Arctigenin: A Potential Component with Multifaceted Therapeutic Properties

Acharya Balkrishna, Vidhi Dobhal, Sonam Verma, Deepika Srivastava, Shalini Singh, Vedpriya Arya

ABSTRACT

Medicinal plants are an excellent source of new therapeutic drugs because of their phytochemical constituents. Arctium lappa L. (common name-burdock) is a perennial medicinal herb commonly found in China, Japan, Korea traditionally used as promising health supplement, promising health supplement. Major active constituent of A. lappa L. seeds are arctigenin which exhibits pharmacological potential such as anti-inflammatory, anticancer, antimicrobial and hepatoprotective properties. The purpose of this study is to provide an up-to-date evaluation of the literature on the pharmacological activities of Arctigenin from Arctium lappa L. Literature is collected from Google scholar, Science Direct, Research Gate, PubMed, Google, and Scifinder databases published between 2012 and 2021 (Jan). Keywords used to retrieve the data are pharmacological profile, arctigenin, and Arctium lappa L. The antioxidant, anti-inflammatory, anti-tumor, hepatoprotective, renoprotective, neuroprotective, and CNS depressant properties of arctigenin demonstrated its pharmacological significance among traditional science. According to different research, arctigenin is effective in the treatment of a variety of chronic disorders, including cancer (stomach, lungs, liver, and colon) and inflammatory diseases (rashes, and other skin conditions.). Future experiments based on the mechanism pathway responsible for the protective role of arctigenin's will help the scientist to uncover its health benefits.

Keywords: Arctium lappa, Arctigenin, Botanical description, Medicinal uses, Pharmacological profile.

INTRODUCTION

Herbal medicine, encompasses ancient medical systems such as Ayurveda, Chinese herbal medicine, and Kampo[1], which uses different plant parts and their extracts or fractions for therapeutic benefits[2]. Herbal medicine is well-known for its potential role as a complementary treatment for a variety of ailments. Traditional methods have also grown in popularity and recognition in recent years in terms of socioeconomic standing. These extracts have a range of action mechanisms[3]. Stir-heating, charring, steaming, boiling, and calcining are examples of traditional Chinese medicine treatments, dispensing, and preparations that have been used to improve the effectiveness and/or minimise the toxicity of crude medicines. It is commonly used to get rid of ‘wind-heat,’ ease sore throat inflammation and swelling, and detoxify the body[3].

With 1600 genera and over 23000 species worldwide, the Asteraceae family is one of the largest flowering plant families[4]. The genus Arctium L., popularly known as "burdock," is a group of biennial herbs that can be found along roadsides, streams, and waste sites, as well as in forests in temperate Europe and Asia and in subtropical and tropical locations. Arctium species contain nonvolatile compounds such as acetylenic compounds, lignans, phytosterols, fatty acids, polysaccharides, flavonoids, caffeyloquinic acid derivatives, terpenes/terpenoids, and volatile compounds such as carboxylic and fatty acids, hydrocarbons, aldehydes, methoxyxyprazines, sesquiterpenes and monoterpenes. The Arctium genus possessed pharmacological properties including gastroprotective, hepatoprotective, anti-allergic, anti-cancer, anti-diabetic, antimicrobial, anti-oxidant, antiviral, and anti-inflammatory effects [5].

