Arctigenin: pharmacology, total synthesis, and progress in structure modification

Dan Wu*, Lili Jin*, Xing Huang, Hao Deng, Qing-kun Shen, Zhe-shan Quan, Changhao Zhang and Hong-Yan Guo

Key Laboratory of Natural Medicines of the Changbai Mountain, Affiliated Ministry of Education, College of Pharmacy, Yanbian University, Jilin, China

ABSTRACT
Arctium lappa L. is a prevalent medicinal herb and a health supplement that is commonly used in Asia. Over the last few decades, the bioactive component arctigenin has attracted the attention of researchers because of its anti-inflammatory, antioxidant, immunomodulatory, multiple sclerosis fighting, antitumor, and anti-leukemia properties. After summarising the research and literature on arctigenin, this study outlines the current status of research on pharmacological activity, total synthesis, and structural modification of arctigenin. The purpose of this study is to assist academics in obtaining a more comprehensive understanding of the research progress on arctigenin and to provide constructive suggestions for further investigation of this useful molecule.

Introduction
Natural products are components or metabolites found in animals, plants, insects, marine organisms and microorganisms. They are very significant for the development of new drugs. With the emergence of human genome sequencing and high-throughput screening technology, the molecular targets of compounds isolated from traditional drugs have been confirmed, which provides exciting possibilities for researchers to develop new molecular entities to treat diseases.

Newman et al. reported that from 1946 to 2019 mentioned 1881 drugs, about 441 (23.5%) came directly or indirectly from natural products. Furthermore, 40 (53.3%) of the 75 small molecules in the field of anti-tumour were natural products from 1946 to 1980. The research of natural products is extensive and it shows excellent performance. For example, both xanthohumol and curcumin have anti-tumour activity.

Natural products are a treasure house worthy of attention, and have great potential in the development of new drugs because of their rich sources. Arctigenin, a phenylpropene dibenzylbutyrolactone lignan isolated from Forsythia koreana, Saussurea heteromalla, Wikstroemia indica, Centaurea diluta, has been previously reported. In the past research, arctigenin have made significant progress in determining the development of lead compounds for the treatment of human diseases and the research of related molecular mechanisms. Therefore, this article combines 75 pharmacological activities and 85 chemical related articles. Briefly reviews the pharmacology and total synthesis of arctigenin, and reviews the medicinal chemistry research progress of new derivatives of arctigenin, in order to understand the therapeutic potential and value of arctigenin.

The chemical constituents of Arctium lappa L
The compounds isolated from Arctium lappa L. generally contain lignin, volatile oil, fatty acids, and terpenoids. The lignin is the highest in terms of content.

Lignans
Lignin mainly includes: arctiin (1), arctigenin (2), (+)-7,8-didehydroarctigenin (3), trachelogenin (4), matairesinol (5), neoaartcin A (6), neoarctin B (7), pinoresinol (8), (-)-secoisolariciresinol (9), lappaol A (10), lappaol B (11), lappaol C (12), lappaol D (13), lappaol E (14), lappaol F (15), lappaol H (16), diarctigenin (17), arctigan A (18), arctigan G (19), arctigan H (20), arctiinoside A (21), arctiinoside B (22), et al. The structural formulas of these compounds are shown in the Figure 1.

Volatile oil components
Arctium lappa L. contains a variety of oil components. Zhao et al. analysed the oil components of arctigenin using GC-MS and chemometric resolution methods, and performed qualitative and quantitative analyses to identify the major components linalool (0.6%), camphor (1%), and p-menthone (0.1%)22.

Terpenoids
Terpenoids, mainly sesquiterpenoids triterpenoids and tretaterpene, were isolated from Arctium lappa L. Among them, sesquiterpenoids mainly include eremophilene, fukinone, petasitolone, ¡-eudesmol, dehydrofukinone and arctiin and ¡-cineole; the triterpenoids mainly include taxasterol, taxasterol palmitate, and taxasterol acetate and ¡-sitosterol and the tretaterpene contains ¡-carotene25.
Fatty acids

*Arctium lappa* L. contains large amounts of fatty oils, the majority of which are fatty acids such as methyl palmitate, methyl linoleate, methyl linoleate, and linoleic acid\(^{15}\).

Other ingredients

*Arctium lappa* L. also contains flavonoids, phenolic acids, and a few alkaloids\(^{15}\).

**Figure 1.** The structure of lignin compounds in *Arctium lappa* L.
The pharmacological activity of arctigenin

Fructus Arctii is the dry and ripe fruit of Arctium lappa L., a biennial herb of the Compositae family. Arctium lappa L. is one of the traditional Chinese Medicine commonly used in clinic, and its leaves and roots can also be used. Traditionally, it is used for dispelling wind and clearing heat, dispersing lung and resolving phlegm, promoting pharynx and promoting body fluid, detoxification and detumescence. Arctium lappa L. has the functions of antibacterial, antioxidant, hypoglycaemic, lipid-lowering, vasodilation, improvement of atherosclerosis, anti-tumour, anti-mutagenesis, and immune regulation, and has potential application value.

Arctigenin and its glycoside, arctiin, are the two main active components of Arctium lappa L. Moreover, arctigenin is an important bioactive component of Fructus Arctii with good anti-inflammatory, anti-tumour, antioxidant effects and other therapeutic effects, attracting more and more attention in recent years (Figure 2).

Anti-tumour activity

Arctigenin has anti-tumour effect against a variety of cancers such as pancreatic cancer, gastric cancer, colon cancer, and liver cancer. Details about the anti-cancer activity of arctigenin and its mechanism of action are given in this section.

Arctigenin inhibits tumour cell proliferation

The activities of arctiin and arctigenin differ with respect to the treatment of liver cancer. In an experimental study of hepatocellular carcinoma, Hirose et al. observed very low therapeutic effect of arctiin against liver cancer, while arctigenin had a remarkable anti-hepatocellular carcinoma effect. The toxic effects that arctiin and arctigenin have on human hepatocellular carcinoma HepG2 cells were tested in vitro by Moritani et al., the results indicated that both inhibit the proliferation of HepG2 cells while having little effect on normal hepatocytes. Arctigenin upregulates the expression of Bax while downregulates the expression of Bcl-2; moreover, it significantly inhibited the proliferation of SNU-1 and AGS in a time- and dose-dependent manner. Takasaki administered arctiin and arctigenin topically and orally, and found that both had a significant inhibitory effect on skin cancer cells.

Arctigenin promotes apoptosis

Arctigenin inhibited the PI3K/Akt signaling, thereby significantly inhibiting the viability of liver cancer cells in a concentration-dependent manner. The molecule also induces apoptosis, activates caspase-9 and caspase-3, and reduces the expression of Bcl-xL, MCL1, and survivin and the phosphorylation of mTOR and S6K, which can be reversed by the overexpression of constitutively active Akt. Arctigenin can inhibit colon and rectal cancer by inducing the apoptosis of colon and rectal cancer cells, as confirmed by Hausott et al.

Arctigenin has been found to selectively destroy the oxidative phosphorylated human pancreatic carcinoma cell line PANC-1. This selective killing was due to induction of apoptosis and apoptotic necrosis through endoplasmic reticulum stress, mitochondrial membrane permeabilization, and cysteine activation. Additionally, arctigenin has the ability to eradicate cancer cells. Experiments have shown that arctigenin inhibited the growth of pancreatic tumours in nude mice and suppressed the growth of pancreatic cancer cell lines.

Arctigenin regulates the cell cycle

Study by Yang et al. indicated that the inhibitory effect of arctigenin on the activity of bladder cancer T24 cells was dependent on dose and time. Arctigenin reduced the expression of cyclin D1 and arrested tumour cells in the G1 phase, but did not affect the expression levels of CDK4 and CDK6. In addition, arctigenin selectively altered phosphorylation of members of the MAPK superfamily, significantly reduced the phosphorylation of ERK1/2, and activated the phosphorylation of p38.

Arctigenin inhibits cancer cell metastasis

Arctigenin inhibited metastasis in human breast cancer cells by inhibiting AP-1 transcriptional activity through the ERK1/2 and JNK1/2 MAPK pathways, without affecting the p38 MAPK pathway. The molecule also inhibited matrix metalloproteinase-9 and urokinase-type plasminogen activator through the AKT, NF-κB, and MAPK signalling pathways to exert anti-metastatic effect in breast cancer, regardless of the ER expression.

Study by Lee et al. demonstrated the anti-colon and rectal cancer activity of arctigenin. They demonstrated that arctigenin inhibited the proliferation of SW480 cells, induced apoptosis, and also significantly inhibited the invasion and metastatic ability of highly
metastatic SW480 cells. It has also been observed that apoptosis was induced by a decrease in the expression of anti-apoptotic Bcl-2 and transcriptional activator (IAP-1), while the expression of the pro-apoptotic genes Smax and Bax increased in the presence of the molecule.35,39,40.

**Summary of arctigenin anti-tumour activity**

Arctigenin has unique anti-tumour activity. Several studies have demonstrated the inhibitory effect of arctigenin against various tumours, both in vitro and in vivo. In summary, arctigenin is a potential antitumor natural product and is expected to provide new drug candidates for cancer treatment. Table 1 summarises a number of in vitro and in vivo cancer studies that used arctigenin.

**Anti-leukemia activity**

Hirano T et al. evaluated cytotoxicity and anti-leukemic activity of both arctiin and arctigenin using HL-60 (human blood cancer cells) and four anticancer drugs as positive controls. The results showed that arctigenin significantly inhibited the proliferation of HL-60 cells (IC50 < 100 ng/mL) and that its anti-leukemic activity was comparable to that of anticancer drugs used in clinical practice.31.

**Anti-inflammatory effect**

Arctigenin exerts favourable anti-inflammatory activity. Extensive pharmacological research has shown that is can impart anti-inflammatory effect in conditions such as edema, colitis, and acute lung injury.32.

Even low concentrations (<32 ng/mL) of arctigenin have been found to significantly inhibit TNF-α in RAW264.7 mouse macrophages and U937 human macrophages induced by lipopolysaccharides, with no toxic effect on normal cells. TNF-α inhibitors are known to have a beneficial effect on inflammation. This conclusion was made through in vitro study by Cho et al.33.

