

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

Kenneth Waititu^{1*}, Caroline Mugo¹, Daisy Nyawira², Peter Mwethera³

¹Animal Sciences Department, Kenya Institute of Primate Research, Nairobi, Kenya

²Center for Biodiversity, National Museums of Kenya, Nairobi, Kenya

³Department of Reproductive Health and Biology, Kenya Institute of Primate Research, Nairobi, Kenya

Email: *waitituken@gmail.com

How to cite this paper: Waititu, K., Mugo, C., Nyawira, D. and Mwethera, P. (2024) Antidiabetic Properties of *Bidens pilosa* and Its Polyacetylenic Compounds for Management of Diabetes: Systematic Review. *Journal of Biosciences and Medicines*, 12, 164-179. <https://doi.org/10.4236/jbm.2024.122013>

Received: December 6, 2023

Accepted: February 5, 2024

Published: February 8, 2024

Copyright © 2024 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

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 phytochemicals 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; up-regulating prandial 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-prandial 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-triynone, 2- β -D-Glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triynone have been reported to improve glycaemic 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”, “anti-diabetic 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 glucosides 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**).

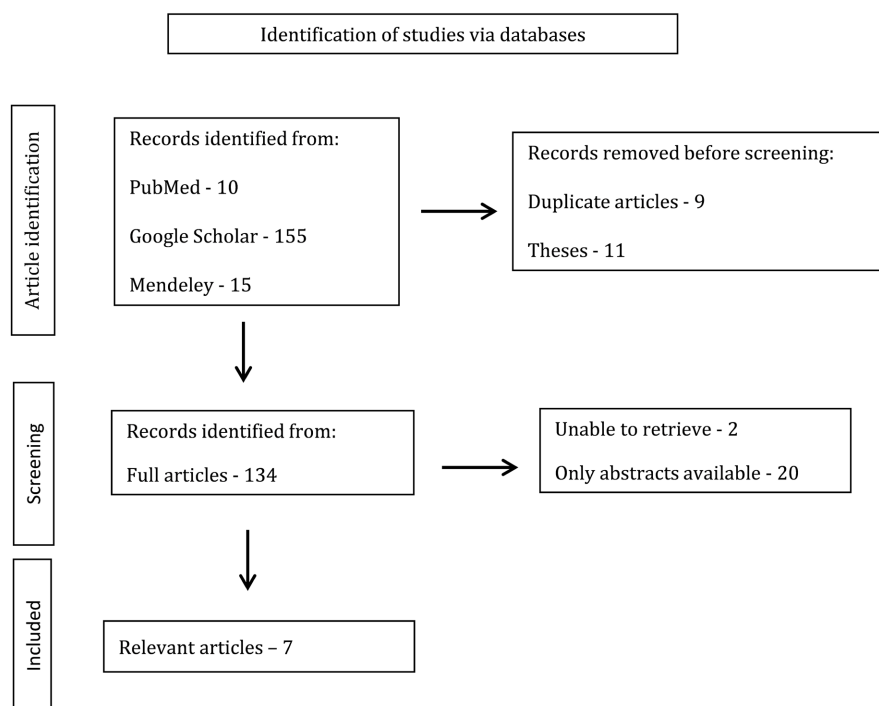


Figure 1. PRISMA flowchart for the review methodology.

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% <i>B. pilosa</i> 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 <i>B. pilosa</i> formulation (probetacell) orally at a daily dose of 400 mg, <i>ter in die</i> , 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 <i>Cα</i> (PKC α) and its activators, calcium, and diacylglycerol (DAG). Cytopiloyne treats type 2 diabetes via regulation of insulin production involving the calcium/DAG/PKC α cascade in β -cells as well as maintaining islet architecture.
[28]	Single oral dose <i>B. pilosa</i> 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 <i>B. pilosa</i> 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 μ g/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

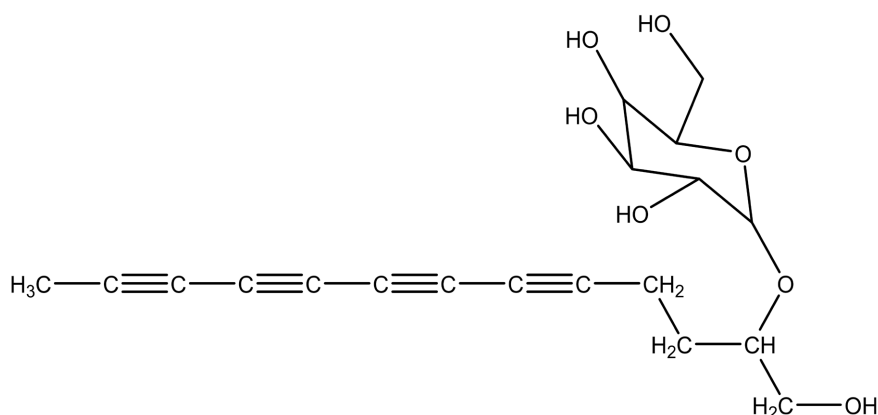


Figure 2. The structure of cytopiloyne [38].

