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# Atractylodis Rhizoma: A review of its traditional uses, phytochemistry, pharmacology, toxicology and quality control

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## ABSTRACT

**Ethnopharmacological relevance:** Atractylodis Rhizoma (AR), mainly includes *Atractylodes lancea* (Thunb.) DC. (*A. lancea*) and *Atractylodes chinensis* (DC.) Koidz. (*A. chinensis*) is widely used in East Asia as a diuretic and stomachic drug, for the treatment of rheumatic diseases, digestive disorders, night blindness, and influenza as it contains a variety of sesquiterpenoids and other components of medicinal importance.

**Aim of the review:** A systematic summary on the botany, traditional uses, phytochemistry, pharmacology, toxicology, and quality control of AR was presented to explore the future therapeutic potential and scientific potential of this plant.

**Materials and methods:** A review of the literature was performed by consulting scientific databases including Google Scholar, Web of Science, Baidu Scholar, Springer, PubMed, ScienceDirect, CNKI, etc. Plant taxonomy was confirmed to the database "The Plant List".

**Results:** Over 200 chemical compounds have been isolated from AR, notably sesquiterpenoids and alkynes. Various pharmacological activities have been demonstrated, especially improving gastrointestinal function and thus allowed to assert most of the traditional uses of AR.

**Conclusions:** The researches on AR are extensive, but gaps still remain. The molecular mechanism, structure-activity relationship, potential synergistic and antagonistic effects of these components need to be further elucidated. It is suggested that further studies should be carried out in the aspects of comprehensive evaluation of the quality of medicinal materials, understanding of the "effective forms" and "additive effects" of the pharmacodynamic substances based on the same pharmacophore of TCM, and its long-term toxicity in vivo and clinical efficacy.

## 1. Introduction

Genus *Atractylodes* (Compositae) comprises eight species of perennial herbs distributed in East Asia (Hiraoka, 1993) and is classified into two major groups, Cangzhu and Bai-zhu (common Chinese names). Dried rhizomes of *Atractylodes* plants, including *Atractylodes lancea* (Thunb.) DC. (*A. lancea*), *Atractylodes chinensis* (DC.) Koidz. (*A. chinensis*), *Atractylodes japonica* Koidz. (*A. japonica*), and *Atractylodes macrocephala* Koidz. (*A. macrocephala*) etc, have been used as important

crude drugs prescribed in Chinese, Japanese, Korean and Thai traditional medicine. *A. lancea* and *A. chinensis* are perennial plants, known to be widely distributed in China, are prescribed in the Chinese, Japanese and Korean Pharmacopoeia as the botanical origins of the crude drug, Cangzhu (Sojutsu in Japanese) and collectively termed Atractylodis Rhizoma (AR) in present paper.

*A. japonica* and *A. macrocephala* are prescribed in the Japanese and Korean Pharmacopoeia as the botanical origin of the crude drug, Baizhu (Byakujutsu in Japanese and Baekchul in Korean). Traditional Chinese medicine (TCM) theory states that both groups have a similar mode of

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**Abbreviations**

AR	Atractylodis Rhizoma	IEC-6	intestinal epithelial
AM	Atractylodis Macrocephalae Rhizoma	5-LOX	5-lipoxygenase
ATL-I	atractylenolide I	GLUT-4	glucose transporter type 4
CCA	cholangiocarcinoma	CYP3A	cytochrome P450 3A
MPO	myeloperoxidase	NLRP3	nucleotide-binding domain-like receptor protein 3
MCP	monocyte chemoattractant protein	TSLP	thymic stromal lymphopoietin
HMC-1	human mast cell line	Bcl-2	B-cell lymphoma 2
TLR4	toll like receptor 4	p-PKB	phospho-protein kinase B
COX-2	cyclooxygenase-2	p-ERK	phospho-extracellular regulated protein kinases
ASNA	adrenal sympathetic nerve activity	p-JAK2	phospho-janus kinase 2
IAV	influenza A virus	p-STAT3	phospho-signal transducer and activator of transcription 3
TLR7	toll-like receptor 7	MMP-2	matrix metalloproteinase-2
IFN- $\beta$	interferon- $\beta$	Mcl-1	myeloid cell leukemia 1
CNS	central nervous system	Bcl-xL	B-cell lymphoma-extra large
TCM	traditional Chinese medicine	CDK1	cyclin-dependent kinase 1
IUPAC	international Union of Pure and Applied Chemistry	Cdc25c	cell division cycle 25C
PTPLB	protein tyrosine phosphatase-like, member b	G-CSF	granulocyte-colony stimulating factor
TNF- $\alpha$	necrosis factor- $\alpha$ ; interleukin-8 (IL-8)	TRPC1	transient receptor potential canonical 1
PGE2	prostaglandin E2	PLC- $\gamma$ 1	phospholipase C- $\gamma$ 1
JNK	c-Jun N-terminal kinase	EGF	epidermal growth factor
NQO1	NAD(P)H-quinone oxidoreductase 1	TFF2	trefoil factor 2
HUVEC	human umbilical vein endothelial cells	TRPC1	transient receptor potential canonical 1
AMPK	AMP-activated protein kinase	TLC	thin layer chromatography
ACC	acetyl-CoA carboxylase; carboxylase	ICAM-1	intercellular adhesion molecule-1
MCP	monocyte chemoattractant protein	MIP-2	macrophage inflammatory protein 2
HA	Hubei type AR	DOI	1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane
MA	maoshan type AR	TRPA1	transient receptor potential cation channel subfamily a member 1
CRF	corticotropin-releasing factor	ATR	Atractylode

action for invigorating the spleen and eliminating dampness. However, it has been reported that the former crude drug has anti-sudorific activity and the latter exhibits diaphoretic activity (Mizukami et al., 1996), and they have been used for different clinical purposes. AR has been used as an important crude drug for the treatment of rheumatic diseases, digestive disorders, night blindness, and influenza in TCM (Xiao et al., 2002) and was listed in Shennong Bencao Jing, the first Chinese Pharmacopoeia. In the Korean and Japanese Pharmacopoeias, the AR has been prescribed in traditional medicine as a diuretic and stomachic drugs (Kitajima et al., 2003c). In Thai traditional medicine, the main use of *A. lancea* is for the treatment of fever and cold (Kesara et al., 2017). These ethnopharmacological uses of AR either as a single extract or as a component in herbal medicine formula are explained by its properties in eliminating dampness, invigorating spleen, and expelling wind according to the theory of TCM. However, “Zhu” medicine materials have a long history of application and have always been confused. The Latin names of AR are miscellaneous. The multiple components contained in the AR contributed to its beneficial effects including a series of sesquiterpenoids, alkyne, triterpenoids, aromatic glycosides, oligosaccharides, and polysaccharides (Jun et al., 2018a). But the available literature is not sufficient to explain its medical claims. And the corresponding structures have not been fully introduced and summarized yet. Although recent researches reveal that the extracts from AR could also exert improving gastrointestinal function, anti-tumor activity, immunomodulatory activity, anti-inflammatory activity, antibacterial activity (Jun et al., 2018). The findings have not yet been established links between traditional uses and modern scientific knowledge of AR. And the toxicity and safety of the chemicals have not been defined (Zhu et al., 2018). On the other hand, the drugs distributed in the market have hugely varied in contents of the major essential oil compounds, posing a challenge for the cultivation of AR with constant quality (Nishikawa et al., 1975). A systematic review of *A. macrocephala* has been previously

reported (Zhu et al., 2018). This paper reviews the available recent literature on botany, traditional use, phytochemistry, pharmacological activity and its possible mechanisms, toxicity of AR with an emphasis on the biological activity and its application in TCM, quality control, and to critically analyse the reported studies. Its other possible clinical applications and future research directions also were proposed to provide a valuable and comprehensive compilation of research findings on AR to improve its medical value and use.

## 2. Botany

Genus *Atractylodes* is the main source of *Atractylodis Rhizoma* (known as “Cangzhu” in China, “Khod-Kha-Mao” in Thailand and “Sojutsu” in Japan) (Ahmed et al., 2016) and *Atractylodis Macrocephalae Rhizoma* (AM, known as “Baizhu” in China, “Byakujutsu” in Japan and “Baekchul” in Korea) in China, Japan, and Korea (Table 1), both being long used as a stomachic. In the Japanese Pharmacopoeia, *Atractylodes Lancea* Rhizome is the rhizome of *Atractylodes lancea* De Candolle, *Atractylodes chinensis* Koidzumi or their interspecific hybrids. *Atractylodes Rhizome* is the rhizome of *Atractylodes japonica* Koidzumi ex Kitamura (Wa-byakujutsu) or *Atractylodes macrocephala* Koidzumi (*Atractylodes ovata* De Candolle) (Kara-byakujutsu) (Shimato et al., 2018). *Atractylodes Rhizome* is the rhizome of *Atractylodes lancea* De Candolle or of *Atractylodes chinensis* Koidzumi. *Atractylodes Rhizome* White is the rhizome of *Atractylodes japonica* Koidzumi or *Atractylodes macrocephala* Koidzumi in Korean Pharmacopoeia. However, *A. japonica* is not included in the Pharmacopoeia of the People's Republic of China (Since, 2015 Edition) and Taiwan Herbal Pharmacopoeia (Committee, 2015).

A comparison of the components in the rhizomes of Chinese *Atractylodes* has been made by thin layer chromatography (TLC) and gas-liquid chromatography (GLC). The results were in accordance with

**Table 1**

Atractylodis rhizoma and atractylodis macrocephalae rhizoma in pharmacopoeia of China, Japan and Korea.

Pharmacopoeia	Crude drug	Scientific names
Pharmacopoeia of the People's Republic of China	Atractylodis Rhizoma	<i>Atractylodes lancea</i> (Thunb.) DC. or <i>Atractylodes chinensis</i> (DC.) Koidz.
	Atractylodis Macrocephalae Rhizoma	<i>Atractylodes macrocephala</i> Koidz.
Japanese Pharmacopoeia	Atractylodes Lancea Rhizome	<i>Atractylodes lancea</i> De Candolle or <i>Atractylodes chinensis</i> Koidzumi or their interspecific hybrids
	Atractylodes Rhizome	<i>Atractylodes japonica</i> Koidzumi ex Kitamura (Wa-byakujutsu) or <i>Atractylodes macrocephala</i> Koidzumi ( <i>Atractylodes ovata</i> De Candolle) (Kara-byakujutsu)
Korean Pharmacopoeia	Atractylodes Rhizome	<i>Atractylodes lancea</i> De Candolle or <i>Atractylodes chinensis</i> Koidzumi
	Atractylodes Rhizome White	<i>Atractylodes japonica</i> Koidzumi or <i>Atractylodes macrocephala</i> Koidzumi

their morphological features and pharmaceutical merits. *A. macrocephala*, with its leaves pinnately incised, is characterized by the presence of rich atractylon and absence or lack of atractylodin. As for *A. lancea* and *A. chinensis* with their leaves not incised or only lobed, are characterized by high contents of atractylodin,  $\beta$ -eudesmol, and hinesol, but poor in atractylon (Fu et al., 1981). In addition, *A. lancea*, *A. chinensis*, and *A. macrocephala* are the three most widely used medicinal species of the *Atractylodes* genus. Their similar morphological features cause disagreement as whether they are three unique species, leading to their frequent misuses in medical products (Wang et al., 2020). *A. macrocephala* is distinguishable from other *Atractylodes* plants by RAPD analysis (Kohjyouma et al., 1997), and the phylogenetic relationship between *A. lancea* and *A. japonica* is suggested to be closer than that between *A. japonica* and *A. macrocephala* (Kitajima et al., 2003b). further examined the water-soluble portion of *A. macrocephala* to determine the chemotaxonomic relationships among them. And confirmed that the chemotaxonomic relationship between *A. lancea* and *A. japonica* can be considered to be close. The basic term “zhu” was the only one used when atractylodes was first recorded in the ancient Shennong Bencao Jing (ca. 100 A.D.) (Chang et al., 2015); the division between these two related herb materials first occurred in the Mingyi Bielu (500 A.D.). At that time, the tuber-like rhizomes of these plants were specified as either Baizhu (bai = white) and Chizhu (chi = red), referring to the color observed in the sliced rhizomes, the red being due to spots of accumulated oils. Later, Chizhu was renamed Cangzhu (cang = gray or black), which refers to the appearance of the outer skin of the rhizome, a dark gray-black color. “Baizhu” in the Song Dynasty gradually turned into a cultivated product. After the Yuan (1271–1368 A.D.) and Ming Dynasties (1368–1644 A.D.), “Cangzhu” and “Baizhu” were divided into two herbs with different effects. After the Ming and Qing Dynasties (1636–1912 A.D.), “Mao Cangzhu” was recommended in Jiangsu province, while AM highly praised wild species in Zhejiang Province. Later it was found that this herb includes two species, *A. lancea* and *A. chinensis*, separately in China and people have used these together as AR (ECONCMMBC, 1999). According to “The Plant List” ([www.theplantlist.org](http://www.theplantlist.org)), *Atractylodes amurensis* (Freyn ex Kom.) H.S.Pak, *Atractylodes carlinoides* (Hand.-Mazz.) Kitam., *Atractylodes japonica* Koidz. ex Kitam., *Atractylodes koreana* (Nakai) Kitam., *Atractylodes lancea* (Thunb.) DC., is accepted names for the plant, with more than ten synonyms. Generally, cultivated or wild *A. lancea*, also known as Mao Cangzhu in Chinese, is mainly produced in Jiangsu, Hubei, Zhejiang, Anhui, and other places. *A. lancea* is irregularly curved, cylindrical

rhizome, 3 cm–10 cm in length and 10 mm–25 mm in diameter. The external surface is dark grayish-brown to dark yellow-brown. A transverse section reveals nearly orbicular, with pale brown to red-brown secretes as fine points. Often white cotton-like crystals are produced on its surface if *A. lancea* stored long time with fragrant smelling and sweet tasty. *A. chinensis* (Bei Cangzhu) is mainly produced in Hebei, Shanxi, Inner Mongolia, Liaoning, and other places. *A. chinensis* is irregularly cylindrical rhizome, 4 cm–9 cm in length and 10 mm–40 mm in diameter. The external surface is black-brown to yellow-brown. The fragrance is light, pungent, and bitter (Fig. 1) (Committee, 2018). Due to the different origins of *A. lancea* and *A. chinensis*, the leaf shapes and active ingredients are different. So it is appropriate to treat it differently and consider “Bei Cangzhu” as a variant of “Mao Cangzhu” (Fu et al., 1981).

