Received: 28 February 2019 | Revised: 9 May 2019 | Accepted: 26 May 2019

DOI: 10.1002/ptr.6416

REVIEW

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Arctium lappa contributes to the management of type 2 diabetes mellitus by regulating glucose homeostasis and improving oxidative stress: A critical review of in vitro and in vivo animal-based studies

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Diabetes is a metabolic disease highly widespread worldwide, and the most common form is the type 2 diabetes mellitus (T2DM). A large number of synthetic drugs are currently available for the treatment of diabetes; however, they present various side effects and, for this reason, people are increasingly inclined to search natural alternative treatments. Among these, *Arctium lappa* (*A. lappa*) has interesting anti-diabetic activities, exerted by improving glucose homeostasis and reducing insulin-resistance. In addition, *A. lappa* exerts a marked antioxidant activity, an effect known to play a pivotal role in the treatment of T2DM. The purpose of this review is to analyse scientific evidence in order to evaluate the role of *A. lappa* and its bioactive compounds in management of T2DM. The literature search performed provided only in vitro and animal-based studies. No clinical studies have been conducted in order to investigate the effect of *A. lappa* on T2DM patients. However, available literature provides evidence for further clinical trials in order to confirm these claimed activities on humans.

KEYWORDS

antioxidant, *Arctium lappa*, glucose homeostasis, oxidative stress, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disease that affects a large number of people in the world, and it is therefore considered an epidemic (Aschner, 2017). T2DM is characterized by decreased β-cells insulin secretion ability and/or insulin-resistance, resulting in chronically elevated blood glucose levels (American Diabetes Association, A.D.A, 2014; American Diabetes Association, A.D.A, 2017). Persistent hyperglycaemia is recognized as one of the main causes of oxidative stress, which drastically impairs biologically structures, causing several T2DM complications (Aronson, 2008; Baynes & Thorpe, 1999; Ceriello, 2000; Maritim, Sanders & Watkins, 2003).

Abbreviations: **T2DM**, type 2 diabetes mellitus; **AMPK**, 5′ adenosine monophosphate-activated protein kinase; **GPAT**, glycerol-3-phosphate acyltransferase; **HMGCR**, 3-hydroxy-3-methylglutarul-CoA reductase; **ACC1**, acetyl-CoA aarboxylase-1; **GLUT**, glucose transporter; **ARE**, *A. lappa* root extract; **HOMA-IR**, homeostasis model assessment–insulin resistance; **HFD**, high-fat diet; **TL**, total lignans; **HbA1c**, glycated haemoglobin; **GLP-1**, glucagon-like peptide; **TAS2R**, taste receptor type 2; **ROS**, reactive oxygen species; **ABTS**, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic) acid; **TE**, Trolox equivalents; **DCM**, dichloromethane; **EtOH**, ethanol; **DPPH**, 2,2-diphenyl-1-picrylhydrazyl; **FRAP**, ferric reducing antioxidant power; **MeOH**, methanol; **ORAC**, oxygen radical absorbance capacity; **SOD**, superoxide dismutase; **GHS-Px**, glutathione peroxidase; **CAT**, catalase; **MDA**, malondialdehyde; **TAOC**, total antioxidant capacity; **GR**, glutathione reductase

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TABLE 1 In vitro and in vivo studies demonstrating the anti-diabetic effect of *A. lappa*

