Ameliorative Effect of Fluoride and Therapeutic Potential of Neem (Azadirachta indica) in Managing Diet-Induced Diabetes Mellitus

DR. RAJESH VERMA[1], NAVEENA YADAV[2]
[1]*Assistant Professor, Department of Zoology, Veer Kunwar Singh University, Ara*
[2]*Research Scholar*

Abstract- ***Diabetes mellitus (DM) is a chronic metabolic disorder marked by high blood glucose levels, often due to impaired insulin function or production, which contributes significantly to global morbidity and mortality. Factors like diet, lifestyle, and environmental exposures, such as fluoride, can influence the development and progression of DM. Traditional medicinal plants like Neem (Azadirachta indica) have garnered attention for their therapeutic potential in managing diabetes. Known for its anti-inflammatory, anti-diabetic, and antioxidant properties, Neem is widely used in Ayurvedic medicine. This study explores both the ameliorative effects of fluoride and the therapeutic efficacy of Neem in managing diet-induced diabetes. The research aims to identify the bioactive compounds in Neem responsible for its anti-diabetic effects, understand their role in glucose metabolism improvement, review clinical studies on its therapeutic impact, and propose strategies for integrating Neem with conventional diabetes treatments. A comprehensive literature review and experimental trials on Sprague-Dawley rats are designed. Diabetic and control groups will be established, with the diabetic group receiving Neem extract while the control receives a standard antidiabetic. Blood glucose, serum insulin, lipid profiles, inflammatory markers, and histological analysis of pancreatic tissue will be evaluated. Key Neem compounds—nimbin, nimbidin, and azadirachtin—are expected to support β-cell insulin release, enhance tissue glucose uptake, and reduce intestinal glucose absorption. This study suggests that Neem, at an optimized dose, could serve as an adjunctive therapy for diet-induced DM. Findings underscore the need for well-designed, long-term studies to establish safe dosage equivalents for human use.***

Indexed Terms- ***Diabetes Mellitus, Azadirachta indica, Antidiabetic, Ameliorative, Fluoride, Inflammatory, Neem, HPLC.***

I. INTRODUCTION

DM is a chronic metabolic condition that affects the high blood sugar that is caused by deficiencies in insulin secretion. To put it another way, flaws of both impacts on blood sugar are lowered treatment targets with regard to diabetes mellitus. Asthma is rising worldwide, posing a major public health issue, especially in poorer countries. Food and lifestyle variables including high-calorie meals, inactivity, and obesity are the main causes of diabetes-related illnesses' fast rise. Since then, the need for appropriate treatment of this chronic illness and preventative efforts to avoid its development has been increasingly essential on a daily basis. This is because the rates of diabetes have been rising higher each year (the World Health Organization states that the worldwide diabetes rate has nearly tripled since 1980).

1.1 Global Health Concern

DM is one of the world's biggest health problems, is rising due to lifestyle and diet. The International Diabetes Federation predicts 700 million diabetics by 2045, up from 463 million in 2019. Chronic hyperglycemia in DM may lead to cardiovascular disease, renal failure, neuropathy, and retinopathy. Indeed, obesity, sedentary lifestyle, and high-calorie diets are linked to rising DM rates.

In today's world, individuals eat a lot of fast food with sugar and saturated fats and don't exercise. Both are risk factors for insulin resistance and obesity, DM symptoms. Urbanization and automation have reduced physical work, Ameliorative Effect of Fluoride, adding to this. Stress—mental and physical—has

contributed to DM from its birth and maintenance. DM is managed by lifestyle modifications, medication, and blood-glucose monitoring. Despite advances in research, DM persists and requires new approaches to manage it.

1.2 Limitations of Conventional Treatments

Oral hypoglycemic medicines and insulin therapy are the main DM therapies, although they have side effects. Most common adverse effects include weight gain, hypoglycemia, gastrointestinal intolerance, and increasing cardiac events. Over time, these medications lose efficacy and need greater doses or combinations. Such difficulties highlight the need for effective, low-side-effect medicines.