### 3. Traditional uses

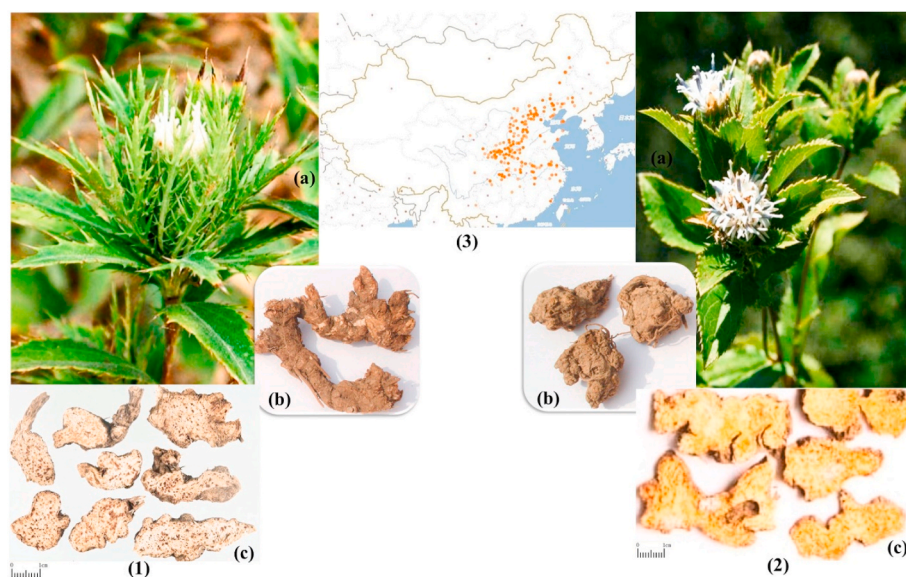
#### 3.1. Medicinal history of AR

Beginning from the ancient times, the traditional use of AR constantly develops and changes with the deepening of cognition. AR is listed as a top grade in Shennong Bencao Jing (Gu, 1955), in which it was recorded as “removing wind-cold and resolving dampness, dead muscle spasm, and jaundice. The decoctions are taken for a long time, lighting body and prolonging life without hunger.” AR is pungent and fragrant. It can relax muscle and induce perspiration. It can dispel the cold and pathogenic wind on the surface of the skin. However, the effect of sweating is not obvious. AR is most suitable for treating cold and dampness because it is good at dehumidification. According to the Yaopin Hua Yi (Jia, 2015), AR is the main drug from the treatment of the syndrome of dampness, turbidity, and stagnation of middle-jiao (the upper part of the abdominal cavity). Mingyi Bielu (Tao, 2013) documented “curing headache, eliminating phlegm and water-retention, removing the swelling of wind and water between the skin, eliminating heart disease and vomiting in cholera, warming the stomach and eliminating food”. AR could invigorate spleen-Qi, and activate the spleen and stomach. The Yang is clear and rising, nourishing and clearing orifices, leading to a clear-sight. The Taiping Shenghui Fang (Wang et al., 1958) recorded it as “treating night blindness” and Jingyan Fang recorded “treating internal and external barriers to the eyes”. AR eliminates dampness with aromatics by avoiding filth and pestilence. Bencao Qiuyuan (Zhao, 2009) added the treatment of “injury from food, heat, and diarrhea, spleen dampness and blood”. The records of doctors from all dynasties reflected the main treatment scopes of AR. Therefore, the Materia Medica in the Ming and Qing Dynasties summarized the functions of AR as drying dampness and strengthening the spleen, eliminating pollution and turbidity, eliminating wind dampness, relieving symptoms, and clarifying the eyes.

#### 3.2. Compatibility and application of AR

These functions also reflected in the application of ancient herbal medicine containing AR in typhoid fever, internal and external barriers of the eyes, diarrhea, arthralgia, beriberi, and edema. Jiang et al. (2016) searched the database management system of Puji Fang, and obtained 951 pieces of AR compound, which was used for 347 kinds of diseases. The compound containing AR has the most treatments for deficiency syndromes, including tonifying asthenia and Qi, strengthening and tonifying Yuanyang, and ear asthenia. In addition, AR is mainly indicated for typhoid fever (including miscellaneous treatment of typhoid fever, moderate cold, and the common cold), internal and external barriers (including eye blindness and bird blindness), spleen and stomach weakness (including spleen and stomach deficiency and food fatigue), diarrhea, and paralysis, jaundice, cold deficiency, toothache, vomiting, cough, hemorrhoids, phlegm, spasm, bleeding, dystocia, constipation, chancre disease, rhinorrhea, endless lochia, thirst,





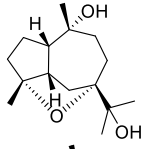
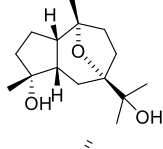
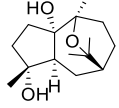
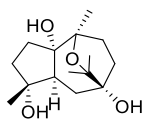
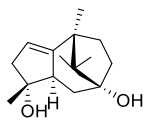
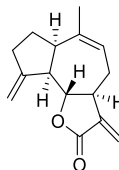
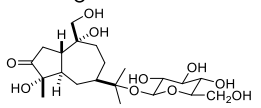
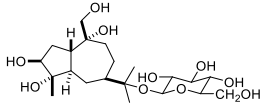
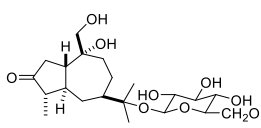
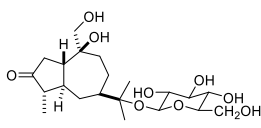
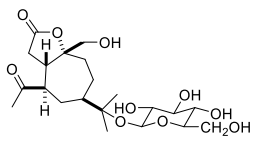
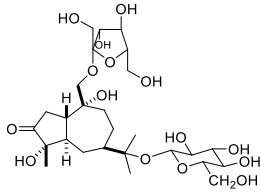
**Fig. 1.** The above-ground portion (a), medicinal portion (b), and commercial herbal pieces (c) of (1) *A. chinensis* and (2) *A. lancea*. Distribution of *Atractylodes* Rhizoma resources (3).

heatstroke, and palpitation were also indicated. The indications were classified into 43 categories in total. When AR is used for treating diseases, syndromes, and symptoms, it is compatible with different herbs. It is often compatible with *Phellodendri Chinensis* Cortex and *Coptidis Rhizoma* for clearing heat and drying dampness and with *Magnoliae Officinalis* Cortex and *Citri Reticulatae* Pericarpium for fortifying the spleen and drying dampness (Zhao et al., 2019). The compatible application of AR mainly includes drying dampness and activating spleen, dispersing dampness, removing blockage, exorcising evils, relieving depression, nourishing the stomach and supplementing deficiency, and enriching the liver to brighten the eyes. AR must be used to trap the spleen with dampness (Zhuang et al., 2015). For example, Pingwei Powder comes from AR, *Magnoliae Officinalis* Cortex and *Citri Reticulatae* Pericarpium, and it is used to remove dampness and regulate Qi. In the treatment of diarrhea with dampness, AR is associated with *Citri Reticulatae* Pericarpium, *Poria* or *Plantaginis Herba*, and *Liuyi* Powders. *Zingiberis Rhizoma* or *Cinnamomi Cortex* is also added for cold-dampness. If heat is converted into dampness stagnancy, AR is combined with *Paeoniae Radix Alba*, *Coptidis Rhizoma* and *Scutellariae Radix*. For people who have experience dampness and evil trapped in the spleen, abdominal pain, and diarrhea. AR harmonizes the liver and spleen when combined with *Paeoniae Radix Alba*, *Scutellariae Radix*, *Cinnamomi Cortex*, and *Saposhnikovia Radix*. AR is good at dispersing cold and dampness and benefiting the joints, especially for dampness arthralgia (Zhuang et al., 2015). AR can induce sweat and dehumidification and dispel the evil wind. It is also compatible with *Notopterygii Rhizoma et Radix* and *Saposhnikovia Radix*, such as Nine-Ingredient *Notopterygium* Decoction. For example, the extracts with single AR are used to treat severe pain and joint swelling, and they can be combined with AM and *Notopterygii Rhizoma et Radix*; AM, *Ephedrae Herba*, and *Cinnamomi Ramulus*; or AM, *Poria*, and *Alismatis Rhizoma*. *Ermiao Powder* is composed of AR and *Phellodendri Chinensis* Cortex. It is effective in treating phlegm arthralgia, foot dampness, and leg sores. *Baihu Jia Cangzhu* Decoction treats damp-temperature disease with AR being compatible with *Gypsum Fibrosum* and *Anemarrhenae Rhizoma*. However, the functions of AR in eliminating filth, promoting Qi and relieving depression have not been appreciated. AR has a fragrant smell and good nature but it is not conservative. If used to prevent diseases, AR can be worn or fumigated in a medicine bag made of AR and *Acori Tatarinowii Rhizoma* and *Artemisiae Argyi Folium*. *Yueju Pill* is mainly made of AR, and it can invigorate the spleen. If the spleen is healthy, the

other four viscera are healthy, and the melancholia resolves itself. The Chinese traditional incense consisting mainly of AR, *Phellodendri Chinensis* Cortex, and *Artemisiae Argyi Folium* has demonstrated the advantages of Chinese medicine in “avoid poisonous gas” in the prevention of the novel coronavirus COVID-19 (Zhang et al., 2020). “AR could warm the stomach, transport food and increase appetite” when combined with *Galli Gigerii Endothelium Corneum*, and it can promote appetite and increase the effect of *Galli Gigerii Endothelium Corneum* on relieving food and guiding stagnation (Tao, 2013). The combination of AR and *Poria* can strengthen the spleen and stomach, promote the clearance and reduction in turbidity, regulate the acquired constitution, generate vigorous Qi and blood, nourish the viscera and limbs, and resolve the deficiency. AR can be used for the treatment of blindness, freckles, dry eyes, and other eye diseases. Ground AR and *Ephedrae Herba* are combined into powder, mixed with wine, and used to treat dry eyes. In Zhengzhi Zhunsheng (Wang, 1993), single AR was used to treat night blindness, while stir-fried AR combined with AM, *Cicadae Periostracum*, and *Coptidis Rhizoma*, was used in powder form to treat painful eyes and corneal opacity.