Plant morphology- Arctium lappa (burdock) L., also known as “niupang” in Chinese and “gobo” in Japanese[6]. It is a European and Asian native that is increasingly spreading through North America[7]. Burdock is an herbaceous biennial plant with pubescent to subglabrous epigal portions that grows up to 150 cm tall. The basal leaves are oval, cordate, and hollow petioles with a diameter of 50 cm. The stems are branching and have corymbose capitula at the end. Florets are the same length as the involucral bracts. The roots are slender (about 0.71 m long and 0.20 m across), very crisp, and have a sweet, mild, and pungent flavour[8].
Ethnomedically, *A. lappa* (a.k.a. Burdock) root is eaten in many parts of Asia and is used in folk medicine to treat infectious diseases\(^7\). In several parts of Asia, the root is eaten and used to treat infectious diseases, while the seeds are used as an herbal medicine to treat inflammatory disorders\(^9\)\(^{10}\). Eastern Asian countries produce and eat plants as food (particularly China, Japan, and Korea). The plant is also abundantly medicinal and edible in China's Shandong and Jiangsu provinces\(^9\). Burdock contains polyphenols, burdock aldehydes, and other nutrients in addition to protein, oligosaccharides, and other nutrients. Burdock extract demonstrates biological effects like anti-cancer, anti-inflammatory, antiparasitic, antimicrobial, anti-diabetic and hepatoprotective activities\(^{11}\)\(^{12}\)\(^{13}\). Sore throats, boils, rashes, and other skin disorders have all been treated with this plant in the past. Burdocks commonly used in traditional Chinese medicine to treat burns, tumors, eczema, gout, and hepatitis. The plant is generally referred to as ‘bardana’ in Brazil, and it has been used as a digestive stimulant, dehydrative, diuretic and in dermatological conditions\(^{11}\)\(^{12}\)\(^{13}\). In traditional medicine, seeds are employed as a diuretic, antipyretic, or detoxifying agent\(^{14}\).

A. *lappa* root is high in phenols, saponins, lignans, tannin, and flavonoids, according to phytochemical studies\(^{13}\). The primary active compounds identified from this plant include arctigenin (ARG), tanin, arctin, chlorogenic acid, caffeic acid, beta-eudesmol, trachelogenin, inulin, stisotoster-beta-D-glucopyranoside, diarctigenin and lappao. Among them, two important lignans present in the roots, ARG and arctin, are known to have anti-inflammatory, anti-allergic, anticancer, and anti-metastatic activities. Burdock leaves, fruit/seeds, and burdock roots are also used for various medicinal purposes\(^{13}\).

Most of the pharmacological activity of ARG (the key component of *A. lappa*) has been studied in recent years\(^{17}\). Arctigenin is a compound extracted from seeds of *Arctium lappa* L. (Asteraceae), a Chinese, Japanese, and Korean medicinal herb. Arctigenin has been proven to have anti-oxidant, anti-inflammatory, and anti-tumor characteristics. ARG is thought to have anti-tumor properties by preventing Nuclear factor-kB (NF-kB) from translocating to the nucleus. ARG promotes apoptosis and anti-metastatic effects in breast cancer cell\(^{13}\). The current review article aims to include an up-to-date literature review on ARG's detailed pharmacological activities, with an emphasis on its significance. May 2021.

**Figure 1:** *Arctium lappa* L. and its active constituent, Arctigenin

**METHODOLOGY**

This review paper was prepared by integrating and analysing prior research on ‘Arctigenin’ compound from *Arctium lappa* L., its medicinal uses and scientific validity. Several data sources, including Google Scholar, Science Direct, Research Gate, PubMed, Chem draw, and other Google search engines, were used to examine a total of 67 published articles in between 2012 to 2021. Using a collection of keywords, including ‘A. lappa’ L., ‘Arctigenin’, ‘Botanical description’, ‘Medicinal uses’, ‘Pharmacological profile’, etc., only published works in English were selected as search targets across many databases. Although we acknowledge that there may be some additional data in less accessible forms, such as unpublished research, the literature search in this paper was restricted to scientific publications included in the aforementioned databases that may be available to the scientific community as references.

**ARCTIGENIN AND ITS SCIENTIFIC EVIDENCES**

‘Arctigenin’, the main constituent obtained from seeds of *Arctium lappa* L. that have been used as an herbal medicine or functional food to treat various diseases such as inflammation, cancer, diabetes as well as showed protective effect on different organ i.e., liver, kidney, heart. We have reviewed the pharmacological profile of this compounds that has been described in Table 1.

