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Review

Arctium lappa (Burdock): Insights from ethnopharmacology potential, chemical constituents, clinical studies, pharmacological utility and nanomedicine

Nermeen Yosri [a], Sultan M. Alsharif [b], Jianbo Xiao [c], Syed G. Musharraf [d], Chao Zhao [e], Aamer Saeed [f], Ruichang Gao [g], Noha S. Said [h], Alessandro Di Minno [i,j], Maria Daglia [i,k], Zhiming Guo [g], Shaden A.M. Khalifa [l], Hesham R. El-Seedi [h,k,m,n,*]

[a] *Chemistry Department of Medicinal and Aromatic Plants, Research Institute of Medicinal and Aromatic Plants (RIMAP), Beni-Suef University, Beni-Suef 62514, Egypt*
[b] *Biology Department, Faculty of Science, Taibah University, Al Madinah 887, Saudi Arabia*
[c] *Department of Analytical Chemistry and Food Science, Faculty of Food Science and Technology, University of Vigo, Vigo, Spain*
[d] *H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan*
[e] *College of Marine Sciences, Fujian Agriculture and Forestry University, Fuzhou 350002, China*
[f] *Chemistry Department, Quaid-i-Azam University, Islamabad 45320, Pakistan*
[g] *School of Food and Biological Engineering, Jiangsu University, Zhenjiang 212013, China*
[h] *Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Kom 32512, Egypt*
[i] *Department of Pharmacy, University of Napoli Federico II, Via D. Montesano 49, 80131 Naples, Italy*
[j] *CEINGE-Biotecnologie Avanzate, Naples 80131, Italy*
[k] *International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang 212013, China*
[l] *Department of Molecular Biosciences, Stockholm University, The Wenner-GrenInstitute, SE-106 91 Stockholm, Sweden*
[m] *Pharmacognosy Group, Department of Pharmaceutical Biosciences, Uppsala University, Biomedical Centre, Box 591, SE 751 24 Uppsala, Sweden*
[n] *International Joint Research Laboratory of Intelligent Agriculture and Agri-products Processing (Jiangsu Education Department), Zhenjiang 212013, China*

Abbreviations: Covid-19, Coronavirus disease of 2019; TCM, traditional Chinese medicine; EMA, European Medicines Agenc,; DCMQA, 4,5-*O*-dicaffeoyl-1-*O*-[4-malic acid methyl ester]-quinic aci,; DPPH, 1,1–diphenyl-2–picryhydrazyl; H_2O_2,, hydrogen peroxide; NMDA, N-methyl-D aspartate; JNK, C-Jun N-terminal kinase; ERK 1/2, Extracellular signal-regulated kinase 1/2; MAPKs, Mitogen-activated protein kinases; AMPK), Mammalian target of rapamycin; mTOR, Adenosine monophosphate-activated protein kinase; miRNA, Micro ribonucleic acid; GSK-3β, Glycogen synthase kinase-3 beta; AKT, Protein kinase B; ERK1/2, Extracellular signal-regulated protein kinases 1 and 2; ABTS, 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; Nrf2/HO-1, Nuclear factor-erythroid-2-related factor 2/ heme oxygenase-1; SREBP-1, Sterol Regulatory Element-Binding protein-1; IL-6, Interleukin-6; (IL-1β, Interleukin-1β; TNF-α, Interleukin-10 (IL-10) Tumor Necrosis Factor-α; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ATPase, Adenosine 5′-TriPhosphatase; mROS, Mitochondrial Reactive Oxygen Species; PI3K/AKT, Phosphoinositide 3-kinase/ Protein kinase B; NF-κB, Nuclear Factor Kappa- B; COX-2, cyclooxygenase-2; MAPK, Mitogen-Activated Protein Kinase; AMPK, Adenosine monophosphate activated protein kinase; MDA, Malondialdehyde; NO, Nitric oxide; SOD, Superoxide dismutase; GSH, Glutathione; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; GSH-Px, Glutathione peroxidase; AR, Androgen Receptor; VEGF, Vascular Endothelial Growth Factor; EGF, Epidermal Growth Factor; NGF, Nerve Growth Factor; FGF-β, Fibroblast Growth Factor-β; PDGF-BB, Platelet-Derived Growth Factor-BB; GST-P), preneoplastic glutathione-S-transferase pi; PNLs, Preneoplastic lesions; GLP-1, glucagon-like peptide-1; HOMA-IR, Homeostasis Model Assessment–Insulin Resistance; UCP1, Uncoupling Protein 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, Peroxisome Proliferator Activated Receptor gamma; C/EBPα), Sterol Regulatory Element-Binding Protein-1; SREBP-1, CCAAT/Enhancer Binding Proteins alpha; SCD-1, Stearoyl-CoA Desaturase 1; NPs, Nanoparticles; XRD, X-Ray Diffraction; TEM, Transmission Electron Microscopy; FTIR, Fourier Transform Infrared; SEM, Scanning Electron Microscope; XPS, X-ray Photoelectron Spectroscopy; AFM, Atomic Force Microscopy; UV, Ultraviolet; EDX, Energy Dispersive X-Ray; MHA, Muller-Hinton agar; PG, Propylene glycol; scCO2, supercritical CO2; EtOH, Ethanol; AcOEt, Ethyl acetate; LDH, Lactate dehydrogenase; MMP, Matrix Metalloproteinase; ROS, Reactive oxygen species; OGD/R, Oxygen glucose deprivation/reoxygenation; MQA, 1,5-O-dicaffeoyl-3-O-[4-malic acid methyl ester]-quinic acid; CNQX, Cyanquixaline; b.w., Body weight; ASALP, Alkali-soluble polysaccharides; AST, Aspartate transaminase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; LPS, Lipopolysaccharide; PNG, Pectolinarigenin; TNBS, 2,4,6-trinitrobenzenesulfonic acid; DMEM, Dulbecco's Modified Eagle Medium; IκBα, Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; DAI, Diseased activity index; DSS, Dextran sulfate sodium; MPO, Myeloperoxidase; PBS, Phosphate-buffered saline; PCV2, Porcine circovirus type 2; CHOL, Cholesterol; TC, Total cholesterol; FBG, Fasting Blood Glucose; Homa-IR, Homeostasis model assessment for insulin resistance; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; PBG, Postprandial blood glucose; HbA1c, Glycosylated hemoglobin; GK, Goto- Kakizaki; OGTT, Oral glucose tolerance test; IPGTT, Intraperitoneal Glucose Tolerance Test; SGPT, Serum glutamic pyruvic transaminase; DMSO, Dimethyl sulfoxide.

* Corresponding author at: Pharmacognosy Group, Department of Pharmaceutical Biosciences, Uppsala University, Biomedical Centre, Box 591, SE 751 24 Uppsala, Sweden.

E-mail address: hesham.el-seedi@farmbio.uu.se (H.R. El-Seedi).

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ABSTRACT

Arctium lappa L. is a medicinal edible homologous plant, commonly known as burdock or bardana, which belongs to the Asteraceae family. It is widely distributed throughout Northern Asia, Europe, and North America and has been utilized for hundreds of years. The roots, fruits, seeds, and leaves of *A. lappa* have been extensively used in traditional Chinese Medicine (TCM). *A. lappa* has attracted a great deal of attention due to its possession of highly recognized bioactive metabolites with significant therapeutic potential. Numerous pharmacological effects have been demonstrated *in vitro* and *in vivo* by *A. lappa* and its bioactive metabolites, including antimicrobial, anti-obesity, antioxidant, anticancer, anti-inflammatory, anti-diabetic, anti-allergic, antiviral, gastroprotective, hepatoprotective, and neuroprotective activities. Additionally, *A. lappa* has demonstrated considerable clinical efficacies and valuable applications in nanomedicine. Collectively, this review covers the properties of *A. lappa* and its bioactive metabolites, ethnopharmacology aspects, pharmacological effects, clinical trials, and applications in the field of nanomedicine. Hence, a significant attention should be paid to clinical trials and industrial applications of this plant with particular emphasis, on drug discovery and nanotechnology.

1. Introduction

Arctium lappa L. is a medicinal edible homologous plant that belongs to the Asteraceae family and is abundant all over the world, particularly in Asia. *A. lappa* L. (Fig. 1) is a shrub that grows to roughly 1 m in height, with roots that can extend to 45–50 cm in depth and 3–6 cm in diameter. These have a cylindrical outline, brown skin and an interior which varies from white to yellowish-white depending on the age of the plant [1]. Notably, the *A. lappa* plant has several common names according to its origin. For example, in China it is referred to as Niubang, in Japanese it is called gobo, and in Russia it is known as repejnik [2,3]. For a long time and across various cultures, burdock has received a great deal of attention in folk medicine; and has been used to improve well-being, treat fever, dizziness, throat pain, infection, diabetes, diuretic, anti-inflammation, toothache, swelling, boils, cuts, wounds and hair loss [4].

Through numerous preclinical studies (*in vitro* and *in vivo*), burdock has been found to exhibit a plethora of biological activities and pharmacological functions, including anti-inflammatory [5], anti-constipation [6], anti-cancer [7], management of male erectile dysfunction [8], angiogenic [9], antioxidant [10], ameliorating cerebral ischemia [11], and proapoptotic and antiangiogenic effects against breast cancer cells [12]. These effects are mostly ascribed to its richness of arctiin (PubChem CID: 100528), arctigenin (PubChem CID: 28125531), pectin (PubChem CID: 441476), fructooligosaccharides, inulin (PubChem CID: 132932783), dicaffeoyl acids and fructofuranan [13], chlorogenic acid (PubChem CID: 1794427), cynarin (PubChem CID: 5281769) [14], and flavonoids (rutin (PubChem CID: 5280805), myricetin (PubChem CID: 5281672), quercetin (PubChem CID: 5280343), apigenin (PubChem CID: 5280443), and kaempferol (PubChem CID: 5280863)) [15].

Randomized clinical studies have also been conducted to evaluate the potential of burdock against certain diseases such as influenza [16], viral pneumonia [17], Covid-19 [18], *Acne vulgaris* [19], knee osteoarthritis [20], and abdominal obesity [21]. Moreover, *A. lappa* L. has had a significant impact in the field of nanotechnology, contributing to antimicrobial, anticancer and anti-diabetic nanomedicine. As a part of our ongoing projects on chemical and pharmacological studies of plants used in the traditional medicine [22–28]. The current review critically discusses the ethnobotanical importance, chemistry, biological activity (*in vitro*, *in vivo*), clinical trials and nanomedical applications of *A. lappa* L. Moreover, we intend to illustrate its isolated bioactive compounds

Fig. 1. *Arctium lappa* L.
Adopted from Plants of the World Online (POWO)); https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:178385–1/images [29].

