INVITED REVIEW

Mechanistic insights on burdock (*Arctium lappa* L.) extract effects on diabetes mellitus

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Abstract Diabetes mellitus (DM) type 2 is amongst the most common chronic diseases, being responsible for various problems in humans and contributing to increased mortality rates worldwide. Fructooligosaccharide, which can be produced from the roots of burdock (*Arctium lappa* L.), has been shown to have a wide range of pharmacological proprieties, including antiviral, anti-inflammatory, hypolipidemic, and antidiabetic effects. Moreover, burdock also contains chlorogenic acid, which has been used in traditional medicine as an antioxidant. Considering its natural origin and minimal toxicity, burdock fructooligosaccharides (BFO) has gained considerable attention from researchers owing its wide, efficient, and beneficial action against DM. Although the effectiveness of fructooligosaccharide and chlorogenic acid has been extensively discussed, limited information is available on the application of burdock for DM treatment. In this review, we discuss the beneficial contributions, and the recent in vitro and in vivo analytical findings on *A. lappa* extract as DM therapy.

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Introduction

Currently, diabetes mellitus (DM) is associated with significant health and societal burdens worldwide. The number of patients with diabetes has been rapidly increasing, affecting up to 9.3% (463 million people) of the global population in 2019, a rate that is projected to continue to increase to approximately 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (Saeedi et al., 2019). DM can be classified as type 1 and type 2 DM (T2DM), which are characterized by no secretion of insulin and insulin deficiency/resistance, respectively (ADA, 2021). All patients with T2DM have high risk of developing various complications, such as nephropathy, retinopathy, and cardiovascular disorders, as long term hyperglycemia leads to tissue and organ damage (ADA, 2021; Juster-Switlyk and Smith, 2016). Indeed, 44% of T2DM patients experience progressive impairment of their renal function, which can ultimately lead to diabetic nephropathy and renal disease (Tang and Lai, 2012).

To date, inhibition of carbohydrate, polysaccharide, and disaccharide absorption is the main strategy to control the blood glucose levels (Deng et al., 2015; Ortiz-Andrade et al., 2007; Satoh et al., 2015). As starch hydrolysis into glucose can be influenced by the enzyme α-glucosidase, inhibition of its enzymatic activity is an effective strategy to control normal blood glucose levels in diabetic patients (Kim et al., 2005; Satoh et al., 2015). Within the past three decades, some synthetic α-glucosidase inhibitors, such as acarbose, miglitol, and voglibose, have been developed (Lordan et al., 2013; Yuan et al., 2021); however, they have been associated with some serious side effects

including gastrointestinal problems caused by disturbances on the microbiome *Lactobacillaceae*, *Ruminococcaceae*, and *Veillonellaceae* populations (Zhang et al., 2017). Therefore, identification of natural α-glucosidase inhibitors without such adverse secondary effects is warranted. Inulin-type fructans (Fig. 1) or *Compositae* plants have shown positive effects on preventing metabolic disorders due to the presence of bioactive compounds (Yuan et al., 2021). For example, chlorogenic acids (CGA), which is an umbrella term for a class of phenolic acids that are commonly found in coffee, including 5-*O*-caffeoylquinic acid (5-CQA), have been extensively studied owing its commercial availability and health benefits (Lu et al., 2020). Recent studies have also shown that fructooigosaccharides (Ding et al., 2021) and bioactive polyphenols, in particular CGA, obtained from burdock exhibit antidiabetic effects (Boonphang et al., 2021; Hussain and Hafeez, 2021; Martina et al., 2019; Saravanakumar et al., 2021; Singh et al., 2021; Yuan et al., 2021). In this review article, we systematically discuss the beneficial effects of burdock extract against T2DM, which may pave the way for the development of enhanced therapies in the future. Accordingly, in this review we provide a critical perspective of the most recent advances on the in vitro and in vivo assessment of burdock therapeutic effects.

