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Review Paper

Formulation Development and Comprehensive Characterization of an Ion-Activated Ophthalmic in Situ Gel of *Strychnos potatorum* Linn.: Integrated In Vitro Mechanistic Studies and In Vivo Antidiabetic Evaluation

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder associated with persistent hyperglycemia and progressive microvascular complications, particularly diabetic retinopathy. The present investigation aimed to scientifically evaluate the antidiabetic potential of standardized methanolic seed extract of *Strychnos potatorum* Linn. and to develop a sustained ophthalmic in situ gel formulation for possible management of diabetes-associated ocular complications. Phytochemical analysis revealed substantial phenolic (92.4 ± 2.6 mg GAE/g) and flavonoid content (47.9 ± 2.1 mg QE/g). In vitro evaluation demonstrated dose-dependent inhibition of α -amylase (IC_{50} : 178 μ g/mL) and α -glucosidase (IC_{50} : 146 μ g/mL), along with enhanced glucose uptake in L6 skeletal muscle cells (71% increase at 200 μ g/mL). In vivo assessment in streptozotocin-induced diabetic Wistar rats over 28 days showed significant reduction in fasting blood glucose, improvement in lipid profile, restoration of hepatic glycogen, and partial pancreatic β -cell regeneration ($p < 0.01$). The ophthalmic ion-activated in situ gel formulated using gellan gum exhibited acceptable physicochemical properties, sustained release (82.9% over 8 h), and was found non-irritant according to OECD TG 405 ocular irritation guidelines. The results suggest that *Strychnos potatorum* possesses multitargeted antidiabetic activity and can be successfully incorporated into a safe ophthalmic delivery system.

INTRODUCTION

Diabetes mellitus is a chronic endocrine disorder characterized by impaired glucose metabolism

resulting from insufficient insulin secretion, insulin resistance, or both. Persistent hyperglycemia leads to oxidative stress and inflammation, which progressively damage vital

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organs. Among the complications, diabetic retinopathy remains one of the leading causes of preventable blindness. Current pharmacotherapy primarily targets glycemic control but often fails to provide adequate protection against microvascular complications. In this context, medicinal plants containing polyphenolic compounds offer promising multitargeted therapeutic potential. *Strychnos potatorum* has

been traditionally used in Ayurveda for excessive thirst, urinary disturbances, and ocular irritation—clinical features closely associated with metabolic imbalance. The seeds contain flavonoids, tannins, alkaloids, and phenolic compounds known for antioxidant and enzyme inhibitory effects. However, systematic pharmacological validation and formulation-based delivery strategies remain underexplored.



Fig1 *Strychnos potatorum* Linn.

1. Botanical Profile Description

Strychnos potatorum Linn. , a member of the family Loganiaceae, is a deciduous tree of moderate size that generally grows to a height of approximately 10–15 meters. The tree is distinguished by its straight trunk and coarse greyish-brown bark. Its branches spread outward, forming a moderately dense canopy. Younger plant parts are typically smooth and hairless, whereas older portions become hard and woody with maturity. The leaves are simple and arranged oppositely along the stem. They are elliptic to ovate in shape, possessing entire margins and a smooth surface texture. The leathery nature of the leaves, along with clearly visible venation, enables the plant to withstand dry climatic conditions. The flowers are small, greenish-white in color, and usually occur in axillary or terminal cymes. After

the flowering stage, the plant produces spherical berries that contain one or occasionally two seeds. The seeds represent the most therapeutically important component of the plant. They are flat, disc-shaped, and covered with fine silky hairs, which provide them with a distinctive appearance. Traditionally, these seeds have been utilized in various medicinal preparations, particularly in ophthalmic treatments and in the purification of water due to their natural clarifying properties. Geographically, *Strychnos potatorum* is widely distributed across the Indian subcontinent and neighboring regions of South Asia. It commonly grows in dry deciduous forests, scrublands, and plains, preferring well-drained soils and semi-arid environmental conditions. In India, the species is frequently found in states such as Andhra Pradesh, Tamil Nadu, Karnataka, Maharashtra, Madhya Pradesh, and certain parts of

Uttar Pradesh. The species demonstrates considerable adaptability to diverse ecological conditions, which contributes to its broad distribution and sustained availability. Its prevalence in areas with long-standing traditional medical practices has further enhanced its recognition as an important medicinal plant. The wide geographical presence of *Strychnos potatorum* continues to support ongoing research into its therapeutic and pharmaceutical potential.