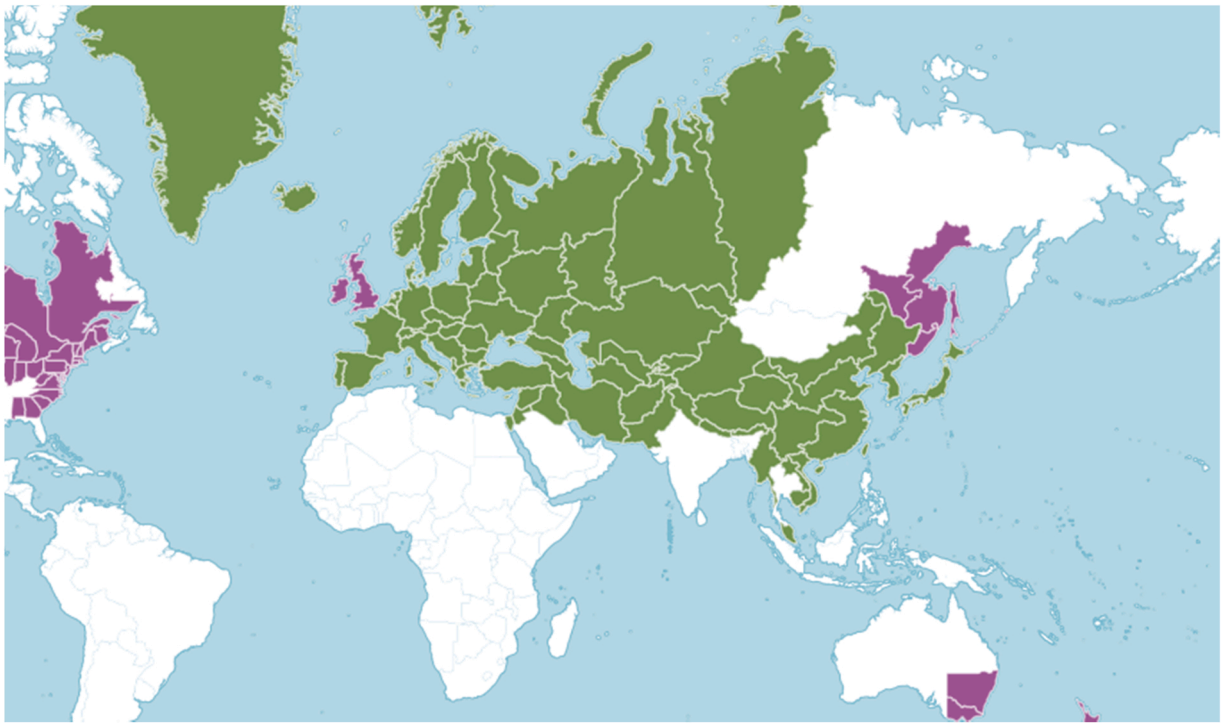

Fig. 2. World distribution of burdock
Adopted from Plants of the World Online (POWO); https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:178385–1 [29].

enlisted in state-of-the-art clinical studies.

2. Taxonomy, botanical and ethnopharmacological aspects

Arctium lappa L., is a perennial traditional herb belonging to the kingdom: *Plantae*; Phylum: *Tracheophyta*; Class: *Magnoliopsida*; Order: *Asterales*; Family: *Asteraceae*; Genus: *Arctium*; and species *Arctium lappa* L. [30]. Burdock, a shrub plant that grows up to about one meter high, and has a branched and shirred stem with a diameter of 1–2 cm. It has a major root, with few branches, which reaches down to 45–50 cm depth, and 3–6 cm in diameter [31]. For centuries, burdock has been widely utilized as a vegetable, snack food, and as part of a popular health beverage, as well as being used as a traditional medicinal herb in Eastern Asian countries, particularly in Traditional Chinese Medicine (TCM) [32,33]. Generally, *A. lappa* L. traditionally consumed to improve well-being, treat fever, dizziness, throat pain, infection and diabetes [34]. Additionally, burdock leaves, seeds and roots have traditionally been used in both European and Asian traditional herbal medicine as a diuretic, to treat inflammation and to "detoxify the blood" [35]. Moreover, In Latvian Folk medicine, *A. lappa* L. is locally known as *lielais dižddadzis* where the leaves and roots are utilized as a decoction and juice to treat dysentery, toothache, swelling, boils, cuts, wounds and hair loss [36].

A. lappa L. is native to Europe and Asia (Fig. 2), and was rapidly spread across North America by early European settlers (Fig. 1) since it was traditionally used to treat infections such as sore throat, boils, rashes and various skin disorders [37], Its root is a popular ingredient in Asian foods, while the leaves are ingested as infusions or applied as an ointment [38]. *A. lappa* L. roots have been widely planted and used as a popular edible traditional medicinal plant worldwide for hundreds of years and are considered to be a variety of healthy and nutritious food, containing a good amount of caffeoylquinic acid derivatives [39]. Burdock is used in TCM for its anti-inflammatory, anticancer, anti-viral, antidiabetic and immune-enhancing activities, as well as regulating blood sugar and anti-tumor, resisting infection, alleviating sore throat and eliminating phlegm, it is used in traditional Korean medicine as a

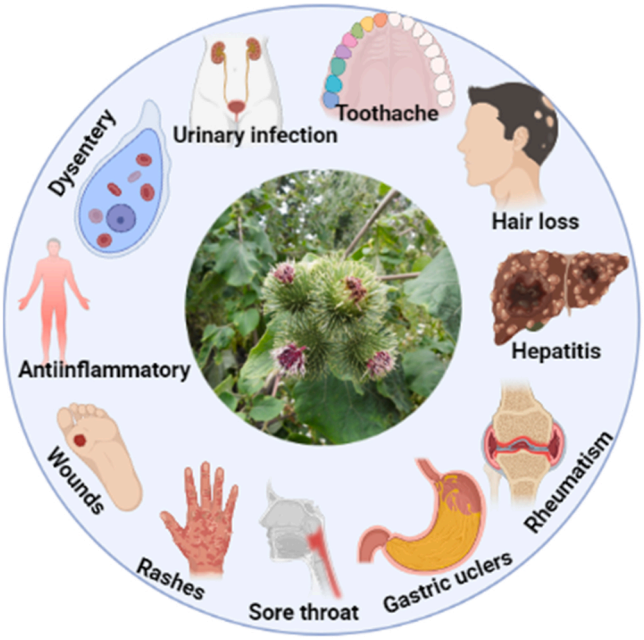

Fig. 3. Traditional uses of burdock (*Arctium lappa* L.,) created with Biorender.com.

diuretic, anti-inflammatory or detoxifying agent [40–43]. *A. lappa* L has been used for hundreds of years as a nutritive vegetable and as edible traditional medicine, serving as a diuretic, carminative, anti-infection, anti-inflammatory, and as an anti-tuberculosis agent [44].

The dried root of 1-year-old burdock is traditionally used to treat diseases such as sore throat and infections such as rashes, boils, and various skin problems (Fig. 3) [45]. In general, the roots, buds, and seeds of *A. lappa* have widely been employed in traditional medicine for treatment of hepatitis, hypertension, gout, and inflammatory diseases,

Table 1
Basic health merits of *A. lappa* L. with their underlying mechanisms (*in vitro* studies).

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
Antibacterial	Leaves/ AcOEt fraction	A paste containing AcOEt fraction and propylene glycol (No microbial growth after 14 days) Control: PG	NR	[68]
Antimicrobial	Leaves/ Extract and fractions	Dose: 50 µL of 10 mg/mL hexanoic fraction Inhibition diameter: 1.4 mm against *S. aureus* and *E. faecalis* Control: PG	NR	[69]
Antibacterial	Leaves/ Extract and fractions	Against *S. epidermidis* ATCC 12228 (Whole extract) MIC= 128 µg GAE/ mL (Aqueous fraction) MIC= 32 µg GAE/ mL Control: MHA+PG (4.1 mL + 0.9 mL)	NR	[70]
Antibacterial	Leaves/ Extract	Against *Staphylococcus aureus* Dose: 40 µL (1 g extract in 3 g DMSO) Best inhibition diameter: 31.6 mm (scCO2 +EtOH extract at 25 MPa/ 313.15 K) NC: DMSO	NR	[71]
Antimicrobial	Roots/ Non-polar fractions	The best MIC= 0.16 mg/mL of AcOEt fraction against *Pseudomonas aeruginosa* PC: Kanamycin (6 mg/mL) and Streptomycin (6 mg/mL)	NR	[72]
Antifungal	Roots/ Extract	Dose: 50 µL Inhibition zone= 22 and 17.1 mm (Against *Aspergillus niger* and *Penicillium hirsutum,* respectively) PC: Miconazole nitrate NC: EtOH: H_2O (1:1)	NR	[73]
Antibacterial	Roots/ Extract	Dose: 50% and 100% showed bactericidal activity against *Eschericha coli* and *Salmonella abony enterica*	NR	[74]
Antiviral	Fruits/ Extract	400 mg/mL hydroalcoholic extract showed similar antiviral effect to acyclovir at 50 mg/mL (PC)	NR	[75]
Antibacterial and antibiofilm	Leaves/ 70% ethanol fraction	Antibacterial: MIC= 2 mg/mL against *E. coli* and *Salmonella typhimurium*. Antibiofilm: At 2 mg/mL of leaf fraction, the growth and development of *E. coli* and *Salmonella typhimurium* biofilms were inhibited by 78.7 and 69.9%, respectively PC: Experiment without leaf fraction NC: Experiment without inoculation	NR	[76]
Antibiofilm	Leaves/ 34% ethanol fraction	Dose= 1 mg/mL Inhibition= 100% PC: Experiment without leaf fraction NC: Experiment without inoculation	NR	[77]
Antibacterial	Leaves and stems/ Extract	Dose= 166 mg/mL Inhibition diameter= 4.2 mm MIC= 166 mg/mL *against Bacillus cereus* PC: 10 µg Penicillin (10.4 mm inhibition); 10 µg Gentamicin (32.4 mm inhibition); 5 µg Ciprofloxacin (30.4 mm inhibition); 5 µg Ofloxacin (28.4 mm inhibition); 5 µg Erythromycin (30.4 mm inhibition) -The extract is here considered to be inactive compared to PC	NR	[78]
Neuroprotective	Roots/ Extract	-160 µg/mL AcOEt extract increased cell viability to 86.78%. -20 µg/mL AcOEt extract decrease LDH release to 40.67%. -80 µg/mL increased the fluorescence intensity of intracellular MMP to 89.46%. -Pretreatment with 20, 40 and 80 µg/mL AcOEt extract significantly suppressed the phosphorylation of p38, JNK and ERK 1/2. -80 µg/mL AcOEt extract decreased ROS generation of the control from 260.02% to 126.37%	↑ cell viability and MMP; ↓ LDH and ROS release; Inhibit phosphorylation of p38, JNK and ERK 1/2	[79]
Neuroprotective	Roots/ Extract	-Inhibition rate of $ABTS^{\cdot+}$ was 80.72% at 160 µg/mL AcOEt extract. -ROS production reduced from 196.7% to 121.54% at 80 µg/mL AcOEt extract. -MMP increased to 83.82% at 20, 40, 80 µg/mL of AcOEt extract. Caspase-3 activity was inhibited by 62.27% at 80 µg/mL of AcOEt extract. Treatment with 20, 40, and 80 µg/mL AcOEt extract	↑ cell viability, MDA, and MMP; ↓ ROS, Bcl-2/ Bax ratio, cytochrome *c* release, caspase-3 and caspase-9 activities; Inhibit $ABTS^{\cdot+}$	[80]

