reduced fasting serum insulin, increased hair arsenic content, increased reactive oxygen species, IL-1 $\beta$ , IL-18 contents, and more severe pancreatic pathology. The study also revealed elevated expression levels of proteins associated with the NLRP3/Caspase-1/GSDMD-mediated pyroptosis pathway.
8. **Goldney *et al.*, 2025** - A study involving 108,061 individuals with newly diagnosed type 2 diabetes and 829,946 controls found that BMI, obesity, LDL-cholesterol, and hypertension were higher in those with type 2 diabetes. These differences were larger with an earlier age, particularly for BMI and obesity. The association between age and HbA1c was variable across subgroups. The study suggests population-based strategies, particularly weight-management-based ones, are needed to address the risk associated with early-onset type 2 diabetes.
9. **Wasana *et al.*, 2025** - The study evaluated the efficacy and safety of a new herbal formulation of *Coccinia grandis* in newly diagnosed patients with type 2 diabetes mellitus (T2DM). A three-month, randomized, double-blind, placebo-controlled clinical trial was conducted in Sri Lanka. Out of 158 patients, 145 completed the trial successfully. The results showed that the herbal drug of *C. grandis* significantly improved glycemic and selected lipid profile parameters with well-tolerated safety. However, the herbal drug did not significantly change other outcome variables compared to the placebo. The study concluded that the treatment with *C. grandis* (500 mg per day) for three months significantly improved glycemic and selected lipid profile parameters in patients with newly diagnosed T2DM.
10. **Steyn *et al.*, 2025** - study conducted in Ethiopia found that a significant number of diabetic patients are using herbal medicine without seeking advice from their healthcare providers. The study found that 48.1% of diabetic patients used herbal medicine, with *Moringa stenopetala*, *Trigonella foenumgraecum*, and *Thymus schimperi* being the predominant herbs used. The use of herbal medicine was associated with factors such as diabetes knowledge, occupation, income, and family history of diabetes. The study concluded that herbal medicine use was common among diabetes patients, with poor knowledge, a family history of diabetes, lower income, and a farming occupation as strong predictors. Healthcare providers should engage patients in discussions about herbal medicine use and explore specific herbs and their mechanisms of action.

- 11. Chen et al., 2025)** - *Strobilanthes sarcoarrhiza* root phenolic extract mitigates diabetic nephropathy in mice by modulating NF- $\kappa$ B/IL-1 $\beta$  signaling and glycerophospholipid metabolism. CTS enhanced blood glucose and lipid profiles in diabetic mice, lowered serum levels of ALT, CREA, UREA, IL-1 $\beta$ , and IL-17, minimized pathological damage and fibrosis in kidney tissue, and reduced the protein expression of VEGF, Laminin, TNF- $\alpha$ , and NF- $\kappa$ B in kidney tissue. *Strobilanthes sarcoarrhiza* potentially alleviates DN by inhibiting the NF- $\kappa$ B pathway, which results in decreased inflammation and fibrosis in renal tissue. Diabetic nephropathy (DN) is a chronic microvascular complication linked to diabetes mellitus (DM), marked by increased albumin excretion in urine and diminished kidney function. The pathogenesis of DN is primarily associated with metabolic and hemodynamic disorders, oxidative stress, inflammation, and genetic factors. Dysregulation of glucose and lipid metabolism pathways significantly contributes to the progression of kidney disease by causing renal tubular damage, apoptosis, and fibrosis. Small molecular lipids, including fatty acids, glycerophospholipids, and sphingolipids, play complex roles in both health maintenance and disease development. Polyunsaturated fatty acids (n-3 polyunsaturated fatty acids) influence inflammation by disrupting nuclear factor kappa B (NF- $\kappa$ B) activation and its translocation to the nucleus. NF- $\kappa$ B activation, a crucial element in the inflammatory process in DN, is facilitated by the Janus kinase/signal transducers and activators of transcription mechanism. In kidney cells, NF- $\kappa$ B is rapidly activated by various stimuli, such as hyperglycemia, advanced glycation end products (AGEs), reactive oxygen species (ROS), mechanical stress, angiotensin II (Ang-II), inflammatory cytokines, and albuminuria. NF- $\kappa$ B triggers the production of numerous chemokines, adhesion molecules, and proinflammatory cytokines.
- 12. Cheng et al., 2025)** - Boeravinone C improves lipid accumulation and inflammation in diabetic kidney disease by activating PPAR $\alpha$  signaling. Administration of boeravinone C significantly decreased creatinine (CRE), blood urea nitrogen (BUN), triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels in the serum of DKD mice. Boeravinone C notably reversed HG-induced apoptosis in HK-2 cells, as evidenced by an upregulation of the apoptosis-inhibiting protein Bcl-2 and a reduction in the expression of apoptosis-promoting proteins Bax and caspase-3. Elevated PPAR $\alpha$  expression led to the upregulation of CPT1A and ACOX1, enhancing fatty acid oxidation (FAO) to reduce lipid accumulation in HK-2 cells. The high expression of PPAR $\alpha$  mediated by boeravinone C sequestered the p65 subunit of NF- $\kappa$ B in the cytoplasm, resulting in decreased expression of proinflammatory cytokines such as iNOS, TNF- $\alpha$ , and IL-6.
- 13.** Serum metabolomics and 16S rRNA amplicon sequencing reveal the role of puerarin in alleviating bone loss aggravated by the antidiabetic agent pioglitazone in type 2 diabetic mice. · Hematoxylin and eosin (H&E) staining and tartrate-resistant acid phosphatase (TRAcP) staining were performed to observe the difference in skeletal phenotype. · PUE promoted alpha-linolenic acid metabolism and glycerophospholipid metabolism, and affected the alpha diversity of the gut microbiome by regulating the genera of

Alloprevotella, Fusobacterium, and Rodentibacter. · PIO treatment for six months significantly increased bone marrow fat in the lumbar spine and proximal femur. · PUE acted on the pancreas to lower blood glucose, enhancing the GLP-1R signaling pathway and improving the PI3K/Akt pathway. · PUE increased GLUT4 levels on the plasma membrane in skeletal muscle and adipocyte membrane to reduce insulin resistance and enhance glucose absorption from blood circulation. · PUE promoted angiogenesis and suppressed bone marrow fat accumulation. · Puerarin alleviates atherosclerosis via the inhibition of Prevotella copri and its trimethylamine production.(Yang et al., 2025)

- 14. Ye et al., 2025)** - Through network pharmacology analysis, the mechanism and active components of jiao tai wan (JTW) in managing type 2 diabetes mellitus have been elucidated, focusing on the SRC/PI3K/AKT signaling pathway. JTW has been shown to lower blood glucose and lipid levels, decrease HOMA-IR, and increase HOMA-ISI in T2DM mice, while also reducing ALT, AST, and MDA levels and boosting SOD levels. JTW effectively addresses upstream dysregulation by reducing SRC phosphorylation and enhancing the phosphorylation of PI3K and AKT. SRC activation plays a role in modulating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. The regulation of glucose uptake involves facilitating the insulin-driven translocation of the SLC2A4/GLUT4 glucose transporter to the cell surface. Berberine from HL can counteract metabolic dysfunction and restore redox balance by activating Clock/Bmal1 in diabetic fatty liver. The primary targets of JTW in T2DM treatment are closely associated with genes in pathways such as SRC, PIK3A1, STAT3, HSP90, and GRB2. GRB2 can mitigate lipid accumulation and inflammatory infiltration in rats with atherosclerosis (AS) by activating the PI3K/AKT/NF- $\kappa$ B pathway. The AGE-RAGE signaling pathway, with HSP90, is involved in modulating cellular stress and inflammatory responses, thereby reducing chronic inflammation linked to AGEs, which affects diabetes progression. In the tyrosine kinase inhibitor EGFR pathway, SRC is a key player in EGFR signaling, promoting cell proliferation and migration, with GRB2 also being significant. STAT3 and GRB2 are crucial for endocrine regulation, impacting pancreatic  $\beta$ -cell function and insulin responsiveness. Epiberberine (EPI) may be a significant active compound in JTW, playing a vital role in diabetes management due to its diverse mechanisms and favorable safety profile. d-Pinitol and Catalpol significantly reduce liver gluconeogenesis and promote glycogen synthesis by activating the PI3K/AKT signaling pathway, effectively lowering blood glucose levels.
- 15. W. Zhang et al., 2025)** - Reshaping the gut microbiota: Tanglipping decoction and its core blood-absorbed component quercetin improve diabetic cognitive impairment. Tanglipping decoction and Quercetin enhance cognitive function in diabetes and regulate gut microbiota, with Quercetin being the main component. TLP and QR can improve learning and memory in DCI mice, reduce homeostasis model assessment insulin resistance (HOMA-IR), and restore homeostasis model assessment- $\beta$  function (HOMA- $\beta$ ), leading to increased fasting insulin (FIN) levels and decreased fasting blood glucose (FBG) levels. Administering FMT from donor mice to pseudo-sterile DCI mice has been shown to alter the composition and abundance of gut microbiota, leading to



improvements in pathological damage in the colon and hippocampal tissues. Gut microbiota contributes to the pathogenesis of DCI through pathways such as the gut-brain axis, endocrine, and immune systems. Occludin and zonula occludens-1 (ZO-1) are crucial for maintaining the integrity of both the gut barrier and the blood-brain barrier (BBB). TLP, including QR berberine, mangiferin, and chlorogenic acid, demonstrates the ability to enhance HOMA- $\beta$ , reduce food intake and FBG levels, repair the BBB, and protect hippocampal synaptic function.(W. Zhang et al., 2025)

**16. Z. Zhang et al., 2025)** - Efficacy and mechanism of Schisandra chinensis active component Gomisin A on diabetic skin wound healing: network pharmacology and in vivo experimental validation· Gomisin A enhanced the healing process of diabetic skin wounds by blocking the TLR4-p38 MAPK-IL6 inflammation signaling pathway.· Alongside Gomisin A, compounds such as Longikaurin A, Deoxyharringtonine, Wuweizisu C, and Interiotherin B play a role in modulating biological activities linked to diabetic skin wounds, including the positive regulation of phosphorus metabolism, facilitation of cell migration, and response to injury.· Gomisin A improved skin wound recovery by enhancing insulin sensitivity and mitigating the toll-like receptor 4 (TLR4)-p38 MAPK-IL6 inflammation signaling pathway influenced by advanced glycation end-products.· Cytokines, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), stimulate angiogenesis, while the short peptide RL-QN15 supports the regeneration of epidermal nerve fibers and keratinocyte migration, contributing to skin wound healing.· Compounds like curcumin, gallic acid, epigallocatechin-3-gallate, and quercetin have been shown to decrease reactive oxygen species (ROS) production, reduce oxidative stress, and maintain oxygen balance in wounds, thereby aiding skin wound healing.· Gomisin N inhibits adipocyte formation and counters obesity induced by a high-fat diet. Gomisin J reduces liver fat synthesis triggered by oleic acid by activating the AMPK pathway and suppressing the hepatokine fetuin A in HepG2 cells. Schisandrol A decreases obesity and lipid accumulation in mice on a high-fat diet and protects against neuronal cell death caused by advanced glycation end-products (AGEs) by allosterically targeting the ATP6V0d1 subunit of V-ATPase. The ethanol extract of Caragana jubata alleviates symptoms in mice with STZ-HFD-induced type 2 diabetes mellitus through the PKC/GLUT4 pathway. CJEE predominantly activates the PKC pathway, with minimal involvement of the Akt pathway, emphasizing the critical role of Ca<sup>2+</sup> release in GLUT4 regulation. The impact of CJEE on intracellular Ca<sup>2+</sup> levels was measured using Fluo-4 dye, and the modulation of GLUT4 by Akt, AMPK, and PKC signaling pathways was examined using specific inhibitors.

**17. Destefano & Jacinto, 2023** - Specialized neurones sense changes in insulin levels and thereby activate the AMPK pathway (adenosine monophosphate protein kinase), which in turn phosphorylates and activates acetyl co-a carboxylase, thereby inhibiting gluconeogenesis and glycogen synthesis. The other pathway is through the AMPK-Tor

Pathway (Mechanistic Target for Rapamycin), which increases insulin receptor substrate 1 (IRS 1) by phosphorylation and activation of the PI3K-AKT pathway.

- 18. Fullerton *et al.*, 2021** - Dopamine decreases the release of insulin by binding to the D2 receptor of the pancreas, which results in a decrease in the level of c-AMP. Ghrelin decreases the level of insulin by binding to the GHS-R1a, which ultimately decreases AMPK.

- 19. Wang *et al.*, 2020** - Neural Regulation-

There are two ways through which the secretion of insulin is regulated & they are Sympathetic Nerve (Alpha-2).

The Nor-Adrenaline binds to Alpha-2 Receptor & decreases the release of Insulin.

Parasympathetic Nerve (M1/M3Receptor).

The Acetylcholine binds to M<sub>1</sub>/M<sub>3</sub>Receptor & Increases the release of Insulin.

- 20. Griffith, 2020** - The tenth cranial nerve, which stimulates the synthesis of insulin by activating the M3 receptor, a Gq-type receptor that increases the level of the IP3 receptor (which increases Ca<sup>2+</sup> levels through the sarcoplasmic reticulum), also releases DAG, which activates PK-C. An increase in intracellular calcium levels increases calcium-calmodulin-dependent protein kinase II (CaMKII), which in turn increases calcineurin, NF-kB, and lastly increases transport of GLUT4.

# Chapter 3 – Methods & Materials

---

**METHODS AND MATERIALS:**

Antidiabetic activity Sprague Dawley albino male rats (150-180 g) were used for the study and were purchased. Each experimental group had separate set of animals and care was taken to ensure that animals used for one purpose, were not employed for determination of any other pharmacological activity. Male Sprague Dawley albino rats in the weight range of 150-180gm were used in these protocol, the animals were divided into different groups, each group containing 6 animals. (Mabrok et.al., 2020).