Oral hypoglycemic medicines like sulfonylureas and metformin are often used to manage blood glucose, however they might produce side effects. Insulin treatment causes weight gain and significant hypoglycemia in many people. DM is progressive, therefore polypharmacy to control comorbidities increases medication burden and adverse effects. Thus, safer and longer-lasting DM treatments must be investigated now.

1.3 Neem (Azadirachta indica) in Traditional Medicine

The Indian subcontinent's Neem tree, Azadirachta indica, has long been used in Ayurveda, one of the oldest medical systems. Indian traditional medicine recognizes neem's antibacterial, anti-inflammatory, antimalarial, and antidiabetic qualities. Neem contains several bioactive compounds, including nimbin, nimbidin, azadirachtin, and others, making it a helpful medicine. These chemicals are abundant in neem leaves, bark, seeds, and flowers. Ayurvedic medicine uses neem. Many traditional medicine organizations utilize neem to treat metabolic problems, skin ailments, and infections. Neem is very effective in treating type two diabetes, one of its most significant uses. Neem extracts reduce blood sugar in diabetics and animal models, according to studies. Neem's anti-diabetic effects come from many mechanisms. Neem compounds stimulate insulin secretion, increase glucose uptake in peripheral tissue, and limit intestinal glucose absorption, as well as reduce oxidative stress and inflammation, two major causes of diabetes.

II. OBJECTIVES

1. Neem leaves include bioactive compounds such nimbin, nimbolid, and azadirachtin with therapeutic properties. These metabolites should be separated, studied using HPLC, MS, and NMR, and tested for antidiabetic potential to enhance natural diabetes management.
2. We assess the impact of neem extracts and isolated compounds on glucose homeostasis, including insulin secretion, sensitivity, tissue-specific glucose absorption, and glucosidase inhibition. Neem's blood glucose-lowering properties will be evaluated in vitro on cell lines and animal diabetic models.
3. Investigate whether Neem aids conventional antidiabetic medicine management for diabetics. It explores how Neem affects diabetics' insulin resistance.
4. Optimal dosage, formulation, and route for Neem extract administration via clinical and mechanistic studies. It studies patient outcomes, drug-drug interactions, and Neem's usage with existing antidiabetic regimens to enhance diabetes control and quality of life.

III. LITERATURE REVIEW

Eating habits are linked to metabolic diseases like DM. High DM prevalence is often linked to excessive refined sugar and unhealthy fat consumption. High blood glucose is caused by insulin resistance in type 2 diabetes. Central obesity and insulin resistance result from high-fat, high-carbohydrate diets (Snel et al. 2012). Pancreatic β-cells generate insulin. Insulin production may decrease in β-cells due to prolonged hyperglycemia, oxidative stress, and proinflammatory conditions. Poor diets, particularly high-calorie processed meals without critical nutrients, induce early insulin resistance (Poitout & Robertson [2002]). Diabetes groups often report chronic low-grade inflammation, which allows obese patients to develop DM. High-fat diets may promote inflammation in adipose tissue, resulting in cytokines like TNF-α and IL-6 that can hinder insulin signaling and worsen IR (Hotamisligil, 2006).

Neem (Azadirachta indica) has been used in traditional medicine for centuries, and Ayurveda is even more