Authors	Type of study	Experimental model	Extract/compound	Observed effect
Tousch et al. (2014)	In vitro	L6 myocytes	*Arctium lappa* root extract rich in caffeoylquinic acid derivatives	Increased glucose uptake
		Hepatocytes from rats	*A. lappa* root extract rich in caffeoylquinic acid derivatives	Reduced glucose output induced by glucagon
	In vivo	Mice	Intraperitoneal and oral administration of dried *Arctium lappa* root extract rich in caffeoylquinic acid derivatives	Improvement in oral glucose tolerance
Tang et al. (2011)	In vitro	H9C2 and C2C12 cell line	Arctigenin	Promotion of AMPK phosphorylation
Franco et al. (2018)	In vitro	Inhibition assay	*A. lappa e*thanol and hexane extracts	Inhibition of α-glucosidase activity
Kuo et al. (2012)	In vitro	HepG2 cells	*A. lappa n*-hexane extract	Activation of AMPK
Xu et al. (2008)	In vivo	Alloxan-induced diabetic mice	Total lignans from Fructus arctii (2.0, 1.0, and 0.5 g/kg) for 10 days	Decreased blood glucose levels; increased plasma levels of insulin
Xu et al. (2014)	In vivo	Goto-Kakizaki type 2 diabetic mice	Total lignans from Fructus arctii (300 mg/kg) for 12 weeks	Decreased blood glucose levels and HbA1c; improvement in glucose tolerance; insulin and GLP-1 release stimulation
Xu et al. (2015)	In vivo	Goto-Kakizaki type 2 diabetic mice	Arctigenic acid (50 mg/kg) for 12 weeks	Decreased FBG and HbA1c; improvement in oral glucose tolerance
Ahangarpour et al. (2017)	In vivo	Diabetic mice model	A. lappa hydro-alcoholic extract (200 and 300 mg/kg) for 28 days	Reduced glycaemia ($p < .001$ for both 200 and 300-mg extract); increased insulinemia ($p < .05$ for 200-mg extract); improved HOMA-IR ($p < .05$ for 300-mg extract)
Bok et al. (2017)	In vivo	Mice	A. lappa water extract (50 mg/kg/day and 250 mg/kg/day) for 8 weeks	Decreased HFD-induced weight gain and blood glucose levels
Gao et al. (2018)	In vivo	KKAy type 2 diabetic and obese mice	Total lignans from Fructus arctii (250 and 125 mg/kg) for 11 weeks	Decreased FBG, HbA1c and body weight; improvement in oral glucose tolerance; increased insulin secretion

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

A large number of synthetic drugs are currently used for the treatment of diabetes; however, they present various side effects and, for this reason, people are increasingly inclined to search natural alternative treatments (Ota & Ulrih, 2017). Among these, *A. lappa* could be considered a good candidate as natural treatment for the management of T2DM.

Arctium lappa L. (*A. lappa*), also known as burdock, bardana, or Fructus arctii, is an herbaceous plant belonging to the *Asteraceae* botanical family, very popular in Asia as food and medical plant. The plant can grow up to a height of 1 m; it has large leaves and spherical inflorescences, of purple colour. Seeds are oval and covered with yellow hair. In China, *A. lappa* is also known as "Niubang" and its use has largely been applied in traditional Chinese medicine treatments for over 3,000 years (Chan et al., 2011). In Ppytotherapy, dried root, leaves, fruits, and seeds from *A. lappa* are used (Chan et al., 2011). Each part of the plant has a different composition, especially in terms of biologically active compounds; indeed, a large variety of bioactive compounds are contained in the phytocomplex, such as terpenoids (beta-eudesmol, $C_{15}H_{24}O$, present in fruits), sterols (sitosterol-beta-D-glucopyranoside, $C_{35}H_{60}O_6$, contained in roots), lignans, polyphenols, and fructans (Chan et al., 2011). Generally, *A. lappa* is a safe plant. Only minimal side effects, such as dermatitis or urticaria, have been reported (Chan et al., 2011). Toxicity studies conducted on mice have demonstrated the absence of adverse effects with <250 mg/kg *A. lappa* water extract administration for 8 weeks (Bok et al., 2017); moreover, administration of 280 mg/kg arctigenin, one of the main component of *A. lappa*, for 2 weeks, does not cause side effects (Xu et al., 2015).

