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Medicinal Plants with Diuretic and Hypoglycaemic Activities: Mitigating Hyperglycaemia Induced by Diuretics

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ABSTRACT: Diuretic therapy, while essential for managing conditions such as hypertension and edema, often induces hyperglycaemic as a side effect, posing significant challenges for patients with diabetes or prediabetes. This review explores the potential of medicinal plants possessing diuretic and hypoglycaemic properties as a promising strategy to mitigate diuretic-induced hyperglycemia. A comprehensive analysis of relevant literature identifies several plant species known for their diuretic effects, such asSamanea Saman, H. antidysentrica, Achyranthes Aspera, Taraxacum Officinale, and Urtica Dioica, and their concurrent hypoglycaemic activities.These plants control glucose metabolism while preserving renal function through a variety of mechanisms that are revealed by scientific investigations into their pharmacological activities. Moreover, scientific and clinical research demonstrates the safety and effectiveness characteristics of these plants, emphasizing their potential as adjuvant medicines in medical scenarios. This synthesis aims to provide a foundation for future research and therapeutic interventions aimed at optimizing diuretic therapy while managing hyperglycemic complications effectively.

Keywords: -Diuretic,Hyperglycaemia, Hypoglycaemia

I. INTRODUCTION

Any drug that raises urine flow and thus increases the excretion of water is called a diuretic. Among the most widely prescribed medications are diuretics, most of which work by decreasing the reabsorption of sodium chloride at various nephron sites, which raises urine salt levels and therefore causes water loss [1].Diuretics are commonly used to treat conditions including edema, hypertension, congestive heart failure, and disorders of the kidney and liver.[2]Diuretics are part of therapeutic strategies to help balance fluid, help shift fluid out of the interstitium, and control fluid overload characterized as ankle swelling, ascites, and pulmonary edema. This results in significant symptom relief and improves patients' quality of life overall.[3]Nowadays many commercial diuretic drugs are available in the market, such as the high-ceiling loop and thiazides diuretic. These commercial diuretic drugs have a variety of side effects such as hypokalemia, metabolic alkalosis, and dehydration (hypovolemia), leading to hypotension, fever, cough, unusual bleeding, hyperglycemia, excessive weight loss, nausea, and vomiting.[2]

Drug-induced hyperglycemia is one of the global issues, increasing the risk of infections, metabolic coma, microvascular and macrovascular complications, and even death. People with certain risk factors are particularly susceptible to developing diabetes mellitus, including those with a sedentary lifestyle, a body mass index (BMI) over 27 kg/m2, impaired glucose tolerance or fasting glucose, a family history of diabetes, a history of vascular disease, gestational diabetes, or at least one risk factor for metabolic syndrome. These individuals are especially vulnerable to drug-induced hyperglycemia because some medications can worsen pre-existing insulin resistance or pancreatic dysfunction.[4]

Diuretics are widely prescribed for various cardiovascular conditions but are associated with metabolic side effects, including an increased risk of developing diabetes mellitus.[5] The search for alternative therapies has led to exploring medicinal plants known for theirdiuretic actions, which may also offer hypoglycemic benefits, thus presenting a

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promising avenue for managing fluid retention without compromising glucose homeostasis.[1]

II. MATERIALS AND METHODS

The current study utilized a comprehensive and systematic literature search. Various databases such as PubMedand Google Scholar were searched using terms such as diuretic, hyperglycemia, hypoglycemia, traditional uses, and medicinal plants.The identified medicinal plants were grouped based on the diuretic and hypoglycaemic actionsand data from both in vitro and/or in vivo studies were compiled.This information, along with basic details about medicinal plants, was collected and carefully analyzed.Scientific names and synonyms were verified through www.plantlist.org and www.tropicos.org. References of selected articles were manuallysearched for additional relevant studies.

Mechanisms of diuretic-induced hyperglycemia

Thiazide diuretics are among the most commonly used antihypertensives.[6] In a recent meta-analysis of antihypertensive trials, thiazides were associated with a higher risk of diabetes than placebo.[7]The mechanisms behind diuretic-induced hyperglycemia appear to involve decreased insulin production, secondary to diuretic-induced hypokalaemia.[8,9]

Other pathways that could lead to thiazide-induced hyperglycemia include increased levels of free fatty acids, which are known to reduce insulin secretion in response to glucose-marked decreases in insulin sensitivity, and increased hepatic glucose production and/or catecholamine secretion and action [10],[11].

