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Antidiabetic Properties of *Bidens pilosa* and Its Polyacetylenic Compounds for Management of Diabetes: Systematic Review

Kenneth Waititu[1*], Caroline Mugo[1], Daisy Nyawira[2], Peter Mwethera[3]

[1]Animal Sciences Department, Kenya Institute of Primate Research, Nairobi, Kenya
[2]Center for Biodiversity, National Museums of Kenya, Nairobi, Kenya
[3]Department of Reproductive Health and Biology, Kenya Institute of Primate Research, Nairobi, Kenya
Email: *waitituken@gmai.com

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Abstract

Bidens pilosa is a member of the *Asteraceae* family that is widely distributed across the tropics. It has been utilized by different communities both as food and medicinal herb. This plant and its polyacetylenic compounds hold potential as a natural antidiabetic intervention that can be used to combat this global public health problem. Bioactive compounds found in this plant constitute promising interventions for combating obesity which is a major risk factor for the development of type 2 diabetes. These phytocompounds can work independently or synergistically to modulate appetite, lipase activity, adipogenesis and adipocyte apoptosis. However, the efficacy, mode of action and scope of management of diabetes by these compounds remains elusive. The current review aims to summarize data on efficacy in the management of diabetes, an antidiabetic candidate polyacetylenic compound and possible biological activities as an antidiabetic agent from the available literature. Much emphasis has been directed to cytopiloyne as a representative of polyacetylenic compounds extracted from *Bidens pilosa* and its activity on diabetic animal models. The majority of the studies conducted on animal models described antidiabetic mechanisms that range from hypoglycemic to secretagogue activity of cytopiloyne in a dose-dependent manner. A clinical trial pilot indicated improved glycemic control of *Bidens pilosa* formulation among diabetic patients in the study. *Bidens pilosa* and its compounds are highly potent antidiabetic agent(s) that should be graduated to an intervention for management of diabetes through pre-clinical and clinical trials to elucidate its efficacy and safety.

Keywords

Antidiabetic, Cytopiloyne, *Bidens pilosa*, Polyacetylenic Compounds

1. Introduction

Diabetes is a chronic metabolic disorder characterized by sustained high blood sugar levels, glycosuria, polyphagia, polyuria and polydipsia with the potential to cause diverse complications including blindness, terminal nephropathies, neuropathies and cardiovascular diseases [1] [2]. Type 1 diabetes that is often reported among young patients is characterized by absolute insulin deficiency resulting from autoimmune destruction of pancreatic β-cells [3] [4]. Currently, management of type 1 diabetes requires using multiple insulin injections; upregulating pradial insulin to carbohydrate intake and insulin analogs [5] [6] [7]. However, such treatment requires adequate training of patients on how to match the dosage with carbohydrate meals, pre-pradial blood glucose levels and anticipated activity [8]. Type 2 diabetes that affects over 90% of diabetic patients [9] is caused by a deficiency in insulin activity occasioned by insulin resistance by target tissues [10] [11]. Dysregulation of glycemic control often seen in obesity and type 2 diabetes results from decreased GLUT4 and insulin-stimulated glucose transport in adipocytes [12]. Risk factors for the development of type 2 diabetes include obesity, a sedentary lifestyle, and environmental factors and it is the most prevalent form among the elderly but recent studies have reported increasing cases among children and teenagers [13] [14]. Hyperglycemia has been linked to the generation of highly active intermediate compounds leading to non-functional proteins resulting in the formation of protein-adducts which promote the formation of the highly modified advanced glycation end products (AGEs) [15] [16]. Pathophysiology of diabetes and development of complications arise due to oxidative stress pathway [17] [18], polyol pathway activity [19], formation of AGEs [16], activation of protein kinase C isoforms [20] and augmentation of the hexosamine pathway flux [21]. Natural products or their derivatives can act as antioxidants that possess integrative and complementary medicinal properties in the protection against these complications [22]. Currently available synthetic anti-diabetic interventions for type 2 diabetes such as biguanides, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1), and dopamine-2 agonists, dipeptidyl peptidase 4 (DPP-4), and sodium-glucose cotransporter-2 (SGLT 2) have been alluded to cause side effects including cancer, hepatitis, allergy, among others following prolonged consumption [23] [24]. Medicinal products developed from naturally occurring bioactive compounds are mused to be less toxic compared to synthetic drugs thus the growing consideration for their utilization as promising interventions for the management of various disease conditions including diabetes [25]. *Bidens pilosa* also commonly known as black-jack is a highly invasive plant that is considered a weed widely distributed in tropical and subtropical regions with its leaves and flowers being commonly used as natural herbal remedies [26] [27]. Utilization of *B. pilosa* herbal preparations for management of different conditions including diabetes has been reported among local communities from Africa, Asia and America [28] [29] [30] [31]. Additionally, *B. pilosa* is used both as

