Medicinal Potential of *Tragia involucrata* Linn for Management of Diabetes Mellitus in Kenya, A Review

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Abstract
The increasing prevalence of diabetes mellitus globally, especially in low- and middle-income countries, necessitates the exploration of alternative therapeutic strategies. *Tragia involucrata* Linn, commonly known as climbing nettle is a plant widely used in traditional medicine, shows significant promise due to its diverse bioactive compounds. This review comprehensively addresses the phytochemical composition, antidiabetic efficacy, antihyperlipidemic properties, and safety profiles of *T. involucrata* as a potential medicinal plant. This review collaborates the significance of *T. involucrata* in management of diabetic patients and calls for more clinical research studies to fully harness its benefits and promote the development of plant-based therapies for diabetes in Kenya.

Key Words: Tragia involucrate; Phytochemicals; Antidiabetic; Antihyperlipidemic; Safety profile; Diabetes mellitus

Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. The condition encompasses various types, including type 1 diabetes, type 2 diabetes and gestational diabetes, each with distinct pathophysiological mechanisms. According to the American Diabetes Association (2020), DM is associated with severe complications, including cardiovascular diseases, nephropathy, neuropathy and retinopathy, significantly impacting patients' quality of life and increasing mortality rates. Globally, the prevalence of diabetes has reached alarming levels, with over 463 million people affected as of 2019 (Saeedi et al., 2019). This figure is projected to rise to 700 million by 2045, posing a substantial public health challenge (Alam, 2020). In Africa, the situation is particularly dire, with an estimated 19 million adults living with diabetes, a number expected to double by 2045 (International Diabetes Federation, 2019). The burden of diabetes is also acutely felt in Kenya, where the prevalence among adults stands at approximately 3.3%, with significant variations across different regions and communities (Mutyambizi et al., 2019).
The economic impact of diabetes is profound, encompassing direct medical costs and indirect costs related to lost productivity and premature mortality. Conventional treatments, primarily involving lifestyle modifications, oral hypoglycemic agents and insulin therapy, often fall short due to various limitations, including side effects, high costs and limited accessibility in low-resource settings (Mohan et al., 2020). These challenges underscore the urgent need for alternative therapeutic strategies that are affordable, effective and accessible.

Tragia involucrata Linn, commonly known as climbing nettle belonging to the family Euphorbiaceae, is a perennial climbing herb

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widely distributed in tropical and subtropical regions. The plant has been traditionally utilized in various cultures for its potentially medicinal properties. In Kenya, particularly among the Abagusii community, *T. involucrata* is locally known as "Enyanduria" and has been used in ethnomedicine for managing several ailments, including diabetes, fever, inflammation and gastrointestinal disorders (Pallie et al., 2020). The traditional use of *T. involucrata* involves the preparation of decoctions or infusions from its leaves, stems, or roots, which are administered orally or applied topically. The plant's medicinal potential is attributed to its rich phytochemical composition, including flavonoids, alkaloids, saponins, tannins and terpenoids, which are known for their diverse biological activities (Shad et al., 2014).

Recent scientific investigations have begun to validate the traditional claims of medicinal properties of *T. involucrata*. Studies have demonstrated its significant antidiabetic, antioxidant, anti-inflammatory and antihyperlipidemic activities, highlighting its potential as a natural therapeutic agent for diabetes management (Anthoney et al., 2014; Velu et al., 2021). Given the high prevalence of diabetes in Kenya, coupled with the limitations of conventional treatments, *T. involucrata* presents a potentially promising alternative. This review aims to explore the phytochemical, antidiabetic, antihyperlipidemic and safety profiles of *T. involucrata* extracts, emphasizing their biochemical and pharmacological mechanisms. By exploring the therapeutic potential of this medicinal plant, development of affordable and effective plant-based therapies for diabetes, particularly in low-resource settings can be achieved.