(*continued on next page*)

Table 1 (*continued*)

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
		supressed Bax/Bcl-2 ratio, increased MDA levels and cell viability.		
Neuroprotective	Roots/ Caffeoylquinic acid derivatives[1–3]	-Compounds 1 and 2 reduced H_2O_2-induced human neuroblastoma SH-SY5Y cell death at EC_{50} equal to 17.27 and 18.25 μ, respectively relative to vehicle control. -Compound 3 displayed protective effect against NMDA-induced cell injury with EC_{50} of 18.4 μM relative to vehicle control.	↓ H_2O_2 and NMDA	[81]
Neuroprotective	NR/ Arctigenin[4]	-Arctigenin showed the best neuroprotective activity on glutamate-induced neurotoxicity in primary cultures of rat cortical cells (57.5% protection) when applied 1 hr before exposure to glutamate at dose of 1 μM. -In cerebral cortical membrane preparation arctigenin binds to KA receptors with IC_{50} = 83 nM compared to CNQX IC_{50} = 90 nM and inhibit [^{3}H]-kainate binding to the receptors 1 hr before glutamate insult. -Arctigenin (10 μM) scavenged H_2O_2 (50 μM) in culture medium in the absence of cells for 1 hr. by 28.2%.	Bind to kainate receptors and reduce H_2O_2	[82]
Neuroprotective	NR/ Arctigenin[4]	0.5 μmol/L arctigenin reduced degree of cell death compared to naive control.	Regulate miRNA-16 and miRNA-199a expression	[83]
Neuroprotective	Roots/ 4, 5-O-dicaffeoyl-1-O-[4-malic acid methyl ester]-quinic acid[5]	-Pretreatment with compound 5 (10, 20, and 40 μM) increased cell viability to 68.20%, 81.76%, and 93.84%, respectively against NMDA-induced cytotoxicity in SH-SY5Y cells. -Pretreatment with 20 μM compound 5 decreased ROS levels induced by NMDA from 330.3% to 167.2% and improved MMP levels to 76.81%, up-regulate GluN2B, down-regulate GluN2A. While decrease cytochrome *c* release, caspase-9, caspase-3 expression.	Modulate GluN2A and GluN2B-containing NMDA receptors	[39]
Neuroprotective	Roots/ 4, 5-O-dicaffeoyl-1-O-[4-malic acid methyl ester]-quinic acid[5]	Cell viability increased while ROS and LDH decreased by increasing compound 5 concentrations to 10, 20, and 40 μM in human SH-SY5Y cells.	Inhibit OGD/R-induced oxidative stress and mitochondrial damage by ↑ cell viability; ↓ LDH and ROS release	[11]
Neuroprotective	Roots/ 1,5-O-dicaffeoyl-3-O-[4-malic acid methyl ester]-quinic acid[6]	-MQA decreases LDH release, Bax/Bcl-2 ratio, caspase-3, caspase-9, and ERK1/2 expression while increases cell viability and phosphorylation of AKT and GSK-3β at 20 μM. -20 μM MQA decreased apoptotic cells and ROS level to 26.04% and 162.04% while increased SOD activities and MDA production, and MMP to 85.63%, 211.59%, and 80.74%.	↓ cytochrome *c* release, phosphorylation of ERK1/2, caspase-3 and caspase-9 expressions, and dephosphorylation of AKT and GSK-3β	[84]
Antioxidant	Roots/ Extract	$EC_{50=}$ 4.79 μg/mL PC: Trolox ($EC_{50=}$ 1.13 μg/mL) and lycopene ($EC_{50=}$ 21.28 μg/mL)	Quench DPPH	[85]
Antioxidant	Roots/ Extract	At a dose of 1.0 mg water and hot water extracts, a scavenging effect on superoxide and H_2O_2 by 60.4–65.0% and 80.5%, was exhibited respectively	Termination of free-radical reactions and quenching of reactive oxygen species	[86]
Antioxidant	Roots/ Extract	DPPH assay Dose: 0.5 mL Antioxidant capacity: 76.23% phosphomolybdate method Antioxidant capacity: Which Dose: 0.3 mL 296.5 mg/g ascorbic acid	76.23% scavenging effect on DPPH	[73]
Antioxidant	Leaves/ Extract	EtOH soxhlet extract showed the best antioxidant capacity DPPH assay Dose: 250 μg/mL Antioxidant capacity: 46.41% IC_{50} = 0.273 mg/mL Phosphomolybdenum method Dose: 300.39 $mg_{tocopherol}/g_{extract}$ PC: *α*-tocopherol NC: DPPH solution + 2.5 mL EtOH	↓ DPPH and Phosphomolybdenum	[71]
Antioxidant	Roots/ Fructan	Hydroxyl radical scavenging assay Dose: 2.5 mg/mL Scavenging rate= 99.19% for ALP1 PC: Ascorbic acid showed similar inhibition rate $ABTS^{\bullet+}$scavenging assay Dose: 5 mg/mL Inhibition rate= 72.5% for ALP1 PC: Trolox inhibition rate of 90% at 0.3125 mg/mL Chelating ability assay Dose: 1.25 mg/mL Inhibition rate= 100% for ALP1 PC: EDTA inhibition rate of 90% at 0.3125 mg/mL	Moderate $ABTS^{\cdot+}$ scavenging and potent hydroxyl radical scavenging ability	[87]
Antioxidant	Roots/ Polysaccharides	Dose: 2 mg/mL DPPH radical-scavenging activity= 78.30%, 76.34%, and	↓ DPPH, and superoxide radicals	[60]

(*continued on next page*)

Table 1 (*continued*)

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
		57.81% for ALP60–1, ALP40–1, and ALP80–1. IC_{50} = 1.12, 0.76, and 1.26 mg/mL for ALP40–1, ALP60–1, and ALP80–1.		
Antioxidant	Leaves/ Onopordopicrin[7]	Dose: 0.125–0.5 μg/mL inhibited the H_2O_2-mediated loss of myoblast cell viability	Activation of the Nrf2/HO-1 signaling and protecting human myoblasts against H_2O_2-induced stress	[88]
Antioxidant	Roots/ Caffeoylquinic acid derivatives[8–12]	Dose: 100 μM Antioxidant activity of compounds 8, 9, 10, 11 were equal and lower than compound 12	NR	[89]

NR: Not Reported

Note: Abbreviations: 1,1–diphenyl-2–picryhydrazyl (DPPH); hydrogen peroxide (H_2O_2); *N*-methyl-*D* aspartate (NMDA); *C*-Jun *N*-terminal kinase (JNK); Extracellular signal-regulated kinase 1/2 (ERK 1/2); Mitogen-activated protein kinases (MAPKs); Adenosine monophosphate-activated protein kinase (AMPK), Mammalian target of rapamycin (mTOR); Micro ribonucleic acid (miRNA); Glycogen synthase kinase-3 beta (GSK-3β); Protein kinase B (AKT); Extracellular signal-regulated protein kinases 1 and 2 (ERK1/2); 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS); Nuclear factor-erythroid-2-related factor 2/ heme oxygenase-1 (Nrf2/HO-1)); Muller-Hinton agar (MHA); Propylene glycol (PG); supercritical CO_2 ($scCO_2$); Ethanol (EtOH); Ethyl acetate (AcOEt); Lactate dehydrogenase (LDH); Matrix Metalloproteinase (MMP); reactive oxygen species (ROS); Oxygen glucose deprivation/reoxygenation (OGD/R); 1,5-*O*-dicaffeoyl-3-*O*-[4-malic acid methyl ester]-quinic acid (MQA); cyanquixaline (CNQX)

also serving as a blood purifier, and they have been used as a remedy for rheumatism, scurvy, venereal disease, and sores, with the leaves being used for the healing of wounds, burns, and gastric ulcers [46–48]. Since the roots are traditionally used to treat diseases such as sore throat and infections such as rashes, boils and various skin problems, the seed and fruits are also used for skin conditions, as well as in cold/flu formulae [49]. *A. lappa* L. has been extensively cultivated for over 3000 years in Asia, is not only a nutritious vegetable but also an important part of Traditional Chinese Medicine (TCM) [50,51].

Arctium lappa roots are used in Europe for the management of dermatological and blood disorders; its leaves are used as an anti-inflammatory agent in traditional medicine to treat gastrointestinal disorders in Brazil. Both fruits and roots are used to treat diabetes mellitus in Asian countries. The European Medicines Agency (EMA) recommends the roots of *Arctium lappa* as adjunct therapy for seborrheic skin conditions and urinary tract infections [52]. *A. lappa* is among commonly used traditional medicines in Iraq for treatment of diseases related to cancer or that may lead to cancer, such as skin diseases, blood-related diseases, inflammatory diseases, immune disorders, and infectious diseases [53]. *A. lappa* roots have been used for hundreds of years as traditional medicines by multiple European, Asian and North American cultures for a variety of purposes including to improve the immune system and enhance metabolism, as well as for its anti-inflammatory and anticancer effects [54]. *A. lappa* L., is also called Niubang in Chinese, gobo in Japanese, burdock in English and repejnik in Russian, and this plant has been cultivated in China, Japan, and Korea as a root vegetable or traditional herb medicinal plant for centuries, remaining popular unto the present day. Its seeds, known as Niubangzi, have been used widely as a diuretic, diaphoretic, and a blood purifying agent [3]. The root has been used in Russian traditional medicine as a diuretic and diaphoretic [2].

Arctiin is one of the main active components extracted from the dried ripe fruit of *A. lappa* L. commonly called greater burdock. As a component in the Chinese pharmacopoeia, Arctiin exerts traditional therapeutic actions, to "ease the throat, dissipate nodules, remove toxic materials, expel wind and heat", As a traditional medicine, Arctiin has been widely used in Asia, Europe and North America for centuries [55].

3. Phytochemical constituents

According to Moro et al., fresh burdock root contains moisture (78.13 ± 1.18), protein (2.46 ± 0.01), lipids (0.06 ± 0.01), ash (1.13 ± 0.08), total dietary fiber (17.43 ± 1.65) and digestible carbohydrates (0.79), for each 100 gm [56]. *A. lappa* is considered to provide a rich pool of bioactive constituents, for example lignans, which are represented in the major compounds of this plant by arctigenin among others, a phenylpropanoid dibenzyl butyrolactone lignan and one of the major active ingredients extracted from the fruits and seeds of *A. lappa* L. Notably, arctigenin and arctiin are two of the bioactive compounds that exist in burdock extracts [55,57,58]. In addition to lignans, burdock contains high amounts of monosaccharides and polysaccharides, mainly consisting of mannose (PubChem CID: 18950), glucose (PubChem CID: 5793), fructose (PubChem CID: 2723872) and galactose (PubChem CID: 6036) compounds with potent antioxidant activity [59,60].

