Acta Pharmacologica Sinica (2018) 39: 787–801
 1671-4083/18
www.nature.com/aps

Review Article

Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiin from *Arctium lappa* L

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Abstract

Arctigenin (AR) and its glycoside, arctiin, are two major active ingredients of *Arctium lappa* L (*A lappa*), a popular medicinal herb and health supplement frequently used in Asia. In the past several decades, bioactive components from *A lappa* have attracted the attention of researchers due to their promising therapeutic effects. In the current article, we aimed to provide an overview of the pharmacology of AR and arctiin, focusing on their anti-inflammatory effects, pharmacokinetics properties and clinical efficacies. Compared to acrtiin, AR was reported as the most potent bioactive component of *A lappa* in the majority of studies. AR exhibits potent anti-inflammatory activities by inhibiting inducible nitric oxide synthase (iNOS) via modulation of several cytokines. Due to its potent anti-inflammatory effects, AR may serve as a potential therapeutic compound against both acute inflammation and various chronic diseases. However, pharmacokinetic studies demonstrated the extensive glucuronidation and hydrolysis of AR in liver, intestine and plasma, which might hinder its *in vivo* and clinical efficacy after oral administration. Based on the reviewed pharmacological and pharmacokinetic characteristics of AR, further pharmacokinetic and pharmacodynamic studies of AR via alternative administration routes are suggested to promote its ability to serve as a therapeutic agent as well as an ideal bioactive marker for *A lappa*.

Keywords: arctigenin; arctiin; *Arctium lappa* L; Fructus Arctii; anti-inflammatory agents; pharmacokinetics; clinical efficacy

Acta Pharmacologica Sinica advance (2018) 39: 787–801; doi: 10.1038/aps.2018.32; published online 26 Apr 2018

Introduction

Arctigenin (AR) (Figure 1), a phenylpropanoid dizbenzylbutyrolactone lignan, was first identified in *Arctium lappa* L (*A lappa*), a popular medicinal herb and health supplement frequently used for anti-influenza treatment in Asia, especially China, Korea and Japan. AR and its glycoside, arctiin, are listed as both the chemical marker compounds and major active ingredients of Fructus Arctii in Chinese Pharmacopeia[1]. In the past several decades, bioactive components from *A lappa*, especially AR, have attracted the attention of researchers due to their promising therapeutic effects on inflammation[2-4], infection[5-7], metabolic disorders[8-10], and central nervous system dysfunctions[11-13].

AR and arctiin have been extensively studied for their anti-inflammatory effects in both *in vitro* and *in vivo* models. Inflammation is a series of protective responses of the body against exogenous pathogens and to repair tissue damage resulting from infection or trauma. Acute inflammation is characterized by vasodilatation, fluid exudation and neutrophil infiltration[14]. Severe inflammation can cause organ injury, shock and even death, presenting major management problems[14]. Furthermore, when the inflammatory response does not eradicate the primary stimulus, a chronic form of inflammation ensues and contributes to further tissue damage. A number of chronic diseases, including atherosclerosis, cancer, type II diabetes, and Alzheimer's disease, have a pathophysiologically important inflammatory component[15]. Therefore, developing novel compounds targeting the inflammatory response can be beneficial for the treatment of acute inflammation and infection, as well as many widespread chronic diseases. Studies on the pharmacology of AR and arctiin as natural compounds with significant anti-inflammatory effects may contribute to the development of novel anti-inflammatory therapeutics.

Pharmacokinetic profiles, including the absorption, distribution, metabolism and excretion properties, determine the efficacy and safety of a potential therapeutic. Extensive *in vitro* and *in vivo* studies have been conducted on AR and arctiin

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Received 2017-10-30 Accepted 2018-01-07

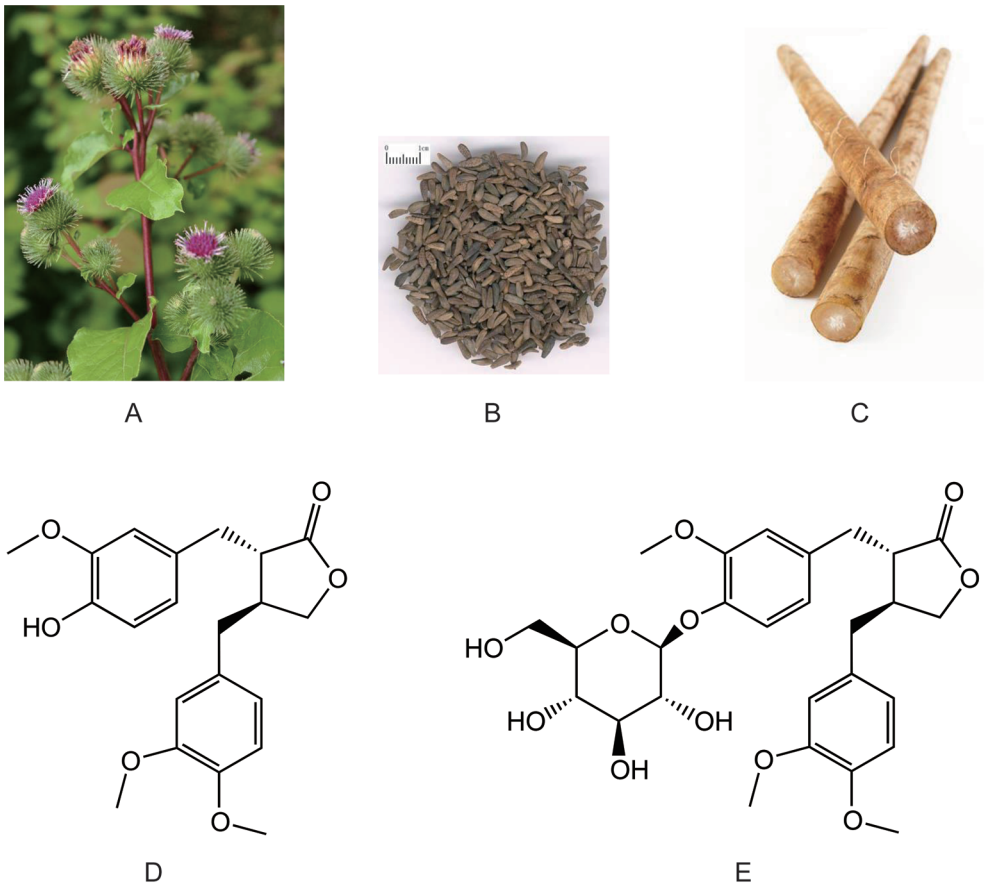

Figure 1. *Arctium lappa* L: plant (A), fruit (Fructus Arctii) (B), root (C), and two major bioactive compounds, AR (D) and arctiin (E).

to elucidate their absorption, metabolite profiles, and plasma concentration profiles, as well as the mechanisms involved. The results of these studies provide comprehensive data on the pharmacokinetic properties of AR and arctiin, leading to further optimization strategies for the use of these natural compounds as potential anti-inflammatory therapeutics.