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 insulinitis, 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 (PKC α) 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 phytochemicals 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]. Secretagogue 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 phytochemicals [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.

References

- [1] Kerner, W., Brückel, J. and German Diabetes Association (2014) Definition, Classification and Diagnosis of Diabetes Mellitus. *Experimental and Clinical Endocrinology & Diabetes*, **122**, 384-386. <https://doi.org/10.1055/s-0034-1366278>
- [2] Kharroubi, A.T. and Darwish, H.M. (2015) Diabetes Mellitus: The Epidemic of the Century. *World Journal of Diabetes*, **6**, 850-867. <https://doi.org/10.4239/wjd.v6.i6.850>
- [3] Inzucchi, S.E. and Majumdar, S.K. (2016) Current Therapies for the Medical Management of Diabetes. *Obstetrics and Gynecology*, **27**, 780-794. <https://doi.org/10.1097/AOG.0000000000001332>
- [4] Chillarón, J.J., Flores Le-Roux, J.A., Benaiges, D. and Pedro-Botet, J. (2014) Type 1 Diabetes, Metabolic Syndrome and Cardiovascular Risk. *Metabolism*, **63**, 181-187. <https://doi.org/10.1016/j.metabol.2013.10.002>
- [5] DeWitt, D.E. and Hirsch, I.B. (2003) Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus: Scientific Review. *JAMA*, **289**, 2254-2264. <https://doi.org/10.1001/jama.289.17.2254>
- [6] Gilroy, C.A., Luginbuhl, K.M. and Chilkoti, A. (2015) Controlled Release of Biologics for the Treatment of Type 2 Diabetes. *Journal of Controlled Release*, **240**, 151-164. <https://doi.org/10.1016/j.jconrel.2015.12.002>
- [7] Mooradian, A.D., Bernbaum, M. and Albert, S.G. (2006) Narrative Review: A Rational Approach to Starting Insulin Therapy. *Annals of Internal Medicine*, **145**, 125-134. <https://doi.org/10.7326/0003-4819-145-2-200607180-00010>
- [8] Xu, L., Li, Y., Dai, Y. and Peng, J. (2018) Natural Products for the Treatment of