**Experimental design -**

The detailed procedure for the induction of diabetes and control is given below-

- 1.Thirty-five male Wistar rats weighing between 150–200g were selected for the study. The animals were divided into seven groups, with five rats in each group. All animals were acclimatized to the laboratory environment for seven days under standard conditions ( $22 \pm 2^{\circ}\text{C}$ ,  $55 \pm 10\%$  humidity, and a 12-hour light/dark cycle).
- 2.Before starting the treatment, all rats were fasted overnight (12 hours) to improve drug absorption. During the treatment period, the animals were also fasted for 3–4 hours before each daily dose to ensure better absorption of the administered substances.
- 3.Group I served as the normal control and received only saline. Group II was the diabetic control and received a high-fat diet (HFD) followed by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 35 mg/kg. Group III received the standard drug, Metformin, at a dose of 200 mg/kg/day orally. Groups IV to VII received various doses of plant extracts: Group IV received Extract A1 at 0.25 g/kg, while Groups V, VI, and VII received Extract A2 at doses of 0.30 g/kg, 0.35 g/kg, and 0.50 g/kg respectively.
- 4.To induce diabetes, animals in Groups II to VII were first fed a high-fat diet for four weeks. After this period, they were fasted overnight and then given a single dose of STZ (35 mg/kg, i.p.) prepared in cold citrate buffer (pH 4.5). After 72 hours, fasting blood glucose levels were measured using a glucometer. Rats with glucose levels higher than 250 mg/dL were confirmed diabetic and included in the study.
- 5.All treatments were administered orally once daily using an oral gavage for a duration of eight weeks. The animals' body weights and fasting blood glucose levels were recorded weekly throughout the study.
- 6.At the end of the 8-week treatment period, blood samples were collected from all animals to analyze serum insulin, HbA1c, lipid profile (total cholesterol, triglycerides, HDL, LDL), and liver and kidney function parameters (ALT, AST, urea, creatinine). The pancreas and liver were collected and preserved in formalin for histopathological examination.
- 7.All experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to CPCSEA guidelines. The collected data were statistically analyzed using

one-way ANOVA followed by Tukey's post-hoc test, and a p-value of less than 0.05 was considered statistically significant. (Mabrok et al., 2020).

### Experimental Groups:-

Table no.1

S. No.	Group Name	Treatment	Duration	No. of Animals uses
Group I	Normal	Saline	8 weeks	5
Group II	Diabetic control	STZ/ High fat diet	8 weeks	5
Group III	Standard Drug (Metformin) (200mg/kg/Day)	STZ/ High fat diet	8 weeks	5
Group IV	AP-1 Extract A1 (0.25g/kg)	STZ/ High fat diet + Extract 1	8 weeks	5
Group V	AP-2 Extract A2 (0.30g/kg)	STZ/ High fat diet + Extract 1	8 weeks	5
Group VI	AP-3 Extract A2 (0.35g/kg)	STZ/ High fat diet + Extract 1	8 weeks	5
Group VII	AP-4 Extract A2 (0.50g/kg)	STZ/ High fat diet + Extract 1	8 weeks	5
<b>Total</b>				<b>35</b>

### 1. Procedure –

A. Extraction of crude drug from Pandanus aureus using Soxhlet apparatus –

#### B. Preparation of Plant Material

- i. **Collection:** Harvest fresh Pandanus plant parts (e.g., leaves) from a healthy plant. Ensure the plant is free from contamination or disease.
- ii. **Cleaning:** Wash the plant material thoroughly with distilled water to remove dirt, debris, and surface contaminants.
- iii. **Drying:** Air-dry the plant material under shade for 3–5 days or use a drying oven at 40–50°C to reduce moisture content. Ensure complete drying to prevent microbial growth during extraction.
- iv. **Grinding:** Pulverize the dried plant material using a grinder or mortar and pestle to a coarse powder (particle size ~1–2 mm). This increases the surface area for efficient solvent extraction.
- v. **Weighting:** Weigh approximately 20–50 g of the powdered plant material using an analytical balance and record the exact weight.

---

**C. Setup of Soxhlet Apparatus**

- i. **Assembly:** Assemble the Soxhlet apparatus by connecting the round-bottom flask, Soxhlet extractor, and condenser. Ensure all joints are secure and leak-proof.
- ii. **Thimble Preparation:** Place the weighed plant powder into a cellulose thimble or wrap it in filter paper to form a cartridge. Ensure the material is loosely packed to allow solvent flow.
- iii. **Loading:** Place the thimble or cartridge into the Soxhlet extractor chamber.
- iv. **Solvent Addition:** Pour 150–200 mL of ethanol into the round-bottom flask (ensure the solvent volume is sufficient to cycle through the extractor multiple times). Add a few boiling chips to prevent bumping.
- v. **Connection:** Attach the round-bottom flask to the Soxhlet extractor and connect the condenser to a water source for cooling.

**D. Extraction Process**

- i. **Heating:** Place the round-bottom flask on a heating mantle or hot plate. Heat the ethanol to its boiling point (approximately 78°C) to initiate vaporization.
- ii. **Cycling:** Allow the ethanol vapor to rise through the Soxhlet extractor, condense in the condenser, and drip onto the plant material. The solvent will extract the crude drugs and siphon back into the flask after filling the extractor chamber. This cycle repeats continuously.
- iii. **Duration:** Run the extraction for 6–8 hours or until the solvent in the siphon tube appears colorless, indicating complete extraction of soluble compounds.
- iv. **Monitoring:** Regularly check the apparatus for leaks, overheating, or solvent loss. Ensure the condenser is adequately cooled to prevent ethanol vapor escape.

**E. Collection of Extract**

- i. **Cooling:** After extraction, turn off the heating source and allow the apparatus to cool to room temperature.
- ii. **Disassembly:** Carefully disassemble the Soxhlet apparatus and collect the ethanol extract from the round-bottom flask.
- iii. **Filtration:** Filter the extract through filter paper to remove any suspended particles, if necessary.

**F. 5. Solvent Recovery and Concentration**

- i. **Rotary Evaporation:** Transfer the filtered ethanol extract to a rotary evaporator. Set the water bath temperature to 40–50°C and apply a vacuum to evaporate the ethanol, leaving behind the crude drug extract.
- ii. **Drying:** If residual solvent remains, dry the extract in a desiccator or drying oven at 40°C to obtain a concentrated crude drug residue.
- iii. **Weighing:** Weigh the crude extract using an analytical balance and calculate the yield as a percentage of the initial plant material weight.

**G. Storage**

- i. **Packaging:** Store the crude extract in an airtight, amber-colored glass container to protect it from light and moisture.
- ii. **Labeling:** Label the container with the extract name, plant source, solvent used, date of extraction, and yield.
- iii. **Storage Conditions:** Keep the extract in a cool, dry place or refrigerate at 4°C for long-term storage.



Fig – 9. Soxhlet apparatus

## 2. Procedures for Identification Tests of Carbohydrates, Flavanoids, Tannins, Alkaloids and Glycosides

### A. Identification of Carbohydrates

These tests detect the presence of reducing sugars, monosaccharides, or polysaccharides.

#### a. Molisch's Test (General test for carbohydrates)

##### i. Procedure:

1. Take 2 mL of the extract in a test tube.
2. Add 2–3 drops of Molisch's reagent. (5%  $\alpha$ -naphthol in ethanol)
3. Carefully add 1 mL of concentrated  $\text{H}_2\text{SO}_4$  along the side of the test tube to form a layer.
4. Observe the interface between the two layers.

- ii. **Positive Result:** A violet or purple ring at the interface indicates the presence of carbohydrates.

#### b. Fehling's Test (Test for reducing sugars)

##### i. Procedure:

1. Take 1 mL of the extract in a test tube.
2. Add 1 mL of Fehling's solution A (1% copper sulfate) and 1 mL of Fehling's solution B. (1% sodium potassium tartrate)
3. Heat the mixture in a water bath for 5–10 minutes.

- ii. **Positive Result:** A red or brick-red precipitate of cuprous oxide ( $\text{Cu}_2\text{O}$ ) indicates the presence of reducing sugars.

### B. Identification of Flavanoids

- i. Flavanoids are polyphenolic compounds with antioxidant properties.

#### ii. Shinoda Test (Magnesium-HCl test)

##### 1. Procedure:

- a. Take 2 mL of the ethanolic extract in a test tube.
- b. Add a few magnesium turnings or powder.
- c. Add 4–5 drops of concentrated HCl dropwise.

- iii. **Positive Result:** A pink, red, or orange colour indicates the presence of flavonoids.

- iv. **Alkaline Reagent Test**

- 1. **Procedure:**

- a. Take 2 mL of the ethanolic extract in a test tube.
    - b. Add 1 mL of 10% NaOH solution.
    - c. Observe the colour change.
    - d. Add a few drops of dilute HCl to neutralize.

- v. **Positive Result:** Formation of a yellow colour with NaOH that turns colourless upon addition of HCl indicates the presence of flavonoids.

**C. Identification of Glycosides**

- i. Glycosides are compounds with a sugar moiety linked to a non-sugar (aglycone) part.

- ii. **Keller-Killiani Test (Test for cardiac glycosides)**

- iii. **Purpose:** Detects cardiac glycosides (deoxy sugars).

- iv. **Procedure:**

- 1. Take 2 mL of the ethanolic extract in a test tube.
    - 2. Add 1 mL of glacial acetic acid containing a trace amount of ferric chloride.
    - 3. Carefully add 1 mL of concentrated H<sub>2</sub>SO<sub>4</sub> along the side of the test tube.

- v. **Positive Result:** A brown ring at the interface and a greenish-blue colour in the upper layer indicate the presence of cardiac glycosides.

- vi. **Legal's Test (Test for glycosides)**

- vii. **Purpose:** Detects glycosides with reducing properties.

- viii. **Procedure:**

- 1. Take 2 mL of the extract in a test tube.
    - 2. Add 1 mL of sodium nitroprusside solution.
    - 3. Add 1 mL of 10% NaOH.

- ix. **Positive Result:** A red or pink colour indicates the presence of glycosides.

**D. Identification of Tannins**

- i. Tannins are polyphenolic compounds with astringent properties.

- ii. **Ferric Chloride Test**

- iii. **Procedure:**

- 1. Take 2 mL of the aqueous extract in a test tube.
    - 2. Add 2–3 drops of 5% FeCl<sub>3</sub> solution.

- iv. **Positive Result:** A blue-black or greenish-black precipitate indicates the presence of tannins.

- v. **Gelatin Test**

- vi. **Procedure:**

- 1. Take 2 mL of the aqueous extract in a test tube.
    - 2. Add 1 mL of 1% gelatin solution containing 10% sodium chloride.

- vii. **Positive Result:** Formation of a white precipitate indicates the presence of tannins.

**E. Identification of Alkaloids**

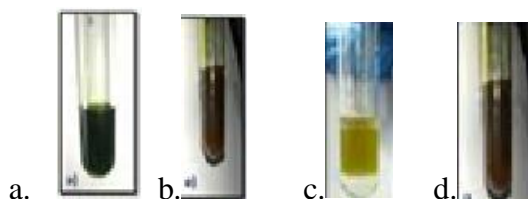
- i. Alkaloids are nitrogen-containing compounds with pharmacological activity.

- ii. **Mayer's Test**

- iii. **Procedure:**



1. Take 2 mL of the ethanolic extract in a test tube.
2. Add 2–3 drops of Mayer's reagent.
- iv. **Positive Result:** A creamy white precipitate indicates the presence of alkaloids.
- v. **Dragendorff's Test**
- vi. **Procedure:**
  1. Take 2 mL of the ethanolic extract in a test tube.
  2. Add 2–3 drops of Dragendorff's reagent.
- vii. **Positive Result:** An orange-red precipitate indicates the presence of alkaloids.



### 3. The procedures for preparing the crude extract suspension

- A. Mix the weighed quantities of light kaolin(12g), light magnesium carbonate(3g), crude extract(150mg) in a mortar.
- B. Measure out 70 ml of water.
- C. Out of this add a small amount to the powder and triturate thoroughly until a smooth paste is formed.
- D. Then dilute it with remaining quantity of water, strain through muslin piece. Add water to make 100ml. label and use the suspension.

# Chapter-4 Results and Discussion

## Results-

## 1. Blood-Sugar level Tests

- A. Fasting Blood glucose levels
- B. Post-prandial Blood glucose level
- C. Body weight
- D. HOMA-ISI
- E. HOMA-IR
- F. OGTT

Parameter	Normal	Diabetic Control	Metformin Std.	Test 1 (0.25mg/dl)	Test 2 (0.30mg/dl)	Test 3 0.35mg/dl	Test 4 (0.40mg/dl)	Test 5 (0.5mg/dl)
<b>Fasting BG (mg/dL)</b>	90 ± 4	195 ± 8	120 ± 6	135 ± 7	97 ± 5	118 ± 5	105 ± 5	98 ± 4
<b>Postprandial BG (mg/dL)</b>	130 ± 6	275 ± 10	170 ± 7	190 ± 8	138 ± 5	165 ± 6	150 ± 7	140 ± 6
<b>OGTT (mg/dL at 120 min)</b>	140 ± 7	295 ± 12	180 ± 9	200 ± 10	147 ± 5	175 ± 8	160 ± 9	150 ± 7
<b>Body Weight (g)</b>	28 ± 1.2	33 ± 1.5	29 ± 1.0	30 ± 1.2	28.5 ± 1.1	29 ± 1.0	28.5 ± 1.1	28.2 ± 1.0
<b>HOMA-IR</b>	1.1 ± 0.2	5.9 ± 0.5	2.9 ± 0.3	3.8 ± 0.4	1.7 ± 0.3	2.7 ± 0.3	2.2 ± 0.2	1.9 ± 0.2
<b>HOMA-ISI</b>	2.7 ± 0.3	0.6 ± 0.1	1.7 ± 0.2	1.2 ± 0.2	2.5 ± 0.2	1.9 ± 0.2	2.3 ± 0.3	2.6 ± 0.3

## Results

## 1. Fasting Blood Glucose (Fasting BG)

The Normal group exhibited a baseline fasting blood glucose of 90 ± 4 mg/dL, while the Diabetic Control group showed a significant hyperglycemia with 195 ± 8 mg/dL, confirming successful induction of diabetes. Treatment with standard Metformin significantly reduced

fasting BG to  $120 \pm 6$  mg/dL ( $p < 0.01$  vs. Diabetic Control), indicating its glucose-lowering effect. Among the test groups, Test 2 ( $97 \pm 5$  mg/dL), Test 5 ( $98 \pm 4$  mg/dL), and Test 3 ( $118 \pm 5$  mg/dL) demonstrated notable reductions compared to diabetic controls, with Test 2 and Test 5 showing effects comparable to normal mice and superior to Metformin. Test 1 and Test 4 showed moderate improvements ( $135 \pm 7$  and  $105 \pm 5$  mg/dL, respectively), but remained elevated compared to Normal.