Fig. 1 carbohydrate structure of burdock roots (Li et al., 2013)

Dietary sources of fructooligosaccharides and bioactive compounds

Fruits, vegetables, and honey contain trace amounts of fructooligosaccharides within their natural components, and many higher plants may also comprise fructooligosaccharides as reserved carbohydrates. The most common sources of fructooligosaccharides are asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato, rye, and burdock (Mussatto and Mancilha, 2007; Sangeetha et al., 2005), among which the most commercial fructooligosaccharide sources are chicory root (*Cichorium intybus* L.) (Moser et al., 2014), Jerusalem artichoke (*Helianthus tuberosus* L.) (Rubel et al., 2014), and burdock roots (Moro et al., 2022). Generally, fructooligosaccharide concentrations range between 0.3 and 6%; for chicory, these values are between 5 and 10%, while for Jerusalem artichoke and burdock roots, these values can reach 20% (Dominguez et al., 2014) and 0.71 g/100 g (Moro et al., 2022), respectively.

The main dietary sources of bioactive compounds such as polyphenols include different herbs, foods, dicotyledonous ferns and plants species, namely berry fruits, tea, apple, cocoa, citrus fruits, roasted beans, pears, carrots, worm-wood, artichoke, potatoes, eggplant, betel, kiwi fruits, tobacco leaves, burdock, eucommia, coffee beans, tomatoes, honeysuckle, and grapes (Barreto et al., 2021; Bento-Silva et al., 2021; Moro et al., 2022; Nwafor et al., 2022; Stefanov et al., 2022). Among these sources, green coffee contains approximately 6–12% (w/w) of total CGAs (Raskar and Bhalekar, 2019), whereas fresh coffee contains approximately 8.19–23.778 mg/200 mL and instant coffee contains 9.45–41.05 mg/200 mL (Mills et al., 2015). Fruits and vegetables are also a good source of 5-CQA, with eggplant having a high concentration of 5-CQA (1.4–28.0 mg/g) (Plazas et al., 2013), and carrot (0.3–18.8 mg/g), artichoke (1.1–1.8 mg/g), and pepper (0.7–0.9 mg/g) also making a significant contribution to 5-CQA intake in the human diet. Additionally, apples, pears, peaches, plums, cherries, tomatoes, and potatoes contain a reasonable quantity of 5-CQA (Kumar et al., 2020). Specifically, apples contain primarily 5-CQA (0.41–1.16 mg/g), 3-CQA and 5-CQA are predominant in peaches, and plums predominantly contain 3-CQA (0.54 mg/g) but also have 5-CQA (0.073 mg/g) (Upadhyay and Mohan Rao, 2013).

Burdock (*Arctium lappa*) is a medicinal plant that contains several bioactive polyphenols, such as chlorogenic acid and its derivatives (Herrera-Balandrano et al., 2021; Wang et al., 2001). Burdock cultivated in Japan contains 1.5–4.7 mg/g (dry weight) of chlorogenic acid along with other derivatives (Wang et al., 2001), whereas Bulgarian burdock was shown to have 5.0 ± 0.2 mg/g (dry weight) (Petkova et al., 2022) and total phenolic content was found to
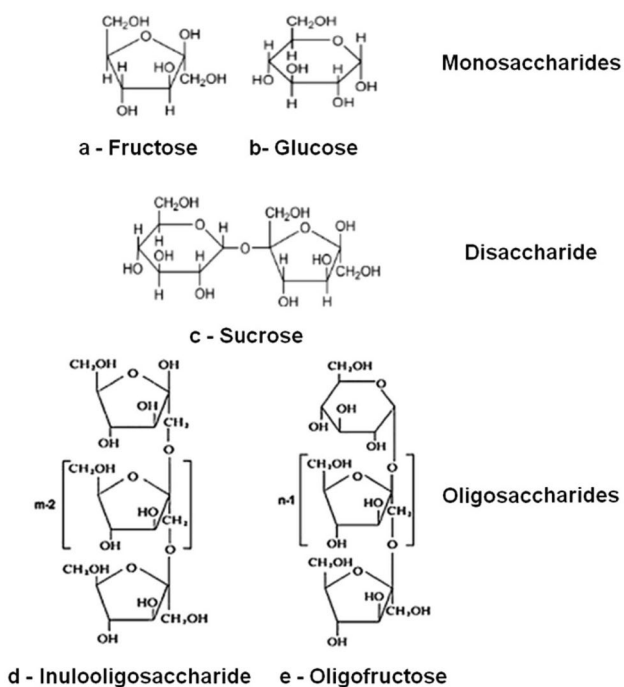
be approximately 150 mg/g of dry plant sample produced in France (Tousch et al., 2014). Moreover, Mondal and Eun (2021) reported that the total phenolic content of *A. lappa* produced in Korea was 9.28 ± 0.16 mg GAE/g of the sample dry weight. The bioactive polyphenols identified from burdock are shown in Table 1.

