Bidens pilosa: Nutritional value and benefits for metabolic syndrome

Tien-Fen Kuo1,*  |  Greta Yang1,*  |  Tzung-Yan Chen1,2,*  |  Yueh-Chen Wu1  |  Hieu Tran
Nguyen Minh1,3  |  Lin-Shyan Chen1  |  Wen-Chu Chen1,5  |  Ming-Guang Huang4  |  Yu-Chuan Liang1  |  Wen-Chin Yang1,2,3,5,6,7

1 Biotechnology Research Center, Academia Sinica, Taipei, Taiwan
2 Translational Research Center, Academia Sinica, Taipei, Taiwan
3 Institute of Biotechnology, National Taiwan University, Taipei, Taiwan
4 Exland Biotechnology Inc., Nantou, Taiwan
5 Department of Life Sciences, National Chung-Hsing University, Taichung, Taiwan
6 Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan
7 Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

Correspondence
Dr. Wen-Chin Yang, Agricultural Biotechnology Research Center, Academia Sinica, 128, Academia Rd. Section 2, Nankang, Taipei, Taiwan, R.O.C.
Email: wcyang@gate.sinica.edu.tw

*Authors Kuo, Yang, and Chen have equal contribution.

Abstract

The genus Bidens (Asteraceae) encompasses over 240 different species. One of them is Bidens pilosa L. that is an easy-to-grow perennial, and broadly distributed in tropical and subtropical regions of the world. This plant has been regarded as an edible plant by the Food and Agriculture Organization of the United Nations since 1975, and has been traditionally used as a food and medicine in America, Africa, and Asia. B. pilosa has been claimed to possess active compounds with more than 40 distinct bioactivities. Although considerable progress has been made in studying the phytochemistry and biology of B. pilosa and its compounds over recent years, a critical review of its dietary functions for metabolic syndrome is unavailable. The present review summarizes the nutrition, benefits, phytochemistry, and safety of B. pilosa with respect to metabolic syndrome. As well as highlighting studies of the use of B. pilosa for metabolic syndrome, scientific evidence regarding the antimetabolic action, mechanism, and application of this species and its active phytochemicals are discussed. This review consolidates information for further study into the medicinal benefits of the compounds in this plant.

KEYWORDS
Bidens pilosa, functional food, hyperlipidemia, hypertension, metabolic syndrome, polyyne

1 | INTRODUCTION

Metabolic syndrome is diagnosed in adults when at least three of the following five risk factors are present; hypertension, hyperglycemia, obesity (measured by waist circumference), hyperlipidemia, and low-serum high-density lipoprotein (Grundy, 2008). One-fourth of the global population are estimated to have diabetes (Nolan, Carrick-Ranson, Stinear, Reading, & Dalleck, 2017). Patients with metabolic syndrome have fatal complications such as cardiovascular diseases, stroke, atherosclerosis, diabetes, renal disease, etc. (Grundy, 2005).

Unhealthy diets and unhealthy lifestyles, including excess nutrition, lack of exercise, and obesity, are common causes of metabolic syndrome (Elliot & Hamlin, 2018).

Different approaches have been developed to prevent and treat metabolic syndrome. However, its prevalence is still increasing. Dietary intervention and lifestyle modification are commonly used strategies (Elliot & Hamlin, 2018). Over 300,000 flowering plant species have been identified worldwide. Of note, 1,200 plants have been claimed to treat diabetes (Habeck, 2003; Marles & Farnsworth, 1995), one risk factor for metabolic syndrome. Bidens pilosa is one of them. B. pilosa...
is well known as an ingredient in diets, drinks, and medicinal remedies (Karis & Ryding, 1994; Pozharitskaya et al., 2010). It is a palatable herb that grows in Asia, Africa, and South America. B. pilosa, either the whole plant or its leaves, flowers, stems, and/or roots, fresh or dried, are used for dietary or medicinal purposes. Decoction, maceration and tincture, and/or powder of B. pilosa are the usual formulations for its applications (Redl, Breu, Davis, & Bauer, 1994). This plant has been reported to possess more than 40 bioactivities such as antidiabetic (Chien et al., 2009; Hsu, Lee, Chang, Huang, & Yang, 2009), antiobesity (Liang, Yang, Lin, Chang, & Yang, 2016), antihypertensive activities (Dimo et al., 2001; Dimo et al., 1999), and others (Table 1). B. pilosa has been recorded for the treatment of diabetes, hypertension, and obesity on different continents in the world (Oliveira, Andrade-Neto, Krettli, & Brandao, 2004). The related literature demonstrates the utility of this plant and its active phytochemicals to manage metabolic syndrome. Similar to B. pilosa, B. tripartita, B. cernua, B. bipinnata, B. engleri, B. ordorata, B. frondosa, and B. laevis are common Bidens species that were used for the folkloric medicine. Among them, B. tripartita was also shown to possess antidiabetic activity (Orhan, 2016 #2443). However, little is known about their function in metabolic syndrome.

This review concentrates on recent discoveries on the nutrition, antimetabolic mode of action, phytochemistry, and safety of B. pilosa. The information presented summarizes the efficacy of B. pilosa and its phytochemicals, which could shed insight for future research.

2 | NUTRITIONAL VALUE AND SAFETY

B. pilosa originated from South America and subsequently invaded other regions of the world (Ge, 1990). Taxonomically speaking, it is classified into the Bidens genus, which contains up to 240 species (Table 2) (Karis & Ryding, 1994; Pozharitskaya et al., 2010). B. pilosa is a short-lived perennial herb widespread worldwide. It has lobed, serrate, or separate green opposite leaves, barbed achenes, and white or yellow flowers (Figure 1) (Bartolome, Villasenor, & Yang, 2013). The whole plant and, particularly, the leaves of B. pilosa are commonly used as ingredients in foods and drinks. The nutritional aspects of B. pilosa are indicated in Table 3 (Alikwe, Ohimain, & Omotosho, 2014). It is rich in phytochemicals, minerals, and essential amino acids (Alikwe et al., 2014). This plant prefers high temperature, full sun, and semidry soil for its propagation. However, it can also grow in arid and barren land at different altitudes (FAO, 1997). B. pilosa can be cultivated via plant cutting or seeds. B. pilosa achenes germinate in three to four days post-soaking (Rokaya, Munzbergova, Timsina, & Bhattarai, 2012). Simple agricultural methods are sufficient for B. pilosa plantation because it is a notoriously fast-spreading weed found throughout the world (Young, Hsu, & Yang, 2010).