- Type 2 Diabetes Mellitus: Pharmacology and Mechanisms. *Pharmacological Research*, **130**, 451-465. <https://doi.org/10.1016/j.phrs.2018.01.015>
- [9] Thomas, C.C. and Philipson, L.H. (2015) Update on Diabetes Classification. *Medical Clinics of North America*, **99**, 1-16. <https://doi.org/10.1016/j.mcna.2014.08.015>
- [10] Roden, M. and Shulman, G.I. (2019) The Integrative Biology of Type 2 Diabetes. *Nature*, **576**, 51-60. <https://doi.org/10.1038/s41586-019-1797-8>
- [11] Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K.B., *et al.* (2020) Pathophysiology of Type 2 Diabetes Mellitus. *International Journal of Molecular Sciences*, **21**, Article No. 6275. <https://doi.org/10.3390/ijms21176275>
- [12] Santoro, A. and Kahn, B.B. (2023) Adipocyte Regulation of Insulin Sensitivity and the Risk of Type 2 Diabetes. *New England Journal of Medicine*, **388**, 2071-2085. <https://doi.org/10.1056/NEJMra2216691>
- [13] Amutha, A. and Mohan, V. (2016) Diabetes Complications in Childhood and Adolescent Onset Type 2 Diabetes—A Review. *Journal of Diabetes Complications*, **30**, 951-957. <https://doi.org/10.1016/j.jdiacomp.2016.02.009>
- [14] Van Belle, T.L., Coppieters, K.T. and Von Herrath, M.G. (2011) Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies. *Physiological Reviews*, **91**, 79-118. <https://doi.org/10.1152/physrev.00003.2010>
- [15] Salazar, J., Navarro, C., Ortega, Á., Nava, M., Morillo, D., Torres, W., Hernández, M., *et al.* (2021) Advanced Glycation End Products: New Clinical and Molecular Perspectives. *International Journal of Environmental Research and Public Health*, **18**, Article No. 7236. <https://doi.org/10.3390/ijerph18147236>
- [16] Singh, V.P., Bali, A., Singh, N. and Jaggi, A.S. (2014) Advanced Glycation End Products and Diabetic Complications. *Korean Journal of Physiology & Pharmacology*, **18**, 1-14. <https://doi.org/10.4196/kjpp.2014.18.1.1>
- [17] Engwa, G.A., Ennwekegwa, F.N. and Nkeh-Chungag, B.N. (2022) Free Radicals, Oxidative Stress-Related Diseases and Antioxidant Supplementation. *Alternative Therapies in Health and Medicine*, **28**, 114-128.
- [18] Asmat, U., Abad, K. and Ismail, K. (2016) Diabetes Mellitus and Oxidative Stress—A Concise Review. *Saudi Pharmaceutical Journal*, **24**, 547-553. <https://doi.org/10.1016/j.jsps.2015.03.013>
- [19] Yan, L.J. (2018) Redox Imbalance Stress in Diabetes Mellitus: Role of the Polyol Pathway. *Animal Models and Experimental Medicine*, **1**, 7-13. <https://doi.org/10.1002/ame2.12001>
- [20] Das Evcimen, N. and King, G.L. (2007) The Role of Protein Kinase C Activation and the Vascular Complications of Diabetes. *Pharmacology Research*, **55**, 498-510. <https://doi.org/10.1016/j.phrs.2007.04.016>
- [21] Dierschke, S.K. and Dennis, M.D. (2022) Retinal Protein O-GlcNacylation and the Ocular Renin-Angiotensin System: Signaling Cross-Roads in Diabetic Retinopathy. *Current Diabetes Reviews*, **18**, e011121190177. <https://doi.org/10.2174/1573399817999210111205933>
- [22] Unuofin, J.O. and Lebelo, S.L. (2020) Antioxidant Effects and Mechanisms of Medicinal Plants and Their Bioactive Compounds for the Prevention and Treatment of Type 2 Diabetes: An Updated Review. *Oxidative Medicine and Cellular Longevity*, **2020**, Article ID: 1356893. <https://doi.org/10.1155/2020/1356893>
- [23] Osadebe, P.O., Odoh, E.U. and Uzor, P.F. (2014) Natural Products as Potential Sources of Antidiabetic Drugs. *Journal of Pharmaceutical Research International*, **1**,

