Review

Chemical composition and pharmacological activities of *Atractylodes lancea*: A review

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Abstract

***Atractylodes lancea* (called Cangzhu in China) is a medicinal plant that has long been used as tonic agent in various ethno-medical systems in East Asia, especially in China, for the treatment of gastrointestinal dysfunction, cancer, osteoporosis, obesity and fetal irritability. We used the TCMSP database to search for the main active ingredients and traditional Chinese medicine targets of *Atractylodes macrocephala*. There are a total of 38 related articles, of which 27 are closely related to chemical composition and activity. This study reviews the chemical components and pharmacological effects of *A. lancea*, aiming to provide reference for its further research and development.**

Keywords: *Atractylodes lancea*; chemical composition; pharmacological activities

1 Introduction

The genus *Atractylodes lancea* (*A. lancea*), which consists of eight species, are perennial herbs widely distributed throughout Korea, China and Japan [1,2]. *A. lancea* has been cultivated in temperate and subtropical areas for more than 700 years [3]. It is one of the best known herbs in East Asia and in particular in China. The rhizome of this plant, named “Baizhu” in traditional Chinese medicine (TCM), has been used for thousands of years to treat a wide spectrum of diseases including spleen hypofunction, loss of appetite, abdominal distension, diarrhea, dizziness and heart palpitation [4,5]. *A. lancea* has diverse pharmacological activities [6-10]. These activities include improving gastrointestinal function, anti-tumor activity, anti-inflammatory activity, anti-aging activity, anti-oxidative activity, anti-osteoporotic activity, anti-bacterial activity, gonadal hormone regulation, tocolytic effects, neuroprotective activity such as protection against Alzheimer’s disease, anti-obesity activity, immunomodulatory activity and energy-enhancing metabolism.

Phytochemical investigations have revealed that *A. lancea* contains sesquiterpenoids, triterpenoids, polyacetylenes, coumarins, phenylpropanoids, flavonoids, flavonoid glycosides, steroids, benzoquinones and polysaccharides [11-18]. However,

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Received: 2024-01-25 Accepted: 2024-03-22

only a few of these compounds have been tested for their bioactivity, and their corresponding structures have not been fully summarized and comprehensively presented in other publications. Although *A. lancea* has proved to be effective in treating various infections, toxicity and safety of the chemical constituents in its extracts have not been determined. In addition, there is insufficient research on the quality control of *A. lancea*, and there is a lack of critical pharmacological evaluation on the relation between these constituents and the traditional use of *A. lancea*.

2 Chemical composition

A. lancea is known for its rich medicinal active components, and its main chemical constituents are sesquiterpenoids, triterpenoids, polyacetylenes, coumarins, phenylpropanoids, flavonoids, flavonoid glycosides, steroids, benzoquinones and other diverse compounds [11-18]. These compounds contribute to the unique pharmacological effects and medicinal value of *A. lancea*.

2.1 Sesquiterpenoids

Research indicates that sesquiterpenoids are significant active ingredients in *A. lancea*. The main sesquiterpenoids include Δ-guaiene (**1**), *β*-selinene (**2**), *β*-maaliene (**3**), *β*-eudesmol (**4**), *β*-elemene (**5**), *β*-chamigrene (**6**), *β*-caryophyllene (**7**), *α*-humulene (**8**), *α*-guaiene (**9**), *α*-eudesmol (**10**), *α*-chamigrene (**11**), *γ*-selinene (**12**), hinesol (**13**), guaiol (**14**), guaiene (**15**), cyperene (**16**), *β*-humulene (**17**), and humuleneoxide (**18**). The structural formulas of these sesquiterpenoids are shown in Fig. 1.