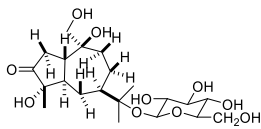
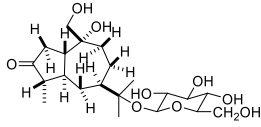
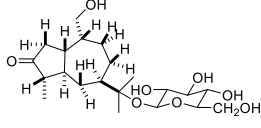
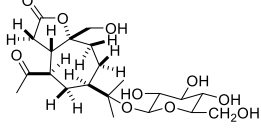
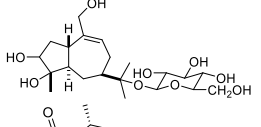
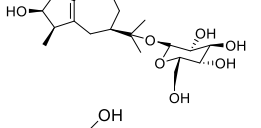
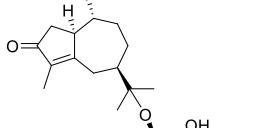
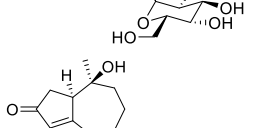
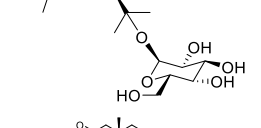
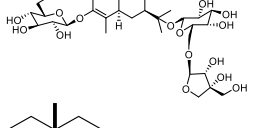
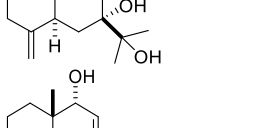
In conclusion, most of the traditional clinical functions of AR are still currently being used. However, the core viewpoints of AR dehumidification are not unified. AR is generally believed to be good at removing the dampness in upper Jiao (chest above the diaphragm, including heart, lungs, head, face), while Li Gao, the founder of “Spleen Stomach Theory” of TCM, believed that AR is an essential medicine for treating flaccidity syndrome (Li, 2007). AR could rule the dampness in the three parts. If the dampness is in the upper Jiao, dampness phlegm could be easily produced to dry the dampness and conduct phlegm. If the dampness is in the middle Jiao, the stagnation of Qi is used for diarrhea, to broaden the middle Jiao and strengthen the spleen. If the dampness is in the lower part, the foot and knee are flaccid and soft. *Phellodendri Chinensis* Cortex, which can strengthen the foot and knee, can be used to treat this flaccidity. AR’s Qi is strong and vigorous, and the effect of sweating is optimal. The effect of invigorating the middle Jiao is weaker than that of AM. However, the research on treating flaccidity by removing the dampness of the lower Jiao is insufficient. The clinical dosage of AR is also related to the difference in the diseases and types of syndrome and symptoms. Zhao et al. (2019) collected ancient books and clinical experience and concluded that the AR dosage should be 5–25 g when drying dampness, fortifying the spleen, enriching Yin and supplying Yang to treat gynecological diseases (such as infertility,

**Table 2**The terpenoids and their glycosides from *Atractylodis Rhizoma*.

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Guaiacane sesquiterpenes and their glycosides	1	4 $\alpha$ ,7 $\alpha$ -epoxyguaiane-10 $\alpha$ ,11-diol		<i>A. lancea</i> (Wang et al., 2008)
	2	7 $\alpha$ ,10 $\alpha$ -epoxyguaiane-4 $\alpha$ ,11-diol		
	3	10 $\beta$ ,11 $\beta$ -epoxyguaiane-1 $\alpha$ , 4 $\alpha$ -diol		
	4	10 $\beta$ ,11 $\beta$ -epoxyguaiane-1 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ -triol		
	5	1-patchoulene-4 $\alpha$ ,7 $\alpha$ -diol		
	6	eremanthin		<i>A. japonica</i> (Toda et al., 2017)
	7	atractyloside A [(1S,4S,5R,7R,10R)-4,10,11,14-tetrahydroxyguai-3-one 11-O- $\beta$ -D-glucopyranoside]		<i>A. lancea</i> (Kitajima et al., 2003b) <i>A. japonica</i> (Kitajima et al., 2003a)
	8	atractyloside B [(1S,3S,4S,5R,7R,10R)-guai-3,4,10,11,14-pentol 11-O- $\beta$ -D-glucopyranoside]		
	9	(1S,4S,5S,7R,10R)-10,11,14-trihydroxyguai-3-one 11-O- $\beta$ -D-glucopyranoside		
	10	(1S,4S,5R,7R,10R)-11,14-dihydroxyguai-3-one 11-O- $\beta$ -D-glucopyranoside		
	11	(1S,5R,7R,10R)-secoatractylolactone 11-O- $\beta$ -D-glucopyranoside		
	12	atractyloside A 14-O- $\beta$ -D-fructofuranoside		
	13	10-epi-atractyloside A [(1S,4S,5R,7R,10S)-4,10,11,14-tetrahydroxyguai-3-one 11-O- $\beta$ -D-glucopyranoside]		

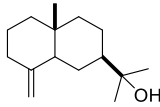
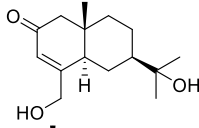
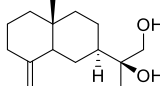
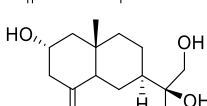
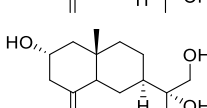
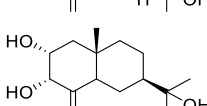
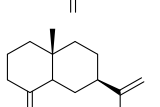
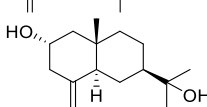
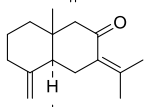
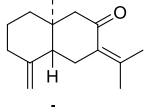
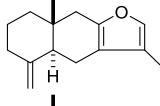
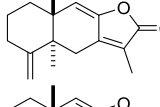
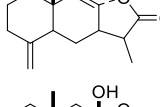
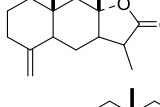
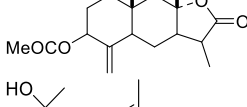
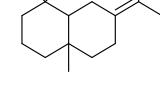

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Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	14	(1S,4S,5S,7R,10R)-10,11,14-trihydroxyguaia-3-one 11-O-β-D-glucopyranoside		
	15	(1S,4S,5S,7R,10S)-10,11,14-trihydroxyguaia-3-one 11-O-β-D-glucopyranoside		
	16	(1S,5R,7R,10R)-secoatractylolactone 11-O-β-D-glucopyranoside		
	17	3,4,11,14-tetrahydroxyguaia-9-en-11-O-β-D-glucopyranoside		<i>A. lancea</i> (Chen, 2007)
	18	(3R,4R,7R,10R)-2-hydroxypancherione-11-O-β-D-glucopyranoside		<i>A. lancea</i> (Xu et al., 2016a)
	19	(1S,7R,10R)-11,15-dihydroxy-4-guaien-3-one 11-O-β-D-glucopyranoside		
	20	(1R,7R,10S)-10,11-dihydroxy-4-guaien-3-one 11-O-β-D-glucopyranoside		
	21	(5R,7R,10S)-3-O-β-D-glucopyranosylisoptercarpolone-11-O-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside		<i>A. lancea</i> (Jiang et al., 2018)
Cineole sesquiterpenes and their glycosides	22	eudesm-4 (15)-ene-7α,11-diol		<i>A. lancea</i> (Wang et al., 2008)
	23	eudesm-4 (15),7-diene-9α,11-diol		
	24	eudesm-4 (15),7-diene-11-ol-9-one		

(continued on next page)

Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	25	$\beta$ -eudesmol		<i>A. lancea</i> (Duan et al., 2008)
	26	14-hydroxy-isoptercarpolone		<i>A. lancea</i> (Kamauchi et al., 2015)
	27	kudtdiol		
	28	(11R)-2,11,12-trihydroxy- $\beta$ -selinene		
	29	2,11,13-trihydroxy- $\beta$ -selinene		
	30	3 $\alpha$ -hydroxy-pterocarpol		
	31	4 (15),11-eudesmadien		<i>A. lancea</i> (Van Minh et al., 2004)
	32	pterocarpol [(2S,4aS,6R,8aS)-6-(2-hydroxypropan-2-yl)-8a-methyl-4-methylidene-1,2,3,4a,5,6,7,8-octahydronaphthalen-2-ol]		<i>A. lancea</i> (Yahara et al., 1989)
	33	eudesma-4(14),7(11)-dien-8-one		<i>A. japonica</i> (Endo and Hikino, 1979)
	34	(+)-eudesma-4(14),7(11)-dien-8-one		
	35	atractylon [(4aS,8aR)-3,8a-Dimethyl-5-methylene-4,4a,5,6,7,8,8a,9-octahydronaphtho [2,3-b]furan]		<i>A. lancea</i> (Resch et al., 1998)
	36	atractylenolide I		<i>A. lancea</i> (Resch et al., 1998); <i>A. chinensis</i> (Meng et al., 2010)
	37	atractylenolide II		<i>A. japonica</i> (Endo et al., 1979)
	38	atractylenolide III		<i>A. japonica</i> (Yosioka et al., 1959); <i>A. lancea</i> (Hikino et al., 1964)
	39	atractylenolide IV		<i>A. lancea</i> (Hikino et al., 1964)
	40	eudesm-7 (11)-en-4-ol		<i>A. japonica</i> (Hong et al., 2012)
	41	$\alpha$ -bisabolol		<i>A. lancea</i> (Takeda et al., 2001)

(continued on next page)



Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	42	atractyloside C		<i>A. lancea</i> (Kitajima et al., 2003b)
	43	atractyloside G		
	44	atractyloside G 2-O-β-D-glucopyranoside		
	45	atractyloside D		<i>A. lancea</i> (Yahara et al., 1989)
	46	atractyloside I		
	47	atractyloside E		
	48	(5R,7R,10S)-isoptercarpolone-β-D-glucopyranoside [(5R,7R,10S)-11-hydroxyeudesm-3-en-2-one-11-O-β-D-glucopyranoside]		<i>A. japonica</i> (Kitajima et al., 2003a)
	49	cis-atractyloside I		
	50	(2R,3R,5R,7R,10S)-Atractyloside G 2-O-β-Glucopyranoside		
	51	(3S)-3-hydroxyatractylenolide III 3-O-D-glucopyranoside [(3S,5R,8R,10R)-3,8-dihydroxyeudesma-4(15),7(11)-diene-8,12-olide 3-O-β-D-glucopyranoside]		<i>A. lancea</i> (Xu, 2017)
	52	officinose C		
	53	atractyloside F		
	54	(3S,4R,5S,7R)-13-hydroxylhinesolone-11-O-β-D-glucopyranoside		<i>A. lancea</i> (Yahara et al., 1989)
	55	(5R,7R,10S)-3-hydroxyisoptercarpolone-3-O-β-D-glucopyranoside		
	56	(5R,7R,10S)-6''-O-β-D-apiofuranosylatractyloside I		
	57	(5R,7R,10S)-6''-O- acetylatractyloside I		

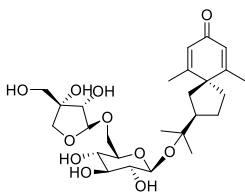
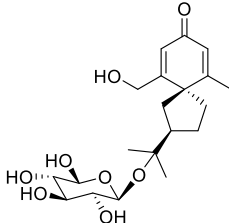
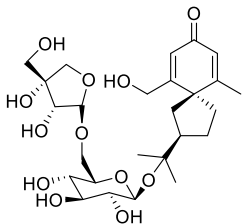
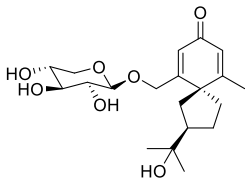
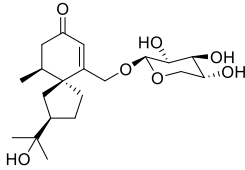
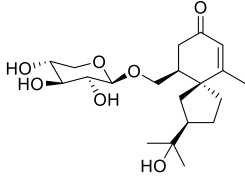
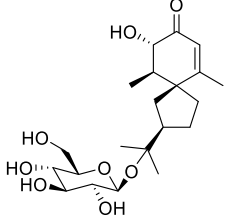
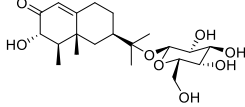
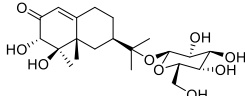
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Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	58	(5R,7R,10S)-6'-O- acetylratractyloside I		
	59	(5R,7R,10S)- isopteroecarpolone-11-O-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside		
	60	(5R,7R,10S)-14-hydroxyisopteroecarpolone-11-O-β-D-glucopyranoside		
	61	(5R,7R,10S)-14-carboxyisopteroecarpolone-11-O-β-D-glucopyranoside		
	62	(2S,7R,10S)-2-hydroxylcarissone-11-O-β-D-glucopyranoside		
	63	(2R,7R,10S)-2-hydroxylcarissone-11-O-β-D-glucopyranoside		
	64	(1R,7R,10R)-1-hydroxylcarissone-11-O-β-D-glucopyranoside		
Spirosane sesquiterpenes and irimophenone sesquiterpenes of vetiver and their glycosides	65	hinesol		<i>A. lancea</i> (Hashimoto et al., 1999)
	66	hinesolone		<i>A. lancea</i> (Long et al., 2018)
	67	2-oxo-12-hydroxy-hinesol		<i>A. lancea</i> (Kamauchi et al., 2015)
	68	2-oxo-15-hydroxy-hinesol		
	69	(7R)-3,4-dehydrohinesolone-11-O-β-D-glucopyranoside		<i>A. lancea</i> (Xu et al., 2016a)