Although research interest in AR, arctiin and *A lappa* has been growing rapidly, there are few published review articles on their pharmacological characteristics. In the current article, we aim to provide an overview of the pharmacology of AR and arctiin, especially their anti-inflammatory effects, pharmacokinetics properties and clinical efficacy.

Distribution of AR and arctiin in plants

AR and arctiin belong to the family of lignans, which is a class of phytoestrogens characterized by their dibenzylbutane skeleton. Lignans were first identified in plants and are believed to play a role in the construction of plant cell wall as the precursor of lignin. The contents of AR and arctiin, as well as the total lignans, were found to be the highest in the fruit of *A lappa* among all the plant parts[16]. AR and arctiin account for approximately 0.5%–2% (*w*/*w*) and 2%–10% (*w*/*w*) of the dry weight of the fruit, respectively, depending on place of origin, processing methods, and other factors[17, 18]. AR is regarded as marker compound in dozens of other medicinal herbs, probably due to its promising therapeutic activities[19, 20]. AR and arctiin have been identified in not only *A lappa* but also more than 38 other plant species, among which 71% belong to the Asteraceae family. Table 1 summarizes the distribution of AR and arctiin in different plant species from eight families, including Aspleniaceae, Asteraceae, Convolvulaceae, Linaceae, Oleaceae, Styracaceae, Taxacea, and Thymelaeaceae. In the family Asteraceae, *Centaurea* is a genus that includes many AR- and arctiin-containing plants, although the AR and arctiin contents are lower than that in *A lappa*. Fruits and seeds had high levels of AR and arctiin[2, 21], while the other parts, such as flower, leaves, stem, and roots, had low levels (Table 1). As shown in Table 1, many of these AR- and arctiin-containing plants are recorded as medical plants in their growing areas and are well-recognized for the treatment of diseases, such as rheumatic arthritis, inflammatory diseases, infection, and others.

Effect of AR and arctiin against inflammatory diseases

Effect of AR and arctiin on acute inflammation and its mechanism

Multiple studies have found that *A lappa* exhibits anti-inflammatory activities, which were attributed to AR in most research focusing on the traditional Chinese herb[22-24]. The anti-inflammatory effect and the reported mechanism of AR are summarized in Table 2.

The anti-inflammatory effects of AR were demonstrated in

Table 1. Plants species containing AR or arctiin and their medical usages.

Family	Species	Parts	Compounds (content, *w*/*w*)	Medical usages	Ref
Aspleniaceae	*Asplenium trichomanes*	Frond	AR	The frond is used as expectorant, anti-cough remedy, laxative, and emmenagogue in the Italian folk medicine, as well as abortifacient in North America.	[89]
Asteraceae	*Arctium lappa*	Fruit	Arctiin (2%–10%), AR (0.5%–2%)	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 used for skin conditions as well as in cold/flu formulae of traditional Chinese medicine.	[2, 21, 90-93]
		Root	Arctiin (0.04%)		
		Stem	Arctiin (0.06%)		
		Flower	Arctiin (0.05%), AR (0.05%)		
	Arctium tomentosum	Root	Arctiin (0.68%)	The root and leaf are used for therapy of rheumatism and paraesthesia of skin in Xinjiang, China.	[94]
		Seed	Arctiin (10.3%), AR (0.2%)		
	Carduus micropterus	Aerial parts	Arctiin, AR	No medical use has been reported for this species.	[95]
	Centaurea affinis	Aerial parts	AR (0.007%)	No use has been reported for specific species.	[96]
	Centaurea americana	Seed	Arctiin (0.2%), AR (0.015%)	Many species of the genus *Centaurea* have long been used in traditional medicine to cure diabetes, diarrhoea, rheumatism, malaria, hypertension *etc*.	[97]
	Centaurea arenaria	Whole plant	Arctiin, AR		[98]
	Centaurea cuneifolia	whole plant	AR		[97, 99]
	Centaurea dealbata	Fruit	Arctiin, AR		[100]
	Centaurea macrocephala	Seed	Arctiin (0.3%)		[101]
	Centaurea nigra	Seed	Arctiin (0.3%), AR (0.06%)		[102]
	Centaurea phrygia	Flower	AR		[103]
	Centaurea ptosimopappa	Aerial parts	AR		[104]
	Centaurea scabiosa	Fruit	AR		[100]
	Centaurea sclerolepis	Fruit	Arctiin		[97, 100]
	Centaurea scoparia	Aerial parts	AR		[105]
	Centaurea schischkinii	Seed	Arctiin, AR		[19, 96]
	Centaurea scoparia	Aerial parts	AR (0.004%)		[106]
	Centaurea tweediei	Aerial parts	AR		[97, 107]
	Cirsium oleraceum	Fruit	Arctiin (3.9%), AR (0.1%)	No medical use has been reported for this species.	[108]
	Cirsium palustre	Fruit	Arctiin (2.8%), AR (0.07%)	No medical use has been reported for this species.	[100]
	Saussurea conica	Whole plant	AR	No medical use has been reported for this species.	[109]
	Saussurea medusa	Aerial part	Arctiin, AR (0.7%)	The aerial part has been used for the treatment of rheumatoid diseases in Northwest China and Nepal.	[55]
	Saussurea salicifolia	Aerial part	Arctiin, AR	The aerial part has been used to treat gynaecological diseases, hepatitis, and gallbladder disorder in Mongolian traditional medicine.	[110, 111]
	Saussurea involucrata	Seed	Arctiin (0.24%)	No medical use has been reported for this species.	[112]
	Onopordum cynarocephalum	Aerial part	AR	A decoction or a tea of the whole plant is used in folk medicine for digestion, cough sedating, and in biliary diseases in Lebanon. The decoction or infusion of flowering tops is used for the alleged treatment of malarial fever and for washing exanthematic skin.	[113]
	Onopordon laconicum	Aerial part	AR	No medical use has been reported for this species.	[114]
	Onopordon sibthorpianum	Aerial part	AR	No medical use has been reported for this species.	[114]
Convolvulaceae	*Ipomoea cairica*	Whole plant	AR	No medical use has been reported for this species.	[42]
Linaceae	*Linum usitatissimum*	Seed	AR	Traditionally been used for the management of diarrhea and gastrointestinal infections.	[115]

