IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 1, November 2026
Impact Factor: 8.2

A Review of Preclinical Evidence and Translational Gaps

Miss. Gunjal Priyanka B[1] and Mr. Bhane Aniket R[2], Mrs. Puja Khemnar K[3]
Student, Department of Pharmacy[1]
Guide, Department of Pharmacy[2]
Assistant Professor[3]
Pravara Education Society's, Institute of Pharmacy, Loni, Maharashtra, India
Dr. Babasaheb Aambedkar Technology University, Lonere, Raigad
priyankagunjal46@gmail.com and aniketbhane4@gmail.com

Abstract : *Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycaemia arising from impaired insulin secretion, insulin action, or both. Plant-derived products are investigated as possible sources of complementary antidiabetic agents because they contain chemically diverse constituents that may influence glucose regulation and diabetes-associated tissue injury. This review critically summarizes the preclinical evidence supplied for Azadirachta indica (neem) and Garcinia indica (kokum), with emphasis on glycaemic control, insulin-related pathways, oxidative stress, lipid abnormalities and organ-protective outcomes. Neem studies in chemically induced and diet-associated diabetic rodents report reductions in blood glucose, improvements in lipid indices, restoration of antioxidant enzymes and changes in insulin-signalling proteins. However, one neonatal streptozotocin model found that a 0.8% neem leaf preparation improved beta-cell morphology but did not restore glucose homeostasis, illustrating that outcomes depend on the model and preparation. Kokum studies report that aqueous fruit extract lowered fasting and postprandial glucose and restored erythrocyte glutathione in diabetic rats; other studies found glucose-, lipid- and renal-profile improvements with fruit-rind extracts, while a seed methanolic extract also reduced glucose in streptozotocin-treated rats. These findings are promising but remain preclinical. Differences in plant part, extraction solvent, dose, duration and diabetes model limit direct comparison. The evidence base lacks adequate standardization, pharmacokinetic characterization, long-term toxicology and controlled human efficacy data. Neither plant should be considered a proven substitute for established diabetes treatment. Further work should prioritize authenticated and chemically standardized extracts, reproducible dose-response studies, mechanistic validation, safety assessment and carefully designed clinical trials.*

Keywords: Azadirachta indica; Garcinia indica; neem; kokum; diabetes mellitus; antihyperglycaemic activity; oxidative stress; preclinical evidence; translational research

1. INTRODUCTION

Diabetes mellitus is a heterogeneous metabolic disease in which chronic elevation of blood glucose is associated with disturbances in carbohydrate, lipid and protein metabolism. Type 2 diabetes commonly involves insulin resistance together with inadequate compensatory insulin secretion. Persistent hyperglycaemia contributes to vascular and metabolic complications affecting the kidneys, eyes, nerves and cardiovascular system. Although established medicines are effective for many patients, the search for additional therapeutic leads continues, including the investigation of medicinal plants and food-derived bioactive compounds.

Azadirachta indica A. Juss., commonly known as neem, belongs to the family Meliaceae and is widely used in traditional systems of medicine. Different parts of the tree, particularly leaves and bark, have been investigated for

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 1, November 2026 Impact Factor: 8.2

biological activities. The supplied studies examine aqueous, ethanolic and chloroform-derived leaf preparations, as well as aqueous bark extract. Their outcomes include antihyperglycaemic effects, modulation of insulin-signalling proteins, improvement in antioxidant defence and changes in diabetes-associated complications.

Garcinia indica Choisy., commonly known as kokum, is a tropical evergreen tree of the Clusiaceae family, particularly associated with parts of western India. The fruit rind is used as food and in traditional preparations. The supplied literature identifies constituents such as garcinol, hydroxycitric acid and anthocyanin pigments, and describes antioxidant and other pharmacological activities. Direct antidiabetic evidence in the supplied set is based mainly on animal experiments using fruit, fruit rind or seed preparations.

