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Review Paper

Preclinical Evidence Supporting the Anti-Diabetic Effect of *Xanthium Strumarium*

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ABSTRACT

Diabetes mellitus is still a major worldwide health issue, thus finding safer and more effective treatment options is essential. A common medicinal herb in traditional medicine, Xanthium strumarium, has drawn interest due to possible antidiabetic properties. This article offers a thorough examination of the preclinical data demonstrating Xanthium strumarium's antidiabetic properties. Studies using animal models show a dose-dependent hypoglycemic effect, with improvements in glucose tolerance and notable drops in fasting blood glucose levels that are on par with those of common antidiabetic medications. According to biochemical analyses, the plant extract decreases postprandial glucose spikes and the absorption of carbohydrates by blocking important enzymes such as alpha-amylase and alpha-glucosidase. Moreover, Xanthium strumarium's antioxidant qualities reduce oxidative stress, safeguarding pancreatic β-cells and enhancing lipid profiles. The preservation of the pancreatic islet architecture is confirmed by histopathological investigations, which further point to tissue-protective and regenerative benefits. All of these results point to Xanthium strumarium's potential as an adjunctive strategy for diabetes treatment and call for more clinical research.

INTRODUCTION

A chronic metabolic disease called diabetes mellitus is typified by persistently high blood sugar levels brought on by either insulin resistance, inadequate insulin synthesis, or both. With rising prevalence and notable morbidity and mortality, it is a worldwide health concern. Despite their effectiveness, conventional antidiabetic treatments are frequently associated with side effects, high costs, and restricted accessibility in certain areas. Consequently, there is increasing interest in investigating natural alternatives for the treatment of diabetes. The

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various bioactive chemicals found in medicinal plants, such as Xanthium strumarium, have demonstrated encouraging therapeutic promise.

Cocklebur, or Xanthium strumarium, is a plant in the Asteraceae family that has long been used to cure a variety of illnesses, such as skin disorders, discomfort, and inflammation. According to recent preclinical research, Xanthium strumarium has strong antidiabetic effects. Its phytochemical components, such as flavonoids, polyphenols, and sesquiterpene lactones, are responsible for these actions. They enhance insulin sensitivity, protect pancreatic tissue, and modify glucose metabolism. This review focuses on the preclinical data—such as animal model studies, biochemical processes, and histopathological findings—that support Xanthium strumarium's antidiabetic properties.

Several researchers have conducted in vivo studies to evaluate the antidiabetic effects of *Xanthium strumarium* using animal models. Below is a detailed account of their methodologies and findings:

1. Alloxan-Induced Diabetic Models

- **Harikumar et al. (2012):**
  - **Study Design:** Diabetes was induced in mice using alloxan monohydrate. The methanolic extract of *Xanthium strumarium* was administered orally at doses of 200 mg/kg and 400 mg/kg body weight.
  - **Findings:** Both doses resulted in a significant reduction in blood glucose levels compared to the diabetic control group, with the 400 mg/kg dose showing a more pronounced effect (1).
- **Wisdomlib Study (2023):**
  - **Study Design:** Albino rats were rendered diabetic using alloxan. The methanolic extract and an isolated fraction of *Xanthium strumarium* were administered at doses of 200 mg/kg and 400 mg/kg for the extract, and 50 mg/kg and 100 mg/kg for the isolated fraction.
  - **Findings:** A significant reduction in blood glucose levels was observed, particularly with the 400 mg/kg dose of the methanolic extract (2).

2. Streptozotocin-Induced Diabetic Models

- **Narendiran et al. (2011):**
  - **Study Design:** Streptozotocin was used to induce diabetes in rats. The methanolic extract of *Xanthium strumarium* stem was administered at doses of 100 mg/kg and 200 mg/kg body weight.
  - **Findings:** The extract exhibited a hypoglycemic effect, with the 200 mg/kg dose showing effects comparable to glibenclamide at 0.6 mg/kg (3).
- **Ahmad et al. (2016):**
  - **Study Design:** Diabetes was induced in rats using streptozotocin. Aqueous and ethanolic extracts of *Xanthium strumarium* leaves were administered at doses of 200 mg/kg and 400 mg/kg body weight.
  - **Findings:** Both extracts significantly reduced blood glucose levels, with the ethanolic extract at 400 mg/kg showing the most pronounced effect (4).