(To be continued)

Family	Species	Parts	Compounds (content, *w*/*w*)	Medical usages	Ref
Oleaceae	*Forsythia intermedia*	Flower, leave	Arctiin	No medical use has been reported for this species.	[116]
	Forsythia koreana	Fruit	Arctiin, AR	*Forsythia* fruits from the three species are known in China, Korea, and Japan as an anti-inflammatory, diuretics, antidote, and anti-bacteria medicine in traditional herbal medicine.	[25, 33]
	Forsythia suspense	Fruit	AR (0.36%)		[25]
	Forsythia viridissima	Fruit, flower	Arctiin, AR		[8, 116, 117]
Styracaceae	*Styrax japonica*	Stem bark	Arctiin	The stem bark has been used to treat inflammatory diseases.	[118]
Taxaceae	*Torreya nucifera*	Bark	Arctiin, AR	The fruits are widely used in folk medicine for the treatment of tapeworm infestation in Korea.	[119]
	Torreya jackii	Leaves	AR	No medical use has been reported for this species.	[120]
Thymelaeaceae	*Wikstroemia indica*	Whole plant	AR (0.06%)	Has long been employed as an antipyretic, detoxicant, expectorant, vermifuge, and abortifacient agent in clinical practice in China.	[121]

Table 2. Summary of the studies on anti-inflammatory effects and related mechanisms of AR.

Model	Cell line/species	Dose	Effect	Mechanism	Ref
LPS-induced inflammation	RAW264.7	0.01 to 1 μmol/L	Suppression of NO production	Inhibition of iNOS protein expression; suppression of IκBα phosphorylation and p65 nuclear translocation	[30]
		0.01 to 1 μmol/L	NR	Decrease of TNF-α production and mRNA level; inhibition of binding between AP-1 and its consensus oligonucleotide; inhibition of phosphorylation and activation of MAPKs	[36]
		0.1 to 10 μmol/L	Inhibition of NO and PGE_2 production	Reduction of iNOS and COX-2 expression; inhibition of NF-κB expression and binding; Suppression of phosphorylation of IκB, IKK and activation of MAPKs	[33]
		0.3 to 32 μmol/L	Inhibition of NO production	Inhibition of TNF-α production	[22]
		10 to 50 μmol/L	Inhibition of iNOS activity; slight inhibition on COX-2 activity	Suppression of iNOS expression, IL-1β and IL-6 gene expression; reduction of phosphorylation and nucleus translocation of JAK, STAT1 and STAT3	[4]
		50 μmol/L	Inhibition of iNOS activity	Suppression of iNOS expression; promotion of ubiqitination and degradation of iNOS by CHIP-associated proteasomes	[32]
		3 to 100 μmol/L	Inhibition of iNOS activity; no inhibition of COX-2 activity	Suppression of iNOS expression; inhibition of TNF-α and IL-6 production	[31]
	U937	1 to 16 μmol/L	NR	Inhibition of TNF-α production	[22]
	Mice peritoneal macrophage	10 to 20 μmol/L	NR	Decrease of IL-1β, IL-6, and TNF-α level with increased IL-10 and CD204; inhibition of NF-κB activation and p65 nuclear translocation; suppression of PI3K and AKT phosphorylation	[2]
Silica-induced inflammation	RAW264.7	0.1 to 10 μmol/L	Inhibition of ROS production	NR	[25]
Concanavalin A and LPS induced proliferation	Mice primary splenocyte	0.5 to 16 μmol/L	Inhibition of T cell and B cell proliferation	NR	[22]

(To be continued)

Model	Cell line/species	Dose	Effect	Mechanism	Ref
Anti-CD3/CD28 Ab induced proliferation	Primary human T lymphocyte	8.25 to 25 μmol/L	Inhibition of lymphocytes proliferation	Suppression of IL-2 and IFN-γ production and gene expression; decrease of NF-AT-mediated reporter gene expression	[3]
TGF-β1-induced EMT-like changes in renal tubular epithelial cells	Human proximal tubular cell line HK-2	0.5 to 1 μmol/L	Protection against TGF-β1-induced MCP-1 upregulation and the resulting EMT-like phenotypic changes	Inactivation of the ROS/ERK1/2 MAPK/NF-κB pathway	[122]
TNF-α induced inflammation	BEAS-2B cells	50 μmol/L	NR	Inhibition of PI3K/AKT and Ras/MAPK pathways; inhibition of NF-κB activation	[35]
Acetic acid-induced inflammation	Rats	12.5, 25, 100 mg/kg, *po*, single dose	Decrease of writhing response and capillary permeability accentuation	NR	[25]
Arachidonic acid-induced ear edema	Rats	0.1–1 mg/ear painting, single dose	Decrease of edema volume, tissue MPO and EPO activities	NR	[25]
Carrageenan-induced paw edema	Rats	10, 30, 100 mg/kg, *po*, single dose	Decrease of paw edema volumn	NR	[25]
LPS-Induced acute lung injury	Rats	30, 100 mg/kg, iv, single dose	Reduced histological damage, myeloperoxidase activity, and wet-to-dry weight ratio of lung tissues	Decrease of TNF-α, IL-1β, and IL-6 levels; down-regulation of NF-κB and p65 expression; activation of AMPKα	[37]
	Mice	50 mg/kg, ip, single dose	Decreased infiltration of inflammatory cells into BALF; production of pro-inflammatory cytokines; reduced the malondialdehyde level; increased superoxide dismutase and catalase activities and glutathione peroxidase/glutathione disulfide ratio in the lung	Significantly reduction of NO production and iNOS expression; enhancement of heme oxygenase-1 expression, and decrease of MAPKs phosphorylation	[27]
LPS-induced colitis	Mice	5 mg/kg, ip, single dose	NR	Suppression of blood IL-1β and TNF-α level TNBS-induced colitis	[2]
	Mice	30, 60 mg/kg, *po*, qd, 3 days	Reduced loss of body weight, colon shortening, macroscopic scores and MPO activity	Inhibition of IL-1β, TNF-α and IL-6 expression and increase of IL-10 and CD204 expression; inhibition of NF-κB activation, as well as PI3K, AKT and IKKβ phosphorylation	[2]
Dextran sulphate sodium-induced colitis	Mice	25, 50 mg/kg, *po*, qd, 10 days	Reduced loss of body weight, disease index and histological damage; recovered intestinal epithelial cells; decreased infiltration of neutrophils and macrophages	Down-regulation of cytokines expressions, including TNF-α and IL-6 at protein and mRNA levels; suppression of MAPKs phosphorylation and NF-κB activation; blockage of Th1 and Th17 responses; inhibition of mTORC1 associated with down-regulation of Th1/ Th17 responses	[26, 123]
Convection enhanced delivery induced brain injury	Mice	20, 40, 80 mg/kg, *po*, qd, 14 days	Reduced brain water content and hematoma; accelerated wound closure; reduced number of allograft inflammatory factor- and MPO-positive cells	Decrease of number of allograft inflammatory factor and MPO-positive cells, TNF-α and IL-6 level; Elevation of IL-10 level	[28]