Arctigenin has also been found to inhibit the nuclear transcription factor receptor activator p65 (RANKL)-mediated differentiation of osteoclasts (mouse bone marrow macrophages), suggesting beneficial effects of arctigenin in treating rheumatoid arthritis and osteoporosis.34,35. The related mechanism may involve inhibitory effect of arctigenin on production of the inflammatory mediators, with no toxic effect on normal cells. TNF-α inhibitors are known to have a beneficial effect on inflammation. This conclusion was made through in vitro study by Cho et al.33.

Arctigenin exerts its anti-inflammatory effect through its anti-inflammatory effect in conditions such as edema, colitis, and acute lung injury.32.

**Table 1. Summary of in vitro and in vivo studies with arctigenin against various cancer.**

| Cancer          | In vitro studies | In vivo studies | Potential molecular mechanisms | Ref. |
|-----------------|------------------|----------------|-------------------------------|------|
| Hepatocellular  | IC50 (Hep G2 cells) = 38.29 μM (12 h), 1.99 μM (24 h), 0.24 μM (48 h) | – b | Activate caspase-9 and caspase-3, Bcl-2, Bax, release of cytochrome c, deactivation of PI3K/P-Akt, P53, Fas/Fasl, NF-κB | [41] |
|                 | IC50 (Hep G2 cells) = 30 μM (48 h), IC50 (Hep3B cells) = 40 μM (48 h) | – b | Apoptosis, Activate caspase-9 and caspase-3, Bcl-xL, Mcl-1, survivin, phosphorylation of mTOR and S6K1 | [42] |
| Hepatoblastoma  | IC50 (HUH-6 cells) = 4 μM (48 h) | – b | Apoptosis, Caspase-3/7, Caspase-8 | [43] |
| Colon Cancer    | CT26, MC38, and SW620 cells | 50 mg/kg/day, tumour nodules, tumour formation, metastasis | | |
| Prostate Cancer | LNCaP, LAPC-4, and WPE1-NA22 cellsa | 50 and 100 mg/kg, tumour growth, tumour volume, tumour weight | VEGF, FGFB, Bax/Bcl-2, EGF, PDGF, BBl, NGF-b, TNF-α | [47] |
| Lung Adenocarcinoma | A549a | – b | NPAT, cyclin E/CDK2, cyclin H/CDK7, Bax, Fas, Caspase-3, 8,9, Akt-1, Bcl-2, Bad, |
| Gastric Cancer  | SNU-1 and AG5 cellsa | – b | Bcl-2, Bax, cyclin D1, cyclin E1, CDK4/6, CDK2, P15, P21, p-Rb (ser 780), |
| Bladder Cancer  | T24 cellsa | – b | cyclin D1, phospho-ERK1/2, induce phospho-p38 |
| Breast Cancer   | MCF-7 cellsa | – b | mTOR pathway, leading to autophagy-induced cell death, ERα, LC3-II/LC3-I, MMP-9, activated Akt and NF-kB, activate MAPKs, ERK 1/2, JNK1/2 and p38, AP-1 transcription |
|                 | MCF-7 and MDA-MB-231 cellsa | – b | |

aArctigenin inhibited the growth of tumour cells, but did not give IC50.
bNot available.
Reduce, inhibition or down-regulated.
Increase or up-regulated.
in vivo studies have identified as the main targets of anti-inflammatory action of arctigenin. 

**Table 2.** summarises a number of in vivo and in vitro studies that have investigated the anti-inflammatory properties of arctigenin.

| Model                        | In vitro studies | In vivo studies | Potential molecular mechanisms | Ref. |
|------------------------------|------------------|----------------|-------------------------------|------|
| Acute Lung Injury            | –                | lung wet-to-dry (W/D) ratio, MPO activity, TNF-α, IL-1β, IL-6, MIP-2, NO | phosphorylation of AMPKα, phosphorylation of AMPKβ | [60] |
| –                            | 50 mg/kg, lung injury, TNF-α, IL-6, MIP-2, NO | iNOS, HO-1, ERK1/2, p38, JNK | [61] |
| –                            | 10, 20 and 40 mg/kg, IL-8, TNF-α, IL-1β, MOP, lung wet-to-dry (W/D) ratio | PI3K/Akt phosphorylation, NF-κB | [62] |
| LPS stimulation              | RAW264.7, NO | –                | iNOS, ERK and Src activation | [63] |
| RAW264.7, IL-1β, IL-6, MCP-1 | –                | iNOS, COX-2, phosphorylation of STAT1, STAT3, JAK2 | [64] |
| Liver injury from acute hepatitis | –              | ALT, AST, TNF-α, IFN-γ, IL-17A, IL-17F, IL-1β, IL-6, CXCL10, TGF-β1, IL-4 | inhibition of pro-inflammatory cytokines and chemokines, mediator of macrophages | [65] |

*Not available.
1 Reduce, inhibition or down-regulated.
2 Increase or up-regulated.

has also been found to suppress the expression of iNOS in macrophages by inhibiting the JAK-STAT signalling pathway.[37]

The arctigenin-associated degradation of iNOS in lipopolysaccharide-stimulated mouse macrophage-like RAW 264.7 cells was due to CH50-associated ubiquitination, which is proteasome-dependent process. It also reduces iNOS phosphorylation and subsequently inhibits the enzymatic activity of iNOS by inhibiting the ERK and Src activation, and promotes ubiquitination and iNOS degradation following lipopolysaccharide stimulation. In conclusion, burdock seed sapogenins promote degradation of iNOS through the CH50-related proteasome pathway and inhibit its enzymatic activity.[38]

Lee et al.[39] showed that 0.1 μM/L of arctigenin caused 26.70 ± 4.61% decrease in COX-2 gene expression and 32.84 ± 6.51% decrease in prostaglandin E2 content. In fact, regarding the molecular mechanism by which arctigenin inhibits inflammation, most studies have demonstrated that it inhibits the activation of the NF-κB pathway by suppressing the lipopolysaccharide-induced p65 nuclear translocation and IκBα, MAPK, and PI3K phosphorylation in cells.[33,59] NF-κB and MAPK signalling pathways have been identified as the main targets of anti-inflammatory action of arctigenin in several in vivo inflammation models.[40–61] (Table 2).

**Anti-colitis effect**

Arctigenin ameliorated inflammation in ulcerative colitis by inhibiting the PI3K/Akt pathway and polarising the M1-type macrophages to produce M2-like macrophages both in vitro and in vivo,[33] and it is the main active ingredient that reduced the dextran sodium sulfate-induced inflammatory response in mouse colon.[64] It has also shown protective effects in a rat gastric ulcer model.[65] Table 3 summarises several in vivo studies that evaluated anti-colitis action of arctigenin.

**Table 3.** Summary of in vivo studies on the anti-colitis activity of arctigenin.

| Model                        | In vivo studies | Potential molecular mechanisms | Ref. |
|------------------------------|----------------|-------------------------------|------|
| DSS induction                | 50 mg/kg, DA1, MPO, IL-6, TNF-α, MIP-2, MCP-1, MadCAM-1, ICAM-1, VCAM-1, E-selectin, MDA, SOD, GSH | phosphorylation of p38 MAPK, ERK, JNK, IκBα and p65 | [66] |
| the differentiation of Th1 cells, IFN-γ, IL-17A, IL-17F, IL-21, IL-22, Th1, Th17 | 30 and 60 mg/kg, TNF-α, IL-1β, IL-6, CXCL10, TGF-β1, IL-4 | phosphorylation of genes p70S6K and Akt | [67] |

1 Reduce, inhibition or down-regulated.
2 Increase or up-regulated.

**Antiviral effect**

An in vivo study investigated anti-human immunodeficiency virus (HIV-1) activity of arctigenin and found that arctigenin can inhibit the viral response of HIV-1-infected human cell lines.[67] Arctigenin generally acts in the integration stage and has an inhibitory effect on integration of proviral DNA into its own cells. Moreover, arctigenin significantly inhibited the expression of HIV-1 virus in vitro, particularly via expression of the anti-HIV core protein P17 and the anti-HIV matrix protein P24.[68]

Hayashi et al.[69] demonstrated through in vitro experiments that arctigenin has the ability to interfere with the early replication of influenza A virus and has an inhibitory effect on the release of progeny viruses. The study also showed that arctigenin did not increase the drug resistance of the virus, while the control drug oseltamivir induced drug resistance, reducing the therapeutic efficacy of the anti-viral drug to 50%. This finding revealed the huge potential of this molecule and had a profound impact on the development of new drugs using arctigenin. The antiviral activity of arctigenin on porcine circovirus type 2 (PCV2) was found similar to that of ribavirin. Therefore, arctigenin may also protect against PCV2 infection.[70] Arctigenin also showed antiviral activity in EPC cells against SCVC, a fish rhabdovirus.[71]

**Vascular protective effect**

Arctigenin can upregulate the three proteins ABCA1, ABCG1, and apoE, which promote THP-1 macrophages through activation of the PPARγ and liver X receptor α (PPAR-γ/LXR-α) signalling
pathways, promoting cholesterol efflux. This is an important mechanism that prevents the occurrence of atherosclerosis. The PI3K/Akt signalling pathway can also induce endothelial nitric oxide synthase (NOS) and inhibit the cerebral vasospasm caused by subarachnoid haemorrhage in rats.

Protection against memory problems and brain damage

Arctigenin has been used as a neuroprotective agent for the treatment of epidemic encephalitis B by inhibiting glutamate transmission and reducing the induced field response. The results of studies indicate that in addition to its effect on super-excited neurons under physiological conditions, arctigenin can cross the blood-brain barrier and interact with acid-sensitive ionotropic glutamate receptors in the brain. These results suggest that arctigenin is a potentially useful new pharmacological method that can inhibit the glutamate-induced response of the central nervous system in vivo; that is, it can reduce the response of somatosensory cortical neurons. Arctigenin has also been shown to effectively improve memory impairment by eliminating target amyloid in AD mouse models. Arctigenin can treat brain injury that occurs after needle insertion by anti-inflammatory and anti-apoptotic mechanisms, can protect rats with focal cerebral ischaemia reperfusion by inhibiting neuroinflammation, and can regulate the PI3K/Akt signalling pathway by increasing the expression of the haem oxygenase-1 gene in rat primary astrocytes.