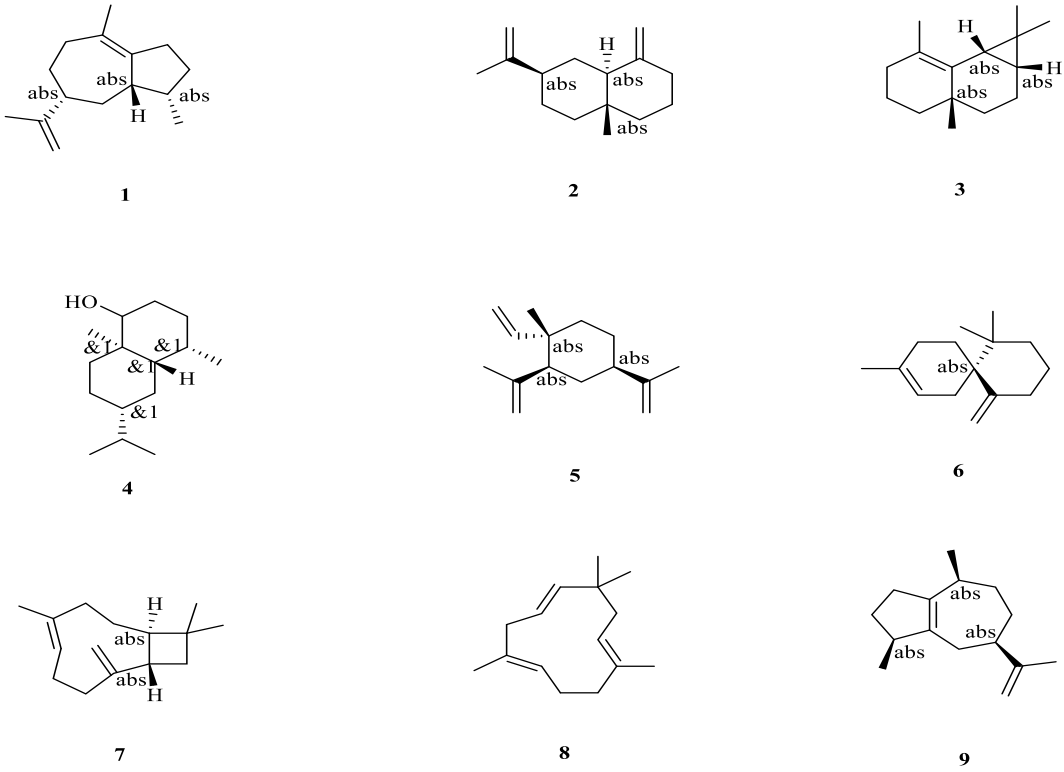
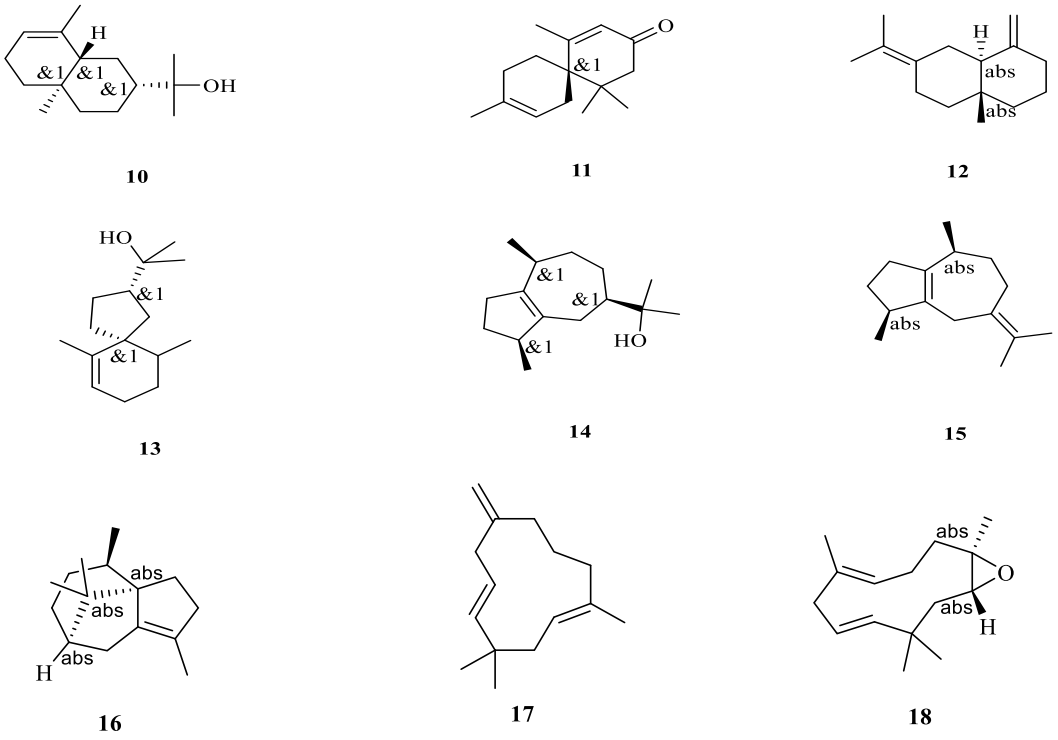


Fig. 1 Structures of sesquiterpenoids isolated from *A. lancea*

(to be continued)



Continued fig. 1

2.2 Diterpenoid

Research indicates that diterpenoid in *A. lancea* mainly include: pteris diterpenoid (**19**) and 1*β*-hydroxybaccatinl (**20**), atractylone (**21**), and atractylon (**22**). The structural formulas of these triterpenoids are shown in Fig. 2.