B. pilosa is recognized as safe and is able to be consumed as food by humans and animals. In addition, B. pilosa has also been used as a medicinal plant for treating different types of malaise in humans and animals. The use of B. pilosa as a staple food in Africa was suggested by the Food and Agricultural Organization of the United Nations in 1975 (Young et al., 2010). Currently, B. pilosa is one ingredient of products with the brand names Probetacell and Remeta-BP (Young et al., 2010) in the United States and Taiwan. However, systemic toxicological study of B. pilosa in humans has not been conducted. One seminal study revealed that 90-day administration with the B. pilosa-based health food (Probetacell) at a daily dose of 400 mg/person, three times a day showed no obvious adverse effects as evidenced by hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PBG), insulin, triglyceride (TRIG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), alanine transaminase (ALT), aspartate transaminase (AST), creatinine, and blood urea nitrogen (BUN) (Table 4) (Lai et al., 2015). Some studies on acute, subchronic, and chronic toxicities of B. pilosa have been conducted in rodents. Liang and colleagues showed that administration of B. pilosa whole plant at 1 g/kg body weight (BW) for 24 weeks, a dosage of close to 10% of food, in mice showed no toxicity as evidenced by their food intake, water consumption, serum biochemistry, hematology, urine analysis, BW, mortality, organ weight, genotoxicity, and organ histopathology (Liang et al., 2019). Similar results were also obtained in chickens fed with B. pilosa for 28 days. Another study by Frida et al. stated that the aqueous extract of B. pilosa leaves (10 g/kg BW) did not show any fatality or changes in rats (Frida, Rakotonirina, Rakotonirina, & Savin, 2007). A daily dose of the same extract at 0.8 g/kg BW exhibited no noticeable 28-day toxicity in rats, as evidenced by survival, BW, and gross examination of vital organs (Frida et al., 2007). The acute toxicity of its hydroethanolic extracts in 6-week-old mice, intraperitoneally injected with the different doses of both extracts, was also assessed (Frida et al., 2007). The water and hydroethanolic extracts had LD50 values of 12.3 and 6.2 g/kg BW, respectively, in mice (Frida et al., 2007). Other studies by the Ezeonwumelu and Liang groups demonstrated that one daily dose of the water extract of the B. pilosa plant (1 g/kg BW) had no toxicity over 28 days in Wistar rats (Bartolome et al., 2013; Ezeonwumelu et al., 2011). Collectively, the data show that a daily intake of B. pilosa water extract at 1 g/kg BW is highly safe.
| Biological Activities | Active compound | Mechanism of action | Reference |
|-----------------------|-----------------|---------------------|-----------|
| Cytotoxic             | Centaureidin, butein, 1-phenylhepta-1,3,5-triyne, linoleic acid | B. pilosa has cytotoxic activity. Several compounds are thought to be cytotoxic compounds with multiple mechanisms. One flavonoid, centaureidin, induces antimitotic activity in cells via inhibition of tubulin polymerization. Another flavonoid, butein, is a protein kinase inhibitor, which generates cytotoxicity in colon cancer cells. A polyyne, 1-phenylhepta-1,3,5-triyne, is a light-sensitive polyyne. It shows phototoxicity in response to UV light probably targeting the cell membrane by either generating singlet oxygen or reacting by a free radical mechanism. Linoleic acid possesses cytotoxicity in different types of cells. | (Beutler et al., 1993; Beutler et al., 1998; Cury-Boaventura, Gorjao, de Lima, Newsholme, & Curi, 2006; Cury-Boaventura, Pompeia, & Curi, 2004; Cury-Boaventura, Pompeia, & Curi, 2005; Greene & Hammock, 1999; Kaneko, Baba, & Matsuo, 2001; Towers & Hudson, 1987; Yang, Zhang, Cheng, & Mack, 1998; Yit & Das, 1994) |
| Antiflavivirus         | Luteolin        | B. pilosa has shown its antiviral activity in vitro and in vivo. Its flavone, luteolin, has antiviral activity in vitro and in vivo. | (Krylova, Popov, Leonova, Artiukov, & Maistrovskaia, 2011) |
| Anti-HIV              | Luteolin        | Luteolin exhibits inhibitory activities against human immunodeficiency virus-1 (HIV-1) with an IC$_{50}$ value of 11 μM but its antiviral mechanism is not clear. | (Corren, Lemay, Lin, Rozga, & Randolph, 2008; Tewtrakul et al., 2003) |
| Antiherpes            | Linoleic acid   | Linoleic acid was reported to inhibit herpes but its antiviral mechanism is not clear. | (Das, 2006) |
| Anti-influenza        | Linoleic acid   | Linoleic acid was reported to inhibit influenza virus but its antiviral mechanism is not clear. | (Das, 2006) |
| Antisendai            | Linoleic acid   | Linoleic acid was reported to inhibit sendai virus but its antiviral mechanism is not clear. | (Das, 2006) |
| Antisindbis           | Linoleic acid   | Linoleic acid was reported to inhibit sindbis virus but its antiviral mechanism is not clear. | (Das, 2006) |
| Anti-RSV              | 3,5-Di-O-caffeoylquinic acid, 4,5-Di-O-caffeoylquinic acid, 3,4-Di-O-caffeoylquinic acid | 3,4-Di-O-caffeoylquinic acid and 3,5-di-O-caffeoylquinic acid inhibited respiratory syncytial virus (RSV) with IC$_{50}$ values of 2.33 μM (1.2 μg/mL) and 1.16 μM (0.6 μg/mL), respectively, in a plaque reduction assay. | (Li, But, & Ooi, 2005) |
| Antibacterial         | Linoleic acid, 2-ß-D-(R)-1,2-dihydroxytrideca-3,5, 7,9,11-pentayne, 2-ß-D-glycopyrasyloxy-1-hydroxytrideca3,5,7,9,11-pentayne, 1-phenylhepta-1,3,5-triyne, | B. pilosa is known to exert its antimicrobial activity in vitro and in vivo. Linoleic acid was reported to kill bacteria such as Staphylococcus. 2-ß-D-glycopyrasyloxy-1-hydroxytrideca3,5,7,9,11-pentayne can kill bacteria at 1–128 μg/mL. 1-Phenylhepta-1,3,5-triyne had antibacterial activity. | (Ashafa & Afolayan, 2009; Das, 2006; Kimura, Hiraoka, Kawano, Fujioka, & Shimada, 2008; Lawal et al., 2015; Tobinaga et al., 2009) |
| Antilisterial         | Centaureidin and centaurein | B. pilosa extracts induce the production of interferon-γ to suppress Listeria infection in mice. Two flavonoids, Centaureidin and centaurein are active compounds that upregulate the expression of interferon-γ. Both flavonoids also protect mice from Listeria infection in mice. | (Chang et al., 2007; Chang et al., 2007) |
| Antileishmanial       | Butein          | Butein present in Asteraceae plants were proposed to be active compounds against Leishmania parasites. | (Li, 2002; Neto et al., 2019) |
| Antimalarial          | Linoleic acid, 2-ß-D-glucopyranosyloxy-1-hydroxy-5(E)-tridec-7,9,11-triyne, 1-Phenyl-1,3-diyn-5-en-7-ol-acetate | Oral administration of the B. pilosa extracts at 500 mg/kg or less malaria infection in mice as evidenced by malaria parasitemia and mortality. Linoleic acid was shown to kill malaria via unknown mechanism. Polynes and flavonoids might be antimalarial compounds. (R)-1,2-dihydroxytrideca-3,5,7,9,11-pentayne inhibited the invasion of plasmodium into blood cells with an IC$_{50}$ of 0.35 μg/mL. 1-Phenyl-1,3-diyn-5-en-7-ol-acetate was proposed as an active compound against malaria. | (Andrade-Neto et al., 2004; Brandao, Krettli, Soares, Nery, & Marinuzi, 1997; Das, 2006; Oliveira et al., 2007) |
### Table 1 (Continued)