Numerous caffeoylquinic acids [61,62] have also been isolated from different parts of burdock, for example, 4,5-*O*-dicaffeoyl-1-*O*-[4-malic acid methyl ester]-quinic acid (DCMQA) which had been isolated from roots of burdock by Yang et al. It has been mentioned that dicaffeoyl compounds demonstrate vital pharmacological effects including neuroprotective activity, since they have been found to ameliorate cerebral ischemia [11], as well as alleviate memory loss via reduction of oxidative stress [63]. 3-*O*-caffeoylquinic acid (chlorogenic acid), 1,5-*O*-dicaffeoylquinic acid, 3-*O*-caffeoylquinic acid methyl ester (PubChem CID: 6476139), 1,3-*O*-dicaffeoylquinic acid (PubChem CID: 6474640), 1,5-*O*-dicaffeoyl-3-*O*-(4-maloyl)-quinic acid, 4,5-*O*-dicaffeoylquinic acid (PubChem CID: 6474309), 1,5-*O*-dicaffeoyl-3-*O*-succinylquinic acid, and 1,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid, 1,4-*O*-dicaffeoyl-3--succinyl methyl ester quinic acid and 1,5-*O*-dicaffeoyl-3-*O*-succinyl methyl ester quinic acid, and other caffeoylquinic acids have been derived from the methanol extract of *A. lappa* L. roots [64].

Fructooligosaccharides are inulin compounds that have been isolated from burdock several times and provide an antidiabetic effect (inhibiting α-glucosidase activity with an IC_{50} of 0.4996 mg/mL) [65]. In a comparison study conducted by Stefanov et al., it was reported that supercritical CO_2 extraction of burdock roots and seeds yields effective values for biomass and quality of chemical constituents, compared to traditional methods (Soxhlet procedure) [66]. It should be noted that the secondary metabolites of burdock vary greatly among burdock plant parts and phenological stages. According to Bhatt et al., the roots of burdock exhibit markedly high contents of triterpenoids during the vegetative stages, including betulinic acid (PubChem CID: 64971), oleanolic acid (PubChem CID: 10494), and lupeol (PubChem CID: 259846) compared with such yields during the reproductive phase [67]. Nevertheless, the stem is rich in flavonoids including rutin, myricetin, quercetin, apigenin, and kaempferol [15].

4. Pharmacological activities

4.1. In vitro studies

4.1.1. Antimicrobial effects

A. lappa leaves could be used as phytotherapeutic agents in intracanal dressings as they inhibit intracanal microbial growth when compared with calcium hydroxide, that showed mild microbial growth

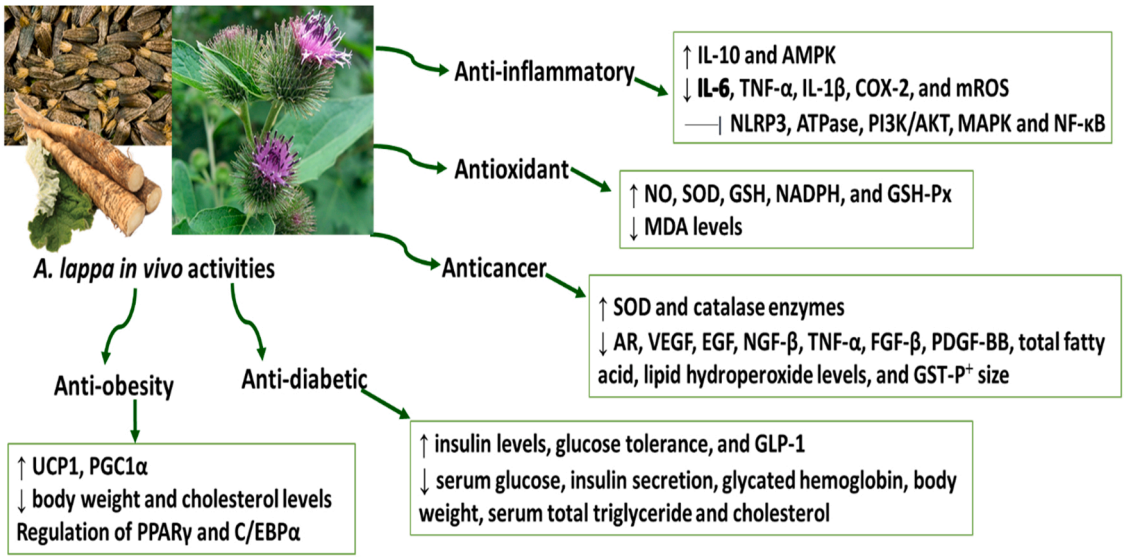

Fig. 4. Various *A. lappa in vivo* studies with their mechanisms.

as an intracanal dressing [68]. Additionally, it demonstrated potential microbial inhibition against different endodontic pathogens found in the oral cavity during endodontic infections [69]. *A. lappa* leaf extract was found to enhance the antimicrobial efficacy of common antibiotics on different Gram-positive and Gram-negative bacterial strains [70]. In another study, *A. lappa* leaves extracted using supercritical CO_2 +EtOH revealed a significant antibacterial effect against *Staphylococcus aureus* [71]. Non-polar fractions of *A. lappa* root extract were effective against different microorganisms including *Salmonella* spp., *S. aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Bacillus cereus*, *Proteus vulgaris*, and *Candida albicans* [72]. *A. lappa* root extract exhibited antifungal activity against *Aspergillus niger* and *Penicillium hirsutum* with inhibition zones of 22 and 13.1 mm, respectively [73]. The hydroalcoholic extract of *A. lappa* roots displayed a bactericidal effect against *E. coli* and *Salmonella abony* [74]. The fruit extract of *A. lappa* was tested against *Herpes simplex* virus type-1 and exhibited a significant reduction in viral load when applied at concentrations of 400, 50, and 3.125 μg/mL, and an antiviral effect similar to acyclovir (positive control 50 μg/mL) when applied at a concentration of 400 μg/mL [75]. A 70% ethanol fraction of *A. lappa* leaves showed potent antibacterial and antibiofilm effects, with MICs of 2 mg/mL against *E. coli* and *Salmonella typhimurium* [76]. In a different study, a 34% ethanol fraction of *A. lappa* leaves provided a complete inhibition of *S. typhimurium* biofilm formation at a concentration of 1 mg/mL [77]. The MICs of *A. lappa* leaf and stem extract on *Pseudomonads aeraginosa*, *Haemophilus influenza*, *Bacillus subtilis*, *B. cereus*, *Klebsiella pneumonia*, and *S. aureus* were 500, 230, 600, 166, 666, and 333 mg/mL, respectively [78]. The antimicrobial effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 1.

4.1.2. Neuroprotective effects

An ethyl acetate extract of *A. lappa* roots demonstrated a neuroprotective effect against glutamate-induced oxidative stress in PC12 cells through the suppression of phosphorylation of p38, JNK, and ERK 1/2 MAPKs [79]. The effects of *A. lappa* root ethyl acetate extract against cerebral ischemia was investigated, and the extract demonstrated a neuroprotective effect via inhibition of neuronal apoptosis and suppression of AMPK/mTOR-mediated autophagy [11]. *A. lappa* root ethyl acetate extract also was found to inhibit H_2O_2-induced apoptosis by enhancing the Bcl-2/Bax ratio, reducing cytochrome *c* release, and caspase-3 and caspase-9 activities in H_2O_2 -induced cell injury in SH-SY5Y cells [80]. *A. lappa* root caffeoylquinic acid derivatives (1,3,5-tri-*O*-caffeoylquinic acid[1] (PubChem CID: 10190081), 1,4,5-tri-*O*-caffeoylquinic acid[2] (PubChem CID: 10283355) and 3,5-di-*O*-caffeoyl-1-*O*-maloylquinic acid[3]) showed neuroprotective activity against the neurotoxicity of hydrogen peroxide and *N*-methyl-*D*-aspartate, by reducing H_2O_2-induced human neuroblastoma SH-SY5Y cell death and NMDA-induced cell injury [81]. Arctigenin[4], which is purified from *A. lappa,* exhibited a neuroprotective effect on glutamate-injured primary cultures of rat cortical cells by binding to kainate receptors and partly scavenging free radicals [82]. The neuroprotective effects of arctigenin[4] against trauma injury in human neuroblastoma SH-SY5Y cells was attributed to regulating miRNA-16 and miRNA-199a expression, reducing the inflammatory response and accelerating injury repair in a scratch-induced injury model [83]. 4,5-*O*-dicaffeoyl-1-*O*-[4-malic acid methyl ester]-quinic acid[5] was extracted from *A. lappa* roots and exhibited a neuroprotective effect via modulating GluN2A and GluN2B-containing NMDA receptors [39]. 1,5-*O*-dicaffeoyl-3-*O*-[4-malic acid methyl ester]-quinic acid[6] is isolated from *A. lappa* roots and was found to mitigate H_2O_2-induced apoptosis via promoting Bcl-2/Bax ratio and decreasing cytochrome *c* release, phosphorylation of ERK1/2, caspase-3 and caspase-9 expressions, and dephosphorylation of AKT and GSK-3β [84]. The neuroprotective effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 1. The chemical structures of the bioactive compounds are drawn in Fig. 5.

4.1.3. Antioxidant effects

The hydroethanolic extract of *A. lappa* roots exerted antioxidant activity by quenching the stable radical DPPH, with the antioxidant properties of the extract commonly attributed to the presence of flavonoids and phenolics such as quercetin, rutin, chlorogenic acid, caffeoylquinic acid derivatives, and caffeic acid [85]. Fierascu and collaborators concluded that the hydroalcoholic extract of *A. lappa* roots exhibited a 76.23% scavenging effect on DPPH radicals, with a total antioxidant capacity of 296.5 mg/g ascorbic acid equivalent, via the phosphomolybdate method [73]. In another study, cold water and hot water extracts of *A. lappa* roots demonstrated 80% scavenging activity on DPPH radicals, 60.4–65.0% scavenging activity on superoxide, 80.5% scavenging effect on H_2O_2, and significant scavenging effect on the hydroxyl radicals, causing termination of free-radical reactions and quenching of reactive oxygen species [86]. *A. lappa* leaves extracted using supercritical CO_2+EtOH demonstrated significant antioxidant effects, and this effect was attributed to their high phenolic content [71]. Fructan was purified from *A. lappa* roots and showed antioxidant activity in the form of moderate $ABTS.^+$ scavenging activity [87]. The polysaccharides extracted from *A. lappa* roots showed scavenging effects

Table 2
Basic health merits of *A. lappa* L. with the underlying mechanisms (*in vivo* studies).