Arctium lappa beneficial properties are rather known; indeed, antioxidant, antiinflammatory, and anticancer (Chan et al., 2011) activities have been attributed to the plant. Not recently, however, studies provided evidence about the anti-diabetic activity of *A. lappa*. In traditional Chinese medicine, *A. lappa* is largely used as anti-diabetic natural remedy (Chan et al., 2011). Xiao-Ke tea is one of the traditional phytotherapic remedy used in China for treatment of T2DM, in which *A. lappa* is the main component (Hale et al., 1989).

In this paper, by the analysis of current scientific evidence we sought to evaluate the role of *A. lappa* in the management of T2DM and its complications, such as oxidative stress. Particularly, a literature search has been conducted in official scientific databases, including PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Science Direct (http://www.sciencedirect.com). Articles in English were identified using specific keywords ("*Arctium lappa*," "Burdock," "Fructus arctii," "type 2 diabetes mellitus," "hyperglycaemia," "oxidative stress," and "antioxidant activity") and their combinations.

2 | ANTI-DIABETIC EFFECTS OF *A. LAPPA*: SCIENTIFIC EVIDENCE

There is scarce evidence about the anti-diabetic effect of *A. lappa*. The literature search only provided four in vitro studies and seven in vivo studies, as summarized in Table 1; these latter were all conducted on animal-based model. No clinical studies were found; however, all available evidence is concordant.

2.1 | In vitro studies

The main bioactive compound with anti-diabetic activity is sitosteol-beta-D-glucopyranoside, which acts by inhibiting α-glucosidase (Chan et al., 2011), an enzyme involved in hydrolysis of glycogen, leading to the release of single units of glucose. The inhibition of α-glucosidase activities is considered an efficacious strategy for the management of T2DM, and it is exerted by several phytochemicals (Shori, 2015). Franco et al. (2018) demonstrated that *A. lappa* ethanol and hexane extracts exerted an α-glucosidase inhibitory activity (20.8 ± 0.4% and 25.1 ± 1.1%, respectively).

Among the molecular targets for the management of T2DM, stimulation of the 5′ adenosine monophosphate-activated protein kinase (AMPK) is one of the most important. AMPK inhibits specific enzymes involved in anabolic processes, such as glycerol-3-phosphate acyltransferase, in triacylglycerols synthesis; 3-hydroxy-3-methylglutarul-CoA reductase (HMGCR), in sterols synthesis and acetyl-CoA carboxylase 1 (ACC1), in fatty acid synthesis; on the other hand, it improves glucose uptake by stimulating glucose transporter (GLUT)-1 action and GLUT4 translocation on muscle cell membranes (Mihaylova & Shaw, 2011). It has been demonstrated that arctigenin is able to promote the AMPK phosphorylation in H9C2 and C2C12 cell lines by Ca^{2+}/calmodulin-dependent protein kinase kinase and liver kinase B 1-dependent pathways (Tang et al., 2011). The same result in activation of AMPK has been also found by Kuo et al. (2012) in HepG2 cells treated with *A. lappa n*-hexane fraction.

The anti-hyperglycaemic activity of an *A. lappa* root extract (ARE) rich in caffeoylquinic acid derivatives was tested on L6 myocytes and rat-derived hepatic cell lines. In particular, in muscle cells ARE increased the uptake of glucose, and in hepatocytes it reduced the output of glucose induced by glucagon (Tousch et al., 2014).

2.2 | In vivo studies

Several studies investigated the effects of *A. lappa* extract or its bioactive components in improving glycaemic homeostasis in murine models. In this context, recently, two animal-based studies showed the effect of *A. lappa* hydro-alcoholic (Ahangarpour et al., 2017) and water (Bok et al., 2017) extract. In the first one, 200 and 300 mg/kg of hydro-alcoholic extract were administered to diabetic mice for 28 days. After the treatment period, reduced glycaemia ($p < .001$ for both 200 and 300 mg/kg of extract), increased insulinemia ($p < .05$ for 200 mg/kg extract) and improved insulin-resistance, evaluated by using the Homeostasis Model Assessment–Insulin Resistance (HOMA-IR; $p < .05$ for 300 mg/kg extract) were found. The authors explained these anti-diabetic effects by amelioration of β-cell function, stimulation of insulin secretion, reduction of insulin resistance, and reduction of glucose intestinal absorption (Ahangarpour et al., 2017). In the other study, 8-week administration of *A. lappa* water extract