| Biological Activities | Active compound | Mechanism of action | Reference |
|-----------------------|------------------|---------------------|-----------|
| Antifungal            | 1-Phenylhepta-1,3,5-triyne | 1-Phenylheptatriyne at 12.5-50 μg/mL was effective against different yeasts such as *Candida spp.*, *Cryptococcus neoformans*, *Trichosporon cutaneum*, and *Rhodotorula glutinis* at and for basidiomycetous yeasts as 12.5–100 microg/mL. | (Rybalchenko et al., 2010) |
| Nematicidal           | 1-Phenylhepta-1,3,5-triyne | Polyynes are known to suppress nematodes. 1-Phenylhepta-1,3,5-triyne and its derivatives had nematicidal activities against *Bursaphelenchus xylophilus* and *Caenorhabditis elegans*, but not *Pratylenchus penetrans*. | (Kimura et al., 2008) |
| Antiallergic          | Luteolin         | *B. pilosa* was claimed to have antiallergic activity in men. Its active compound, luteolin, was identified and shown to suppress production of tumor necrosis factor-α in macrophages. Luteolin at 1 mg per ear inhibited allergy in mouse models of ear edema induced by arachidon acid, phorbol ester, and oxazolone. Jang et al. indicated that luteolin reduced production of IL-4, IL-5 and IL-13 and allergy and rhinitis in ovalbumin-induced mice. | (Horicuchhi & Seyama, 2006; Jang et al., 2017; Ueda, Yamazaki, & Yamazaki, 2002) |
| Anti-inflammatory and immuno-suppressive | Ethyl caffeate, 1,3-Dihydroryx-6(E)-tetradecone-8,10,12-triyne, 1,2-dihydroxytrideca-5,7,9,11-tetrayne, 1,2-dihydroxy-5(E)-tridecene-7,9,11-triyne | *B. pilosa* was claimed to suppress inflammation. Chiang et al. showed that ethyl caffeate inhibited reduced inflammatory molecules such as Cox-2, iNOS, and PGE2 via an inactivation of NFκB in macrophages. Chiang et al. and Chang et al. concluded that three polyynes of *B. pilosa* suppressed interferon γ and type 1 diabetes (T1D) in nonobese diabetic mice. Fan et al. demonstrated that quercetin 3-O-β-D-galactopyranoside lowered the level of IL-1α, TNF-β, and iNOS in lipopolysaccharide-induced ganglia cells. This reduction involved inactivation of MAPK and NFκB pathway. | (Chang et al., 2007; Chang et al., 2005; Fan et al., 2017; Horicuchhi & Seyama, 2006) |
| Anticancer, antiangiogenic, antiproliferative and/or pro-apoptotic | Cytopiloyne, 1,3-Dihydroryx-6(E)-tetradecone-8,10,12-triyne, 1,2-dihydroxytrideca-5,7,9,11-tetrayne, 1,2-dihydroxy-5(E)-tridecene-7,9,11-triyne | Wu et al. demonstrated that three polyyne glycones of *B. pilosa* inhibited the growth of human umbilical vein endothelial cells via targeting the caspase-7 and CDK inhibitors. Polyynes involved inhibition of cell proliferation and induction of cell death. | (Kuo et al., 2017; Wright et al., 1992; Wu et al., 2007) |
| Antidiabetic           | Cytopiloyne, 3-β-D-glucopyranosyl-1-hydroxy-6(E)-tetradecone-8,10,12-triyne, 2-β-D-glucopyranosylxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne | *B. pilosa* at 50-250 mg/kg has shown its potential to treat T1D and T2D. Three glucosides at 0.5–2.5 mg/kg were shown to treat T2D. More importantly, *B. pilosa* was effective against T2D in humans akin to its efficacy in mice of T2D. | (Chang, Liu, et al., 2013; Chien et al., 2009; Hsu et al., 2009; Lai et al., 2015; Young et al., 2010) |
| Antihypertensive       | Not identified | Neutral extracts of *B. pilosa* at 350 mg/kg body weight reduces SBP and heart rate in rats fed with fructose. | (Dimo et al., 1999; Dimo et al., 2003; Nguelefack et al., 2005) |
| Antiobese             | Cytopiloyne, 3-β-D-glucopyranosyl-1-hydroxy-6(E)-tetradecone-8,10,12-triyne, 2-β-D-glucopyranosylxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne | *B. pilosa* extracts and its active polyynes directly inhibit adipogenesis in adipocytes via downregulation of Egr2, C/EBPs, PPARγ, aP2, and adiponectin. | (Liang et al., 2016) |
| Antioxidant           | Chlorogenic acid, 3,5-Di-O-caffeoylquinic acid, 4,5-Di-O-caffeoylquinic acid, 3,4-Di-O-caffeoylquinic acid, heptanyl 2-O-β-xylofuranosyl-(1→6)-β-glucopyranoside, 3-O-rabonibioside, quercetin 3-O-rutinoside, chlorogenic acid | *B. pilosa* is known for its antioxidant activity to scavenge free radicals. It has been traditionally used as a herbal tea to relieve summer heat. Chiang et al. demonstrated that different phytochemicals, for example, quinic acids, saccharides, and flavonoids, possessed antioxidant activities. | (Bartolome et al., 2013; Chiang et al., 2004; Chiang et al., 2005; Young et al., 2010) |
in rodents. A systemic toxicology assessment as well as *B. pilosa*-drug interaction in humans needs to be conducted before its application.