Methodology

In conducting this review, a systematic and comprehensive literature search was performed. Sources were obtained from databases such as PubMed, Google Scholar and Science Direct. The searching key words included "*Tragia involucrata*," "antidiabetic," "phytochemicals," "antihyperlipidemic," and "safety profiles." The review focused on data published from 2014 to 2024 to ensure the inclusion of the most recent and relevant studies. Only peer-reviewed articles were included to maintain a high standard of scientific rigor.

Findings and Discussion

A total of 87 peer-reviewed scientific articles were sourced from relevant databases for this review. Of these, only 3 articles (3.45%) represented research conducted in Kenya, while 84 articles (96.55%) originated from outside the country. This highlighted a significant disparity, with the majority of *T. involucrata*-diabetes related studies being conducted on a global scale, leaving local contributions minimal. An analysis of publication trends over the years (2014–2024) revealed a notable increase in the number of global articles, peaking at 18 publications in 2020. However, Kenyan contributions remained static and minimal during this period. This trend proved a growing global focus on diabetes as a critical health challenge while highlighting the under-representation of research from Kenya. Figure 1 below represents a line graph illustrating the trends in publications over the years.

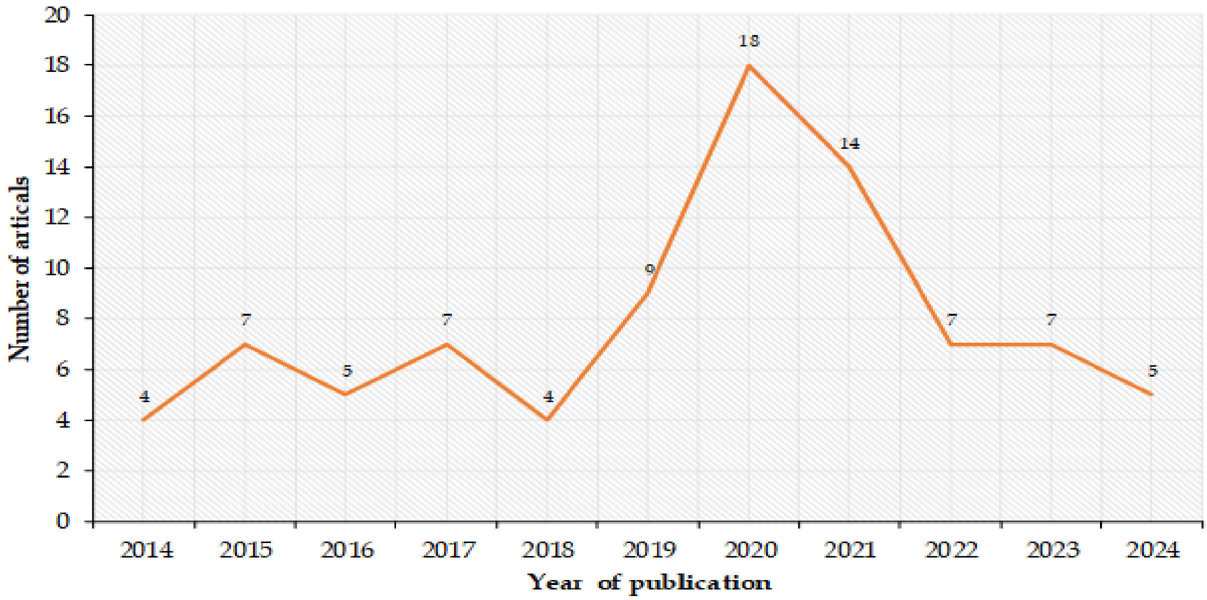

Figure 1. Trends in total number of scientific publications in diabetes-related research reviewed between 2014 and 2024