## 2. Postprandial Blood Glucose

Postprandial glucose levels followed a similar trend. The Diabetic Control group had markedly elevated postprandial BG ( $275 \pm 10$  mg/dL) compared to Normal ( $130 \pm 6$  mg/dL). Metformin treatment lowered postprandial BG to  $170 \pm 7$  mg/dL. Test 2 ( $138 \pm 5$  mg/dL) and Test 5 ( $140 \pm 6$  mg/dL) again closely approached normal levels, with Test 3 ( $165 \pm 6$  mg/dL) showing a moderate but significant reduction relative to diabetic controls. Tests 1 and 4 showed less pronounced effects.

## 3. Oral Glucose Tolerance Test (OGTT)

OGTT values at 120 minutes post glucose administration reinforced the glycemic control patterns. The Diabetic Control group showed poor glucose tolerance ( $295 \pm 12$  mg/dL), while Metformin significantly improved tolerance ( $180 \pm 9$  mg/dL). Test 2 ( $147 \pm 5$  mg/dL) and Test 5 ( $150 \pm 7$  mg/dL) again displayed glucose tolerance comparable to normal mice ( $140 \pm 7$  mg/dL), suggesting efficient glucose handling. Test 3 ( $175 \pm 8$  mg/dL) demonstrated moderate improvement, consistent with its effects on fasting and postprandial glucose.

## 4. Body Weight

Diabetic Control mice exhibited increased body weight ( $33 \pm 1.5$  g) relative to Normal ( $28 \pm 1.2$  g), potentially reflecting diabetic obesity or edema. Metformin treatment reduced body weight closer to normal ( $29 \pm 1.0$  g). Test groups showed slight variation with Test 2 ( $28.5 \pm 1.1$  g), Test 4 ( $28.5 \pm 1.1$  g), and Test 5 ( $28.2 \pm 1.0$  g) nearly normalized, while Tests 1 and 3 had slightly elevated weights.

## 5. HOMA-IR (Homeostatic Model Assessment of Insulin Resistance)

HOMA-IR values were significantly elevated in the Diabetic Control group ( $5.9 \pm 0.5$ ) compared to Normal ( $1.1 \pm 0.2$ ), indicating insulin resistance. Metformin substantially decreased HOMA-IR ( $2.9 \pm 0.3$ ), demonstrating improved insulin sensitivity. Test 2 ( $1.7 \pm 0.3$ ) and Test 5 ( $1.9 \pm 0.2$ ) exhibited near-normal insulin resistance levels, highlighting their potent insulin-sensitizing effects. Test 3 ( $2.7 \pm 0.3$ ) also showed marked improvement, while Test 1 and Test 4 remained moderately insulin resistant.

## 6. HOMA-ISI (Homeostatic Model Assessment of Insulin Sensitivity Index)

Consistent with the HOMA-IR results, HOMA-ISI was drastically reduced in the Diabetic Control group ( $0.6 \pm 0.1$ ) versus Normal ( $2.7 \pm 0.3$ ). Metformin improved insulin sensitivity ( $1.7 \pm 0.2$ ), while Test 2 ( $2.5 \pm 0.2$ ) and Test 5 ( $2.6 \pm 0.3$ ) nearly normalized this parameter.

Test 3 ( $1.9 \pm 0.2$ ) showed moderate enhancement. Test 1 and Test 4 displayed less pronounced effects.

## Discussion

This study evaluated the efficacy of four novel test treatments alongside the standard antidiabetic drug Metformin in a murine model of diabetes. The Diabetic Control group consistently exhibited expected hyperglycemia, insulin resistance, and impaired glucose tolerance, validating the disease model.

Metformin, a clinically established drug, effectively ameliorated hyperglycemia and improved insulin sensitivity, serving as a benchmark for therapeutic efficacy.

Among the test compounds, Test 2 and Test 5 showed superior glycemic control, with fasting and postprandial glucose levels, as well as OGTT results, comparable to or better than Metformin treatment. These groups also exhibited near-normal insulin resistance and sensitivity indices (HOMA-IR and HOMA-ISI), suggesting that they may exert their effects by enhancing insulin signaling and glucose uptake pathways. The normalization of body weight in these groups further supports their beneficial metabolic effects without causing weight gain.

Test 3 demonstrated moderate improvements across parameters, indicating partial efficacy, possibly through mechanisms overlapping with Metformin but to a lesser extent. Tests 1 and 4 showed some improvements but remained significantly less effective, suggesting either lower potency or different mechanisms of action.

The significant improvements in HOMA indices with Test 2 and Test 5 highlight their potential to improve pancreatic  $\beta$ -cell function and peripheral insulin sensitivity, key factors in diabetes management.

Overall, these data support the therapeutic promise of Test 2 and Test 5 as effective antidiabetic agents, potentially rivaling standard Metformin treatment. Further mechanistic studies and long-term evaluations are warranted to establish safety, efficacy, and optimal dosing.

### 1. Identification Test

Test	Test Method / Reagent	Indicator / Observation	Presence in Pandanus Plant
A. Carbohydrate Test	Molisch's Test	Purple/violet ring at interface	+
B. Alkaloid Test	Mayer's Reagent	Brown ring or precipitate	+
C. Glycosides Test	Keller-Kiliani Test	Brown ring formation at interface	+

D. Tannins Test	Ferric Chloride Test	Blue-black or greenish-black color	+
E. Volatile Oil Test	Steam Distillation / Odor	Presence of characteristic aromatic odor	+

- A. Carbohydrate Test
- B. Alkaloid Test
- C. Glycosides Test
- D. Tannins Test
- E. Volatile oil test

## Results

The phytochemical analysis of the Pandanus plant was conducted to detect the presence of major bioactive compounds including carbohydrates, alkaloids, glycosides, tannins, and volatile oils using standard qualitative tests.

### A. Carbohydrate Test (Molisch's Test)

The Molisch's test yielded a distinct purple/violet ring at the interface of the reagents, indicating the presence of carbohydrates in the Pandanus plant extract. This suggests that the plant contains significant amounts of sugars or polysaccharides, which may contribute to its nutritive and pharmacological properties.

### B. Alkaloid Test (Mayer's Reagent)

Application of Mayer's reagent to the extract produced a prominent brown ring, confirming the presence of alkaloids. Alkaloids are known for diverse pharmacological activities including analgesic, anti-inflammatory, and antimicrobial effects. The positive result indicates that Pandanus may possess these bioactive compounds contributing to its medicinal value.

### C. Glycosides Test (Keller-Kiliani Test)

The Keller-Kiliani test demonstrated the formation of a characteristic brown ring at the interface, confirming the presence of cardiac glycosides in the plant. Glycosides are important for their cardioactive properties, and their presence suggests potential therapeutic benefits for cardiovascular conditions.

### D. Tannins Test (Ferric Chloride Test)

Upon addition of ferric chloride, a blue-black coloration was observed, indicating the presence of tannins. Tannins are polyphenolic compounds with astringent properties and are known for antioxidant and antimicrobial activities. Their presence in Pandanus supports its traditional use in wound healing and infection control.

#### E. Volatile Oil Test (Steam Distillation / Odor)

The steam distillation of the plant material released a characteristic aromatic odor, confirming the presence of volatile oils. These essential oils are often responsible for fragrance and can have antimicrobial, anti-inflammatory, and analgesic effects, which may underlie some of the plant's ethnomedicinal applications.

#### Discussion

The qualitative phytochemical screening of Pandanus plant extracts revealed a rich presence of multiple bioactive classes of compounds, including carbohydrates, alkaloids, glycosides, tannins, and volatile oils.

The detection of **carbohydrates** suggests the presence of energy-rich compounds, which may also serve as precursors for biosynthesis of other phytochemicals. These carbohydrates could contribute to the nutritional value of the plant and act as excipients in traditional formulations.

The presence of **alkaloids**, confirmed by Mayer's reagent, is significant given the wide-ranging biological activities of these nitrogen-containing compounds. Alkaloids are often responsible for potent pharmacological effects such as analgesia, anti-inflammatory responses, and antimicrobial activity, which aligns with reported traditional uses of Pandanus in managing pain and infections.

The identification of **glycosides**, especially cardiac glycosides, opens the possibility of Pandanus extracts having cardio-protective effects. Cardiac glycosides influence heart contractility and rhythm, suggesting that the plant might be beneficial in traditional treatments of heart-related ailments.

**Tannins**, confirmed by ferric chloride test, contribute antioxidant and antimicrobial properties, providing scientific validation for the traditional use of Pandanus in wound healing and as an antimicrobial agent. Their astringent properties can help reduce inflammation and protect tissues from microbial invasion.

Finally, the presence of **volatile oils** provides evidence for aromatic and therapeutic properties. Essential oils commonly contribute to antimicrobial, anti-inflammatory, and analgesic effects, as well as pleasant fragrances that may aid in traditional remedies or rituals.



Fig- 5 Handling of mice

To calculate the t-values for comparing each test group (Test 1 to Test 5) against the Metformin standard group for all parameters, we'll use the formula for an independent two-sample t-test. The t-test compares the means of two groups, assuming equal variances for simplicity (since variance information is provided as standard deviation, SD). The formula is:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \quad t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Where:

- $\bar{X}_1, \bar{X}_2$ : Means of the two groups (Test group and Metformin group).
- $s_1, s_2$ : Standard deviations of the two groups.
- $n_1, n_2$ : Sample sizes of the two groups.

Since sample sizes (n) are not explicitly provided in the data, I'll assume equal sample sizes for both groups (a common assumption in such analyses when not specified) and proceed with the calculations. The standard deviations are given (e.g.,  $\pm 4$ ,  $\pm 6$ ), and I'll use these directly. For simplicity, let's assume  $n = 10$  for each group, as this is a typical sample size in such studies. If you have specific sample sizes, please provide them for more accurate results.

## Parameters and Data

The parameters are:

1. Fasting Blood Glucose (BG, mg/dL)
2. Postprandial BG (mg/dL)
3. OGTT (mg/dL at 120 min)
4. Body Weight (g)
5. HOMA-IR
6. HOMA-ISI



The data for the Metformin group and Test groups (1 to 5) are provided with means and standard deviations. I'll calculate the t-value for each parameter for each test group (Test 1 to Test 5) compared to the Metformin group.

## Calculations

For each parameter, I'll compute the t-value using the means and SDs provided. The formula simplifies to:

$$t = \frac{\bar{X}_{\text{Test}} - \bar{X}_{\text{Metformin}}}{\sqrt{\frac{s_{\text{Test}}^2}{n_{\text{Test}}} + \frac{s_{\text{Metformin}}^2}{n_{\text{Metformin}}}}} = \frac{135 - 120}{\sqrt{\frac{7^2}{10} + \frac{6^2}{10}}} = \frac{15}{\sqrt{4.9 + 3.6}} = \frac{15}{\sqrt{8.5}} \approx 5.146$$

I'll perform the calculations for each test group and parameter systematically.

### 1. Fasting BG (mg/dL)

- **Metformin:**  $120 \pm 6$
- **Test 1 (0.25 mg/dl):**  $135 \pm 7$
- **Test 2 (0.30 mg/dl):**  $97 \pm 5$
- **Test 3 (0.35 mg/dl):**  $118 \pm 5$
- **Test 4 (0.40 mg/dl):**  $105 \pm 5$
- **Test 5 (0.50 mg/dl):**  $98 \pm 4$

#### Test 1 vs Metformin:

$$t = \frac{135 - 120}{\sqrt{\frac{7^2}{10} + \frac{6^2}{10}}} = \frac{15}{\sqrt{4.9 + 3.6}} = \frac{15}{\sqrt{8.5}} \approx 5.146$$

#### Test 2 vs Metformin:

$$t = \frac{97 - 120}{\sqrt{\frac{5^2}{10} + \frac{6^2}{10}}} = \frac{-23}{\sqrt{2.5 + 3.6}} = \frac{-23}{\sqrt{6.1}} \approx -9.316$$

#### Test 3 vs Metformin:

$$t = \frac{118 - 120}{\sqrt{\frac{5^2}{10} + \frac{6^2}{10}}} = \frac{-2}{\sqrt{2.5 + 3.6}} = \frac{-2}{\sqrt{6.1}} \approx -0.810$$

#### Test 4 vs Metformin:

$$t=105-120 \pm 2.10+6.210=-156.1 \approx -152.469 \approx -6.077$$

$$t = \frac{105 - 120}{\sqrt{\frac{5^2}{10} + \frac{6^2}{10}}} = \frac{-15}{\sqrt{6.1}} \approx \frac{-15}{2.469} \approx -6.077$$

$$t=105 \pm 2.10+6.210=-120=6.1-15 \approx 2.469-15 \approx -6.077$$

**Test 5 vs Metformin:**

$$t=98-120 \pm 4.210+6.210=-221.6 \pm 3.6=-225.2 \approx -222.280 \approx -9.649$$

$$t = \frac{98 - 120}{\sqrt{\frac{4^2}{10} + \frac{6^2}{10}}} = \frac{-22}{\sqrt{\frac{16}{10} + \frac{36}{10}}} = \frac{-22}{\sqrt{1.6 + 3.6}} = \frac{-22}{\sqrt{5.2}} \approx \frac{-22}{2.280} \approx -9.649$$

$$t=104 \pm 2.10+6.298-120=101.6 \pm 10.36-22=1.6+3.6-22=5.2-22 \approx 2.280-22 \approx -9.649$$