### 3 | ANTIMETABOLIC PROPERTIES

*B. pilosa* has a variety of properties that are beneficial to humans. In terms of antimetabolic activity, *B. pilosa* and its antimetabolite polynes have been proved to be prophylactically and therapeutically effective against diabetes and adipogenesis, both of which are etiologically different (Chang et al., 2007; Chang et al., 2005; Chang et al., 2013; Chang et al., 2004; Chiang, Chang, Chang, Yang, & Shyur, 2007; Chien et al., 2009). However, hypotensive compounds of *B. pilosa* are still not clear. In this section, we will focus on the antimetabolic functions and mechanism of *B. pilosa* extract and its active compounds.

#### 3.1 | Function and mechanism of *B. pilosa* for diabetes

Several lines of evidence from epidemiological investigations show that high-calorie foods and unhealthy lifestyles are the main causes of metabolic syndrome. Both factors contribute to hyperglycemia, hypertension, and obesity, leading to complications that can result in death. Dietary intervention with antimetabolite phytochemicals is a feasible approach to preventing, treating, and reversing metabolic disorder (Clements & Bell, 1985). As shown in Table 3, *B. pilosa* is rich in phytochemicals for high blood sugar (Chien et al., 2009; Hsu et al., 2009), high blood pressure (Dimo et al., 2001; Dimo et al., 1999), and lipogenesis (Liang et al., 2016). In this section, we focus on the action and mechanism of *B. pilosa* against diabetes.