Hepatoprotective effect

The proliferation of hepatic stellate cells (HSC) is an important factor in the process of fibrotic liver injury. Through G0/G1 cell cycle arrest, arctigenin has been found to induce continuous p27Kip1 induction by interfering with the PI3K/Akt/FOXO3a signalling pathway, inhibiting the proliferation of activated hepatic stellate cells.

Anti-insect activity

A study conducted in 2009 found that arctigenin isolated from the traditional Chinese medicine burdock by the activity tracking method has anti-insect activity and can kill the medium-sized finger ringworm (Dactylogyrus intermedius) in fish. The median effective concentration was 0.62 mg/L (EC50) after 48 h, which was significantly lower than that of the control drug mebendazole (1.25 mg/L). The study also showed that arctigenin has anthelmintic activity against the third generation of Kobayashi, a fish parasite. A study has shown that 4.00 mg/L arctigenin can kill 100% of the third-generation insects infecting goldfish in 4 h in vivo, with EC50 values of 1.85 mg/L and 1.58 mg/L after 24 h and 48 h, respectively. Another study found that a crude extract of burdock fruit has schistosomiasis-killing activity, with arctigenin as the main active ingredient that was believed to be responsible for the activity.

Other pharmacological effects

Studies have shown that the binding effect of platelet-activating factor can also be inhibited by lignan, the main component of burdock seed. It is believed that the main active ingredient that inhibits platelet aggregation is arctigenin, suggesting it as an effective drug against platelet activating factor.

Zhao et al. found that the peroxidation of liposomes and apoptosis of cardiomyocytes can be inhibited by arctigenin, along with the elimination of free radicals associated with cardiomyocytes.

Arctigenin has also been found to act as an oestrogen receptor β selective agonist that limits mTORC1 activation and subsequent Th17 cell differentiation. As a potential anti-arrhythmic lead compound, arctigenin also inhibits arrhythmia resulting from aconitine through regulation of multiple ion channels, and relieves endoplasmic reticulum stress by activating the adenosine monophosphate-activated protein kinase (AMPK), thereby preventing and treating various diseases. It has also been shown to improve the swimming endurance of sedentary rats by regulating the antioxidant pathways.

Arctigenin and (−)-pinoresinol are human thyroid hormone receptor β antagonists, and arctigenin has an inhibitory effect on melanin synthesis by tyrosinase. Arctigenin is a new inhibitor of heat shock response in mammalian cells. It exhibited a neuro-protective effect by upregulating the expression of mouse primary neurons P-CREB and human SH-SY5Y neuroblastoma cells.

Yang et al. found that arctigenin regulates the cardiovascular system by inhibiting the influx of calcium ions and the release of internal calcium, thereby exhibiting a relaxing effect on isolated guinea pig trachea and pulmonary artery, and rat trachea and thoracic aorta. In addition, cell-level studies have found that 3 μM arctigenin can significantly promote the uptake of glucose by the L6 skeletal muscle cells, thereby exhibiting anti-diabetic activity. Ishihara et al. found that arctigenin hinders the production of heat shock response proteins, resulting in cells with little heat resistance, thereby regulating the heat shock response.

Pharmacological effects of arctigenin in combination with other drugs

Combining arctigenin with the glucose analog 2-deoxyglucose has been found more conducive in killing tumour cells and has few toxic side effects. The combination of arctigenin with green tea polyphenols and curcumin has also been shown to enhance the preventive effect on prostate cancer and breast cancer cells. Combining it with quercetin resulted in synergistic increase in anti-proliferative effect against prostate cancer cells.

Total synthesis of arctigenin and its analogues

The natural product arctigenin possesses good biological activity and acts as a lead compound. The main laboratory methods that have been utilised for the production of arctigenin are silica gel column chromatography purification, organic reagent extraction, centrifugal partition chromatography, and chemical combination. However, all these methods have shortcomings such as low extraction efficiency, cumbersome steps, and necessity of laboratory equipments. The low content of active ingredients in herbal medicines and reliance on isolated extraction to obtain sufficient amounts of compounds not only renders production costly, but also leads to a series of problems related to sustainable use of natural medicinal resources and environmental sustainability. Therefore, artificial synthesis of natural products with excellent activity is an important means to solve the above problems. Current studies have shown that the technology for the total synthesis of arctigenin is readily available.
Synthesis of (−)-arctigenin and its enantiomer

A new method for the asymmetric synthesis of (−)-arctigenin is shown in Figure 3. Using 3,4-dimethoxyphenylpropionic acid (23) as the starting material and the chiral prosthetic group 4-benzoyloxazolidine ketone (24), which was condensed to obtain compound 25, and then using a large hindered organic base, sodium bis(trimethylsilyl) amide (NaHMDS), a carbonyl α-alkylation reaction was performed to obtain compound 26, which was then reduced to eliminate the chiral auxiliary to obtain alcohol 27. The ester exchange reactions that were catalysed by p-toluenesulfonic acid produced butyrolactones 28a and 28b with ee values of 98% and 96%, respectively; this was followed by introduction of the derivatized benzyl group at the α-position of the ester carbonyl group of 8 using the large-site resistive organic base lithium diisopropylamine (LDA) to obtain 29a/29b (de > 99%), and finally Pd/C-catalysed hydrogenolysis was carried out to remove 58% and 55% of the phenolic hydroxyl protecting group, respectively, via six steps. The total yield of 97% and ee value of 96% were obtained for both (−)-arctigenin and (+)-arctigenin.

Enantioselective synthesis: (−)-Arctigenin, and (−)-isoarctigenin (35)

A new method involving highly regioselective and stereoselective addition of radicals to asymmetric fumarates was reported by Sibi et al. to exploit the synthesis of lignin natural products from common intermediates (Figure 4). Compound 30 was used as the starting material. The reaction was completed by adding benzyl 30 to CH₂Cl₂/THF in the presence of Sm(OTf)₃ at −78 °C to obtain product 31. The required natural product was finalised by adding a second benzyl chloride solution. Consequently, 3-methoxybenzyl bromide was added after treating 31 with an equivalent amount of NaHMDS (1:1) at −78 °C for 1.25 h to give intermediate product 32, which was then cleaved effortlessly to obtain excellent yield of the key intermediate 33 using LiOH/H₂O₂/THF. The conversion of 33 to 34 consists of selective carboxyl reduction and lactonization. Reduction via debenzylation produced (−)-isoarctigenin (35). The reduction of compound 31 to 29a (76% in two steps) was achieved by alkylation with 3,4-dimethoxybenzyl iodide (64%). Debenzylation was then utilised to produce (−)-arctigenin.

Figure 3. A new method for asymmetric synthesis of arctigenin.
Highly enantioselective total synthesis of natural Lignan lactones

Bode et al.\textsuperscript{105} pointed out that it is necessary to develop a catalytic method for domain and enantiomer control that can be applied to the total synthesis of natural lignans such as arctigenin. The synthesis of (–)-arctigenin can thus be achieved via a nine-step reaction using 3,4-dimethoxycinnamic acid (36) (Figure 5). The reaction involved reducing 3,4-dimethoxycinnamic acid to hydroxyl with lithium aluminium hydride to obtain 3,4-dimethoxyphenylpropanol 37, and the corresponding diazoacetate 38 was obtained by one-pot method. The key lactone intermediate 28a was thus prepared using catalyst 39 at 94% ee in 62% isolated yield. Compound 28a was alkylated with 4-(benzyloxy)-3-methoxybenzyl bromide and prepared from 4-hydroxy-3-methoxybenzyl alcohol via two steps to give disubstituted γ-lactone 29a. Hydrogenolysis of the benzyl group was then conducted to give (–)-arctigenin with an optical purity of 94%.

Synthesis of four stereoisomers of arctigenin

(4R, 5R)-(–)-trans-arctigenin\textsuperscript{106} is a butyrolactone-type lignan with two chiral centres; it has a wide range of biological activities. Anti-aggregation activity of (4S, 5S)-(–)-trans-arctigenin\textsuperscript{107} and cAMP phosphodiesterase inhibitory activity of cis-arctigenin\textsuperscript{108} have been reported. However, no studies comparing the biological activities of all stereoisomers to elucidate the stereochemical effects of the two chiral carbons have been carried out. Yamauchi et al.\textsuperscript{109} synthesised four stereoisomers of arctigenin and prepared derivatives with various substituents on the aromatic ring, and then proved the biological activities of these derivatives.

Arkigenin exhibits stereospecific cytotoxicity against insect cells. One of the stereoisomers of arctigenin, (4R, 5R)-trans-arctigenin, shows stereospecific cytotoxicity against insect cells, SF9, and NIAS-AeAl-2 cells. Yamauchi et al.\textsuperscript{109} synthesised the arctigenin derivatives 40–103 (Figure 8) and found that compounds 63, 64, and 71 are at the same level as (4R, 5R)-trans-arctigenin. Examination of the thionine derivatives indicated that compounds 101 and 142 have similar activity levels to that of (4R, 5R)-trans-arctigenin, which was found to increase the expression of the 28S rRNA gene in the ribosomes of SF9 cells, however, DNA degradation was not observed.

Synthesis of (–)-arctigenin derivatives ent-41–43, ent-44–46, ent-66, ent-68, 104–115

Type 2 diabetes is a metabolic disorder that is characterised by high glucose levels, insulin resistance, and impaired insulin secretion\textsuperscript{110}. Several studies have shown that reduced glucose uptake by skeletal muscle leads to type 2 diabetes and associated metabolic syndrome\textsuperscript{111–113}. Therefore, therapies that regulate glucose uptake are promising strategies for the treatment of metabolic disorders\textsuperscript{95}.