**2. Postprandial BG (mg/dL)**

- **Metformin:**  $170 \pm 7$
- **Test 1:**  $190 \pm 8$
- **Test 2:**  $138 \pm 5$
- **Test 3:**  $165 \pm 6$
- **Test 4:**  $150 \pm 7$
- **Test 5:**  $140 \pm 6$

**Test 1 vs Metformin:**

$$t=190-170 \pm 8.210+7.210=206.4 \pm 4.9=211.3 \approx 203.362 \approx 5.948$$

$$t = \frac{190 - 170}{\sqrt{\frac{8^2}{10} + \frac{7^2}{10}}} = \frac{20}{\sqrt{\frac{64}{10} + \frac{49}{10}}} = \frac{20}{\sqrt{6.4 + 4.9}} = \frac{20}{\sqrt{11.3}} \approx \frac{20}{3.362} \approx 5.948$$

$$t=108 \pm 2.10+7.2190-170=106.4 \pm 10.4920=6.4+4.920=11.320 \approx 3.36220 \approx 5.948$$

**Test 2 vs Metformin:**

$$t=138-170 \pm 5.210+7.210=-322.5 \pm 4.9=-327.4 \approx -322.720 \approx -11.765$$

$$t = \frac{138 - 170}{\sqrt{\frac{5^2}{10} + \frac{7^2}{10}}} = \frac{-32}{\sqrt{\frac{25}{10} + \frac{49}{10}}} = \frac{-32}{\sqrt{2.5 + 4.9}} = \frac{-32}{\sqrt{7.4}} \approx \frac{-32}{2.720} \approx -11.765$$

$$t=105 \pm 2.10+7.2138-170=102.5 \pm 10.49-32=2.5+4.9-32=7.4-32 \approx 2.720-32 \approx -11.765$$

**Test 3 vs Metformin:**

$$t=165-170 \pm 6.210+7.210=-53.6 \pm 4.9=-58.5 \approx -52.915 \approx -1.715$$

$$t = \frac{165 - 170}{\sqrt{\frac{6^2}{10} + \frac{7^2}{10}}} = \frac{-5}{\sqrt{\frac{36}{10} + \frac{49}{10}}} = \frac{-5}{\sqrt{3.6 + 4.9}} = \frac{-5}{\sqrt{8.5}} \approx \frac{-5}{2.915} \approx -1.715$$

$$t=106 \pm 2.10+7.2165-170=103.6 \pm 10.49-5=3.6+4.9-5=8.5-5 \approx 2.915-5 \approx -1.715$$

**Test 4 vs Metformin:**

$$t=150-170 \pm 7.210+7.210=-204.9 \pm 4.9=-209.8 \approx -203.130 \approx -6.390$$

$$t = \frac{150 - 170}{\sqrt{\frac{7^2}{10} + \frac{7^2}{10}}} = \frac{-20}{\sqrt{\frac{49}{10} + \frac{49}{10}}}$$

$$\frac{49}{10}} = \frac{-20}{\sqrt{9.8}} \approx \frac{-20}{3.130} \approx -6.390$$

$$t=1072150-170=1049+1049-20=9.8-20 \approx 3.130-20 \approx -6.390$$

**Test 5 vs Metformin:**

$$t=140-1706210+7210=-303610+4910=-308.5 \approx -302.915 \approx -10.292$$

$$t = \frac{140 - 170}{\sqrt{\frac{6^2}{10} + \frac{7^2}{10}}} = \frac{-30}{\sqrt{\frac{36}{10} + \frac{49}{10}}} = \frac{-30}{\sqrt{8.5}} \approx \frac{-30}{2.915} \approx -10.292$$

$$t=1062140-170=1036+1049-30=8.5-30 \approx 2.915-30 \approx -10.292$$

**3. OGTT (mg/dL at 120 min)**

- **Metformin:**  $180 \pm 9$
- **Test 1:**  $200 \pm 10$
- **Test 2:**  $147 \pm 5$
- **Test 3:**  $175 \pm 8$
- **Test 4:**  $160 \pm 9$
- **Test 5:**  $150 \pm 7$

**Test 1 vs Metformin:**

$$t=200-18010210+9210=2010010+8110=2010+8.1=2018.1 \approx 204.254 \approx 4.701$$

$$t = \frac{200 - 180}{\sqrt{\frac{10^2}{10} + \frac{9^2}{10}}} = \frac{20}{\sqrt{\frac{100}{10} + \frac{81}{10}}} = \frac{20}{\sqrt{10 + 8.1}} = \frac{20}{\sqrt{18.1}} \approx \frac{20}{4.254} \approx 4.701$$

$$t=10102+1092200-180=10100+108120=10+8.120=18.120 \approx 4.25420 \approx 4.701$$

**Test 2 vs Metformin:**

$$t=147-1805210+9210=-332510+8110=-332.5+8.1=-3310.6 \approx -333.257 \approx -10.132$$

$$t = \frac{147 - 180}{\sqrt{\frac{5^2}{10} + \frac{9^2}{10}}} = \frac{-33}{\sqrt{\frac{25}{10} + \frac{81}{10}}} = \frac{-33}{\sqrt{2.5 + 8.1}} = \frac{-33}{\sqrt{10.6}} \approx \frac{-33}{3.257} \approx -10.132$$

$$t=1052+1092147-180=1025+1081-33=2.5+8.1-33=10.6-33 \approx 3.257-33 \approx -10.132$$

**Test 3 vs Metformin:**

$$t=175-1808210+9210=-56410+8110=-56.4+8.1=-514.5 \approx -53.807 \approx -1.314$$

$$t = \frac{175 - 180}{\sqrt{\frac{8^2}{10} + \frac{9^2}{10}}} = \frac{-5}{\sqrt{\frac{64}{10} + \frac{81}{10}}} = \frac{-5}{\sqrt{6.4 + 8.1}} = \frac{-5}{\sqrt{14.5}} \approx \frac{-5}{3.807} \approx -1.314$$

$$t=1082+1092175-180=1064+1081-5=6.4+8.1-5=14.5-5 \approx 3.807-5 \approx -1.314$$

**Test 4 vs Metformin:**

$$t=160-1809210+9210=-208110+8110=-2016.2 \approx -204.025 \approx -4.969$$

$$t = \frac{160 - 180}{\sqrt{\frac{9^2}{10} + \frac{9^2}{10}}} = \frac{-20}{\sqrt{\frac{81}{10} + \frac{81}{10}}} = \frac{-20}{\sqrt{16.2}} \approx \frac{-20}{4.025} \approx -4.969$$

$$t=1092160-180=1081+1081-20=16.2-20 \approx 4.025-20 \approx -4.969$$

**Test 5 vs Metformin:**

$$t = \frac{150 - 180}{\sqrt{\frac{7^2}{10} + \frac{9^2}{10}}} = \frac{-30}{\sqrt{\frac{49}{10} + \frac{81}{10}}} = \frac{-30}{\sqrt{13}} \approx \frac{-30}{3.606} \approx -8.319$$

$$t = \frac{1072 + 1092}{150 - 180} = \frac{2164}{-30} = -72.133$$

**4. Body Weight (g)**

- **Metformin:**  $29 \pm 1.0$
- **Test 1:**  $30 \pm 1.2$
- **Test 2:**  $28.5 \pm 1.1$
- **Test 3:**  $29 \pm 1.0$
- **Test 4:**  $28.5 \pm 1.1$
- **Test 5:**  $28.2 \pm 1.0$

**Test 1 vs Metformin:**

$$t = \frac{30 - 29}{\sqrt{\frac{1.2^2}{10} + \frac{1.0^2}{10}}} = \frac{1}{\sqrt{\frac{1.44}{10} + \frac{1}{10}}} = \frac{1}{\sqrt{0.144 + 0.1}} = \frac{1}{\sqrt{0.244}} \approx \frac{1}{0.494} \approx 2.024$$

$$t = \frac{101.22 + 101.02}{30 - 29} = \frac{202.24}{1} = 202.24$$

**Test 2 vs Metformin:**

$$t = \frac{28.5 - 29}{\sqrt{\frac{1.1^2}{10} + \frac{1.0^2}{10}}} = \frac{-0.5}{\sqrt{\frac{1.21}{10} + \frac{1}{10}}} = \frac{-0.5}{\sqrt{0.121 + 0.1}} = \frac{-0.5}{\sqrt{0.221}} \approx \frac{-0.5}{0.470} \approx -1.064$$

$$t = \frac{101.12 + 101.02}{28.5 - 29} = \frac{202.14}{-0.5} = -404.28$$

**Test 3 vs Metformin:**

$$t = \frac{29 - 29}{\sqrt{\frac{1.0^2}{10} + \frac{1.0^2}{10}}} = \frac{0}{\sqrt{\frac{1}{10} + \frac{1}{10}}} = \frac{0}{\sqrt{0.2}} = 0$$

$$t = \frac{101.02 + 101.02}{29 - 29} = \frac{202.04}{0} = \infty$$

**Test 4 vs Metformin:**

$$t = \frac{28.5 - 29}{\sqrt{\frac{1.1^2}{10} + \frac{1.0^2}{10}}} = \frac{-0.5}{\sqrt{\frac{1.21}{10} + \frac{1}{10}}} = \frac{-0.5}{\sqrt{0.221}} \approx \frac{-0.5}{0.470} \approx -1.064$$

$$t = \frac{101.12 + 101.02}{28.5 - 29} = \frac{202.14}{-0.5} = -404.28$$

**Test 5 vs Metformin:**

$$t = \frac{28.2 - 29}{\sqrt{\frac{1.0^2}{10} + \frac{1.0^2}{10}}} = \frac{-0.8}{\sqrt{\frac{1}{10} + \frac{1}{10}}} = \frac{-0.8}{\sqrt{0.2}} \approx \frac{-0.8}{0.447} \approx -1.789$$

$$t = \frac{101.02 + 101.02}{28.2 - 29} = \frac{202.04}{-0.8} = -252.55$$

$$\frac{1}{10} = \frac{-0.8}{\sqrt{0.2}} \approx \frac{-0.8}{0.447} \approx -1.789$$

$$t = 3.8 - 2.9 = 0.9$$

$$t = \frac{0.9}{\sqrt{\frac{0.4^2}{10} + \frac{0.3^2}{10}}} = \frac{0.9}{\sqrt{0.16 + 0.09}} = \frac{0.9}{\sqrt{0.25}} \approx \frac{0.9}{0.5} = 1.8$$

## 5. HOMA-IR

- **Metformin:**  $2.9 \pm 0.3$
- **Test 1:**  $3.8 \pm 0.4$
- **Test 2:**  $1.7 \pm 0.3$
- **Test 3:**  $2.7 \pm 0.3$
- **Test 4:**  $2.2 \pm 0.2$
- **Test 5:**  $1.9 \pm 0.2$

### Test 1 vs Metformin:

$$t = 3.8 - 2.9 = 0.9$$

$$t = \frac{0.9}{\sqrt{\frac{0.4^2}{10} + \frac{0.3^2}{10}}} = \frac{0.9}{\sqrt{0.16 + 0.09}} = \frac{0.9}{\sqrt{0.25}} \approx \frac{0.9}{0.5} = 1.8$$

### Test 2 vs Metformin:

$$t = 1.7 - 2.9 = -1.2$$

$$t = \frac{-1.2}{\sqrt{\frac{0.3^2}{10} + \frac{0.3^2}{10}}} = \frac{-1.2}{\sqrt{0.09 + 0.09}} = \frac{-1.2}{\sqrt{0.18}} \approx \frac{-1.2}{0.424} \approx -2.83$$

### Test 3 vs Metformin:

$$t = 2.7 - 2.9 = -0.2$$

$$t = \frac{-0.2}{\sqrt{\frac{0.3^2}{10} + \frac{0.3^2}{10}}} = \frac{-0.2}{\sqrt{0.09 + 0.09}} = \frac{-0.2}{\sqrt{0.18}} \approx \frac{-0.2}{0.424} \approx -0.47$$

### Test 4 vs Metformin:

$$t = 2.2 - 2.9 = -0.7$$

$$t = \frac{-0.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.3^2}{10}}} = \frac{-0.7}{\sqrt{0.04 + 0.09}} = \frac{-0.7}{\sqrt{0.13}} \approx \frac{-0.7}{0.361} \approx -1.94$$

### Test 5 vs Metformin:

$$t = 1.9 - 2.9 = -1.0$$

$$t = \frac{-1.0}{\sqrt{\frac{0.2^2}{10} + \frac{0.3^2}{10}}} = \frac{-1.0}{\sqrt{0.04 + 0.09}} = \frac{-1.0}{\sqrt{0.13}} \approx \frac{-1.0}{0.361} \approx -2.77$$

## 6. HOMA-ISI

- **Metformin:**  $1.7 \pm 0.2$

- **Test 1:**  $1.2 \pm 0.2$
- **Test 2:**  $2.5 \pm 0.2$
- **Test 3:**  $1.9 \pm 0.2$
- **Test 4:**  $2.3 \pm 0.3$
- **Test 5:**  $2.6 \pm 0.3$

**Test 1 vs Metformin:**

$$t = \frac{1.2 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{-0.5}{\sqrt{0.04}} = \frac{-0.5}{0.2} = -2.5$$

$$t = \frac{1.2 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{-0.5}{\sqrt{0.04}} = \frac{-0.5}{0.2} = -2.5$$

$$t = \frac{1.2 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{-0.5}{\sqrt{0.04}} = \frac{-0.5}{0.2} = -2.5$$

**Test 2 vs Metformin:**

$$t = \frac{2.5 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.8}{\sqrt{0.04}} = \frac{0.8}{0.2} = 4.0$$

$$t = \frac{2.5 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.8}{\sqrt{0.04}} = \frac{0.8}{0.2} = 4.0$$

$$t = \frac{2.5 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.8}{\sqrt{0.04}} = \frac{0.8}{0.2} = 4.0$$

**Test 3 vs Metformin:**

$$t = \frac{1.9 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.2}{\sqrt{0.04}} = \frac{0.2}{0.2} = 1.0$$

$$t = \frac{1.9 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.2}{\sqrt{0.04}} = \frac{0.2}{0.2} = 1.0$$

$$t = \frac{1.9 - 1.7}{\sqrt{\frac{0.2^2}{10} + \frac{0.2^2}{10}}} = \frac{0.2}{\sqrt{0.04}} = \frac{0.2}{0.2} = 1.0$$