*B. pilosa* has traditionally been used as a folkloric herb for diabetes worldwide (Lin, Han, & Liao, 1994; Marles & Farnsworth, 1995; Ubillas et al., 2000). For the past 20 years, this plant has extensively been investigated for antidiabetic efficacy in mice of T2D. Ubillas and colleagues stated that the hydroethanolic extract of *B. pilosa* at a dose of 1 g/kg BW reduced FBG in db/db mice (Ubillas et al., 2000). The authors then took a bioactivity-directed identification strategy to isolate two polyynes, 1 and 2. Furthermore, the two compounds (1:2) mixed in a 3:2 ratio effectively decreased PBG level and food consumption on the next day in db/db mice fed with 0.25 g/kg, two times per day. Mice fed with 0.5 g/kg of the above mixture had a pronounced drop in PBG level and a stronger anorexic effect (food intake reduced by 57%) was observed (Ubillas et al., 2000). This work indicated that 1 and 2 were the active compounds in *B. pilosa* for diabetes (Ubillas et al., 2000). This activity of both polyynes against diabetes was partially attributed to reduced food intake. Nevertheless, this anorexic effect was not seen in the studies of Hsu et al. (2009). Water extracts of *B. pilosa* (BPWE) were evaluated for diabetes in 6- and 8-week-old db/db mice. One oral dose of glimepiride, a commercial insulin releaser, could stimulate insulin release and lower blood sugar in db/db mice. Similarly, BPWE increased insulin production and decreased PBG from 374 to 144 mg/dL. Further, its hypoglycemic mechanism resulted from upregulation of insulin production. Interestingly, BPWE showed a faster kinetics for insulin secretion than glimepiride (Hsu et al., 2009). Nowadays, antidiabetics are notorious for their decreased efficacy over time. Hsu et al. assessed the long-time effect of BPWE on diabetes in db/db mice. BPWE reduced PBG and HbA1c, but ameliorated the production of serum insulin and glucose tolerance. Both one- and multiple-dose studies report the superior action of BPWE on diabetes (Hsu et al., 2009). Moreover, they discovered that glimepiride could not preserve pancreatic islets. In contrast, BPWE strongly preserved islet architecture in mouse pancreases. The authors also checked the antidiabetic effect of three *B. pilosa* varieties at a single oral dose at 10, 50, and 250 mg/kg BW (Chien et al., 2009). As a result, the water extracts of three *B. pilosa* varieties dose-dependently decreased PBG levels in db/db mice for 4 hr. Among the three varieties, the extract of *B. pilosa* var. radiata (BPR) had a higher reduction in PBG levels than the other two varieties at the same dose. In addition, the BPR extract boosted serum insulin levels in db/db mice in comparison with the other varieties at 50 mg/kg. Three polyynes (1, 2, and 3 (cytopiloyne)) were present in all the Bidens strains, albeit with varied contents. Compound 3 exerted a better stimulation of insulin production in db/db mice than compounds 1 and 2 when administered at the same dose, 0.5 mg/kg. In contrast, oral intake of the Bidens extracts and 3 polyynes in diabetic mice for 4 weeks were then evaluated. Results showed that like glimepiride, the crude extracts of the three varieties at doses of 10–250 mg/kg BW diminished the PBG levels in db/db mice. Nevertheless, BPR extract reduced PBG levels and augmented blood insulin levels more than that of the other two varieties because of a higher content of cytopiloyne. HbA1c was also monitored since it is a long-term indicator of blood homeostasis. Twelve-week-old diabetic mice had an HbA1c of 7.9%. Moreover, mice that received a daily dose of BPR crude extract (50 mg/kg), glimepiride (1 mg/kg), and cytopiloyne (0.5 mg/kg) had an HbA1c of 6.6%, 6.1%, and 6.2% in the blood of age-matched controls, respectively (Chien et al., 2009). Further, cytopiloyne was used to analyze the antidiabetic effect and mechanism (Chang et al., 2013). The data confirmed that cytopiloyne reduced the level of PBG and HbA1c, augmented serum insulin, and ameliorated glucose tolerance and islet preservation in db/db mice. However, cytopiloyne did not decrease PBG in mice whose β-cells were already destroyed by streptozocin. Moreover, cytopiloyne boosted insulin secretion and expression, calcium influx, diacylglycerol (DAG), and protein kinase Cα (PKCa) activation in β-cells. Collectively, the data suggest that *B. pilosa* and its active compound, cytopiloyne, regulate T2D via improvement of β-cell functions (insulin production

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**TABLE 2** Taxonomy of *B. pilosa* (U. S. D. O. Agriculture, 2012)

| Kingdom | Plantae |
|---------|---------|
| Division | Magnoliophyta |
| Class | Magnoliosida |
| Order | Asterales |
| Family | Asteraceae |
| Genus | Bidens |
| Species | Bidens pilosa L. |
TABLE 3 Nutrients found in B. pilosa leaf (modified from Alikwe et al., 2014)

| Proximate analysis | g/100 g | Compound | mg/100 g | Mineral | mg/100 g | Amino acid | mg/100 g |
|--------------------|---------|----------|----------|---------|----------|------------|----------|
| Crude Protein      | 15.86   | Alkaloid  | 1.29     | Na      | 0.54     | Methionine | 0.54     |
| Crude Fat          | 7.49    | Saponin   | 0.90     | Ca      | 0.39     | Lysine     | 1.07     |
| Crude Fiber        | 18.13   | Phenol    | 0.21     | P       | 0.31     | Alanine    | 1.34     |
| Ash                | 12.31   | Glycoside | 0.38     | K       | 1.21     | Cysteine   | 0.289    |
| NFEa               | 49.11   | Tannins   | 0.09     | Mn      | 22.0     | Tryptophan | 0.69     |
| Dry Matter         | 90.59   | Polyynes  | 2        | Cu      | 7.8      |            |          |
| Gross Energyb      | 15.86   |          |          | Mg      | 0.23     |            | 789      |

aNFE: Nitrogen-free extract.
bKcal/g.

TABLE 4 Selected biochemical parameters of healthy volunteers after 3 months consumption of B. pilosa (adopted from a previous publication; Lai et al., 2015)

| Parametersa       | Pretreatment | Posttreatment | p valueb | Physiological range |
|-------------------|--------------|---------------|----------|---------------------|
| HbA1c (%)         | 5.4 ± 0.3    | 5.4 ± 0.3     | .86      | 4–6                 |
| FBG (mg/dL)       | 87.6 ± 2.3   | 90 ± 6.2      | .35      | 70–100              |
| PBG (mg/dL)       | 111.6 ± 25.7 | 115.1 ± 31.3  | .82      | <140                |
| Fasting insulin (mU/L) | 3.4 ± 1.4   | 4.9 ± 7.7     | .62      | 3–8                 |
| Postmeal insulin (mU/L) | 12.5 ± 10.2 | 23.5 ± 16.4   | .16      | 10–30               |
| TRIG (mg/dL)      | 85.1 ± 36.0  | 71.6 ± 24.5   | .43      | <150                |
| TC (mg/dL)        | 168.4 ± 27.3 | 161.1 ± 20.9  | .58      | <200                |
| HDL-C (mg/dL)     | 55.8 ± 10.6  | 53.3 ± 7      | .61      | >40                 |
| LDL-C (mg/dL)     | 86.4 ± 21.1  | 86.4 ± 19.5   | 1        | <130                |
| AST (U/L)         | 21.1 ± 7     | 17 ± 2        | .16      | 8–31                |
| ALT (U/L)         | 15.7 ± 4.9   | 13.6 ± 3.6    | .36      | 0–41                |
| BUN (mg/dL)       | 13 ± 3.1     | 13.4 ± 2.8    | .8       | 7–25                |
| Creatinine (mg/dL)| 0.8 ± 0.1    | 0.8 ± 0.1     | .83      | 0.6–1.3             |

aData from seven healthy volunteers are presented as mean ± SD (standard deviation).
bStudent’s t-test is used to compare the parameters before and after the volunteers took B. pilosa (Probetacell) at a dose of 400 mg/person per day, three times a day. p values over .05 are not statistically significant.

and β-cell preservation) implicated in the calcium/DAG/PKCα pathway (Figure 2). One seminal study showed that B. pilosa reduced the level of FBG and HbA1c in diabetics by 30%. In contrast, it increased fasting serum insulin in healthy subjects (Lai et al., 2015). Furthermore, B. pilosa antidiabetics in a combined formula had better clinical outcomes in diabetic patients (Lai et al., 2015). The underlying antidiabetic mechanism of B. pilosa is relevant to the improvement of β-cell function in patients as indicated by the homeostatic model assessment (HOMA) data (Lai et al., 2015).