Medicinal plants with dual-action

As alternate sources of treatment regimens, medicinal plants employed in traditional medicine are gaining popularity, particularly when supported by scientific proof of their clinical value. This is becauseseveral natural substances used in folk medicine are efficient, occasionally have comparatively less negative clinical effects, and are frequently reasonably priced.[12]However, research in ethnobotany and ethnopharmacology has shown that numerous medicinal plants from various regions possess both diuretic and hypoglycaemic effects. This suggests promising avenues for discovering therapeutic agents that could effectively manage both diabetes and diuresis simultaneously.[13]

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Table No:1.1 Plants with Both Diuretic and Hypoglycemic Activity

PLANT	FAMILY	PLANT PART WITH DIURETIC EFFECT	PLANT PART WITH HYPOGLYCAEMIC EFFECT	REF
Abutilon indicum	Malvaceae	leaf	leaf	[14,27]
Allium sativum	Alliaceae	Bulb	Bulb	[`13]
Benincasa hispida	Cucurbitaceae.	fruit	fruit	[15]
Boerhavia diffusa Linn	Nyctaginaceae.	leaf	leaf	[16,28]
Centella asiatica	Apiaceae	leaf	leaf	[17]
Ipomoea aquatica	Convolvulaceae	whole plant	leaf	[18]
Xanthium strumarium	Compositae	whole plant	whole plant	[19,20]
Samanea Saman (Jacq) Merr	legumes	bark	leaf	[19,21]
Holarrhena Antidysenterica	Apocyanaceae	seed	seed	[19,22]
Achyranthes aspera linn	Amaranthaceae	whole plant	whole plant	[19,23]
Taraxacum officinale	daisy	whole plant	whole plant	[24]
Urtica dioica	Urticaceae	whole plant	whole plant	[25,26]

- **ABUTILON INDICUM**

Abutilon indicum, a member of the Malvaceae family, is commonly known as Country Mallow in English, Kanghi in Hindi, and Atibala in Sanskrit. This plant exhibits both diuretic and hypoglycemic properties.

The leaf extract of A. indicum was evaluated for its diuretic effect, where the aqueous extract at 400 mg/kg showed a statistically significant effect compared to the reference standard, Furosemide. Additionally, the hypoglycemic activity of A. indicum leaf extracts in rats was assessed, with both alcoholic and aqueous extracts demonstrating a significant reduction in blood glucose levels. [14,27]

FigureNo:1.1 Abutilon indicum

- **ALLIUM SATIVUM**

Allium sativum (Meaning pungent) belongs to the Alliaceae family and genus Allium, and is generally known in the developing world for its characteristic flavor, a medicinal plant, and a source of vegetable oil.The herb has hypoglycemic and diuretic properties.

Several animal studies support the effectiveness of garlic in reducing blood glucose levels in streptozotocin-induced and alloxan-induced diabetes mellitus in rats and mice. Most studies showed that garlic can lower blood glucose levels in diabetic mice, rats, and rabbits. Additionally, garlic has been reported to act as a diuretic, helping to eliminate excess body fluids, making it a potentially useful resource for conditions such as rheumatism, gout, arthritis, dropsy, and edema.[13]

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FigureNo:1.2 Allium sativum

- **BENINCASA HISPIDA**

Benincasa hispida also known as Winter melon, Ash gourd, Wax gourd, White pumpkin. Belongs to the familyCucurbitaceae.

When rats were administered 0.75% v/v ethylene glycol in their drinking water to induce chronic hyperoxaluria, the concurrent oral administration of Benincasa hispida extract at doses of 250 and 500 mg/kg body weight for 35 days significantly reduced the urinary excretion and kidney retention levels of oxalate, protein, and calcium. Additionally, elevated serum levels of sodium, creatinine, calcium, and phosphorus were significantly reduced by the extracts. Furthermore, the stem chloroform extract of Benincasa hispida demonstrated significant hypoglycemic activity in normal male Wistar rats, with the maximum reduction in blood glucose levels observed at a dose of 200 mg/kg body weight.[15]

Figure No:1.3 Benincasa hispida

- **BOERHAVIA DIFFUSA LINN**

Boerhavia diffusa Linn. Also known as Punarnava, Red Spiderling, or Spreading Hogweed. Belongs to Family: Nyctaginaceae.