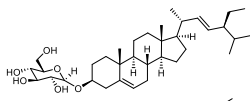
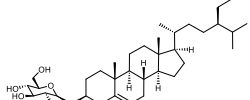
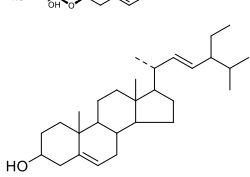
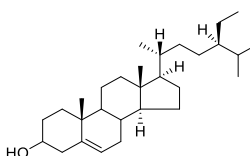
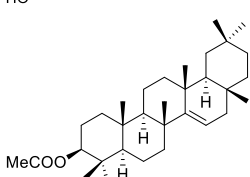
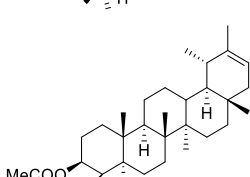
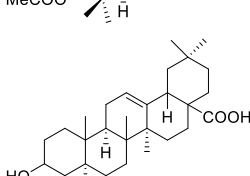
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Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	70	(7R)-3,4-dehydrohinesolone-11-O- $\beta$ -D-glucopyranosideideyranoside-hydroxyeud		
	71	(5R,7R)-14-hydroxy-3,4-dehydrohinesolone-11-O- $\beta$ -D-glucopyranoside		
	72	(5R,7R)-14-hydroxy-3,4-dehydrohinesolone-11-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	73	(5R,7R)-14-hydroxy-3,4-dehydrohinesolone-14-O- $\beta$ -D-xylopyranoside		
	74	(4S,5S,7R)-15-hydroxylhinesolone-15-O- $\beta$ -D-xylopyranoside		
	75	(4S,5S,7R)-14-hydroxylhinesolone-14-O- $\beta$ -D-xylopyranoside		
	76	(3S,4R,5S,7R)-13-hydroxylhinesolone-11-O- $\beta$ -D-glucopyranoside		
	77	(3S,4R,5R,7R)-3,11-dihydroxy-11,12-dihydronootkatone-11-O- $\beta$ -D-glucopyranoside		
	78	(3S,4R,5S,7R)-3,4,11-trihydroxy-11,12-dihydronootkatone-11-O- $\beta$ -D-glucopyranoside		

(continued on next page)

Table 2 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Triterpenoids and steroids	79	stigmasterol 3-O- $\beta$ -D-glucopyranoside		<i>A. lancea</i> (Duan et al., 2008)
	80	daucoesterol [3 $\beta$ -( $\beta$ -D-glucopyranosyloxy)stigmast-5-en]		
	81	stigmasterol [(3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-Ethyl-6-methyl-2-heptanyl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta [a]phenanthren-3-ol]		
	82	$\beta$ -sitosterol [(3S,8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta [a]phenanthren-3-ol]		
	83	traxerol acetate [(3S,4aR,6aR,8aR,12aR,12bS,14aR,14bR)-4,4,6a,8a,11,11,12b,14b-Octamethyl-1,2,3,4,4a,5,6,6a,8,8a,9,10,11,12,12a,12b,13,14,14a,14b-icosahydro-3-picenyl acetate]		
	84	$\phi$ -traxasteryl acetate (heterolupeol)		
	85	oleanolic acid [(3 $\beta$ )-3-hydroxy-olean-12-en-28-oic acid]		

polycystic ovary syndrome, and primary dysmenorrhea). It is 12–15 g when diffusing impediment and unblocking the collaterals, clearing heat, and draining dampness to treat rheumatoid arthritis and gouty arthritis.

## 4. Phytochemistry

### 4.1. Terpenoids and their glycosides

AR is rich in volatile oil and other small polar components. The reported volatile oil components were mainly identified using GC-MS. The identified compounds in eight samples accounted for 89.36%–95.79% of the total volatile oil. Sesquiterpene is the main component of relatively high boiling point in AR volatile oil, with strong aroma and biological activity. The chemical profiles of the essential oil from *A. lancea* showed that wild grown plants produced mostly significant amounts of sesquiterpenes, with the top three being hinesol (68.5%),  $\beta$ -eudesmol (13.1%) and elemol (6.2%) (Jia et al., 2004).

Guaiacane sesquiterpenes are isolated and identified earlier from AR, and they belong to azulene derivatives, an aromatic skeleton compound composed of five and seven-membered rings. Wang et al. (2008) obtained sesquiterpenes (1–5) from *A. lancea*, and confirmed that the

compounds have no cytotoxic activity on P388 and A549 cells through cytotoxic experiments. Kitajima et al. (2003b) isolated various water-soluble guaiacum sesquiterpenoids from the rhizomes of *A. lancea* and *A. japonica*, and analyzed the structure of the rhizomes (Table 2, 7–16). Compounds 13 and 14 were isolated from *A. japonica*, and compounds 18–21 were isolated from *A. lancea* for the first time. Pharmacological experiments showed that compounds 18 and 20 have no significant inhibitory effect on protein tyrosine phosphatase-like, member b (PTPLB) and  $\beta$ -glucosidase. Wang et al. (2008) isolated and identified cineole sesquiterpenes from AR. Duan et al. (2008) analyzed the structure of compound 25. Endo and Hikino (1979) determined the absolute configuration of compounds 33 and 34 via circular dichroism. Endo et al. (1979) isolated atractylenolide II (37) from *A. japonica* for the first time and analyzed its structure. Atractylolide III (38) was isolated from *A. Japonica* for the first time by Yosiooka et al. (1959). And both atractylolide III and atractylone had acaricidal activity (Meng et al., 2010). Kitajima et al. (2003a) isolated a series of eucalyptosyl sesquiterpene glycosides from AR and analyzed the chemical structure of compounds (42–50), among which compounds (43, 44, 46) were first isolated from *A. lancea* methanol extract, as shown in Table 2. Compounds 54–64 were isolated from 30% n-butanol fraction of *A. lancea* and their structures were analyzed (Xu, 2017). At present, 14 species of

spiroane sesquiterpenes (Table 2, 65–78) have been found in *A. lancea*. Compounds 77 and 78 are irimophenol alkane sesquiterpenes. The triterpenoid saponins in AR are mainly tetracyclic triterpenoids, pentacyclic triterpenoids, and tetracyclic triterpenoids. Six triterpenoids (Table 2, 79–84) were isolated from *A. lancea* by Duan et al. (2008), and their chemical structures were analyzed. The information of the sesquiterpenoid biosynthesis is largely unknown. Ahmed et al. (2016) investigated the transcriptome of different tissues of *A. lancea*. All the enzymes that took part in the terpenoid biosynthesis and five different known sesquiterpenoids were identified via cytosolic mevalonic acid and plastidal methylerythritol phosphate pathways. Besides, 6864 simple sequence repeats were found to be great potential markers in *A. lancea*. Jia et al. (2016) demonstrated that endophytic bacterium-triggered ROS could directly oxidize oxygen-free sesquiterpenoids and increase the oxygenous sesquiterpenoid content and diversity in *A. lancea*. Takeda et al. (1996) transplanted the rhizomes of *A. lancea*, *A. chinensis* and *A. koreana* growing in China from 18 populations in the same experimental field. Main essential oil components: the sesquiterpenes and the polyacetylene of atractylodin were determined. The analytical data of 306 cultivated plants were compared with plants collected in their habitat. *A. lancea* varied significantly in the contents of the components after cultivation. Compared to this, *A. chinensis* had constant content values. Three types of *A. lancea* and two types of *A. chinensis*, which are distinguished by the characteristics of the components in the wild conditions, were statistically recognized after cultivation. From these results, it was determined that the geographical variation in the components of these species mainly reflects genetic variability.

#### 4.2. Alkynes and their glycosides

Alkynes include unsaturated alcohols, ketones, acids, esters, benzene, furans and other functional groups in addition to unsaturated triple bonds and double bonds. The triple and double bonds are relatively stable, and thus they can be extracted, separated, and identified by conventional phytochemical techniques. The polyacetylenes were classified by their chemical backbones and the species of genus *Atractylodes* where the compounds were contained were presented. The polyacetylenes of diene-diyne types were classified into furan-ring-attached, alcohol-attached, acetyl-attached, and two more functional groups-attached compounds. A part of atractylodin-related acetylenes, which contained a furan-ring at the terminal carbon, consisted of nine carbons. Among them, atractylodin was the most reported and it is contained in *A. lancea*, *A. chinensis*, *A. japonica* and *A. koreana* (Kim, 2016). Other polyacetylenes comprised 14 carbons with double bonds at C-6 and C-12, and triple bonds at C-8 and C-10. Diacetyl atractylodiol (100) comprised 13 carbons and (2E, 8E)-decadiene-4,6-diyne-1,10-diol-1-O- $\beta$ -D-glucopyranoside (101) was the only polyacetylene consisted of 10 carbons and glucosamine. However, no diene-diyne types were reported to be contained in AM (Table 3, 86–122). As shown in Table 3, most compounds of triene-diyne type polyacetylenes (123–162) originated from *A. lancea* and possessed 14 carbons with triple bonds at C-4 and C-6, double bonds at C-2, C-8, and C-12. Seneciolyloxy, isovaleryloxy, methylpropionyl, methylbutyryl, and acetoxy were the main functional groups of these compounds and were positioned at C-12 or C-14. Another 14 carbon polyacetylenes with triple bonds at C-8 and C-10, double bonds at C-4, C-6, and C-12. And the main functional groups were isovaleryloxy, acetoxy, methylbutyryloxy, or seneciolyloxy. Monoene-diyne type polyacetylenes and their glycosides were reported to be a single double bond and two triple bonds, consisting of 9, 10, 12, and 13 carbons, with furan ring or sugars attached (Table 3, 163–175). Kitajima et al. (2003b) obtained enyne-derived glycoside (Table 3, 169) from the water-soluble components of AR for the first time and determined their skeleton structure. Besides, several polyacetylenes with C10 chain alkyne, C13 chain alkyne, C14 chain alkyne, furan cycloalkyne, and thiophene cycloalkyne were isolated from 30% ethanol fraction of

the n-butanol fraction of Cangzhu 80% ethanol extracts (Xu, 2017). Resch et al. (1998) showed that compounds 184 and 185 have 5-lipoxygenase and cyclooxygenase activities. Chen et al. (2012) revealed that compounds 86, 88–107, and 187–188 have anti-*Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* activities. *A. lancea* essential oil data were first collected from the literature referring to the bioinformatic methods to study the variation rules and classify the chemotype of *A. lancea* essential oil. Then, the essential oil among different populations or individuals in the same population was compared. (1) Large varieties in *A. lancea* essential oil, which involved components and their content, were found among populations or even among the individuals in the same population. (2) The total essential oil and the six major components in it (elemol, atractylon, hinesol,  $\beta$ -eudesmol, selina-4(14), 7(11)-dienone and atractylodin) varied continuously in different geographical populations. (3) The total essential oil of *A. lancea* decreased from South China to North China. Two chemotypes of *A. lancea* essential oil were mainly found in China, one was Hubei chemotype (HBA), which has hinesol and  $\beta$ -eudesmol as the main components, with a little atractylodin and almost without atractylon and selina-4(14), 7(11)-dienone. The other type was Mt. Maoshan chemotype (MA), which is characterized by atractylon and atractylodin as main components with little hinesol,  $\beta$ -eudesmol and other components (Guo et al., 2008).

#### 4.3. Aromatic glycosides and acyl sugar compounds

Naturally occurring carbohydrates with aromatic aglycones are a class of important compounds, such as antibiotics (e.g., vancomycin and chromomycin), and some plant-derived phenolic hydroxyl compounds are also glycosylated (e.g., arbutin, sennoside A, and glucoside). Kitajima et al. (2003b) isolated compounds (Table 4, 190–198) from *A. lancea* and analyzed its structure. Some known compounds (201–203) of aromatic glycosides were identified from *A. lancea* by Feng et al. (2018). *A. lancea* also contains acyl sugar derivatives (Table 5).

#### 4.4. Other compounds

AR also contains other compounds (Table 6), including osthol (210), amino acids (212, 213), and other water-soluble compounds. Duan et al. (2008) first isolated compound (219) from *A. lancea*. Some new compounds were also isolated from *A. lancea*, including lignans, phenolic acids, and pyrazines. An intestinal immune system modulating arabino-3,6-galactan, containing shorter (AF-GN-1 and 3), and longer (AF-GN-2) oligosaccharide fractions were isolated from *A. lancea* (Taguchi et al., 2004). AF-GN-3 mainly contains eight oligosaccharides (oligo-1–8) and the monosaccharides (Ara and Gal). AF-GN-2 contains oligosaccharides (oligo-9–15) and small proportions of oligo-3–8. It also contains a large amount of the fraction of longer oligosaccharides. An acidic polysaccharide (ALP-3) and a neutral polysaccharide (ALP-1) were purified from *A. lancea* (Qin et al., 2019) and the results showed that ALP-1 exhibits a linear backbone composed of (2  $\rightarrow$  1)-linked  $\beta$ -D-fructofuranose. The backbone of ALP-3 was elucidated as  $\rightarrow$ 4)-GalAp-(1  $\rightarrow$  3, 4)-Rhap-(1  $\rightarrow$ , and with branch chain substituted at O-3 position of  $\rightarrow$ 3, 4)-Rhap-(1  $\rightarrow$ . The branch chain consists of  $\rightarrow$ 3, 5)-Araf-(1  $\rightarrow$ ,  $\rightarrow$ 5)-Araf-(1  $\rightarrow$ , and Araf-(1  $\rightarrow$ . A series of oligo-saccharides DP 3–15 were separated from *A. lancea* and identified as FOS, which consisted of linear  $\beta$ -(2, 1)-linked fructofuranosyl units mostly carry a terminal single  $\alpha$ -(1–2)-linked  $\alpha$ -glucopyranosyl unit (Zhuang et al., 2019). The ACPS was extracted via ultrasonic method in enzymolysis *A. lancea*. ACPS structure can be expressed as  $\alpha$ -D-Glcp-(1  $\rightarrow$  2)-[ $\beta$ -D-Fruf-(1  $\rightarrow$  2)- $\beta$ -D-Fruf-]n-(1  $\rightarrow$  2)- $\beta$ -D-Fruf. Atractylis polysaccharide could inhibit the proliferation of human ovarian cancer, liver cancer in cellular level (Xu, 2015).