- 2075-2095. <https://doi.org/10.9734/BJPR/2014/8382>
- [24] Safavi, M., Foroumadi, A. and Abdollahi, M. (2013) The Importance of Synthetic Drugs for Type 2 Diabetes Drug Discovery. *Expert Opinion on Drug Discovery*, **8**, 1339-1363. <https://doi.org/10.1517/17460441.2013.837883>
- [25] Ahda, M., Jaswir, I., Khatib, A., Ahmed, Q.U., Mahfudh, N. and Ardini, Y.D. (2023) A Review on Selected Herbal Plants as Alternative Anti-Diabetes Drugs: Chemical Compositions, Mechanisms of Action, and Clinical Study. *International Journal of Food Properties*, **26**, 1414-1425. <https://doi.org/10.1080/10942912.2023.2215475>
- [26] Mtenga, D.V. and Ripanda, A.S. (2022) A Review on the Potential of Underutilized Blackjack (*Bidens pilosa*) Naturally Occurring in Sub-Saharan Africa. *Heliyon*, **8**, e09586. <https://doi.org/10.1016/j.heliyon.2022.e09586>
- [27] Yanqing P., Todd, L.L. and Rik, R.T. (2009) Naturally Occurring and Synthetic Polyyne Glycosides. *Canadian Journal of Chemistry*, **87**, 1565-1582. <https://doi.org/10.1139/V09-117>
- [28] Chien, S.C., Young, P.H., Hsu, Y.J., Chen, C.H., Tien, Y.J., Shiu, S.Y., *et al.* (2009) Anti-Diabetic Properties of Three Common *Bidens pilosa* Variants in Taiwan Region. *Phytochemistry*, **70**, 1246-1254. <https://doi.org/10.1016/j.phytochem.2009.07.011>
- [29] Chiang, Y.M., Chang, C.L.T., Chang, S.L., Yang, W.C. and Shyr, L.F. (2007) Cytopylyne, A Novel Polyacetylenic Glucoside from *Bidens pilosa*, Functions as a T Helper Cell Modulator. *Journal of Ethnopharmacology*, **110**, 532-538. <https://doi.org/10.1016/j.jep.2006.10.007>
- [30] Yang, W.C. (2014) Botanical, Pharmacological, Phytochemical, and Toxicological Aspects of the Antidiabetic Plant *Bidens pilosa* L. *Evidence-Based Complementary and Alternative Medicine*, **2014**, Article ID: 698617. <https://doi.org/10.1155/2014/698617>
- [31] Waititu, K., Jerono, C., Kituku, D., Nzuve, M., Mambo, F., Ngugi, P., *et al.* (2018) Phytochemical Composition of *Kalanchoe pinnata* and *Bidens pilosa* Leaves Associated with Management of Diabetes. *Biomedicine and Biotechnology*, **6**, 15-20.
- [32] Chung, C.Y., Yang, W.C., Liang, C.L., Liu, H.Y., Lai, S.K. and Chang, C.L.T. (2016) Cytopylyne, A Polyacetylenic Glucoside from *Bidens pilosa*, Acts as a Novel Anticandidal Agent via Regulation of Macrophages. *Journal of Ethnopharmacology*, **184**, 72-80. <https://doi.org/10.1016/j.jep.2016.02.036>
- [33] Ganjewala, D., Kumar, S., Ambika, K., Luthra, R., Resource, H., Group, D., *et al.* (2008) Plant Polyacetylenic Glycosides Occurrence, Biosynthesis and Biological Activities. *Pharmacologyonline*, **131**, 113-131.
- [34] Xuan, T.D. and Khanh, T.D. (2016) Chemistry and Pharmacology of *Bidens pilosa*: An Overview. *Journal of Pharmaceutical Investigation*, **46**, 91-132. <https://doi.org/10.1007/s40005-016-0231-6>
- [35] Wang, R., Wu, Q.X. and Shi, Y.P. (2010) Polyacetylenes and Flavonoids from the Aerial Parts of *Bidens pilosa*. *Planta Medica*, **76**, 893-896. <https://doi.org/10.1055/s-0029-1240814>
- [36] Ubillas, R.P., Mendez, C.D., Jolad, S.D., Luo, J., King, S.R., Carlson, T.J., *et al.* (2000) Antihyperglycemic Acetylenic Glucosides from *Bidens pilosa*. *Planta Medica*, **66**, 82-83. <https://doi.org/10.1055/s-0029-1243117>
- [37] Chang, S.L., Chang, C.L.T., Chiang, Y.M., Hsieh, R.H., Tzeng, C.R., Wu, T.K., *et al.* (2004) Polyacetylenic Compounds and Butanol Fraction from *Bidens pilosa* Can Modulate the Differentiation of Helper T Cells and Prevent Autoimmune Diabetes in Non-Obese Diabetic Mice. *Planta Medica*, **70**, 1045-1051. <https://doi.org/10.1055/s-2004-832645>