Abbreviation: iv: intravenous administration; *po*: oral administration; ip: intraperitoneal; qd: once daily. NR: not reported.

various disease models, including local edema, colitis, acute lung injury, and brain trauma. AR was effective in relieving symptoms such as writhing response, capillary permeability accentuation, and edema volume in local tissue inflammation of rats induced by various stimulators[25]. Protective effects of AR against LPS-induced acute lung injury through suppression of MAPK, HO-1, and iNOS signaling was observed[26, 27]. Furthermore, AR reduced the infiltration of leukocytes into

local tissues, a typical hallmark of acute inflammation. This was observed in various colitis mouse models by the decreased activity of myeloperoxidase (MPO), eosinophil peroxidase (EPO), and cluster of differentiation 68 (CD68), indicators of neutrophils, eosinophils and macrophages, respectively[2, 26, 28]. In addition, AR reduced brain water content and hematoma and accelerated wound closure in convection-enhanced delivery induced brain injury in mice through regulation of various inflammatory factors and numbers of MPO-positive cells[28].

The anti-inflammatory effect of AR was first shown to be mediated through the suppression of NO production via inhibition of inducible nitric oxide synthase (iNOS) at both the expression and activity levels. These findings have been confirmed in multiple *in vitro* studies that were primarily conducted on a lipopolysaccharide (LPS)-induced inflammatory model of RAW264.7 cells[22, 29-32], an immortalized murine macrophage cell line, and on U937 cells[22], a human pro-macrophage cell line. The modulatory effects of AR on cyclooxygenase-2 (Cox-2)[31, 33] have also been reported, but there is controversy regarding the effect of AR on Cox-2. Although both studies were carried out on the same LPS-induced RAW 267.4 cells, Zhao *et al* reported that AR did not affect Cox-2 expression or enzyme activity at 3–100 μmol/L[31], whereas Lee *et al* found that 0.1 μmol/L of AR could decrease COX-2 expression and PGE_2 production by 26.70%±4.61% and 32.84%±6.51%, respectively[33]. Other *in vitro* anti-inflammatory effects of AR include inhibition of LPS-induced primary murine splenocyte proliferation[22], inhibition of anti-CD3/CD28 antibody-induced primary human T lymphocyte proliferation[3], and polarization of M1 macrophages to M2-like macrophages[2]. The anti-inflammatory effect was also confirmed on silica-induced and peptidoglycan-induced inflammatory cell models[25]. In addition, AR was reported to have immunomodulatory effects towards type I–IV allergic inflammation[34], as well as inhibiting mast cell-mediated allergic responses[35].

Molecular mechanisms accounting for the anti-inflammatory effect of AR have been widely investigated in the past decade. Generally, upon sensing infection or tissue damage, transcription factors such as nuclear factor κB (NF-κB) are activated to induce the expression of genes participating in the inflammatory response (*eg*, iNOS and COX-2). Cytokine-mediated feed-forward loops can amplify and coordinate this inflammatory response[15]. The anti-inflammatory effect of AR has been attributed to its potent *in vitro* and *in vivo* modulating effects on several important cytokines, such as tumor necrosis factor-α (TNF-α)[2, 22, 26, 28, 31, 36, 37], interleukin-6 (IL-6)[2, 26, 28, 29, 31, 37], interleukin-1β (IL-1β)[2, 29, 37], and interleukin-10 (IL-10)[2, 28]. Inhibitory effects of AR on the expression levels of other cytokines, such as interleukin-2 and interferon-γ (IFN-γ), were also found *in vitro*[3]. Multiple upstream mechanisms for the modulating effect of AR on cytokines were proposed. Both *in vivo* and *in vitro* studies showed that AR inactivated NF-kB by inhibiting p65 nuclear translocation, suppressing I-κ phosphorylation[2, 26, 30, 37], suppressing phosphorylation of mitogen-activated protein kinases (MAPKs)[26, 36], and inhibiting phosphorylation of phosphatidylinositide 3-kinases (PI3K) and protein kinase B (AKT)[2, 26]. Other proposed mechanisms include suppression of the Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) pathway[4, 29], promotion of degradation of iNOS synthase through the carboxyl terminus of Hsc70-interacting protein (CHIP)-associated proteasome[32], and activation of adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPKα)[37]. However, there are few studies on the anti-inflammatory effects of arctiin. In three studies, arctiin was reported to have similar anti-inflammatory effects to those of AR *in vitro* and *in vivo*[33, 38, 39].

Effect of AR and arctiin against exogenous pathogens

AR, arctiin, and *A lappa* also demonstrated inhibitory effects on microorganism (Table 3), including viruses and bacteria, common exogenous stimuli for inflammatory responses. Studies attributed the anti-viral effects of *A lappa* to the major component AR. AR was reported to have strong anti-viral activities against influenza A in both *in vitro* and *in vivo* settings, and the mechanism of the anti-influenza effect of AR was related to the direct inhibitory effect on viral replication[5, 6, 40]. Furthermore, protective effects of AR against more lethal pathogens, such as human immunodeficiency virus and Japanese encephalitis virus, were also reported with *in vitro* and *in vivo* models[7, 41-43]. AR demonstrated inhibitory effects on the bacteria *Helicobacter pylori*, but this effect was not sufficient to attenuate the gastric carcinogenesis in Mongolian gerbils[44]. Other anti-bacterial activities of *A lappa* against pathogens such as *Escherichia coli* and *Pseudomonas aeruginosa* were all demonstrated using the extract of the herb on *in vitro* disk diffusion models[45-48]. In addition, inhibitory effects of *A lappa* on other microorganisms, such as fungi, were also demonstrated[46]. However, whether these effects are attributed to AR and arctiin is still unclear.

