PLANT ALKALOIDS: AN ANTI-DIABETIC POTENTIAL

Abstract

The chronic metabolic disease known as diabetes mellitus, which is characterised by hyperglycemia, is a severe health burden that affects people all over the world. As a result of the limits and bad effects that relate to the treatments that are now available, the quest for new antidiabetic agents continues, despite the achievements that have been made in pharmacotherapy. It has come to people's notice that plant alkaloids have the potential to have medicinal benefits, including characteristics that may help prevent diabetes. The purpose of this study is to offer a complete overview of the possible anti-diabetic effects of plant alkaloids by investigating their mechanisms of action, preclinical and clinical data, and potential future applications. A comprehensive search of scientific databases led to the discovery of pertinent research that were published in journals that were subjected to peer review. Plant alkaloids, such as berberine, metformin, and quinolizidine alkaloids, have shown promise anti-diabetic benefits via a variety of mechanisms. These mechanisms include insulin sensitization, blockage of glucose absorption, and modification of signalling pathways that are important in glucose homeostasis. In addition, alkaloids have qualities that contribute to their overall therapeutic success in the treatment of diabetes. These features include antioxidant, anti-inflammatory, and lipid-lowering effects. To evaluate the effectiveness and safety of plant alkaloids as supplementary or alternative therapy for diabetes, more clinical studies are necessary, despite the positive preclinical evidence that has been collected. By gaining an understanding of the pharmacological characteristics and mechanisms of action of plant alkaloids, it is possible to pave the way for the creation of

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new antidiabetic medicines that are more effective and more tolerable.

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I. INTRODUCTION

The term "alkaloids" refers to a large number of chemical entities that Pelletier described as follows: cyclic organic molecules that include nitrogen in a negative oxidation state. Alkaloids are a classified set of substances. According to their chemical composition, these substances are characterised by a basicity that originates from a heterocyclic tertiary nitrogen atom (with a few notable exceptions, such as colchicine and xanthines). Depending on where they come from, alkaloid compounds may be either naturally occurring, biomimic, or manufactured [1]. Furthermore, they are secondary metabolites that contribute to the protective process. They have a profound influence on biological processes. The majority of the approximately 16,000 alkaloids that are known to exist come from plants, although some arise from algae, bacteria, and other sources. Indole alkaloids, isoquinoline alkaloids, tropane alkaloids, and steroidal alkaloids are the several types of alkaloids that may be found based on their backbone. The alkaloids that make up the biggest quantities are the indole and isoquinoline alkaloids [17]; around 8100 alkaloids are classified into these classes [2]. The metabolic illness known as diabetes mellitus is characterised by high amounts of sugar in the blood. Resistance to the effect of insulin, deficiencies in insulin synthesis, and dysfunctions in glucagon secretion are all potential causes of this condition. The majority of the time, it is the consequence of a combination of more than one of these characteristics. If the condition is not properly handled, complications including as retinopathy, renal failure, and neuropathy may develop [15]. The World Health Organisation estimates that diabetes was directly responsible for the deaths of around 1.6 million people in the World in the year 2016. There is an estimated prevalence of 3.8% in Africa, 7.3% in Europe, 10.7% in the Middle East and North America, 11.5% in North America and the Caribbean, 9.6% and 9.1% in South America and Southeast Asia, respectively [3]. South America and Southeast Asia have the highest prevalence rates.

- **Alkaloids:** Alkaloids represent a diverse group of naturally occurring organic compounds that contain nitrogen atoms, often found in plants [1]. They exhibit a wide range of pharmacological activities and have been studied extensively for their potential therapeutic applications [7,14]. Alkaloids are classified into several types based on their chemical structures, origins, and biological activities [16]. In this essay, we will explore the major types of alkaloids, including their structures, sources, and pharmacological properties.

- **Indole Alkaloids:** Indole alkaloids are derived from the amino acid tryptophan and are characterized by the presence of an indole ring. They are commonly found in plants such as the Apocynaceae, Rubiaceae, and Loganiaceae families [1]. Examples include:

- **Tryptamine**: Found in plants like Banisteriopsis caapi and Mimosa hostilis, tryptamine serves as a precursor to various other indole alkaloids.