at two dosages (50 and 250 mg/kg/day) significantly decreased high-fat diet-induced weight gain and blood glucose levels (Bok et al., 2017). In addition, ARE rich in caffeoylquinic acid derivatives exerts anti-hyperglycaemic effect, both after acute (intraperitoneal) and subchronic (oral) administration (Tousch et al., 2014).

Total lignans (TL) from *A. lappa* dried fruits, obtained by an ethanol extraction, improved glucose homeostasis in alloxan-induced diabetic mice (Xu et al., 2008). In particular, three different dosages (0.5, 1.0, and 2.0 g/kg) were administered for 10 days, and glucose and insulin blood levels were monitored. In diabetic mice, but not in normal mice (control group), decreased blood glucose levels and increased plasma insulin levels were found, with a dose-dependent relationship (Xu et al., 2008). Similarly, Xu, Ju, Wang, Gu, and Feng (2014) showed that administration of TL (300 mg/kg twice daily before each meal) in diabetic animal model (Goto-Kakizaki rats), for 12 weeks, induced a significant amelioration in glycaemic profile by reducing both blood glucose levels and glycated haemoglobin (HbA1c) and by improving oral glucose tolerance. In addition, authors also found increased insulin secretion and glucagon-like peptide (GLP)-1 release (Xu et al., 2014). Although the authors did not stress this aspect, it worth noting that an increase in GLP-1 release has been reported to be an efficacious therapeutic strategy for the management of T2DM (Ezcurra, Reimann, Gribble & Emery, 2013; Troke, Tan & Bloom, 2014). This action might be also considered for medical plants and certain foods. In particular, a recent narrative review highlights the effects of natural bitter compounds in stimulating intestinal bitter taste receptors (taste receptor type 2, TAS2R), resulting in increased incretine release, including GLP-1 (Barrea et al., 2019). Potentially, thus, the increased GLP-1 release observed by Xu and colleagues could be explained by an interaction of these compounds with TAS2R; however, further studies are needed.

The anti-diabetic activity of TL from *A. lappa* dried fruit was also recently investigated by Gao and colleagues (2018). Diabetic and obese mice (KKAy rodent model) were treated for 11 weeks with 125 and 250 mg/kg TL. After the treatment period, authors found a statistically significant reduction of fasting glycaemia, HbA1c, and body weight and improved oral glucose tolerance. In addition, a stimulatory effect was observed on several pathways, including phosphatidylinositol 3 kinase/protein kinase B and AMPK (Gao et al., 2018). Among the lignans, arctigenin is considered one of the most important compounds of *A. lappa* extract showing hypoglycaemic activity. In particular, Xu et al. (2015) showed that oral administration of arctigenic acid (50 mg/kg, twice daily for 12 week) in Goto-Kakizaki rats reduced blood glucose and HbA1c levels, by stimulating insulin secretion.

In summary although limited as number, all experimental studies available, both in vitro and in vivo, are strongly suggestive of the high potential of *A.lappa* components as antidiabetic remedies. Results obtained in vitro, on cell cultures, have found confirmation in vivo, in different animal models of diabetes. Unfortunately, to date, there are no clinical studies available; nonetheless, encouraging results obtained from experimental studies open the way for future clinical studies.