food and medicine for animals and humans [30]. Bioactivities of the extracts from *B. pilosa* include anti-hyperglycemia, anti-hypertensive, anti-ulcerogenic, hepatoprotective, immunomodulatory and anti-inflammatory, anti-leukemic, anti-malarial, anti-bacterial, anti-microbial, anticancer and anti-oxidative [29] [32] [33]. These extracts have been widely studied and polyacetylenes constitute a significant fraction of phytocompounds in this plant [33]. Polyacetylenes form a distinct group of chemically reactive natural products found in plants including *B. pilosa* that occur as aliphatic acetylenes containing triple or double bonds with their cyclic, aromatic and glucoside rings or heterocyclic end groups [34]. Aerial *B. pilosa* plant parts are rich in polyacetylenic glucosides [34] [35]. Polyacetylenes isolated from *B. pilosa* have demonstrated anti-diabetic properties [36] [37] thus emerging as potent natural bioactive compounds for management of the disease. Cytopiloyne is a novel polyacetylene that was isolated from *B. pilosa* that appears to be highly potent in the prevention of type 1 diabetes via T-cell regulation [38]. *B. pilosa* and its three polyacetylenes; 2-*β*-D-Glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (GHT; also known as cytopiloyne), 3-*β*-D-Glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne, 2-*β*-D-Glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne have been reported to improve glycemic control in diabetic mice [30] [39] [40]. The ability of cytopiloyne to modulate immunological response via T helper cells selective differentiation of T helper (Th0) cells into type II T helper (Th2) cells presents it as an excellent remedy for the management of type 1 diabetes [41]. This review seeks to highlight the bioactive properties of *B. pilosa* and its polyacetylenic compounds as a potential antidiabetic agent.

2. Methods

This systematic review was performed by online searches of PubMed and Google Scholar databases. The descriptors "Biological properties of cytopiloyne", "antidiabetic AND cytopiloyne", "cytopiloyne". The inclusion criteria were research articles on antidiabetic and anti-obesity activity of cytopiloyne or glucosides extracted from *B. pilosa*. The search returned 155 articles and the preselection was made by reading the abstracts and full-text research publications, while excluding reviews. The preferred reporting items for systematic and meta-analysis (PRISMA) framework used data collection for this review is presented in **Figure 1**. Studies that focused on antidiabetic properties of *B. pilosa* and its polyacetylenic glucosisdes that were included in this review are listed in **Table 1**.

3. Results and Discussion

Previous studies have reported antidiabetic activity of *B. pilosa* and its compounds. However, despite discovery of different phytocompounds present in *B. pilosa,* understanding of their biological activity in management of diabetes remains unclear. Studies that have been selected in this review demonstrate that *B. pilosa* and its polyacetylenic compounds are capable of ameliorating diabetes via T-cell regulation, insulin secretion and management of obesity (**Table 1**).