The chloroform extract of Boerhavia diffusa (BD) leaves has shown dose-dependent hypoglycemia in experimentally diabetic rats. Glibenclamide (25 µg/kg) and BD leaf extract (200 mg/kg) resulted in glucose reductions of 59.01% and 38.63%, respectively, by the fourth week. Additionally, the authors found significant diuretic activity in the BD leaf extract (a water-insoluble portion of the alcoholic extract) collected during the rainy season. Rats treated with the leaf extract (300 mg/kg) exhibited a 90.3% increase in urine volume, while the extract of leaves and flowers showed a 67.22% increase in urine volume. [16,28]

Figure No:1.4 Boerhavia diffusa Linn

- **CENTELLAASIATICA**

Centella Asiaticais also known as Gotu Kola, Indian Pennywort, or Asiatic Pennywort. Belongs to the family Apiaceae (Umbelliferae). It is a small, herbaceous, perennial plant characterized by its fan-shaped, green leaves with

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serrated edges. It typically grows in moist, tropical, and subtropical areas.

The aqueous extracts of Centella Asiatica leaves possess good diuretic activity. The anti-diabetic properties of the leaf extract were evaluated in alloxan-induced diabetic rats by administering the extract at concentrations of 250, 500, and 1000 mg/kg. Three hours after ingestion, a reduction in blood glucose levels was observed by 32.6%, 38.8%, and 29.9%, respectively.[17]

Figure No: 1.5Centella asiatica

- **IPOMOEA AQUATICA**

Ipomoea aquaticais also known as Water Spinach, Kangkong, Water Convolvulus, and Chinese Watercress. Belongs to the family Convolvulaceae.

The methanol extract of Ipomoea aquatica demonstrated notable diuretic activity in Swiss albino mice, surpassing the effects of the standard diuretic furosemide by increasing electrolyte excretion and urine volume. In addition, methanol extracts from its leaves exhibited potent hypoglycemic effects in Swiss albino mice, with doses of 200 mg/kg and 400 mg/kg significantly lowering blood glucose levels, particularly effective at 400 mg/kg. Furthermore, a boiled whole extract of Ipomoea aquatica showed oral hypoglycemic effects in healthy male Wistar rats, leading to significant reductions in serum glucose concentrations with both single (33%, $P < 0.0027$) and multiple (25%, $P < 0.02$) doses. The optimal dose was found to be 3.4 g/kg, with maximum activity observed two hours after administration.[18]

Figure No:1.6 Ipomoea aquatic

- **XANTHIUM STRUMARIUM**

Xanthium strumarium, a prevalent weed in India from the Compositae family, is utilized medicinally, particularly its roots and fruits.

In a study, Xanthium strumarium L. was evaluated for its diuretic activity in albino rats. The extract was administered at doses of 250 mg/kg and 500 mg/kg body weight, while frusemide, a standard diuretic, was given at 5 mg/kg body weight. The petroleum ether extract showed significant increases in diuresis, natriuresis (sodium excretion), kaliuresis (potassium excretion), and glomerular filtration rate compared to normal saline. Additionally, caffeic acid isolated from X. strumarium was studied for its antidiabetic effects in streptozotocin-induced and insulin-resistant rat models. Results indicated that caffeic acid administered intravenously at doses ranging from 0.5 to 3.0 mg/kg could lower plasma glucose levels by enhancing glucose utilization. [19,20]

Figure No:1.7 Xanthium strumarium

- **SAMANEA SAMAN (JACQ) MERR**

Samanea Saman (Jacq) Merr is a large, umbrella-shaped tree that can grow over 20 meters tall. It has a thick trunk approximately 1.5 meters in

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diameter and a wide, spreading canopy that offers ample shade. The bark is rough and deeply furrowed.

B. Komarapalayam et al. evaluated the diuretic activity of Samanea saman (Jacq) Merr bark in albino rats using the in-vivo Lipschitz test model. The study found that methanol extract of the bark at concentrations of 200 mg/kg and 400 mg/kg body weight significantly increased urine volume and electrolyte excretion compared to the control group. Furosemide, used as the standard at a dose of 20 mg/kg body weight, showed that the methanol extract of Samanea saman at higher doses might have comparable diuretic activity to furosemide. Additionally, the methanol leaf extract of Samanea saman demonstrated anti-diabetic activity in both in vitro and in vivo studies. The α-amylase inhibition showed increasing concentrations at 50 µg/ml, 100 µg/ml, 150 µg/ml, 200 µg/ml, and 250 µg/ml. When administered to diabetic-induced rats at doses of 250 mg/kg and 500 mg/kg body weight, the extract significantly reduced blood glucose levels ($p<0.001$) at 1 and 2 hours and ($p<0.05$) at 30 minutes compared to the control group. [19,21]

Figure No:1.8 Samanea Saman (Jacq) Merr

- **HOLARRHENA ANTIDYSENTERICA**

Holarrhena Antidysenterica belonging to the familyApocyanaceae, commonly known as bitter oleander andlocally as Kurchi, is a small deciduous tree found inHimalaya and sub-Himalaya tract.