3 | THE ROLE OF *A. LAPPA* IN CONTRASTING THE OXIDATIVE STRESS

Oxidative stress is a pathological condition due to an imbalance between production and elimination of oxidants, such as reactive oxygen species (ROS) and reactive nitrogen species (Johansen, Harris, Rychly, & Ergul, 2005; Limon-Pacheco & Gonsebatt, 2009; Valko et al., 2007). Physiologically, ROS and reactive nitrogen species are produced in small amounts, because endogenous antioxidant systems are able to contrast their actions. On the other hand, elevated amounts of free radicals cause the oxidation of lipids, proteins, and nucleic acids, thereby producing toxic molecules and causing DNA damages (Limon-Pacheco & Gonsebatt, 2009; Valko et al., 2007).

There is evidence that in diabetic subjects the hyperglycaemia is the main cause of oxidative stress (Esposito et al., 2002; Ganjifrockwala, Joseph & George, 2017). In particular, chronic hyperglycaemia is implicated in mechanisms that are considered to be the cause of oxidative stress, including glucose auto-oxidation, increased protein glycation, intensified glucose input into the polyol pathway, and advanced glycosilation end product formation (Aronson, 2008; Baynes & Thorpe, 1999; Ceriello, 2000; Maritim, Sanders & Watkins, 2003). Therefore, nutraceuticals or dietary sources of antioxidant may represent a useful natural approach for the management of T2DM. In this contest, the nutraceutical potential of *A. lappa* appears prominent considering that in addition to the aforementioned anti-diabetic effect, this medical plant also exerts a marked antioxidant activity.

Several studies investigated the antioxidant activity of *A. lappa*. As summarized in Table 2, however, different assays were performed, and for the same assay, the results were expressed in different ways. In addition, different plant parts were used and various extraction methods were performed. Thus, the comprehension of the *A. lappa* antioxidant and antiradical potential might not be easy and direct for nontechnicians.

Ferracane, Graziani, Gallo, Fogliano, and Ritieni (2010) evaluated the radical scavenging activity of different *A. lappa* plant parts by using the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic) acid (ABTS) assay; they found that the antioxidant activity ranged from 0.0016 to 0.0289 mmol Trolox equivalent (TE) per 100 g dry weight in roots and leaves, respectively.

The majority of available studies exploring the antioxidant activity of *A. lappa* were conducted on extracts from roots, with different extraction methods. Predes, Ruiz, Carvalho, Foglio, and Dolder (2011) tested the antioxidant activity of (a) dichloromethane (DCM), ethanol (EtOH), and water (plant/solvent, 1:2); (b) DCM, EtOH, and water (plant/solvent, 1:5); (c) water (plant/solvent, 1:5); and (d) 70% EtOH (plant/solvent, 1:5) extracts, by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. Among these, only the 70% EtOH extract showed a marked antiradical activity. In particular, EtOH extract EC_{50} was 4.79 ± 0.15 μg/ml compared with Trolox (1.13 ± 0.1 μg/ml). EC_{50} is the antioxidant amount needed to reduce the concentration of DPPH by 50%. In addition, the time necessary to reach the EC_{50} (TEC_{50}) was 5 and 0.1 min for EtOH extract and Trolox, respectively, and the antiradical efficiency (AE),

calculated as follow: AE = 1/(EC_{50} × TEC_{50}), was 0.0418 ± 0.001 (EtOH extract) and 8.98 ± 0.84 (Trolox; Predes et al., 2011). Similar results were found in other studies in which root hydro-EtOH extractions were performed, although in different proportions. In particular, the water/EtOH (1:1, v/v) extract antioxidant activity assessed by DPPH and phosphomolybdate method was 76.23 ± 0.29% and, respectively, 269.5 mg/g ascorbic acid equivalent (Fierascu et al., 2018).