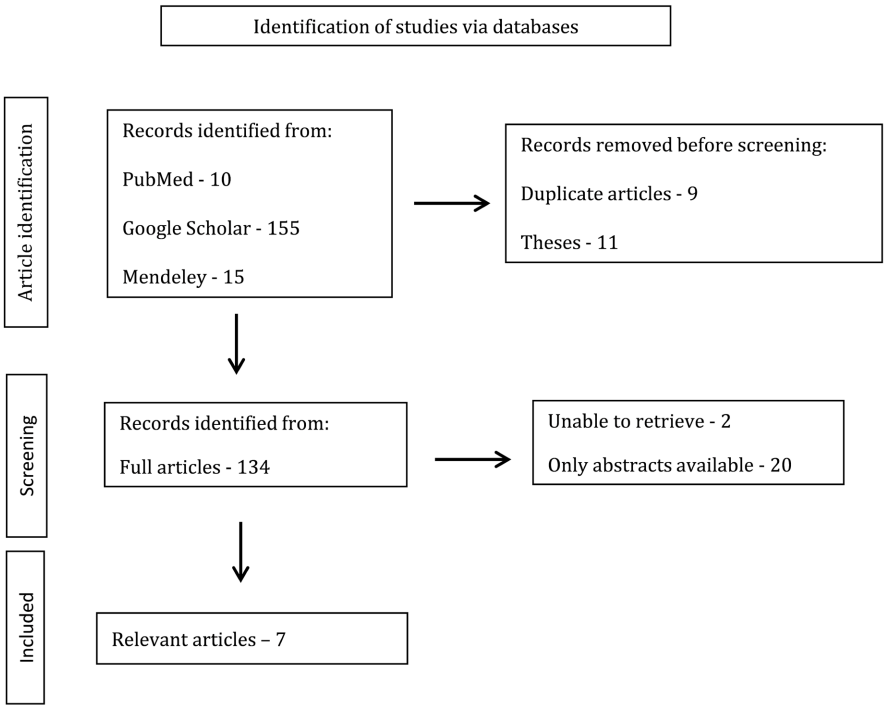

Figure 1. PRISMA flowchart for the review methodology.

Table 1. Data from studies on antidiabetic activity of *B. pilosa* and its compounds identified.

Reference	Highlight results
[42]	Treatment of ob/ob mice with 2.5% *B. pilosa* significantly reduced visceral and subcutaneous fat but not brown fat. Body weight, body fat and serum lipids in treated ob/ob mice appeared well regulated. Treatment of mouse 3T3-L1 pre-adipocytes with cytopiloyne/GHT reduced adipogenesis in adipocytes via down-regulation of Egr2, CCAAT/enhancer-binding Proteins (C/EBPs) and peroxisome proliferator-activated receptor-gamma (PPAR-γ) as well as their downstream genes, aP2 and adiponectin.
[43]	Fasting blood glucose and glycosylated hemoglobin A1c (HbA1c) levels of patients with type 2 diabetes that took a *B. pilosa* formulation (probetacell) orally at a daily dose of 400 mg, *ter in die*, for 3 months were well regulated.
[40]	Cytopiloyne reduced postprandial blood glucose levels, increased blood insulin, improved glucose tolerance, suppressed the level of HbA1c, and protected pancreatic islets in db/db mice. Cytopiloyne dose dependently increased insulin secretion and expression in β-cells by triggering the activity of protein kinase Cα (PKCα) and its activators, calcium, and diacylglycerol (DAG). Cytopiloyne treats type 2 diabetes via regulation of insulin production involving the calcium/DAG/PKCα cascade in β-cells as well as maintaining islet architecture.
[28]	Single oral dose *B. pilosa* methanolic crude extracts and its polyacetylenic compounds reduced blood glucose levels in db/db mice by increasing insulin release whereas reduction of HbA1c was observed as a long-term effect.
[44]	Treatment of db/db mice with *B. pilosa* water extract improved glucose tolerance, decreased HbA1c and protected the structure of pancreatic islet and enhance insulin secretion.
[38]	Administration of Intramuscular or intraperitoneal injection of cytopiloyne at 25 μg/kg body weight per dose three times per week completely prevented the development of diabetes in 30 weeks old non-obese diabetic (NOD) mice. This could be attributed to suppressions of Th1 differentiation and depletion of serum interferon-Gamma (IFN-γ) which is essential in development of type 1 diabetes.
[29]	Antidiabetic activity of cytopiloyne is due to its immunomodulatory role in T-cell differentiation of naive T helper (Th0) cells into type I T helper (Th1) cells or type II T helper (Th2) cells.

3.1. Cytopiloyne

Cytopiloyne, also known as 2-β-D-Glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (GHT) is a novel amorphous colorless polyacetylenic glucoside isolated from the *B. pilosa* variant radiata plant of Asteraceae family [28] [29] [45]. It is a tetrayne with a methyl group at one terminus and a vicinal diol at the other with the molecular formula, $C_{19}H_{22}O_7$ (**Figure 2**) according to high-resolution Fast atom bombardment (FAB) mass spectrometry [29]. Various polyacetylenic glucosides have two or three triple bonds at the polyacetylene part but cytopiloyne has 4 triple bonds at Carbons C5, C7, C9 and C11 [33]. Cytopiloyne has been reported to effectively control and prevent type 1 diabetes in non-obese diabetic mice and be effective in controlling type 2 diabetes in db/db mice, a leptin receptor-deficient mouse model for the study of type 2 diabetes [28] [29] [38].