**Anti-inflammatory activity**

Arctigenin exerted significant anti-inflammatory effect on LPS stimulated RAW264.7 macrophages cells (in-vitro) and thioglycolate induced acute peritonitis in C57BL/6 mice (in-vivo) by inhibiting phosphorylation of p65 and p38 and suppressing neutrophils, macrophages, and chemokines, pro-inflammatory cytokines as compared to the normal control group\(^{11}\). In another study, ARG administration at 50 mg/kg was found to be anti-inflammatory against lipopolysaccharide (LPS)- induced endotoxin shock in the bone marrow-derived MDSCs (in-vitro) and lipopolysaccharide (LPS)- induced acute inflammation in C57BL/6 mice (in vivo) when compared with LPS group\(^{15}\). Similarly, ARG administration (50 mg/kg) displayed anti-inflammatory activity on lipopolysaccharide (LPS)-induced acute lung injury in male C57BL/6 wild-type mice, by inhibiting different inflammatory parameters such as MDA, iNos, NO, phosphorylation of mitogen-activated protein kinase (MAPKs and SOD, CAT, GSH/GSSG) when compared with LPS treated group\(^{16}\). ARG (10 μM) showed significant anti-inflammatory potential against LPS-stimulated peritoneal macrophages through inhibition of IL-1β, IL-6, TNF-a expression, PI3K, AKT and IKKβ phosphorylation while stimulating IL-10 and CD204 expression. In animal study, ARG at 5 mg/kg suppressed blood IL-1β, TNF-a level, PI3K, AKT and IKKβ phosphorylation as well as NF-κB activation while increased IL-10 and CD 204 expression in 2,4,6-trinitrobenzene sulfonic acid (TNBS)- induced colitis in the mice when compared with diseased group\(^{17}\).

**Anti-cancer activity**

Arctigenin from *A. lappa* showed significant inhibition on proliferation of glioma cells (U87MG and T98G) by inducing autophagy and apoptosis through the AKT/mTOR pathway (concentration at 400 μM) as compared to the control group\(^{13}\). ARG significantly inhibited proliferation, invasion, and the stemness of cancer cells via decreasing the tumor-promoting cytokines GM-CSF, MMP-3, MMP-9, and TSLP both in murine mammary cancer cell line and in human breast cancer cell-tumor-bearing BALB/c female mice\(^{18}\). When compared to doxorubicin, ARG at 10-200 M boosted the cytotoxic effect of doxorubicin-induced cell death by causing extended p21 expression and p38-mediated AIF-dependent cell death in MDA-MB-231 human breast cancer cells\(^{19}\). Additionally, ARG showed anti-metastasis and anti-epithelial–mesenchymal transition in hepatocellular carcinoma through inhibiting migration and invasion of cells with epithelial up-regulation while, down-regulating the mesenchymal marker proteins. It also activated the Wnt/-catenin signalling pathway, resulting in the down-regulation of -catenin target genes such as c-Myc, cyclin D1, MMP-9, and ZO-1. In an in-vivo study, it significantly reduced tumour metastasis in mice liver while inhibiting the growth of subcutaneously transplanted tumors\(^{20}\). In addition, ARG exerts anticancer effects by proliferation and induced apoptosis in TNBC cells\(^{21}\). By inhibiting MMP-9 and 9-urokinase plasminogen activator (Upa) through the Akt, NF-B, and MAPK signaling pathways, ARG effectively inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cell migration and invasion in oestrogen receptor-positive MCF-7 cells\(^{22}\). In another study, ARG in two-drug combinations with doxorubicin showed...
synergistic effects in inhibiting CaCo2 cells and CEM/ADR 5000 multidrug-resistant cells[23]. Likewise, ARG (10 μM) exhibited significant (p≤0.05) anticancer activity by inhibiting human ovarian cancer cell (OVCAR3 and SKOV3 cells) proliferation as well as STAT3 phosphorylation and expression levels of survivin protein and iNOS compared to the control[24]. Furthermore, ARG (0.10-20 μM) inhibited proliferation in KSHV-infected PEL cells under glucose deprivation by lowering cellular ATP, mitochondrial membrane potential, and triggering caspase-9-mediated apoptosis. ARG suppress extracellular signal-regulated kinase (ERK) activity and p38 mitogen-activated protein kinase (p38 MAPK) signaling pathways by inhibiting their phosphorylation[25].