In 2016, Jang and colleagues performed an *A. lappa* root hydro-EtOH extraction under reflux, isolating eight different caffeoylquinic acid derivatives. The antioxidant activity of these compounds ranged

TABLE 2 In vitro studies exploring the antioxidant activity of *A. lappa*

Authors	Part of plant	Extraction method	Antioxidant assay	Results
Ferracane et al. (2010)	Roots and leaves	Extraction with 70% methanol by RT sonication	ABTS (mmol TE per 100 g)	0.0016 (roots) 0.0289 (leaves)
Predes et al. (2011)	Roots	70% ethanol extraction (1:5, plant solvent)	DPPH (EC_{50}, μg/ml; TEC_{50}, min; AE)	EC_{50}: 4.79 ± 0.15; TEC_{50}: 5; AE: 0.0418 ± 0.001
Li et al. (2013)	Whole plant	Boiling water extraction	FRAP (μmol Fe (II) per g) ABTS (μmol TE per g)	207.71 ± 19.86 167.89 ± 18.78
Takebayashi et al. (2013)	Roots	Hexane/dichloromethane (1:1) followed by methanol/water/acetic acid (99:9.5:0.5)	ORAC (μmol TE per g) DPPH (μmol TE per g)	66.07 ± 12.74 19.37 ± 19.37
Liu et al. (2014)	Roots	Hot water extraction	Hydroxyl radical scavenging assay (%) ABTS (%) Chelating ability on ferrous ions (%)	At 2.5 mg/ml extract = 99.19% At 5.5 mg/ml extract = 72.5% At 1.25–5.0 mg/ml extract = nearly 100%
Jiang et al. (2016)	Roots	55% ethanol extraction	DPPH (mM) ABTS (mM) FRAP (mM of $FeSO_4$ equivalents)	Min.: 9.210 ± 3.840; max: 46.362 ± 3.992 Min.: 1.130 ± 0.183; max: 1.187 ± 0.008 Min.: 3.810 ± 1.013; max: 6.792 ± 1.749
Jimenez-Zamora, Delgado-Andrade and Rufian-Henares (2016)	N.D.	Boiling water extraction by infusion for 7 min	ABTS (mmol TE per L) DPPH (mmol TE per L) FRAP (mmol TE per L)	1.06 ± 0.00 1.26 ± 0.02 1.00 ± 0.11
Fierascu et al. (2018)	Roots	Water-ethanol (1:1) extraction	DPPH (% antioxidant potential) Phosphomolybdate method (total antioxidant capacity expressed as mg of ascorbic acid equivalent)	76.26 ± 0.29 269.5
Franco et al. (2018)	Leaves	Ethanol (Et) or hexane (Hex) static maceration for seven days	FRAP (μmol TE per g) DPPH (%) ORAC (μmol TE per g)	Et: 58.7 ± 1.2; Hex: 15.2 ± 2.2 Et: 72.8 ± 1.2; Hex: 22.8 ± 7.3 Et: 926.9 ± 48.3; Hex: 867.9 ± 36.6
Rodriguez et al. (2018)	Roots	$scCO_2$ as solvent and methanol as co-solvent	DPPH (IC_{50})	IC_{50} = 0.13 mg extract per ml

Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic) acid; AE: antiradical efficiency; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC_{50}: the antioxidant amount needed to reduce the concentration of DPPH by 50%; FRAP: Ferric Reducing Antioxidant Power; ORAC: oxygen radical absorbance capacity; $scCO_2$: supercritical CO_2 RT: room temperature; TE, Trolox equivalents; TEC_{50}: the time necessary to reach the EC_{50}.