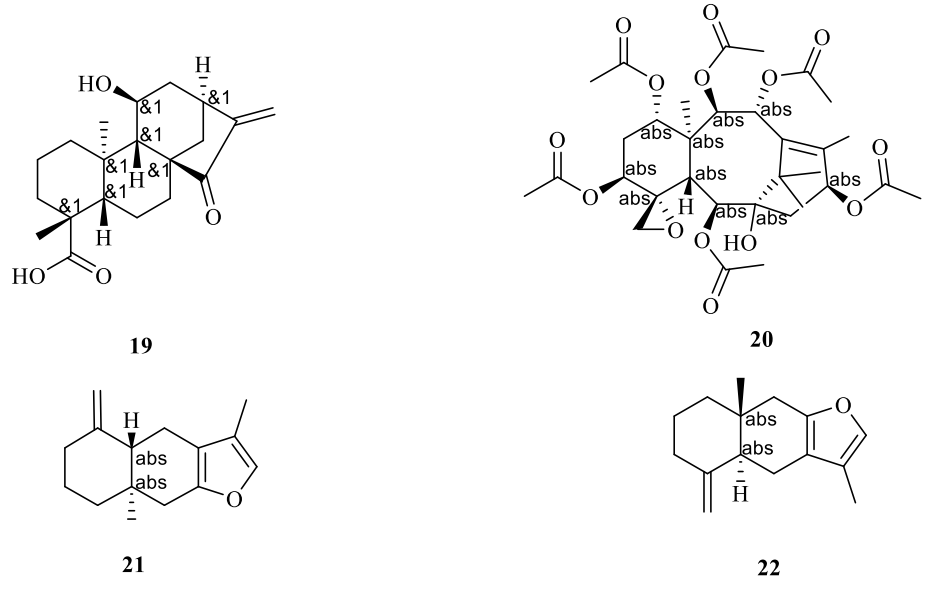
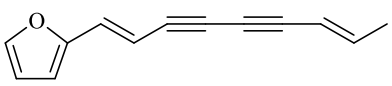


Fig. 2 Structures of triterpenoids isolated from *A. lancea*

2.3 Polyacetylenes

A. lancea contains polyacetylenes such as atractylodin (**23**), and atractylodinol (**24**), with their structures detailed in Fig. 3.



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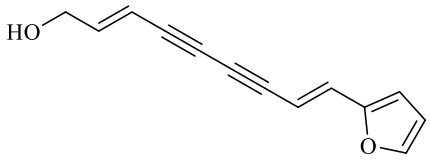

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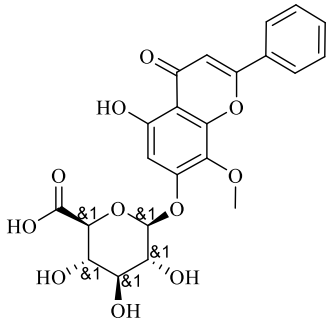
Fig. 3 Structures of polyacetylenes isolated from *A. lancea*

2.4 Coumarins and Phenylpropanoids

This category includes: oroxindin (**25**), methyl 3, 4, 5-trimethoxycinnamate (**26**), and elemicin (**27**). Fig. 4 shows their structural formulas.



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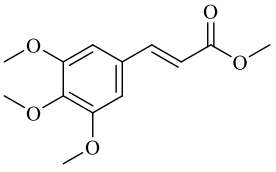

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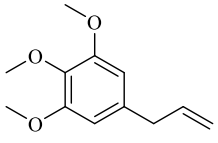

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Fig. 4 Structures of coumarins and phenylpropanoids isolated from *A. lancea*

2.5 Flavonoids and Flavonoid Glycosides

Flavonoids and flavonoid glycosides in *A. lancea* comprise wogonin (**28**), as depicted in Fig. 5.

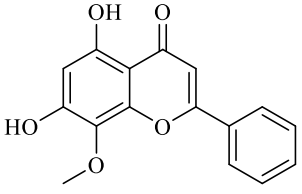

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Fig. 5 Structures of flavonoids and flavonoid glycosides isolated from *A. lancea*

2.6 Steroids

Steroids such as daucosterol (**29**), daucosterin (**30**), stigmasterol (**31**), and 24-hydroxycholesterol (**32**) are also present, with their structures in Fig. 6.