Hepatoprotective activity

The ARG was found to be hepatoprotective in NCTC-1469 cells, the cell viability was increased similarly, ARG and SD-Na (100mg/kg) treatment reduced the generation of inflammatory mediators and the TLR4/MyD88/NF-B signalling pathway in C57BL6 mice with toxoplasma gondii-induced liver injury (in vivo)[26]. Likewise, ARG showed significant protective activity against concanavalin A (ConA)-induced liver injury via suppression of immune cells, congestion, necroinflammation of livers and improved hepatic function in male BALB/c mice at 10 μg/g administered dose[27]. In WRL68 hepatocytes, ARG at 50 μM concentration inhibited OA-induced lipid aggregation, lipid peroxidation, and inflammation. It also reduced the expression of U937 lymphocyte chemoattractant, ICAM-1, IL-1, IL-6, IL-6sR, IL-7, IL-8, and sterol regulatory element-binding protein-1, thus significantly increasing the expression of carnitine palmitoyltransferase 1 and peroxisome proliferator-activated receptor alpha. ARG controls cell survival, lipid metabolism, oxidative stress, and inflammation by activating phosphoinositide 3-kinase/protein kinase B (P3K/AKT), AMP-activated protein kinase AMPK pathways, and phosphorylation levels of Akt and AMPK[28].

Nephroprotective activity

Arctigenin shows nephroprotective behavior and found to increase PP2A activation and reduced p65 NF-B mediated inflammatory response and high glucose-induced migration in the cultured podocytes through interaction with Drebrin-1[29]. It also had cytoprotective effects on high glucose-induced cell apoptosis and inhibited ER stress in db/db animals with diabetes-related renal damage[30]. Furthermore, when compared to the I/R population, pretreatment with ARG at a high dose exacerbated I/R-induced acute kidney injury by increasing tubular cell apoptosis while reducing infiltrating inflammatory cells and proinflammatory cytokines[31]. It was also discovered, it protected the kidney from injury by minimizing tubular dilatation, epithelial atrophy, collagen deposition, and tubulointerstitial compartment expansion, as well as inhibiting various pro-inflammatory cytokines[32].

Neuroprotective activity

Arctigenin showed anti-depression and anti-anxiety-like properties in male ICR mice at 10 and 30 mg/kg which might possible to have protective action towards central nervous system[33]. ARG attenuated microglial activation and neuro-inflammation by suppressing the TLR4/NF-kB and TNFα/NF-kB signaling pathways in Toxoplasma gondii infection induced depression in animal studies[34]. Arctigenin reduced infarct volume, neurological score, and brain water content and attenuated ischemic stroke induced neuroinflammation and NLRP3 inflammasome activation via the SIRT1 pathway[35]. Studies revealed that, ARG protected PC12 cells of Rattus norvegicus adrenals tumours from ethanol-induced injury by promoting cell proliferation, increasing the cell distribution ratio at the G2/M and S phases, and thus significantly reducing apoptosis and necrosis in ethanol-treated cells[36]. In another study, ARG potently reversed scopolamine-induced memory deficits in mice in a passive avoidance test by 62 % and 73 %, respectively[37]. Moreover, arctigenin had a substantial protective effect on cerebral ischemia-reperfusion rats by inhibiting neuroinflammation[38].