3.2. Antidiabetic Activity of Cytopiloyne

Diabetes mellitus is disease that results from the impairment of either the secretion or action of insulin in the body and characterized by metabolism of aberrant protein, lipids and glucose [28] [46]. Type 1 diabetes is a disease that results from the destruction of insulin producing pancreatic β-cells by immune cells that exhibit a strong autoimmune reaction [47] [48]. Inflammatory response mounted by the immune cells infiltration of pancreatic islet results in gradual depletion of the β-cell mass and ultimately low or absence of insulin production [49] [50]. Glycemic control is hampered since insulin is the exclusive hormone that lowers plasma glucose concentration, and glucose homeostasis is maintained primarily as a result of regulated insulin secretion [11]. Pancreatic β-cells recognize extracellular glucose concentration and secrete insulin as required at a given time [51]. Non-glucose nutrients, hormones and neural inputs also modulate glucose-stimulated insulin secretion (GSIS) but this is impaired in diabetic patients [50] [52]. Type 1 diabetes pathology similar to humans is often observed in NOD mice develop spontaneous autoimmunity dominated by autoantibodies and circulating auto reactive T-cells that target β-cell antigens [53] thus making

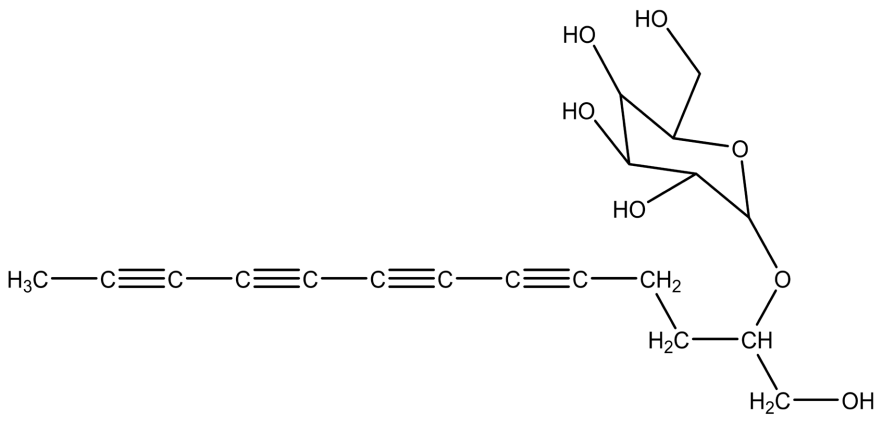

Figure 2. The structure of cytopiloyne [38].

it an ideal model for the disease and potential intervention studies. Previous studies have reported that *B. pilosa* extracts can be used to treat both type 1 and type 2 diabetes in mice [44] [54]. Their potential is emphasized by the available clinical trials data that have indicated that treatment of diabetic patients with *B. pilosa* formulation significantly increased pancreatic β-cell function as evidenced by the homeostatic model assessment beta (HOMA-β) values [32] [40]. Such findings present *B. pilosa* and its polyacetylenic glucosides as potential agents to treating diabetes by acting on pancreatic β-cells [54]. Lower doses of cytopiloyne of 0.1 mg/kg have been reported to significantly reduce postprandial blood glucose levels in diabetic db/db mice compared to glimepiride (2.5 mg/kg) implying their high efficacy at minimal concentrations. Cytopiloyne has been associated with better blood insulin levels improvement compared to glimepiride and highly effective long-term glycemic controls observed in db/db mice. Glycemic control by cytopiloyne has been attributed to its insulin secretagogue activity based on previous studies in mice and rats [40]. In addition to increasing insulin secretion by β-cells as it happens with the current secretagogues, cytopiloyne promotes its biosynthesis [40] [55]. Cytopiloyne has been shown to be effective against diabetes and decrease the symptoms associated with autoimmune disease in NOD mice with diabetes [56] [57]. It is the most potent and most effective polyene active in the modulation of both immune and β-cells of the other two as shown in both db/db and NOD mice which are both animal models for diabetes [28] [29] [58]. Glycemic control in type 1 diabetes by *B. pilosa* and its polyacetylenic compounds is achieved through T-cell regulation, long-term therapeutic action and through increased insulin expression and protection of pancreatic β-cells in type 2 diabetes [32]. The compound exhibits combination therapeutic targets via both immune and β-cells which give better protection against type 1 diabetes [40]. Lower dose of *B. pilosa* plant extract is highly effective in management of type 1 diabetes as it has been reported that 200 mg/kg treatment of rats with alloxan induced diabetes showed better recovery compared to 400 mg/kg [59]. Ability of *B. pilosa* to regulate insulin secretion and protect pancreatic islets makes it a potential candidate for management of type 2 diabetes [44]. Drugs that are currently used to treat diabetes have either unfulfilled efficacy or undesired side effects or both [60] implying that research and development of new remedies such as cytopiloyne is warranted.