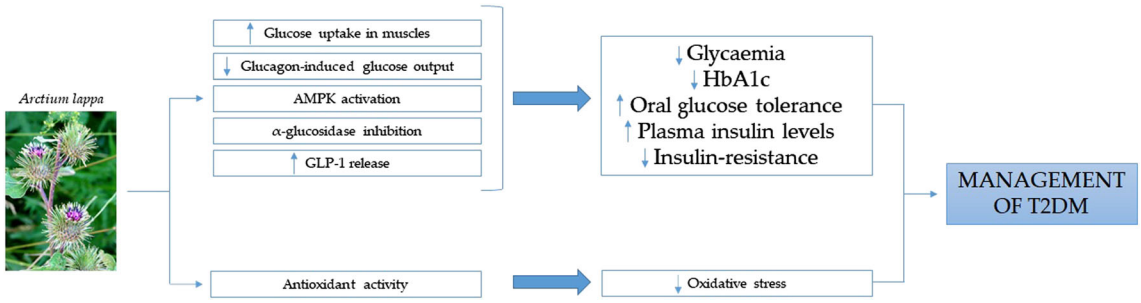

FIGURE 1 Mechanisms of action by which *A. lappa* could contribute to the management of Type 2 diabetes mellitus (T2DM). AMPK: 5′ adenosine monophosphate-activated protein kinase; GLP-1, glucagon-like peptide; HbA1c, glycated haemoglobin [Colour figure can be viewed at wileyonlinelibrary.com]

from 9.210 ± 3.840 to 46.362 ± 3.992 mM (DPPH assay), 1.130 ± 0.183 to 1.187 ± 0.008 mM (ABTS assay), and 3.810 ± 1.013 to 6.792 ± 1.749 mM $FeSO_4$ equivalents (Ferric Reducing Antioxidant Power, FRAP assay).

Extraction methods using hexane as part of the mixture were also performed. In particular, a hexane/DCM (1:1) extraction followed by a methanol (MeOH)/water/acetic acid (95:9.5:0.5) extraction was performed on *A. lappa* root. The antioxidant activity evaluated by using DPPH and oxygen radical absorbance capacity (ORAC) assays was 19.37 and 66.07 μmol TE per g, respectively (Takebayashi et al., 2013). Franco et al. (2018) evaluated the antioxidant activity of EtOH and hexane (Hex) extracts of leaves from *A. lappa*, obtained by a 7-day static maceration. The two extracts showed different antioxidant capacity evaluated by FRAP (15.2 ± 2.2 and 58.7 ± 1.2 μmol TE per g, for Hex and EtOH extract, respectively), DPPH (22.8 ± 7.3 and 72.8 ± 1.2%, for Hex and EtOH extract, respectively), and ORAC (867.9 ± 36.6 and 926.9 ± 48.3 μmol TE per g, for Hex and EtOH extract, respectively; Franco et al., 2018), suggesting that EtOH is more effective for extraction of bioactive compounds with a marked antioxidant activity. Moreover, Rodriguez et al. (2018) demonstrated that supercritical extraction using CO_2 as solvent and MeOH as co-solvent is effective to obtain an extract with a high antioxidant activity, evaluated by using DPPH (IC_{50}: 0.13 mg/ml).

Some authors evaluated the antioxidant capacity of *A. lappa* extracts obtained with hot-water extractions (Jimenez-Zamora, Delgado-Andrade & Rufian-Henares, 2016; Li et al., 2013; Liu et al., 2014). Particularly, whole plant extract antioxidant activity was 207.71 ± 19.86 μmol Fe (II) per g (FRAP) and 167.89 ± 18.78 μmol TE per g (ABTS; Li et al., 2013). On the other hand, antioxidant assays were performed on water infusion, and following results, expressed as mmol TE per l, were found: 1.00 ± 0.00 for ABTS, 1.26 ± 0.02 for DPPH and 1.00 ± 0.11 for FRAP (Jimenez-Zamora, Delgado-Andrade & Rufian-Henares, 2016). Interestingly, Liu et al. (2014) conducted a study using a water extract, in order to evaluate the antioxidant activity of polysaccharides from *A. lappa* root. At first, the researchers evaluated this activity with in vitro assays, including hydroxyl radical scavenging assay, ABTS, and chelating ability on ferrous ions, finding a strong activity, particularly 99.19% (at 2.5 mg/ml, compared with ascorbic acid), 72.5% (at 5.0 mg/ml, compared with Trolox), and nearly 100% (at 1.25–5.0 mg/ml, compared with EDTA). In addition, the same group conducted an in vivo study on IRC mice treated with D-galactose (500 mg/kg) in order to stimulate oxidative stress. Mice were treated with three dosages of the water-extracted polysaccharides from *A. lappa* (100, 200, and 400 mg/kg) for 8 weeks. The activity of endogenous defences against ROS, including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), the levels of malondialdehyde (MDA; a marker of peroxidation), and total antioxidant capacity (TAOC) were evaluated. The authors found significant increases in SOD, GSH-Px, CAT, and TAOC and decreased levels of MDA (Liu et al., 2014). Similar results were found in further in vitro studies conducted on two different cell lines (Tian et al., 2014; Wang et al., 2007). In particular, in 3T3 cells 24-hr treatment with 0–200 μg/ml methanol extract of *A. lappa* root significantly increased the activity of GSH, GSH-Px, glutathione reductase, glutathione transferase, and CAT, in a dose-dependent manner (Wang et al., 2007). In PC12 cells increased activity of GSH-Px and SOD, and decreased levels of MDA were found after pretreatment with a hydro-EtOH extract of *A. lappa* root, partitioned with ethyl acetate. In addition, treatment with 20, 40, and 80 μg/ml of this extract also reduced ROS accumulation in a dose-dependent manner (Tian et al., 2014).