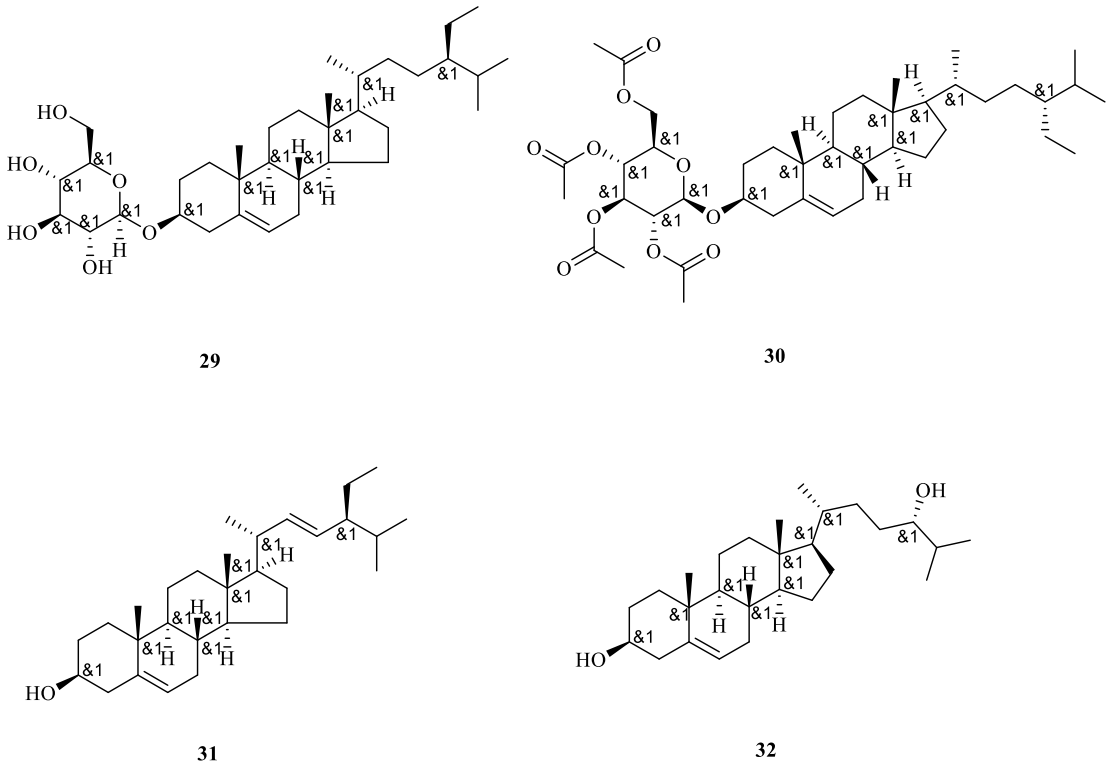

Fig. 6 Structures of steroids isolated from *A. lancea*

2.7 Other Compounds

Additional compounds in *A. lancea* include atractyloside (**33**), atractyloside A (**34**), uridine (**35**), tryptophan (**36**), adenine nucleoside (**37**), elemol (**38**), anillic acid (**39**), elenolide (**40**), furol (**41**), 5-pyridin-3-yloxyfuran-2-carbaldehyde (**42**), syringin (**43**), icariside (**44**), 3-O-*β*-D-glucopyranoside (**45**), and 6,6′-dimethoxygossypol (**46**). Their structural formulas are provided in Fig. 7.