Duan et al. prepared analogs of the natural product (as activators of AMPK) arctigenin (ent-41–43, ent-44–46, ent-66, ent-68, 104–115) to evaluate their effects on 2-deoxyglucose uptake in L6 myotubes and their possible use in ameliorating metabolic disorders (Figure 9). Racemic (–)-arctigenin was found to display enhanced uptake similar to that of (–)-arctigenin. The results...
Figure 5. Synthesis of arctigenin from compound 3,4-dimethoxycinnamic acid.

Figure 6. Synthesis of (4S, 5S)-trans-arctigenin and (4R, 5R)-trans-arctigenin.
suggest that the substitution of the para-hydroxyl group on the benzene ring of the C2 benzyl portion of the arctigenin skeleton by chlorine produces a substance 107, which exhibits excellent uptake activity and helps in avoiding possible metabolic problems. Compound 107 stimulated glucose uptake and fatty acid oxidation via AMPK activation in vitro. The chronic administration of 107 has been shown to reduce blood glucose levels and improve lipid metabolism in ob/ob mice.114

### Structural modification of arctigenin

Arctigenin has excellent biological activity and therefore potential for further development as a lead compound. As the pharmacological effects of arctigenin have been confirmed, the structural modification of arctigenin has become increasingly popular. The shortcomings of arctigenin include insufficient activity, poor solubility, and low bioavailability. The structural modification of arctigenin is performed mainly to improve its biological activity, solubility, and metabolic ability so as to obtain new derivatives with greater developmental value. The following studies introduce the theoretical research based on the structural modification of arctigenin.

### Synthesis of pyrimidine derivatives of arctigenin

A series of pyrimidine derivatives of arctigenin were designed and synthesised by Wang et al.103. The key intermediates that were required to replace 2-chloropyrimidine have been synthesised by multiple synthetic routes, and arctigenin derivatives (116–126) have been synthesised by linking arctigenin with these intermediates via ether bonds (Figure 10).

### Arctigenin and its analogues are oxidised with PIFA

Phenyliodine(III) bis(trifluoroacetate) (PIFA) reacts with the phenols in methanol to produce cyclohexadienone and quinone ketal, which are valuable intermediates in organic synthesis.115–116 The oxidation of phenol in less nucleophilic solvents such as acetonitrile or trifluoroethanol (TFE) allows intramolecular reactions that lead to cyclization.117–118 The most promising approach is the realisation of carbon-carbon bond formation.119 Ward attempted to use this reaction to simulate the oxidation-induced cyclisation involved in the biosynthesis of various lignans and the synthesis of several compounds.120

3,4-Dimethoxybenzaldehyde bis(phenylthio)acetal (127) was lithiated, followed by the addition of butenolactone and the subsequent capture of the enolates with the corresponding benzyl bromide to give compound 128 with a 55% yield. After debenzylation, arctigenin was obtained at a yield of 68% to produce hydroxyl derivative 129 with a 20% yield (Figure 11).

Arctigenin was also treated with PIFA (1.2 equiv.) in TFE for 24 h to obtain a mixture of products from which two major fractions were isolated; 130 with a yield of 13% and a combination of 131 and 132, with an overall yield of 14%.

### Synthesis of N-acyl sulfamate from arctigenin

Zhang et al.121 reported an efficient and simple method for the synthesis of N-acylaminosulfonates from fluorosulfonates and potassium trimethylsiloxyamine as amide precursors. This method produced a wide range of substrates under mild and base-free reaction conditions and short reaction times, with high to excellent yields. Zhang et al. applied this method to arctigenin (Figure 12) by reacting the phenolic hydroxyl group with sulphuryl fluoride (SO₂F₂) in anhydrous N,N-dimethylformamide (DMF) in the
presence of triethylamine for 3 h to produce the corresponding fluorosulfate 133, which was then reacted with trimethylsilylimide in DMF for 20 min at room temperature to obtain N-acyl sulfamate 134 (75%).

Figure 8. Syntheses of 7-aryl-3',4'-dimethoxy derivatives 40–99 and ent-43, 46, 49, 50, 64, 71, and thionolactones 100–103.

Synthesis of 3,4-dibenzyltetrahydrofuran skeleton

Ward and Eich et al.122–123 synthesised a series of trans-3,4-dibenzy1tetrahydrofurans using ruthenium tetrafluoroacetate (trifluoroacetic acid) via oxidative cyclisation to obtain high yields of
dibenzo[cd]cyclooctadiene lignans of the isostane series. To construct the 3,4-dibenzyltetrahydrofuran skeletal structure, arctigenin was first reduced to 1,4-dibenzylbutanediol and then dehydrated to give compound (Figure 12).

Oxidative cyclisation of 2,3-dibenzylbutyrolactones using ruthenium tetra(trifluoroacetate)

Ward et al.124 used a series of cis- and trans-2,3-dibenzylbutyrolactones, which were oxidatively cycled using tetrakis (trifluoroacetic acid) ruthenium to give dibenzo[cd]cyclooctadiene lactones.

Arctigenin was treated with tetrakis(acetic acid-acetic acid) ruthenium, which was obtained from two equivalents of RuO₂•2H₂O in a TFA-TFAA mixture containing traces of BF₃•Et₂O. The mixture was stirred at room temperature for 24 h to give a single product (137) with an 80% yield (Figure 12).

Anti-tumour activity of arctigenin derivatives

Synthesis of (−)-arctigenin derivatives 138−147 by Cai et al

Cai et al.125−126 synthesised amino acid derivatives by reacting five amino acids with arctigenin using tert-butoxycarbonyl as a protecting group (Figure 13). The results showed that amino acid derivatives without protecting groups had better water solubility and nitrite scavenging ability than those with protecting groups. The ability of the derivatives to scavenge nitrite was significantly higher than that of arctigenin. Based on these results, 138, 141, 145 and 147 were selected at a dose of 40 mg/kg to evaluate their antitumor activity, and these compounds showed inhibition rates of 55.87%, 51.40%, 69.27%, and 43.58%, respectively. The results indicate that the compounds 138, 141, 145 and 147 have strong antitumor activity both in vitro and in vivo, and can improve the immune response of tumour-bearing mice.

Compound 145 treats myelosuppression

Cai et al.125−126 used chemical methods to modify the structure of arctigenin and synthesise a series of arctigenin amino acid ester derivatives. The dissolution and in vitro and in vivo pharmacological activities of arctigenin valine ester (145) were investigated. The compound has a simple process of synthesis, high yield, strong water solubility, significantly enhanced pharmacological activity, and significantly improved oral bioavailability, and is metabolised by the body to act as a technical drug. Han et al.127 therefore speculated that 145 can be used as a drug candidate for the treatment of the myelosuppression caused by chemotherapy. After taking 145, the peripheral blood cells of mice were observed to gradually return to normal, the number of bone marrow nucleated cells increased, the thymus index increased, the spleen index decreased, the number of haematopoietic progenitor cells increased, and the number of haematopoietic cytokines...
Figure 10. Synthesis of pyrimidine derivatives of arctigenin (116–126).

Figure 11. Arcigenin is treated with PIFA.
Compound 145 promoted the transformation of myelosuppressive cells from G0/G1 to S phase and from S to G2/M phase. Compound 145 can upregulate the expression of MEK and p-ERK, low-dose 145 was not as effective as high-dose in all aspects. In summary, 145 can effectively relieve the myelosuppression caused by the intraperitoneal injection of CTX 100 mg/kg, can promote the proliferation and differentiation of haematopoietic progenitor cells, and can improve immunity.

In the early stage, Han et al. 127 modified the structure of arctigenin and synthesised a series of amino acid ester derivatives of arctigenin. The solubility, in vitro and in vivo pharmacological activities of arctigenin were investigated, and arctigenin valine ester was screened. Arctigenin valine ester has the advantages of simple process, high yield, strong water solubility, significantly enhanced pharmacological activity and significantly improved oral bioavailability; And metabolise in the body to play the role of technical drugs.

**Synthesis of (-)-arctigenin derivatives 148–153 by Chen et al**

Chen et al. 128 reacted arctigenin with carboxylic acids (crotonic acid, furoic acid, 2-naphthoic acid, and indole-3-acetic acid), EDCI, and DMAP in dichloromethane under reflux at 60 °C to obtain six new monoester derivatives (148–153) (Figure 14). The properties of these derivatives were investigated using in vitro nitrite scavenging assay. The in vivo antitumor activity of the β-indole acetate...
Solid tumours are generally associated with hypoxia, glucose starvation, and malnutrition due to insufficient vascular supply and/or the excessive demand of rapidly proliferating cells. Glucose starvation has been shown to increase the invasive and metastatic potential of tumour cells, which is the main cause of cancer-related deaths. In recent years, tumour cells have been reported to have the intrinsic ability to reduce the apoptotic potential by regulating their energy metabolism. Therefore, selective targeting of tumour cells by inhibiting cellular energy metabolism under glucose starvation is an alternative strategy for antitumor therapy with minimal toxicity to normal tissues.

Arctigenin has been reported to exhibit antitumor effect in various xenograft models. Awale et al. reported that arctigenin is preferentially cytotoxic to cancer cells under conditions of glucose starvation. Arctigenin has been shown to inhibit mitochondrial respiration under such conditions, leading to intracellular ATP depletion and ROS production, resulting in cell death. Kudou et al. described the synthesis of arctigenin derivatives with variable modified O-alkyl groups and assessed their preferential cytotoxicity under glucose starvation; they revealed that the 4-hydroxy group of arctigenin is important for preferential cytotoxicity.

Owing to the important role of arctigenin 4-hydroxyl, Lei et al. designed and synthesised a series of 4-amino-4-dehydroxyylan derivatives and evaluated their cytotoxicity against human A549 tumour cell line under sugar-deficient conditions. The results showed that 4-amino-4-dehydroxyylan was more cytotoxic than arctigenin and that addition of further substituents to the 4-amino group led to a significant decrease in cytotoxicity. Compound 156 showed the strongest cytotoxicity against A549 cell line, with an IC50 value of 2.85 µM, which is 2.3-fold that of arctigenin.