Overall, more than 200 compounds have been isolated and identified from AR, and the majority of them are volatile oil. Some volatile components of AR were identified only via GC-MS alone by comparison with

the databases which were only tentative identification and could not give unambiguous structures. These kinds of compounds were not listed in the tables. Transcriptomic analyses were furthermore performed via RNA-Seq to reveal the molecular mechanism regulating sesquiterpenoid formation of *A. lancea*. A total of 857 unigenes were identified to be involved in sesquiterpenoid formation via analysis of differentially expressed genes. A putative sesquiterpenoid biosynthetic pathway was proposed, including mevalonate, 2-C-methyl-d-erythritol-4-phosphate, sesquiterpene synthase, cytochrome P450, and the peroxisome pathway (Chen et al., 2017). However, increasing studies showed that macromolecular substances (e.g., polysaccharides and proteins) play an indispensable role in the quality formation of TCM (Zhang et al., 2020). The biomacromolecules in AR have wide bioactivity-related efficacy but yet to be fully appreciated compared with small molecule components.

## 5. Pharmacology

Modern pharmacological studies supported the broad pharmacological effects of AR on various diseases. The pharmacological activities of *A. lancea* have previously been reviewed (Jun et al., 2018; Koon-rungsesomboon et al., 2014). In vitro or vivo studies on animal models demonstrated promising activities of the crude extracts (ethanolic, water, benzene, and methanol) of *A. lancea* and its major constituents ( $\beta$ -eudesmol, atractylodin, atractylon, and hinesol) on cancers, inflammation, fever and pain, gastrointestinal system, nervous system, cardiovascular system, and various microorganisms (*Staphylococcus aureus*, *E. coli*, *C. albicans*, *Saccharomyces cerevisiae* and *Rhodotorula glutinis*). The pharmacological activities of AR and its constituents on the gastrointestinal system (delay of gastric emptying, stimulation of intestinal motility, inhibition of gastric secretion, and antiulcer property) strongly supported their clinical use for the alleviation of digestive symptoms in traditional medicine (Kimura and Sumiyoshi, 2012; Plengsuriyakarn et al., 2012).

### 5.1. Improving gastrointestinal function

In the system of TCM, spleen deficiency plays an important role in the development of gastrointestinal dysfunction. Ancient Chinese doctors believed that AR can be used for dampness blocking, abdominal distention, and diarrhea. *A. japonica* has been commonly used to treat the gastrointestinal (GI) disorders in Korean traditional medicine. Modern researches also found that AR could protect the intestinal tract and promote intestinal movement and has anti-diarrhea activity through anti-inflammation (Deng et al., 2016). AR extracts have been shown to delay gastric emptying and stimulate small intestinal motility in a dose-dependent manner. The extract (1000 mg/kg) could inhibit the intestinal dyskinesia caused by atropine, and the extract (500 mg/kg) could block the gastric emptying and intestinal dyskinesia caused by 5-hydroxytryptamine (5-HT) (Kimura and Sumiyoshi, 2012). The n-butanol extract of AR has a broad-spectrum anti-ulcer effect and could inhibit protease activity and eliminate gastric acid. Choi et al. (2011) suggested that ethyl acetate extracts of *A. japonica* (AJEA) may specifically act on the distal colon longitudinal muscles (DCLM) among gastrointestinal smooth muscles, and AJEA-induced DCLM contraction is likely mediated, at least, by activation of ChAT and acetylcholinergic muscarinic receptors. Aqueous extract of *A. lancea* was also shown to increase the levels of gastric hormone motilin and gastrin while decreasing the levels of somatostatin and corticotrophin-releasing factor, which results in improving the gastric emptying condition. And polyacetylenic compounds contributed to its activity (Nakai et al., 2003). Essential oil extracted from *A. lancea* delayed gastric emptying are preformed mainly via inhibition of the release of central corticotrophin-releasing factor and activation of the vagal pathway, which is also involved in the release of gastrointestinal hormones such as motilin, gastrin, and somatostatin (Zhang et al., 2008).

AR decoction has a curative effect on histamine-induced gastric acid

hypersecretion and ulcer with a mucosal lesion as the main factor (Piao and Piao, 1996). Intestinal epithelial (IEC-6) cells play a major role in gastrointestinal disease to accelerate wounds and mucosal ulcer healing. A recent study found that atractylenolide I (ATL-I) could promote IEC-6 cell proliferation and migration by increasing cytosolic free  $\text{Ca}^{2+}$  concentration and enhancing transient receptor potential canonical 1 (TRPC1) and phospholipase C- $\gamma$ 1 (PLC- $\gamma$ 1) activity in IEC-6 cells (Song et al., 2017). Satoh et al. (2000) found that hinesol could resist gastric ulcer by inhibiting  $\text{H}^+$ ,  $\text{K}^+$ -ATPase and  $\text{Mg}^{2+}$ -ATPase and  $\text{Ca}^{2+}$ -ATPase activity. AR exerted anti-gastric ulcer effect by decreasing inflammatory mediators [i.e. tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), prostaglandin E2 (PGE2), and interleukin-8 (IL-8), IL-6] and increasing trefoil factor 2 (TFF2) and epidermal growth factor (EGF) in the rat model (Yu et al., 2015). A series of oligosaccharides (DP 3–15) were isolated from *A. lancea* and identified as FOS. They could selectively stimulate the growth and/or activity of intestinal microflora and provide a health benefit to the host (Zhuang et al., 2019). It is increasingly clear that FOS could reduce or prevent gastroenteritis, inflammatory bowel disease, reduce the risk of colon cancer, and potential pathogenic gastrointestinal bacteria (Pöhnl et al., 2017). Atractylodiol and diacetyl-atractylodiol from *A. japonica* could stimulate the contractility of the distal colon in rats by inhibiting nitrgergic-purinergeric relaxation. Atractylodin, acetylactylodinol, atractylodinol, and 4, 6, 12-tetradecatriene-8, 10-diyne-1, 3, 14-triol from *A. lancea* could promote delayed gastric emptying (Kim, 2016). These acetylenes, even though the traditional therapeutic properties cannot be entirely explained, are considered key elements for pharmacological accounts of the effects of AR that have been used to treat gastrointestinal disorders. These activities are consistent with the AR quality of natural and cultured products.

### 5.2. Immunomodulatory activity

AR is commonly used as a TCM for strengthening spleen. The spleen, a vital secondary lymphoid organ, works in innate immune response owing to its participation in immune memory and phagocytosis. AR and AM pharmaceutical uses differ in traditional Japanese Kampo medicine and TCM, with less apparent scientific evidence. Shimato et al. (2018) compared the immunomodulatory activity between Byakujutsu (*A. macrocephala* and *A. japonica*) and Sojutsu (*A. chinensis*, *A. lancea*, and the hybrids). The extract of *A. japonica* significantly induced granulocyte-colony stimulating factor (G-CSF) secretion from MCE301 cells in a concentration-dependent manner and had significantly higher activity than *A. macrocephala*. However, these effects of Byakujutsu samples were not significantly different from those of Sojutsu samples. The methanol extract of *A. lancea* could inhibit nitric oxide (NO) production in lipopolysaccharide-stimulated murine macrophage-like RAW264.7 cells and induce G-CSF secretion in murine normal colonic epithelial MCE301 cells. A neutral polysaccharide (ALP-1) and an acidic polysaccharide (ALP-3) were purified from *A. lancea*. ALP-3 exhibited macrophage proliferation in a dose-dependent manner, and stimulated phagocytic, NO and cytokines production on RAW264.7 cells. In addition, ALP-1 and ALP-3 could activate T cells in Peyer patch cells and promote the production of CSF. ALP-3 is better than ALP-1 in regulating the intestinal immune system (Qin et al., 2019). An intestinal immune system modulating arabino-3, 6-galactan (ALR-5IIa-1-1) has been found in rhizomes of *A. lancea* and the active clusters of polysaccharides were investigated (Taguchi et al., 2004; Yu et al., 1998).

### 5.3. Anti-tumor activity

Several conventional anticancer drugs for patients were and are extracted from plants. These include vincristine, paclitaxel, and camptothecin, all of which have been approved by the U.S. Food and Drug Administration (Dholwani et al., 2008). Moreover, some TCMs have been proved to have good anticancer activity in laboratory and clinical trials. The potential anticancer and antiangiogenesis properties of



**Table 3**The alkynes and their glycosides from *Atractylodis Rhizoma*.

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Polyacetylenes of diene-diyne types and their glycosides	86	atractylodin 2-[(1E,7E)-nona-1,7-dien-3,5-diynyl]furan		<i>A. lancea</i> (Takeda, 1994); <i>A. chinensis</i> (Nishikawa et al., 1975); <i>A. lancea</i> (Kawanishi, 1994); <i>A. koreana</i> (Kawanishi, 1994) <i>A. lancea</i> (Resch et al., 2001)
	87	(1Z)-atractylodin 2-[(1Z,7E)-nona-1,7-dien-3,5-diynyl]furan		
	88	9-nor-atractylodin		
	89	atractylodinol [(2E,8E)-9-(furan-2-yl)nona-2,8-dien-4,6-diyn-1-ol]		<i>A. lancea</i> , <i>A. chinensis</i> (Nishikawa et al., 1976)
	90	(1Z)-atractylodinol [(2E,8Z)-9-(furan-2-yl)nona-2,8-dien-4,6-diyn-1-ol]		
	91	acetylactylodinol [(2E,8E)-9-(furan-2-yl)nona-2,8-dien-4,6-diynyl] acetate		<i>A. lancea</i> , <i>A. chinensis</i> (Nishikawa et al., 1976)
	92	(1Z)-acetylactylodinol [(2E,8Z)-9-(furan-2-yl)nona-2,8-dien-4,6-diynyl] acetate		
	93	(6E,12E)-tetradecadiene-8,10-diyne-1,3-diol		<i>A. chinensis</i> (Meng et al., 2010); <i>A. japonica</i> (Jeong et al., 2010); <i>Atractylodis Rhizoma</i> (Sakurai et al., 1994b) <i>A. chinensis</i> (Meng et al., 2011)
	94	(6E,12Z)-tetradecadiene-8,10-diyne-1,3-diol		
	95	(6Z,12Z)-tetradecadiene-8,10-diyne-1,3-diol		
	96	(6E,12E)-tetradecadiene-8,10-diyne-1,3-diol diacetate		<i>A. chinensis</i> (Meng et al., 2010)
	97	(6E,12E)-3-acetoxytetradeca-6,12-dien-8,10-diyn-1-ol		
	98	(6E,12E)-1-acetoxytetradeca-6,12-dien-8,10-diyn-3-ol		<i>Atractylodis Rhizoma</i> (Sakurai et al., 1994a)
	99	1,4-acetoxytetradeca-6,12-diene-8,10-diyne		
	100	diacetyl atractylodiol [(5E,11E)-3-acetyloxytrideca-5,11-dien-7,9-diynyl] acetate		<i>A. japonica</i> (Yosioka et al., 1974)
	101	(2E,8E)-decadiene-4,6-diyne-1,10-diol 1-O-β-D-glucopyranoside		<i>A. lancea</i> (Kitajima et al., 2003b)
	102	atractylodinol [1-(2-Furyl)-(1E,7E)-nonadiene-3,5-diyne-9-ol]		<i>A. lancea</i> (Chen et al., 2012)
	103	1-(2-Furyl)-(1E,7E)-nonadiene-3,5-diyne-9-al		

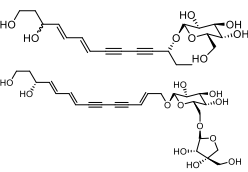
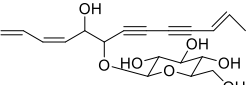
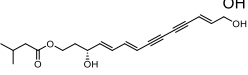
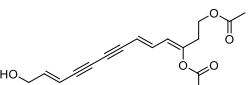
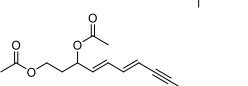
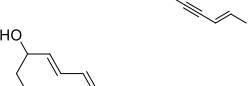

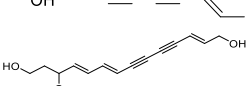
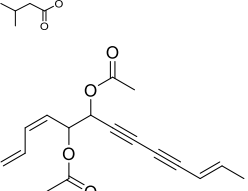
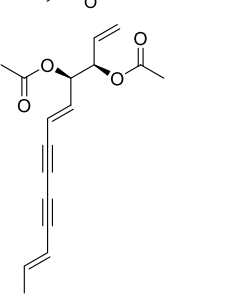
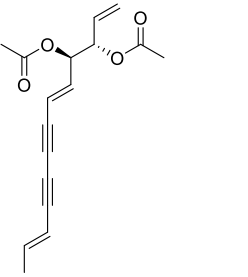
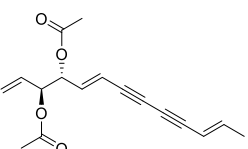