- [38] Chang, C.L.T., Chang, S.L., Lee, Y.M., Chiang, Y.M., Chuang, D.Y., Kuo, H.K., *et al.* (2007) Cytopiloyne, A Polyacetylenic Glucoside, Prevents Type 1 Diabetes in Non-obese Diabetic Mice. *Journal of Immunology*, **178**, 6984-6993. <https://doi.org/10.4049/jimmunol.178.11.6984>
- [39] Bartolome, A.P., Villaseñor, I.M. and Yang, W.C. (2013) *Bidens pilosa* L. (Asteraceae): Botanical Properties, Traditional Uses, Phytochemistry, and Pharmacology. *Evidence-Based Complementary and Alternative Medicine*, **2013**, Article ID: 340215. <https://doi.org/10.1155/2013/340215>
- [40] Chang, C.L.T., Liu, H.Y., Kuo, T.F., Hsu, Y.J., Shen, M.Y., Pan, C.Y., *et al.* (2013) Antidiabetic Effect and Mode of Action of Cytopiloyne. *Evidence-Based Complementary and Alternative Medicine*, **2013**, Article ID: 685642. <https://doi.org/10.1155/2013/685642>
- [41] Wei, W.S.V., Yang, W.C., Sheu, J.H., Shyur, L.F. and Yang, N.S. (2008) Cytopiloyne, A Polyacetylenic Glucoside from *Bidens pilosa*, Modulates T Cell Differentiation through Suppression of IL-12 Expression in Human Dendritic Cells. *Planta Medica*, **74**, PA6. <https://doi.org/10.1055/s-0028-1084006>
- [42] Liang, Y.C., Yang, M.T., Lin, C.J., Chang, C.L.T. and Yang, W.C. (2016) *Bidens pilosa* and Its Active Compound Inhibit Adipogenesis and Lipid Accumulation via Down-Modulation of the C/EBP and PPAR γ Pathways. *Scientific Reports*, **6**, Article No. 24285. <https://doi.org/10.1038/srep24285>
- [43] Lai, B.Y., Chen, T.Y., Huang, S.H., Kuo, T.F., Chang, T.H., Chiang, C.K., *et al.* (2015) *Bidens pilosa* Formulation Improves Blood Homeostasis and β -Cell Function in Men: A Pilot Study. *Evidence-Based Complementary and Alternative Medicine*, **2015**, Article ID: 832314. <https://doi.org/10.1155/2015/832314>
- [44] Hsu, Y.J., Lee, T.H., Chang, C.L.T., Huang, Y.T. and Yang, W.C. (2009) Anti-Hyperglycemic Effects and Mechanism of *Bidens pilosa* Water Extract. *Journal of Ethnopharmacology*, **122**, 379-383. <https://doi.org/10.1016/j.jep.2008.12.027>
- [45] Kumar, C.R., Tsai, C.H., Chao, Y.S. and Lee, J.C. (2011) The First Total Synthesis of Cytopiloyne, An Anti-Diabetic, Polyacetylenic Glucoside. *Chemistry*, **17**, 8696-8703. <https://doi.org/10.1002/chem.201100986>
- [46] Grossman, L.D., Roscoe, R. and Shack, A.R. (2018) Complementary and Alternative Medicine for Diabetes. *Canadian Journal of Diabetes*, **42**, S154-S161. <https://doi.org/10.1016/j.jcjd.2017.10.023>
- [47] La Noce, M., Nicoletti, G.F., Papaccio, G., Del Vecchio, V. and Papaccio, F. (2022) Insulinitis in Human Type 1 Diabetic Pancreas: From Stem Cell Grafting to Islet Organoids for a Successful Cell-Based Therapy. *Cells*, **11**, Article No. 3941. <https://doi.org/10.3390/cells11233941>
- [48] Roep, B.O., Thomaidou, S., Van Tienhoven, R. and Zaldumbide, A. (2021) Type 1 Diabetes Mellitus as a Disease of the β -Cell (Do Not Blame the Immune System?). *Nature Reviews Endocrinology*, **17**, 150-161. <https://doi.org/10.1038/s41574-020-00443-4>
- [49] Shen, M.Y., Lin, Y.P., Yang, B.C., Jang, Y.S., Chiang, C.K., Mettling, C., *et al.* (2012) Catenarin Prevents Type 1 Diabetes in Nonobese Diabetic Mice via Inhibition of Leukocyte Migration Involving the MEK6/P38 and MEK7/JNK Pathways. *Evidence-Based Complementary and Alternative Medicine*, **2012**, Article ID: 982396. <https://doi.org/10.1155/2012/982396>
- [50] Campbell-Thompson, M., Fu, A., Kaddis, J.S., Wasserfall, C., Schatz, D.A., Pugliese, A., *et al.* (2016) Insulinitis and β -Cell Mass in the Natural History of Type 1 Diabetes. *Diabetes*, **65**, 719-731. <https://doi.org/10.2337/db15-0779>