Anti-inflammatory activities of AR and arctiin on chronic diseases

AR and arctiin have also been associated with beneficial effects on some chronic diseases, such as metabolic disorders and central nervous system dysfunctions, partially due to their anti-inflammatory activity. AR and arctiin demonstrated their effects on ameliorating metabolic disorders in various cell lines[49-51], *ob/ob* mice, and streptozotoxin (SZT)-induced diabetic rats[8-10]. Neuroprotective effects of AR were demonstrated on cultured neuron cells, cerebral ischemia rats, memory deficit mice, experimental autoimmune encephalomyelitis in mice, Aβ-induced AD mice, and transgenic Alzheimer's disease mice[11-13, 52, 53]. Multiple mechanisms for these neuroprotective effects were proposed, including scavenging free radicals, down-regulating pro-inflammatory cytokines, regulating AMPK and PPAR-γ/ROR-γt signaling, reducing Tau hyperphosphorylation and inhibiting Aβ production[11-13, 52-54]. In addition, although AR and *A lappa* demonstrated their potential anti-cancer activities on various cancer cell lines, there is still a lack of sufficient evidence for their anti-cancer activities on *in vivo* models[21, 55-59].

In summary, AR was reported as the most potent bioactive component of *A lappa* in the majority of studies, while the bioactivities of arctiin were lower than those of AR in most

Table 3. Summary of the studies on pharmacological effect of AR and arctiin against exogenous pathogens.

Pathogen	Compound	Model	Dose	Findings	Ref
Japanese encephalitis virus (JEV)	AR	BALB/c mice	10 mg/kg, ip	AR treatment provided complete protection from JEV infection, reduced virus titres and demonstrated neuron rescue and gliosis reducing effects.	[41]
	AR	Mouse Neuro2a cells	0.1%	AR decreased viral titre.	[41]
Human immunodeficiency virus (HIV)	AR	HTLV-III B/H9-Jurkat cell system	0.5 μmol/L	The expression and reverse transcriptase activity of HIV-1 proteins p17 and p24, was inhibited by AR.	[42]
	AR	3'-processing and integration assays	100 μmol/L	AR suppressed the integration of proviral DNA into the cellular DNA genome but was inactive in the cleavage (3'-processing) and integration (strand transfer) assays.	[43]
	AR	CHME5 cells	5–20 μmol/L	AR regulated the upstream PI3K enzyme to abolish the cytoprotective phenotype of HIV virus type 1 Tat-expressing CHME5 cells.	[7]
Influenza A	Arctiin	BALB/c mice	5 mg/d, *po*	Lethal infection was decreased, virus production was reduced, antibody response was elevated by treatment of arctiin.	[5]
	AR	NIH mice	10, 100 μg/kg, *po*	Lung consolidation due to viral infection was significantly inhibited by AR. Survival time of infected mice was prolonged by AR treatment.	[6]
	AR	MDCK cells	5, 25, 50 μmol/L	IC_{50} of AR were 3.8 μmol/L and 2.9 μmol/L in plaque yield reduction assay. Synergistic effect of AR with oseltamivir was found.	[5]
	AR	Hemagglutination titer	6.7–53.6 μmol/L	Hemagglutination titer was inhibited, indicating direct inhibitory effect against influenza virus replication of AR.	[40]
Helicobacter pylori	AR	Mongolian gerbil	10 μmol/L, 0.1% in diet	AR showed inhibitory effect of H. pylori colonies at 10 μmol/L, but failed to attenuate neoplasia *in vivo*.	[44]
porcine circovirus type 2	AR	Mice	200 μg/kg, ip	Significant inhibition of PCV2 proliferation in the lungs, spleens and inguinal lymph nodes.	[124]

Abbreviation: ip: intraperitoneal injection; *po*: oral administration.

reports evaluating both compounds. AR demonstrated potent effects on inflammatory responses. The anti-inflammatory effect of AR may function synergistically with its anti-viral effect to manage some infectious conditions. However, inflammatory responses also have a role in the progression of several chronic diseases, and AR may serve as an auxiliary treatment for these chronic diseases, including metabolic disorders and central nervous system dysfunctions.

Pharmacokinetic properties of AR and arctiin

Despite the research attention AR has received due to its promising therapeutic potential, biopharmaceutic and pharmacokinetic investigations of AR and arctiin are rare. In this section, we will discuss the pharmacokinetic properties of arctiin and AR, including the absorption, distribution, metabolism and excretion characteristics, focusing on the biotransformation of arctiin and AR. Furthermore, comparison will be made among the pharmacokinetic profiles of AR after various routes of administration.

Pharmacokinetic properties of arctiin

AR was regarded as the only metabolite in most *in vivo* pharmacokinetic studies of arctiin, due to its much higher concentration in plasma compared with that of arctiin[5, 60]. However, *in vitro* incubation studies of arctiin or AR with intestinal content or feces revealed that intestinal microbiota mediated the biotransformation of arctiin to AR in the intestine[61, 62], followed by demethylation and a series of other biotransformation processes leading to the formation of enterolactone **(3)**[63-65]. Wang *et al* reported three metabolites in rat urine and feces after oral administration of 30 mg/kg arctiin **(1)**, including AR **(2)**, enterolactone **(3)** and (2R,3R)-2-(3′-hydroxybenzyl)-3-(3″,4″-dimethoxybenzyl)-butyrolactone, an intermediate metabolite[66] (Figure 2).

Pharmacokinetic properties of AR

The pharmacokinetic properties of AR are summarized in Table 4. After oral ingestion, efficient absorption of AR was demonstrated in a Caco-2 cell monolayer transport study and a rat *in situ* intestinal perfusion model[67, 68]. The duodenum was found to be the best absorption segment of AR among all the intestinal segments[67]. Although the Caco-2 cell monolayer model showed that no significantly active efflux was involved during the absorption of AR, with an efflux ratio of 1.17[68], an *in situ* intestinal perfusion model showed that absorption of AR in the duodenum was significantly improved by co-treatment with the P-glycoprotein (P-gp) inhibitor verapamil[67], suggesting AR is a potential P-gp substrate.