2. MATERIALS AND METHODS

2.1 Plant Material and Extraction

Authenticated seeds were shade-dried, powdered, and extracted using Soxhlet apparatus with 70% methanol for 8 hours. The extract was concentrated under reduced pressure.

Percentage yield: 12.9% w/w.

2.2 Phytochemical Standardization

Table :1 Phytochemical Standardization

Parameter	Result
Total Phenolic Content	92.4 ± 2.6 mg GAE/g
Total Flavonoid Content	47.9 ± 2.1 mg QE/g
Alkaloids	Present
Tannins	Present
Saponins	Present

3. In Vitro Antidiabetic Evaluation

3.1 α -Amylase Inhibition

Table2 α -Amylase Inhibition

Concentration (μ g/mL)	% Inhibition
50	23.7 ± 1.4
100	41.5 ± 2.0

200	64.8 ± 2.5
400	80.4 ± 2.7
Acarbose	85.2 ± 2.2

3.2 Glucose Uptake in L6 Myotubes

Table3 Glucose Uptake in L6 Myotubes

Treatment	% Increase vs Control
Control	100
Extract 100 μ g/mL	135 ± 5
Extract 200 μ g/mL	171 ± 6
Metformin	186 ± 7

4. In Vivo Antidiabetic Study

4.1 Experimental Design

- Wistar rats (n = 6/group)
- Streptozotocin 45 mg/kg (i.p.)
- 28-day treatment

Groups:

1. Normal control
2. Diabetic control
3. Extract 200 mg/kg
4. Extract 400 mg/kg
5. Metformin 100 mg/kg

4.2 Fasting Blood Glucose (mg/dL)

Table 4 Fasting Blood Glucose

Group	Day 0	Day 14	Day 28
Normal	95 ± 4	96 ± 3	94 ± 3
Diabetic	285 ± 9	322 ± 11	351 ± 12
Extract 200	282 ± 8	214 ± 7	158 ± 6
Extract 400	287 ± 7	181 ± 6	128 ± 5
Metformin	284 ± 9	165 ± 5	111 ± 4



Significance: $p < 0.01$ vs diabetic control.

4.3 Lipid Profile (Day 28)

Table5 Lipid Profile

Parameter	Diabetic	Extract 400	Metformin
Total Cholesterol	238 ± 8	170 ± 5	154 ± 4
Triglycerides	209 ± 7	145 ± 5	138 ± 4
HDL	26 ± 2	44 ± 3	48 ± 2

4.4 Hepatic Glycogen

Table6 Hepatic Glycogen

Group	mg/g tissue
Normal	49.3 ± 2.1
Diabetic	18.9 ± 1.7
Extract 400	42.6 ± 2.4

5. Development of Ophthalmic In Situ Gel

5.1 Formulation Composition

- Gellan gum: 0.5% w/v
- HPMC: 0.3% w/v
- Extract equivalent: 1% w/v
- Benzalkonium chloride: 0.01%
- pH adjusted to 7.2

5.2 Physicochemical Evaluation

Table5 Physicochemical Evaluation

Parameter	Result
Appearance	Clear
pH	7.2 ± 0.1
Drug Content	$98.1 \pm 1.4\%$

Gelation Time	19 sec
Viscosity (sol)	37 cps
Viscosity (gel)	176 cps
Drug Release (8 h)	82.9%
Release Model	Higuchi ($R^2 = 0.968$)

5.3 Ocular Irritation Study (OECD TG 405)

Mean Scores (24–72 h average)

Table6 Ocular Irritation Study

Parameter	Mean Score
Corneal Opacity	0.00
Iris	0.00
Conjunctival Redness	0.25
Chemosis	0.12
Discharge	0.00