Other activities

Arctigenin possess several other therapeutic properties such as antihypertensive, vasorelaxant, cytoprotective, gastroprotective, antioxidant, osteoprotective, antifibrosis, and anti-alzheimer activities[39-42]. Researchers have shown that spontaneously hypertensive rats (SHR), arctigenin when administered with 50 mg/kg and prevented hypertension while increasing eNOS and decreasing NADPH oxidase protein production, ROS production[39]. Similarly, ARG protects by inhibiting Ca2+ influx partly through L-type calcium channel as well as enhancing Ca2+ efflux, Arctigenin show relaxant effect in guinea pigs[40]. Furthermore, when ARG was tested against ethanol and acetic acid-induced ulcers in the experimental animals, it was found to prevent these gastric lesions. In addition, ARG decreased MDA and increased superoxide dismutase levels in serum, while TNF-α, interleukin-6 (IL-6 & IL-10) and C-reactive protein expression levels were significantly lower in the ARG group relative to the vehicle group[42]. Using nitrite scavenging activity and acetylcholinesterase activity, ARG showed antioxidant and enzyme inhibitory activity[43]. ARG blocked acetylcholinesterase and also showed antioxidant activity[44]. Similarly, Arctigenin inhibit RANKL-induced osteoclastogenesis and hydroxyapatite resorption, as well as prevent titanium particle–induced bone degradation[44].

Table 1: Some Scientific Evidences of Arctigenin

<table>
<thead>
<tr>
<th>Biological Profile</th>
<th>Experimental models</th>
<th>Mechanism</th>
<th>References</th>
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<tr>
<td>Anti-inflammatory</td>
<td>LPS stimulated RAW264.7 cells</td>
<td>ATG inhibits the phosphorylation of p65 and p38 in LPS-stimulated RAW264.7 cells</td>
<td>[11]</td>
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<td></td>
<td>TG-Induced acute peritonitis in C57BL/6 mice</td>
<td>ATG inhibited tissue inflammatory cell infiltration, expression of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), CD11b+ Ly6G+ neutrophils percentage and F4/80+ macrophages in the spleen, chemokines CCL3 &amp; CCL4 expression and the adhesion molecule CD62L on the surface of CD11b-positive monocytes.</td>
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<td></td>
<td>LPS-induced endotoxin shock in bone marrow cells</td>
<td>ARG ameliorate LPS-induced inflammation through accumulating MDCs, especially granulocytic and enhancing the immunosuppressive function of MDCs.</td>
<td>[15]</td>
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<tr>
<td></td>
<td>LPS-induced acute inflammation in C57BL6 mice.</td>
<td>ARG stimulates accumulation of MDCs through upregulating mIL-127-5p which targets the 3′UTR of interferon regulatory factor-8 (IRF8) , M1 macrophage polarization by elevating the expression of arginase 1 (Arg-1) and inducible nitric oxide synthase (iNOS) in spleen of LPS-induced mice.</td>
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Figure 2: Spectrum of Arctigenin's pharmacological activities
LPS-induced acute lung injury in C57BL/6 mice. Inhibited MDA, iNOS, NO, phosphorylation of mitogen-activated protein kinases (MAPKs) and stimulated SOD, CAT, GSH/GSSG in the lung, expression of heme oxygenase-1.

LPS-stimulated peritoneal macrophages 2,4-dinitrobenzenesulfonic acid-induced colitis in mice. Inhibited IL-1β, IL-6 and TNF-α expression, PI3K, Akt and IKKα phosphorylation, p-PI3K antibody binding and the nuclear translocation of NF-κB p65 with increase in IL-10 and CD204 expression in LPS-stimulated peritoneal macrophages. Inhibited IL-1β and TNF-α level, colon shortening, macroscopic scores, myeloperoxidase activity, TNBS-induced IL-1β, TNF-α and IL-6 expression, as well as PI3K, Akt and Iκκβ phosphorylation and NF-κB activation with increase in IL-10 and CD204 expression in colitic mice.

Glioma cells (U87MG and T98G) Inhibited proliferation, invasion and migration and arrested the cell cycle through inducing apoptosis in glioma cells.