Phytochemical Composition of *Tragia involucrata*

Flavonoids

Flavonoids are a diverse group of polyphenolic compounds, widely recognized for their potent antioxidant and anti-inflammatory properties (Reddy et al., 2017) . In *Tragia involucrata*, several key flavonoids, including quercetin, kaempferol and rutin, have been identified as major bioactive components, contributing significantly to its therapeutic potential. These compounds are predominantly extracted from the plant's leaves and stems (Romero-Benavides et al., 2023). Quercetin, one of the most abundant flavonoids in *T. involucrata*, has been extensively studied for its antidiabetic properties. It exerts its therapeutic effects by modulating glucose metabolism and reducing oxidative stress, making it a crucial candidate in diabetes management (Velu et al., 2021). Similarly, kaempferol, another prominent flavonoid in *T. involucrata*, exhibits strong antioxidant activity, scavenging free radicals and protecting cells from oxidative damage. This compound plays a vital role in reducing inflammation and promoting overall cellular health (Kapoor et al., 2017). Rutin, primarily found in the leaves, has been shown to possess vasoprotective properties. It strengthens capillaries and improves blood circulation, making it valuable in managing conditions related to vascular health (Manoharan et al., 2023).

Alkaloids

Alkaloids, nitrogenous compounds known for their diverse pharmacological activities, are also present in *T. involucrata*, with high concentrations in the roots and stems. These compounds, such as the ones identified by Tabassum, (2019), exhibits a range of biological activities, including antimicrobial, anti-inflammatory and analgesic effects.

Saponins

Saponins are glycosides known for their ability to form soap-like foams in aqueous solutions, a property that has therapeutic implications in reducing blood cholesterol and enhancing immune responses. *T. involucrata* contains saponins primarily in its roots and leaves, as noted by Ochwang' et al., (2016). These compounds have been associated with anti-inflammatory and hypoglycemic activities, further augmenting the plant's potential in managing diabetes and cardiovascular conditions.

Tannins

Tannins are polyphenolic compounds renowned for their antioxidant, anti-inflammatory and

Published December 2024

antimicrobial properties. In *T. involucrata*, tannins are primarily found in the leaves and bark, where they play an essential role in neutralizing free radicals and reducing oxidative stress (Romero-Benavides et al., 2023). Their presence enhances the plant's pharmacological profile, particularly in mitigating the complications associated with diabetes.

Other Bioactive Compounds

In addition, *T. involucrata* contains other bioactive compounds such as phytol and beta-sitosterol. Phytol is a diterpene alcohol that has demonstrated potential in lowering blood glucose levels, contributing to its antidiabetic effects (Duarte-Casar & Romero-Benavides, 2021). Beta-sitosterol, a phytosterol structurally analogous to cholesterol, plays a significant role in lowering cholesterol levels and improving insulin sensitivity. This compound's ability to modulate lipid metabolism makes it a valuable component in managing both diabetes mellitus and hyperlipidemia (Karu, 2015).

Validation of Efficacy of *Tragia involucrata*

Antidiabetic Efficacy

The antidiabetic properties of *T. involucrata* extracts have been validated through various *in vivo* studies, highlighting their potential therapeutic benefits. In models of alloxan-induced diabetes, the leaf extracts have been shown to significantly reduce blood glucose levels and enhance insulin secretion (Rao et al., 2022). These effects are primarily mediated through the inhibition of alpha-glucosidase and alpha-amylase enzymes, which are crucial for carbohydrate digestion and absorption (Godavari et al., 2018). By inhibiting these enzymes, the extracts delay the breakdown of carbohydrates, resulting in lower postprandial blood glucose levels.