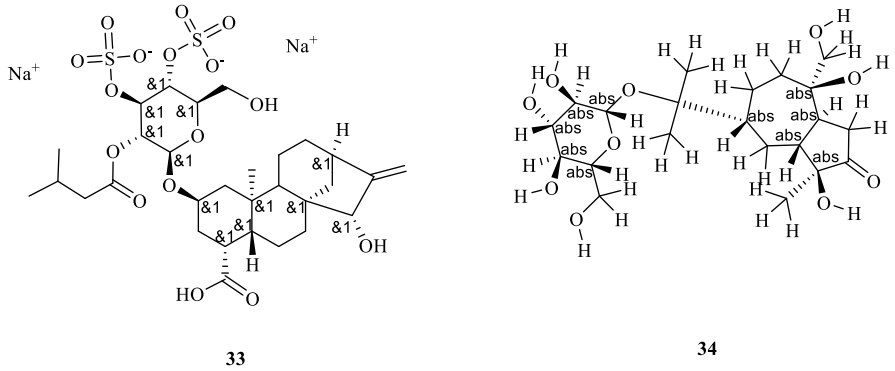

Fig. 7 Structures of other compounds isolated from *A. lancea*

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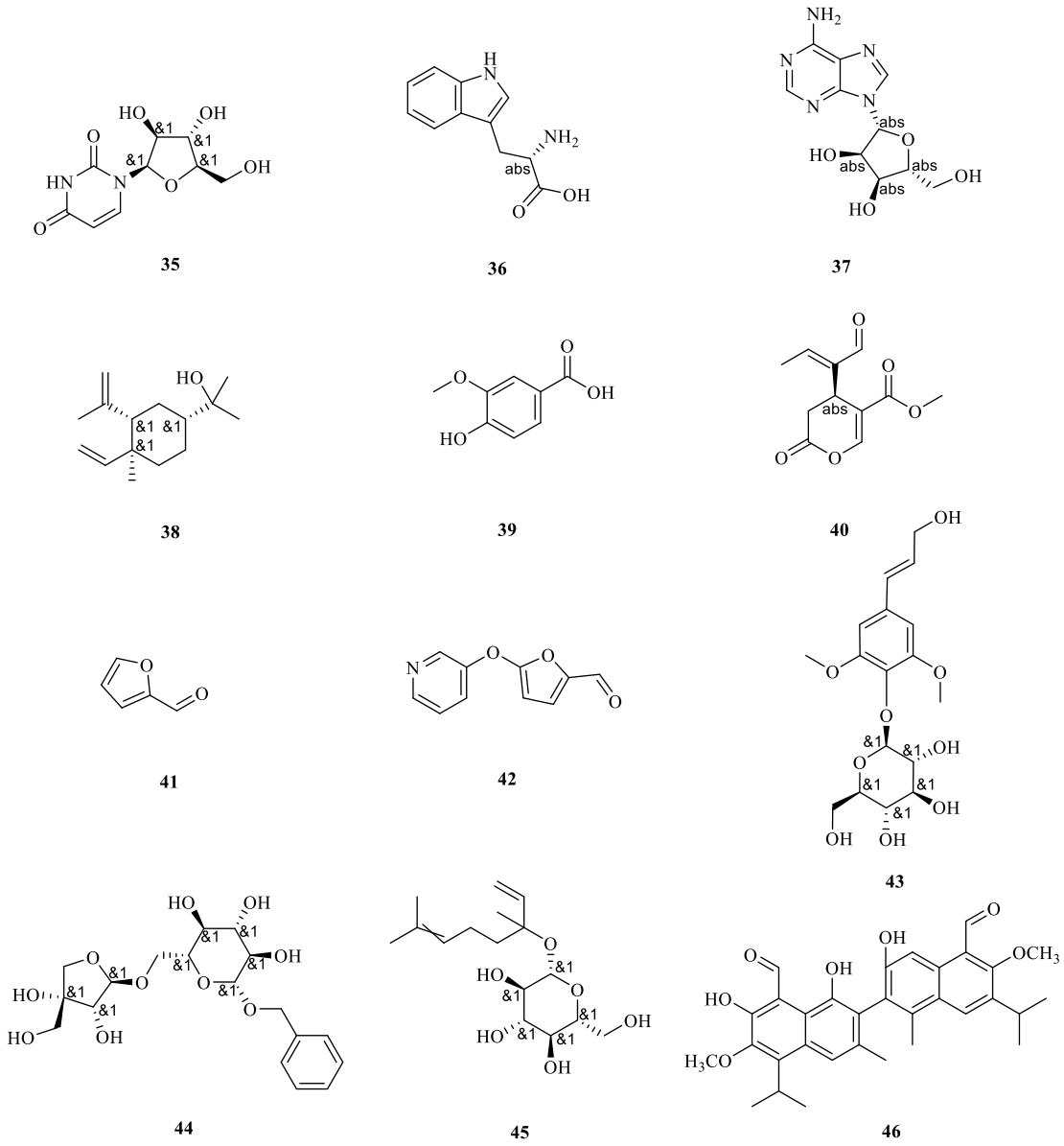

Continued fig. 7

3 Pharmacological activity

A. lancea is a widely used medicinal plant in traditional Chinese medicine, with functions of strengthening the stomach, diuresis, detumescence, and antiperspiration. In recent years, the pharmacological activities of *A. lancea* and its extracts have attracted the attention of modern scientific research, and it has been found that they have various biological activities, including improving gastrointestinal function, anti-tumor properties, immunomodulation, anti-inflammatory effects, neuroprotective qualities against Alzheimer's disease, anti-aging and anti-oxidative effects, regulation of gonadal hormones and tocolysis, treating obesity and enhancing energy metabolism, as well as anti-osteoporotic and antibacterial activities. These studies not only demonstrate the

potential of *A. lancea* as a natural drug, but also provide a scientific basis for its clinical application.