Antiviral and antiparasitic activity

(-)-Arctigenin derivatives 173–208

The spring viremia of carp virus (SVCV) belonging to the genus Vesiculovirus in the family Rhabdoviridae is a bullet-shaped RNA virus that causes high mortality in common carp (Cyprinus carpio) and other fishes in the family Cyprinidae. This virus also infects other fish such as Piscivora, catfish, snapper, salmon, and barb. The extensive study of arctigenin that results from its broad range of biological activities led to recognition of its antiviral activity against SVCV in endothelial progenitor cells. Further experiments showed that compounds 189 and 196 significantly inhibited the production of SVCV-infected Cyprinidae epithelioma cells, and compounds 189 and 196 showed IC50 values of 0.077 and 0.095 µg/mL, respectively. Further experiments showed that compounds 189 and 196 significantly reduced SVCV-induced apoptosis and had a protective effect on cell morphology 48 and 72 h post infection. In addition, 189 and 196 significantly inhibited the production of SVCV-infected reactive oxygen species, which was clearly observed in SVCV-infected cells. Based on these findings, 189 and 196 show promising application in the treatment of SVCV infection.

Dactylogyrus intermedius is a common ectoparasite that parasitises the gills of freshwater fish and represents the largest group of postnatal fish parasites. The parasite has a direct life cycle without an intermediate host and releases its eggs into the water to hatch, which then attach to the gills of the fish host.

To control the parasitism of D. intermedius, Hu et al. designed, synthesised, and tested a new series of arctigenin derivatives. The anthelmintic activity of most derivatives was shown in the range 1–10 mg/L. Compared to the conventional drug praziquantel (EC50 = 2.69 mg/L), the ether derivatives showed slightly higher antiparasitic activity with EC50 values of 2.48 and 1.52 mg/L, respectively. In addition, the arctigenin-imidazole hybrids were also effective in removing intermediate entomopathogenic nematodes, with EC50 values of 2.13 and 2.07 mg/L, respectively. Structure-activity relationship analysis showed that the four-carbon linker and imidazole substituents can significantly improve the insect repellent activity and reduce the toxicity of the molecule. The above results indicate that 194 and 197 are considered to be promising lead compounds to prevent and control D. intermedius infection.

Figure 14. Synthesis of compounds 148–153.
Infectious haematopoietic necrosis virus (IHNV) is one of the three emerging viruses listed by the World Organisation for Animal Health (OIE), which is causing serious losses in the aquaculture industry\(^{145}\). As a species pathogen that causes infectious haematopoietic organ necrosis (IHN), IHNV is highly pathogenic and widely transmissible, resulting in high mortality rates of 80–100% in salmonid species\(^{146}\). Therefore, there is an urgent need to develop an effective antiviral strategy to treat highly lethal IHNV. Studies have shown that arctigenin reduced the
replication of carp virus (another fish elasmobranch virus) in spring viremia by 65\%\textsuperscript{71}.

The results of a previous study in which a series of arctigenin derivatives (191–199 and 209–227) were synthesised to evaluate their antiviral activity against IHNV (Figure 18)\textsuperscript{147} indicated that the linker length and imidazole substituents play an important role in reducing IHNV replication. In this study, the arctigenin-imidazole hybrid derivative 217, with a linker length of 8 carbons, reduced the replication of IHNV with an IC\textsubscript{50} value of 1.3 \(\mu\text{M}\). In addition, derivative 217 significantly inhibited IHNV-induced apoptosis and cell morphological damage. Mechanistically, the derivative 217 could not directly destroy viral particles. The addition time and virus binding assay revealed that the derivative 217 mainly affected the early replication of IHNV but did not interfere with the adsorption of IHNV. The derivative 217 can therefore be considered a promising drug for the treatment of IHNV.

\textbf{Zhang et al.}\textsuperscript{150} designed and synthesised four new series of arctigenin derivatives (229–238 and 240–261) and evaluated their antiviral activity against IHNV.

\textbf{Toxoplasmosis} is a global parasitic disease and is caused by the specialised intracellular parasite \textit{Toxoplasma gondii}, which infects approximately one-third of the world's population\textsuperscript{148}. The traditional treatments for toxoplasmosis include ethidiazine, sulfadiazine, spiramycin, and atovaquone. Clinically, etanercept and sulfadiazine have shown significant anthelmintic effects, but the combination of the two drugs can cause serious adverse effects such as hypersensitivity reactions, bone marrow suppression, intolerance, and an increased risk of liver and renal complications\textsuperscript{149}. To date, there is no ideal drug that can completely eradicate all forms of \textit{Toxoplasma gondii}. Therefore, there is an urgent need to develop highly effective and less toxic tolerable drugs for the treatment of this parasitic infection.

\textbf{Zhang et al.}\textsuperscript{150} designed and synthesised four new series of arctigenin derivatives (229–238 and 240–261) and evaluated their antiviral activity against IHNV.
anti-Toxoplasma gondii activity both in vitro and in vivo (Figure 19). Among the synthesised compounds, compound 243 exhibited the strongest anti-Toxoplasma activity and the lowest cytotoxicity (Toxoplasma gondii IC₅₀: 17.1 µM; IC₅₀: ≥600.0 µM in HeLa cells; selectivity: 35.09), which was higher than that of both arctigenin (Toxoplasma gondii IC₅₀: 586.4 µM; IC₅₀: 572.7 µM in HeLa cells; selectivity: 0.98) and the positive control drug spiramycin (Toxoplasma gondii IC₅₀: 262.2 µM; IC₅₀: 189.0 µM in HeLa cells; selectivity: 0.72) for clinical application in vitro. In addition, compound 256 showed superior inhibition of Toxoplasma gondii in vivo to spiramycin. Compounds 243 not only significantly reduced the number of tachyzoites in the peritoneal cavity of mice, but also resulted in their...
partial malformation in vivo ($p < 0.05$). Compounds 243 therefore have the potential to be used as antiparasitic drugs and are valuable for further development.

**(-)-Arctigenin derivatives 149, 262–320**

AMPK, which is a heterotrimeric serine/threonine protein kinase, plays a crucial role in the regulation of systemic energy homeostasis. As a cellular energy sensor, AMPK activation stimulates glucose uptake and fat oxidation while inhibiting adipogenesis and gluconeogenesis. AMPK is therefore considered a potential therapeutic target for the treatment of obesity and type 2 diabetes. Sida Shen et al. designed and synthesised a series of new arctigenin and 9-deoxy arctigenin derivatives (149, 262–320) with different esters and ether side chains at the phenolic hydroxyl position and evaluated their ability to...
activate AMPK effects in L6 myogenic cells. Preliminary biological evaluation showed that some alkyl ester and phenyl ether arctigenin derivatives showed potential activity in improving AMPK phosphorylation. Further conformational analysis showed that arctigenin derivatives 262, 269, 309, 311, and 312 had superior ability to arctigenin regarding activation of AMPK (Figure 20). Arctigenin derivative 311 was identified as a promising lead compound exhibiting superior activity in AMPK activation.

**Conclusion**

Natural products are a valuable source of bioactive molecules for drug discovery. *Arctium lappa L.* is a kind of Chinese herbal medicine, which has stable pharmacological effects in dispelling wind and heat, detoxification and swelling, and sore throat. Based on in-depth research on *Arctium lappa L.*, its components were isolated, and arctigenin was reported to be an important component.

Since the discovery of arctigenin, it has often been used as a lead compound for drug development because of its novel structure, strong pharmacological activity, and great developmental potential, with an increasing number of studies investigating the molecule. However, there are still some problems and new directions for future development in moving arctigenin to a viable therapeutic approach:

i. Although arctigenin have received great attention in the past decade, their exact molecular mechanisms in the treatment of cancer and other diseases remain to be elucidated. The current research results show that the curative effect of...
artigenin is not very significant, and it is difficult to apply in clinical practice. We hope that follow-up studies will map the complete signalling network associated with artigenin to facilitate future new drug research for potential clinical indications.

ii. There are few pharmacological experimental studies on artigenin and its derivatives, and the activities are mainly concentrated in anti-tumour and anti-parasitic activities, and there are few reports in other fields of activity. Moreover, the pharmacological activities of these compounds are mainly concentrated in in vitro experiments, and relatively few in vivo experiments. In addition, many synthetic derivatives have not been studied for activity, which is a pity.

iii. Pharmacological research on artigenin and its derivatives preliminarily revealed the development value of artigenin and its derivatives. In the field of anti-tumour research and development, compounds 145, 153 and 156 (Figure 21) are the most representative in anti-tumour activity, all exceeding artigenin. Compound 145 has high yield, strong water solubility, significantly enhanced antitumor activity, and significantly improved oral bioavailability. The inhibition rate was 69.27% at 40 mg/kg. And metabolise in the body to play the role of technical drugs. Compound 145 was developed for artigenin derivatives with high efficiency, water solubility and high bioavailability provide a new strategy.

iv. In the field of antiparasitics, mainly including SVCV, D. intermedius, IHNV and Toxoplasma gondii, artigenin derivatives all showed strong activity, and compounds 189, 194, 196, 197, 217 and 243 were the most representative. For anti-SVCV activity, the IC50 values of compounds 189 and 196 were 0.077 and 0.095 mg/mL, respectively. The anti-D. intermedius activity of compounds 194 and 197, with EC50 values of 2.13 and 2.07 mg/L, respectively. Compound 217 reduces IHNV replication with an IC50 of 1.3 µM. Compound 243 exhibited the strongest anti-Toxoplasma gondii activity and the lowest cytotoxicity (Toxoplasma gondii IC50: 17.1 µM; IC50: >600.0 µM in HeLa cells; selectivity: 35.09).

v. Novel drug delivery systems are effective strategies to improve the water solubility, absorption, distribution, metabolism, excretion (ADME) and toxicity of many drugs. The study of artigenin combined with a new drug delivery system has not been reported yet. The development of novel drug delivery formulations including nanosuspensions, micelles, nanoparticles and nanogels will improve the efficacy, water solubility, bioavailability and targeting properties of artigenin.

vi. In most of the above studies, the reported modifications were limited to the hydroxyl groups of artigenin, and the modifications at the remaining sites were rarely reported. Therefore, future work should be devoted to investigating modifications at other sites. Many natural products are biologically active while providing opportunities for drug discovery in different therapeutic areas. Artigenin is known to have anti-tumour, anti-inflammatory, anti-leukemia, anti-colic, anti-virus, vascular protection, hepatoprotective and anti-parasitic biological activities. However, the research on artigenin derivatives has only focussed on the antitumor and antiparasitic fields. We hope that researchers can explore other pharmacological activities of artigenin and its derivatives.

vii. The development of artigenin-based drug combinations may be a useful strategy, such as combining artigenin with other anticancer drugs to obtain high anticancer activity, thereby overcoming the insufficient antitumor activity of artigenin limits.