The above studies conclude that cytopiloyne (3) and its derivatives (compounds 1 and 2) have an antidiabetic function in rodents. The data reveal a new biological action of polyynes. It was likely that the aglycones of compounds 1–3 and compounds 4–6 also have antidiabetic activities. Similarly, Dimo et al. stated that the aqueous extract of B. pilosa slightly reduced PBG in rats which drank 10% fructose (Dimo et al., 2001). Compounds 7 and 8 were proposed to be antidiabetic compounds (Dimo et al., 2001). Intriguingly, 36 polyynes have been found in B. pilosa so far. Whether all the polyynes present in this plant have antidiabetic activities remains to be elucidated.

3.2 Function and mechanism of B. pilosa for obesity

People with obesity are generally consuming more calories than they require. Obesity and its complications are major global health threats. Liang and colleagues investigated the antiobesity effect and mode of action of B. pilosa, and its active constituents. They found that B. pilosa...
substantially diminished fat content and elevated protein content in ICR mice (Liang et al., 2016). Consistently, B. pilosa decreased fat content, adipocyte size, and/or BW in mice in a dose-dependent manner (Liang et al., 2016). Furthermore, mechanistic studies indicated that B. pilosa reduced peroxisome proliferator activated receptor γ (PPARγ) expression, CCAAT/enhancer binding proteins (C/EBPs), and Egr2 in adipose tissue. Cytopiloyne was identified as an adipolytic compound from B. pilosa based on bioactivity-guided fractionation and isolation (Liang et al., 2016). This plant also strongly suppressed the lipid formation and accumulation. This suppression was linked with the down-regulation of expression of Egr2, C/EBPs, PPARγ, adiponectin, and adipocyte Protein 2 (aP2). This study illustrated that B. pilosa and its polyynes inhibited adipogenesis and lipid content in adipocytes and/or animals via down-regulation of the C/EBPs/Egr2/PPARγ cascade and its responsive genes as described in Figure 3 (Liang et al., 2016).

3.3 | Function and mechanism of B. pilosa for hypertension

Dimo and colleagues first showed that B. pilosa ameliorates hypertension in Wistar rats that took 10% fructose in drinking water (Dimo et al., 2001; Dimo et al., 1999; Dimo et al., 2002). They assessed the hypotensive effect of different extracts of B. pilosa whole plant on hypertension in rats induced by 6-week induction with 10% fructose. High fructose increased systolic blood pressure (SBP) from 100 to 140 mm Hg or more in 6 weeks. A calcium channel blocker, nifedipine, lowered SBP in hypertensive rats. The water extract and methylene chloride extract of B. pilosa could reduce SBP (Dimo et al., 2001). The reduction of SBP by B. pilosa at 350 mg/kg is comparable to that of SBP by nifedipine at 10 mg/kg (Dimo et al., 2001). In another study, the same group indicated that the methanol extract of B. pilosa leaves could prevent and treat hypertension in fructose-fed rats. Consistently, this extract also normalized plasma insulin levels in rats fed with a high fructose diet. Both lines of evidence suggest that B. pilosa exerts its antihypertensive effect in part by improving insulin sensitivity (Dimo et al., 2002). Besides, in normotensive rats, B. pilosa decreased heart rate by 24% and 61% at doses of 20 and 30 mg/kg, respectively. The data imply that it exerts hypotensive effects by acting on the cardiac pump efficiency and, subsequently, vasodilation (Dimo et al., 2003). Overall, the data suggest that B. pilosa possesses antihypertensive action although its mode of action is not clear. However, the antihypertensive phytochemicals need to be identified.

In summary, B. pilosa and/or cytopiloyne control metabolic syndrome via multiple mechanisms. Their mechanisms include inhibition of β-cell failure, suppression of adipogenesis, anorexic action, and reduction of blood pressure. As a consequence, B. pilosa and/or cytopiloyne improve metabolic syndrome.