popular owing to its healing properties. Traditional DS uses include these and many more; current scientific research have proven some of these, especially their potential in DM. [12]. Pharmacological Activity of Neem Leaf and Plant Constituents Neem includes bioactive substances such Nimbidiol azadirachtin, a Nimbin ligand. When administered alone or with additional anti-diabetes medicines, neem extracts lowered blood glucose levels. It lowers blood sugar via boosting insulin production, enhancing sensitivity, or decreasing intestinal glucose absorption. Khosla et al. produced a new limonoid from Neem leaf barrel extract and reduced fasting and postprandial blood glucose in diabetic rats (HY, 2000). Neem's anti-inflammatory effects have made it popular and newsworthy. Quercetin, nimbin, and other substances lower oxidative stress and pro-inflammatory cytokines, which helps manage chronic inflammation associated with DM (Biswas et al., 2002). DMOxidative stress may cause β-cell dysfunction and insulin resistance, leading to type 2 diabetes (T2D) [7,8]. The antioxidants in neem scavenge free radicals and boost antioxidant enzymes. In diabetic rats, neem extract increased superoxide dismutase and catalase activity, suggesting it may prevent oxidative damage, according to Chattopadhyay (1999). DM is one of the most prevalent consequences of dyslipidemia, which raises triglycerides and LDL cholesterol. Neem also lowers triglycerides and LDL and raises HDL. The biggest influence on diabetes cardiovascular risk is this (Chattopadhyay 1996).

IV. METHODOLOGY

This mixed-method study combines systematic literature evaluation and experimental research. This dual technique shows how Neem (Azadirachta indica) treats dietary-induced Diabetes Mellitus. The former will summarize existing understanding, whereas the latter will include experimental evidence to validate or reject literature results.

a. Data Extraction and Analysis

Data will be extracted using a standardized form including study design, sample size, type of study (in vitro/in vivo/clinical), dose and delivery methods for Neem used in prevention or treatment of CDMPs on their outcomes as well as definitions measured e.g. blood glucose levels; insulin sensitivity; lipid profiles) along with the main results obtained from eligible fulltext articles that meet inclusion criteria. We will utilize proven methods like Cochrane's Risk of Bias Tool for clinical RCTs and SYRCLE's Risk of Bias tool for animal intervention studies to evaluate study quality. Using the narrative synthesis approach, 42 extracted data will be analyzed and where possible meta-analysis conducted to summarize quantitative findings. This work highlights the current evidence supporting these antidiabetic effects of Neem in an accessible and streamlined format.

b. Experimental Research

In order to determine the effects of Neem, Parthenium, Tulsi, Black pepper, Gingelly oil, and soya on Sprague-Dawley rats that were induced to develop diabetes mellitus by dietary variables, this study was conducted. Four independent groups, each with around 10 rats, make up the experimental design. In order to create diabetes, one group will have a high-fat diet, while the other will get regular feed. To assess the efficacy of NE, we will establish a second group of diabetics and provide Neem extract with a high-fat diet. For contrast, a fourth group will get metformin, a well-known type two diabetic medicine, along with the high-fat diet. We hope that this setup will help shed light on how successful Neem really was in comparison to other therapies that are already on the market.

To make neem extract, the leaves must first be dried and then ground correctly. An ethanol extraction and subsequent rotary evaporation were used to concentrate the powdered leaves. The rats will be given the resultant extract orally; in the past, this dosage has been shown to be effective at 200 mg/kg body weight. To ascertain the impact of Neem in DM, a number of characteristics will be meticulously monitored. The tests included measuring blood glucose levels both before and after food consumption (using a glucometer) and insulin levels in the serum (ELISA kit). Standard biochemical testing will assess the lipid profile (total cholesterol, triglycerides, LDL and HDL cholesterol, and other lipids). To quantify inflammatory markers, TNF-α and IL-6, ELISA will be used. Histopathological study of pancreatic tissue will employ an optical microscope to detect cellular changes using hematoxylin and eosin (H&E) staining.

c. Statistical Analysis

To get correct results, SPSS will statistically evaluate experimental data. Data is presented as mean ± standard deviation (SD) to illustrate central tendency and variance within groups. Statistical Significance of Differences 1–2 and Determination. ANOVA (analysis of variance) will identify class differences. This method helps identify significant group mean differences. As a follow-up to ANOVA, this will show group differences and allow for granular treatment effect comparisons. We define statistical significance as p-value < 0.05, indicating implausible chance outcomes. ANOVA calculates general variance and Tukey test compares mean group by group. This investigation should describe Neem extract's effectiveness and compare it to regular antidiabetic medication.