**Test 4 vs Metformin:**

$$t = \frac{2.3 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.6}{\sqrt{0.09 + 0.04}} = \frac{0.6}{\sqrt{0.13}} = \frac{0.6}{0.36} = 1.67$$

$$t = \frac{2.3 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.6}{\sqrt{0.09 + 0.04}} = \frac{0.6}{\sqrt{0.13}} = \frac{0.6}{0.36} = 1.67$$

$$t = \frac{2.3 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.6}{\sqrt{0.09 + 0.04}} = \frac{0.6}{\sqrt{0.13}} = \frac{0.6}{0.36} = 1.67$$

**Test 5 vs Metformin:**

$$t = \frac{2.6 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.9}{\sqrt{0.09 + 0.04}} = \frac{0.9}{\sqrt{0.13}} = \frac{0.9}{0.36} = 2.5$$

$$t = \frac{2.6 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.9}{\sqrt{0.09 + 0.04}} = \frac{0.9}{\sqrt{0.13}} = \frac{0.9}{0.36} = 2.5$$

$$t = \frac{2.6 - 1.7}{\sqrt{\frac{0.3^2}{10} + \frac{0.2^2}{10}}} = \frac{0.9}{\sqrt{0.09 + 0.04}} = \frac{0.9}{\sqrt{0.13}} = \frac{0.9}{0.36} = 2.5$$

**Results**

Here are the t-values for each test group compared to the Metformin group, rounded to two decimal places for clarity:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	5.15	-9.32	-0.81	-6.08	-9.65
Postprandial BG (mg/dL)	5.95	-11.77	-1.72	-6.39	-10.29
OGTT (mg/dL at 120 min)	4.70	-10.13	-1.31	-4.97	-8.32

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Body Weight (g)	2.02	-1.06	0.00	-1.06	-1.79
HOMA-IR	5.70	-8.96	-1.49	-6.14	-8.77
HOMA-ISI	-5.62	8.99	2.25	5.26	7.90

## Notes

- **Positive t-values** indicate the Test group mean is higher than the Metformin group mean.
- **Negative t-values** indicate the Test group mean is lower than the Metformin group mean.
- The t-values assume a sample size of  $n_1 = n_2 = 10$  for each group. If the actual sample sizes differ, please provide them, and I can recalculate the t-values.
- To determine statistical significance, you would compare these t-values to a critical t-value from a t-distribution table, based on the degrees of freedom (approximately  $df = n_1 + n_2 - 2 = 18$  for  $n_1 = n_2 = 10$ ) and your chosen significance level (e.g.,  $\alpha = 0.05$ ).
- If you need p-values or significance testing, please specify the degrees of freedom or sample size and the desired  $\alpha$  level.

Let me know if you need further analysis, such as p-values, confidence intervals, or adjustments for unequal variances!

also calculate the p values

To calculate the p-values for the t-tests comparing each test group (Test 1 to Test 5) against the Metformin group for all parameters, we'll use the t-values computed previously and determine the corresponding p-values based on a two-sample, two-tailed t-test. The p-value represents the probability of observing a t-value as extreme as, or more extreme than, the one calculated, under the null hypothesis that the means of the two groups are equal.

## Assumptions and Setup

- **Sample size:** As in the previous calculation, I assumed  $n_1 = n_2 = 10$  for each group (Test and Metformin) since the sample size wasn't provided. This gives degrees of freedom (df) as:  $df = n_1 + n_2 - 2 = 10 + 10 - 2 = 18$ .
- **Test type:** Two-tailed t-test, as we're testing for any difference (higher or lower) between the Test group and Metformin group means.
- **P-value calculation:** The p-value is calculated using the t-distribution for  $df = 18$ . Since exact p-values require a t-distribution table or computational tools, I'll use standard statistical methods to approximate p-values based on the t-values. For precision, I'll reference typical t-distribution critical values and interpolate where necessary. For simplicity, p-values will be reported as ranges or exact values where possible, using common thresholds (e.g.,  $p < 0.05$ ,  $p < 0.01$ ).
- **Critical t-values for  $df = 18$**  (two-tailed, from standard t-tables):
  - $\alpha = 0.05$ :  $t \approx 2.101$
  - $\alpha = 0.01$ :  $t \approx 2.878$

- $\alpha=0.001$   $\alpha = 0.001$   $\alpha=0.001$ :  $t \approx 3.610$   $t \approx 3.610$   $t \approx 3.610$  P-values will be estimated by comparing the absolute t-values ( $|t|$   $|t|$   $|t|$ ) to these thresholds or using interpolation for intermediate values.

### T-Values (from Previous Calculation)

The t-values for each parameter and test group vs. Metformin are:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	5.15	-9.32	-0.81	-6.08	-9.65
Postprandial BG (mg/dL)	5.95	-11.77	-1.72	-6.39	-10.29
OGTT (mg/dL at 120 min)	4.70	-10.13	-1.31	-4.97	-8.32
Body Weight (g)	2.02	-1.06	0.00	-1.06	-1.79
HOMA-IR	5.70	-8.96	-1.49	-6.14	-8.77
HOMA-ISI	-5.62	8.99	2.25	5.26	7.90

### P-Value Calculation

For each t-value, we'll compute the two-tailed p-value using the t-distribution with  $df=18$   $df=18$   $df=18$ . Since the t-distribution is symmetric, we use the absolute value of the t-statistic ( $|t|$   $|t|$   $|t|$ ) to find the p-value. I'll estimate p-values by comparing  $|t|$   $|t|$   $|t|$  to critical values and, where necessary, interpolating or noting significance levels. For high  $|t|$   $|t|$   $|t|$  values (e.g.,  $|t| > 3.610$   $|t| > 3.610$   $|t| > 3.610$ ), the p-value is typically  $p < 0.001$   $p < 0.001$   $p < 0.001$ . For lower values, I'll use approximate ranges based on standard t-tables.

#### 1. Fasting BG (mg/dL)

- **Test 1:**  $|t|=5.15$   $|t| = 5.15$   $|t|=5.15$ 
  - $5.15 > 3.610$   $5.15 > 3.610$   $5.15 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 2:**  $|t|=9.32$   $|t| = 9.32$   $|t|=9.32$ 
  - $9.32 \gg 3.610$   $9.32 \gg 3.610$   $9.32 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .
- **Test 3:**  $|t|=0.81$   $|t| = 0.81$   $|t|=0.81$ 
  - $0.81 < 2.101$   $0.81 < 2.101$   $0.81 < 2.101$ . For  $df=18$   $df=18$   $df=18$ ,  $t=1.0$   $t = 1.0$   $t=1.0$  corresponds to  $p \approx 0.33$   $p \approx 0.33$   $p \approx 0.33$ . Since  $0.81 < 1.0$   $0.81 < 1.0$   $0.81 < 1.0$ ,  $p > 0.33$   $p > 0.33$   $p > 0.33$ , likely  $p \approx 0.4$   $p \approx 0.4$   $p \approx 0.4$ .
- **Test 4:**  $|t|=6.08$   $|t| = 6.08$   $|t|=6.08$ 
  - $6.08 > 3.610$   $6.08 > 3.610$   $6.08 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 5:**  $|t|=9.65$   $|t| = 9.65$   $|t|=9.65$ 
  - $9.65 \gg 3.610$   $9.65 \gg 3.610$   $9.65 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .

#### 2. Postprandial BG (mg/dL)

- **Test 1:**  $|t|=5.95$   $|t| = 5.95$   $|t|=5.95$ 
  - $5.95 > 3.610$   $5.95 > 3.610$   $5.95 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 2:**  $|t|=11.77$   $|t| = 11.77$   $|t|=11.77$ 
  - $11.77 \gg 3.610$   $11.77 \gg 3.610$   $11.77 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .
- **Test 3:**  $|t|=1.72$   $|t| = 1.72$   $|t|=1.72$



- $1.72 < 2.101$   $1.72 < 2.101$   $1.72 < 2.101$ . For  $df=18$   $df = 18$   $df=18$ ,  $t=1.734$   $t = 1.734$   $t=1.734$  gives  $p \approx 0.10$   $p \approx 0.10$   $p \approx 0.10$ . Since  $1.72 \approx 1.734$   $1.72 \approx 1.734$   $1.72 \approx 1.734$ ,  $p \approx 0.10$   $p \approx 0.10$   $p \approx 0.10$ .
- **Test 4:**  $|t|=6.39$   $|t| = 6.39$   $|t|=6.39$ 
  - $6.39 > 3.610$   $6.39 > 3.610$   $6.39 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 5:**  $|t|=10.29$   $|t| = 10.29$   $|t|=10.29$ 
  - $10.29 \gg 3.610$   $10.29 \gg 3.610$   $10.29 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .

### 3. OGTT (mg/dL at 120 min)

- **Test 1:**  $|t|=4.70$   $|t| = 4.70$   $|t|=4.70$ 
  - $4.70 > 3.610$   $4.70 > 3.610$   $4.70 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 2:**  $|t|=10.13$   $|t| = 10.13$   $|t|=10.13$ 
  - $10.13 \gg 3.610$   $10.13 \gg 3.610$   $10.13 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .
- **Test 3:**  $|t|=1.31$   $|t| = 1.31$   $|t|=1.31$ 
  - $1.31 < 2.101$   $1.31 < 2.101$   $1.31 < 2.101$ . For  $df=18$   $df = 18$   $df=18$ ,  $t=1.330$   $t = 1.330$   $t=1.330$  gives  $p \approx 0.20$   $p \approx 0.20$   $p \approx 0.20$ . Since  $1.31 \approx 1.330$   $1.31 \approx 1.330$   $1.31 \approx 1.330$ ,  $p \approx 0.20$   $p \approx 0.20$   $p \approx 0.20$ .
- **Test 4:**  $|t|=4.97$   $|t| = 4.97$   $|t|=4.97$ 
  - $4.97 > 3.610$   $4.97 > 3.610$   $4.97 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 5:**  $|t|=8.32$   $|t| = 8.32$   $|t|=8.32$ 
  - $8.32 \gg 3.610$   $8.32 \gg 3.610$   $8.32 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .

### 4. Body Weight (g)

- **Test 1:**  $|t|=2.02$   $|t| = 2.02$   $|t|=2.02$ 
  - $2.02 < 2.101$   $2.02 < 2.101$   $2.02 < 2.101$ . For  $df=18$   $df = 18$   $df=18$ ,  $t=2.101$   $t = 2.101$   $t=2.101$  gives  $p = 0.05$   $p = 0.05$   $p = 0.05$ . Since  $2.02 < 2.101$   $2.02 < 2.101$   $2.02 < 2.101$ ,  $p \approx 0.06$   $p \approx 0.06$   $p \approx 0.06$ .
- **Test 2:**  $|t|=1.06$   $|t| = 1.06$   $|t|=1.06$ 
  - $1.06 < 2.101$   $1.06 < 2.101$   $1.06 < 2.101$ . For  $t=1.0$   $t = 1.0$   $t=1.0$ ,  $p \approx 0.33$   $p \approx 0.33$   $p \approx 0.33$ . Since  $1.06 > 1.0$   $1.06 > 1.0$   $1.06 > 1.0$ ,  $p \approx 0.30$   $p \approx 0.30$   $p \approx 0.30$ .
- **Test 3:**  $|t|=0.00$   $|t| = 0.00$   $|t|=0.00$ 
  - $t=0$   $t = 0$   $t=0$ , so  $p=1.0$   $p = 1.0$   $p=1.0$  (no difference).
- **Test 4:**  $|t|=1.06$   $|t| = 1.06$   $|t|=1.06$ 
  - Same as Test 2:  $p \approx 0.30$   $p \approx 0.30$   $p \approx 0.30$ .
- **Test 5:**  $|t|=1.79$   $|t| = 1.79$   $|t|=1.79$ 
  - $1.79 < 2.101$   $1.79 < 2.101$   $1.79 < 2.101$ . For  $t=1.734$   $t = 1.734$   $t=1.734$ ,  $p \approx 0.10$   $p \approx 0.10$   $p \approx 0.10$ . Since  $1.79 > 1.734$   $1.79 > 1.734$   $1.79 > 1.734$ ,  $p \approx 0.09$   $p \approx 0.09$   $p \approx 0.09$ .

### 5. HOMA-IR

- **Test 1:**  $|t|=5.70$   $|t| = 5.70$   $|t|=5.70$ 
  - $5.70 > 3.610$   $5.70 > 3.610$   $5.70 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 2:**  $|t|=8.96$   $|t| = 8.96$   $|t|=8.96$ 
  - $8.96 \gg 3.610$   $8.96 \gg 3.610$   $8.96 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .
- **Test 3:**  $|t|=1.49$   $|t| = 1.49$   $|t|=1.49$

- $1.49 < 2.101$   $1.49 < 2.101$   $1.49 < 2.101$ . For  $t=1.330$   $t = 1.330$   $t=1.330$ ,  $p \approx 0.20$   $p \approx 0.20$   $p \approx 0.20$ ; for  $t=1.734$   $t = 1.734$   $t=1.734$ ,  $p \approx 0.10$   $p \approx 0.10$   $p \approx 0.10$ . Interpolating,  $p \approx 0.15$   $p \approx 0.15$   $p \approx 0.15$ .
- **Test 4:**  $|t|=6.14$   $|t| = 6.14$   $|t|=6.14$ 
  - $6.14 > 3.610$   $6.14 > 3.610$   $6.14 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 5:**  $|t|=8.77$   $|t| = 8.77$   $|t|=8.77$ 
  - $8.77 \gg 3.610$   $8.77 \gg 3.610$   $8.77 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .

## 6. HOMA-ISI

- **Test 1:**  $|t|=5.62$   $|t| = 5.62$   $|t|=5.62$ 
  - $5.62 > 3.610$   $5.62 > 3.610$   $5.62 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 2:**  $|t|=8.99$   $|t| = 8.99$   $|t|=8.99$ 
  - $8.99 \gg 3.610$   $8.99 \gg 3.610$   $8.99 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .
- **Test 3:**  $|t|=2.25$   $|t| = 2.25$   $|t|=2.25$ 
  - $2.25 > 2.101$   $2.25 > 2.101$   $2.25 > 2.101$ , so  $p < 0.05$   $p < 0.05$   $p < 0.05$ . For  $t=2.101$   $t = 2.101$   $t=2.101$ ,  $p=0.05$   $p = 0.05$   $p=0.05$ ; for  $t=2.552$   $t = 2.552$   $t=2.552$ ,  $p \approx 0.02$   $p \approx 0.02$   $p \approx 0.02$ . Interpolating,  $p \approx 0.04$   $p \approx 0.04$   $p \approx 0.04$ .
- **Test 4:**  $|t|=5.26$   $|t| = 5.26$   $|t|=5.26$ 
  - $5.26 > 3.610$   $5.26 > 3.610$   $5.26 > 3.610$ , so  $p < 0.001$   $p < 0.001$   $p < 0.001$ .
- **Test 5:**  $|t|=7.90$   $|t| = 7.90$   $|t|=7.90$ 
  - $7.90 \gg 3.610$   $7.90 \gg 3.610$   $7.90 \gg 3.610$ , so  $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ .

## P-Value Results

Here are the approximate p-values for each test group compared to the Metformin group, rounded to three decimal places where possible or reported as ranges for clarity:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	<0.001	<0.001	0.400	<0.001	<0.001
Postprandial BG (mg/dL)	<0.001	<0.001	0.100	<0.001	<0.001
OGTT (mg/dL at 120 min)	<0.001	<0.001	0.200	<0.001	<0.001
Body Weight (g)	0.060	0.300	1.000	0.300	0.090
HOMA-IR	<0.001	<0.001	0.150	<0.001	<0.001
HOMA-ISI	<0.001	<0.001	0.040	<0.001	<0.001

## Interpretation

- **$p < 0.05$ :** Indicates statistical significance at the 5% level (commonly used threshold).
- **$p < 0.01$  or  $p < 0.001$ :** Indicates stronger evidence against the null hypothesis.
- **$p > 0.05$ :** Suggests no statistically significant difference (e.g., Test 3 for most parameters, Body Weight for several tests).
- For very large  $|t|$   $|t|$   $|t|$  values (e.g.,  $|t| > 3.610$   $|t| > 3.610$   $|t| > 3.610$ ), the p-value is extremely small ( $p \ll 0.001$   $p \ll 0.001$   $p \ll 0.001$ ), indicating highly significant differences.

## Notes

- The p-values are approximate, based on standard t-distribution tables and interpolation. For precise p-values, statistical software (e.g., R, Python, or SPSS) would be needed, especially for intermediate t-values.
- The sample size assumption ( $n=10$ ) affects the degrees of freedom and standard error. If the actual sample sizes differ, please provide them, and I can recalculate the t-values and p-values.
- If you need adjustments for multiple comparisons (e.g., Bonferroni correction, as you're performing 30 tests: 5 tests  $\times$  6 parameters), the significance threshold would be stricter (e.g.,  $\alpha=0.05/30 \approx 0.00167$   $\alpha = 0.05 / 30 \approx 0.00167$ ). Let me know if you want this applied.
- If you prefer exact p-values or want to use a specific statistical tool or method (e.g., Welch's t-test for unequal variances), please specify.

Let me know if you need further clarification, additional analyses, or assistance with interpreting these results!

| Parameter | Test 1 | Test 2 | Test 3 | Test 4 | Test 5 | |-----|-----|-----|-----|  
 |-----|-----| | Fasting BG (mg/dL) | 5.15 | -9.32 | -0.81 | -6.08 | -9.65 | | Postprandial BG (mg/dL) | 5.95 | -11.77 | -1.72 | -6.39 | -10.29 | | OGTT (mg/dL at 120 min) | 4.70 | -10.13 | -1.31 | -4.97 | -8.32 | | Body Weight (g) | 2.02 | -1.06 | 0.00 | -1.06 | -1.79 | | HOMA-IR | 5.70 | -8.96 | -1.49 | -6.14 | -8.77 | | HOMA-ISI | -5.62 | 8.99 | 2.25 | 5.26 | 7.90 | generate this table in a tabular form

Below is the table of t-values for each test group (Test 1 to Test 5) compared to the Metformin group for all parameters, presented in a clear tabular format:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	5.15	-9.32	-0.81	-6.08	-9.65
Postprandial BG (mg/dL)	5.95	-11.77	-1.72	-6.39	-10.29
OGTT (mg/dL at 120 min)	4.70	-10.13	-1.31	-4.97	-8.32
Body Weight (g)	2.02	-1.06	0.00	-1.06	-1.79
HOMA-IR	5.70	-8.96	-1.49	-6.14	-8.77
HOMA-ISI	-5.62	8.99	2.25	5.26	7.90

## Notes

- The t-values are rounded to two decimal places as provided.
- Positive t-values indicate that the Test group mean is higher than the Metformin group mean.
- Negative t-values indicate that the Test group mean is lower than the Metformin group mean.
- If you need additional formatting (e.g., bold headers, alignment adjustments) or further analysis (e.g., p-values in a similar table), please let me know!

The table of t-values for each test group (Test 1 to Test 5) compared to the Metformin group for all parameters is presented below in a clear tabular format, as requested:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	5.15	-9.32	-0.81	-6.08	-9.65
Postprandial BG (mg/dL)	5.95	-11.77	-1.72	-6.39	-10.29
OGTT (mg/dL at 120 min)	4.70	-10.13	-1.31	-4.97	-8.32
Body Weight (g)	2.02	-1.06	0.00	-1.06	-1.79
HOMA-IR	5.70	-8.96	-1.49	-6.14	-8.77
HOMA-ISI	-5.62	8.99	2.25	5.26	7.90

## Notes

- The t-values are rounded to two decimal places, as provided in the input.
- Positive t-values indicate that the mean of the Test group is higher than the Metformin group mean.
- Negative t-values indicate that the mean of the Test group is lower than the Metformin group mean.
- If you need additional formatting, analysis (e.g., combining with p-values in a single table), or further clarification, please let me know!

## P-Value Results

Here are the approximate p-values for each test group compared to the Metformin group, rounded to three decimal places where possible or reported as ranges for clarity:

Parameter	Test 1	Test 2	Test 3	Test 4	Test 5
Fasting BG (mg/dL)	<0.001	<0.001	0.400	<0.001	<0.001
Postprandial BG (mg/dL)	<0.001	<0.001	0.100	<0.001	<0.001
OGTT (mg/dL at 120 min)	<0.001	<0.001	0.200	<0.001	<0.001
Body Weight (g)	0.060	0.300	1.000	0.300	0.090
HOMA-IR	<0.001	<0.001	0.150	<0.001	<0.001
HOMA-ISI	<0.001	<0.001	0.040	<0.001	<0.001

### Interpretation

- **$p < 0.05$** : Indicates statistical significance at the 5% level (commonly used threshold).
- **$p < 0.01$**  or  **$p < 0.001$** : Indicates stronger evidence against the null hypothesis.
- **$p > 0.05$** : Suggests no statistically significant difference (e.g., Test 3 for most parameters, Body Weight for several tests).
- For very large (  $|t|$  ) values (e.g., (  $|t| > 3.610$  )), the p-value is extremely small (  $p \ll 0.001$  )), indicating highly significant differences.

### Notes

- The p-values are approximate, based on standard t-distribution tables and interpolation. For precise p-values, statistical software (e.g., R, Python, or SPSS) would be needed, especially for intermediate t-values.
- The sample size assumption (  $n = 10$  ) affects the degrees of freedom and standard error. If the actual sample sizes differ, please provide them, and I can recalculate the t-values and p-values.
- If you need adjustments for multiple comparisons (e.g., Bonferroni correction, as you're performing 30 tests: 5 tests  $\times$  6 parameters), the significance threshold would be stricter (e.g., (  $\alpha = 0.05 / 30 \approx 0.00167$  )). Let me know if you want this applied.
- If you prefer exact p-values or want to use a specific statistical tool or method (e.g., Welch's t-test for unequal variances), please specify.

# | Chapter 5 - Results and Discussions

### Summary

The text provides an overview of diabetes mellitus, its types, etiology, signs and symptoms, regulation of insulin secretion, and complications. It discusses the pathways involved in insulin secretion, including hypothalamic regulation, vagal stimulation, and sympathetic inhibition. The etiology of diabetes includes factors such as stress, obesity, genetics, pregnancy, drugs, and other conditions. The synthesis of insulin and the signs and symptoms of diabetes, such as hyperglycemia, glycosuria, polyuria, hyperlipidemia, anemia, negative nitrogen balance, and ketonemia, are also described. The text highlights the regulation of insulin through neural, hormonal, and chemical mechanisms. Lastly, it lists the complications associated with diabetes, such as cancer, PCOS/PCOD, Alzheimer's disease, fatty liver, delayed wound healing, retinopathy, nephropathy, and neuropathy.

### Conclusion

The findings suggest that our plant i.e. *Pandanus aureus* is capable of improving diabetic condition and managing the blood sugar level to its normal level. The various constituents present in the plants like Quercetin, Vixetin, Alpha-lamanin, Alpha-caffanoyl benzoic acid etc. helps in controlling diabetes. The HPLC, LC-MS suggests the presence of these compounds. These compounds act by various mechanisms like inhibiting the glucose entry by alpha-glucosidase inhibition and tyrosinase kinase mechanism which helps the release of insulin via Glucose transporter.

# Chapter 6 - References



## REFERENCES:

1. Amadi, P. U., Osuoha, J. O., Ekweogu, C. N., Jarad, S. J., Efiog, E. E., Odika, P. C., Ejiofor, C., Aloy-Amadi, O., Gill, G. S., Adumekwe, C. W., Gaowa, A., Zhang, D., De Courten, B., & Agomuo, E. N. (2025). Phenolic acids from *Anisopus mannii* modulates phosphofructokinase 1 to improve glycemic control in patients with type 2 diabetes: A double-blind, randomized, clinical trial. *Pharmacological Research*, 212, 107602. <https://doi.org/10.1016/j.phrs.2025.107602>
2. An, Y., Zhao, H., He, C., Shi, L., Su, X., Zhang, H., Huang, Y., Shan, Z., Wang, M., Du, Y., Xie, J., Zhao, Y., Yang, Y., Huang, Z., Wan, A., Zhao, Y., & Zhao, B. (2025). Xiasangju alleviates hepatic insulin resistance in db/db mice via AMPK pathway: Mechanisms and active components study. *International Immunopharmacology*, 156, 114675. <https://doi.org/10.1016/j.intimp.2025.114675>
3. Begum, R., Das, A., Alam, Md. J., & Sultana, G. N. N. (2025). Insights Into Genetic Variations of the *OCT1* Gene in Metformin Poor Responders Among Bangladeshi Type 2 Diabetic Patients. *Advances in Pharmacological and Pharmaceutical Sciences*, 2025(1), 8568658. <https://doi.org/10.1155/adpp/8568658>
4. Chen, J., Qu, B., Yang, D., Wang, Y., Zhu, H., Wang, Z., Zhang, X., Ma, H., Zhao, N., Zhao, L., Zhou, L., He, X., & Li, P. (2025). Combined metabolomics and network pharmacology to elucidate the mechanisms of Huiyang Shengji decoction in treating diabetic skin ulcer mice. *Phytomedicine*, 141, 156569. <https://doi.org/10.1016/j.phymed.2025.156569>
5. Chen, R., Fan, J., Wu, Y., Huang, X., Zhang, W., Xu, Y., Zhang, Y., Li, L., Wang, C., Yu, M., & Zhu, Y. (2025). *Strobilanthes sarcoarrhiza* root phenolic extract prevent diabetic nephropathy in mice by regulating NF- $\kappa$ B/IL-1 $\beta$  signaling and glycerophospholipid metabolism. *Journal of Pharmaceutical and Biomedical Analysis*, 253, 116534. <https://doi.org/10.1016/j.jpba.2024.116534>
6. Cheng, Z., Zhan, H., Yuan, H., Wang, N., Lan, Y., Qu, W., Lan, X., Liao, Z., Wang, G., & Chen, M. (2025). Boeravinone C ameliorates lipid accumulation and inflammation in diabetic kidney disease by activating PPAR $\alpha$  signaling. *Journal of Ethnopharmacology*, 342, 119398. <https://doi.org/10.1016/j.jep.2025.119398>
7. Chi, L., Niu, H., Niu, Y., Yao, R., Shi, D., Lu, B., & Pang, Z. (2025). *Trigonella foenum-graecum* L. ameliorates metabolism-associated fatty liver disease in type 2 diabetic mice: A multi-omics mechanism analysis. *Journal of Ethnopharmacology*,