After entering the systemic circulation, AR exhibited a strong binding capacity (99.8%–100%) to plasma. The high plasma binding was found in various species, including human, beagle dog, and rat[69]. The tissue distribution of AR was only investigated after hypodermic or oral administration to rats. After hypodermic injection of 0.806 μmol/kg AR to

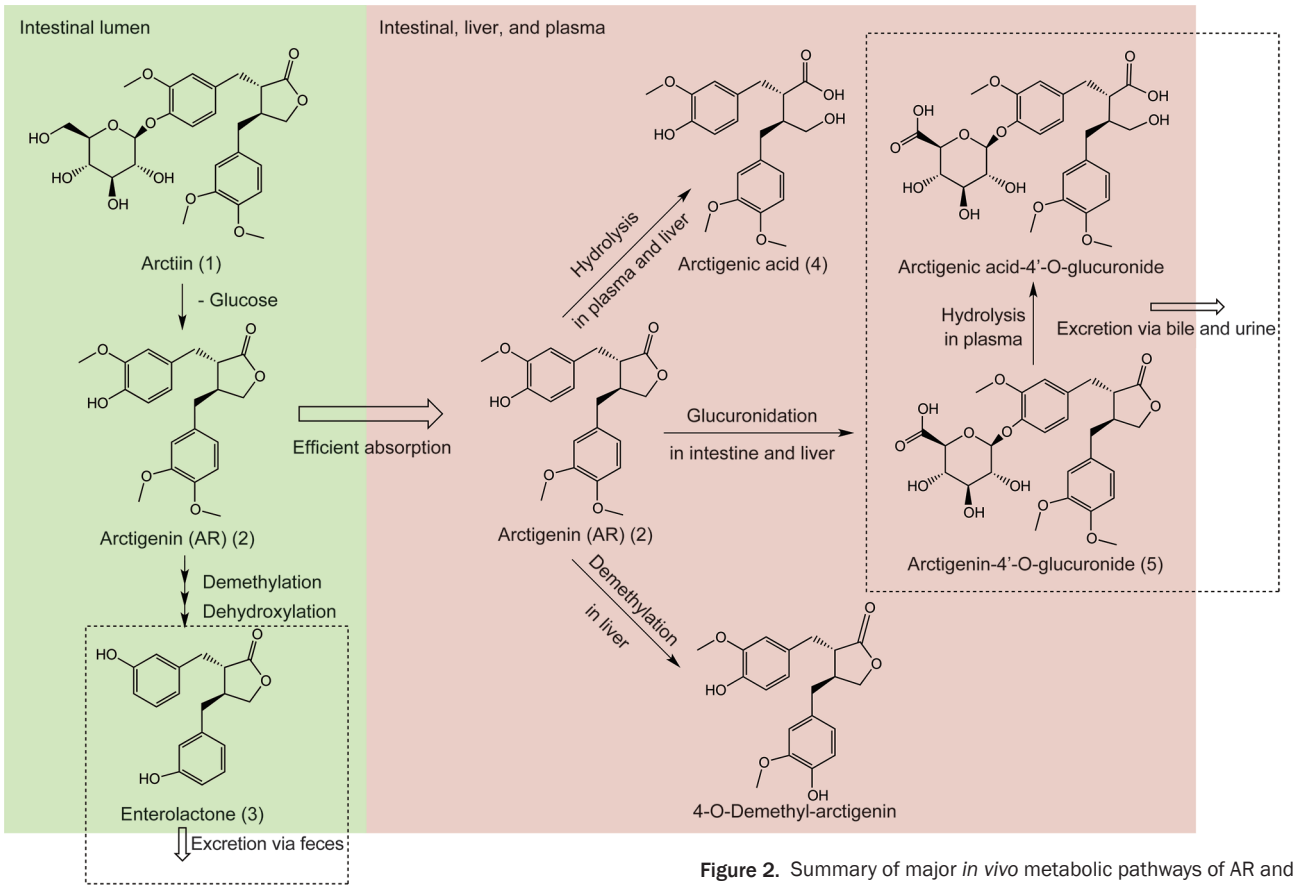

Figure 2. Summary of major *in vivo* metabolic pathways of AR and arctiin.

rats, the AR concentrations were reduced at 6 h to approximately 1/10 of their peak values at 0.25 h in most organs, indicating no accumulation in tissues, and the peak concentration of AR was in the intestine, followed by the heart, liver, pancreas, and kidney[69]. After oral administration of 70 mg/kg AR to rats, the tissue concentration of AR peaked at 30 min and was quickly eliminated within 4 h, and the concentration of AR was highest in the spleen, followed by the liver and the other organs[70].

AR was eliminated via extensive metabolism to various metabolites. The dominant metabolic pathways of AR are summarized in Figure 2. *In vitro* incubation of AR with the intestinal microbiota demonstrated that similar to acrtiin, AR can be biotransformed into a series of demethylation and dehydroxylation products, such as 3'-demethylarctigenin, 3'-demethyl-4'-dehydroxyarctigenin, and eventually to the enterolactone **(3)** anaerobically within 24 h[61, 65, 71]. In rats, extensive first-pass metabolism of AR occurred in both the intestine and liver, with the formation of two major *in vivo* metabolites, namely, arctigenic acid **(4)** and arctigenin-4'-O-glucuronide **(5)**[68, 72-74]. Further *in vitro* and clinical studies confirmed that similar biotransformation also occurred in humans. The hydrolysis of AR was mediated by human paraoxonase 1 in plasma[73], and glucuronidation of AR was mediated by UGT1A9, UGT2B7 and UGT2B17 in the liver and intestine[74]. A phase I clinical trial of the herbal product GBS-01 on pancreatic cancer patients demonstrated that after oral administration of GBS-01 at a dose of 12 g AR per person, the area under the plasma concentration versus time curve (AUC) of arctigenin-glucuronide was almost 1000 times higher than that of AR[75]. Notably, the extent of metabolism of AR might be different between species. As reported by Li *et al*, approximately 62%, 3.7%, 25.9% and 15.7% of the AR remained after incubation in human, monkey, dog, and rat liver microsomes for 90 min[69]. Other minor *in vivo* metabolites found in SD rats include 4-O-demethylarctigenin, arctigenin 4-O'-sulfate, arctigenic acid-4'-O-glucuronide, and 4-O-demethyl-arctigenin-4,4'-O-di-glucuronide[72, 73]. Following rapid formation, fast elimination of the two major metabolites was observed after both intravenous and oral administration of AR to rats. Several glucuronidation products of AR, including arctigenin-4'-O-glucuronide **(5),** were excreted via bile, with potential enterohepatic circulation suggested[72]. These complex metabolic pathways of AR were described and verified by an integrated semi-mechanistic pharmacokinetic model of rats[72] and warrant further verification in human trials.

Due to the extensive first-pass metabolism of AR, it is likely that most AR, either as single compound or as active component in herbal preparations, would be quickly metabolized after oral administration. As shown in Table 5, after oral administration, the plasma concentrations of AR were very low and even undetectable in various animal models, sug-

Table 4. Summary of absorption, distribution, metabolism and elimination of AR.