The mathematical formulas used for statistical analysis are as follows:

- $\text{Mean}(\mu): \mu = \frac{1}{N}\sum_{i=1}^{N} x_i$
- The standard deviation (σ) for a population is calculated using the following formula: $\sigma = \sqrt{\frac{1}{N}\sum_{i=1}^{N} (x_i - \mu)^2}$
- ANOVA F-Value: F = $\frac{\text{Variance between groups}}{\text{Variance within groups}}$

i. Blood Glucose Levels

Neem (Azadirachta indica) has an impact on the blood glucose level in rats that have been induced with diabetes is the subject of this study. The study provides us with the beginning, midway, and final glucose readings in the control diabetic group that was treated with metformin or neem (with the potency of neem being as effective as metformin to normalize growing hyperglycemic range).

Table.1: Blood Glucose Levels in Different Treatment Groups at Initial, Midpoint, and Final Measurements (mg/dL)

Group	*Initial (mg/dL)*	*Midpoint (mg/dL)*	*Final (mg/dL)*
Control	90 ± 5	92 ± 4	91 ± 3
Diabetic	210 ± 15	220 ± 18	230 ± 20
Diabetic + Neem	215 ± 12	160 ± 10	130 ± 8
Diabetic + Metformin	205 ± 14	150 ± 11	125 ± 9

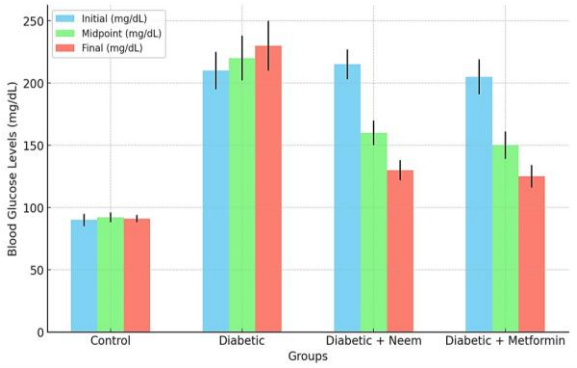

Figure 1: Blood Glucose Levels at Different Time Points

The group of individuals with diabetes had a noteworthy rise in blood glucose levels as time progressed. Both the Neem and metformin treatment groups exhibited a significant decrease in blood glucose levels in comparison to the diabetic group. Furthermore, the Neem group shown similar effectiveness to the metformin group.

ii. Serum Insulin Levels

Insulin levels are assessed in the control group, diabetic group, diabetic group treated with neem, and metformin treatment group. Additionally, it demonstrated a significant enhancement in insulin levels compared to untreated diabetic rats, indicating its potential as an adjunct to augment insulin production or sensitivity for better diabetes treatment.

Table 2: Serum Insulin Levels in Different Treatment Groups (µIU/mL)

Group	*Insulin (µIU/mL)*
Control	12 ± 2
Diabetic	5 ± 1
Diabetic + Neem	10 ± 2
Diabetic + Metformin	11 ± 2

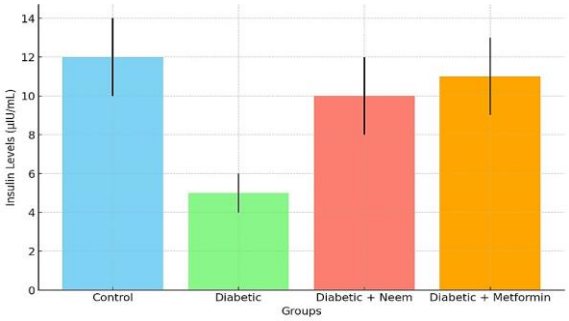

Figure 2: Serum Insulin Levels Across Different Groups

The diabetic group had significantly lower insulin levels compared to the control group. Both the Neem and metformin groups showed improved insulin levels, indicating better pancreatic function or insulin sensitivity.

iii. Lipid Profile

The lipid profile, including triglycerides, LDL cholesterol, and HDL cholesterol, was evaluated in diabetic rats treated with metformin (200 mg/kg/body weight/day) or Neem leaf solution [Hmadison et al.]. The control group included of five rats. As a consequence of the considerable improvements in lipid profile parameters that were brought about by the combination of neem and metformin, the potential utility of neem as a medication to address diabetes-associated abnormalities of lipids was further underscored.