Beneficial effects of burdock extract on health

Herbal medicines are used to treat approximately 80% diseases worldwide. Some of these herbal plants contain different bioactive polyphenols, and have attracted attention for diabetes care (Saravanakumar et al., 2021). Phenols, flavonoids, alkaloids, and saponins are among the components in *A. lappa* root extract (Cao et al., 2012) and evidences from in vitro experimental studies suggest that phenolic compound especially CGA inhibits α-amylase and α-glucosidase activities in a dose-dependent manner

(Cui et al., 2022). Moreover, significant suppression of blood glucose, total cholesterol, triglyceride, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, γ-glutamyl transferase, alkaline phosphatase, total bilirubin, creatinine, urea, uric acid, and feed intake levels were reported in diabetic rats upon treatment with chlorogenic acid for 28 days (Singh et al., 2021). Notably, administration of CGA was also showed to delay the development of other various chronic diseases (Liang and Kitts, 2015). Hence, CGA consumption may promote a broad range of health benefits and can have several biological functions in humans, as they can target the nervous system, cardiovascular system, gastrointestinal tract, as well as the kidneys, liver, muscles, and pancreas (Lu et al., 2020). Some recent reports have also demonstrated the antioxidant (Tomac et al., 2020), anti-inflammatory (Liang and Kitts, 2015), hepato-protective (Bazool Farhood et al., 2019), anticancer (Gouthamchandra et al., 2017; Kushwaha et al., 2021;

Table 1 Bioactive phenols identified in burdock extracts

Components	Burdock extract	References
1-*O*-caffeoylquinic acid	60% methanol	Lin and Harnly (2008)
3-*O*-caffeoylquinic acid	60% methanol	Lin and Harnly (2008)
5-*O*-caffeoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008)
4-*O*-caffeoylquinic acid	60% methanol	Lin and Harnly (2008)
1,4-Di-*O*-caffeoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008)
1,5-Di-*O*-caffeoyl-3-*O*-maloylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
Dimaloyl-dicaffeoylquinic acid isomer 1	70% ethanol	Tousch et al. (2014)
3,5-Di-*O*-caffeoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008)
1,4-Di-*O*-caffeoyl-3-*O*-maloylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
Succinoyl-tricaffeoylquinic acid isomer	70% ethanol	Tousch et al. (2014)
1,5-Di-*O*-caffeoyl-4-*O*-maloylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
1,3-Di-*O*-caffeoyl-4,5-di-*O*-maloylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
Maloyl-dicaffeoylquinic acid isomer	70% ethanol	Tousch et al. (2014)
1,5-Di-*O*-caffeoyl-3-*O*-succinoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008), Maruta et al. (1995)
1,4-Di-*O*-maloyl-3,5-di-*O*-caffeoylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
1,5-Di-*O*-caffeoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008), Maruta et al. (1995)
Dicaffeoyl-succinoyl-malonylquinic acid isomer 1	70% ethanol	Tousch et al. (2014)
Dicaffeoyl-succinoyl-malonylquinic acid isomer 2	70% ethanol	Tousch et al. (2014)
Dimaloyl-dicaffeoylquinic acid isomer 2	70% ethanol	Tousch et al. (2014)
1,5-Di-*O*-caffeoyl-3-*O*-succinoyl-4-*O*-maloylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
1,5-Di-*O*-caffeoyl-4-*O*-succinoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008), Maruta et al. (1995)
Dimaloyl-dicaffeoylquinic acid isomer 3	70% ethanol	Tousch et al. (2014)
Maloyl-tricaffeoylquinic isomer	70% ethanol	Tousch et al. (2014)
1,5-Di-*O*-caffeoyl-3,4-di-*O*-succinoylquinic acid	90% methanol	Jaiswal and Kuhnert (2011)
1,3,5-Tri-*O*-caffeoyl-4-*O*-maloylquinic acid	70% ethanol	Tousch et al. (2014)
1,3,5-Tri-*O*-caffeoyl-4-*O*-succinoylquinic acid	Methanol	Jaiswal and Kuhnert (2011), Lin and Harnly (2008), Maruta et al. (1995)
1,3,5-Tri-*O*-caffeoylquinic acid	60% methanol	Lin and Harnly (2008)