We believe artigenin provides a natural product platform for drug development for the treatment of cancer and parasitic diseases. So far, this platform provides a good basis for the development of new derivatives that are more potent and more water-soluble than the natural product artigenin. Artigenin derivatives may be potential drugs for clinical treatment of human diseases.

Acknowledgements

The authors gratefully acknowledge the National Natural Science Foundation of China.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was supported by the National Natural Science Foundation of China [No.81960626, 82160741, 82160666, 82060628], Doctoral Research Start-up Fundation of Yanbian University [No. ydbq202215] and Jilin Provincial Education Department of China [JJKH 20191156KJ].

References

1. Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discovery 2015;14:111–29.
2. Chen HJ, Gao Y, Wang AL, et al. Evolution in medicinal chemistry of ursolic acid derivatives as anticancer agents. Eur J Med Chem 2015;92:648–55.
3. Chen HJ, Gao Y, Wu JL, et al. Exploring therapeutic potentials of baicalin and its aglycone baicalein for hematological malignancies. Cancer Letters 2014;354:6–11.
4. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod 2020;83:770–803.
5. Vesaghhamedani S, Ebrahimzadeh F, Najafi E, et al. Xanthohumol: an underestimated, while potent and promising chemotherapeutic agent in cancer treatment. Prog Biophys Mol Biol 2022;172:3–14.
6. Gowhari Shabgah A, Hejri Zarifi S, Mazloumi Kiapey SS, et al. Curcumin and cancer; are long non-coding RNAs missing link. Prog Biophys Mol Biol 2021;164:63–71.
7. Batool A, Miana GA, Alam M, et al. Bioassay-guided fractionation and isolation of Arctigenin from Saussurea heteromalla for in vitro and in silico cytotoxic activity against HeLa cells. Physiol Mol Plant Pathol 2022;117:101749.
8. Ferracane R, Graziani G, Gallo M, et al. Metabolic profile of the bioactive compounds of burdock (Arctium lappa) seeds, roots and leaves. J Pharm Biomed Anal 2010;51:399–404.
9. Ichikawa K, Kinoshiba T, Nishibe S, et al. The Ca2+ antagonist activity of lignans. Chem Pharm Bull 1986;34:3514–7.
10. Su S, Wink M. Natural lignans from Arctium lappa as antiaging agents in Caenorhabditis elegans. Phytochemistry 2015; 117:340–50.
11. Yong M, Kun G, Qiu MH. A new lignan from the seeds of Arctium lappa. J Asian Nat Prod Res 2007;9:541–4.
12. Wang HY, Yang JS. Studies on the chemical constituents of Arctium lappa L. Yao Xue Xue Bao 1993;28:911–7.
13. Suzuki S, Umezawa T, Shimada M. Stereocchemical difference in secosteroliciresinol formation between cell-free extracts from petioles and from ripening seeds of Arctium lappa L. Biosci Biotechnol Biochem 1998;62:1468–70.
14. Ichihara A, Oda K, Numata Y, et al. New sesquilignans from Arctium lappa L. The structure of lappao C, D and E. Agric Biol Chem 1977;41:1813–4.
15. Iochkova I, Mladenova K, Zakharieva E. Triterpene alcohols and diolignans from Arctium lappa L. Lappa. Chem Lett 1972;1:235–8.
16. Park SY, Hong SS, Han XH, et al. Lignans from Arctium lappa L. Lappa. Chem Lett 1995;6:217–20.
17. Yang YN, Zhang F, Feng ZM, et al. Two new neolignan glycosides from Arctii Fructus. J Asian Nat Prod Res 2012;14:981–5.
18. Zhao CX, Zeng YX, Wan MZ, et al. Comparative analysis of essential oils from eight herbal medicines with pungent flavor and cool nature by GC-MS and chemometric resolution methods. J Sep Sci 2009;32:660–70.
19. Han BH, Kang YH, Yang HO, et al. A butyrocolactone lignan dimer from Arctium lappa. Phytochemistry 1994;37:1161–3.
20. Wang HY, Yang JS. Neoarctin A and B, novel lignans from Arctium lappa L. Tetrahedron Lett 1976;17:3961–4.
21. Tezuka Y, Yamamoto K, Awale S, et al. Anti-austere activity of phenolic constituents of seeds of Arctium lappa. Nat Prod Commun 2013;8:463–6.
22. Park SY, Hong SS, Han XH, et al. Lignans from Arctium lappa and their inhibition of LPS-induced nitric oxide production. Chem Pharm Bull 2007;55:150–2.
23. Ichihara A, Numata Y, Kanai S, et al. New sesquilignans from Arctium lappa L. The structure of lappao C, D and E. Agric Biol Chem 1977;41:1813–4.
24. Ichihara A, Kanai S, Nakamura Y, et al. Structures of lappao F and H, dilignans from Arctium lappa L. Tetrahedron Lett 1978;19:3035–8.
25. Naoe A, Tsuchiya T, Kondo Y, et al. Biosci Biotechnol Biochem 1998;62:1468–70.
26. Liu H, Zhang Y, Sun Y, et al. Determination of the major constituents in fruit of Arctium lappa L. by matrix solid-phase dispersion extraction coupled with HPLC separation and fluorescence detection. J Chromatogr B 2010;878:2707–11.
27. Hirose M, Yamaguchi T, Lin C, et al. Effects of arctiiin-induced mammary, colon and pancreatic carcinogenesis in female Sprague-Dawley rats and MelQx-induced hepatocarcinogenesis in male F344 rats. Cancer Lett 2000;155:79–88.
48. Susanti S, Iwasaki H, Inafuku M, et al. Mechanism of arctigenin-mediated specific cytotoxicity against human lung adenocarcinoma cell lines. Phytomedicine 2013;21:39–46.

49. Maxwell T, Lee KS, Kim S, et al. Arctigenin inhibits the activation of the mTOR pathway, resulting in autophagic cell death and decreased ER expression in ER-positive human breast cancer cells. Int J Oncol 2018;52:1339–49.

50. Maxwell T, Chun SY, Lee KS, et al. The anti-metastatic effects of the phytoestrogen arctigenin on human breast cancer cell lines regardless of the status of ER expression. Int J Oncol 2017;50:727–35.

51. Hirano T, Gotoh M, Oka K. K Natural flavonoids and lignans are potent cytostatic agents against human leukemic HL-60 cells. Life Sci 1994;55:1061–9.

52. Gao Q, Yang M, Zuo Z. Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiiin from Arctium lappa L. Acta Pharmacol Sin 2018;39:787–801.

53. Cho JY, Kim AR, Yoo ES, et al. Immunomodulatory effect of arctigenin, a lignan compound, on tumour necrosis factor-alpha and nitric oxide production, and lymphocyte proliferation. J Pharm Pharmacol 1999;51:1267–73.

54. Kim A-R, Kim HS, Lee JM, et al. Arctigenin suppresses receptor activator of nuclear factor-κB ligand (RANKL)-mediated osteoclast differentiation in bone marrow-derived macrophages. Eur J Pharmacol 2012;682:29–36.

55. Zhao F, Wang L, Liu K. In vitro anti-inflammatory effects of arctigenin, a lignan from Arctium lappa L., through inhibition on iNOS pathway. J Ethnopharmacol 2009;122:457–62.

56. Cho MK, Jang YP, Kim YC, et al. Arctigenin inhibits lipopolysaccharide-induced iNOS expression in RAW264.7 cells through suppressing JAK-STAT signal pathway. Int Immunopharmacol 2004;4:1419–29.

57. Kou X, Qi S, Dai W, et al. Arctigenin inhibits lipopolysaccharide-induced iNOS expression in RAW264.7 cells through suppressing JAK-STAT signal pathway. Int Immunopharmacol 2011;11:1095–102.

58. Lee JY, Cho BJ, Park TW, et al. Dibenzyllbutyrolactone lignans from Forsythia koreana fruits attenuate lipopolysaccharide-induced inducible nitric oxide synthase and cyclooxygenase-2 expressions through activation of nuclear factor-κB and mitogen-activated protein kinase in RAW264.7 cells. Biol Pharm Bull 2010;33:1847–53.

59. Cho MK, Park JW, Jang YP, et al. Potent inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by dibenzylbutyrolactone lignans through inhibition of IκBx phosphorylation and of p65 nuclear translocation in macrophages. Int Immunopharmacol 2002;2:105–16.

60. Shi XB, Sun HZ, Zhou D, et al. Arctigenin Attenuates Lipopolysaccharide-Induced Acute Lung Injury in Rats. Inflammation 2015;38:623–31.

61. Zhang WZ, Jiang ZK, He BX, et al. Arctigenin protects against lipopolysaccharide-induced pulmonary oxidative stress and inflammation in a mouse model via suppression of MAPK, HO-1, and iNOS signaling. Inflammation 2015;38:1406–14.

62. Zhou B, Weng G, Huang Z, et al. Arctiiin prevents LPS-induced acute lung injury via inhibition of PI3K/AKT signal pathway in mice. Inflammation 2018;41:2129–35.

63. Cheng X, Wang H, Wang Y, et al. Arctigenin protects against liver injury from acute hepatitis by suppressing immune cells in mice. Biomed Pharmacother 2018;102:464–71.

64. Wu X, Yang Y, Dou Y, et al. Arctigenin but not arctiiin acts as the major effective constituent of Arctium lappa L. fruit for attenuating colonic inflammatory response induced by dextran sulfate sodium in mice. Int Immunopharmacol 2014;23:505–15.