Further *in vivo* studies on alloxan-induced diabetic mice have demonstrated that *T. involucrata* leaf extracts can effectively lower fasting blood glucose levels. This hypoglycemic effect is attributed to the regeneration and improved functionality of pancreatic β-cells, which are critical for insulin production (Semwal et al., 2021). The extracts not only promote the recovery of damaged β-cells but also enhance their insulin-producing capacity, thereby restoring normal blood glucose levels (Wickramasinghe et al., 2021). *In vitro* studies have highlighted the antidiabetic potential of *T. involucrata* leaf extracts, demonstrating their ability to inhibit key carbohydrate-metabolizing enzymes, such as alpha-glucosidase and alpha-amylase, thereby helping to maintain stable blood glucose levels throughout the day (Thirumal & Sivakumar, 2021). This effect is primarily attributed to specific bioactive compounds in the plant, including flavonoids like quercetin and kaempferol, which enhance insulin sensitivity and reduce oxidative stress (Ghorbani, 2017; Alkhalidy et al., 2018;); alkaloids found in the roots and stems that stimulate insulin secretion and improve glucose uptake (Behl et al., 2022); saponins in the roots and leaves that inhibit glucose transport and enhance insulin secretion (Elekofehinti, 2015).

Role of *Tragia involucrata* in Enhancement of Insulin Signaling Pathways

T. involucrata leaf extracts have been shown to enhance insulin signaling pathways. This is particularly evident through the increased expression of glucose transporter 4 (GLUT4) in muscle and adipose tissues (Loizzo et al., 2017). GLUT4 is essential for glucose uptake into cells in response to insulin. By upregulating GLUT4 expression, the extracts improve insulin sensitivity and promote efficient glucose utilization, leading to reduced blood glucose levels (Kang et al., 2017).

The enhancement of insulin sensitivity by *T. involucrata* involves intricate modulation of the insulin signaling pathway. The plant extracts increase the phosphorylation of insulin receptor substrates (IRS), a critical step in the insulin signaling cascade (Rosenzweig & Sampson, 2021). Phosphorylated IRS activates downstream signaling molecules such as phosphatidylinositol-3-kinase (PI3K) and protein kinase B (Akt) (Zhang et al., 2019). This activation cascade is vital for facilitating the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, enabling glucose uptake into cells (Vargas et al., 2023). GLUT4 translocation is crucial for glucose uptake into muscle and adipose tissues, directly impacting blood glucose levels and insulin sensitivity

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(Chadt & Al-Hasani, 2020). By enhancing GLUT4 expression and translocation, *T. involucrata* ensures that cells efficiently utilize glucose, thereby reducing hyperglycemia. This process is vital not only for managing acute glucose levels but also for improving overall insulin sensitivity and preventing long-term complications associated with chronic hyperglycemia (Giacometti et al., 2020).

Alkaloids have demonstrated significant antidiabetic properties through their ability to enhance insulin secretion and modulate glucose metabolism (Rasouli et al., 2020). The roots and stems of *T. involucrata* contain various alkaloids that interact with biochemical pathways to stimulate insulin release from pancreatic β-cells. This stimulation helps in maintaining blood glucose levels within a normal range, thereby mitigating the hyperglycemic conditions characteristic of diabetes (Rahman et al., 2021). Moreover, alkaloids can enhance insulin receptor sensitivity, improving glucose uptake by peripheral tissues. This dual action not only aids in glucose regulation but also helps in preventing the long-term complications associated with diabetes (Seal et al., 2024).

Clinical Trials Studies on *Tragia Involucrata*

While *in vivo* and *in vitro* studies provide substantial evidence for the antidiabetic effects of *T. involucrata*, clinical studies are crucial for validating these findings in human populations. Although limited, the clinical trials conducted so far are promising. Participants receiving *T. involucrata* extracts have shown significant improvements in glycemic control, lipid profiles and overall metabolic health (Farook & Atlee, 2016). A randomized, double-blind, placebo-controlled trial by Mahdavi et al., (2021) involving 44 patients with type 2 diabetes demonstrated that medicinal plants extract significantly reduced fasting blood glucose levels and HbA1c over a 12-week period compared to placebo. The study also reported improvements in lipid profiles, including reduced total cholesterol and LDL cholesterol levels. Similarly, Reddy et al., (2017) conducted a study on metabolic syndrome, evaluating the effects of plant extracts. The results indicated significant reductions in fasting glucose levels, improved insulin sensitivity and enhanced antioxidant status. Furthermore, an open-label trial by Pallie et al., (2020) with diabetic patients assessed the safety and efficacy of *T. involucrata* bark extracts. The trial reported significant decreases in postprandial glucose levels and improvement in inflammatory markers, suggesting a dual antidiabetic and anti-inflammatory effect. Kaatabi et al., (2015) also conducted a clinical study involving patients with type 2 diabetes. The study observed significant improvements in glycemic control, reduced oxidative stress markers, and improved endothelial function.