Sadeghi Ekbatan et al., 2018), and anti-obesity (He et al., 2021; Yin et al., 2021) activities of CGA. Flavonoids also are polyphenolic compounds that scavenge free radicals and reduce diabetes complications (Song et al., 2013). A number of investigators have reported flavonoids as potent antioxidants and antidiabetic agents as well as the alkaloid content of plants potentially modulating insulin secretion. In addition, saponins have been found to reduce blood glucose levels (Patel et al., 2012). Therefore, *A. lappa* roots extracts are capable of improving beta cell function because they contain these components.

Convincing results from numerous studies have shown that fructooligosaccharide is an effective dietary protective compound that can successfully inhibit the activity of α-amylase and α-glucosidase enzyme, thereby reducing the blood glucose and bilirubin levels, while promoting creatinine excretion, and increasing blood urea nitrogen and uric acid as well as the high-density lipoprotein cholesterol levels (Singh et al., 2021). In the large profile of active compounds found in burdock's root, Sitosterol-beta-D-glucopyranoside is thought to be the most potent and effective component. It inhibits alpha glucosidase activity strongly. The enzymes involved in glycopeptide and glycogenolysis are alpha glucosidases. The inhibition of glycosidase is a potential treatment for DM and obesity (Chan et al., 2010). Also known as inulin, gamma-lucoside-fructose ester, assists in the regulation of blood glucose levels. Burdock root contains natural carbohydrates called inulin, which may be able to maintain blood glucose levels by acting on cell surface receptors. Silver and Krantz (1956) also reported an increase in short-chain fatty acid production. In a model of alloxan-induced diabetes in mice and rats, total lignan from burdock fruit has been shown to exert anti-diabetic activity. Burdock lignan has been demonstrated to be a safe and effective antidiabetic agent (Xu et al., 2008).

In vitro and in vivo protective effects of burdock

Polyphenols and fructooligosaccharides, the main components of burdock, are biologically active compounds that have several therapeutical effects and properties. Table 2 highlights the beneficial effects of burdock extract against DM, as demonstrated by in vitro and in vivo experimental studies. With regards to its health promoting attributes, the potential of burdock extract against fibrosis, cancer, and cardiovascular disorders has been clinically demonstrated. In particular, several studies conducted in the past few decades have demonstrated the positive significant effects of burdock fructooligosaccharide (BFO) against chronic diseases. In the following sections, we discuss the in vitro and in vivo antidiabetic effect of burdock.

In vitro studies on diabetes mellitus

Carbohydrates are decomposed into glucose molecules due to the activity of α-glucosidase; thus, inhibition of this process by bioactive compounds, such as phytochemicals, can help regulate the blood glucose levels in patients with DM. Sitosteol-beta-D-glycopyranoside is the main bioactive component of burdock that acts against α-glucosidase and shows antidiabetic activity (Annunziata et al., 2019). Moreover, a recent in vitro study reported that burdock leaf extract can effectively inhibit the activity of α-amylase and α-glucosidase, and consequently impact on starch digestion (Cui et al., 2022). The study also demonstrated, by kinetic and spectroscopic experiments, that the compounds present in burdock can bind to both α-amylase and α-glucosidase, thus preventing the hydrolysis of glycogen into glucose. Notably, administration of only 4% burdock leaf extract significantly reduced the digestible starch.

Flavonoid compounds have been pointed out as being responsible for the antioxidant and other biological activities of burdock extract. Ferreres et al. (2012) suggested that kaempferol, myricetin, and quercetin derivatives are the main biologically active components in hydro-methanolic extracts of burdock leaves. In particular, these components were associated with the inhibition of α-amylase and lipase activities, along with antioxidant proprieties (Tan et al., 2017). Franco et al. (2018) showed that ethanol and hexane extracts of burdock have α-glucosidase inhibitory activity ($25.2 \pm 1.1\%$ and $20.8 \pm 0.4\%$, respectively).