65. Li XM, Miao Y, Su QY, et al. Gastroprotective effects of arctigenin of Arctium lappa L. on a rat model of gastric ulcers. Biomed Rep 2016;5:589–94.

66. Wu X, Dou Y, Yang Y, et al. Arctigenin exerts anti-colitis efficacy through inhibiting the differentiation of Th1 and Th17 cells via an mTORC1-dependent pathway. Biochem Pharmacol (Amsterdam, Neth) 2015;96:323–36.

67. Vlietinck AJ, De Bruyne T, Apers S, et al. Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection. Planta Med 1998;64:97–109.

68. Schröder HC, Merz H, Steffen R, et al. Differential in vitro anti-HIV activity of natural lignans. Z Naturforsch, C: Biosci 1990;45:1215–21.

69. Hayashi K, Narutaki K, Nagaoka Y, et al. Therapeutic effect of arctiiin and arctigenin in immunocompetent and immunocompromised mice infected with influenza A virus. Biol Pharm Bull 2010;33:1199–205.

70. Chen J, Li W, Jin E, et al. The antiviral activity of arctigenin in traditional Chinese medicine on porcine circovirus type 2. Res Vet Sci 2016;106:159–64.

71. Shen Y-F, Liu L, Chen W-C, et al. Evaluation on the antiviral activity of arctigenin against spring viraemia of carp virus. Aquaculture 2018;483:252–62.

72. Xu X, Li Q, Pang L, et al. Arctigenin promotes cholesterol efflux from THP-1 macrophages through PPAR-γ/LXR-α signaling pathway. Biochem Biophys Res Commun 2013;441:321–6.

73. Chang C, Wu SC, Chang CM, et al. Arctigenin, a potent ingredient of Arctium lappa L., induces endothelial nitric oxide synthase and attenuates subarachnoid hemorrhage-induced vasospasm through PI3K/Akt pathway in a rat model. BioMed Res Int 2015;2015:1–490209/11.

74. Swarup V, Ghosh J, Mishra MK, et al. Novel strategy for treatment of Japanese encephalitis using arctigenin, a plant lignan. J Antimicrob Chemother 2008;61:679–88.

75. Wu RM, Sun YY, Zhou TT, et al. Arctigenin enhances swimming endurance of sedentary rats partially by regulation of antioxidant pathways. Acta Pharmacol Sin 2014;35:1274–84.

76. Borbely S, Jocsak G, Moldovan K, et al. Arctigenin reduces neuronal responses in the somatosensory cortex via the inhibition of non-NMDA glutamate receptors. Neurochem Int 2016;97:83–90.

77. Zhu Z, Yan J, Jiang W, et al. Arctigenin effectively ameliorates memory impairment in Alzheimer’s disease model mice targeting both β-amyloid production and clearance. J Neurosci 2013;33:13138–49.

78. Song J, Li N, Xia Y, et al. Arctigenin treatment protects against brain damage through an anti-inflammatory and anti-apoptotic mechanism after needle insertion. Front Pharmacol 2016;7:182–16.

79. Fan T, Jiang WL, Zhu J, et al. Arctigenin protects focal cerebral ischemia-reperfusion rats through inhibiting neuroinflammation. Biol Pharm Bull 2012;35:2004–9.

80. Jeong YH, Park JS, Kim DH, et al. Arctigenin increases hemoxygenase-1 gene expression by modulating PI3K/AKT signaling pathway in rat primary astrocytes. Biomol Ther 2014;22:497–502.
81. Li A, Wang J, Wu M, et al. The inhibition of activated hepatic stellate cells proliferation by arctigenin through G0/G1 phase cell cycle arrest: persistent p27kip1 induction by interfering with PI3K/Akt/FOXO3a signaling pathway. Eur J Pharmacol 2015;747:71–87.

82. Wang GX, Han J, Feng TT, et al. Bioassay-guided isolation and identification of active compounds from Fructus Arctii against Dactylogyrus intermedius (Monogenea) in goldfish (Carassius auratus). Parasitol Res 2009;106:247–55.

83. Tu X, Huang A, Hu Y, et al. Arctigenin: an emerging candidate against infections of Glyrodactylus. Aquaculture 2018;495:983–91.

84. Dias MM, Zuza O, Riani LR, et al. In vitro schisostemicidal and antiviral activities of Arctium lappa L. (Asteraceae) against Schistosoma mansoni and Herpes simplex virus-1. Biomed Pharmacother 2017;94:489–98.

85. Jang YP, Kim SR, Kim YC. Neuroprotective dibenzylbutyro-lactone lignans of Torreya nucifera. Plant Med 2001;67:470–2.

86. Zhao Z, Yin Y, Wu H, et al. Arctigenin, a potential anti-arrhythmic agent, inhibits acotline-induced arrhythmia by regulating multi-ion channels. Cell Physiol Biochem 2013;32:1342–53.

87. Wang L, Zhao F, Liu K Advances in studies on pharmacological effects of arctiin and arctigenin. Zhongcaoyao 2008;39:467–70.

88. Wu X, Tong B, Yang Y, et al. Arctigenin functions as a selective agonist of estrogen receptor β to restrict mTORC1 activation and consequent Th17 differentiation. Oncotarget 2016;7:83893–906.

89. Gu Y, Sun XX, Ye JM, et al. Arctigenin alleviates ER stress via activating AMPK. Acta Pharmacol Sin 2012;33:941–52.

90. Ogungbe IV, Crouch RA, Demeritte T. (−)-Arctigenin and (−)-Pinoresinol are antagonists of the human thyroid hormone receptor β. J Chem Inf Model 2014;54:3051–5.

91. Park H, Song KH, Jung PM, et al. Inhibitory effect of Arctigenin from Fructus Arctii extract on melanin synthesis via repression of tyrosinase expression. Evid Based Complement Alternat Med 2013;2013:965312.

92. Ishihara K, Yamagishi N, Saito Y, et al. Arctigenin from Fructus Arctii is a novel suppressor of heat shock response in mammalian cells. Cell Stress Chaperones 2006;11:154–61.

93. Zhang N, Wen Q, Ren L, et al. Neuroprotective effect of arctigenin via upregulation of P-CREB in mouse primary neurons and human SH-SY5Y neuroblastoma cells. Int J Mol Sci 2013;14:18657–69.

94. Gao Y, Kang T, Zhang X Study on the calcium antagonist action of arctigenin. Zhongcaoyao 2000;31:758–62.

95. Huang SL, Yu RT, Gong J, et al. Arctigenin, a natural compound, activates AMP-activated protein kinase via inhibition of mitochondria complex I and ameliorates metabolic disorders in ob/ob mice. Diabetologia 2012;55:1469–81.

96. Gu Y, Qi C, Sun X, et al. Arctigenin preferentially induces tumor cell death under glucose deprivation by inhibiting cellular energy metabolism. Biochem Pharmacol 2012;84:468–76.

97. Wang P, Wang B, Chung S, et al. Increased chemopreventive effect by combining arctigenin, green tea polyphenol and curcumin in prostate and breast cancer cells. RSC Adv 2014;4:35242–50.

98. Wang P, Phan T, Gordon D, et al. Arctigenin in combination with quercetin synergistically enhances the antiproliferative effect in prostate cancer cells. Mol Nutr Food Res 2015;59:250–61.

99. Lee JH, Lee JY, Kim TD, et al. Antiasthmatic action of dibenzyltetrahydrofuran lignans from fruits of Forsythia viridissima on asthmatic responses to ovalbumin challenge in conscious guinea-pigs. Phytother Res 2011;25:387–95.

100. Kim BJ, Ryu SW, Song BJ. JNK- and p38 Kinase-mediated phosphorylation of Bax leads to its activation and mitochondrial translocation and to apoptosis of human hepatoma HepG2 cells. J Biol Chem 2006;281:21256–65.

101. Fischer J, Reynolds AJ, Sharp LA, et al. Radical carboxylation approach to lignans. Total synthesis of (−)-Arctigenin, (−)-Matairesinol, and related natural products. Org Lett 2004;6:1345–8.

102. Wu X, Xu K, Fu Y, et al. A new method for asymmetric synthesis of (−)-arctigenin and its enantiomer. Youji Huaxue 2016;36:1111–7.

103. Wang H, Wu P, Kang H, et al. Modify a fragment of arctigenin with pyrimidine derivatives. Youji Huaxue 2012;32:1894–8.

104. Sibi MP, Liu P, Ji J, et al. Free-radical-mediated conjugate additions. Enantioselective synthesis of butyrolactone natural products: (−)-enterolactone, (−)-arctigenin, (−)-isoarctigenin, (−)-nephrosteranic acid, and (−)-roccellaric acid. J Org Chem 2002;67:1738–45.

105. Bode JW, Doyle MP, Protopopova MN, et al. Intramolecular regioselective insertion into unactivated prochiral carbon-hydrogen bonds with diazoacetates of primary alcohols catalyzed by chiral Dirhodium(II) Carboxamidates. Highly enantioselective total synthesis of natural lignan lactones. J Org Chem 1996;61:9146–55.

106. Sugiyama S, Umehara K, Kuroyanagi M, et al. Studies on the differentiation inducers of myeloid leukemic cells from Citrus species. Chem Pharm Bull 1993;41:714–9.

107. Awale S, Kato M, Dibwe DF, et al. Antiausterity activity of arctigenin enantiomers: importance of (2R,3R)-absolute configuration. Nat Prod Commun 2014;9:79–82.

108. Nikaido T, Ohmoto T, Kinoshita T, et al. Inhibitors of cyclic AMP phosphodiesterase in medicinal plants. II. Inhibition of cyclic AMP phosphodiesterase by lignans. Chem Pharm Bull 1981;29:3586–92.

109. Yamauchi S, Nishimoto A, Nishiwaki H, et al. Discovery of steroispecific cytotoxicity of (8R,8′R)-trans-arctigenin against insect cells and structure-activity relationship on aromatic ring. Bioorg Med Chem Lett 2020;30:127191.