Model	Dose	Findings	Ref
Absorption			
Caco-2 cell monolayer	50 μg/mL	AR efficiently passed through the cell monolayer with P_{app} of $(1.76\pm0.48)\times10^{-5}$ (apical to basolateral) and $(1.50\pm0.61)\times10^{-5}$ (basolateral to apical).	[68]
In situ SD rat intestinal perfusion model	25 μg/mL	Efficient absorption of AR was observed with extensive intestinal first-pass metabolism demonstrated.	[68]
In situ intestinal perfusion on normal and diabetic SD rats	5, 10, 20 μg/mL	AR belongs to easily absorbed agents. Duodenum was the best absorption segment of AR. The P_{eff} and K_a of AR were increased by 60% and 52% in duodenum with co-treatment of verapamil. The absorption of AR was promoted in diabetic rats.	[67]
Distribution			
In vitro plasma incubation	0.0672, 0.269, 1.075 μmol/L	AR exhibited a strong binding capacity (99.8%–100%) with plasma, including human, beagle dog, and rat.	[69]
Wistar rat	0.806 μmol/kg, ih	AR concentration in the intestine was the highest, followed by heart, liver, pancreas, and kidney. No accumulation of AR in tissues after 6 h.	[69]
SD rat	30, 50, 70 mg/kg, *po*	AR was rapidly distributed into organs, and C_{max} in tissues was observed at 30 min. The content of AR in spleen was the highest.	[70]
Metabolism and elimination			
Human fecal inoculum incubation	0.2 to 0.35 mmol/L	Three metabolites of AR were identified under anaerobic condition: enterolactone (**3**), 3'-demethyl-4'-dehydroxyarctigenin and 3'-demethylarctigenin.	[65]
Eubacterium ARC-2 incubation	0.6 mmol/L	After 24-h incubation, AR was transformed to 4', 4'-dihydroxylenterolatone through 3 types of demethylation products under anaerobic condition.	[61, 71]
Rat intestinal content solution		After 4-h incubation, AR was stable in rat small and large intestinal content solution, while arctigenic acid was converted back to arctigenin in rat large intestinal content. All three glucuronides, were hydrolysed back to corresponding parent compounds.	[72]
In situ SD rat intestinal perfusion model	25 μg/mL	Extensive intestinal first-pass metabolism of AR to arctigenic acid (**4**) and arctigenin-4'-O-glucuronide (**5**) was identified.	[68]
Human recombinant paraoxonase 1	0.27 to 134.4 μmol/L	Paraoxonase 1 was confirmed to be the enzyme responsible for AR hydrolysis.	[73]
V79 Chinese hamster cells with rat Cyp2b1	1 mmol/L	AR was converted to 3'-demethyl-arctigenin in cells expressing rat Cyp2b1.	[125]
Rat liver/intestine microsome	0.269 to 67.2 μmol/L	Extensive glucuronidation of AR was observed in both liver and intestine microsome. No further glucuronidation or demethylation of arctigenic acid (**4**) in liver and intestine microsome.	[72]
Rat liver cytosol incubation	10 nmol/L	3'-Demethyl-arctigenin was converted back to AR.	[126]
Human liver/intestine microsomes	100 μmol/L	AR was metabolized to 4′-O-glucuronide (**5**) in human liver and intestinal microsome mainly via UGT1A9, UGT2B7 and UGT2B17.	[74]
Human, monkey, dog, and rat liver microsome	100 μmol/L	Around 62%, 3.7%, 25.9% and 15.7% of AR remained after incubated in human, monkey, dog, and rat liver microsome for 90 min.	[69]
SD rats	3 mg/kg, *po*	Arctigenic acid (**4**) and arctigenin-4'-O-glucuronide (**5**) was identified as major metabolites in rat plasma after oral administration of AR. 4-O-demethylarctigenin was also identified *in vivo*.	[73]
SD rats	0.48 to 2.4 mg/kg, iv; 2.4 to 12 mg/kg, *po*	Rapid formation of arctigenic acid (**4**) and arctigenin-4'-O-glucuronide (**5**) with quick elimination of both parent and metabolites were observed after both intravenous and oral administrations. No quantifiable AR was identified after oral administration due to extensive first-pass metabolism	[72]
SD rats	0.96 mg/kg, iv	Arctigenin-4'-O-glucuronide (**5**), arctigenic acid-4'-O-glucuronide, 4-O-demethyl-arctigenin -4,4'-O-di-glucuronide, and trace amount of arctigenic acid (**4**) were found in bile at 0–15 min.	[72]
Wistar rat	0.806 μmol/kg ih	Within 72 h after drug-delivery, the urine accumulative excretion ratio was 1.93% and the excretory amount of AR in faeces and bile were 0.248% and 0.182%, respectively.	[69]

Abbreviation: iv: intravenous administration; ih: hypodermic injection; *po*: oral administration.

gesting poor oral bioavailability. The pharmacokinetic profile of AR in humans after oral administration was investigated in a phase I clinical trial of the herbal product GBS-01. After oral administration of GBS-01 at a dose of 12 g AR per person, the peak concentration of AR in the plasma of the pancreatic cancer patients was 66.56±26.81 ng/mL, and the AUC was 487.97±368.86 ng*h/mL[75]. Given the low molecular weight of AR and its high permeability demonstrated in the absorption models, the poor oral bioavailability of AR should be mainly due to its extensive first-pass metabolism rather than limita-

Table 5. Pharmacokinetic parameters of AR after different routes of administration in rat, dog, and human.

Species	Route	Dose (μmol/kg)	Pharmacokinetic parameters					Ref
			C_{max} (μmol/L)	T_{max} (min)	$T_{1/2}$ (min)	AUC (min* μmol/L)	Bioavailability	
Beagle dogs	iv	0.403	N/A	N/A	96±24.84	15.64±2.08[a]	N/A	[69]
	sl	0.20 (2.687 μmol/dog)	0.04±0.01	60±16.44	61.8±19.26	6.56±1.16[a]	N/A	
		0.403 (5.374 μmol/dog)	0.07±0.24	112±53.64	70.8±24.36	12.01±2.26[a]	72.5%	
		0.81 (10.748 μmol/dog)	0.10±0.02	130.2±70.20	84±34.98	23.22±3.06[a]	N/A	
	ih	0.134	0.03±0.01	60±0	94.8±31.74	4.76±0.75[a]	N/A	
		0.403	0.11±0.03	70.2±15.48	74.4±12.18	16.93±5.42[a]	108%	
		1.209	0.25±0.04	75±16.44	117±25.44	35.63±4.21[a]	N/A	
Wistar rats	iv	2.687	N/A	N/A	217.8±74.04	66.26±18.7[a]	N/A	[69]
	ih	2.687	1.26±0.30	15±0	116.4±21.72	77.87±24.67[a]	116%	
	po	2.687	Concentrations were lower than the lowest limit of quantitation at most time points.					
Wistar rats	iv	0.8	0.87±0.18	N/A	40.8±10.0	13.1±3.6[b]	N/A	[127]
SD rats	iv	0.32	N/A	N/A	9.35±2.15	9.32±2.80[a]	N/A	[72]
		0.64	N/A	N/A	13.4±2.2	19.4±2.9[a]	N/A	
		1.61	N/A	N/A	13.0±1.8	54.1±8.1[a]	N/A	
	po	1.61, 3.22, 8.16	No quantifiable AR was determined.					
SD rats	iv	27	N/A	N/A	627.6±214.8	199.8±49.51[a]	N/A	[67]
	po	538	0.34±0.04	4.32±5.46	414.6±107.4	116.18±38.69[a]	N/A	
Diabetic rats	iv	27	N/A	N/A	469.2±227.4	151.05±46.84[a]	N/A	[67]
	po	538	1.22±0.45	3.42±0.9	322.8±106.2	197.99±48.28[a]	N/A	
Human with	*po*	134 (3 g/person)	0.05±0.01	60±30	430.8	40.1±33.3[b]	N/A	[75]
pancreatic		269 (6 g/person)	0.07±0.02	30±0	183.6 ±176.4	23.0±9.2[b]	N/A	
cancer		538 (12 g/person)	0.18±0.07	52.2±37.2	340.8 ±380.4	78.7±59.5[b]	N/A	