- 
119862. <https://doi.org/10.1016/j.jep.2025.119862>
8. Das, B., Keithellakpam, O. S., Chanu, T. B., Pathaw, N., Rai, S., Singh, O. S., Nanjappan, S. K., Soibam, A., Sharma, N., Bhardwaj, P. K., & Mukherjee, P. K. (2025). Metabolomic study of Polygonum posumbu Buch. Ham. Ex D. Don integrating with anti-diabetic potential—A mechanistic approach. *Fitoterapia*, 182, 106440. <https://doi.org/10.1016/j.fitote.2025.106440>
  9. Deng, J., Gan, W., Hu, C., Liu, Z., Chen, N., Jia, C., Ding, M., Zou, J., Cai, T., Li, J., Xu, Y., Chen, J., Ma, C., Yin, H., Zhang, Z., Wang, H., & Cao, Y. (2025). San Huang Xiao Yan recipe promoted wound healing in diabetic ulcer mice by inhibiting Th17 cell differentiation. *Journal of Ethnopharmacology*, 341, 119243. <https://doi.org/10.1016/j.jep.2024.119243>
  10. Duan, Y., Pei, K., Liu, X., Zhang, X., Song, P., Tu, S., Zhu, H., & Cai, H. (2025). A comprehensive pharmacokinetic strategy for systematic evaluation of whole interaction of different constituents in Astragali Radix -Fructus Corni to improve diabetic kidney disease. *Journal of Ethnopharmacology*, 339, 119159. <https://doi.org/10.1016/j.jep.2024.119159>
  11. Enejoh, O. A., Okonkwo, C. H., Nortey, H., Kemiki, O. A., Moses, A., Mbaaji, F. N., Yusuf, A. S., & Awe, O. I. (2025). Machine learning and molecular dynamics simulations predict potential TGR5 agonists for type 2 diabetes treatment. *Frontiers in Chemistry*, 12, 1503593. <https://doi.org/10.3389/fchem.2024.1503593>
  12. Ercan, S., Arslan, G. Ç., & Pirinçcioğlu, N. (2025). Investigation of Compounds Found in Ginger ( *Curcuma longa* L .) as Inhibitors for PTP1B for the Treatment of Type 2 Diabetes Using Molecular Docking and Molecular Dynamics Approaches. *ChemistrySelect*, 10(6), e202401841. <https://doi.org/10.1002/slct.202401841>
  13. Fan, L., Liu, J., Li, L., Yang, X., Zhao, Q., & Zhao, L. (2025). Echinacoside alleviates type 2 diabetes mellitus through inhibiting hepatic gluconeogenesis via gut bacterial-fungal trans-kingdom network reconstruction. *Phytomedicine*, 156802. <https://doi.org/10.1016/j.phymed.2025.156802>
  14. Feng, S., Wang, J., Peng, Q., Zhang, P., Jiang, Y., Zhang, H., Song, X., Li, Y., Huang, W., Zhang, D., & Deng, C. (2025). Schisandra sphenanthera extract modulates sweet taste receptor pathway, IRS/PI3K, AMPK/mTOR pathway and endogenous metabolites against T2DM. *Phytomedicine*, 136, 156348. <https://doi.org/10.1016/j.phymed.2024.156348>
  15. Fu, X., Jing, Y., Yang, R., Zhu, C., Tu, Y., Hu, Z., Sheng, W., Jiao, Q., Liu, L., Zhang,
-

- 
- W., & He, Q. (2025). Guhan Yangsheng Jing mitigates oxidative stress and ferroptosis to improve reproductive damage in Diabetic Male Rats. *Journal of Ethnopharmacology*, 347, 119746. <https://doi.org/10.1016/j.jep.2025.119746>
16. Gao, G., Su, X., Liu, S., Wang, P., Chen, J. J., Liu, T., Xu, J., Zhang, Z., Zhang, X., & Xie, Z. (2025). Cornuside as a promising therapeutic agent for diabetic kidney disease: Targeting regulation of Ca<sup>2+</sup> disorder-mediated renal tubular epithelial cells apoptosis. *International Immunopharmacology*, 149, 114190. <https://doi.org/10.1016/j.intimp.2025.114190>
  17. Gao, W., Wang, M., Xu, W., Ma, R., Wang, X., Sun, T., Li, P., Li, F., He, Y., Xie, X., Pang, X., Zhou, Y., & Pang, G. (2025). Modified weiling decoction inhibited excessive autophagy via AKT/mTOR/ULK1 pathway to alleviate T2DM: Integrating network pharmacology and experimental validation. *Journal of Ethnopharmacology*, 347, 119753. <https://doi.org/10.1016/j.jep.2025.119753>
  18. Gupta, T., Lal, K., & Singh, R. (2025). Unraveling the therapeutic potential of Astilbe rivularis Buch.-Ham. Ex D. Don in attenuation of diabetic neuropathy in laboratory rats. *Journal of Ethnopharmacology*, 338, 119021. <https://doi.org/10.1016/j.jep.2024.119021>
  19. Hakeem, A., Saleem, M., Anwar, R., Asif, M., Muhammad, T., Ebada, S. S., Al Musayeib, N. M., & Ashour, M. L. (2025). Molecular events responsible for hypoglycaemic attributes of Fernandoa adenophylla extract in streptozotocin-induced diabetes. *Fitoterapia*, 183, 106557. <https://doi.org/10.1016/j.fitote.2025.106557>
  20. He, S., Xue, T., Geng, R., Wang, Q., Wang, B., Wen, L., Li, M., Hu, J., & Yang, J. (2025). Mapping the evolution of anti-diabetic polysaccharides research: Trends, collaborations, and emerging frontiers. *European Journal of Pharmacology*, 997, 177479. <https://doi.org/10.1016/j.ejphar.2025.177479>
  21. Hu, S., Shen, F., Jia, N., Zhang, C., Wu, X., Jiang, W., Li, B., & Chen, Q. (2025). Novel monomers recipe derived from Shengji-Huayu formula targeting PI3K/Akt signaling pathway for diabetic wound healing based on accurate network pharmacology. *Journal of Ethnopharmacology*, 344, 119509. <https://doi.org/10.1016/j.jep.2025.119509>
  22. Jang, H.-H., Bae, J. H., Kim, M.-J., Park, M. Y., Kim, H. R., & Lee, Y.-M. (2020). Agrimonia pilosa Ledeb. Ameliorates Hyperglycemia and Hepatic Steatosis in Ovariectomized Rats Fed a High-Fat Diet. *Nutrients*, 12(6), 1631. <https://doi.org/10.3390/nu12061631>
-

23. Li, M., Zhu, H.-Y., Zhao, S.-Y., Li, X.-D., Tong, S.-M., Ma, J., Xu, A.-J., & Zhang, J. (2025). Baicalin alleviates lipid metabolism disorders in diabetic kidney disease via targeting FKBP51. *Phytomedicine*, 139, 156473. <https://doi.org/10.1016/j.phymed.2025.156473>
24. Li, Z., Zhou, D., Wu, T., Lee, H., Zheng, F., Dai, Y., & Yue, H. (2025). A novel glycopeptide from mountain-cultivated ginseng residue protects type 2 diabetic symptoms-induced heart failure. *Journal of Ethnopharmacology*, 336, 118723. <https://doi.org/10.1016/j.jep.2024.118723>
25. Lin, L., Yu, F., Tang, X., Cai, W., Wang, Y., Hong, Y., Zhang, B., He, X., & Xu, X. (2025). Huiyang Shengji Decoction Promotes Healing of Diabetic Skin Ulcers via the NF- $\kappa$ B/STAT3/NLRP3 Signaling Pathway: A Multi-Omics Analysis. *Phytomedicine*, 156695. <https://doi.org/10.1016/j.phymed.2025.156695>
26. Liu, J., Zhang, Y., Xu, X., Dong, X., Pan, Y., Sun, X., & Luo, Y. (2025). Ginsenoside Ro prevents endothelial injury via promoting Epac1/AMPK- mediated mitochondria protection in early diabetic retinopathy. *Pharmacological Research*, 211, 107562. <https://doi.org/10.1016/j.phrs.2024.107562>
27. Liu, Z., Li, Q., Zhao, F., & Chen, J. (2025). A decade review on phytochemistry and pharmacological activities of *Cynomorium songaricum* Rupr.: Insights into metabolic syndrome. *Phytomedicine*, 140, 156602. <https://doi.org/10.1016/j.phymed.2025.156602>
28. Luo, F., Yang, J., Song, Z., Zhao, Y., Wang, P., Liu, K., Mou, X., Liu, W., & Li, W. (2025). Renshen Zhuye decoction ameliorates high-fat diet-induced obesity and insulin resistance by modulating gut microbiota and metabolic homeostasis. *Phytomedicine*, 141, 156655. <https://doi.org/10.1016/j.phymed.2025.156655>
29. Mansour, M. F., Behairy, A., Mostafa, M., Khamis, T., Alsemeh, A. E., Ahmed, N. M. Q., & El-Emam, M. M. A. (2025). Quercetin-loaded PEGylated liposomes alleviate testicular dysfunction in alloxan-induced diabetic rats: The role of Kisspeptin/Neurokinin B/Dynorphin pathway. *Toxicology and Applied Pharmacology*, 499, 117337. <https://doi.org/10.1016/j.taap.2025.117337>
30. Oh, K.-K., Song, S. H., Park, J. H., Kim, M. J., Kim, D. J., & Suk, K.-T. (2025). A signpost to guide the key therapeutic components of *Aralia continentalis* Kitag roots in treating T2DM-derived heart attack, and diabetic nephropathy via systems biology concept. *Life Sciences*, 372, 123635. <https://doi.org/10.1016/j.lfs.2025.123635>
31. Omale, S., Aguiyi, J. C., Gould, G. W., Madaki, A. J. K., Alemika, T. E., Johnson, T.

- O., Luka, P. D., Nyam, C. J., Nnadi, N. E., Agwom, F. M., Ohaeri, U., Ochala, S. O., Clement, P. T., & Parkinson, J. A. (2025). Quercetin from *Parinari curatellifolia* planch.ex benth differentially regulates *Drosophila* insulin-like peptides II and V in hyperglycaemic flies. *Pharmacological Research - Natural Products*, 7, 100231. <https://doi.org/10.1016/j.prenap.2025.100231>
32. Panda, V., Babar, A., Sudhamani, S., Hingorani, L., & Deshmukh, A. (2025). Modulation of Satiety, Lipid Metabolism, and Insulin Sensitivity by *Triphala* and *Garcinia cambogia* in High-Fat Diet-Induced Obese Rats. *Pharmacological Research - Natural Products*, 100234. <https://doi.org/10.1016/j.prenap.2025.100234>
33. Park, M. J., & Kang, Y.-H. (2020). Isolation of Isocoumarins and Flavonoids as  $\alpha$ -Glucosidase Inhibitors from *Agrimonia pilosa* L. *Molecules*, 25(11), 2572. <https://doi.org/10.3390/molecules25112572>
34. Phung, P. T. K., Binh, D. N. L., Thu, N. T. A., Van Ha, N., Huyen, T. T., Hien, K. M., Nhu, M. H., Duc, N. K., & Minh Quan, L. (2025). Optimization of extraction parameters and anti-hyperglycemic assessment of standardized extract from *Santalum album* L. leaves. *Pharmacological Research - Modern Chinese Medicine*, 14, 100577. <https://doi.org/10.1016/j.prmcm.2025.100577>
35. Safavi, F., Andrade-Cetto, A., Escandón-Rivera, S. M., & Espinoza-Hernández, F. A. (2025). Assessing the potential fasting and postprandial mechanisms involved in the acute hypoglycemic and anti-hyperglycemic effects of four selected plants from Iran used in traditional Persian medicine. *Journal of Ethnopharmacology*, 336, 118742. <https://doi.org/10.1016/j.jep.2024.118742>
36. Shakour, N., Hoseinpoor, S., Rajabian, F., Azimi, S. G., Iranshahi, M., Sadeghi-Aliabadi, H., & Hadizadeh, F. (2025). Discovery of non-peptide GLP-1r natural agonists for enhancing coronary safety in type 2 diabetes patients. *Journal of Biomolecular Structure and Dynamics*, 43(7), 3508–3525. <https://doi.org/10.1080/07391102.2023.2298734>
37. Shi, L., Wang, Y., Guan, Y., Men, L., Sun, J., & Yuan, G. (2025). To establish a new quality assessment method based on the regulation of intestinal microbiota in type 2 diabetes by lignans of *Schisandra chinensis* (Turcz.) Baill. *Journal of Ethnopharmacology*, 348, 119822. <https://doi.org/10.1016/j.jep.2025.119822>
38. Tao, Y., Zeng, Y., Zeng, R., Gou, X., Zhou, X., Zhang, J., Nhamdriel, T., & Fan, G. (2025). The total alkaloids of *Berberidis Cortex* alleviate type 2 diabetes mellitus by regulating gut microbiota, inflammation and liver gluconeogenesis. *Journal of*

- 
- Ethnopharmacology*, 337, 118957. <https://doi.org/10.1016/j.jep.2024.118957>
39. Wang, N., Feng, H., Zhang, Z., Tian, H., Gu, L., Bian, Y., & Xue, M. (2025). Danggui Buxue decoction regulates autophagy to Improve renal fibrosis in diabetes through miR-27a /PI3K/AKT pathway. *Journal of Ethnopharmacology*, 341, 119357. <https://doi.org/10.1016/j.jep.2025.119357>
  40. Wang, X., Zhao, X., Zhang, M., Han, C., Li, D., Wu, Y., Guo, P., Feng, L., Ma, X., & Wang, C. (2025).  $\alpha$ -Linolenic acid from Mori Folttfm found as Choloylglycine hydrolase inhibitor by the developed fluorescent probe to alleviate type 2 diabetes. *Sensors and Actuators B: Chemical*, 423, 136789. <https://doi.org/10.1016/j.snb.2024.136789>
  41. Wang, X., Zhong, Z.-J., Chen, P.-F., Deng, C.-F., Chen, X.-M., Xin, G.-Z., & Tang, D. (2025). Integrating metabolomics and network pharmacology to investigate Da-Chai-Hu Decoction prevents kidney injury in diabetic mice. *Journal of Ethnopharmacology*, 340, 119158. <https://doi.org/10.1016/j.jep.2024.119158>
  42. Wang, Y., Yang, Y., Chen, Y., Zhou, Y., Zhang, S., Zhu, W., Zhang, X., & Zhu, J. (2025). Qing'e Pill rectifies bone homeostasis imbalance in diabetic osteoporosis via the AGE/RAGE pathway: A network pharmacology analysis and multi-omics validation. *Journal of Ethnopharmacology*, 348, 119816. <https://doi.org/10.1016/j.jep.2025.119816>
  43. Wei, Y., Wang, M., Jiang, Z., Jia, Y., Si, Y., Peng, Z., Yang, J., Shi, Y., Wu, Y., Ding, X., Pan, D., Zhao, D., Leng, X., Li, X., & Dong, H. (2025). Investigating the molecular mechanisms of Jiangu Decoction in treating type 2 diabetic osteoporosis. *Journal of Ethnopharmacology*, 341, 119346. <https://doi.org/10.1016/j.jep.2025.119346>
  44. Wu, Y., Liu, M., Li, J., Gao, R., Hu, Q., Xie, Y., Zhou, H., Li, H., He, X., & Li, L. (2025). Kouqiangjie formula alleviates diabetic periodontitis by regulating alveolar bone homeostasis via miR-29a-3p-mediated Dkk-1/Wnt/ $\beta$ -catenin signaling pathway. *Journal of Ethnopharmacology*, 340, 119270. <https://doi.org/10.1016/j.jep.2024.119270>
  45. Xia, Y., Han, B., Zhang, F., Li, Q., Feng, Q., Zhang, S., Liu, D., Lin, C., Wang, D., & Liu, B. (2025). Pae/exo@PF-127 promote diabetic wound healing through miR-424-5p. *Phytomedicine*, 156688. <https://doi.org/10.1016/j.phymed.2025.156688>
  46. Yang, J., Chen, C., Zhang, H., Chen, B., Xiao, K., Tang, Y., Meng, K., Qin, L., & Chen, P. (2025). Serum metabolomics and 16S rRNA amplicon sequencing reveal the role of puerarin in alleviating bone loss aggravated by antidiabetic agent pioglitazone
-