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
Anti-inflammatory	The whole plant/ Powder	100 mg/kg per 200 μL of the plant powder prevented significant elevations in IL-6 and TNF-α at day 8. Control: 200 μL of water.	↓ IL-6 and TNF-α	[90]
Anti-inflammatory	Leaves and stems/ Extract	2.5–10 μg/mL extract suppressed IL-1β induced by NLRP3 as well as activation of caspase-1 while inhibited ATP-induced pyroptosis and ASC translocation, oligomerization, and speck formation in a dose dependent manner PC: A pan-caspase inhibitor (zVAD-Fmk); KCl; MCC950	Inhibits NLRP3 ATPase; ↓ mROS and IL-1β	[91]
Anti-inflammatory	Roots/ Microemulsion	1 mL/100 g b.w. of microemulsions showed a similar paw oedema evolution with the diclofenac treated group. PC group: Rats treated with the microemulsions Vehicle The reference substance: Diclofenac NC: Distilled water	NR	[73]
Anti-inflammatory	Roots/ Alkali-soluble polysaccharides	400 mg/kg b.w. of ASALP reduced thymus index, elevated spleen index, ALT, AST, TNF-α, IL-1β, and IL-6 secretion nearly to normal levels while increased IL-10 secretion in LPS-induced inflammatory mice compared to normal control mice	↓ IL-6, IL-1β, and TNF-α; ↑ IL-10	[5]
Anti-inflammatory	Roots/ Water-soluble polysaccharide	-Cell viability for (100, 200, 400, and 800 μg/mL) of water-soluble polysaccharide was above 94%. -High doses (200, 400, 800, and 1600 μg/mL) showed significant suppression on NO release. -IL-6, IL-1β, and TNF-α were decreased and IL-10 secretion was enhanced by water-soluble polysaccharide in a dose dependent manner. NC: mice were given water, standard foods, and saline solution.	↓ IL-6, IL-1β, and TNF-α; ↑ IL-10	[92]
Anti-inflammatory	Seeds/ Arctigenin[4] (Isolated lignan)	-Arctigenin 30 mg/kg inhibited LPS- and PGN-induced proinflammatory cytokines by 71% and 68% for IL-1β and 81% and 62% for TNF-α. -30 and 60 mg/kg arctigenin inhibited body weight loss, colon shortening, myeloperoxidase activity, PI3K, AKT, and NF-κB activation in TNBS-induced colitis mice. Control: Vehicle	Inhibits PI3K/AKT pathway and polarizes M1 macrophages to M2-like macrophages	[93]
Anti-inflammatory	NR/ Arctigenin[4]	Arctigenin 2.0 mg/kg body weight per mouse reduced IL-1β, IL-6, IL-8 and TNF-α in mice serum and supressed translocation of p65 from the cytoplasm to the nucleus and the phosphorylation of IκBα. NC: DMEM	Inhibits NF-κB	[94]
Anti-inflammatory	Fruit/ Ethanol extract and arctigenin[4]	-25, 50, 100 mg/kg of ethanol extract decreased -DAI score in a dose-dependent manner as compared with the DSS group, and showed a significant protective effect on days 7, 8, and 9. -100 mg/kg extract prevented colon shortening in DSS group. -50, 100 mg/kg extract reduced MPO activities in colonic tissues. -50 mg/kg arctigenin recovered the loss of body weight, decreased the DAI scores, completely reversed TNF-α and IL-6, suppressed both IκBα and p65 phosphorylation, inhibited colon shortening, reduced MPO activity, and improved the pathological changes of colonic tissues in mice colitis induced by DSS. - 25 and 50 mg/kg arctigenine inhibited the phosphorylation of p38 MAPK, ERK and JNK by 21.74% and 45.37% against p38 MAPK, 35.70% and 36.66% against ERK, and 41.40% and 50.89% against JNK, respectively. PC: Mesalazine	Inhibits MAPK and NF-κB	[95]
Anti-inflammatory	NR/ Arctigenin[4]	Arctigenine (30 and 100 mg/kg) pretreatment reduced the production of TNF-α to (1463.98 and 577.01), IL-1β (1373.39 and 511.57), and IL-6 (1243.06 and 426.35) in a dosedependent manner	↑ AMPK, inhibits NF-κB, and prevents IκBα phosphorylation	[96]
Anti-inflammatory	Leaves/ Lactone sesquiterpene onopordopicrin[7] fraction	-Onopordopicrin fraction (25 and 50 mg/kg) reduced MPO by (0.97 and 1.18 U/mg) and TNF-α by (0.12 and 0.26), respectively in TNBS-induced colitis rats. -50 mg/kg onopordopicrin fraction reduced COX-2 overexpression Control: Tween	↓ COX-2 overexpression	[97]
Anti-inflammatory	Roots/ crude extract			[98]

(*continued on next page*)

Table 2 (*continued*)

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
		The extract (125, 250, and 500 mg/kg) inhibited oedema by (29.39, 37.17, 41.21%) compared to diclofenec 20 mg/kg b.w. reduced oedema by 55.9% after 4 h NC: Saline	Inhibiting some pro-inflammatory mediators by polyphenols	
Anti-inflammatory	Roots/ crude extract	The extract (100, 300, and 1000 mg/kg) inhibited oedema by (22.33, 23.99, 25.01%) compared to indomethacin 10 mg/kg reduced oedema by 34.21% after 4 hr NC: Saline	Radical scavenger mechanism	[99]
Anti-inflammatory and anti-tumor	Bark/ Extract	Hydroalcoholic extract (300 mg/kg/1 mL/pouch) reduced leukocytes and neutrophils and inhibited IL-6, TNF-α, and IL-1β in the LPS-stimulated animals. Control: LBS and PBS	↓ IL-6, TNF-α, and IL-1β, edema formation and NO production	[100]
Antioxidant	Roots/ Extract	The aqueous extract (2 g), chloroform (200 mg), and flavone extract (300 mg) reduced MDA to (9.3, 9.27, and 9.11 μmol/mL), while increased NO to (35.38, 35.84, and 36.51 μmol/mL), SOD to (217.2, 216.3, and 220.2 U/mL), GSH to (3.36, 3.48, and 3.55 mg/L), NADPH (3.41, 3.54, and 3.63 μmol/mL), and GSH-Px to (718.5, 751.1, and 763.9 U). PC: Simvastatin. Control group fed standard chow (0% cholesterol).	↑ NO, SOD, GSH, NADPH, and GSH-Px; ↓ MDA levels	[101]
Antioxidant	Roots/ Water-soluble polysaccharide	- Water-soluble polysaccharide (100, 200, and 400 mg/kg body weight) increased SOD to (75.19, 99.42, and 104.17 U/mL), GSH-Px to (2102.89, 2124.33, and 2960.34 U/mL), and CAT to (14.39, 18.35, and 22.16 U/mL), while decreased MDA to (58.7, 57.62, and 52.43 nmol/mL) in serums of aging mice while in livers of aging mice SOD increased to (111.3, 145.89, and 184.27 U/mg protein), GSH-Px increased to (266, 274.99, and 332.65 U/mg protein), and CAT increased to (18.27, 18.45, and 19.30 U/mg protein), while MDA decreased to (19.56, 17.99, and 17.6 nmol/g protein). PC: Ascorbic acid. Model group: D-Galactose 500 mg/kg/d Normal group: Saline.	↑ Antioxidant enzyme activities and ↓ MDA levels	[87]
Anti- tumor	Bark/ Extract	Hydroalcoholic extract (50 mg/kg/300 μL) suppressed tumor growth by 38% after 20 days and enhanced mice survival after 30 days Control: PBS	↓ tumor growth and ↑ mice survival	[100]
Anticancer	Roots/ Extract	The root ethanolic extract (100 or 200 mg/kg body weight/ 2 weeks) decreased hepatocyte proliferation (Ki-67) inside remodeling PNL ($P = .059$) leading to 48% and 75% reductions, remodeling GST-P^+ PNL ($P = .008$) size, liver total fat acids levels ($P < 0.001$), while enhanced the activity of antioxidant SOD ($P = 0.020$) and catalase enzymes in the liver ($P = 0.040$) Vehicle: 5% DMSO	↓ Total fatty acid, lipid hydroperoxide levels, and GST-P^+ size; ↑ SOD and catalase enzymes and remodeling PNLs	[50]
Anticancer	Seeds/ Arctigenin[4]	Arctigenin at 50 or 100 mg/kg b.w. daily inhibited tumor growth by 50% and 70% after 6 weeks compared to control. Vehicle (2% DMSO in corn oil).	↓ AR, VEGF, EGF, NGF-β, TNF-α, FGF-β, and PDGF-BB	[102]
Antitumor	Seeds/ Lappaol F[13]	Lappaol F (5 or 10 mg/kg) once daily for 15 days inhibited tumor growth by 54% and 64%, respectively, relative to vehicle-treated cohorts. Tumor volume and weight decreased by increasing lappaol F dose without any observed toxicity or weight loss in mice. Vehicle: (5% DMSO + 5% Tween 80 in 5% glucose solution, 5 mL/kg/d.	NR	[103]
Anti-diabetic	Roots/ Extract	- The root extract 200 mg/kg increased insulin level to 19.89 μIU/mL in diabetic mice - 300 mg/kg extract increased leptin level to 2.26 U/L and decreased ALP and SGPT to 99.62 and 51.23 U/L Control group: Saline PC: Glibenclamide (0.25 mg/kg)	↑ Insulin levels and ↓ serum glucose	[105]
Anti-diabetic	Roots/ Extract rich in caffeoylquinic acids	Dried root extract (0.75 mg/kg) decreased the increase in plasma glucose ($p < 0.05$) from minute 10–30 in IPGTTs and at 15 mg/kg reduced hyperglycemia from minute 60–90 ($p < 0.05$) in OGTTs. Control: Saline. PC: Metformin (100 mg/kg).	↑ Glucose tolerance and ↓ insulin secretion	[104]
Anti-diabetic	Fructus Arctii/ Lignan	17.28 g/kg total lignan increased insulin level to 32.44 mU/L, HDL to 1.7 mmol/L; decreased TC to 4.71 mmol/L, TG to 1.27 mmol/L, and blood glucose in alloxan-induced hyperglycemic rats. PC: Glibenclamide (6.75 mg/kg). Blank: Saline solution. Model: Diabetic control.	↑ Glucose tolerance and serum insulin; ↓ blood glucose	[107]
Anti-diabetic	Fructus Arctii/ Lignan	Total lignan (300 mg/kg/ twice daily for 12 weeks) decreased FBG by 51.4%, PBG by 54.6%, HbA1c ($p < 0.01$), body weight		[108]

(*continued on next page*)

Table 2 (*continued*)