3.3. Antidiabetic Role of Cytopiloyne in T Helper Cell Regulation

Type 1 diabetes is a T-cell mediated autoimmune disease characterized by destruction and/or dysregulation of the insulin producing β-cells found in the pancreatic islets of Langerhans [61] [62]. Inflammation of the islets, termed insulitis, involves infiltration of $CD4^+$ and $CD8^+$ T-cells, B-cells, dendritic cells (DC) and macrophages, as well as production of islet-specific autoantibodies [63] [64] [65]. Hyperglycemia and overt diabetes are established when 80%–90% of β-cell mass is rendered nonfunctional [66]. Detection of $CD4^+$ and $CD8^+$

T-cells infiltration into the islets of type 1 diabetes subjects underscores their important role development of type 1 diabetes [67] [68]. Expanded effector T-cell (Teff) response to β-cell autoantigens, such as proinsulin and insulin is a prominent finding in childhood type 1 diabetes [69] [70]. $CD4^+$ and $CD8^+$ T-cells are essential for β-cell destruction, and respond to similar β-cell autoantigens in NOD mice, a spontaneous model of type 1 diabetes [71] [72] [73] [74]. $CD4^+$ cells can differentiate into type 1 (Th1) or type 2 (Th2) helper cells categorized by both function and the profile of the cytokines [29] [75]. Th1 cells and their cytokines including IFN-γ promote type 1 diabetes in NOD mice whereas Th2 cells and their cytokines such as IL-4 and IL-10 have been reported to suppress this disease in previous studies [75] [76] [77]. Compounds that can modulate T helper cell differentiation have a great potential to treat immune diseases that are brought about by T helper cells [29]. Cytopiloyne inhibits the differentiation of $CD4^+$ cells into Th1 cells but promotes their differentiation into Th2 cells [29] [78] [79] thus presenting it as a potent antidiabetic agent. Cytopiloyne is reported to inhibit IFN-γ expression [29] [78] and promote Th2 cell differentiation and the transcription of the cytokine Interleukin-4 (IL-4) [29] [32] [79]. Increased serum levels of IL-4 antagonize the function of IFN-γ in the differentiation of T-cells [29] [30] in a dose-dependent manner [38]. Cytopiloyne also works by partially depleting $CD4^+$ T-cells via the modulation of T-cell proliferation and differentiation in the long term which leads to islet preservation [30]. Macrophages and neutrophils are also increased in the pancreatic lymph nodes and spleens of NOD mice. Infiltration by $CD4^+$ T-cells is reduced, and the islet integrity is increased. This makes cytopiloyne a preventive compound against diabetes [38] [78]. $CD4^+$ T-cell depletion can also be partially attributed to the up-regulation of the expression of the Fas Ligand protein in pancreatic islet cells [30] [38]. GATA-3 and T-bet genes are master genes for Th2 and Th1 cell differentiation respectively. Cytopiloyne increases the transcription of GATA-3 significantly but not the T-bet gene. This further accounts for the preferential differentiation of Th2 cells and expression of IL-4 but not Th1 cell differentiation and expression of IFN-γ [30] [38] thus underscoring the important role of cytopiloyne in the management of type 1 diabetes.