3.1 Improving gastrointestinal function

A. lancea is a commonly used stomachic drug. It can stimulate the movement and secretion of the gastrointestinal tract, enhance appetite, and improve digestive function. The main active components of *A. lancea* are lactone compounds, such as atractylenolides (-I, -II, -III), which can activate the cholinergic nerves of the gastrointestinal tract, enhance the tension and peristalsis of the gastrointestinal tract, and thus promote the emptying of the gastrointestinal tract [19]. In addition, *A. lancea* can also inhibit the secretion of gastric acid, protect the gastric mucosa, and prevent the occurrence of gastric ulcers [20]. *A. lancea* can also regulate the balance of intestinal flora, inhibit the growth of harmful bacteria, increase the number of beneficial bacteria, and thus improve the barrier and immune functions of the intestine [21]. Therefore, *A. lancea* can effectively improve gastrointestinal function and treat dyspepsia, gastric ulcer, gastritis, enteritis and other diseases.

3.2 Anti-tumor activity

A. lancea has obvious anti-tumor activity. It can inhibit the proliferation, invasion and metastasis of various tumor cells, induce the apoptosis and autophagy of tumor cells, and enhance the immune response of the body. *A. lancea*'s anti-tumor activity may be attributed to its lactone compounds, such as atractylenolide I. This compound can induce the mitochondrial-mediated apoptosis of tumor cells by regulating the expression of Bcl-2 family proteins, activating caspases, and increasing the production of reactive oxygen species [22]. Atractylenolide I can also induce the autophagy of tumor cells by activating the AMPK/mTOR signaling pathway, and inhibit the epithelial-mesenchymal transition of tumor cells by down-regulating the expression of Snail and Twist [23]. Atractylenolide II can inhibit the angiogenesis of tumor cells by down-regulating the expression of VEGF and MMP-9, and inhibit the invasion and metastasis of tumor cells by suppressing the NF-κB and MAPK signaling pathways [24]. Atractylenolide III can enhance the immune response of the body by stimulating the production of cytokines, such as IL-2, IL-12 and IFN-γ, and activating the natural killer cells and cytotoxic T lymphocytes [25]. Therefore, *A. lancea* has a broad-spectrum and multi-target anti-tumor effect and a certain therapeutic potential for various types of cancer.

3.3 Immunomodulatory effects

A. lancea has significant immunomodulatory effects. It can regulate the immune system of the body, and enhance the resistance and immune response of the body. *A. lancea*'s immunomodulatory effects may be related to the synergistic effect of its various components, such as lactone compounds, volatile oil and polysaccharides. *A. lancea* can affect the non-specific and specific immunity of the body by stimulating the activity of immune cells, such as macrophages, lymphocytes and natural killer cells, promoting the production of immune molecules, such as cytokines and antibodies, regulating the balance of Th1/Th2 cytokines and inhibiting the expression of immune suppressive factors [26]. Therefore, *A. lancea* can effectively regulate the immune function of the body, and has a certain effect on the treatment of immune-related diseases, such as infection, inflammation, allergy and autoimmune disease.

3.4 Anti-inflammatory activity

A. lancea has obvious anti-inflammatory

activity. It can inhibit the occurrence and development of inflammation and reduce the symptoms and damage of inflammation. *A. lancea*'s anti-inflammatory activity may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds can inhibit the synthesis and release of inflammatory mediators, such as prostaglandins, leukotrienes and histamine, thereby reducing the severity of inflammation [27]. In addition, *A. lancea* can also inhibit the activation of inflammatory signaling pathways, such as NF-κB, MAPK and JAK/STAT, and reduce the expression of inflammatory factors, such as TNF-α, IL-1β and IL-6, thereby inhibiting the development of inflammation [28]. Therefore, *A. lancea* has anti-inflammatory effects and is effective in treating various inflammatory diseases, such as arthritis, hepatitis, pancreatitis and pneumonia.