Biological activity	Part/ bio-gradients	Doses/ conditions	Mechanism	Reference
		($p < 0.05$); improved OGT; and increased serum insulin 4.05-fold and C-peptide 3.66-fold after 1 hr of glucose gavage. PC: Nateglinide (50 mg/kg). Normal control: Saline solution. Model control: 0.5% methylcellulose.	↓ Intestinal absorption of glucose; ↑ glucose tolerance, insulin secretion, and GLP-1	
Anti-diabetic	Fructus Arctii/ Lignan	Total lignan (250 mg/kg/ once daily for 11 weeks) reduced FBG by 19.24%, HbA1c, and body weight; improved OGT; increased HDL to 4.03 mmol/L; and decreased TC to 5.23 mmol/L, LDL to 1.23 mmol/L, TG to 2.6 mmol/L and free fatty acid to 364.33 μmol/L in mice serum. Normal control: Saline solution PC: Metformin (200 mg/kg) Model:Type 2 diabetic control	↓ FBG, HbA1c, and body weight; ↑ OGT and insulin secretion	[113]
Anti-diabetic	Fructus Arctii/ Arctigenic acid[14]	Arctigenic acid (50 mg/kg/ twice daily for 12 weeks) reduced FBG by 37.6%, PBG by 43.7%, HbA1c, and increased serum C-peptide 1 h to 2.88-fold in glucose fed hyperglycemic GK rats compared to PC and model group. PC: Nateglinide. Model group: type2 diabetic control.	↑ Glucose tolerance, insulin secretion; ↓ blood glucose and glycosylated hemoglobin	[109]
Anti-diabetic	Roots/ Extract	The hot water extract (50 mg/kg + 60% fat diet group) was within the safety range and decreased body weight and blood glucose to 35.9 g and 341 mg/dL compared to 60%-fat diet group in which body weight and blood glucose were 37.9 g and 474 mg/dL after 8 weeks. Control group: Normal diet group	↓ Body weight and serum glucose	[106]
Anti-diabetic	Roots/ Fructooligosaccharide	800 mg/kg/day fructooligosaccharide reduced TG, TC, and LDL-C to 0.60, 3.32, and 1.82 mmol/L and FBG from 23.97 mmol/L before treatment to 19.77 mmol/L after treatment, and reduced HOMA-IR, while increased HDL-C to 1.47 mmol/L and improved OGT compared to model group. PC: Acarbose Model: High-fat diet Control diet: Saline	↓ Fasting blood glucose, body weight, serum total triglyceride and cholesterol; ↑ glucose tolerance	[65]
Anti-obesity	Roots/ Polysaccharide	Polysaccharide was given by 100 mg/kg body weight per day after establishing diabetes (blood glucose > 16.5 mmol/L) and showed similar levels of TC, TG, and LDL to that of normal group and the ratio of liver weight to body weight was close to normal compared to diabetic group. Normal group: Saline.	Regulate SREBP-1 and SCD-1	[59]
Anti-obesity	Arctii Fructus/ Extract	After 10 weeks the mice weight in ethanol extract group (100 mg per kg per day extract + 60% HFD) was 29.86 g while in HFD group was 33.76 g. Additionally, TG, LDL, and TC were decreased by ethanol extract as well.	Regulation of PPARγ and C/EBPα.; ↑ UCP1 and PGC1α	[110]
Anti-obesity	Roots/ Extract	After 8 weeks in the high dose group that received high-fat diet and aqueous extract (8 g/kg) there was reduction in body weight (328 g) and CHOL levels (1.81 mM) compared to model group showed body weight (381 g) and CHOL levels (2.33 mM). PC: fed the high-fat diet and simvastatin (10 mg/kg). Also CHOL levels Model group received a high-fat diet only. Control group: Normal diet.	↓ Body weight and cholesterol levels; ↑ differential expression of genes	[111]
Antiviral	Fruit/ Arctigenin[4]	Arctigenin (200 μg/kg) inhibited PCV2 proliferation in the lungs, spleens and inguinal lymph nodes, with an effect similar to ribavirin (1000 μg/mL) NC: Saline.	NR	[112]

Note: Abbreviations: Sterol Regulatory Element-Binding protein-1 (SREBP-1); Stearoyl-CoA Desaturase 1 (SCD-1); Interleukin-6 (IL-6); Interleukin-1β (IL-1β); Interleukin-10 (IL-10) Tumor Necrosis Factor-α (TNF-α); NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3); Adenosine 5′-TriPhosphatase (ATPase); Mitochondrial Reactive Oxygen Species (mROS); Phosphoinositide 3-kinase/ Protein kinase B (PI3K/AKT); Nuclear Factor Kappa- B (NF-κB); cyclooxygenase-2 (COX-2); Mitogen-Activated Protein Kinase (MAPK); Adenosine monophosphate activated protein kinase (AMPK); Malondialdehyde (MDA); Nitric oxide (NO); Superoxide dismutase (SOD); Glutathione (GSH); Nicotinamide Adenine Dinucleotide Phosphate (NADPH); Glutathione peroxidase (GSH-Px); Androgen Receptor (AR); Vascular Endothelial Growth Factor (VEGF); Epidermal Growth Factor (EGF); Nerve Growth Factor (NGF); Fibroblast Growth Factor-β (FGF-β); Platelet-Derived Growth Factor-BB (PDGF-BB); preneoplastic glutathione-S-transferase pi (GST-P)$^{+}$; Preneoplastic lesions (PNLs); glucagon-like peptide-1 (GLP-1); Homeostasis Model Assessment–Insulin Resistance (HOMA-IR); Uncoupling Protein 1 (UCP1); peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α); Peroxisome Proliferator Activated Receptor gamma (PPARγ); CCAAT/Enhancer Binding Proteins alpha (C/EBPα), Sterol Regulatory Element-Binding Protein-1 (SREBP-1); Stearoyl-CoA Desaturase 1 (SCD-1); Not reported (NR); Body weight (b.w.); Alkali-soluble polysaccharides (ASALP); Aspartate transaminase (AST); Alanine aminotransferase (ALT); Alkaline phosphatase (ALP); Lipopolysaccharide (LPS); Pectolinarigenin (PNG); 2,4,6-trinitrobenzenesulfonic acid (TNBS); Dulbecco's Modified Eagle Medium (DMEM); Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα); Diseased activity index (DAI); Dextran sulfate sodium (DSS); Myeloperoxidase (MPO); Phosphate-buffered saline (PBS); Porcine circovirus type 2 (PCV2); Cholesterol (CHOL); Total cholesterol (TC); Fasting Blood Glucose (FBG); Homeostasis model assessment for insulin resistance (Homa-IR); High-density lipoprotein cholesterol (HDL-C); Low-density lipoprotein cholesterol (LDL-C); Postprandial blood glucose (PBG); Glycosylated hemoglobin (HbA1c); Goto- Kakizaki (GK); Oral glucose tolerance test (OGTT); Intraperitoneal Glucose Tolerance Test (IPGTT); Alkaline phosphatase (ALP), Serum glutamic pyruvic transaminase (SGPT); Dimethyl sulfoxide (DMSO)

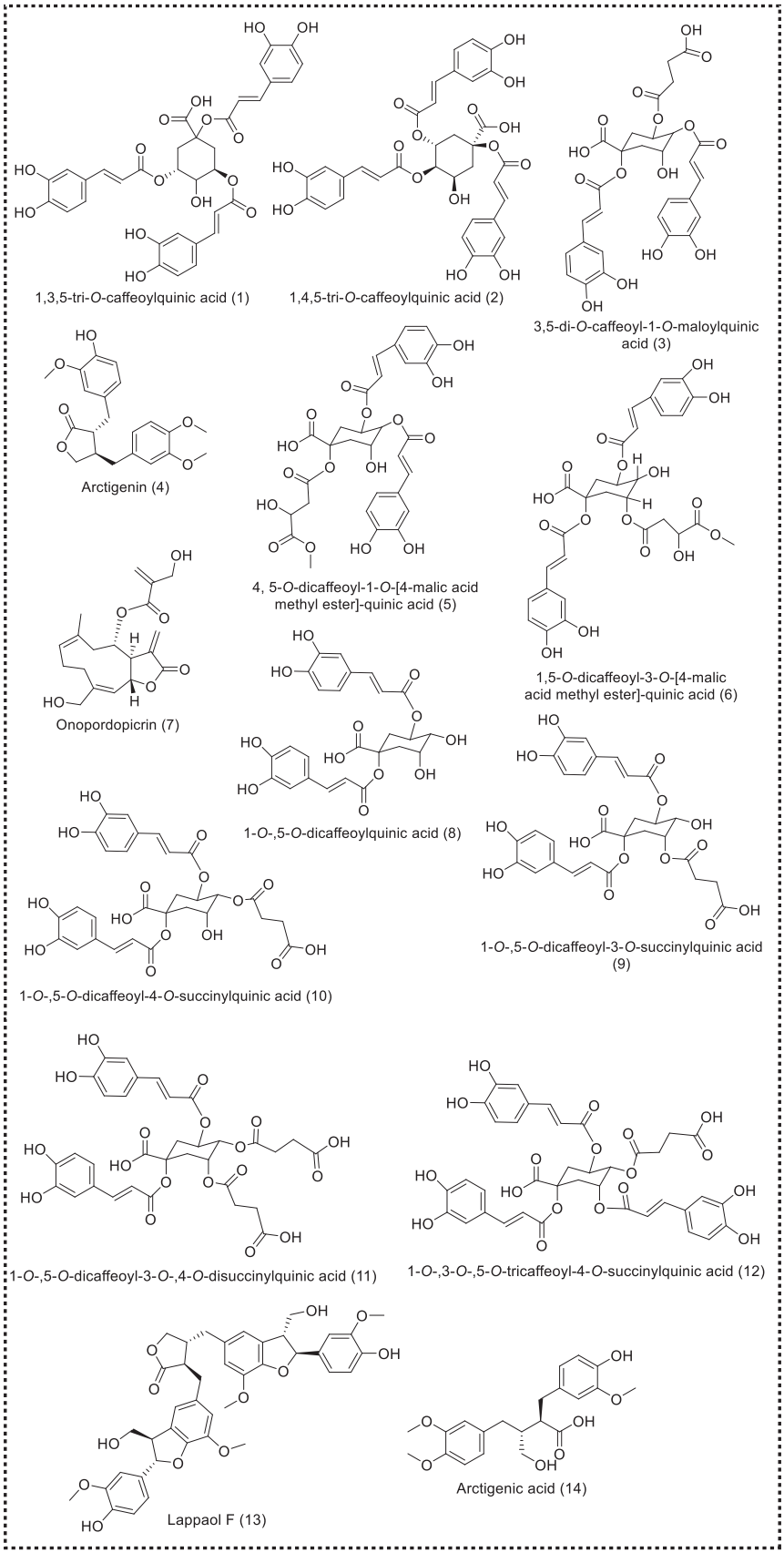

Fig. 5. Chemical structures of *A. lappa* bioactive compounds with unique pharmacological effects.

on DPPH and superoxide radicals [60]. Onopordopicrin[7] (PubChem CID: 6440861) is a sesquiterpene lactone isolated from *A. lappa* leaves, and it was found to exert antioxidant activity via activation of the Nrf2/HO-1 signaling pathway in a primary human muscle cell model exposed to H_2O_2 oxidative stress [88]. Maruta and other collaborators isolated five caffeoylquinic acid derivatives (1-*O*-,5-*O*-dicaffeoylquinic acid[8], 1-*O*-, 5-*O*-dicaffeoyl-3-*O*-succinylquinic acid[9] (PubChem CID: 102296939), 1-*O*-,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid[10], 1-*O*-,5-*O*-dicaffeoyl-3-*O*-, 4-*O*-disuccinylquinic acid[11], and 1-*O*-,3-*O*-,5-*O*-tricaffeoyl-4-*O*-succinylquinic acid[12]) from *A. lappa* roots. These derivatives were found to possess diverse antioxidant efficacies in a hexane/2-propanol solution of methyl linoleate in the presence of a radical initiator [89]. The antioxidant effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 1. The chemical structures of the bioactive compounds are drawn in Fig. 5.