3.4. Cytopiloyne as an Insulin Secretagogue

Cytopiloyne stimulates insulin transcription and expression in the β-cells of the pancreas through protein kinase alpha (PKCα) in a glucose dependent manner. Cytopiloyne, like blood glucose, also increases the levels of intracellular calcium and diacylglycerol (DAG) in a dose-dependent manner in mice [32] [40]. Cytopiloyne reduces blood glucose levels and leads to elevated levels of insulin in the blood in db/db mice in relation to dosage [30]. Data from previous studies indicated that combining cytopiloyne with other therapies that target metabolism could be better in the treatment of type 2 diabetes [40]. Treatment of diabetic db/db mice with *B. pilosa* aqueous extract increased insulin secretion, improved

glucose tolerance and reduced the levels of HbA1c in the blood [44]. These findings indicate that phytocompounds extracted from *B. pilosa* may also be used in the long-term control of glycemia in type 2 diabetes. A *B. pilosa* formulation that promoted secretion of insulin and preservation of pancreatic islets in humans without any obvious side effects has been developed [43]. The formulation reduced fasting blood glucose levels and HbA1c in diabetic humans but increased the levels of fasting insulin in the serum of healthy subjects. The use of high doses of cytopiloyne may however lead to hypoglycemia as high doses lead to insulin secretion even in the absence of glucose [40]. Secretogouge activity coupled with maintenance of pancreatic islets integrity provides an edge for cytopiloyne over the available insulin sensitizers for the management of type 2 diabetes.

3.5. Anti-Obesity Effect of Cytopiloyne

Obesity is a major risk factor for the development of type 2 diabetes with 90% of patients being classified as either obese or overweight [80] [81]. Sustained weight loss is quite challenging because of its complex interactions between biology, behavior and obesogenic environment. Anti-obesity treatments are usually accompanied by biological changes such as reducing total energy expenditure via hormones secreted by adipocytes, thyroid and gut and neural activity in brain centers that affect food intake [82] [83]. Current drugs used in weight loss act on reduction of fat absorption, suppression of appetite and increasing energy expenditure [84] [85]. Despite their efficacy, weight-loss drugs are often accompanied by undesirable side effects as well as cost-effectiveness concerns [86] [87]. Type 2 diabetes is characterized by β-cell dysfunction and peripheral tissue insulin resistance resulting in hyperglycemia, dyslipidemia among other complications [88] [89]. A wealth of information indicates that plants and their compounds can decrease food intake and fat absorption, increase lipid metabolism and stimulate energy expenditure [90]. Therefore, plants and their compounds are considered to be a natural, alternative way to control obesity. Initial stages of adipogenesis are regulated by PPAR-γ and C/EBPs followed by the formation of mature adipocytes a process that involves fatty acid binding protein 4 (FABP4), adiponectin and fatty acid synthase (FAS) [91] [92]. Increased lipids accumulation in adipocytes thus increased in secretion of adipokines and interference with insulin signaling. Insulin resistance develops leading to a high demand for insulin production that is associated with type 2 diabetes [92] [93]. Previous studies using ob/ob mice, a mouse model of obesity revealed that administration of *B. pilosa* controlled their body weight in a dose-dependent manner [42]. Cytopiloyne has been reported to hydrolyze fat by suppressing adipogenesis. Its activity has been attributed to reducing the expression of Egr2 thus leading to the downregulation of C/EBPs, PPAR-γ, adiponectin and adipocyte protein 2 (ap2) expression during the development of adipocytes in the body [42]. Natural weight loss herbal and dietary interventions are not uncommon as either for-

kloric preparations or extracted phytocompounds [94] [95]. Plants and their compounds can exert anti-obesity action via reduction of appetite and fat digestion/absorption and/or increase of lipid breakdown and energy expenditure [96] [97]. Available data on the anti-obesity activity of *B. pilosa* and its compounds presents it as a viable intervention for combating type 2 diabetes.

4. Conclusion

Plant-derived natural compounds represent a safe, effective and affordable intervention for various conditions that pose a public health crisis. Previous studies have reported that *B. pilosa* and polyacetylenic compounds are highly effective in the management of type 1 diabetes and alleviating obesity, a key risk factor for the development of type 2 diabetes. Cytopiloyne appears to be the most potent compound with high antidiabetic activity and with the ability to regulate adipogenesis thus alleviating obesity, a major risk factor for the development of type 2 diabetes. There is a need to conduct further studies to elaborate on the mode of action, bioavailability and potential long-term adverse effects of cytopiloyne.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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