- **Ergotamine:** Produced by the fungus Claviceps purpurea, ergotamine has vasoconstrictive properties and is used in the treatment of migraines.

- **Lysergic acid diethylamide (LSD):** A potent psychedelic compound derived from ergot alkaloids, LSD interacts with serotonin receptors in the brain, leading to altered perception and consciousness.

- **Isoquinoline Alkaloids [17]:** Isoquinoline alkaloids are derived from the amino acids phenylalanine and tyrosine [13] and are characterized by a benzylisoquinoline skeleton. They are abundant in plants of the Papaveraceae, Ranunculaceae, and Berberidaceae families. Examples include:

- **Morphine:** Found in opium poppy (Papaver somniferum), morphine is a potent analgesic and narcotic alkaloid used to relieve severe pain.

- **Berberine:** Present in plants like goldenseal (Hydrastis canadensis) and Oregon grape (Mahonia aquifolium), berberine exhibits antimicrobial, anti-inflammatory, and antidiabetic properties [28,31].

- **Sanguinarine:** Found in bloodroot (Sanguinaria canadensis), sanguinarine possesses antimicrobial and anticancer activities and has been studied for its potential in oral health products.

- **Tropane Alkaloids:** Tropane alkaloids are bicyclic compounds derived from ornithine and are commonly found in plants of the Solanaceae family. They contain a tropane ring system and exhibit anticholinergic properties. Examples include:

- **Atropine:** Derived from plants like deadly nightshade (Atropa belladonna) and jimsonweed (Datura stramonium), atropine acts as a competitive antagonist of muscarinic acetylcholine receptors and is used to dilate the pupils and treat bradycardia.

- **Scopolamine**: Also known as hyoscine, scopolamine is found in plants like henbane (Hyoscyamus niger) and belladonna (Atropa belladonna). It is used to prevent motion sickness and nausea and has hallucinogenic properties.

- **Cocaine:** Derived from the coca plant (Erythroxylum coca), cocaine is a powerful stimulant and local anesthetic that blocks the reuptake of dopamine, serotonin, and norepinephrine, leading to euphoria and increased alertness.

- **Pyrrolidine Alkaloids**: Pyrrolidine alkaloids contain a pyrrolidine ring and are derived from ornithine or proline. They are found in various plant families, including the Solanaceae and Convolvulaceae. Examples include:

- **Nicotine:** Found in tobacco (Nicotiana tabacum), nicotine is a highly addictive stimulant that acts on nicotinic acetylcholine receptors in the central nervous system, leading to increased heart rate and blood pressure.

- **Anabasine:** Present in plants like tobacco and certain species of lupine, anabasine is a toxic alkaloid that acts as a nicotinic acetylcholine receptor agonist.

- **Piperidine Alkaloids:** Piperidine alkaloids are characterized by a piperidine ring and are derived from lysine. They are found in plants of the Piperaceae family, including black pepper (Piper nigrum) and kava (Piper methysticum). Examples include:

- **Piperine:** Found in black pepper, piperine is responsible for the spice's pungency and exhibits antioxidant and anti-inflammatory properties. It also enhances the bioavailability of certain drugs and nutrients [4, 26].

- **Coniine:** Derived from hemlock (Conium maculatum), coniine is a neurotoxic alkaloid that acts as a nicotinic acetylcholine receptor antagonist, leading to paralysis and respiratory failure in high doses.

- **Lupinine:** Found in various species of lupine, lupinine has been studied for its potential as an antidepressant and antihypertensive agent.

- **Quinoline Alkaloids**: Quinoline alkaloids contain a quinoline ring and are derived from tryptophan. They are found in plants such as Cinchona species and have antimalarial properties. Examples include:

- **Quinine:** Obtained from the bark of Cinchona trees, quinine has been used for centuries to treat malaria. It acts by inhibiting the growth and replication of the malaria parasite Plasmodium.

- **Quinidine**: Also derived from Cinchona bark, quinidine is used to treat certain types of arrhythmias by prolonging the cardiac action potential and slowing conduction in the heart.