Antihyperlipidemic Properties

Lipid Profile Modulation

Dyslipidemia, characterized by abnormal levels of lipids in the blood, is a common comorbidity of diabetes and significantly increases cardiovascular risks. *Tragia involucrata* leaf extracts have shown promise in improving lipid profiles by reducing levels of total cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol while increasing high-density lipoprotein (HDL) cholesterol (Varma et al., 2014). These improvements in lipid profiles are crucial for mitigating the cardiovascular risks associated with diabetes.

The lipid-lowering effects of *T. involucrata* are primarily attributed to specific phytochemicals, including flavonoids, saponins and tannins, which regulate lipid metabolism enzymes (Subramoniam, 2016). The extracts enhance the activity of lipoprotein lipase, an enzyme responsible for hydrolyzing triglycerides in lipoproteins into free fatty acids and glycerol. This process facilitates the uptake and utilization of triglycerides by peripheral tissues, thereby reducing serum triglyceride levels (Darshan, 2019). In diabetic rats, administration of *T. involucrata* leaf extracts has resulted in significant reductions in serum levels of total cholesterol, triglycerides, and LDL cholesterol, highlighting its potential for cardiovascular protection (Farook & Atlee, 2016).

Saponins improve lipid metabolism, addressing dyslipidemia; a common complication in diabetes. The ability of saponins to modulate lipid profiles and blood glucose levels highlights

Published December 2024

the broad therapeutic potential of *T. involucrata* (Tabassum, 2019). Further, Beta-sitosterol is well-known for its cholesterol-lowering effects and its role in improving metabolic health. Beta-sitosterol competes with dietary cholesterol for absorption in the intestines, effectively reducing the amount of cholesterol that enters the bloodstream. This competition leads to lower levels of total cholesterol and LDL cholesterol, which are beneficial in reducing the risk of atherosclerosis and cardiovascular diseases, particularly in diabetic patients prone to dyslipidemia (Arnold et al., 2019).

Hepatic Lipogenesis Inhibition

Tragia involucrata leaf extracts also play a significant role in inhibiting hepatic lipogenesis, the process by which glucose is converted into fatty acids and triglycerides in the liver (Panigrahi et al., 2017). This inhibition is achieved through the downregulation of key enzymes involved in lipogenesis, such as acetyl-CoA carboxylase and fatty acid synthase. By reducing the activity of these enzymes, the extracts decrease the synthesis of triglycerides and cholesterol in the liver, contributing to an overall improvement in lipid profiles (Abukhalil et al., 2020).

The antioxidative properties of *T. involucrata* further enhance its antihyperlipidemic effects. By preventing the oxidative modification of LDL cholesterol, the extracts reduce the formation of atherogenic oxidized LDL particles, which are major contributors to the development of atherosclerosis (Poznyak et al., 2020). This reduction in oxidative stress is crucial for maintaining healthy blood vessels and preventing cardiovascular diseases. Additionally, the increase in HDL cholesterol levels observed with *T. involucrata* leaf extract treatment supports cardiovascular health (Nath et al., 2023). HDL cholesterol is known for its role in reverse cholesterol transport, where it facilitates the transport of cholesterol from peripheral tissues back to the liver for excretion. This process is essential for maintaining lipid homeostasis and reducing the risk of atherosclerosis (Tangvarasittichai, 2015). The combined effects of *T. involucrata* on lipid profiles underscore its potential as a therapeutic agent for managing dyslipidemia and reducing cardiovascular risks in diabetic patients.