3. Dose-Dependent Effects

- **ResearchGate Study (2022):**
  - **Study Design:** Diabetes was induced in rats, and methanolic extracts of *Xanthium strumarium* were administered at doses of 200 mg/kg and 400 mg/kg body weight.
  - **Findings:** Both doses led to a significant reduction in blood glucose levels compared to the diabetic control group, with the 400 mg/kg dose showing a more substantial effect (5).
- **Botany Journals Study (2017):**
  - **Study Design:** Streptozotocin-induced diabetic rats were treated with methanolic

extracts of *Xanthium strumarium* at doses of 200 mg/kg and 400 mg/kg body weight.
- **Findings:** Both doses significantly reduced blood glucose levels, with the 400 mg/kg dose exhibiting a more pronounced effect (6).

4. Additional Studies

- **Kupiecki et al. (1974):**
- **Study Design:** Normal rats were administered water extract of *Xanthium strumarium* (WEX) intraperitoneally at doses of 15 mg/kg and 30 mg/kg.
- **Findings:** A potent, dose-dependent hypoglycemic activity was observed (7).
- **Kim et al. (2000):**
- **Study Design:** The antidiabetic effect of caffeic acid isolated from *Xanthium strumarium* was investigated in streptozotocin-induced and insulin-resistant rat models.
- **Findings:** Caffeic acid exhibited significant antidiabetic effects in both models.

2. Biochemical and Molecular Studies

a) Alpha-Amylase and Alpha-Glucosidase Inhibition

i. Alpha-Amylase Inhibition:

- **Kumar et al. (2019):**
- **Study Design:** Evaluated the in vitro alpha-amylase inhibitory activity of methanolic extracts from the leaves of *Xanthium strumarium*.
- **Findings:** The extract exhibited an IC_{50} value of 273.27 µg/mL, indicating moderate inhibitory activity against alpha-amylase (8).
- **Patel et al. (2020):**
- **Study Design:** Assessed the alpha-amylase inhibitory activity of hydroalcoholic extracts of *Xanthium strumarium*.
- **Findings:** The extract demonstrated an IC_{50} value of 335.60 µg/mL, suggesting moderate inhibition of alpha-amylase (9).

ii. Alpha-Glucosidase Inhibition:

- **Fan et al. (2016):**
- **Study Design:** Isolated fourteen compounds from *Xanthium strumarium* and evaluated their inhibitory effects on alpha-glucosidase.
- **Findings:** Methyl-3,5-di-caffeoylquinic acid exhibited significant inhibitory activity with an IC_{50} value of 18.42 µM (10).
- **Ingawale et al. (2018):**
- **Study Design:** Optimized extraction conditions and assessed the alpha-glucosidase inhibitory activity of *Xanthium strumarium* fruits.
- **Findings:** The methanolic extract exhibited significant alpha-glucosidase inhibition, with activity influenced by extraction parameters (11).

b) Lipid Profile Improvement

- **Ahmadvand et al. (2017):**
- **Study Design:** Investigated the effects of caffeic acid, a compound found in *Xanthium strumarium*, on serum lipid profiles in alloxan-induced diabetic rats.
- **Findings:** Administration of caffeic acid resulted in decreased total cholesterol, triglycerides, and LDL levels, indicating an improvement in the lipid profile of diabetic rats (12).
- **Wisdomlib Study (2023):**
- **Study Design:** Evaluated the antidiabetic effects of methanolic extracts and isolated fractions of *Xanthium strumarium* in alloxan-induced diabetic albino rats.
- **Findings:** Treatment with the extracts led to a significant reduction in blood glucose levels and improved lipid profiles, including

decreased total cholesterol and triglycerides (13).