- [51] Bulfoni, M., Bouyioukos, C., Zakaria, A., Nigon, F., Rapone, R., Del Maestro, L., Ait-Si-Ali, S., Scharfmann, R. and Cosson, B. (2022) Glucose Controls Co-Translation of Structurally Related mRNAs via the mTOR and eIF2 Pathways in Human Pancreatic Beta Cells. *Frontiers in Endocrinology*, **13**, Article ID: 949097. <https://doi.org/10.3389/fendo.2022.949097>
- [52] Komatsu, M., Takei, M., Ishii, H. and Sato, Y. (2013) Glucose-Stimulated Insulin Secretion: A Newer Perspective. *Journal of Diabetes Investigations*, **4**, 511-516. <https://doi.org/10.1111/jdi.12094>
- [53] Chen, Y.G., Mathews, C.E. and Driver, J.P. (2018) The Role of NOD Mice in Type 1 Diabetes Research: Lessons from the Past and Recommendations for the Future. *Frontiers in Endocrinology*, **9**, Article No. 51. <https://doi.org/10.3389/fendo.2018.00051>
- [54] Oh, Y.S. (2015) Plant-Derived Compounds Targeting Pancreatic Beta Cells for the Treatment of Diabetes. *Evidence-Based Complementary and Alternative Medicine*, **2015**, Article ID: 629863. <https://doi.org/10.1155/2015/629863>
- [55] Li, Y., Hong, W. and Li, L.-C. (2021) Pharmacogenomics of Insulin Secretagogues in Pharmacodynamics, Pharmacokinetics and Adverse Reactions. *Austin Journal of Pharmacology and Therapeutics*, **9**, Article No. 1152.
- [56] Chang, C.L.T., Kuo, H.K., Chang, S.L., Chiang, Y.M., Lee, T.H., Wu, W.M., *et al.* (2005) The Distinct Effects of a Butanol Fraction of *Bidens pilosa* Plant Extract on the Development of Th1-Mediated Diabetes and Th2-Mediated Airway Inflammation in Mice. *Journal of Biomedical Science*, **12**, 79-89. <https://doi.org/10.1007/s11373-004-8172-x>
- [57] Rodríguez-Mesa, X.M., Contreras, B.L.A., Mejía, A., Pombo, L.M., Modesti, C.G. and Santander, G.S.P. (2023) Immunomodulatory Properties of Natural Extracts and Compounds Derived from *Bidens pilosa* L.: Literature Review. *Pharmaceutics*, **15**, Article No. 1491. <https://doi.org/10.3390/pharmaceutics15051491>
- [58] Apaya, M.K., Kuo, T.F., Yang, M.T., Yang, G., Hsiao, C.L., Chang, S.B., *et al.* (2020) Phytochemicals as Modulators of β -Cells and Immunity for the Therapy of Type 1 Diabetes: Recent Discoveries in Pharmacological Mechanisms and Clinical Potential. *Pharmacology Research*, **156**, Article ID: 104754. <https://doi.org/10.1016/j.phrs.2020.104754>
- [59] Ajagun-Ogunleye, M.O., Tirwomwe, M., Mitaki, R.N., Ejekwumadu, J.N., Kasozi, K.I., Pantoglou, J., *et al.* (2015) Hypoglycemic and High Dosage Effects of *Bidens pilosa* in Type-1 Diabetes Mellitus. *Journal of Diabetes Mellitus*, **5**, 146-154. <https://doi.org/10.4236/jdm.2015.53018>
- [60] Padhi, S., Nayak, A.K. and Behera, A. (2020) Type II Diabetes Mellitus: A Review on Recent Drug-Based Therapeutics. *Biomedicine and Pharmacotherapy*, **131**, Article ID: 110708. <https://doi.org/10.1016/j.biopha.2020.110708>
- [61] Clark, M., Kroger, C.J. and Tisch, R.M. (2017) Type 1 Diabetes: A Chronic Anti-Self-Inflammatory Response. *Frontiers in Immunology*, **8**, Article No. 1898. <https://doi.org/10.3389/fimmu.2017.01898>
- [62] Eisenbarth, G.S. (2004) Type 1 Diabetes: Molecular, Cellular and Clinical Immunology. *Advances in Experimental Medicine and Biology*, **552**, 306-310.
- [63] Richardson, S.J., Willcox, A., Bone, A.J., Morgan, N.G. and Foulis, A.K. (2011) Immunopathology of the Human Pancreas in Type-I Diabetes. *Seminars in Immunopathology*, **33**, 9-21. <https://doi.org/10.1007/s00281-010-0205-0>
- [64] Pugliese, A. (2017) Autoreactive T Cells in Type 1 Diabetes. *Journal of Clinical Investigations*, **127**, 2881-2891. <https://doi.org/10.1172/JCI94549>