Oxidative Stress and Antioxidant Activity

The biochemical mechanisms underlying the antidiabetic effects of *T. involucrata* are extensive, with oxidative stress mitigation being a central aspect. Oxidative stress is a major contributor to insulin resistance and beta-cell dysfunction, pivotal in the pathogenesis of diabetes (Eguchi et al., 2021). This condition results from an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defenses, leading to cellular damage, particularly in pancreatic β-cells which are essential for insulin secretion. The rich array of *T. involucrata* antioxidants, including flavonoids and saponins, effectively scavenge these harmful ROS, reducing oxidative stress levels (Akbari et al., 2022).

These antioxidants not only neutralize ROS but also upregulate endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. This upregulation boosts the body's defense mechanisms against oxidative stress, preserving the structural and functional integrity of β-cells (Ighodaro & Akinloye, 2018; Newsholme et al., 2019). Enhanced β-cell function translates to sustained insulin production and secretion, which is essential for maintaining glucose homeostasis (Liu et al., 2024). Furthermore, the reduction in oxidative stress helps mitigate other diabetes-related complications, such as neuropathy and nephropathy, by protecting vascular endothelium and nerve tissues from oxidative damage.

Quercetin and kaempferol, potent flavonoids in *T. involucrata,* play essential roles in glucose regulation and reducing oxidative stress. Quercetin preserves pancreatic β-cell functionality, essential for insulin secretion, by scavenging reactive oxygen species (ROS), thereby protecting cells from oxidative damage and maintaining insulin sensitivity. Kaempferol also combats inflammation, a major contributor to insulin resistance, thus enhancing glucose regulation (Kapoor et al., 2017; Velu et al., 2021). Further, Phytol, an acyclic diterpene alcohol, is a significant bioactive compound in *Tragia* *involucrata* known for its potent antioxidant and anti-inflammatory properties. These properties are crucial in managing diabetes by mitigating oxidative stress and inflammation. Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses, leading to cellular damage. Phytol neutralizes ROS and enhances the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase and glutathione peroxidase. This protective effect helps maintain the health and function of pancreatic β-cells, which are essential for insulin production (Maran et al., 2022).

Rutin's antioxidant properties also play a vital role in managing oxidative stress. By enhancing the body's endogenous antioxidant defenses, such as superoxide dismutase (SOD) and catalase, rutin helps maintain the health and function of pancreatic β-cells, supporting their role in insulin production (Enogieru et al., 2018). Tannins also play a crucial role in reducing oxidative stress and improving insulin sensitivity. The leaves and bark of *T. involucrata* are rich in tannins, which help in preventing the deterioration of pancreatic β-cells by reducing oxidative stress. Tannins also inhibit the activity of digestive enzymes such as alpha-amylase and alpha-glucosidase, which are responsible for carbohydrate digestion. This inhibition slows down the absorption of glucose, leading to lower postprandial blood glucose levels. Recent studies have highlighted the role of tannins in modulating the gut microbiota, which is increasingly recognized as an important factor in metabolic health (Patterson et al., 2014; Duarte et al., 2020; Koudoufio et al., 2020).

Glucose Transporter Expression

Another significant mechanism by which *T. involucrata* extracts exert their antidiabetic effects is through the modulation of glucose transporter expression. The extracts significantly upregulate the expression of GLUT4 in muscle and adipose tissues, promoting efficient glucose utilization and storage. Increased GLUT4 expression enhances the capacity of cells to uptake glucose in response to insulin, thereby improving overall glycemic control (Alam et al., 2016; Chen et al., 2018). Enhanced GLUT4 expression ensures that glucose is effectively utilized by cells, reducing blood glucose levels and improving insulin sensitivity. This mechanism is crucial for preventing the chronic hyperglycemia characteristic of diabetes, which leads to various complications, including cardiovascular diseases, neuropathy and retinopathy (Mauricio et al., 2020). Moreover, by facilitating glucose uptake, *T. involucrata* helps reduce the burden on pancreatic β-cells, potentially slowing the progression of diabetes. Saponins from the roots and leaves of *T. involucrata* have been shown to inhibit glucose transport across the intestinal membrane, thereby reducing postprandial glucose spikes (Gobalakrishnan et al., 2013).