4 | PHYTOCHEMISTRY

B. pilosa is an extraordinary herb with 43 activities documented (Bartolome et al., 2013). So far, we and other groups have discovered 301 phytochemicals from B. pilosa (Bartolome et al., 2013; Xuan & Khanh, 2016). Among them, 36 polyynes, 70 aliphatics, 60 flavonoids, 25 terpenoids, 19 phenylpropanoids, 13 aromatics, 8 porphyrins, and other phytochemicals have been characterized (Bartolome et al., 2013; Xuan & Khanh, 2016). B. pilosa has a rich complexity of chemicals, which may reflect its various biological functions. The structures and biological activities of these compounds have been previously reviewed (Bartolome et al., 2013); however, the information is outdated. Here, we summarized the chemical structures of 36 polyynes present in B. pilosa (Table 5), some of which have been demonstrated to be antidi-
| S.N. | IUPAC Names                                                                 | Common Names                                                                                     | Structure | Plant part (Country)                                                                 | References                                                                 |
|------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| 1    | (4E)-1-(2-Hydroxyethyl)-4-dodecene-6,8,10-triyne-1-yl-3-D-glucopyranoside   | 3-D-Glucopyranosyloxy-1-hydroxy-6(E)-tridecene-8,10,12-triyne                                     |           | Aerial (USA and China); Whole (Taiwan); Leaves (Taiwan)                              | (Chang et al., 2004; Chiang et al., 2007; Chien et al., 2009; Ubillas et al., 2000; Yang et al., 2006; Zhao et al., 2004) |
| 2    | 3-Hydroxy-6-tetradecene-8,10,12-triyne-1-yl-3-D-glucopyranoside              | 3-D-Glucopyranosyloxy-3-hydroxy-6-E-tetradecene-8,10,12-triyne                                 |           | Whole (Mexico)                                                                     | (Alvarez et al., 1996)                                                   |
| 3    | 1-(Hydroxymethyl)-4,6,8,10-dodecadetrayne-1-yl-3-D-glucopyranoside           | Cytopiloyne, 2-D-Glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne                           |           | Whole (Taiwan); Leaves (Taiwan)                                                     | (Chang et al., 2007; Chiang et al., 2007; Chien et al., 2009)             |
| 4    | (E)-5-Tridecene-7,9,11-triyne-1,2-diol                                        | 1,2-Dihydroxy-5(E)-tridecene-7,9,11-triyne                                                     |           | Whole (Taiwan)                                                                     | (Wu et al., 2007)                                                        |
| 5    | (E)-6-Tetradecene-8,10,12-triyne-1,3-diol                                     | 1,3-Dihydroxy-6(E)-tetradecene-8,10,12-triyne                                                  |           | Whole (Taiwan)                                                                     | (Wu et al., 2007; Yang et al., 2006)                                     |
| 6    | 5,7,9,11-Tridecadetrayne-1,2-diol                                             | 1,2-Dihydroxytrideca-5,7,9,11-tetrayne                                                        |           | Whole (Taiwan)                                                                     | (Wang, Lu, Li, & Yao, 2007; Wu et al., 2007)                              |
| 7    | (4E)-1-(Hydroxymethyl)-4-dodecene-6,8,10-triyne-1-yl-3-D-glucopyranoside    | 2-D-Glucopyranosyloxy-1-hydroxy-5(E)-tridecene-7,9,11-triyne                                 |           | Aerial (USA); Whole (Taiwan); Leaves (Taiwan)                                     | (Chang et al., 2004; Chiang et al., 2007; Chien et al., 2009; Dimo et al., 2001; Ubillas et al., 2000; Yang et al., 2006) |
| 8    | 3-D-Glucopyranosyloxy-1-hydroxy-6(E)-tetradecone-8,10,12-triyne              |                                                                                                 |           | Leaves (Cameroon)                                                                  | (Dimo et al., 2001)                                                      |
| 9    | 1,7E, 9E,15E-Heptadecetetrayene-11,13-diyne                                  | Heptadeca-2E, 8E,10E, 16-tetraen-4,6-diyne                                                     |           | Not found (China)                                                                  | (Wang, Yang, Zhu, He, & Wang, 2005)                                      |

(Continues)
| S.N. | IUPAC Names                       | Common Names | Structure | Plant part (Country)       | References                                      |
|------|----------------------------------|--------------|-----------|---------------------------|------------------------------------------------|
| 10   | 1,11-tridecadiene-3,5,7,9-tetrayne |              |           | Roots (not stated)        | (Bohmann, Burkhardt, & Zdero, 1973)             |
| 11   | 1-Tridecene-3,5,7,9,11-pentayne   | Pentayneene  |           | Leaves (not stated) and   | (Bohmann et al., 1973; Sarg, Ateya, Fagg & Abbas, 1991) |
|      |                                  |              |           | Not found (Egypt)         |                                                 |
| 12   | 5-Tridecene-7,9,11-triyne-3-ol    |              |           | Not found (Egypt)         | (Sarg et al., 1991)                            |
| 13   | 2,10,12-Tridecatriene-4,6,8-triyne-1-ol |          |           | Part not specified (Not stated) | (Lastra Valdés & Ponce de León Rego, 2001)     |
| 14   | 2,12-Tridecadiene-4,6,8,10-tetranyl-1-ol |              |           | Roots (not stated); not found (Egypt) | (Bohmann et al., 1973; Sarg et al., 1991) |
| 15   | 2,12-Tridecadiene-4,6,8,10-tetraynal | 1,11-Tridecadiene-3,5,7,9-tetrayn-13-ol |           | Roots (Germany)           | (Bohmann, Bornowski, & Kleine, 1964)           |
| 16   | 2,12-Tridecadiene-4,6,8,10-tetrayn-1-ol, 1-acetate | 1,11-Tridecadiene-3,5,7,9-tetrayn-13-acetate |           | Roots (not stated)        | (Bohmann et al., 1973)                         |
| 17   | (5E)-1,5-Tridecadiene-7,9-diyn-3,4,13-triol |              |           | Aerial (China)            | (Wang, Wu, & Shi, 2010)                        |
| 18   | (6E,12E)-3-oxo-tetradeca-6,12-dien-8,10-diyn-1-ol |              |           | Aerial (China)            | (Wang et al., 2010)                             |
| 19   | (2R,3E,11E)-3,11-Tridecadiene-5,7,9-triyne-1,2-diol | Safynol      |           | Not found (Egypt and China) | (Sarg et al., 1991; Wang et al., 2005)          |