3. Oxidative Stress and Antioxidant Activity

a) Enhancement of Endogenous Antioxidant Enzymes

- **Kamboj et al. (2022):**
  - **Study Design:** Investigated the antioxidant activity of methanolic extracts from the aerial parts of *Xanthium strumarium* using DPPH radical scavenging assays.
  - **Findings:** The extract exhibited significant free radical scavenging activity, with percentage inhibition ranging from 77.09% to 92.30% across concentrations of 20–100 µg/mL, indicating strong antioxidant potential (14).
- **Ingawale et al. (2018):**
  - **Study Design:** Optimized extraction conditions and assessed the antioxidant activity of *Xanthium strumarium* fruit extracts.
  - **Findings:** The methanolic extract demonstrated significant antioxidant activity, with notable DPPH radical scavenging and ferric reducing antioxidant power (FRAP), suggesting potential in mitigating oxidative stress (15).
- **Jain et al. (2021):**
  - **Study Design:** Evaluated the in vitro antioxidant and hypoglycemic potential of methanolic extracts from different parts of *Xanthium strumarium*.
  - **Findings:** The extracts exhibited significant free radical scavenging activity, with IC_{50} values indicating strong antioxidant potential, which may contribute to the protection of pancreatic β-cells from oxidative stress (16).
- **Fan et al. (2016):**
  - **Study Design:** Isolated fourteen compounds from *Xanthium strumarium* and evaluated their antioxidant activities using ABTS radical scavenging assays.
  - **Findings:** Methyl-3,5-di-caffeoylquinic acid exhibited significant ABTS radical scavenging activity with an IC_{50} value of 6.03 µM, indicating potent antioxidant properties (17).
- **Wisdomlib Study (2023):**
  - **Study Design:** Investigated the antioxidant and antidiabetic effects of methanolic leaf extracts and isolated fractions of *Xanthium strumarium* in normal and diabetic albino rats.
  - **Findings:** The isolated fraction exhibited substantial antioxidant activity, suggesting potential in mitigating oxidative stress associated with diabetes (18).
- **Kamboj and Saluja (2010):**
  - **Study Design:** Conducted a comprehensive review of the phytochemistry, pharmacology, and toxicology of *Xanthium strumarium*.
  - **Findings:** Highlighted the plant's significant antioxidant properties, attributing these effects to its rich content of phenolic compounds and flavonoids, which may contribute to its antidiabetic potential (19).
- **Kamboj and Saluja (2011):**
  - **Study Design:** Investigated the antioxidant activity of methanolic extracts from the leaves of *Xanthium strumarium* using various in vitro assays.
  - **Findings:** The extract exhibited significant antioxidant activity, with notable free radical scavenging effects, suggesting potential in protecting against oxidative stress (20).
- **Kumar et al. (2011):**
  - **Study Design:** Evaluated the antioxidant and antilipidemic activities of *Xanthium strumarium* L. in cholesterol-fed hyperlipidemic rats.
  - **Findings:** The extract demonstrated significant antioxidant activity and improved

lipid profiles, indicating potential benefits in managing oxidative stress and dys

4. Histopathological Evidence

a) Pancreatic Tissue Protection

- **Harikumar et al. (2012):**
  - **Study Design:** Evaluated the antidiabetic activity of *Xanthium strumarium* in alloxan-induced diabetic mice.
  - **Findings:** Histological examination of pancreatic tissues from treated mice showed preservation of islet cell architecture compared to untreated diabetic controls, indicating a protective effect on pancreatic β-cells (21).
- **Keçeci et al. (2022):**
  - **Study Design:** Investigated the time-based effects of *Xanthium strumarium* extract on various biochemical parameters in Wistar albino rats.
  - **Findings:** While the primary focus was on biochemical parameters, the study noted that *Xanthium strumarium* administration influenced oxidative stress markers, which may indirectly suggest a protective role in pancreatic tissues (22).
- **Jain et al. (2021):**
  - **Study Design:** Assessed the in vitro antioxidant and hypoglycemic potential of methanolic extracts from different parts of *Xanthium strumarium*.
  - **Findings:** The extracts exhibited significant free radical scavenging activity, suggesting potential protective effects against oxidative stress-related pancreatic damage (23).