The purpose of this review is to bring these findings together, compare the evidence for the two plants, identify important methodological limitations and outline the work needed before any clinical application can be considered.

II. REVIEW APPROACH AND SCOPE

This is a focused narrative review of the ten PDF sources supplied for the assignment. The source set includes original animal studies on neem and kokum, together with an updated pharmacological review of G. indica. The studies were grouped by plant, plant part, extraction method, experimental model, treatment duration and reported outcomes. No new animal or human data were generated. Because the supplied papers use different models and preparations, the findings are described study by study rather than pooled statistically. This is not a systematic review or meta-analysis, and no formal risk-of-bias scoring was performed.

III. PHYTOCHEMICAL AND PHARMACOLOGICAL BACKGROUND

3.1 Neem (Azadirachta indica)

Neem contains multiple classes of secondary metabolites, including limonoids and other terpenoid-related constituents, alongside phenolic compounds and flavonoids. The supplied experimental papers generally evaluate crude extracts or solvent fractions rather than a single purified antidiabetic molecule. This is important because aqueous, ethanolic and chloroform extracts can differ substantially in chemical composition and biological activity. Mishra et al. reported that the 95% ethanolic leaf extract was the most active among the preparations initially screened; subsequent fractionation identified a chloroform fraction for more detailed testing. Pérez-Gutiérrez and colleagues likewise reported stronger activity with the chloroform leaf extract than with the other solvent extracts they compared.

Proposed biological actions in the supplied neem studies include improved insulin signalling, increased glucose uptake, restoration of antioxidant enzymes, reduced lipid peroxidation and inhibition of advanced glycation end-product formation. These mechanisms are supported by experimental observations in cells and rodents, but the precise active constituents and their contribution to each effect remain incompletely established.

3.2 Kokum (Garcinia indica)

The supplied updated review describes garcinol, isogarcinol, hydroxycitric acid, xanthones and anthocyanins such as cyanidin-3-sambubioside and cyanidin-3-glucoside among the reported constituents of G. indica. The composition of an extract will depend on the plant part, maturity, processing and extraction conditions. In the antidiabetic studies, aqueous fruit extract, methanolic seed extract, and aqueous or ethanol fruit-rind extracts were examined. These are not interchangeable preparations, and results from one extract should not automatically be attributed to all kokum products.

Antioxidant activity is a recurring theme in the kokum literature. Kirana and Srinivasan focused on erythrocyte reduced glutathione (GSH), while Deore et al. discussed antioxidant potential as a possible contributor to improvements in glucose, lipid and renal parameters. Such findings suggest a possible role in limiting oxidative injury, but they do not establish that antioxidant activity alone explains the glucose-lowering effects.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 1, November 2026
Impact Factor: 8.2

IV. PRECLINICAL EVIDENCE FOR NEEM

4.1 Glycaemic control and insulin signalling

Satyanarayana et al. investigated aqueous neem leaf extract in a high-fat and fructose-associated type 2 diabetes model in male rats. The extract was administered orally at 400 mg/kg body weight once daily for 30 days. The authors reported improvement in fasting blood glucose, oral glucose tolerance, serum insulin and lipid profile. They also observed normalization of several insulin-signalling components in skeletal muscle, including the insulin receptor, insulin receptor substrate-1 (IRS-1), phosphorylated IRS-1, phosphorylated Akt and glucose transporter 4 (GLUT4). Glycogen concentration and glucose oxidation in gastrocnemius muscle were also assessed. These observations provide mechanistic evidence that the extract may influence peripheral insulin action and glucose utilization in this particular model.

Mishra et al. compared crude leaf powder and aqueous, 50% ethanolic and 95% ethanolic extracts in experimental models. The 95% ethanolic extract showed the strongest activity in the initial screening. Its chloroform fraction was then examined in more detail. The study reported increased glucose uptake in L6 muscle cells and increased IRS, AKT and GLUT4 expression at mRNA and protein levels. In rodent experiments, the fraction improved hyperglycaemia and selected lipid, hepatic and renal parameters. These findings support further investigation of neem fractions, but the active molecules and their exposure-response relationships were not established.