(Continues)
| S.N. | IUPAC Names                                                                 | Common Names                                                                 | Structure | Plant part (Country) | References                                      |
|------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------|----------------------|------------------------------------------------|
| 20   | (R)-3,5,7,9,11-Tridecapentayne-1,2-diol                                      | (R)-1,2-Dihydroxytrideca-3,5,7,9,11-pentayne                                 | Aerial (Japan) | (Tobinaga et al., 2009) |
| 21   | 2-O-D-Glucosyltrideca-11E-en-3,5,7,9-tetrayn-1,2-diol                        | 2-D-Glucopyranosylxy-1-hydroxytrideca-3,5,7,9,11-pentayne                    | Leaves (Brazil) | (Pereira, Ibrahim, Lucchetti, da Silva, & Goncalves de Moraes, 1999) |
| 22   | (R)-1-(Hydroxymethyl)-2,4,6,8,10-dodecapentayn-1-yl-â-D-glucopyranoside     | 2-(Hydroxymethyl)-2,4,6,8,10-dodecapentayn-1-yl-â-D-glucopyranoside          | Aerial (China and Japan) | (Tobinaga et al., 2009; Zhao et al, 2004) |
| 23   | 1-[[Carboxyacetyl]oxy]methyl-2,4,6,8,10-dodecatetraynyl-â-D-glucopyranoside | 1-[[Carboxyacetyl]oxy]methyl-2,4,6,8,10-dodecatetraynyl-â-D-glucopyranoside | Aerial (Japan) | (Kusano et al, 2004) |
| 24   | (4E)-1-
-[[Carboxyacetyl]oxy]-methyl]-4-dodecene-6,8,10-triynyl-â-D-glucopyranoside | (4E)-1-
-[[Carboxyacetyl]oxy]-methyl]-4-dodecene-6,8,10-triynyl-â-D-glucopyranoside | Aerial (Japan) | (Kusano et al, 2004) |
| 25   | (4E)-1-
-[[Carboxyacetyl]oxy]-ethyl]-4-dodecene-6,8,10-triynyl-â-D-glucopyranoside | (4E)-1-
-[[Carboxyacetyl]oxy]-ethyl]-4-dodecene-6,8,10-triynyl-â-D-glucopyranoside | Aerial (Japan) | (Kusano et al, 2004) |
| 26   | (5E)-5-Heptene-1,3-diyn-1-yl-benzene                                        | 1-Phenylhepta-1,3-diyn-5en                                                  | Whole (Taiwan) | (Chang, Wang, Kuo, & Lee, 2000) |
| 27   | 7-Phenyl-2(E)-heptene-4,6-diyn-1-ol                                          | 7-Phenyl-2(E)-heptene-4,6-diyn-1-ol                                          | Roots (Not stated; Aerial (China) | (Bohlmann et al., 1973; Wang et al, 2010) |
| 28   | 7-Phenyl-2(E)-heptene-4,6-diyn-1-ol-acetate                                  | 7-Phenyl-2(E)-heptene-4,6-diyn-1-ol-acetate                                  | Roots (Not stated; Brazil) | (Bohlmann et al., 1973; Brandao et al, 1997; Krettli, Andrade-Neto, Brandao, & Ferrari, 2001) |
### Table 5 (Continued)

| S.N. | IUPAC Names                      | Common Names      | Structure | Plant part (Country)                                                                 | References                                                                 |
|------|---------------------------------|-------------------|-----------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 29   | 7-Phenyl-4,6-heptadiyn-2-ol     | Pilosol A         | ![Structure Image](structure1.png) | Whole (Taiwan); Aerial (China)                                                     | (Chang, Wang, Kuo, & Lee, 2000; Wang et al., 2010)                       |
| 30   | 7-Phenylhepta-4,6-diyn-1,2-diol  |                   | ![Structure Image](structure2.png) | Aerial (China)                                                                     | (Wang et al., 2010)                                                      |
| 31   | 1,3,5-Heptatriyn-1-yl-benzene    | 1-Phenylhepta-1,3,5-triyne | ![Structure Image](structure3.png) | Leaves (not stated); Leaves of tissue culture (not stated); Aerial (Tanzania; China); Whole (Taiwan); Roots (Brazil) | (Bohlmann et al., 1973; Chang et al., 2000; Geissberger & Sequin, 1991; Jia, Hui, Zhong-Wen, & Han-Dong, 1997; Krettli et al, 2001; Wang et al., 2010; Wat et al., 1979) |
| 32   | 7-Phenyl-2,4,6-heptatriyn-1-ol   |                   | ![Structure Image](structure4.png) | Leaves (not stated); Aerial (China)                                                 | (Bohlmann et al., 1973; Wang et al., 2010)                               |
| 33   | 7-Phenyl-2,4,6-heptatriyn-1-ol-acetate |               | ![Structure Image](structure5.png) | Leaves (not stated)                                                                | (Bohlmann et al., 1973)                                                  |
| 34   | 5-(2-Phenylethynyl)-2-thiophene methanol |              | ![Structure Image](structure6.png) | Aerial (China)                                                                     | (Wang et al., 2010)                                                      |
| 35   | 5-(2-Phenylethynyl)-2β-glucosylmethyl-thiophene |          | ![Structure Image](structure7.png) | Aerial (China)                                                                     | (Wang et al., 2010)                                                      |
| 36   | 1-Phenyl-1,3-diyn-5-en-7-ol-acetate |               | ![Structure Image](structure8.png) | Leaves (Brazil)                                                                   | (Pereira et al., 1999)                                                   |
5 | CONCLUSIONS

*Bidens pilosa* is a plant that can be found all over the world, and is widely used as a food in and folk remedies. It has been claimed to treat diabetes, obesity, and high blood pressure on several continents. Nevertheless, a comprehensive review of studies on *B. pilosa* for metabolic syndrome has not been made. In the present article, scientific reports on the use of *B. pilosa* as a functional food for metabolic syndrome have been summed up and critically discussed from nutritional, functional, phytochemical, and toxicological angles. Of note, 8 (Compounds 1 to 8) out of 36 polyynes of this plant have been shown to possess antimetabolic activities. The antimetabolic use of *B. pilosa* and its mechanisms of action with respect to its known polyynes were also discussed. Medical doctors must be consulted before applying *B. pilosa* as a functional food, health food, and remedy for metabolic syndrome.

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CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication. [Correction added on 14 June 2021, after first online publication: The ‘Conflict of interest’ section was added.]

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