Alkaloids, as their name suggests, are compounds with a chemical nature resembling alkalis, often characterized by their basic properties and ability to form salts with acids. These nitrogen-containing heterocyclic organic compounds are primarily derived from plants and exhibit diverse pharmacological activities [7,14]. Alkaloids are classified based on their carbon-nitrogen skeleton and are often colourless, crystalline solids that are slightly soluble in neutral or alkaline aqueous solutions but readily soluble in various organic solvents. Among their numerous pharmacological activities, alkaloids have gained attention for their potential in managing diabetes mellitus (DM) and its associated complications [15].

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both [24]. According to the International Diabetes Federation (IDF), the global prevalence of diabetes is steadily increasing, with approximately 537 million adults aged 20-79 years living with the condition in 2021, a number projected to rise to 643 million by 2030 [11]. DM is associated with various complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy, contributing to significant morbidity and mortality.

The current pharmacotherapy for diabetes includes oral antidiabetic agents such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and injectable therapies like insulin and glucagon-like peptide-1 (GLP-1) receptor agonists. While these medications effectively lower blood glucose levels [19] and reduce the risk of complications, they are associated with following mechanisms:

II. MECHANISMS OF ACTION OF PLANT ALKALOIDS IN DIABETES MANAGEMENT

Plant alkaloids exert their antidiabetic effects through various mechanisms, targeting different aspects of glucose homeostasis and metabolic pathways. The following subsections highlight some of the key mechanisms underlying the antidiabetic potential of plant alkaloids [23,27,32].

1. Insulin Sensitization

Insulin resistance, characterized by impaired insulin signaling and reduced responsiveness of target tissues to insulin, plays a central role in the pathogenesis of type 2 diabetes (T2DM). Several plant alkaloids have been shown to improve insulin sensitivity by enhancing insulin signaling pathways or activating downstream mediators involved in glucose uptake and metabolism.

2. Berberine

Berberine a quaternary ammonium salt alkaloid found in several medicinal plants, including Berberis species [2,10], has gained attention for its insulin-sensitizing effects. Berberine activates adenosine monophosphate-activated protein kinase (AMPK) [18,32], a key regulator of cellular energy metabolism, leading to increased glucose uptake and utilization in skeletal muscle and adipose tissue. Additionally, berberine inhibits hepatic gluconeogenesis by suppressing the expression of key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). These mechanisms contribute to the overall improvement in insulin sensitivity and glycemic control observed with berberine supplementation in both preclinical and clinical studies [28,31].

3. Metformin

Metformin a synthetic biguanide derivative derived from the plant alkaloid galegine found in Galega officinalis (French lilac), is a first-line oral antidiabetic agent widely used for the management of T2DM [23,27,32]. Metformin primarily exerts its effects by activating AMPK, leading to inhibition of hepatic gluconeogenesis and promotion of glucose uptake in peripheral tissues. Additionally, metformin enhances insulin sensitivity by increasing the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, facilitating glucose uptake in skeletal muscle and adipose tissue. The combined effects of metformin on hepatic glucose production and peripheral glucose utilization contribute to its efficacy in lowering blood glucose levels and improving insulin sensitivity in diabetic patients.

III. INHIBITION OF GLUCOSE ABSORPTION

Another strategy employed by plant alkaloids to reduce postprandial hyperglycemia involves inhibiting the absorption of dietary carbohydrates in the gastrointestinal tract. By delaying or reducing the digestion and absorption of carbohydrates, alkaloids can attenuate the rise in blood glucose levels following meals, thereby improving overall glycemic control [19].

1. Quinolizidine Alkaloids

These are a class of alkaloids commonly found in plants of the Fabaceae family, have been investigated for their potential antidiabetic effects. Studies have shown that quinolizidine alkaloids such as lupinine and sparteine inhibit α-glucosidase and α-amylase enzymes, which are responsible for carbohydrate digestion in the small intestine [6]. By inhibiting these enzymes, quinolizidine alkaloids reduce the rate of glucose absorption from the gut, leading to lower postprandial glucose excursions and improved glycemic control. Additionally, quinolizidine alkaloids may modulate gut hormone secretion, including glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which regulate satiety and glucose homeostasis.