DISCUSSION

The present investigation was designed to integrate pharmacological validation with advanced ophthalmic drug delivery development using *Strychnos potatorum* Linn. seed extract as a candidate phytotherapeutic agent. The results collectively demonstrate that the extract possesses significant antidiabetic activity mediated through complementary mechanisms, and that it can be successfully incorporated into a stable, ion-activated ophthalmic in situ gel system with favorable safety characteristics. The in vitro enzyme inhibition findings provide initial mechanistic insight into the antihyperglycemic potential of the extract. The observed dose-dependent inhibition of α -amylase and α -glucosidase suggests a capacity to delay intestinal carbohydrate digestion and subsequent glucose absorption. Such inhibition is clinically relevant because suppression of postprandial glucose

excursions is a key therapeutic target in diabetes management. The IC_{50} values obtained in this study indicate moderate yet significant inhibitory potency, likely attributable to the high phenolic and flavonoid content identified during phytochemical standardization. Polyphenolic compounds are known to interact with digestive enzymes through hydrogen bonding and hydrophobic interactions, thereby reducing catalytic efficiency. In addition, flavonoids may modulate glucose transporter activity and intracellular signaling pathways involved in carbohydrate metabolism. The glucose uptake assay performed in L6 skeletal muscle cells further strengthens the mechanistic understanding of the extract's action. Enhancement of glucose uptake suggests improved peripheral utilization, potentially mediated through insulin-sensitizing pathways or upregulation of GLUT4 translocation. Skeletal muscle represents a major site of insulin-dependent glucose disposal; therefore, stimulation of glucose uptake at this level reflects a physiologically meaningful antidiabetic effect. The magnitude of improvement observed in treated cells indicates that the extract does not act solely through enzyme inhibition but also influences cellular metabolic pathways. The *in vivo* streptozotocin-induced diabetic model provided translational validation of the *in vitro* findings. Streptozotocin selectively damages pancreatic β -cells, resulting in persistent hyperglycemia and metabolic disturbances resembling type 1 diabetes with certain features of type 2 metabolic dysfunction. The significant reduction in fasting blood glucose observed in extract-treated groups demonstrates systemic antihyperglycemic efficacy. Notably, the higher dose exhibited substantial improvement comparable to standard metformin treatment. Restoration of hepatic glycogen levels indicates improved insulin sensitivity and enhanced glucose storage capacity in the liver. The improvement in

lipid parameters, including reduced total cholesterol and triglycerides along with elevated HDL levels, suggests beneficial modulation of diabetic dyslipidemia. Since dyslipidemia contributes to oxidative stress and vascular damage, its correction may indirectly protect against diabetic microvascular complications. Histopathological evaluation revealed partial regeneration and structural restoration of pancreatic islets in treated animals. Although complete recovery was not observed, preservation of islet architecture implies cytoprotective or regenerative activity. This protective effect may be linked to antioxidant mechanisms, given the substantial phenolic content of the extract. Oxidative stress plays a pivotal role in β -cell dysfunction due to the inherently low antioxidant defense capacity of pancreatic tissue. Therefore, phytoconstituents with free radical scavenging properties may attenuate cellular damage and improve functional recovery. Beyond systemic antidiabetic activity, the formulation aspect of this research adds translational value. Diabetic retinopathy involves chronic microvascular injury, inflammation, and oxidative stress within ocular tissues. Conventional eye drops often suffer from rapid precorneal elimination and limited bioavailability. The ion-activated *in situ* gel system developed in this study addresses these limitations by undergoing sol-to-gel transition upon contact with tear fluid ions. This transition increases viscosity and prolongs residence time on the ocular surface, enhancing drug availability. Physicochemical characterization confirmed that the formulation maintained a near-physiological pH and appropriate viscosity, ensuring ocular compatibility and patient comfort. Sustained release behavior following Higuchi kinetics indicates diffusion-controlled drug release from the gel matrix. Prolonged release over eight hours may reduce dosing frequency and improve therapeutic compliance. Importantly, ocular

irritation assessment conducted according to OECD TG 405 guidelines demonstrated absence of corneal opacity or significant conjunctival damage. Mild transient redness resolved spontaneously, supporting the safety of the developed formulation. The integration of pharmacological evaluation with drug delivery development represents a strength of this investigation. Many herbal studies remain confined to extract-level biological testing without addressing formulation challenges or safety validation. By combining in vitro enzyme studies, cellular assays, in vivo diabetic modeling, histopathology, formulation optimization, release kinetics, and ocular safety testing, the present work establishes a comprehensive preclinical framework. However, while the findings are promising, mechanistic pathways at the molecular level require further elucidation. The involvement of insulin receptor signaling, AMP-activated protein kinase activation, inflammatory cytokine modulation, and oxidative stress biomarkers were not directly measured. Future investigations incorporating molecular assays, gene expression studies, and oxidative stress markers would strengthen mechanistic conclusions. Overall, the results demonstrate that *Strychnos potatorum* seed extract exhibits multitargeted antidiabetic potential and can be effectively delivered through an ophthalmic in situ gel system. This dual pharmacological and formulation-based approach provides a foundation for further translational development in managing diabetes-associated ocular complications.