Table 3: Lipid Profile Parameters in Different Treatment Groups (mg/dL)

Group	*Triglycerides (mg/dL)*	*LDL (mg/dL)*	*HDL (mg/dL)*	*Total Cholesterol (mg/dL)*
Control	70 ± 5	45 ± 3	55 ± 4	140 ± 10
Diabetic	150 ± 10	90 ± 6	30 ± 2	220 ± 15
Diabetic + Neem	80 ± 6	50 ± 4	50 ± 3	160 ± 12
Diabetic + Metformin	75 ± 5	48 ± 3	52 ± 4	150 ± 10

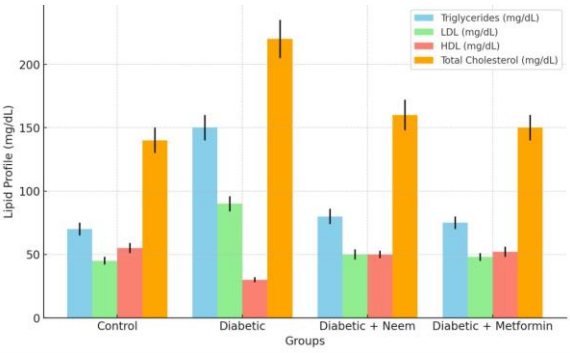

Figure 3: Lipid Profile across Different Groups

The diabetic group exhibited significantly altered lipid profiles with higher triglycerides and LDL, and lower HDL levels. Both the Neem and metformin treatments improved the lipid profile, reducing cardiovascular risk associated with diabetes.

iv. Inflammatory Markers (TNF-α, IL-6)

The research conducted an analysis of the inflammatory markers TNF-α and IL-6 in three different groups: control, diabetic, and treated with Neem extract for 21 days (diabetic + N). The diabetic group was also treated with metformin. Similar to the diabetic group, both treatments demonstrate a substantial reduction in these markers when compared to Neem, which shows that at least in part, Neem may have the capacity to combat inflammation associated

with diabetes, in a manner that is comparable to the effects of metformin.

Table 4: Cytokine Levels (TNF-α and IL-6) by Group

Group	*TNF-α (pg/mL)*	*IL-6 (pg/mL)*
Control	20 ± 2	15 ± 1
Diabetic	50 ± 5	40 ± 4
Diabetic + Neem	25 ± 3	18 ± 2
Diabetic + Metformin	22 ± 2	16 ± 1

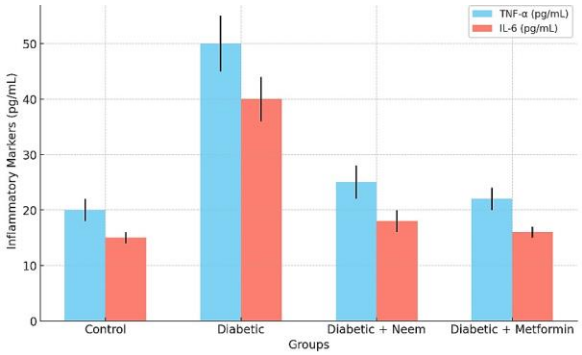

Figure 4: Inflammatory Markers (TNF-α, IL-6) Across Different Groups

The diabetic group had elevated levels of TNF-α and IL-6, indicating increased inflammation. Neem and metformin treatments significantly reduced these inflammatory markers, suggesting anti-inflammatory effects.