4.2 Lipid abnormalities and diabetic complications

Eshrat (2002) studied fresh neem leaf aqueous extract in streptozotocin-induced diabetic rats. Oral administration at 250 mg/kg body weight for 16 weeks was associated with a gradual reduction in blood glucose, improvement in serum total cholesterol, LDL cholesterol, HDL cholesterol and triacylglycerol, and improvement in body weight. The paper also reported reversal of diabetic retinopathy in the experimental animals. This is a notable complication-related observation, but it comes from a single animal study and should not be interpreted as evidence that neem reverses retinopathy in people.

Pérez-Gutiérrez et al. examined neem leaf solvent extracts in streptozotocin-induced diabetic rats over 28 days. The chloroform extract was reported to be the most active. Outcomes included improved glucose and insulin-related measures, changes in hepatic glycogen and antioxidant status, reduced lipid peroxidation and inhibition of advanced glycation end-product formation in the experimental assays. The reported findings provide a possible link between glycaemic effects, oxidative balance and nonenzymatic glycation.

4.3 Antioxidant defence

Shailey and Basir evaluated aqueous neem leaf extract (500 mg/kg) and bark extract (100 mg/kg) for 21 days in alloxan-diabetic rats. Diabetes was associated with increased lipid peroxidation and reduced activities of antioxidant enzymes in liver and kidney tissues. Treatment with neem leaf or bark extracts restored superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and glucose-6-phosphate dehydrogenase (G-6-PD) activities towards control values, while reducing markers of lipid peroxidation. These findings suggest an antioxidant effect in the tested tissues, although the study does not establish long-term prevention of clinical complications.

4.4 Conflicting evidence: beta-cell morphology without glycaemic correction

McCalla et al. evaluated a 0.8% neem leaf extract in a neonatal streptozotocin rat model. The extract improved weight gain and showed beta-cell regenerative or morphological potential, but it did not reduce blood glucose or restore glucose homeostasis. Serum insulin increased only slightly in the treated group, whereas the untreated diabetic group showed a larger increase. The authors concluded that the preparation was not sufficiently potent to treat diabetes in that model, although its beta-cell-related effects merited further study. This result is important because it demonstrates that improvements in pancreatic morphology do not necessarily translate into measurable glycaemic control.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 1, November 2026
Impact Factor: 8.2

V. PRECLINICAL EVIDENCE FOR KOKUM

5.1 Aqueous fruit extract and glutathione restoration

Kirana and Srinivasan studied aqueous G. indica fruit extract in streptozotocin-induced type 2 diabetic rats. The extract was administered orally at 100 or 200 mg/kg for four weeks. Both doses significantly reduced fasting and postprandial blood glucose and restored erythrocyte reduced glutathione. The higher dose produced a more pronounced effect. The study suggests that kokum may influence both glycaemic status and an intracellular antioxidant marker. However, the study was relatively small and short, and it did not establish whether the GSH change directly caused the reduction in glucose.

5.2 Fruit-rind extracts and renal/lipid parameters

Deore et al. investigated aqueous and ethanol extracts of G. indica fruit rind in alloxan-induced diabetic rats. The extracts were administered at 500 mg/kg daily for 21 days. The authors reported significant reductions in fasting blood glucose, total cholesterol, triglycerides, LDL cholesterol, urea and creatinine, while HDL cholesterol was not reduced in the same way. The results suggest antihyperglycaemic, antihyperlipidaemic and renal-profile benefits in this model. The study used a small number of animals per group and a relatively short treatment period; therefore, the findings should be considered preliminary.