In addition to α-glucosidase, regulation of the activity of 5′ adenosine monophosphate-activated protein kinase (AMPK) has also been suggested as an important strategy for T2DM management (Mihaylova and Shaw, 2011). AMPK can inhibit the activity of several enzymes involved in anabolic processes, such as the glycerol-3-phosphate acyltransferase, which participates in triacylglycerols synthesis; 3-hydroxy-3-methylglutaryl-CoA reductase, involved in sterols synthesis; and acetyl-CoA carboxylase 1, which contributes to fatty acid synthesis. Thus, AMPK inhibition results in enhanced activity of the glucose transporter (GLUT)-1 and GLUT-4 translocation on cell membranes, which in turn promotes glucose uptake in the muscles (Mihaylova and Shaw, 2011). The putative mechanisms and effects of 5-CQA via activating AMPK signaling pathway has been shown in Fig. 2. According to reports, CGA affects only insulin-sensitive tissues such as skeletal muscles, livers and adipocytes. However, AMPK has been linked to the calcium-dependent protein kinase kinase-β (CaMKKβ), in addition to the calcium-dependent protein kinase and LKB-1 (Ong et al., 2012). In addition, arctigenin present in burdock extract can promote the activation of AMPK via Ca^{2+}/calmodulin-mediated protein kinase- and liver kinase B1-dependent pathways in in vitro

Table 2 In vitro and in vivo beneficial effects of chlorogenic acid from *Arctium lappa*

| No	Extract/compound	Experimental model	Analytical findings	References
1	Burdock leaf flavonoids	In vitro inhibition assay	α-Amilase (IC_{50}: 92.01 µg/mL) and α-glucosidase (IC_{50}: 29.49 µg/mL) inhibitions in a mixed-type manner	Cui et al. (2022)
2	Burdock fructooligosaccharide	NRK-52E cells	Protection against HG-induced damage by inhibiting apoptosis and oxidative stress via Nrf2/HO-1 signaling	Ding et al. (2021)
3	Hot water extract rich in fructooligosaccharide	Male, C57BL/6 J mice ($n = 80$)	Reduced FBG levels, body weight, and serum total triglyceride and cholesterol	Yuan et al. (2021)
4	Total lignans from Fructus arctii (250 and 125 mg/kg) for 11 weeks	KKAy type 2 diabetic and obese mice	Decreased FBG, HbA1c, and body weight; improved oral glucose tolerance; increased insulin secretion	Gao et al. (2018)
5	*A. lappa* ethanol and hexane extracts	In vitro inhibition assay	Inhibition of α-glucosidase activity	Franco et al. (2018)
6	*A. lappa* hydro-alcoholic extract (200 and 300 mg/kg) for 28 days	Diabetic mice	Reduced glycaemia ($p < 0.001$ for both 200 and 300 mg extracts); increased insulinemia ($p < 0.05$ for 200 mg extract); improved HOMA-IR ($p < 0.05$ for 300 mg extract)	Ahangarpour et al. (2017)
7	*A. lappa* water extract (50 and 250 mg/kg/day) for 8 weeks	Mice	Decreased HFD-induced weight gain and blood glucose levels	Bok et al. (2017)
8	Arctigenic acid (50 mg/kg) for 12 weeks	Goto-Kakizaki type 2 diabetic mice	Decreased FBG and HbA1c; improved oral glucose tolerance	Xu et al. (2015)
9	Total lignans from Fructus arctii (300 mg/kg) for 12 weeks	Goto-Kakizaki type 2 diabetic mice	Decreased blood glucose levels and HbA1c; improved glucose tolerance; stimulation of insulin and GLP-1 release	Xu et al. (2014)
10	*A. lappa* root extract rich in caffeoylquinic acid derivatives	L6 myocytes	Increased glucose uptake	Tousch et al. (2014)
	A. lappa root extract rich in caffeoylquinic acid derivatives	Hepatocytes from rats	Reduced glucose output induced by glucagon	
	Intraperitoneal and oral administration of dried *A. lappa* root extract rich in caffeoylquinic acid derivatives	Mice	Improved oral glucose tolerance	
11	*A. lappa* n-hexane extract	HepG2 cells	Activation of AMPK	Kuo et al. (2012)
12	Arctigenin	H9C2 and C2C12 cells	Promotion of AMPK phosphorylation	Tang et al. (2011)
13	Total lignans from Fructus arctii (2.0, 1.0, and 0.5 g/kg) for 10 day	Alloxan-induced diabetic mice	Decreased blood glucose levels; increased plasma insulin levels	Xu et al. (2008)