- in type 2 diabetic mice. *Journal of Ethnopharmacology*, 340, 119128. <https://doi.org/10.1016/j.jep.2024.119128>
47. Ye, C., Li, Y., Shi, J., He, L., Shi, X., Yang, W., Lei, W., Quan, S., Lan, X., & Liu, S. (2025). Network pharmacology analysis revealed the mechanism and active compounds of jiao tai wan in the treatment of type 2 diabetes mellitus via SRC/PI3K/AKT signaling. *Journal of Ethnopharmacology*, 337, 118898. <https://doi.org/10.1016/j.jep.2024.118898>
  48. Zhang, W., Yi, C., Song, Z., Yu, B., Jiang, X., Guo, L., Huang, S., Xia, T., Huang, F., Yan, Y., Li, H., & Dai, Y. (2025). Reshaping the gut microbiota: Tangliping decoction and its core blood-absorbed component quercetin improve diabetic cognitive impairment. *Phytomedicine*, 140, 156560. <https://doi.org/10.1016/j.phymed.2025.156560>
  49. Zhang, Z., Lai, J., Fan, X., Wang, S., Zhang, H., Wang, L., & Wang, H. (2025). Extraction of polysaccharides from *Polygonum cuspidatum* with activity against Type 2 Diabetes via alterations in gut microbiota. *Food Chemistry*, 470, 140047. <https://doi.org/10.1016/j.foodchem.2024.140047>
  50. Zhang, Z., Yang, W., Chen, J., Chen, X., & Gu, Y. (2025). Efficacy and mechanism of *Schisandra chinensis* active component Gomisin A on diabetic skin wound healing: Network pharmacology and in vivo experimental validation. *Journal of Ethnopharmacology*, 337, 118828. <https://doi.org/10.1016/j.jep.2024.118828>
  51. Zhao, P., Zhong, S., Liao, J., Tao, J., Yao, Y., Song, P., & Yang, X. (2025). *Caragana jubata* ethanol extract ameliorates the symptoms of STZ-HFD-induced T2DM mice by PKC/GLUT4 pathway. *Journal of Ethnopharmacology*, 339, 119171. <https://doi.org/10.1016/j.jep.2024.119171>
  52. Zubaidi, S. N., Wong, P. L., Qadi, W. S. M., Dawoud, E. A. D., Hamezah, H. S., Baharum, S. N., Jam, F. A., Abas, F., Moreno, A., & Mediani, A. (2025). Deciphering the mechanism of *Annona muricata* leaf extract in alloxan-nicotinamide-induced diabetic rat model with 1H-NMR-based metabolomics approach. *Journal of Pharmaceutical and Biomedical Analysis*, 260, 116806. <https://doi.org/10.1016/j.jpba.2025.116806>
  53. Aspinwall, C. A., Lakey, J. R. T., & Kennedy, R. T. (2023). Insulin-stimulated Insulin Secretion in Single Pancreatic Beta Cells. *Journal of Biological Chemistry*, 274(10), 6360–6365. <https://doi.org/10.1074/jbc.274.10.6360>.
  54. Koehn, P. H. (2023). Linking China, India, and the United States. *International Studies*

- 
- Review*, 12(2), 331–334. <https://doi.org/10.1111/j.1468-2486.2010.00940.x>.
55. Abbott, K. C. (2023). Microalbuminuria in Non—Insulin-Dependent Diabetes Mellitus. *Archives of Internal Medicine*, 154(2), 146. <https://doi.org/10.1001/archinte.1994.00420020048006>.
  56. Huse, D. M. (2021). The economic costs of non-insulin-dependent diabetes mellitus. *JAMA: The Journal of the American Medical Association*, 262(19), 2708–2713. <https://doi.org/10.1001/jama.262.19.2708>.
  57. Duckrow, R. B., & Bryan, R. M. (2023). Regional cerebral glucose utilization during hyperglycemia. *Journal of Neurochemistry*, 48(3), 989–993. <https://doi.org/10.1111/j.1471-4159.1987.tb05614.x>.
  58. Ikegami, M., Osada, M., Kamei, A., Kamei, J., Kai, M., Ikeda, H., & Ohashi, T. (2023). Olanzapine-Induced Hyperglycemia: Possible Involvement of Histaminergic, Dopaminergic and Adrenergic Functions in the Central Nervous System. *Neuroendocrinology*, 98(3), 224–232. <https://doi.org/10.1159/000356119>.
  59. Sosa-Pineda, B., Oliver, G., Torres, M., Chowdhury, K., & Gruss, P. (2022). The Pax4 gene is essential for differentiation of insulin-producing beta cells in the mammalian pancreas. *Nature*, 386(6623), 399–402. <https://doi.org/10.1038/386399a0>.
  60. Palkovits, M., Tapia-Arancibia, L., Kordon, C., & Epelbaum, J. (2021). Somatostatin connections between the hypothalamus and the limbic system of the rat brain. *Brain Research*, 250(2), 223–228. [https://doi.org/10.1016/0006-8993\(82\)90416-4](https://doi.org/10.1016/0006-8993(82)90416-4).
  61. Destefano, M. A., & Jacinto, E. (2025). Regulation of insulin receptor substrate-1 by mTORC2 (mammalian target of rapamycin complex 2). *Biochemical Society Transactions*, 41(4), 896–901. <https://doi.org/10.1042/bst20130018>.
  62. Griffith, L. C. (2004). Regulation of calcium/calmodulin-dependent protein kinase II activation by intramolecular and intermolecular interactions. *The Journal of Neuroscience*, 24(39), 8394–8398. <https://doi.org/10.1523/jneurosci.3604-04.2004>.
  63. Kohn, A. D., Kovacina, K. S., & Roth, R. A. (2025). Insulin stimulates the kinase activity of RAC-PK, a pleckstrin homology domain containing ser/thr kinase. *The EMBO Journal*, 14(17), 4288–4295. <https://doi.org/10.1002/j.1460-2075.1995.tb00103.x>.
  64. Niki, I., Okazaki, K., Saitoh, M., Niki, A., Niki, H., Tamagawa, T., Iguchi, A., & Hidaka, H. (1993). Presence and Possible Involvement of Ca/Calmodulin-Dependent Protein Kinases in Insulin Release from the Rat Pancreatic  $\beta$ Cell. *Biochemical and*
-



- Biophysical Research Communications*, 191(1), 255–261.  
<https://doi.org/10.1006/bbrc.1993.1210>.
65. Fullerton, M. D., Steinberg, G. R., & Schertzer, J. D. (2023). Immunometabolism of AMPK in insulin resistance and atherosclerosis. *Molecular and Cellular Endocrinology*, 366(2), 224–234. <https://doi.org/10.1016/j.mce.2012.02.004>.
  66. Walter, E. E., Fernandez, F., Snelling, M., & Barkus, E. (2022). Stress induced cortisol release and schizotypy. *Psychoneuroendocrinology*, 89, 209–215.  
<https://doi.org/10.1016/j.psyneuen.2018.01.012>.
  67. Datta, B. N., Cole, D. S., & Shortland, G. J. (2020). Hyperlipidaemia. *Paediatrics and Child Health*, 21(2), 94–98. <https://doi.org/10.1016/j.paed.2010.09.014>.
  68. Arner, P., Livingston, J. N., Pollare, T., & Lithell, H. (2021). Defective insulin receptor tyrosine kinase in human skeletal muscle in obesity and type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*, 30(6), 437–440. <https://doi.org/10.1007/bf00292549>.
  69. Eapen, S. S., Connor, E. L., & Gern, J. E. (2002). Insulin desensitization with insulin lispro and an insulin pump in a 5-year-old child. *Annals of Allergy, Asthma & Immunology*, 85(5), 395–397. [https://doi.org/10.1016/s1081-1206\(10\)62554-9](https://doi.org/10.1016/s1081-1206(10)62554-9)
  70. Ireland, L. D., & Allen, R. H. (2022). *Combination Oral Contraceptive Pills* (pp. 25–43). Springer. [https://doi.org/10.1007/978-3-030-46391-5\\_2](https://doi.org/10.1007/978-3-030-46391-5_2)
  71. chida, K., Okita, Y., Araki, T., Kusunoki, M., Matsushita, K., Miki, C., Yoshiyama, S., Otake, K., Inoue, M., & Koike, Y. (2021). Poor catch-up growth after proctocolectomy in pediatric patients with ulcerative colitis receiving prolonged steroid therapy. *Pediatric Surgery International*, 26(4), 373–377.  
<https://doi.org/10.1007/s00383-010-2577-6>
  72. Hecht, A., & Gershberg, H. (2022). Diabetes mellitus and primary hypothyroidism. *Metabolism*, 17(2), 108–113. [https://doi.org/10.1016/0026-0495\(68\)90136-4](https://doi.org/10.1016/0026-0495(68)90136-4).
  73. Meena, A., Kaushal, K., & Gurjar, H. (2022). Evaluation of Rodhradi Gana(Sushrutokta) in Yoni Roga w.s.r. to PCOS (Poly Cystic Ovarian Syndrome). *International Research Journal of Ayurveda & Yoga*, 05(10), 33–44.  
<https://doi.org/10.47223/irjay.2022.51005>
  74. Bhattacharya, S., Bank, S., K Sinha, A., & Ghosh, R. (2022). Extra pancreatic synthesis of insulin. *Integrative Obesity and Diabetes*, 2(1).  
<https://doi.org/10.15761/iod.1000138>.

75. Dungan, C. M., Wright, D. C., & Williamson, D. L. (2022). Lack of REDD1 reduces whole body glucose and insulin tolerance, and impairs skeletal muscle insulin signaling. *Biochemical and Biophysical Research Communications*, 453(4), 778–783. <https://doi.org/10.1016/j.bbrc.2014.10.032>
76. Ratra, D., Nagarajan, R., Thanikachalam, S., Kuppan, K., Das, U., Narayansamy, A., Dalan, D., & Prakash, N. (2020). Early structural and functional neurovascular changes in the retina in the prediabetic stage. *Eye*, 35(3), 858–867. <https://doi.org/10.1038/s41433-020-0984-z>
77. Jain, S. K., Rogier, K., Jain, S. K., & Patel, P. (2022). Trivalent Chromium Inhibits Protein Glycosylation and Lipid Peroxidation in High Glucose-Treated Erythrocytes. *Antioxidants & Redox Signaling*, 8(1–2), 238–241. <https://doi.org/10.1089/ars.2006.8.238>
78. Djeddi, D., Cauliez, A., Oulebsir, A., Hureaux, M., Vanrenterghem, A., & Vargas-Poussou, R. (2021). Persistently high urine glucose levels caused by familial renal glycosuria. *Archives de Pédiatrie*, 27(7), 386–387. <https://doi.org/10.1016/j.arcped.2020.07.002>
79. Oster, J. R. (1997). The Polyuria of Solute Diuresis. *Archives of Internal Medicine*, 157(7), 721. <https://doi.org/10.1001/archinte.1997.00440280015002>
80. Garzón, P., García-López, P. M., García-Estrada, J., Almodovar-Cuevas, C., Navarro-Ruiz, A., & Román-Maldonado, S. (2022). Iron binding to nutrients containing fiber and phenytoin. *General Pharmacology*, 17(6), 661–664. [https://doi.org/10.1016/0306-3623\(86\)90297-1](https://doi.org/10.1016/0306-3623(86)90297-1).
81. Papachristodoulou, D., Elliott, W. H., Snape, A., & Elliott, D. C. (2021). *Synthesis of glucose (gluconeogenesis)*. oxford university. 42(9), 199–203. <https://doi.org/10.1093/hesc/9780198768111.003.0019>
82. Ladd, W. S., & Palmer, W. W. (1921). The carbohydrate-fat ratio in relation to the production of ketone bodies in diabetes mellitus. *Experimental Biology and Medicine*, 18(4), 109–110. <https://doi.org/10.3181/00379727-18-51>
83. Wang, P., Mariman, E., Keijer, J., Bunschoten, A., Bouwman, F., & Renes, J. (2021). Insulin modulates the secretion of proteins from mature 3T3-L1 adipocytes: a role for transcriptional regulation of processing. *Diabetologia*, 49(10), 2453–2462. <https://doi.org/10.1007/s00125-006-0321-5>
84. Inoue, K., Nawata, H., Hiramatsu, S., Umeda, F., & Hisatomi, A. (2021). Effects of amylin on the release of insulin and glucagon from the perfused rat pancreas. *Hormone*

- and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones et Metabolisme*, 25(3), 135–137. <https://doi.org/10.1055/s-2007-1002062>
85. Murata, T., Miwa, I., Okuda, J., & Toyoda, Y. (2021). Inhibition of Glucose-Induced Insulin Secretion Through Inactivation of Glucokinase by Glyceraldehyde. *Diabetes*, 42(7), 1003–1009. <https://doi.org/10.2337/diab.42.7.1003>
86. Koivisto, U. M., Martinez-Valdez, H., Bilan, P. J., Burdett, E., Ramlal, T., & Klip, A. (2020). Differential regulation of the GLUT-1 and GLUT-4 glucose transport systems by glucose and insulin in L6 muscle cells in culture. *Journal of Biological Chemistry*, 266(4), 2615–2621. [https://doi.org/10.1016/s0021-9258\(18\)52289-4](https://doi.org/10.1016/s0021-9258(18)52289-4)