5.3 Methanolic seed extract

Shetty and Pushpa evaluated methanolic G. indica seed extract in streptozotocin-induced diabetic albino rats. The study included extract alone and a combination with glibenclamide. Over 28 days, the extract-treated group showed a significant fall in fasting blood glucose, and the combination group also showed a reduction compared with the diabetic control group. Improvement in body weight was reported in the treated groups. This study adds evidence from a different plant part, but its results cannot be directly compared with fruit-rind or aqueous-fruit studies because the extract chemistry and experimental design differ.

5.4 Broader pharmacological context

Lim et al. (2021) reviewed the pharmacological activity of G. indica and summarized antioxidant, anti-inflammatory, hepatoprotective, cardioprotective and other experimental activities. The review is useful for understanding the plant's broader chemical and pharmacological profile. However, evidence for a broad range of biological activities should not be confused with proof of clinical antidiabetic efficacy. The antidiabetic conclusions in the present review are based primarily on the specific animal studies described above.

VI. COMPARATIVE SUMMARY OF KEY PRECLINICAL STUDIES

Plant / study	Preparation and model	Dose and duration	Main reported findings
Neem – Eshrat (2002)	Fresh-leaf aqueous extract; STZ-diabetic rats	250 mg/kg; 16 weeks	Lower glucose; improved lipid measures and body weight; reported improvement in retinopathy.
Neem – Pérez-Gutiérrez et al. (2011)	Solvent leaf extracts; STZ-diabetic rats	Chloroform fraction; 28 days	Improved glycaemic/lipid and oxidative markers; reduced lipid peroxidation and AGE formation.
Neem – Shailey & Basir (2012)	Aqueous leaf and bark extracts; alloxan-diabetic rats	Leaf 500 mg/kg; bark 100 mg/kg; 21 days	Restored antioxidant enzyme activities in liver and kidney; reduced lipid peroxidation.
Neem –	Aqueous leaf extract;	400 mg/kg; 30	Improved glycaemia, lipids and skeletal-

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 1, November 2026 Impact Factor: 8.2

Satyanarayana et al. (2015)	high-fat/fructose type 2 model	days	muscle insulin-signalling markers including IRS-1, Akt and GLUT4.
Neem – Mishra et al. (2015)	95% ethanol leaf extract and chloroform fraction; STZ/high-fructose models and L6 cells	Fraction tested in single- and multiple-dose studies	Improved glucose and selected metabolic/organ-function parameters; increased L6 glucose uptake and IRS/AKT/GLUT4 expression.
Neem – McCalla et al. (2016)	0.8% leaf extract; neonatal STZ rat model	5–13 weeks plus oral treatment phase	Improved beta-cell morphology/regenerative measures but did not restore blood glucose homeostasis.
Kokum – Kirana & Srinivasan (2010)	Aqueous fruit extract; STZ type 2 diabetic rats	100 and 200 mg/kg; 4 weeks	Reduced fasting/postprandial glucose and restored erythrocyte GSH; higher dose more pronounced.
Kokum – Deore et al. (2018)	Aqueous and ethanol fruit-rind extracts; alloxan-diabetic rats	500 mg/kg; 21 days	Reduced glucose, total cholesterol, triglycerides, LDL, urea and creatinine; HDL not similarly reduced.
Kokum – Shetty & Pushpa (2018)	Methanolic seed extract; STZ-diabetic albino rats	28-day study	Reduced fasting blood glucose; extract plus glibenclamide also improved glucose; body-weight improvement reported.

VII. POSSIBLE MECHANISMS AND INTERPRETATION

7.1 Regulation of glucose handling

The strongest direct mechanistic observations in the supplied set come from neem studies reporting changes in IRS-1, Akt and GLUT4, together with increased glucose uptake in L6 cells. These proteins participate in insulin signal transduction and glucose transport in muscle. The findings are consistent with improved peripheral glucose utilization in the studied experimental systems. Kokum studies primarily report changes in blood glucose and do not provide the same depth of insulin-signalling measurements.