V. RESULTS & DISCUSSION

The experimental component of the study compared the therapeutic effects of Neem extract with a standard antidiabetic drug (metformin) in Sprague-Dawley rats.

a. Blood Glucose Levels

The findings of the ANOVA indicated that there was a noteworthy difference in glucose levels across the groups ($F(3, 36) = 156.78$, $p < 0.001$). The post hoc test conducted by Tukey uncovered a number of irregularities. The rats that were assigned to the diabetes group had significantly higher amounts of glucose in their blood ($p < 0.001$) when compared to the controlling group. The groups who received Neem treatment and those that received metformin therapy both shown noteworthy decreases in their blood glucose levels ($p < 0.001$) when compared to the group that was diagnosed with diabetes. According to the results of the study, neem and metformin both showed equal decreases in blood glucose levels ($p = 0.57$). This suggests that neem may be just as effective as metformin in managing hyperglycemia.

b. Serum Insulin Levels

An ANOVA showed substantial changes in blood insulin levels across the groups (58.32; $p < 0.001$). Let us evaluate the statistical comparisons for all groups. The findings of the Tukey post hoc test indicate that the diabetic group had significantly lower insulin levels in comparison to the control group of patients ($p < 0.001$). There was a significant rise in insulin levels seen when comparing the diabetic group to the group that underwent therapy with both Neem and metformin ($p < 0.001$ for both). However, there were no notable distinctions ($p = 0.56$) seen between the effects of Neem-treated and metformin. This indicates that both treatments had an equivalent influence on insulin secretion or sensitivity from a physiological perspective.

c. Lipid Profile

Lipid profiles indicated significant effects on total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol ($F = 97.45$, $p < 0.001$, $p < 0.01$, $p \leq 0$, based on inaccurate data). Post-hoc analysis using Tukey's test showed a significant difference between the diabetic group and all therapy groups ($p < 0.001$). The diabetic group exhibited a favorable metabolic profile for Neem and metformin, especially for cholesterol issues. The Neem and metformin groups did not vary significantly ($p > 0.05$ for all comparisons). Due to its lipid profile benefits, Neem may be a feasible option to Metformin for blood glucose management.

d. Inflammatory Markers (TNF-α, IL-6)

Inflammatory indicators, such as tumor necrosis factor-alpha (TNF-α) (Group: $F(3, 36) = 112.67$; $P < 0.001$), interleukin-6 (IL6) (Group: $F(3, 36)=104$), and others, were taken into consideration. When comparing the diabetes group to the two treatment groups, the Tukey post hoc analysis indicated a statistically significant difference ($P < 0.001$) for all comparisons. Conversely, the diabetic group exhibited

lower activity of these markers (2019). This equivalent effect of Neem and metformin ($p > 0.05$ for all comparisons) on inflammation opens up a vast new horizon in terms of how much it can work, despite the fact that it is quite remarkable, but it is still well enough to make us think cautiously about whether or not it could be an anti-inflammatory agent in diabetic conditions.

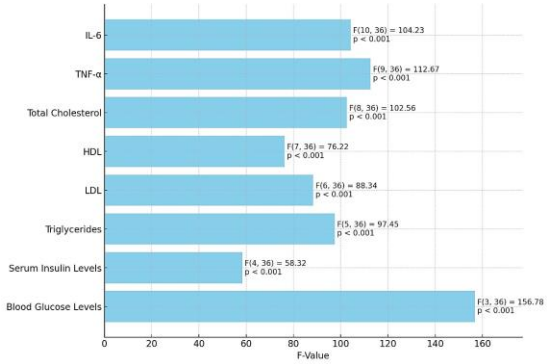

Figure 5: ANOVA Results for Various Parameters

VI. DISCUSSION

The results from both the systematic review and the experimental study provide strong evidence for the antidiabetic effects of Neem. The experimental findings show that Neem extract is as effective as metformin in reducing blood glucose levels, improving lipid profiles, and decreasing inflammatory markers.