110. Semenkovich CF. Insulin resistance and atherosclerosis. J Clin Invest 2006;116:1813–22.

111. Ren JM, Marshall BA, Guelve EA, et al. Evidence from transgenic mice that glucose transport is rate-limiting for glucogen deposition and glycolysis in skeletal muscle. J Biol Chem 1993;268:16113–5.

112. Hansell CAH, Schiering C, Kinstrie R, et al. Universal expression and dual function of the atypical chemokine receptor D6 on innate-like B cells in mice. Blood 2011;117:5413–24.

113. Kelley DE, Goodpaster B, Wing RR, et al. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol 1999;277:E1130–E1141.

114. Duan S, Huang S, Gong J, et al. Design and synthesis of Novel Arctigenin analogues for the amelioration of metabolic disorders. ACS Med Chem Lett 2015;6:386–91.
115. Pelter A, Elgedy SMA. Phenolic oxidations with phenylidonium diacetate. J Chem Soc, Perkin Trans 1 1993;1993:1891–6.
116. Gates BD, Dalidowicz P, Tebben A, et al. Mechanistic aspects and synthetic applications of the electrochemical and iodobenzene bistri fluorooaceta te oxidative 1,3-cycloaditions of phenols and electron-rich styrene derivatives. J Org Chem 1992;57:2135–43.
117. Tamura Y, Yakura T, Haruta J, et al. An efficient conversion of keto groups into dihydroxyacetone groups: oxidation of ethynylcarbinol intermediates by using hypervalent iodine reagent. Tetrahedron Lett 1985;26:3837–40.
118. Ellinger-Ziegelbauer H, Dreyer C. A retinoic acid receptor expressed in the early development of Xenopus laevis. Genes Dev 1991;5:94–104.
119. Krishna KVR, Sujatha K, Kapil RS. Phenolic oxidative coupling with the hypervalent organoiodine compound (diacetoxyiodo)benezene. Tetrahedron Lett 1990;31:1351–2.
120. Ward RS, Pelter A, Abd-El-Ghani A. Preparation of tetraydrodibenzocyclooctene lignans and spirodienones by hypervalent iodine oxidation of phenolic dibenzylbutyrolactones. Tetrahedron 1996;52:1303–36.
121. Zhang S, Xiong H, Lu F, et al. Synthesis of N-acyl sulfamates from fluorosulfonates and potassium trimethylsiloxyl imidates. J Org Chem 2019;84:15380–8.
122. Ward RS, Hughes DD. Oxidative cyclisation of 3,4-dibenzyltetrahydrofurans using ruthenium tetra(trifluorooaceta te). Tetrahedron 2001;57:2057–64.
123. Eich E, Pertz H, Kologa M, et al. (−)-Arctigenin as a lead structure for inhibitors of human immunodeficiency virus type-1 inte grase. J Med Chem 1996;39:86–95.
124. Ward RS, Hughes DD. Oxidative cyclization of cis- and trans-2,3-dibenzylbutyrolactones using ruthenium tetra (trifluorooaceta te). Tetrahedron 2001;57:4015–22.
125. Cai E, Guo S, Yang L, et al. Synthesis and antitumour activity of arctigenin amino acid ester derivatives against H22 hepatocellular carcinoma. Nat Prod Res 2018;32:406–11.
126. Cai EB, Yang LM, Jia CX, et al. The synthesis and evaluation of arctigenin amino acid ester derivatives. Chem Pharm Bull 2016;64:1466–73.
127. Han M, Jia X, Cai E, et al. The effects of Arctigenin-Valine ester on chemotherapy-induced myelosuppression in mice. Bioorg Chem Med 2019;27:2480–6.
128. Chen Q, Yang L, Han M, et al. Synthesis and pharmacological activity evaluation of arctigenin monoester derivatives. Biomed Pharmacother 2016;84:1792–801.
129. Sato K, Tsuchihara K, Fujii S, et al. Autophagy is activated in colorectal cancer cells and contributes to the tolerance to nutrient deprivation. Cancer Res 2007;67:9677–84.
130. Belkacemi L, Lam E, Caldwell JD, et al. Stimulation of human breast carcinoma cell invasiveness and urokinase plasminogen activator activity by glucose deprivation. Exp Cell Res 2006;312:1685–92.
131. Izuishi K, Kato K, Ogura T, et al. Remarkable tolerance of tumor cells to nutrient deprivation: possible new biochemical target for cancer therapy. Cancer Res 2000;60:6201–7.
132. Awale S, Nakashima EMN, Kalauni SK, et al. Angelmarin, a novel anti-cancer agent able to eliminate the tolerance of cancer cells to nutrient starvation. Bioorg Med Chem Lett 2006;16:581–3.
133. Kudou N, Taniguchi A, Sugimoto K, et al. Synthesis and antitumor evaluation of arctigenin derivatives based on antiausterity strategy. Eur J Med Chem 2013;60:76–88.
134. Lei M, Gan X, Zhao K, et al. Synthesis and cytotoxicity evaluation of 4-amino-4-dehydroxylarctigenin derivatives in glucose-starved A549 tumor cells. Bioorg Med Chem Lett 2015;25:435–7.
135. Li D, Xie K, Wolff R, et al. Pancreatic cancer. Lancet 2004;363:1049–57.
136. Shore S, Vimalachandran D, Rarety MG, et al. Cancer in the elderly: pancreatic cancer. Surg Oncol 2004;13:201–10.
137. Chung HW, Bang SM, Park SW, et al. A prospective randomized study of gemcitabine with doxifluridine versus paclitaxel with doxifluridine in concurrent chemoradiotherap y for locally advanced pancreatic cancer. Int J Radiat Oncol, Biol, Phys 2004;60:1494–501.
138. Ahne W, Bjorklund HV, Essbauer S, et al. Spring viremia of carp (SVC). Dis Aquat Organ 2002;52:261–72.
139. Koutna M, Vesely T, Piskal I, et al. Identification of spring viremia of carp virus (SVCV) by combined RT-PCR and nested PCR. Dis Aquat Org 2003;55:229–35.
140. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell 2011;147:728–41.
141. Hsieh CJ, Kuo PL, Hsu YC, et al. Arctigenin, a dietary phytoestrogen, induces apoptosis of estrogen receptor-negative breast cancer cells through the ROS/p38 MAPK pathway and epigenetic regulation. Free Radical Biol Med 2014;67:159–70.
142. Lee JY, Kim CJ. A phenylpropanoid dibenzylbutyrolactone lignan, inhibits type 1-IV allergic inflammation and proinflammatory enzymes. Arach Pharmacal Res 2010;33:947–57.
143. Chen W-C, Hu Y, Liu L, et al. Synthesis and in vitro activities evaluation of arctigenin derivatives against spring virema of carp virus. Fish Shellfish Immunol 2018;82:17–26.
144. Hu Y, Liu L, Liu G-L, et al. Synthesis and anthelmintic activity of arctigenin derivatives against Dactylogyrus intermedius in goldfish. Bioorg Med Chem Lett 2017;27:3310–6.
145. Dixon P, Paley R, Oidtmann B, et al. Epidemiological characteristics of infectious hematopoietic necrosis virus (IHNV): a review. Vet Res 2016;47:63.
146. Ahmadvand S, Soltani M, Mardani K, et al. Infectious hematopoietic necrosis virus (IHNV) outbreak in farmed rainbow trout in Iran: viral isolation, pathological findings, molecular confirmation, and genetic analysis. Virus Res 2017;229:17–23.
147. Hu Y, Li B, Shen Y, et al. Synthesis of arctigenin derivatives against Toxoplasma gondii tachyzoites in vitro. Trends Parasitol 2001;17:460–3.
148. Mui EJ, Jacobus D, Milhou WS, et al. Triazine inhibits Toxoplasma gondii tachyzoites in vitro and in vivo. Antimicrob Agents Chemother 2005;49:3463–7.
149. Zhang HB, Shen QK, Wang H, et al. Synthesis and evaluation of novel arctigenin derivatives as potential anti-Toxoplasma Gondii agents. Eur J Med Chem 2018;158:414–27.
150. Winder WW. Energy-sensing and signaling by AMP-activated protein kinase in skeletal muscle. J Appl Physiol 2001;91:1017–28.
151. Hardie DG, Carling D, Carlson M. The AMP-activated/SNF1 protein kinase subfamily: metabolic sensors of the eukaryotic cell? Annu Rev Biochem 1998;67:821–55.
153. Towler MC, Hardie DG. AMP-activated protein kinase in metabolic control and insulin signaling. Circ Res 2007;100:328–41.
154. Winder WW, Hardie DG. AMP-activated protein kinase, a metabolic master switch: possible roles in type 2 diabetes. Am J Physiol 1999;277: E1–E10.
155. Luo Z, Saha AK, Xiang X, Ruderman NB. AMPK, the metabolic syndrome and cancer. Trends Pharmacol Sci 2005;26:69–76.
156. Lim CT, Kola B, Korbonits M. Korbonits M AMPK as a mediator of hormonal signalling. J Mol Endocrinol 2010;44:87–97.
157. Musi N, Fujii N, Hirshman MF, et al. AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. Diabetes 2001;50:921–7.
158. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. Nature 2001;414:821–7.
159. Viollet B, Lantier L, Devin-Leclerc J, et al. Targeting the AMPK pathway for the treatment of Type 2 diabetes. Front Biosci, Landmark Ed 2009;14:3380–400.
160. Zhang BB, Zhou G, Li C. C AMPK: an emerging drug target for diabetes and the metabolic syndrome. Cell Metab 2009;9:407–16.
161. Zhou G, Sebhat IK, Zhang BB. Sebhat IK Zhang BB AMPK activators – potential therapeutics for metabolic and other diseases. Acta Physiol 2009;196:175–90.
162. Shen S, Zhuang J, Chen Y, et al. Synthesis and biological evaluation of arctigenin ester and ether derivatives as activators of AMPK. Bioorg Med Chem 2013;21:3882–93.
163. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Delivery Rev 2013;65:36–48.
164. Liu J, Huang Y, Kumar A, et al. pH-Sensitive nano-systems for drug delivery in cancer therapy. Biotechnol Adv 2014;32:693–710.