3.5 Anti-Alzheimer's disease and neuroprotective activities

A. lancea has anti-Alzheimer and neuroprotective activities. It can improve cognitive function, and prevent neuronal damage and death. *A. lancea*'s anti-Alzheimer and neuroprotective activities may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds have antioxidant and anti-inflammatory effects, can scavenge reactive oxygen species, inhibit lipid peroxidation, reduce oxidative stress, and suppress the activation of microglia and astrocytes, thereby reducing the neuroinflammation and neurotoxicity [29]. Moreover, *A. lancea* can also modulate the cholinergic system, which is impaired in Alzheimer's disease, by increasing the level of acetylcholine and inhibiting the activity of acetylcholinesterase, thereby enhancing the cholinergic transmission and improving the memory and learning ability [30]. Furthermore, *A. lancea* can also regulate the amyloid-beta metabolism, the main pathological feature of Alzheimer's disease, by inhibiting the formation and aggregation of amyloid-beta, promoting the clearance and degradation of amyloid-beta, and reducing the neurotoxicity of amyloid-beta [31]. Therefore, *A. lancea* can effectively prevent and treat Alzheimer's disease, and has a certain neuroprotective effect on other neurodegenerative diseases, such as Parkinson's disease and stroke.

3.6 Anti-aging and anti-oxidative activities

A. lancea has anti-aging and anti-oxidative activities. It can delay the aging process, improve the quality of life, and prevent the occurrence of age-related diseases. *A. lancea*'s anti-aging and anti-oxidative activities may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds have strong scavenging effects on free radicals, such as superoxide anion, hydroxyl radical and nitric oxide, and can increase the activities of antioxidant enzymes, such as superoxide dismutase, catalase and glutathione peroxidase, and reduce the levels of malondialdehyde, protein carbonyl and advanced glycation end products, which are indicators of oxidative stress and damage [32]. In addition, *A. lancea* can also modulate the expression of genes related to aging, such as SIRT1, FOXO3a and p53, and regulate the signaling pathways involved in aging, such as AMPK, mTOR and NF-κB, thereby affecting the cellular senescence, apoptosis, autophagy, inflammation and metabolism [33]. Therefore, *A. lancea* can effectively prevent and delay aging, and has a certain protective effect on age-related diseases, such as cardiovascular disease, diabete, and neurodegenerative disease.

3.7 Gonadal hormone regulation and tocolytic effects

A. lancea has gonadal hormone regulation and tocolytic effects. It can regulate the reproductive

function, improve the fertility, and prevent the preterm labor. *A. lancea*'s gonadal hormone regulation and tocolytic effects may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds can modulate the secretion and metabolism of gonadal hormones, such as estrogen, progesterone and testosterone, and affect the expression and activity of their receptors, such as ER, PR and AR, thereby influencing the development and function of reproductive organs, such as ovary, uterus and testis [32]. Moreover, *A. lancea* can also inhibit the contraction of uterine smooth muscle, which is induced by various factors, such as oxytocin, prostaglandin and calcium, and relax the uterine tone, thereby preventing the preterm labor and abortion [33]. Therefore, *A. lancea* can effectively regulate the gonadal hormone and uterine function, and has a certain effect on the treatment of reproductive disorders, such as infertility, dysmenorrhea and endometriosis.

3.8 Treating obesity and enhancing energy metabolism

A. lancea has the effects of treating obesity and enhancing energy metabolism. It can reduce the body weight, improve the lipid profile, and prevent the metabolic syndrome. *A. lancea*'s effects of treating obesity and enhancing energy metabolism may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds can inhibit the differentiation and proliferation of adipocytes, reduce the accumulation of lipids, and promote the lipolysis and fatty acid oxidation, thereby reducing the body fat mass and improving the insulin sensitivity [33]. In addition, *A. lancea* can also activate the thermogenesis of brown adipose tissue and beige adipose tissue, which can increase the energy expenditure and heat production, and regulate the expression of genes and proteins involved in thermogenesis, such as UCP1, PGC-1α and PRDM16, thereby enhancing the energy metabolism and preventing the obesity [33]. Therefore, *A. lancea* can effectively treat obesity and enhance energy metabolism, and has a certain effect on the prevention and treatment of metabolic syndrome, such as diabetes, hyperlipidemia and hypertension.