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Table 3 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	104	1-(2-Furyl)-(1E,7Z)-nonadiene-3,5-diyne-9-ol		
	105	1-(2-Furyl)-(1E,7E)-nonadiene-3,5-diyne-9-yl benzoate		
	106	1-(2-Furyl)-(1E,7E)-nonadiene-3,5-diyne-9-yl 4-methylbenzoate		
	107	1-(2-Furyl)-(1E,7E)-nonadiene-3,5-diyne-9-acid		
	108	(1Z)-atractylodinol 1-(2-Furyl)-(1Z,7E)-nonadiene-3,5-diyne-9-ol		<i>A. lancea</i> (Resch et al., 2001)
	109	(1Z)-acetylactracylodinol 1-(2-Furyl)-(1Z,7E)-nonadiene-3,5-diyne-9-yl acetate		
	110	(4E,10E)-dodeca-4,10-dien-6,8-diyne-1,3-diyl diacetate		<i>A. lancea</i> (Meng et al., 2010)
	111	(6E,12E)-aetradecadiene-8,10-diyne-1,3-diol		
	112	(2E,8Z)-deca-2,8-diene-4,6-diyne-1,10-diol-1-O-beta-D-glucopyranoside		<i>A. lancea</i> (Xu, 2017)
	113	(2E,8E)-deca-2,8-diene-4,6-diyne-1,10-diol-1-O-beta-D-apiofuranosyl-(1 -> 6)-beta-D-glucopyranoside		
	114	(2E,8Z)-deca-2,8-diene-4,6-diyne-1,10-diol-1-O-beta-D-apiofuranosyl-(1 -> 6)-beta-D-glucopyranoside		
	115	(8R,9S)-2E,10Z-tridecadiene-4,6-diyne-8,9,12,13-triol-9-O-beta-D-glucopyranoside		
	116	(8R,9S)-2E,10Z-tridecadiene-4,6-diyne-8,9,12,13-triol-8-O-beta-D-glucopyranoside		
	117	(8R,9S)-2E,10Z-tridecadiene-4,6-diyne-8,9,12,13-triol		
	118	(2Z,8E)-deca-2,8-diene-4,6-diyne-1,10-diol-1-O-beta-D-glucopyranoside		
	119	(2E,8E,10R)-tridecatriene-4,6-diyne-1,10,11,12,13-pentol-10-O-beta-D-glucopyranoside		
	120	(2E,8E,10R)-tridecane-2,8-diene-4,6-diyne-1,10,13-di-O-beta-D-xylopyranoside		
	121			

(continued on next page)

Table 3 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Triene-diyne types of atractylodes polyacetylenes and their glycosides	122	(3R,8E,10E)-tetradecadiene-4,6-diyne-3,12,14-triol-3-O- $\beta$ -D-glucopyranoside (2E,8E,12S)-tetradecadiene-4,6-diyne-1,10,14-triol-1-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	123	(1,3Z,11E)-Tridecatriene-7,9-diyne-5-hydroxyl-6-O- $\beta$ -D-glucopyranoside		<i>A. lancea</i> (Ji et al., 2010)
	124	atractyloyn [(3S,4E,6E,12E)-1-isovaleryloxy-tetradeca-4,6,12-triene-8,10-diyne-3,14-diol		<i>A. chinensis</i> (Nakai et al., 2005); Atractylodis Rhizoma (Kim, 2016)
	125	12,14- diacetate- 2E,8E,10E- trien- 4,6-diyne-1-ol		Atractylodis Rhizoma (Kim, 2016)
	126	(4E,6E,12E)-tetradecatriene-8,10-diyne-1,3-diyl diacetate		<i>A. lancea</i> (Resch et al., 2001)
	127	(4E,6E,12E)-Tetradecatriene-8,10-diyne-1,3-diol		
	128	(4E,6E,12E)-Tetradecatrien-8,10-diyne-1-ol		
	129	(4E,6E,12E)-3-isovaleryloxy-tetradeca-4,6,12-triene-8,10-diyne-1,14-diol		
	130	erythro-(1,3Z,11E)-tridecatriene-7,9-diyne-5,6-diyl-diacetate		
	131	erythro-(1,5E,11E)-tridecatriene-7,9-diyne-3,4-diacetate		<i>A. lancea</i> (Lehner et al., 1997)
	132	threo-(1,5E,11E)-tridecatriene-7,9-diyne-3,4-diacetate		
	133	(1,5E,11E)-trideca-1,5,11-trien-7,9-diyne-3,4-diacetate		Atractylodis Rhizoma (Kim, 2016)
	134	(3Z,5E,11E)-tridecatriene-7,9-diyne-1-O-(E)-ferulate		

(continued on next page)

Table 3 (continued)

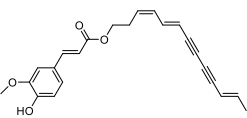
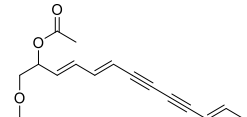
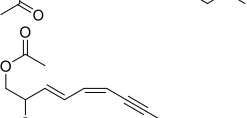
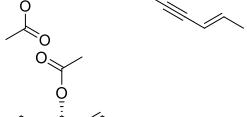
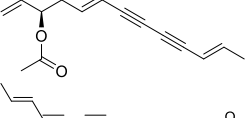
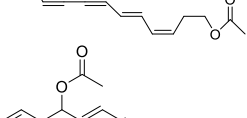
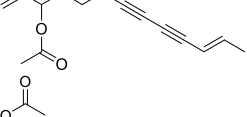
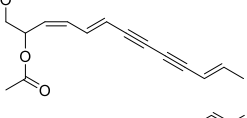
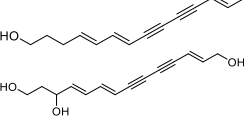
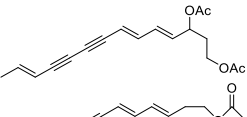
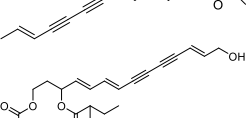
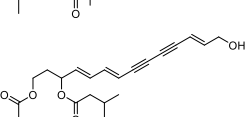
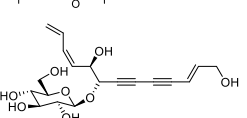
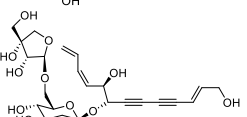
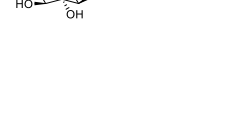
Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
				<i>A. lancea</i> (Resch et al., 2001)
	135	(3E,5E,11E)-tridecatriene-7,9-diyne-1,2-diacetate		<i>A. lancea</i> (Lehner et al., 1997)
	136	(3Z,5E,11E)-tridecatriene-7,9-diyne-1,2-diacetate		<i>A. lancea</i> (Resch et al., 2001)
	137	(3E,5Z,11E)-tridecatriene-7,9-diyne-1,2-diacetate		<i>A. lancea</i> (Lehner et al., 1997)
	138	(2Z,4E,10E)-trideca-2,4,10-trien-6,8-diynyl acetate		Atractylodis Rhizoma (Kim, 2016)
	139	(1,5E,11E)-tridecatriene-7,9-diyne-3,4-diacetate		<i>A. lancea</i> (Resch et al., 2001)
	140	(3E,5Z,11E)-tridecatriene-7,9-diyne-1,2-diyl diacetate		<i>A. lancea</i> (Meng et al., 2010)
	141	(4E,6E,12E)-aetradecatrien-8,10-diyn-1-ol		<i>A. lancea</i> (Meng et al., 2010)
	142	(4E,6E,12E)-tetradeca-4,6,12-trien-8,10-diyne-1,3,14-triol		Atractylodis Rhizoma (Kim, 2016)
	143	(4E,6E,12E)-tetradecadiene-triene-8,10-diol		<i>A. lancea</i> (Meng et al., 2010)
	144	(5E,11E)-trideca-1,5,11-trien-7,9-diyne-3,4-diyl diacetate		Atractylodis Rhizoma (Kim, 2016)
	145	(4E,6E,12E)-1-acetoxy-3-isovaleryloxy-4,6,12-trien-8,10-diyn-14-ol		<i>A. lancea</i> (Xu, 2017)
	146	(4E,6E,12E)-1-acetoxy-3-(2-methylbutyryloxy)-4,6,12-trien-8,10-diyn-14-ol		<i>A. lancea</i> (Xu, 2017)
	147	(8S,9R)-2E,10Z,12-tridecadiene-4,6-diyne-1,8,9-triol-8-O-beta-D-glucopyranoside		
	148	(8S,9R)-2E,10Z,12-tridecadiene-4,6-diyne-1,8,9-triol-8-O-beta-D-apiofuranosyl-(1 -> 6)-beta-D-glucopyranoside		
	149	(8S,9R)-2E,10Z,12-tridecadiene-4,6-diyne-1,8,9-triol-9-O-beta-D-glucopyranoside		(continued on next page)

Table 3 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Monoene-diyne types of aractylodes polyacetylenes and their glycosides	150	(8S,9R)-2E,10Z,12-tridecadiene-4,6-diyne-1,8,9-triol-9-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	151	(10R,11R)-2R,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-10-O- $\beta$ -D-glucopyranoside		
	152	(10R,11R)-2E,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-1-O- $\beta$ -D-glucopyranoside		
	153	(10R,11R)-2E,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-1,10-O-di- $\beta$ -D-glucopyranoside		
	154	(10R,11R)-2E,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-10-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	155	(10R,11S)-2R,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-10-O- $\beta$ -D-glucopyranoside		
	156	(10R,11S)-2E,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-10-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	157	(10S,11R)-2E,8E,12-tridecatriene-4,6-diyne-1,10,11-triol-10-O- $\beta$ -D-glucopyranoside		
	158	(2E,8E,10E,12R)-tridecatriene-4,6-diyne-1,12,13-triol-1,12-di-O- $\beta$ -D-glucopyranoside		
	159	(2E,8E,10E,12R)-tridecatriene-4,6-diyne-1,12,13-triol-1-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	160	(8E,10E)-tetradecadiene-4,6-diyne-3,12,14-triol-3-O- $\beta$ -D-glucopyranoside		
	161	(2E,8E,10E,12R)-tetradeca-2,8,10-triene-4,6-diyne-1,2,14-triol-1-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	162	(2E,8E,10E,12R)-tetradeca-2,8,10-triene-4,6-diyne-1,12,14-triol-1-O- $\beta$ -D-glucopyranoside		
	163	1-(2-Furyl)-(7E)-nonene-3,5-diyne-1,2-diacetate		<i>A. lancea</i> (Lehner et al., 1997); Atractylodis Rhizoma (Kim, 2016)
	164	(2E)-decene-4,6-diyne-1,8-diol-8-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		<i>A. lancea</i> (Kitajima et al., 2003b)
	165	(2E,8R)-decene-4,6-diyne-1,8-diol-8-O- $\beta$ -D-glucopyranoside		<i>A. lancea</i> (Xu, 2017)

(continued on next page)

Table 3 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	166	(2E,8S)-decane-4,6-diyne-1,8-diol-8-O- $\beta$ -D-glucopyranoside		
	167	(2E,8R)-decene-4,6-diyne-1,8-diol-1-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	168	(2E,8R)-decane-4,6-diyne-1,8-diol-O-di- $\beta$ -D-glucopyranoside		
	169	(E)-deca-2-ene-4,6-diyne-1,10-diol-1-O- $\beta$ -D-glucopyranoside		
	170	(E)-deca-2-ene-4,6-diyne-1,10-diol-1-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	171	(2E,10S)-tridecane-2-ene-4,6-diyne-1,10,13-triol-1,13-di-O- $\beta$ -D-xylopyranoside		
	172	(2E,10S)-tridecatriene-4,6-diyne-1,12,13-triol-13-O- $\beta$ -D-glucopyranoside		
	173	(2E,10S)-tridecatriene-4,6-diyne-1,12,13-triol-10-O- $\beta$ -D-glucopyranoside		
	174	(8R,9R)-8,9-dihydroxylatractylodinol-8-O- $\beta$ -D-glucopyranoside		
	175	(8R,9R)-8,9-dihydroxylatractylodinol-9-O- $\beta$ -D-glucopyranoside		
	176	(2E,10S)-tetradecadiene-4,6-diyne-1,10,14-triol-10-O- $\beta$ -D-apiofuranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	177	1-(2-furyl)-(7E)-non-ene-3,5-diyne-1,2-diacetate		
Other alkynes and their glycosides				
	178	(10R)-atracthioenyneside A		<i>A. lancea</i> (Xu, 2017)
	179	(10R)-atracthioenyneside B		
	180	(10S,11R)-atracthioenyneside C		
	181	(10S,11R)-atracthioenyneside D		
	182	(10R,11S)-atracthioenyneside E		
	183	(8S)-decane-4,6-diyne-1,8-diol-O- $\beta$ -D-glucopyranoside		
	184	2,8-dimethyl-6-hydroxy-2-(4-methyl-3-pentenyl)-2H-chromene		<i>A. lancea</i> (Resch et al., 1998)

(continued on next page)



Table 3 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
	185	2-[(2E)-3,7-dimethyl-2,6-octadienyl]-6-methyl-2,5-cyclohexadiene-1,4-dione		
	186	2-[(2'E)-3',7'-dimethyl-2',6'-octadienyl]-4-methoxy-6-methylphenol		
	187	bis (5-[(1E,7E)-nona-1,7-dien-3,5-diyn-1-yl])furan-2-yl) methane		A. lancea (Chen et al., 2012)
	188	bis (5-[(1E,7E)-nona-1,7-dien-3,5-diyn-1-yl])furan-2-yl) isopropane		
	189	(4E,6E,12E)-1-acetoxy-3-senecioyloxytetradeca-4,6,12-trien-8,10-diyn-14-ol		Atractylodis Rhizoma (Kano et al.)