7. Research Gap

Despite extensive traditional usage of *Strychnos potatorum* in metabolic and ocular conditions, several critical scientific gaps existed prior to this investigation:

1. Lack of Integrated Pharmacological Validation:

Previous studies primarily focused on isolated phytochemical identification or basic antioxidant screening. Comprehensive evaluation combining enzyme inhibition, cellular glucose uptake, and in vivo diabetic modeling had not been systematically performed.

2. Absence of Ocular Delivery Research:

Although the plant is traditionally associated with ocular applications, no prior study had developed a modern ophthalmic in situ gel formulation incorporating standardized extract.

3. Limited Mechanistic Insight:

Earlier reports lacked mechanistic exploration at both enzymatic and cellular levels. The present study addresses this gap by correlating digestive enzyme inhibition with peripheral glucose utilization and systemic glycemic control.

4. Insufficient Safety Assessment:

Standardized ocular irritation testing under internationally accepted guidelines (OECD TG 405) had not been reported for this plant extract in ophthalmic dosage form.

5. Formulation–Pharmacology Correlation Gap:

Most herbal antidiabetic research remains disconnected from drug delivery innovation. This study bridges pharmacodynamics with formulation science, demonstrating how bioactive extracts can be translated into clinically relevant dosage forms.

6. Need for Targeted Therapy in Diabetic Retinopathy:

There is limited research exploring plant-derived agents specifically formulated for



prolonged ocular retention in diabetic conditions. The developed ion-activated gel addresses the challenge of short ocular residence time seen with conventional eye drops.

CONCLUSION

The present study successfully established a systematic scientific framework for evaluating the antidiabetic potential of *Strychnos potatorum* Linn. seed extract and translating it into a novel ophthalmic drug delivery system. Through integrated phytochemical standardization, mechanistic in vitro assays, in vivo diabetic modeling, and formulation development, the research provides multidimensional evidence supporting the therapeutic relevance of this medicinal plant. The extract demonstrated significant inhibition of α -amylase and α -glucosidase enzymes, indicating its capacity to reduce postprandial hyperglycemia through delayed carbohydrate digestion. Enhancement of glucose uptake in skeletal muscle cells further suggested improved peripheral glucose utilization. In the streptozotocin-induced diabetic rat model, sustained administration resulted in marked reduction in fasting blood glucose levels, correction of dyslipidemia, restoration of hepatic glycogen stores, and partial preservation of pancreatic islet architecture. These findings collectively confirm that the extract exerts antihyperglycemic effects through complementary mechanisms involving both metabolic regulation and possible cytoprotective activity. Beyond systemic pharmacological validation, the study advances translational applicability by developing an ion-activated ophthalmic in situ gel. The formulation demonstrated appropriate physicochemical properties, rapid gelation upon contact with simulated tear fluid, and sustained drug release over an extended period. Importantly, ocular irritation assessment conducted under

standardized OECD guidelines confirmed the safety and tolerability of the developed system. The sustained release profile and prolonged precorneal retention suggest potential advantages over conventional ophthalmic solutions, particularly in conditions requiring continuous ocular exposure. The novelty of this research lies in its integrative approach—combining phytopharmacology with modern ocular drug delivery science. While most herbal investigations remain confined to extract-level biological evaluation, this work bridges the gap between traditional medicinal claims and pharmaceutical formulation development. The findings provide a strong preclinical basis for further molecular investigations and eventual clinical translation. In summary, *Strychnos potatorum* seed extract exhibits promising antidiabetic activity and can be effectively formulated into a safe and stable ophthalmic in situ gel system. This strategy may contribute to the development of supportive therapeutic options for managing diabetes-associated ocular complications. Future studies focusing on molecular pathway elucidation, long-term toxicity assessment, and controlled clinical trials will be essential to validate its clinical applicability.

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