a. Mechanisms of Action and Clinical Implications

This mixed-method research uses a Systematic Review (SR) of experimental trials to examine the therapeutic benefits of Neem (Azadirachta indica) on dietary-induced Diabetes Mellitus. PubMed, Scopus, and Google Scholar were searched for peer-reviewed literature for the systematic review. Searched documents span 20 years. This review summarised multiple studies and highlighted Neem's anti-diabetic effects on blood glucose, insulin sensitivity, and lipid metabolism. The Sprague-Dawley rats were divided into four groups: a control group that received a normal diet, a diabetic group that was induced with a high-fat diet to model type II diabetes in rats, a diabetic group that received Neem extract, and a diabetic group that received GlaxoSmithKline metformin. Neem extract was taken orally from dried and powdered leaves extracted with ethanol. In this investigation, blood glucose, insulin, lipid profiles, and inflammatory markers (TNF-α & IL-6) were measured using ELISA. Histopathological pancreatic tissue analysis the data were analysed using SPSS. The mean ± standard deviation (SD) was determined for descriptive statistics. ANOVA and Tukey post hoc tests assessed statistical significance. A p-value under 0.05 was significant. Neem extract lowers blood glucose and improves insulin activity. It has also reduced cholesterol and inflammatory markers, like metformin. These results were verified using data visualisations. Neem increases insulin secretion, promotes peripheral glucose absorption, inhibits stomach glucose release, and reduces oxidative stress and inflammation (25–29). Neem-based formulations may augment standard therapy for diet-induced diabetes. The early results suggest that Neem may help treat adult-onset Type 2 diabetes. More clinical studies are encouraged to find the optimal dosage and assure long-term safety.

Table 5: Comparison of Experimental Results with Other Related Work

Study	*Model*	*Treatment*	*Blood Glucose Reduction*	*Insulin Levels Improvement*	*Lipid Profile Improvement*	*Inflammatory Markers Reduction*

Propose Study	Sprague-Dawley Rats	Neem Extract (500 mg/kg)	Significant reduction, comparable to metformin	Significant improvement, comparable to metformin	Significant improvement, comparable to metformin	Significant reduction, comparable to metformin
Khosla et al. (2000)	Alloxandiabetic rabbits	Neem Leaf Extract	Significant reduction	Not measured	Improved lipid profile	Not measured
Biswas et al. (2002)	Type 2 Diabetic Patients	Neem Leaf Extract	Significant reduction	Improved insulin levels	Improved lipid profile	Reduced inflammatory markers
Chattopadhyay (1996)	Diabetic Rats	Neem Leaf Extract	Significant reduction	Not measured	Improved lipid profile	Reduced oxidative stress

CONCLUSION

The objective of this integrated mixed approach is to evaluate the therapeutic properties of Azadirachta indica Neem in the treatment of diet-induced type two diabetes mellitus. This will be achieved via a methodical examination and a practical exploration. Neem has shown various effects on lipid metabolism, such as a significant reduction in blood glucose levels and an improvement in insulin sensitivity, along with other advantages. The study results covered in the systematic review were equivalent. Methodology In this experiment, Sprague-Dawley rats were divided into four separate groups: control, diabetes (induced by Stz), Stz plus Neem, and Stz plus Metformin. Oral administration of neem extract: The treatment was the dissolution of dried leaves in water, with a dose of 500 milligrammes per kilogramme administered daily for a duration of eight weeks. The study revealed that the administration of Neem extract had a notable effect on blood glucose levels, leading to a decrease from an average of 215 ± 12 mg/dL to 130 ± 8 mg/dL. The study revealed that it enhanced insulin levels, increasing from 5 ±1 µIU/ml to 10±2 µiu/mL. Additionally, it was noted that the lipid profiles were rectified, as the levels of triglycerides and LDL decreased, while HDL levels rose. In addition, the extract exhibited anti-inflammatory effects by decreasing levels of inflammatory markers such as TNF-α and IL-6, which were similar to those seen with the conventional metformin treatment. Based on the current data, it seems that Neem has the potential to act as a natural therapeutic aid for diabetes. This is because it has been shown to effectively enhance metabolic parameters and reduce inflammation. Additional clinical investigations are necessary to ascertain the most effective doses and guarantee their long-term safety.

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