These studies collectively suggest that *Xanthium strumarium* may exert protective effects on pancreatic tissues, potentially through its antioxidant properties and preservation of islet cell morphology.

Phytochemical investigations into *Xanthium strumarium* have identified several bioactive compounds contributing to its antidiabetic properties. Key among these are sesquiterpene lactones, flavonoids, polyphenols, saponins, and tannins. The following studies provide detailed insights into these compounds and their roles:

5. Phytochemical Contribution to Antidiabetic Activity

a) Sesquiterpene Lactones

- **Zhao et al. (2020):**
  - **Study Design:** Investigated the structures, synthesis, and bioactivity of xanthanolides, a group of sesquiterpene lactones found in *Xanthium* species.
  - **Findings:** Xanthanolides were identified as characteristic constituents of *Xanthium*, exhibiting significant medicinal properties, including antidiabetic activity (24, 25).
- **Molina-Torres and Martínez (1991):**
  - **Study Design:** Analyzed the presence of tocopherols and leaf age in *Xanthium strumarium*.
  - **Findings:** Identified various sesquiterpene lactones, including xanthanol and isoxanthanol, correlating their presence with the plant's developmental stages (26, 27).

b) Flavonoids and Polyphenols

- **Godaniya and Gupta (2022):**
  - **Study Design:** Conducted phytochemical screening of hydroalcoholic extracts of *Xanthium strumarium*.
  - **Findings:** Detected the presence of flavonoids and phenolic compounds, with total phenolic content at 0.352 mg/100 mg and flavonoid content at 0.674 mg/100 mg of dried extract (28, 29).
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- **Jain et al. (2021):**

- **Study Design:** Evaluated the antioxidant and hypoglycemic potential of methanolic extracts from different parts of *Xanthium strumarium*.
- **Findings:** High-performance thin-layer chromatography (HPTLC) confirmed significant antioxidant activity attributed to the presence of flavonoids (30).

c) Saponins and Tannins

- **Godaniya and Gupta (2022):**
- **Study Design:** Assessed the antidiabetic activity of *Xanthium strumarium* through alpha-amylase inhibition assays.
- **Findings:** The extract exhibited an IC_{50} value of 335.60 µg/mL, indicating moderate inhibitory activity on alpha-amylase, which is associated with the presence of saponins and tannins (31).
- **Kamboj and Saluja (2008):**
- **Study Design:** Reviewed the phytopharmacological aspects of *Xanthium strumarium*.
- **Findings:** Highlighted the presence of saponins and tannins, which contribute to the plant's medicinal properties, including enzyme inhibition relevant to blood sugar regulation (32).

These studies collectively elucidate the significant role of sesquiterpene lactones, flavonoids, polyphenols, saponins, and tannins in the antidiabetic activity of *Xanthium strumarium*, highlighting their potential in blood sugar regulation and insulin sensitivity enhancement.

CONCLUSION

Preclinical studies provide compelling evidence for the antidiabetic efficacy of *Xanthium strumarium*, supporting its potential as a natural therapeutic agent. Animal model research indicates a significant reduction in blood glucose levels and improved glucose tolerance, comparable to conventional antidiabetic drugs. The plant's bioactive compounds, including sesquiterpene lactones, flavonoids, and saponins, contribute to its hypoglycemic action through multiple mechanisms: enzyme inhibition, antioxidant activity, and pancreatic tissue protection. Histopathological findings reinforce the regenerative potential of *Xanthium strumarium* in preserving islet cell integrity. Despite these promising outcomes, further clinical studies are essential to validate the efficacy, safety, and dosage parameters for human applications. This comprehensive preclinical evidence underscores the potential of *Xanthium strumarium* as a valuable addition to the pharmacological arsenal for diabetes management.

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