*A. lancea* extract and its major constituents have been demonstrated in various cancer, for examples, murine blastoma cells Hela (human cervical cells), SGC-7901 (human gastric cancer cells), BEL-7402 (human liver cancer cells), H33, S180, HL-60 leukemic cells, and gastric cancer (Masuda et al., 2015; Zhao et al., 2014). In recent years, *A. lancea* especially as an alternative treatment for cholangiocarcinoma (CCA) patients, seems to be a promising candidate herbal medicine. Results from a series of studies (Na-Bangchang et al., 2017) confirm anti-CCA potential and safety profiles of both the crude extract and the finished product (oral pharmaceutical formulation of the standardized *A. lancea* extract). Phases I and II clinical trials of the product to confirm tolerability and efficacy in healthy subjects and patients with advanced-stage CCA will be carried out soon. AR ethanol extract exhibited an inhibitory effect on opisthorchis viverrini (OV)-induced CCA animal without obvious toxicity after oral administration for 30 days (Ohara et al., 2018).

Atractylenolide I (ATL-I) has an antitumor effect on bladder cancer in vitro and in vivo. The results showed that ATL-I increased the level of p21 and decreased cyclin B1, cyclin-dependent kinase 1 (CDK1), and cell division cycle 25C (Cdc25c) levels and inhibiting bladder cancer cell proliferation. Further study indicated that ATL-I induced G2/M cell cycle arrest. Besides, ATL-I could promote apoptosis by inhibiting PI3K/Akt/mTOR. Animal experiments proved that ATL-I has an inhibitory effect on tumor growth and no obvious toxicity (Zhao et al., 2014). Huang et al. (2016) found that ATL-I could inhibit CML and AML leukemia cell proliferation and growth and induce apoptosis. Fu et al. (2018) found that ATL-I could inhibit melanoma cell migration by suppressing phospho-janus kinase 2 (p-JAK2), phospho-signal transducer, and activator of transcription 3 (p-STAT3), matrix metalloproteinase-2 (MMP-2) and MMP-9. The clinical study of ATL-I in the treatment of gastric cancer cachexia has been carried out. Atractylenolide II (ATL-II) treatment showed a dose-dependent manner inhibitory effect on p-STAT3, myeloid cell leukemia 1 (Mcl-1) and B-cell lymphoma-extra large (Bcl-xL) in B16 and A375 cells. Among them, STAT3 could promote melanoma. A further animal study showed that ATL-II suppressed STAT3 activation and tumor growth (Fu et al., 2014). ATL-II could significantly inhibit cell proliferation, motility and induce apoptosis in a dose and time-dependent manner by modulating Akt/ERK signaling pathway (Tian and Yu, 2017). Atractylenolide III (ATL-III) possessed antitumor activity on human mast cells stimulated by thymic stromal lymphopoietin (TSLP), human mast cell line-1 (HMC-1) by inhibiting mast cell proliferation, phosphorylated signal transducer, IL-13, and activator of transcription (Yoo et al., 2017). It was indicated that hinesol inhibited human leukemia HL-60 cells by reducing nuclear fragmentation and DNA fragmentation, activating c-Jun N-terminal

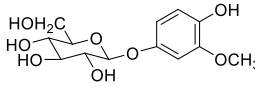
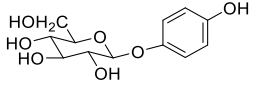
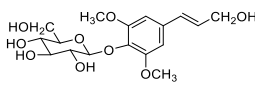
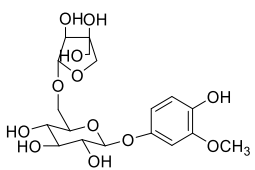
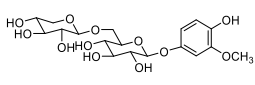
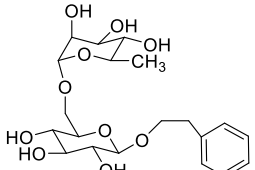
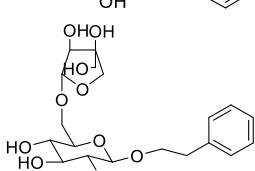
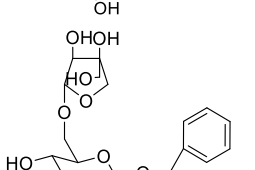
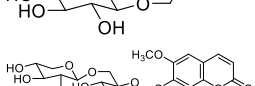
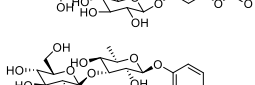
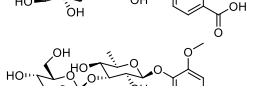
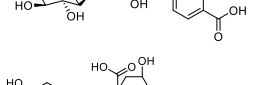
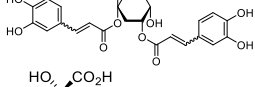
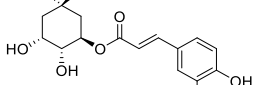
kinase (JNK) (Masuda et al., 2015).  $\beta$ -eudesmol had anti-tumor activity in multiple tumor cell models (CCA, Hep-G2, A549, HT29, HeLa, SGC-7901, and BEL-7402, U266 cells) mainly through regulating apoptosis (Kotawong et al., 2018) and growth factors (Ma et al., 2008) in a time-and dose-dependent manner (Srijwangsa et al., 2018). Moreover,  $\beta$ -eudesmol (2.5–5 mg/kg) treatment significantly inhibited tumor growth in H22 and S180 mice (Ma et al., 2008). Phosphorylation of ERK1/2 and angiogenesis in mice subcutaneous matrix gel plug and mice adjuvant granuloma were inhibited by high concentration of  $\beta$ -eudesmol, suggesting that  $\beta$ -eudesmol can be used as a candidate drug to treat angiogenic diseases (Tsuneki et al., 2005). Pongsakorn et al. (2018) investigated cytotoxic interactions between the three major constituents ( $\beta$ -eudesmol, hinesol and atractylodin) of *A. lancea*. Cytotoxic activities against the human CCA cells CL-6 of the dual and triple combinations with different concentration ratios were evaluated by MTT assay. The mixture of the three compounds produced synergistic interaction with combination index values of  $0.519 \pm 0.10$  and  $0.65 \pm 0.17$  (mean  $\pm$  SD) at the concentrations that inhibit cell growth at the 50% and 90% leveled, respectively.

#### 5.4. Anti-inflammatory activity

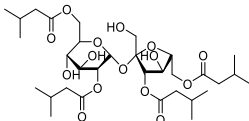
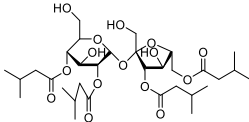
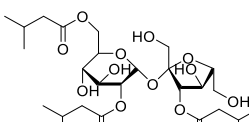
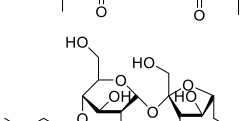
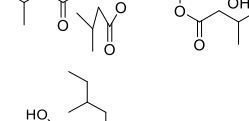
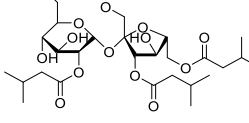
Shimato et al. (2018) compared the anti-inflammatory properties between Byakujutsu and Sojutsu. They found that methanol extract could inhibit the production of NO in macrophage-like RAW264.7 cells stimulated by lipopolysaccharide. The inhibitory effects of Byakujutsu on NO production were significantly higher than those of Sojutsu. This activity of *A. japonica* rhizome was significantly higher than that of *A. macrocephala* and *A. lancea*. The activity of *A. chinensis* was significantly higher than that of *A. lancea*. Chen et al. (2016) prepared n-hexane extracts of the three species (*A. japonica*, *A. chinensis* and *A. macrocephala*) and evaluated their anti-inflammatory effects on lipopolysaccharide (LPS)-induced RAW 264.7 cells. Among them, *A. japonica* most strongly inhibited NO production in LPS-induced RAW 264.7 cells.

Atractylon significantly inhibited NO and prostaglandin E2 production as well as inducible NO synthase and cyclooxygenase-2 expression in LPS-induced RAW 264.7 cells. Atractylon (40 mg/kg) also significantly reduced the acetic-acid-induced writhing response, carrageenan-induced paw edema, and hot-plate latent pain response in mice. The traditional use of *A. lancea* for anti-inflammatory effect is demonstrated to be due mainly to interference with the enzymes in the inflammatory pathway, that is, 5-lipoxygenase (5-LOX) and cyclooxygenase-1 (COX-1) (Resch et al., 1998). The current research showed that atractylodin could inhibit the inflammatory response induced by lipopolysaccharide

**Table 4**The aromatic glycosides and its structure of *Atractylodis Rhizoma*.

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Aromatic glycosides	190	4-hydroxy-3-methoxyphenol- $\beta$ -D-glucopyranoside		<i>A. lancea</i> (Kitajima et al., 2003b)
	191	seguinoside B, 4-hydroxyphenyl 1-O- $\beta$ -D - apiopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside]		
	192	syringin [4-[(1E)-3-Hydroxyprop-1-en-1-yl]-2,6-dimethoxyphenyl- $\beta$ -D-glucopyranoside]		
	193	4-hydroxy-3-methoxyphenol- $\beta$ -D-apiopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranoside		
	194	4-hydroxy-3-methoxyphenyl- $\beta$ -xylopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -glucopyranoside		
	195	icariside F2 [benzyl $\beta$ -D-apiopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside]		
	196	icariside D1 [phenethyl $\beta$ -D-apiopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside]		
	197	phenethyl $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 6)- $\beta$ -D-glucopyranoside		
	198	scopoletin-D-xylopyranosyl-(1 $\rightarrow$ 6)-D-glucopyranoside		<i>A. lancea</i> (Xu et al., 2016b)
	199	p-hydroxybenzoic acid-4-O- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)- $\alpha$ -L-rhamnopyranoside		
	200	vanillic acid-4-O- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)- $\alpha$ -L-rhamnopyranoside		
	201	1,3-di-O-caffeoylquinic acid		<i>A. lancea</i> (Feng et al., 2018)
	202	chlorogenic acid (1S,3R,4R,5R)-3-[3-(3,4-dihydroxyphenyl)prop-2-enoyloxy]-1,4,5-trihydroxycyclohexanecarboxylic acid		
	203	5-O-feruloylquinic acid (1R,3R,4S,5R)-1,3,4-trihydroxy-5-[(2E)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-enoyl]-oxycyclohexane-1-carboxylic acid		

**Table 5**The acyl sugar compounds and its structure of *Atractylodis Rhizoma*.

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Acyl sugar compounds	204	2,6,3',6'-tetra (3-methylbutanoyl) sucrose		<i>A. lancea</i> (Ina, 2009)
	205	2,4,3',6'-tetra (3-methylbutanoyl) sucrose		
	206	2,6,3',4'-tetra (3-methylbutanoyl) sucrose		
	207	2,4,3',4'-tetra (3-methylbutanoyl) sucrose		
	208	2,1',3',6'-tetra (3-methylbutanoyl) sucrose		
	209	3',4',6'-tris (3-methylbutanoyl)-1'-(2-methylbutanoyl) sucrose		