- [65] Gomez-Tourino, I., Arif, S., Eichmann, M. and Peakman, M. (2016) T Cells in Type 1 Diabetes: Instructors, Regulators and Effectors: A Comprehensive Review. *Journal of Autoimmunity*, **66**, 7-16. <https://doi.org/10.1016/j.jaut.2015.08.012>
- [66] Clark, M., Kroger, C.J., Ke, Q. and Tisch, R.M. (2021) The Role of T Cell Receptor Signaling in the Development of Type 1 Diabetes. *Frontiers in Immunology*, **11**, Article ID: 615371. <https://doi.org/10.3389/fimmu.2020.615371>
- [67] Burrack, A.L., Martinov, T. and Fife, B.T. (2017) T Cell-Mediated Beta Cell Destruction: Autoimmunity and Alloimmunity in the Context of Type 1 Diabetes. *Frontiers in Endocrinology*, **8**, Article No. 343. <https://doi.org/10.3389/fendo.2017.00343>
- [68] Willcox, A., Richardson, S.J., Bone, A.J., Foulis, A.K. and Morgan, N.G. (2009) Analysis of Islet Inflammation in Human Type 1 Diabetes. *Clinical & Experimental Immunology*, **155**, 173-181. <https://doi.org/10.1111/j.1365-2249.2008.03860.x>
- [69] Arif, S., Gibson, V.B., Nguyen, V., Bingley, P.J., Todd, J.A., Guy, C., et al. (2017) β -Cell Specific T-Lymphocyte Response Has a Distinct Inflammatory Phenotype in Children with Type 1 Diabetes Compared with Adults. *Diabetic Medicine*, **34**, 419-425. <https://doi.org/10.1111/dme.13153>
- [70] Ke, Q., Kroger, C.J., Clark, M. and Tisch, R.M. (2021) Evolving Antibody Therapies for the Treatment of Type 1 Diabetes. *Frontiers in Immunology*, **11**, Article ID: 624568. <https://doi.org/10.3389/fimmu.2020.624568>
- [71] Anderson, M.S. and Bluestone, J.A. (2005) The NOD Mouse: A Model of Immune Dysregulation. *Annual Review of Immunology*, **23**, 447-485. <https://doi.org/10.1146/annurev.immunol.23.021704.115643>
- [72] Pearson, J.A., Wong, F.S. and Wen, L. (2016) The Importance of the Non Obese Diabetic (NOD) Mouse Model in Autoimmune Diabetes. *Journal of Autoimmunity*, **66**, 76-88. <https://doi.org/10.1016/j.jaut.2015.08.019>
- [73] Crawford, F., Stadinski, B., Jin, N., Michels, A., Nakayama, M., Pratt, P., et al. (2011) Specificity and Detection of Insulin-Reactive CD4+ T Cells in Type 1 Diabetes in the Nonobese Diabetic (NOD) Mouse. *Proceedings of the National Academy of Sciences*, **108**, 16729-16734. <https://doi.org/10.1073/pnas.1113954108>
- [74] Babad, J., Geliebter, A. and DiLorenzo, T.P. (2010) T-Cell Autoantigens in the Non-Obese Diabetic Mouse Model of Autoimmune Diabetes. *Immunology*, **131**, 459-465. <https://doi.org/10.1111/j.1365-2567.2010.03362.x>
- [75] Walker, L.S.K. and Von Herrath, M. (2016) CD4 T Cell Differentiation in Type 1 Diabetes. *Clinical & Experimental Immunology*, **183**, 16-29. <https://doi.org/10.1111/cei.12672>
- [76] Lu, J., Liu, J., Li, L., Lan, Y. and Liang, Y. (2020) Cytokines in Type 1 Diabetes: Mechanisms of Action and Immunotherapeutic Targets. *Clinical & Translational Immunology*, **9**, e1122. <https://doi.org/10.1002/cti2.1122>
- [77] DiMeglio, L.A., Evans-Molina, C. and Oram, R.A. (2018) Type 1 Diabetes. *The Lancet*, **391**, 2449-2462. [https://doi.org/10.1016/S0140-6736\(18\)31320-5](https://doi.org/10.1016/S0140-6736(18)31320-5)
- [78] Wei, W.C., Liu, C.P., Yang, W.C., Shyur, L.F., Sheu, J.H., Chen, S.S., et al. (2015) Mammalian Target of Rapamycin Complex 2 (MTORC2) Regulates LPS-Induced Expression of IL-12 and IL-23 in Human Dendritic Cells. *Journal of Leukocyte Biology*, **97**, 1071-1080. <https://doi.org/10.1189/jlb.2A0414-206RR>
- [79] Bairwa, K., Kumar, R., Sharma, R.J. and Roy, R.K. (2010) An Updated Review on *Bidens pilosa* L. *Der Pharma Chemica*, **2**, 325-337.
- [80] Grant, B., Sandelson, M., Agyemang-Prempeh, B. and Zalin, A. (2021) Managing