7.2 Oxidative stress and glycation

Both plants have been investigated in relation to oxidative stress. Neem leaf and bark extracts restored antioxidant enzyme activities in diabetic rat tissues, and a neem chloroform fraction was reported to influence glutathione-related markers and advanced glycation end-product formation. Kokum aqueous fruit extract restored erythrocyte GSH in diabetic rats. These results are biologically relevant because oxidative stress and glycation are associated with diabetes-related tissue injury. Nevertheless, antioxidant-marker improvement is a surrogate outcome and does not by itself prove prevention of retinopathy, nephropathy or cardiovascular events.

7.3 Lipid and organ-related outcomes

Several neem and kokum studies report improvements in lipid parameters. Neem studies also describe effects on hepatic and renal function markers and an experimental retinopathy outcome. Kokum fruit-rind studies report reductions in urea and creatinine. These results may indicate broader metabolic effects beyond glucose lowering. However, serum biomarkers in rodents are not equivalent to preserved organ function in people, and histological confirmation, longer follow-up and independent replication are needed.

VIII. TRANSLATIONAL GAPS AND LIMITATIONS

Botanical and chemical standardization: The studies use different plant parts and solvents. Aqueous leaf, ethanolic leaf, chloroform fractions, bark, fruit, fruit rind and seeds have different chemical profiles. Future studies should

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 1, November 2026 Impact Factor: 8.2

authenticate botanical material and report extraction yield, chromatographic fingerprints, marker compounds and batch-to-batch consistency.

Model heterogeneity: Alloxan and streptozotocin models produce diabetes through different degrees of pancreatic beta-cell injury and do not fully reproduce human type 2 diabetes. A high-fat/fructose model may better represent insulin resistance, but no single model captures the full clinical disease. Findings should be replicated in complementary models.

Inconsistent efficacy: The neem beta-cell study reported morphological improvement without blood-glucose correction. This conflict suggests that extract composition, dose, route, model and disease stage may strongly influence outcomes. Negative or mixed findings should be retained in future reviews rather than selectively emphasizing positive results.

Dose translation and pharmacokinetics: Animal doses such as 100–500 mg/kg cannot be converted directly into a safe or effective human dose. The supplied studies do not provide sufficient absorption, distribution, metabolism, excretion or active-metabolite data to define human exposure.

Safety and interaction assessment: The supplied evidence does not establish long-term safety in humans, reproductive safety, organ toxicity thresholds or interactions with standard antidiabetic medicines. Combination studies require careful evaluation of additive glucose-lowering effects and other interactions.

Study quality and reproducibility: Many experiments use small animal groups and short treatment periods. Independent replication, transparent randomization and blinding, pre-specified outcomes, adequate sample-size calculations and complete reporting are needed.

Clinical evidence: The supplied source set does not establish efficacy or safety through robust randomized controlled trials in people with diabetes. Animal findings should therefore be regarded as hypothesis-generating, not as clinical recommendations.

IX. FUTURE RESEARCH PRIORITIES

Future investigations should begin with authenticated plant material and reproducible extraction protocols. For neem, the active fraction identified in earlier work should be chemically profiled and compared with aqueous and ethanolic preparations. For kokum, fruit rind, fruit and seed extracts should be characterized separately rather than treated as equivalent. Marker-based standardization and stability testing are essential before formulation development.

Mechanistic studies should distinguish effects on insulin secretion from effects on insulin sensitivity. Relevant outcomes include insulin, C-peptide, glucose tolerance, tissue glucose uptake, IRS-1/Akt/GLUT4 signalling, pancreatic islet histology and oxidative-stress biomarkers. Studies should include both sexes where appropriate, use more than one diabetes model and report dose-response relationships. Safety studies should examine repeated-dose toxicity, liver and kidney function, genotoxicity where justified, and potential interactions with commonly used antidiabetic medicines.

Only after adequate standardization, pharmacology and toxicology should early human studies be considered. Clinical research would need a clearly defined product, quality specifications, appropriate comparator, clinically meaningful glycaemic endpoints such as HbA1c, adequate duration, adverse-event monitoring and transparent reporting. Neem or kokum products should not replace prescribed diabetes medicines on the basis of the current preclinical evidence.