Human breast cancer in murine mammary cancer cell line (4T1) 4T1 tumor bearing BALB/c female mice. ARG inhibited the proliferation, invasion and stenosis of breast cancer cells via decreasing GM-CSF and TSLP via reducing nuclear translocation of NF-κB p65. ARG prolonged the survival as well as hindered tumor growth, size and weight of 4T1 tumor-bearing mice. Immunohistochemistry displayed ARG markedly reduced the expression of Ki-67 in tumor tissues.

Human breast cancer cells (MDA-MB-231). Inhibited breast cancer cell MDA-MB-231 cell viability. MRP1 gene expression, phosphorylation, activator of transcription 3 (STAT3) expressions of RAD51 and survivin, Bcl-2 and Bcl-xL phosphorylations and expressions of Akt and JNK, enhanced uptake of doxorubicin, DNA damage, mitochondrial BAX levels, nuclear AIF levels, p21(cyclin-dependent kinase), p38MAPK.

HepG2 and SMMC 7721 cells Hepatocellular carcinoma in Athymic nu/nu mice. Inhibited the cell viability, migration, invasion of HepG2 and SMMC 7721 cells, β-catenin target genes including c-Myc, cyclin D1, MMP-9, and ZO-1, epithelial-mesenchymal transition. Enhanced activation of Wnt/β-catenin through a GSK3β-dependent pathway. ARG in tumors in mice inhibits growth transplanted tumor and tumor metastasis in liver.

Retinoblastoma cell line (Y79) Inhibited cell viability, BCL-2, cell migration and enhanced apoptosis, BCL-2-associated X protein, IAG1.

HepG2 and Hep3B cell lines Tumor (Hep G2) bearing female BALB/c nude mice. ARG inhibited breast cancer cell MDA-MB-31 and MDA-MB-231 cell lines. ARG inhibited breast cancer cell MDA-MB-31 and MDA-MB-231 cell lines.

Multidrug-resistant CEM/ADR 5000 and Caco2 cells Inhibited the cell proliferation. STAT3 phosphorylation and survivin, iNOS expression, increase apoptosis, caspase-3-dependent apoptosis.

Ovarian OVCA3 and SKOV3 cancer cells Inhibited the cell proliferation, the phosphorylation of STAT3 at residue Y705, induces caspase-3-dependent apoptosis in ovarian cancer cells.

Human lung adenocarcinoma cell lines (A549) Arrested cancer cells proliferation at the GO/G1 phase. Down-regulation of NFAT protein expression and E/Cdk2 or cyclin H/Cdk7, induced apoptosis while its cytotoxicity was enhanced by GSH synthase inhibitor.

Toxoplasma gondii-induced liver damage in C57BL/6 mice. Enhanced cell viability and inhibited proliferation and iNOS, HMGB1 expression, TLR4/NF-κB, ALT, AST levels in liver damaged mice.

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The authors declare that they have no conflict of interest.

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CONCLUSION AND FUTURE PROSPECTIVE

The Articum lappa L., a member of the biggest flowering plant family, the Asteraceae, is commonly known as burdock and plays a significant role in traditional Chinese (NiuBang), Japanese (Gobo), and other Asian medicinal systems. There are various studies in the literature that show the vast range of possible pharmacological uses of Arctigenin as one of the major active natural compounds found in burdock seeds. Among the 18 various pharmacological activities of ARG, anti-inflammatory and antitumor activities were reported to be very high, which is encouraging for the therapeutic application of ARG in the treatment of chronic disorders like cancer, diabetes, and inflammation. According to our review, the compound is beneficial in treating inflammatory and skin disorders as well as cancers of the stomach, lungs, liver, and colon. It also provides information on the potential advantages and disadvantages of using burdock seeds as a functional food. We come to the conclusion that additional research is needed to gain a clearer mechanistic understanding of the reported and unique functions in the prevention and treatment of human diseases, as well as any potential adverse effects.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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