4.2. In vivo studies

For several years, *A. lappa* L. has proven to be a potential candidate for treating several ailments. Many studies have proven the antidiabetic effects of *A. lappa* L. and its main bioactive constituents, such as polysaccharides, which can regulate lipid metabolism in rats via inhibition of sterol regulatory element-binding protein-1 (SREBP-1) and stearoyl-CoA desaturase 1 (SCD-1) [59].

4.2.1. Anti-inflammatory effect

In a murine model of ulcerative colitis induced with dextran sulfate sodium, treatment with *A. lappa* resulted in a reduction in inflammatory cytokines levels (IL-6 and TNF-α) (Fig. 4) [90]. The effect of *A. lappa* leaf and stem extract on NLRP3 inflammasome activation was investigated, demonstrating suppression in NLRP3 ATPase function, mitigation in the mROS, and reduction in LPS-induced increase of plasma IL-1β in a mouse peritonitis model [91]. The root extract of *A. lappa* displayed anti-inflammatory activity similar to the reference substance (diclofenac) as seen through similar paw edema evolution in a dextran-induced inflammation model [73]. The alkali-soluble polysaccharides of *A. lappa* roots exhibited anti-inflammatory activity by alleviating the dysregulation of inflammatory cytokines and oxidative damage, as the polysaccharides down-regulated the secretion of pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α) and increased IL-10 secretion [5]. Another water-soluble polysaccharide extracted from *A. lappa* roots displayed anti-inflammatory effects by accommodating inflammatory cytokine levels in macrophages and mice serum, including the enhancement of anti-inflammatory cytokine (IL-10) secretion and inhibiting the secretion of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) [92]. Arctigenin[4] is a lignan purified from *A. lappa* seeds which exerted anti-inflammatory activity by suppressing the PI3K/AKT pathway and polarizing M1 macrophages to M2-like macrophages [93]. In another study, arctigenin[4] showed anti-inflammatory effects by suppressing a Porcine circovirus type 2 (PCV2) infection that induced the production of proinflammatory cytokines by inhibiting the phosphorylation and nuclear translocation of NF-κB [94]. Arctigenin[4] also exhibited anti-inflammatory effects in a mouse model of colitis via suppressing MAPK and NF-κB pathways [95]. Additionally, arctigenin[4] mitigates acute lung injury induced by lipopolysaccharides in rats via stimulation of AMPK and inhibition of NF-κB pathway accompanied by decreased levels of IL-6, TNF-α, IL-1β [96]. The lactone sesquiterpene onopordopicrin[7] fraction extracted from *A. lappa* leaves demonstrated anti-inflammatory intestinal activity by lowering macroscopic inflammation scores, morphological alterations associated with an increase in mucus secretion, and ameliorating the degree of neutrophil infiltration and cytokine levels. Moreover, it was found to reduce COX-2 overexpression [97]. The anti-inflammatory and antinociceptive effects of *A. lappa* root extract were examined and attributed to the presence of polyphenols such as chlorogenic acid suppressing the synthesis and release of certain pro-inflammatory mediators [98]. The crude extract of *A. lappa* roots exerted anti-inflammatory and liver-protective actions through a radical scavenger mechanism, as well as the overproduction of superoxide and hydroxyl radicals by *A. lappa* extract [99]. *A. lappa* bark extract suppressed inflammation and melanoma progression in mice with lipopolysaccharide-induced inflammation by reducing IL-6, TNF-α, and IL-1β, and edema formation and NO production [100]. The anti-inflammatory effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 2. The chemical structures of the bioactive compounds are drawn in Fig. 5.

4.2.2. Antioxidant effect

The antioxidant activity of *A. lappa* root extract and isolated flavones on high-fat diet-fed quails was assessed and showed an increase in NO, SOD, GSH, NADPH, and GSH-Px levels and a reduction in MDA levels [101]. A fructan with approximately 4600 Da molecular weight, composed of fructose and glucose at a ratio of 13.0:1.0, purified from *A. lappa* roots, demonstrated antioxidant activity via the enhancement of the total antioxidant capacity and antioxidant enzyme activities, also lowering MDA levels in both the blood and liver of aging mice [87]. The antioxidant effects of *A. lappa* extract and its bioactive metabolites are shown in Table 2.

4.2.3. Anticancer effect

A. lappa root extract alleviates preneoplastic lesion development in nonalcoholic steatohepatitis-associated hepatocarcinogenesis in male Wistar rats, due to the reduction in total fatty acid and lipid hydroperoxide levels, while enhancing SOD and catalase antioxidant enzymes in the liver and via intervention due to diminishing preneoplastic glutathione-*S*-transferase pi $(GST\text{-}P)^{+}$ size and remodeling preneoplastic lesions and decreasing hepatocyte proliferation (Ki-67) inside these lesions [50]. The anticancer activity of arctigenin[4] in prostate cancer was evaluated *in vivo* using xenograft mouse models, displaying the best inhibition for tumor growth (60% at week 7% and 70% at week 8 at a dose of 50 mg/kg) when arctigenin[4] administration started before tumor cell implantation. Arctigenin[4] significantly decreased both total and nuclear AR (a key modulator of growth and progression of prostate cancer) expression as well as reduced the expression of multiple growth factors (VEGF, EGF, NGF-β, TNF-α, FGF-β, and PDGF-BB) in tumor tissues, leading to downregulation of proliferative signaling and upregulation of apoptotic signaling in tumors [102]. Lappaol F[13] (PubChem CID: 73425459) is a compound purified from *A. lappa* seeds which has great anticancer potential on nude mice bearing xenografted tumors, as it suppressed tumor growth in mice by 54% and 64% at doses of 5 mg/kg/d and 10 mg/kg/d, respectively [103]. The anticancer effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 2. The chemical structures of the bioactive compounds are drawn in Fig. 5.

4.2.4. Anti-diabetic effect

A. lappa root extract displayed an *in vivo* anti-diabetic activity via improving glucose tolerance and suppressing insulin secretion [104]. The anti-diabetic effect of *A. lappa* root extract was evaluated, and it exhibited a significant decrease in serum glucose and an improvement in insulin levels [105]. In another study *A. lappa* root extract was found to reduce body weight and serum glucose [106]. The total lignan of Fructus Arctii, which is the dried ripe fruit of *A. lappa*, exerted anti-diabetic action in an alloxan-induced diabetic mice model through down-regulating blood glucose levels, while elevating glucose tolerance and serum levels of insulin [107]. In another study on Goto-Kakizaki type 2 diabetic mice, Fructus Arctii total lignan was found to possess significant hypoglycemic potential through stimulating glucose tolerance, insulin secretion, and GLP-1 release, while suppressing intestinal absorption of glucose [108]. The hypoglycemic activity of arctigenic acid[14] (PubChem CID: 141309089) was investigated in Goto-Kakizaki rats and this revealed a promotion in glucose tolerance and insulin secretion, whereas blood glucose and glycosylated hemoglobin were suppressed [109]. *A. lappa* fructooligosaccharide was found to suppress

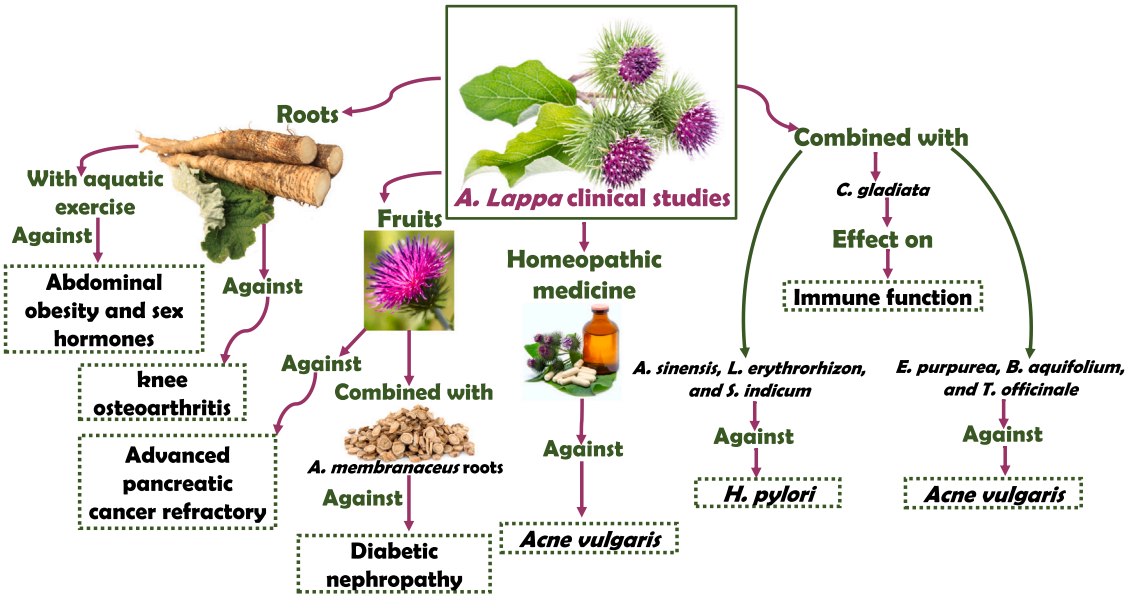

Fig. 6. *A. lappa* and its products in different clinical studies against various ailments.

fasting blood glucose, serum total triglyceride, and body weight, while enhancing glucose tolerance [65]. *A. lappa* polysaccharides displayed anti-diabetic activity via regulation of SREBP-1 and SCD-1 in the liver of diabetic rats [59]. The anti-diabetic effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 2. The chemical structures of the bioactive compounds are drawn in Fig. 5.

Table 3
Screening for *Arctium lappa* L. in clinical studies.