AMPK 5′ adenosine monophosphate-activated protein kinase, *FBG* fasting blood glucose, *GLP-1* glucagon-like peptide-1, *HbA1c* glycated hemoglobin, *HFD* high-fat diet, *HOMA-IR* homeostasis model assessment–insulin resistance

rodent models of cardiomyocytes and muscle cells (Tang et al., 2011). Kuo et al. (2012) reported similar results in a human liver cancer cell line treated with *A. lappa* n-hexane fraction. Interestingly, *A. lappa* root extract showed a significant impact on the glucose uptake in rat myocytes, reducing the glucose levels in rat hepatocytes (Tousch et al., 2014).

In vivo studies on diabetes mellitus

Persistent hyperglycemia can damage the islet β cells due to continuous and excessive insulin secretion to reduce blood glucose, which in turn aggravates the hyperglycemic status and triggers DM development. Hence, chronic complications may occur under persistent hyperglycemia. 5-CQA has been

Fig. 2 Putative mechanisms and effects of 5-CQA via activating AMPK signaling pathway. The phenolic compound 5-CQA activates AMPK, which contributes to main the energy and metabolic homeostasis through modulating the mechanisms above. AMPK, 5′-Adenosine monophosphate-activated protein kinase; *ACC* acetyl-CoA carboxylase, *FASN* fatty acid synthase, *SLC2A4* solute carrier family 2, facilitated glucose transporter member 4, *PPARG* peroxisome proliferator-activated receptor gamma, *G-6-Pase* glucose-6-phosphatase, *ROS* reactive oxygen species, *MDA* malondialdehyde, *NF-κB* nuclear factor kappa, *LTA* lymphotoxin-alpha, also known as TNF-beta, *IL1B* interleukin-1 beta, *IL6* interleukin-6, *SIRT1* NAD-dependent protein deacetylase sirtuin 1, *PPARGC1A* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *NRF-1* nuclear respiratory factor 1, *TFAM* transcription factor A, mitochondrial, *CASP3* caspase-3; BAX, BCL2-associated X protein, *BCL2* apoptosis regulator Bcl-2/B-cell lymphoma 2 (Lu et al., 2020)
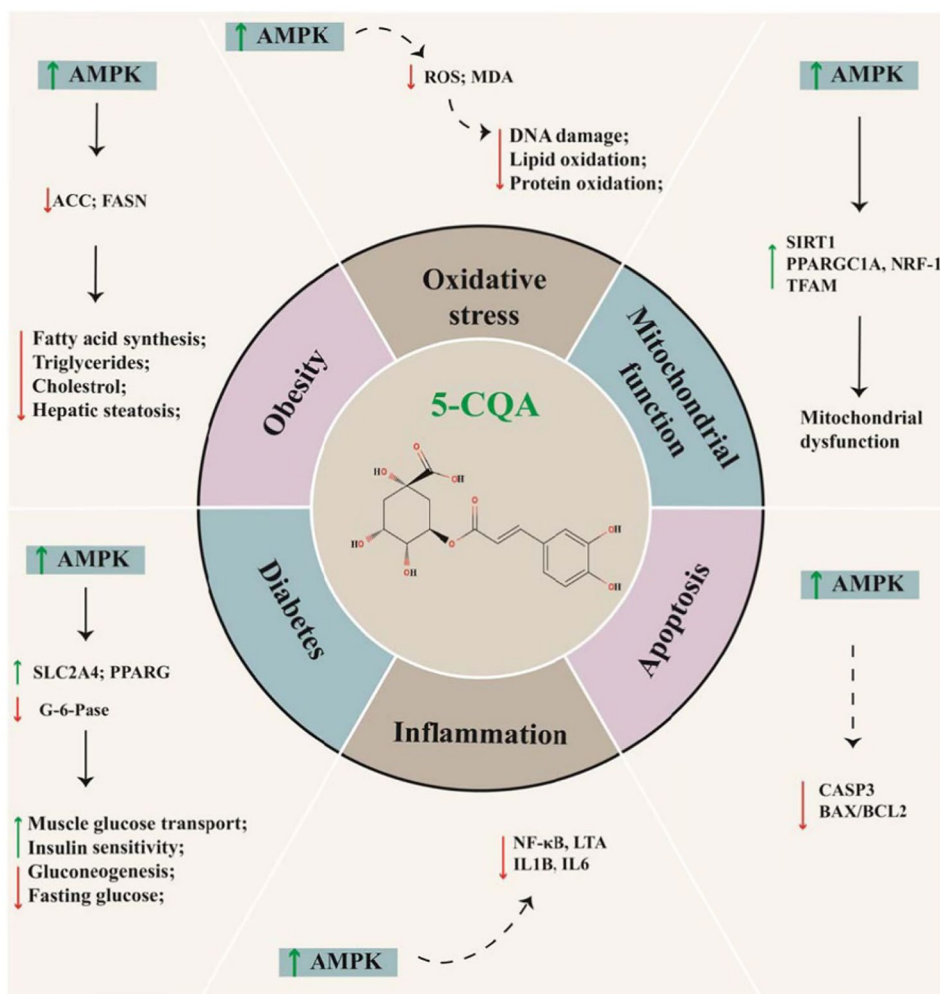
shown to have beneficial effects against DM by promoting the uptake of glucose in the skeletal muscles (Yan et al., 2020). Moreover, fructooligosaccharide and high amounts of polyphenols, especially chlorogenic acid, present in burdock (Cui et al., 2022; Moro et al., 2022) were shown to significantly reduce fasting blood glucose (FBG) levels in male, diabetic C57BL/6 J mice upon 6 weeks of treatment (Yuan et al., 2021). Indeed, the FBG levels were significantly reduced from 23.97 ± 5.65 mmol/L before treatment to 19.77 ± 2.56 mmol/L after treatment in mice treated with a high concentration of burdock oligosaccharides (Yuan et al., 2021).