3.9 Anti-osteoporotic activity

A. lancea has anti-osteoporotic activity. It can prevent the bone loss, improve the bone quality, and protect the bone health. *A. lancea*'s anti-osteoporotic activity may be related to its lactone compounds, such as atractylenolide I, II and III. These compounds can modulate the balance of bone formation and resorption by affecting the differentiation and function of osteoblasts and osteoclasts and regulating the expression of genes and proteins involved in bone remodeling, such as RANKL, OPG, RUNX2 and OCN [34]. Moreover, *A. lancea* can also inhibit the oxidative stress and inflammation in bone tissue, which are the main causes of osteoporosis, by scavenging free radicals, increasing antioxidant enzymes and suppressing inflammatory factors, thereby reducing the bone damage and improving the bone microstructure [34]. Therefore, *A. lancea* can effectively prevent and treat osteoporosis, and has a certain effect on the prevention and treatment of osteoporosis-related fractures and complications.

3.10 Antibacterial activity

A. lancea has antibacterial activity. It can inhibit the growth and reproduction of various bacteria and prevent the bacterial infection. *A. lancea*'s antibacterial activity may be related to its volatile oil, the main component of *A. lancea*'s aroma and flavor, and it contains various monoterpenes and sesquiterpenes, such as

β-eudesmol, elemol and *β*-selinene [35,36]. The volatile oil of *A. lancea* can damage the cell wall and membrane of bacteria, interfere with the bacterial enzyme system and energy metabolism, and inhibit the bacterial biofilm formation and quorum sensing, thereby inhibiting the bacterial viability and virulence [35]. The volatile oil of *A. lancea* has a broad-spectrum antibacterial effect, and it can inhibit various Gram-positive and Gram-negative bacteria, such as *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and has a synergistic effect with some antibiotics, such as *Penicillin* and *Streptomycin* [36]. Therefore, *A. lancea* can effectively inhibit the bacterial infection, and has a certain effect on the treatment of various bacterial diseases, such as skin infection, respiratory infection and urinary tract infection.

3.11 Possible mechanisms of pharmacological activities of A. lancea

A. lancea, a traditional East Asian medicinal herb, contains a plethora of bioactive compounds that exhibit therapeutic effects through intricate interactions with biological targets. The primary active constituents of *A. lancea*, including atractylodin (**23**), *β*-eudesmol (**4**) and atractylenolide I, II, and III, have been identified to engage with specific cellular pathways, thereby eliciting their pharmacological actions [37,38].

The anti-inflammatory properties of *A. lancea* are attributed to its ability to modulate cytokine production. For instance, *A. lancea* extracts have been shown to inhibit the synthesis of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-*α*), interleukin-8 (IL-8) and interleukin-6 (IL-6), while concurrently enhancing the levels of epidermal growth factor (EGF) and trefoil factor 2 (TFF2)1. This modulation likely occurs through the suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*κ*B) signaling pathway, a pivotal regulator of inflammatory responses [39].

The anticancer efficacy of *A. lancea* is mediated through multiple mechanisms. Atractylenolide compounds, in particular, have demonstrated the capacity to induce apoptosis in cancer cells by disrupting mitochondrial membrane potential and activating caspase-dependent pathways. Additionally, these compounds have been observed to arrest the cell cycle at specific checkpoints, thereby inhibiting cellular proliferation. The perturbation of the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways by *A. lancea* constituents further contributes to their antitumor activities [40].

The neuroprotective and antioxidant actions of *A. lancea* are conferred by its constituents' ability to scavenge reactive oxygen species (ROS) and upregulate endogenous antioxidant defenses. Compounds, such as *β*-eudesmol (**4**), exert a protective effect on neuronal cells by mitigating oxidative stress-induced damage and preserving mitochondrial function [41].

In summary, the active components of *A. lancea* interact with a diverse array of biological targets have a broad spectrum of pharmacological effects. These interactions underscore the potential of *A. lancea* as a source for novel therapeutic agents and highlight the need for further research on its mechanism of action and clinical applications.

4 Conclusion

This study reviews the chemical composition and pharmacological activities of *A. lancea* based on existing studies. As traditional Chinese herbal medicine, *A. lancea* is very rich in resources and is widely used clinically. There are a variety of active ingredients in the medicine *A. lancea*. These

ingredients possess antibacterial, antiviral, antiviral and other pharmacological activities. The utility of *A. lancea* is widely recognized by the medical community, but the toxicology of *A. lancea* needs more in-depth and systematic research. In the future, if its safety, effectiveness and efficacy can be further studied and discussed, *A. lancea* will be more widely recognized.

Acknowledgements

This work was financially supported by National Nature Science Foundation of China (81973284) and Scientific Research Foundation of the Education Department of Liaoning Province (LJKZ0944).

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