In summary, there is much evidence for the antioxidant activity of *A.lappa*, in particular of different extracts of plant parts, especially roots; such an effect, might be of relevant clinical significance in the management of T2DM, because it is widely known that persistent hyperglycaemia causes an imbalance between oxidants and antioxidants and the following diabetes-associated organ damage. Thus, under this aspect a nutraceutical compound that ameliorates glucose homeostasis, by a hand, and, by the other hand, exerts antioxidant activity might represents a valuable therapeutic approach for diabetes.

4 | CONCLUSION AND FUTURE PROSPECTIVE

Studies available in scientific literature provide evidence of the *A. lappa* beneficial effects on health. In particular, the plant appears useful in the management of T2DM; thus, folk uses are strongly supported by scientific evidence. In particular, *A. lappa* has been shown to improve glucose homeostasis acting with different mechanisms,

including (a) increased glucose uptake in muscle, (b) reduced glucose output induced by glucagon in hepatocytes, (c) activation of AMPK pathways, (d) inhibition of α-glucosidase activity, and (d) stimulation of GLP-1 release. On the other hand, this medical plant is able to reduce insulin-resistance by ameliorating β-cells function and stimulating weight loss. Moreover, due to the presence of a marked polyphenolic component, *A. lappa* has appreciable antioxidant activity, important to contrast oxidative stress, which is a direct consequence of T2DM (Figure 1).

However, a small number of studies are available and all evidence, to our knowledge, is in vitro or animal-based studies. No studies were conducted on human. This is a weak point that could hinder the spread of *A. lappa* use in clinical practice. However, available literature provides evidence for further clinical trials in order to confirm these claimed activities on humans. In particular, pharmacokinetics studies and clinical randomized, placebo-controlled studies should be conducted on T2DM or prediabetic subjects, obese, or overweight, in order to evaluate the effect of *A. lappa*, or its single bioactive compounds, in the improvement of glycaemic profile and weight control. Results should be adjusted for confounding variables, such as diet, physical activity, and pharmacological treatment, in order to consider the inclusion of *A. lappa* as possible natural treatment for diabetes and its complications.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DISCLOSURE STATEMENT

The authors have nothing to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

The authors' responsibilities were as follows: GA and LB were responsible for the concept of this paper and drafted the manuscript; RC, CC, AA, SS, SMN, GCT, and EN: provided a critical review of the paper. All authors contributed to and agreed on the final version of the manuscript.

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How to cite this article: Annunziata G, Barrea L, Ciampaglia R, et al. *Arctium lappa* contributes to the management of type 2 diabetes mellitus by regulating glucose homeostasis and improving oxidative stress: A critical review of in vitro and in vivo animal-based studies. *Phytotherapy Research*. 2019;1–8. https://doi.org/10.1002/ptr.6416