High glucose levels in the blood can significantly reduce cell viability; however, BFO was shown to protect kidney cells from apoptosis (Ding et al., 2021). Indeed, cell viability increased (63.16%, 72.97%, and 77.98% of the control value at high glucose) in the presence of increasing BFO concentrations (62.5, 125, and 250 µg/mL, respectively). Importantly, BFO protected the kidney cells from the oxidative damage induced by the high glucose levels by significantly inhibiting the production and stabilization of reactive

oxygen species (Tsikas, 2017). Moreover, BFO can enhance the mitochondrial membrane potential, increase the levels of the antioxidant enzymes catalase and superoxide dismutase, and adjust the Bcl-2/Bax ratio, which are critical for the regulation of the antioxidant pathway and cell death.

The antidiabetic activity of *A. lappa* root extract was also evaluated in nicotinamide/streptozotocin (NA/STZ)-induced type 2 diabetes mice (Ahangarpour et al., 2017). Briefly, adult male, NMRI diabetic mice were pretreated with 200 and 300 mg/kg *A. lappa* root extract. Upon continuous treatment for 28 days, the blood glucose levels were significantly reduced regardless of the BFO dose administrated. In addition, BFO were shown to reduce the levels of triglycerides, very low density lipoproteins, and alkaline phosphatases in these diabetic mice. Furthermore, 200 mg/kg of BFO increased the insulin levels, whereas the levels of high-density lipoproteins and leptin increased upon administration of 300 mg/kg of the extract. The main mechanism is the ability of STZ to generate ROS and impair insulin production by beta cells (Patel et al., 2012). Inhibiting glucose absorption from the intestine is another

anti-hyperglycemic mechanisms. However, increasing insulin production and pancreatic tissue function, *A. lappa* root extract may decrease the intestinal absorption of glucose (Ahangarpour et al., 2017).