- Obesity in People with Type 2 Diabetes. *Clinical Medicine*, **21**, e327-e331. <https://doi.org/10.7861/clinmed.2021-0370>
- [81] Reed, J., Bain, S. and Kanamarlapudi, V. (2021) A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, **14**, 3567-3602. <https://doi.org/10.2147/DMSO.S319895>
- [82] Aronne, L.J., Hall, K.D., Jakicic, J., Leibel, R.L., Lowe, M.R., Rosenbaum, M., *et al.* (2021) Describing the Weight-Reduced State: Physiology, Behavior, and Interventions. *Obesity (Silver Spring)*, **29**, S9-S24. <https://doi.org/10.1002/oby.23086>
- [83] Hall, K.D. and Kahan S. (2018) Maintenance of Lost Weight and Long-Term Management of Obesity. *Medical Clinics of North America*, **102**, 183-197. <https://doi.org/10.1016/j.mcna.2017.08.012>
- [84] Enright, C., Thomas, E. and Saxon, D.R. (2023) An Updated Approach to Antiobesity Pharmacotherapy: Moving beyond the 5% Weight Loss Goal. *Journal of the Endocrine Society*, **7**, Bvac195. <https://doi.org/10.1210/jendso/bvac195>
- [85] Walmsley, R. and Sumithran, P. (2023) Current and Emerging Medications for the Management of Obesity in Adults. *Medical Journal of Australia*, **218**, 276-283. <https://doi.org/10.5694/mja2.51871>
- [86] Czepiel, K.S., Perez, N.P., Campoverde, R.K.J., Sabharwal, S. and Stanford, F.C. (2020) Pharmacotherapy for the Treatment of Overweight and Obesity in Children, Adolescents, and Young Adults in a Large Health System in the US. *Frontiers in Endocrinology*, **11**, Article No. 290. <https://doi.org/10.3389/fendo.2020.00290>
- [87] Müller, T.D., Blüher, M., Tschöp, M.H. and DiMarchi, R.D. (2022) Anti-Obesity Drug Discovery: Advances and Challenges. *Nature Reviews Drug Discovery*, **21**, 201-223. <https://doi.org/10.1038/s41573-021-00337-8>
- [88] Son, J. and Accili, D. (2023) Reversing Pancreatic β -Cell Dedifferentiation in the Treatment of Type 2 Diabetes. *Experimental & Molecular Medicine*, **55**, 1652-1658. <https://doi.org/10.1038/s12276-023-01043-8>
- [89] Yun, J.W. (2010) Possible Anti-Obesity Therapeutics from Nature—A Review. *Phytochemistry*, **71**, 1625-1641. <https://doi.org/10.1016/j.phytochem.2010.07.011>
- [90] Gamboa-Gómez, C.I., Rocha-Guzmán, N.E., Gallegos-Infante, J.A., Moreno-Jiménez, M.R., Vázquez-Cabral, B.D. and González-Laredo, R.F. (2015) Plants with Potential Use on Obesity and Its Complications. *EXCLI Journal*, **14**, 809-831.
- [91] Farmer, S.R. (2008) Molecular Determinants of Brown Adipocyte Formation and Function. *Genes & Development*, **22**, 1269-1275. <https://doi.org/10.1101/gad.1681308>
- [92] Moseti, D., Regassa, A. and Kim, W.K. (2016) Molecular Regulation of Adipogenesis and Potential Anti-Adipogenic Bioactive Molecules. *International Journal of Molecular Sciences*, **17**, Article No. 124. <https://doi.org/10.3390/ijms17010124>
- [93] Siersbaek, R., Nielsen, R. and Mandrup, S. (2010) PPARgamma in Adipocyte Differentiation and Metabolism—Novel Insights from Genome-Wide Studies. *FEBS Letters*, **584**, 3242-3249. <https://doi.org/10.1016/j.febslet.2010.06.010>
- [94] Barnes, P.M., Powell-Griner, E., McFann, K. and Nahin, R.L. (2004) Complementary and Alternative Medicine Use among Adults: United States, 2002. *Seminars in Integrative Medicine*, **2**, 54-71. <https://doi.org/10.1016/j.sigm.2004.07.003>
- [95] Hasani-Ranjbar, S., Jouyandeh, Z. and Abdollahi, M. (2013) A Systematic Review of Anti-Obesity Medicinal Plants—An Update. *Journal of Diabetes and Metabolic Disorders*, **12**, Article No. 28. <https://doi.org/10.1186/2251-6581-12-28>

- [96] Karri, S., Sharma, S., Hatware, K. and Patil, K. (2019) Natural Anti-Obesity Agents and Their Therapeutic Role in Management of Obesity: A Future Trend Perspective. *Biomedicine and Pharmacotherapy*, **110**, 224-238.
<https://doi.org/10.1016/j.biopha.2018.11.076>
- [97] Mir, S.A., Shah, M.A., Ganai, S.A., Ahmad, T. and Gani, M. (2019) Understanding the Role of Active Components from Plant Sources in Obesity Management. *Journal of the Saudi Society of Agricultural Sciences*, **18**, 168-176.
<https://doi.org/10.1016/j.jssas.2017.04.003>