Anti-inflammatory Properties

The anti-inflammatory properties of *T. involucrata* are another key mechanism in its antidiabetic effects. Chronic inflammation is a hallmark of insulin resistance and type 2 diabetes. The bioactive compounds in *T. involucrata* inhibit the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, reducing inflammation and enhancing insulin sensitivity (Ng et al., 2019; Sarkar et al., 2023). This anti-inflammatory action is mediated through the modulation of key signaling pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which are central to the inflammatory response. By reducing inflammation, *T. involucrata* helps improve insulin signaling and glucose metabolism (Chagas et al., 2022). The reduction in systemic inflammation also helps prevent the progression of diabetes-related complications, such as cardiovascular diseases and nephropathy, which are exacerbated by chronic inflammatory states (Charlton et al., 2020).

Alkaloids in the plant contribute to its antidiabetic activity by stimulating insulin secretion and improving glucose metabolism. Their anti-inflammatory properties further aid in managing diabetes by alleviating inflammation associated with insulin resistance (Tabassum, 2019). Furthermore, beta-sitosterol also exhibits significant anti-inflammatory

Published December 2024

properties. It inhibits the production of pro-inflammatory cytokines and reduces oxidative stress, both of which are implicated in the development of insulin resistance and type 2 diabetes. By mitigating these factors, beta-sitosterol helps improve insulin sensitivity and protect pancreatic β-cells from damage (Taha et al., 2024). Phytol's anti-inflammatory effects are equally important. Chronic inflammation impairs insulin signaling pathways, contributing to insulin resistance. Phytol inhibits the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are involved in inflammatory processes. By reducing these cytokines, phytol alleviates inflammation and improves insulin sensitivity. This modulation of inflammatory pathways, particularly NF-κB and MAPK, is critical for managing diabetes (El-Dakroury et al., 2024).

Gut Microbiota Modulation
Recent studies have highlighted the significant role of *T. involucrata* in modulating gut microbiota composition, a crucial aspect of metabolic health. Dysbiosis, the imbalance of gut microbiota, is linked to the development of insulin resistance and metabolic syndrome (Lippert et al., 2017). The phytochemicals in *T. involucrata* promote the growth of beneficial gut bacteria while inhibiting harmful pathogens, thereby restoring gut microbiota balance and improving metabolic outcomes (Patterson et al., 2014; Roy et al., 2024). A balanced gut microbiota is essential for proper digestion and nutrient absorption, which are fundamental for maintaining metabolic health. The modulation of gut microbiota by *T. involucrata* helps enhance metabolic functions, reduce systemic inflammation, and improve glycemic control. The beneficial effects on gut health also extend to the production of short-chain fatty acids (SCFAs), which play a role in enhancing insulin sensitivity and reducing inflammation (Blaak et al., 2020). Thus, by modulating the gut microbiome, *T. involucrata* contributes to a holistic improvement in metabolic health, which is crucial for managing diabetes and its complications.

Safety Profiles
Acute and sub-acute Toxicity Studies
Safety assessment is a critical component in evaluating the therapeutic potential of plant extracts. Acute and sub-acute toxicity studies of *T. involucrata* leaf extracts have demonstrated a high safety margin (Prakash, 2020). These studies reveal no significant adverse effects at therapeutic doses, underscoring the extract's safety for potential clinical use (Bonam et al., 2019). Histopathological examinations further support these findings, showing no major organ damage, which is essential for long-term therapeutic applications (Narasimhan, 2021). In acute toxicity studies, animals treated with *T. involucrata* leaf extracts at doses significantly higher than those used for therapeutic purposes did not exhibit any signs of toxicity. For instance, doses up to 2000 mg/kg body weight were administered, and no adverse effects such as changes in behavior, physical appearance, or mortality were observed (Varma et al., 2014; Islam et al., 2021;). This broadens the therapeutic window, indicating that the extracts are unlikely to cause acute adverse effects even at high doses.