Similar results were also reported by Bok et al. (2017). In this study, blood glucose levels were found to be significantly reduced in high-fat diet-induced diabetic rats after 8 weeks of treatment with 50 or 250 mg/kg/day of *A. lappa* water extract. In addition, due to high content of caffeoylquinic acid derivatives, *A. lappa* extract exerts anti-hyperglycemic effects, both after acute (intraperitoneal) and subchronic (oral) administration (Tousch et al., 2014).

Among various complications, obesity due to DM is also a serious problem. Some investigations have suggested that *A. lappa* extract has the potential to treat both diabetes and obesity (Gao et al., 2018). Treatment with 125 and 250 mg/kg of *A. lappa* extract for 11 weeks was shown to promote significant reduction in fasting glycemia, HbA1c levels, and body weight, and improved oral glucose tolerance in KK-Ay rodent models of diabetes and obesity. In addition, the extract also activated several important cellular signals, such as the phosphatidylinositol 3-kinase/protein kinase B and AMPK signaling pathways (Gao et al., 2018). Arctigenin, which is also the main component present in *A. lappa* extract, has also been described as having antidiabetic properties. In particular, oral administration of arctigenic acid (50 mg/kg, twice daily for 12 weeks) in Goto-Kakizaki rats was shown to stimulate insulin secretion and significantly reduce the blood glucose levels (Xu et al., 2015). It is known that arctigenin (2(3H)-furanone, 4-[(3,4-dimethoxyphenyl) methyl] dihydro-3-[(4-hydroxy-3-methoxyphenyl)methyl]-, (3R, 4R)-), the main component of lignan, could be hydrolyzed in vivo, resulting in arctigenic acid (AA). As with nateglinide, AA has an asymmetric carbon and a carboxyl group. Accordingly, AA is speculated to be the principal active metabolite of lignan with similar hypoglycemic properties to nateglinide. Possibly it is the key substance responsible for hypoglycemia (Xu et al., 2015).

In line with these findings, Cao et al. (2012) demonstrated that the administration of burdock root extract (200–400 mg/kg body weight) to STZ-induced diabetic rats induced antidiabetic effects in dose-dependent manner. The effectiveness of the burdock root extract was clearly demonstrated by reduced fasting blood glucose levels, along with beneficial effects on serum insulin, lipid profile, urea and creatinine, liver and skeletal muscle glycogen content, lipid peroxidation of the liver and kidney tissues, as well as by lowering the body weight. In addition, administration of 400 mg/kg of body weight of burdock root extract promoted an overall health outcome, similar to that observed in rats treated with a commercially available antidiabetic drug (glibenclamide, 2.5 mg/kg of body weight). Taken together, these results demonstrate that oral administration of burdock root extract holds potential for managing the underlying features of DM.

As a result of administering *A. lappa* root extract and glibenclamide, serum leptin might be elevated, but may decrease in the diabetic group. There are reports of reduced leptin production in diabetic animals, likely as a result of impaired glucose uptake and adipose tissue metabolism. In addition, insulin increases the serum level of leptin in adipocytes and facilitates glucose uptake and oxidation. According to some studies, *A. lappa* root extract increased serum insulin levels in diabetic mice, so perhaps its beneficial effects on insulin release from beta cells are related to its effect on leptin levels (Benhaddou-Andaloussi et al., 2011).

In conclusion, the active ingredients (isolated from different parts of the plant) found in burdock have been shown to be effective in treating a wide variety of conditions and numerous in vitro and in vivo evidences have suggested that *A. lappa* extract has the potential to impart therapeutic effect in diabetes due to the phytochemical content. Evidences also showed that burdock (*A. lappa*) extract contains inulin-type fructooligosaccharides, bioactive compounds such as chlorogenic acid, caffeic acid and its derivatives, tannins, saponins etc. which may exert positively on muscle glucose transport and insulin sensitivity rather than only inhibit the enzymatic activities. In addition, studying the acute toxicity of burdock root also revealed no toxic effects, which means the consumption of phenolic and flavone containing burdock root in foods and beverages or extract would be beneficial in alleviating diabetic complications. However, future investigations are still necessary to better understand the exact underlying antidiabetic mechanisms and activity pathways of the compounds present in the extracts. Moreover, as the activity of the bioactive compounds can be influenced by the solvent used during the extraction process, an optimal extraction method should be established to investigate the enhanced therapeutic activity of the antidiabetic compounds.

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