X. CONCLUSION

The supplied preclinical literature indicates that neem and kokum possess antidiabetic potential in selected experimental models. Neem has a relatively broad set of reported findings, including glucose lowering, modulation of insulin-signalling proteins, antioxidant effects, improvements in lipid and organ-function markers, and an experimental retinopathy observation. Kokum studies report glucose lowering together with restoration of erythrocyte glutathione and improvements in lipid and renal biochemical parameters. However, the evidence is heterogeneous and includes a neem study in which beta-cell morphological improvement did not translate into glycaemic correction. Differences in plant part, extraction solvent, dose and animal model prevent straightforward comparison. At present, these plants

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 1, November 2026
Impact Factor: 8.2

should be viewed as sources for further pharmacological investigation rather than established diabetes treatments. Standardization, mechanistic confirmation, rigorous safety testing and well-designed clinical trials are necessary to bridge the gap between preclinical promise and clinical use.

REFERENCES

1. Eshrat HM. Reversal of diabetic retinopathy in streptozotocin induced diabetic rats using traditional Indian anti-diabetic plant, Azadirachta indica (L.). Indian Journal of Clinical Biochemistry. 2002;17(2):115–123.
2. Pérez-Gutiérrez RM, Gómez YY, Guzmán MD. Attenuation of nonenzymatic glycation, hyperglycemia, and hyperlipidemia in streptozotocin-induced diabetic rats by chloroform leaf extract of Azadirachta indica. Pharmacognosy Magazine. 2011;7(27):254–259. doi:10.4103/0973-1296.84243.
3. Shailey S, Basir SF. Strengthening of antioxidant defense by Azadirachta indica in alloxan-diabetic rat tissues. Journal of Ayurveda and Integrative Medicine. 2012;3(3):130–136. doi:10.4103/0975-9476.100174.
4. Satyanarayana K, Sravanthi K, Shaker IA, Ponnulakshmi R. Molecular approach to identify antidiabetic potential of Azadirachta indica. Journal of Ayurveda and Integrative Medicine. 2015;6(3):165–174. doi:10.4103/0975-9476.157950.
5. Mishra A, Gautam S, Pal S, Mishra A, Rawat AK, Maurya R, Srivastava AK. Effect of Azadirachta indica leaves on streptozotocin-induced diabetes mellitus and its associated complications. World Journal of Pharmaceutical Sciences. 2015;3(3):500–511.
6. McCalla G, Parshad O, Brown PD, Gardner MT. Beta cell regenerating potential of Azadirachta indica (Neem) extract in diabetic rats. West Indian Medical Journal. 2016;65(1):13–17. doi:10.7727/wimj.2014.224.
7. Kirana H, Srinivasan BP. Aqueous extract of Garcinia indica Choisy restores glutathione in type 2 diabetic rats. Journal of Young Pharmacists. 2010;2(3):265–268. doi:10.4103/0975-1483.66806.
8. Deore AB, Sapakal VD, Naikwade NS. Antidiabetic, antihyperlipidemic and renal protective activities of Garcinia indica Linn. Clusiaceae. International Journal of Pharmaceutical Sciences and Drug Research. 2018;10(1):39–45. doi:10.25004/IJPSDR.2018.100107.
9. Shetty PK, Pushpa VH. Evaluation of the oral hypoglycemic activity of methanolic extract of Garcinia indica seeds in streptozotocin induced diabetic albino rats. International Journal of Basic & Clinical Pharmacology. 2018;7(6):1147–1152. doi:10.18203/2319-2003.ijbcp20182097.
10. Lim SH, Lee HS, Lee CH, Choi CI. Pharmacological activity of Garcinia indica (Kokum): An updated review. Pharmaceuticals. 2021;14(12):1338. doi:10.3390/ph14121338.