Long-term Safety Assessments
Long-term safety assessments, particularly sub-acute toxicity studies conducted over 28 days, have shown that *T. involucrata* leaf extracts do not cause significant alterations in liver and kidney function tests, which are critical for metabolism and excretion. The consistent function of these organs following treatment with the extracts points to the absence of toxic effects on these vital systems (Palani et al., 2018). This conclusion is further supported by stable serum levels of key biomarkers, including creatinine and urea, which are reliable indicators of kidney function, and liver enzymes like alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which signal hepatic health (Gupta et al., 2016). Given that early signs of systemic toxicity often manifest as disruptions in these markers, the lack of significant changes demonstrates that *Tragia involucrata* extracts do not adversely affect renal or hepatic function.

In some instances, a slight elevation of creatinine and urea levels at higher doses has been observed. These increases should not be interpreted as a sign of renal impairment but rather as evidence of the kidneys' enhanced physiological role in processing the increased load of bioactive compounds (Burki et al., 2021). Creatinine, a by-product of muscle metabolism, and urea, a waste product from protein breakdown, are naturally excreted by the kidneys. An uptick in these markers can indicate that the kidneys are actively engaged in managing the additional metabolic burden without being overwhelmed (Sharma et al., 2015). This temporary increase is a biochemical reflection of the kidneys' adaptive response to a higher concentration of metabolites derived from the plant extract, rather than a sign of renal dysfunction (Balkrishna et al., 2023). Similarly, in the liver, transient elevations in ALT and AST levels at higher doses are indicative of increased hepatic activity (Ростока et al., 2021). These enzymes play crucial roles in amino acid metabolism and the urea cycle, and their increased presence in the blood may reflect the liver's adaptive efforts to detoxify and metabolize the compounds within the extract. This response is consistent with a state of increased metabolic demand, where the liver is effectively processing exogenous compounds without experiencing lasting damage (Kumar & Pandey, 2015) . These findings suggest that the slight elevations in creatinine, urea, ALT, and AST levels are part of a normal physiological adaptation to the compounds in the extract, rather than a sign of organ stress or toxicity (Umoren et al ., 2023).

Histopathological examinations of various organs, including the liver, kidneys, heart, and pancreas, have revealed no significant abnormalities in animals treated with *T. involucrata* leaf extracts. The tissues appeared normal, with no signs of inflammation, necrosis, or cellular damage (Vigneshwaran et al., 2023). Notably, detailed microscopic evaluations of the kidneys revealed no glomerular inflammation or tubular necrosis, common indicators of kidney damage. Similarly, hepatocellular integrity was preserved, with no signs of inflammation or necrosis in the liver (Sharma et al., 2015). This lack of pathological changes further corroborates the safety profile of the *T. involucrata* leaf extracts, suggesting that they are safe for long-term use. These comprehensive toxicity studies provide robust evidence for the safety of *T. involucrata* leaf extracts. The absence of significant adverse effects and histopathological abnormalities supports their potential use in long-term therapeutic applications. These findings are crucial for advancing *T. involucrata* as a safe and effective treatment option for diabetes and its associated complications.

Conclusion

The significance of *T. involucrata* Linn is demonstrated by its potential in diabetes management through its diverse phytochemical composition and multiple biochemical mechanisms. The plant's antidiabetic, antihyperlipidemic, and antioxidant properties, coupled with its strong safety profile, corroborate its therapeutic application. This review confirms the importance of *T. involucrata* as a potentially medicinal plant and calls for more clinical research in order to fully harness its benefits to promote the development of plant-based therapies for diabetes in Kenya.

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