Clinical trial/ phase	Disease or condition/dose/ part of plant/ Administration route/time frame	References
Clinical trials/ Dietary supplement/ NR/ Intervention	Hypertension/ 850 mg of burdock twice per day/ oral / 6 W	(https://clinicaltrials.gov, NCT02511860)
Clinical trials Dietary supplement/ NR/ Intervention	Healthy/ Arctigenin 500 mg will be administered for 28 days /oral/ 28 days	(https://clinicaltrials.gov, NCT03703388)
Clinical trials/ drug/ phase 1 trial/ NR	Advanced pancreatic cancer/ 3, 7.5, and 12 g/ fruit/ oral/ two weeks	[114]
Clinical trials/ Drug/ Phase 1/ Intervention	Acne vulgaris/ 6 pills of lappa four times a day for seven days / homeopathic medicine/ oral/ 6 months	[19]; (https://clinicaltrials.gov, NCT01040390)
Clinical trials/ dietary supplement/ NR/ placebo-controlled intervention	Healthy/ 1000 mg per tablet/ *Canavalia gladiata Arctium lappa* extract complex / oral/ one tablet daily for 8 weeks	[13]
Clinical trials/ drug/ NR/ intervention	*H. pylori*/ 10 mL twice daily/ *A. lappa*, *Angelica sinensis*, *Lithospermum erythrorhizon*, and *Sesamum indicum* complex/ oral/ 8 weeks	[115]
Clinical trials/ drug/ NR/ intervention	Knee osteoarthritis/ 3 cups of boiled water daily/ root/ oral/ 42 days	[20,116,117]
Clinical trials/ dietary supplement/ NR/ intervention	Metabolic syndrome/ 100 mL 3 times a day/ root/ 16 week	[21]

Not Reported (NR).

4.2.5. Anti-obesity effect

Arctii Fructus extract exhibited anti-obesity activity in white/brown adipocytes and high-fat diet-induced obese mice through regulation of PPARγ and C/EBPα, as well as increasing the expression levels of thermogenesis related genes such as UCP1 and PGC1α [110]. The effect of aqueous extract of *A. lappa* roots on lipid metabolism was evaluated in serum of rats, and revealed a reduction in body weight and cholesterol achieved by adjusting the differential expression of genes [111]. The anti-obesity effects of *A. lappa* extract and its bioactive metabolites are illustrated in Table 2.

4.2.6. Antiviral effect

The antiviral activity of arctigenin[4] on mice challenge against porcine circovirus type 2 (PCV2) was tested, and demonstrated a significant inhibition in PCV2 proliferation in the lungs, inguinal lymph nodes, and spleen [112].

5. Clinical studies

In an uncontrolled phase I trial, *A. lappa* fruit extract was administrated orally to patients with advanced pancreatic cancer, refractory to gemcitabine, at escalating doses from 3 to 12 g once daily. The doses of 3, 7.5, and 12 g were administrated to three, three, and nine patients respectively, for two weeks. Out of fifteen patients, one had a partial response and 4 patients showed stable disease. No dose-limiting toxicities were observed at any of the three doses [114]. An observational, uncontrolled, interventional clinical study was assessed to evaluate the efficacy of *A. lappa* homeopathic medicine in the treatment of *Acne vulgaris*. *A. lappa,* with potencies ranging from 6c to 1 M, was applied to the participants over the course of 6 months. *A. lappa* exerted positive effects on acne treatment, especially of the inflammatory variety [19]. A randomized, double-blind, placebo-controlled clinical trial was conducted on 100 volunteers to investigate the safety and efficacy of a mixture of *Canavalia gladiata* and *A. lappa* extracts. Volunteers were divided into two groups (extract group and placebo group) with 50 volunteers in each receiving extract or placebo once daily for 8 weeks. The extract complex was safe, and improved immune function via enhancing natural killer cell activity through IL-10 expression [13]. A randomized, double-blind placebo-controlled trial was assessed to determine the effect of *A. lappa*, *Angelica sinensis*, *Lithospermum erythrorhizon*, and *Sesamum indicum* complex on *H. pylori*-infected volunteers.

Table 4
NPs mediated burdock and its application.

Part/ type of extract	NPs	Instrumental analysis	Size (nm)/ shape	Bioactivity	Reference
Arctigenin-loaded nanoparticles	Poly-lysine	AFM, TEM, FTIR, Zeta	33/ spherical	Imaging	[124]
Roots/ aqueous	Ag	UV, XRD, TEM, EDX	21.3/ spherical	Antimicrobial *L. acidophilus* and *S. aureus*	[120]
	Au	UV, XRD, TEM, EDX	24.7/ spherical, triangular, and hexagonal	Antimicrobial *L. acidophilus* and *S. aureus*	
Roots/ aqueous/ polysaccharides	C	FTIR, XPS, TEM,	10–20/ spherical	Inhibit α-glucosidase activity Antidiabetic	[123]
Roots/ aqueous	Au/Pt/ZnO	UV, SEM, TEM, FTIR, AFM,	10–40/ spherical	Cytotoxic Leukemia	[121]
Roots/ aqueous	CeO_2	SEM, XRD, EDX, FTIR	26.2/ cubic	Antimicrobial *S. aureus* and *P. aeruginosa*	[122]

The infected subjects received the complex for 8 weeks. The complex was found to ameliorate urea breath test, antioxidant capacity, healed ulcer wounds, and mitigated inflammation, exhibiting its anti-*H. pylori* activity [115]. A clinical study was established to evaluate the effect of *A. lappa* root tea on clinical signs and symptoms in patients with knee osteoarthritis. 36 patients with knee osteoarthritis were divided into two groups, one received 3 cups of *A. lappa* root tea 30 min after a meal, daily for 42 days, and the control group received 3 cups of boiled water daily. The results showed a significant increase in the mean score of knee injury and osteoarthritis outcome questionnaire, while pain intensity and the mean score of timed "up and go" were decreased in the root tea group [20]. Another trial was performed on knee osteoarthritis patients using *A. lappa* root tea, to evaluate its effect on lipid profile and blood pressure of the patients. 36 patients were divided into intervention and control groups. The intervention group received 3 cups of *A. lappa* root tea half-hour after a meal daily for 42 days, and the other control group received 3 cups of boiled water daily. The consumption of *A. lappa* root tea was suggested to enhance lipid profile and blood pressure status in patients with knee osteoarthritis [116]. *A. lappa* root tea was applied in a different study to evaluate its effect on inflammatory status and oxidative stress in knee osteoarthritis patients. 36 patients were divided into intervention and control groups. The intervention group received 3 cups of *A. lappa* root tea half an hour after a meal, daily for 42 days, and the other control group received 3 cups of boiled water daily. *A. lappa* root tea was found to promote inflammatory status and oxidative stress in patients with knee osteoarthritis [117]. A randomized, double-blind, controlled study was assessed to evaluate the effects of aquatic exercise and *A. lappa* root extract consumption on abdominal obesity and sex hormones in elderly women with metabolic syndrome. The combined effect of aquatic exercise and *A. lappa* root extract consumption exerted no synergistic and/or additive effects on any sex-related outcome measures in women with metabolic syndrome [21]. Clinical studies of *A. lappa* and its products against different ailments are shown in Fig. 6. (Tables 3 and 4).

6. Applications in nanomedicine

In general, natural products represents efficient sources of bioactive constituents which are widely employed as reducing and capping agents for various metallic and non-metallic nanoparticles [118,119]. For example, *A. lappa* L. constitutes an appealing source of compounds that have unique mechanisms of action, which have raised great interest in nanomedical applications. Nguyen et al. employed aqueous extract of burdock root to engineer gold and silver nanoparticles (NPs) via a green strategy. According to XRD and TEM figures, the silver NPs (AgNPs) produced possess a roughly spherical structure with an average diameter of 21.3 nm, but AuNPs have a variety of shapes with an average size of 24.7 nm. FTIR proved that both polyphenols and proteins maintained their role throughout the biosynthesis and stabilization of nanoparticles. Notably, the two types of nanoparticles demonstrated antimicrobial activity toward various types of microorganisms [120]. Similarly, 10 gm of burdock roots, with 100 mL of double distilled water and 5 mM of each $HAuCl_4$, K_2PtCl_6 and $ZnNO_3$, were utilized for the biogenesis of Au/Pt/ZnO NPs. Both TEM and SEM determined the shape and size of the resulting nanoparticles as spherical, ranging from 10 to 40 nm. Additionally, these particles show cytotoxic activity against leukemia cells with an IC_{50} index ranging from 0.95 μmol to1.78 μmol [121]. Furthermore, aqueous extract of burdock roots has been employed to bioengineer ceria nanoparticles (CeO_2-NPs). The sol–gel method was used to encapsulate the ceria biosynthesized NPs with a natural nano-polymer, namely chitosan. Importantly, the enclosed nanocapsules demonstrate microbial inhibition toward *S. aureus* and *P. aeruginosa* bacteria, and could be exploited further against multidrug resistant pathogens [122].

Burdock is considered to be a vital source of polysaccharides, which could be utilized for further bioengineering of carbon nanoparticles. XPS and TEM determined that the size and shape of the CNPs were spherical and 10–20 nm, and the FT-IR figures demonstrated that the functional groups C═O, C═C, C–O, and C–N are the primary groups of the generated NPs. Moreover, these particles show antidiabetic activity via inhibition of α-glucosidase with an IC_{50} value of 0.5677 mg/mL (*in vitro* studies) [123]. Furthermore, arctigenin represents one of the prominent and vital components of *A. lappa* L. Cui et al. were able to coat poly-lysin polymer NPs with arctigenin to assist in the visualization and biomedical labeling of *in vitro* and *in vivo* models [124].

7. Conclusion and future perspectives

Burdock has been thoroughly studied over an extended period and occupies a prominent position in ethnotherapeutic concepts. This review compiled many of its traditional uses, addressing nutritional value, pharmacological activities, chemistry and nanomedicinal applications of burdock. Burdock and its chemical structures (e.g. arctigenin, arctiin, lappaol F, caffeoylquinic acids, polysaccharides, sesquiterpene) certainly demonstrate a wide spectrum of pharmacological activities, with potent efficacies including anticancer, antitumor, anti-inflammatory, anti-diabetic, antiviral, immunoprotective, and anti-obesity effects. These compounds are well thought-out, reliable platforms for the progress of several front-line drugs for the management of proliferative diseases such as cancer. However, taken together, there are relatively few nanoparticles that have undergone biogenesis based on burdock extracts, such as Au/Pt/ZnO NPs, AgNPs, and AuNPs. Finally, we recommend that future studies should be focused on ascertain a) the most effective doses for beneficial role of burdock on each different target use, b) examination of the possible interactions of burdock extracts and their main components with the most common drugs that could potentially be used in combination, and c) address the most common challenges of nanoparticles, nanocomposites and nanocluster fabrication based on this plant.

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CRediT authorship contribution statement

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Conflict of interest statement

The authors declare no conflicts of interest.

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