Abbreviation: iv: intravenous administration; sl: sublingual administration; ih: hypodermic injection; *po*: oral administration. N/A: not applicable.
[a]: $AUC_{0-\infty}$; [b]: AUC_{0-t}.

tions of membrane permeability. Thus, delivering AR through alternative administration routes might be plausible to bypass the first-pass metabolism and improve its bioactivities. Alternative routes for administration of AR, including hypodermic injection and sublingual administration, were tested on experimental animals. The results demonstrated substantially improved AUC and bioavailability of AR after hypodermic or sublingual administration compared with that from the oral administration (Table 5)[69]. These results suggested that optimization of the administration routes for AR may potentially improve its therapeutic efficacy by increasing the systemic and target organ exposure. Further pharmacokinetic/pharmacodynamic studies of AR after different routes of administration are warranted.

Clinical usages

As described previously, AR and arctiin served as marker compounds in the quality control of numerous proprietary Chinese medicines. Most of these products are for treatment of common cold, flu and related symptoms, such as various dosage forms of Yinqiaojiedu decoction[76-78], Lingyang ganmao decoction[79, 80] and Fengreganmao granules[81, 82]. Despite its popularity, Fructus Arctii is not commonly used alone. Therefore, reports on the clinical trials of AR, arctiin or *A lappa* alone are rather limited. As summarized in Table 6, only four clinical trials were identified for evaluation of the therapeutic effects of AR, arctiin or *A lappa*, with diverse indications. Despite their high Jadad scores (2 out of 3 received full score of 5)[83], three randomized controlled trials demonstrating the efficacy of arctiin (0.5–1 g, t.i.d.) or Fructus Arctii (20 g, t.i.d.) against diabetic nephropathy were actually reported by the same group, with a similar study design and dose regiments[84-86]. A recent phase I clinical study co-sponsored by the Japanese National Institute for Cancer Research and Kracie Pharmaceutical Co, Ltd confirmed the safety of an oral product containing a high content of AR (GBS-01) (dose equal to 3 to 12 g daily)[75]. Moreover, a study protocol for evaluating *A lappa*-containing moisturizing cream for dry skin and itch relief in a randomized, double-blind, placebo-controlled trial was published[87]. Similarly, *A lappa* was also demonstrated to effectively treat acne vulgaris in a recent uncontrolled observational interventional study in India[88]. The anti-inflammatory effects of AR, arctiin or *A lappa* have not yet been confirmed in the clinic. Further randomized controlled trials are needed to evaluate the therapeutic efficacy of AR and arctiin.

Conclusions

Inflammatory responses are an important part of various acute

Table 6. Summary of clinical trials on AR- or arctiin-containing products.

Disease	Drug	Study design	Jadad score*	Patient numbers	Oral dose	Duration	Clinical efficacy	Ref
Diabetic nephropathy	Fructus Arctii powder	Randomized controlled	2	Placebo: 61; Treatment: 60	20 g, t.i.d.	8 weeks	Urinary albumin excretion rate (UAER) and 24 h quantitative examination of urinary protein (UPQ) were improved by the treatment, which was significantly better than placebo (P<0.001).	[86]
	Tangjiang-shenkang Granule (125 mg arctiin/g)	Randomized double blind controlled	5	Placebo: 60; Low dose (L): 64; High dose (H): 62	L: 4 g, t.i.d.; H: 8 g, b.i.d.	8 weeks	The treatment efficacy of L and H dose was better than those of placebo (P<0.01). UAER and UPQ were improved by the treatment (P<0.05).	[85]
	Arctiin Granule	Randomized double blind controlled	5	Placebo: 102; Treatment: 307	500 mg/dose, t.i.d.	8 weeks	The treatment efficacy of arctiin granule was better than those of placebo (P<0.01). UAER and UPQ were improved by the treatment (P<0.05).	[84]
Advanced pancreatic cancer refractory to gemcitabine	GBS-01	Uncontrolled Phase I clinical trial	0	15	3–12 g AR qd	4 weeks	No dose limited toxicities observed. Response was found in 1/15 patient while another 4 showed stable disease.	[75]

Abbreviation: b.i.d.: twice a day; t.i.d.: three times a day; qd: once daily.

and chronic disease conditions. AR, as the most potent bioactive component of *A lappa* with anti-inflammatory activities, is a promising therapeutic compound against acute inflammation as well as several chronic diseases. However, pharmacokinetic investigations suggested that the extensive first-pass metabolism of AR would hinder its *in vivo* and clinical efficacy after oral administration. To optimize the *in vivo* and clinical efficacy of AR, alternative administration routes other than oral administration are suggested. AR could be delivered through sublingual or buccal routes that allow rapid onset of the treatment of acute inflammation and influenza; transdermal routes for the treatment of skin conditions; and the intranasal route for targeting central nervous system dysfunctions. In addition, considering the extensive first-pass metabolism of AR and the higher plasma concentrations of metabolites compared with parent compound observed, the potential pharmacological effects of the metabolites of AR should be studied. Further reports with simultaneous monitoring of pharmacokinetics and pharmacological properties are essential for a better understanding of the effects of AR.

Acknowledgements

This work is supported by Direct Grant 3800005 from the Chinese University of Hong Kong and research fund 7010213 from the Health Authority of Hong Kong, China.

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