The crude extract of H. antidysentrica seeds and its fractions (n-hexane, n-butanol, and aqueous) were tested for diuretic effects in Wistar rats, using hydrochlorothiazide at 10 mg/kg body weight as the standard. The crude aqueous ethanolic extract showed a dose-dependent increase in urine output at 30 and 100 mg/kg, indicating a diuretic effect. It also increased urine Na+ and K+ levels, urine volume, pH, and electrolyte levels. Additionally, a recent study reported significant recovery in diabetic rats administered 300 mg/kg and 600 mg/kg doses of the ethanolic extract of the seeds. Weekly treatments significantly decreased blood glucose, serum cholesterol, triglycerides, AST, ALT, alkaline phosphatase, urea, creatinine, and uric acid levels, while the rats' weight increased substantially. [19,22]

Figure No:1.8 Holarrhena Antidysenterica

- **ACHYRANTHES ASPERA LINN**

Achyranthes aspera Linn commonly known asApamarga in Ayurveda is a weed, in Hindi as Latjeera; belongs to the family Amaranthaceae, is an erect orprocumbent, annual or perennial herb, found on roadsides, fields boundaries, and waste places as a weed.

The diuretic activity of Achyranthes aspera was evaluated using a methanolic extract of the whole plant, with the Lipschitz method and furosemide (100 mg/kg b.w.) as the standard drug. At a dose of 400 mg/kg b.w., the extract showed significant diuretic effects in rats compared to the control group. Additionally, another study reported that oral administration of 2-4 g/kg of whole plant powder produced a significant dose-related hypoglycemic effect in both normal and alloxan-treated diabetic rabbits. Both the aqueous and methanol extracts of the plant also decreased blood glucose levels in these rabbits. [19,23]

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Figure No:1.9 Achyranthes aspera Linn

- **TARAXACUM OFFICINALE**

The dandelion, or Taraxacum officinale(G.H. Weber ex Wiggers), is a herbaceous plant that is indigenous to Asia, Europe, and North America. Since ancient times, this herb has been utilized for medicinal purposes. The therapeutic benefits of the plant are attributed to the phytochemicals found in its various sections.

A previous study found that Taraxacum officinale extracts have diuretic activity in a mouse model. And the ethanolic leaf extract of this plant increases urinary frequency and fluid excretion in healthy individuals. Additionally, two studies reported that compounds isolated from Taraxacum officinale exhibit hypoglycemic effects by inhibiting α-glucosidase and α-amylase.[24]

Figure No:1.10 Taraxacum officinale

- **URTICA DIOICA**

Genus Urtica, or "nettle," is a genus of medicinal plants in the Urticaceae family that has been used medicinally since at least Ancient Greece. It has several health advantages.

Urtica dioica has traditionally been used as a diuretic in indigenous medicine. Experimentally, its aqueous extract exhibits natriuretic and diuretic activity in rabbits without affecting the rate of K+. Additionally, in a study on type 2 diabetic model rats, the water extract significantly lowered fasting serum glucose levels on the 14th day (14.05 ± 3.4 mmol/l in the control vs 8.3 ± 1.4 mmol/l in the treated group, p = 0.04). The extract also improved glycaemic and lipidemic status, likely by affecting the histological and functional status of pancreatic β-cells. [25,26]

Figure No:1.11 Urtica dioica

III. CONCLUSION

Diuretics are a cornerstone in the management of various cardiovascular and renal conditions. However, their use, especially with thiazide diuretics, often leads to the undesirable side effect of hyperglycemia. This poses a significant challenge in patients who are at risk of or managing diabetes mellitus, necessitating the exploration of alternative therapies that can mitigate these adverse effects.

The exploration of medicinal plants with dual diuretic and hypoglycemic activities offers a promising strategy for mitigating the hyperglycemia often induced by conventional diuretics. Plants such as Samanea Saman, H. antidysentrica, Achyranthes Aspera, Taraxacum Officinale, and Urtica Dioica,etc... have demonstrated significant potential in preclinical studies, showing efficacy in both increasing urine output and reducing blood glucose levels.The dual properties of these medicinal plants highlight their potential to create a more balanced therapeutic approach for patients requiring diuretic therapy but who are also at risk of hyperglycemia.

However, further clinical research is needed to validate these findings and ensure the safety and efficacy of these plants in human populations. This research will also help elucidate the mechanisms underlying their dual actions, paving the way for optimized treatment protocols.

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Ultimately, the integration of these medicinal plants into conventional medicine could represent a significant advancement in the management of fluid retention and hyperglycemia, improving the quality of care for patients worldwide.

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