- **Regulation of Insulin Secretion:** In addition to enhancing insulin sensitivity and inhibiting glucose absorption, some plant alkaloids have been found to regulate insulin secretion from pancreatic β-cells. By modulating the release of insulin, these alkaloids can effectively lower blood glucose levels and improve glycemic control in diabetic individuals [19].

- **Tinospora Cordifolia:** *T. cordifolia* commonly known as Giloy or Guduchi, is a medicinal plant used in traditional Ayurvedic medicine for the treatment of various ailments, including diabetes [3,25,31]. The alkaloids present in *Tinospora cordifolia* have been shown to possess insulin-mimetic and insulinotropic effects, stimulating both the release and action of insulin in pancreatic β-cells. In vitro studies have demonstrated that alkaloid-rich fractions derived from *Tinospora cordifolia* stimulate insulin secretion from pancreatic β-cells, leading to enhanced glucose uptake and utilization in peripheral tissues [20].

Plant alkaloids (PAs) represent a diverse group of secondary metabolites found abundantly in nature, with over 12,000 identified to date. They are structurally varied compounds, often derived from amino acids, and classified into true, pseudo-, and proto-alkaloids based on their chemical structures. PAs exhibit various pharmacological activities, including anti-diabetic properties, making them valuable for medicinal purposes [7,14].

Among the numerous PAs, certain alkaloids from plants like *Catharanthus roseus, Ervatamia microphylla,* and *Murraya koenigii* [12] show promising hypoglycemic effects [22]. For instance, alkaloids from Catharanthus roseus have been reported to increase insulin levels and decrease glucose levels in diabetic rats. Similarly, Conophylline from *Ervatamia microphylla* has been found to convert pancreatic cells into insulin-producing cells [9,30].

Other alkaloids like mahanimbine from *Murraya koenigii* [12] demonstrate activity against diabetes-associated lipid abnormalities. Additionally, compounds like vindoline and vindolicine from Catharanthus roseus exhibit inhibitory activity against tyrosine phosphatase 1B [5,29], an enzyme linked to diabetes [8,13, 21].

Furthermore, alkaloids from various plants, including Ziziphus oxyphylla and Berberis lyceum Royle, have shown anti-diabetic effects by inhibiting α-glucosidase, controlling hyperglycemia, and improving lipid profiles. Berberine, a well-known alkaloid found in Berberis species, has demonstrated significant anti-diabetic effects in experimental models, including reducing blood glucose levels and improving lipid profiles [2,10].

Moreover, alkaloids from plants like *Coptidis rhizoma* and *Tecoma stans* exhibit inhibitory activity against enzymes like aldose reductase and protein tyrosine phosphatase 1B [5,13], involved in diabetes pathophysiology. These alkaloids show potential in regulating insulin signaling pathways and improving insulin sensitivity [29].

Additionally, Brassica oleracea var. capitata and *Tinospora cordifolia* contain alkaloids with anti-diabetic properties, including insulin-mimicking and insulin-releasing effects. These alkaloids have been found to reduce blood glucose levels [20] and improve insulin secretion in experimental models.

In summary, plant alkaloids represent a vast and diverse group of compounds with significant potential in managing diabetes mellitus and its associated complications. Their varied pharmacological activities, including hypoglycemic [22], anti-glycation, and insulin-mimicking effects, highlight their importance as therapeutic agents in diabetes management. Further research into the mechanisms of action and clinical efficacy of these alkaloids is warranted to harness their full potential in diabetes treatment.

IV.SUMMARY

Plant alkaloids represent a promising avenue for the management of diabetes mellitus and its associated complications. By targeting various aspects of glucose homeostasis and metabolic pathways, alkaloids offer diverse mechanisms of action that complement existing pharmacotherapies for diabetes. Further research into the pharmacological properties and therapeutic potential of plant alkaloids is warranted to develop novel and effective treatments for diabetes and related conditions.

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