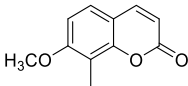
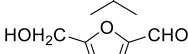
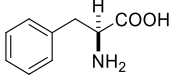
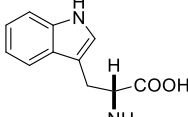
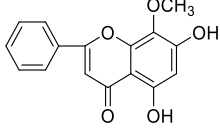
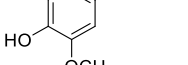
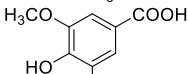
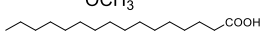
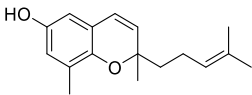
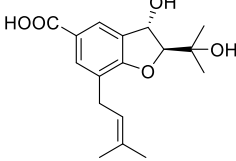
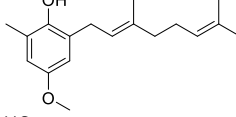
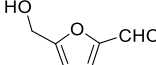
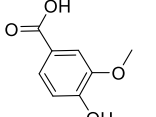
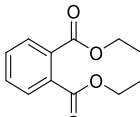
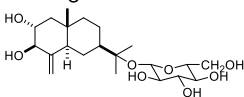
(LPS). Namely, atractylodin inhibited the wet-to-dry weight ratio of lung, myeloperoxidase (MPO) activity, inflammatory cell infiltration, protein leakage, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and monocyte chemoattractant protein (MCP-1) secretion. Its mechanism was that atractylodin could down-regulate nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome and activate toll-like receptor 4 (TLR4) (Tang et al., 2018). Another study reported that atractylodin exhibited anti-inflammatory activity and ameliorated simultaneous dyskinesia in rats with constipation and diarrhea by reducing plasma proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) (Yu et al., 2017). Zhang et al. (2015) indicated that ATL-I could protect acute lung injury by inhibiting TLR4 expression and NF- $\kappa$ B activation. Ji et al. (2016) found that ATL-III inhibited the production of NO, PGE<sub>2</sub>, IL-6, and TNF- $\alpha$  in a dose-dependent manner and had an anti-inflammatory activity on LPS triggered macrophages of RAW264.7 mice. The high concentration of ATL-III (100  $\mu$ M) could inhibit the expression of cyclooxygenase-2 (COX-2) by inhibiting the activation of NF- $\kappa$ B and ERK1/2. Antwi et al. (2017) indicated that stigmasterol could inhibit eosinophils, peribronchiolar, lymphocytes, monocytes proliferation, alveolar infiltration of inflammatory cells, perivascular, vascular cell adhesion molecule-1, ovalbumin (OVA)-specific immunoglobulin E expression and thus inhibit OVA-induced airway inflammatory damage in guinea pigs after intraperitoneal injection. Atractylone inhibited allergic inflammation in OVA-induced animal model while decreased rub scores, IL-1, IL-4, IL-5, IL-6, IL-13, COX-2, intercellular adhesion molecule-1

(ICAM-1), and macrophage inflammatory protein (MIP)-2 expression (Kim et al., 2016). The results exhibited that atractylone could inhibit histidine decarboxylase activity and expression, tryptase and histamine release in PMACI-induced HMC-1 cells and inhibit filamentous actin formation and morphological alteration in stem cell factor-stimulated peritoneal mast cells (RPMCs) animal model (Han et al., 2016). Stigmasterol and  $\beta$ -sitosterol had inhibitory effects on colitis induced by dextran sodium sulfate in C57BL/6J male mice. They critically suppressed colon shortening, colitis, and distal colon via the inactivation of NF- $\kappa$ B and decreased fecal hemoglobin content (Feng et al., 2017). A recent study showed that  $\beta$ -sitosterol had an anti-inflammatory activity based on the rat pleurisy assay and rat paw edema test (Paniagua-Pérez et al., 2017). Polyacetylenes exhibited anti-inflammatory activity with structure-activity relationships: the introduction of an acyl group into a compound increased the inhibitory effect against NO production. Deacylated product of 14- $\beta$ -methylbutyryltetradeca-2E, 8E, 10E-trien-4, 6-diyn-1-ol, due to boiling extraction with water, results in diminished anti-inflammatory activity (Kim, 2016).

### 5.5. Antibacterial activity

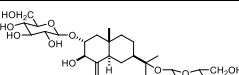
Yin et al. (2000) carried out a systematic multi gradient external antibacterial experiment on the extract of AR. The results showed that AR had different degrees of inhibition on 15 kinds of fungi, and the effect was stronger than that of *Hibiscus cortex*, *Phellodendron bark*, and other

**Table 6**The other compounds and its structure of *Atractylodis Rhizoma*.

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
Other compounds	210	osthol		<i>A. lancea</i> (Resch et al., 1998)
	211	5-hydroxymethyl furaldehyde		<i>A. lancea</i> (Meng et al., 2010)
	212	L-phenylalanine		<i>A. lancea</i> (Kitajima et al., 2003b)
	213	D-tryptophan [(R)-α-amino-3-indolepropionic Acid]		
	214	wogonin [5,7-dihydroxy-8-methoxyflavone]		<i>A. chinensis</i> (Jin, 2002)
	215	3-methoxy-4-hydroxybenzoic acid		<i>A. japonica</i> (Li et al., 2002)
	216	3,5-dimethoxy-4-hydroxybenzoic acid		
	217	palmitic acid		<i>A. lancea</i> (Resch et al., 2001)
	218	atractylochromene [2,8-dimethyl-2-(4-methyl-3-penten-1-yl)-2H-chromen-6-ol]		<i>A. lancea</i> (Resch et al., 1998)
	219	trans-2-hydroxyisoxypyl-3-hydroxy-7-isopentene-2,3-dihydrobenzofuran-5-carboxylic acid		<i>A. lancea</i> (Duan et al., 2008)
	220	2-[(2'E)-3',7'-dimethyl-2',6'-octadienyl]-4-methoxy-6-methylphenol		<i>A. lancea</i> (Resch et al., 2001)
	221	5-hydroxymethyl furaldehyde		<i>A. lancea</i> (Meng et al., 2010)
	222	vanillic acid (4-Hydroxy-3-methoxybenzoic acid)		<i>A. lancea</i> , <i>A. chinensis</i> (Liang et al., 2002)
	223	diethyl phthalate		<i>A. lancea</i> (Yang, 2007)
	224	3-methyl-2-butenyl β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside		<i>A. lancea</i> (Kitajima et al., 2003b)
	225	isopropyl β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside		

(continued on next page)

Table 6 (continued)

Chemical compounds	Nos.	Compounds name	Structure	Origin and Ref.
				
	226	Oligo-1	$\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	<i>A. lancea</i> (Taguchi et al., 2004)
	227	Oligo-2	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	
	228	Oligo-3	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp	
	229	Oligo-4	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	
	230	Oligo-5	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	
	231	Oligo-6	Not determined	<i>A. lancea</i> (Qin et al., 2019)
	232	Oligo-7	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	
	233	Oligo-8	$\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)- $\beta$ -D-Galp-(1 $\rightarrow$ 6)-D-Galp	
	234	ALP-1	linear backbone composed of (2 $\rightarrow$ 1)-linked $\beta$ -D-fructofuranose	
	235	ALP-3	$\rightarrow$ 4)-GalAp-(1 $\rightarrow$ 3,4)-Rhap-(1 $\rightarrow$ , and with branch chain substituted at O-3 position of $\rightarrow$ 3,4)-Rhap-(1 $\rightarrow$ . The branch chain consists of $\rightarrow$ 3,5)-Araf-(1 $\rightarrow$ , $\rightarrow$ 5)-Araf-(1 $\rightarrow$ , and Araf-(1 $\rightarrow$	
	236	FOS	linear $\beta$ -(2,1)-linked fructofuranosyl units mostly carry a terminal single $\alpha$ -(1-2)-linked $\alpha$ -glucopyranosyl unit	Atractylodis Rhizoma (Zhuang et al., 2019)
	237	ACPS	$\alpha$ -D-Glcp-(1 $\rightarrow$ 2)- $\beta$ -D-Fruf-(1 $\rightarrow$ 2)- $\beta$ -D-Fruf-]n-(1 $\rightarrow$ 2)- $\beta$ -D-Fruf	<i>A. lancea</i> (Xu et al., 2016)

traditional Chinese medicines. Stigmasterol exerted the synergistic antibiotic effect (suppressed colony counts, yielding 98.7%) as an adjuvant of ampicillin to gram-negative and gram-positive bacteria. However, the inhibition of ampicillin and stigmasterol alone was ineffective (Yenn et al., 2017). The aqueous extract of *A. lancea* has the activity of anti-microbial infection. Oral administration of 140 mg/kg/d could significantly prolong the life span of mice infected with candida (Inagaki et al., 2001).

### 5.6. Other activities

AR or its compounds have certain biological activities on the nervous system, lung, glucose, and lipid metabolism. The pharmacological activity of the AR on the central nervous system has been demonstrated in various animal models with regards to its effects on the general behavior and spontaneous movement, potentiation of hypnotic action of hexobarbital sodium, and anti-electroshock convulsion. Murayama et al. (2014) indicated that water extract of *A. japonica* showed a stronger inhibitory effect on 1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head-twitch response than that of *A. lancea* corresponding to their major constituents of atractylenolide III and  $\beta$ -eudesmol, and suggested that the major constituents should be active constituents contributing to the antihallucination effects of Byaku- and So-jutsu. Besides, the part B-C ring (butenolide) in ATL III was found to be similar to the structure of serotonin and suggested that the B-C ring may partially play role in antagonistic activity against serotonin receptors. Thus, a rational design of butenolide-related compounds may produce potential lead compounds for new drug development (Murayama et al., 2014). ATL-III presented a neuroprotective effect on learning and memory impairment rats by decreasing ROS production and protein kinase C level (Zhao et al., 2015). The neurological activity of  $\beta$ -eudesmol, including its antagonistic effect on neostigmine-induced neuromuscular failure, was demonstrated in previous studies on the accelerating effect of desensitization of the nicotinic acetylcholine receptor and blockage action during the closed state of the receptor channel or nerve-evoked contraction at the neuromuscular junction (Chiou and Chang, 1992). Ohara et al. (2018) showed that  $\beta$ -eudesmol could inhibit the efferent activity of the adrenal sympathetic nerve in rats through transient receptor potential cation channel subfamily a member 1 (TRPA1) and afferent vagus nerve. Cheng et al. (2016) found that atractylone (40 mg/kg for 5 days) could decrease influenza A virus (IAV)-induced pulmonary injury in mice by inhibiting IL-6, TNF- $\alpha$ , and

IL-1 $\beta$ , but promoting TLR7, IFN- $\beta$ , myeloid differentiation primary response 88 (MYD88) expression. Stigmasterol possessed anti-diabetic activity in vitro and in vivo. Which could reduce and oral glucose tolerance by decreasing blood glucose levels and blood lipid indexes, and alleviating insulin resistance in vivo while increasing glucose transporter type 4 (GLUT-4) translocation and expression in vitro (Wang et al., 2017). A water extract of the oriental crude drug Atractylodes Japonica Rhizomes showed hypoglycemic activity in mice. The extract was fractionated by monitoring the pharmacological activity to obtain three glycans, atractans A, B and C. These constituents exerted significant hypoglycemic actions in normal and alloxan-induced hyperglycemic mice. The *A. lancea* ethanol extracts exhibited an inhibitory effect on lipase with the IC<sub>50</sub> 9.06  $\mu$ g/mL and anti-obesity effect on the obesity mice was presented on the high concentration (500 mg/kg) (Jiao et al., 2014). Water extracts from *A. lancea* reduced triptolide-induced toxicity via down-regulated hepatic cytochrome P450 3A (CYP3A) expression and improved anti-inflammatory activity of triptolide. This suggested that *A. lancea* could inhibit toxicity and increase the therapeutic activity of triptolide (Yenn et al., 2017). Additionally, ATL-I could inhibit 5-lipoxygenase (5-LOX) production to decrease allergic responses (Lim et al., 2012). The pharmacological interaction between the constituents of Keishi-ka-zyutubu-tō (composed of seven crude drugs, namely Glycyrrhizae Radix et Rhizoma, Cinnamomi Cortex, Zingiberis Rhizoma Recens, Atractylodis Rhizoma, etc.) was investigated in in-situ sciatic nerve-gastrocnemius muscle preparations by genetically diabetic KK-CAY mice. When administered intra-arterially, the drug caused a degree of inhibition of the diabetic neuromuscular junction 280 times greater than normal. When further combined with Paeoniae Radix Alba and Glycyrrhizae Radix et Rhizoma, the potency ratio was increased 4.9 times for Cinnamomi Cortex, 5.9 times for Zingiberis Rhizoma Recens, and 8.7 times for Atractylodis Rhizoma. In combination with the representative compounds, the potency ratio of paeoniflorin and glycyrrhizin was increased 6.6 times for cinnamaldehyde, 6.1 times for 8-gingerol and 14 times for  $\beta$ -eudesmol in diabetic muscles. The single effect of  $\beta$ -eudesmol or 8-gingerol was 5.2 times or 3.7 times more potent, respectively, on diabetic muscles than on normal muscles. These results indicated that the preferentially more potent neuromuscular blocking effects of Keishi-ka-zyutubu-tō in diabetic muscles were mainly attributable to  $\beta$ -eudesmol, a major component of Atractylodis Rhizoma (Kimura et al., 1987).

As seen in Table 7, AR has been used as TCM for several thousand years, and current studies indicated that AR and some of its compounds

**Table 7**

Dosage, experimental model, pharmacological action and mechanism of Atractylodis Rhizoma extracts.

Pharmacology	Pharmacological effects	Substances and dosages	Experimental model	Mechanisms	Ref.
Improving gastrointestinal function	Stimulating gastric emptying or small intestinal motility	The extract (500 or 1000 mg/kg) and $\beta$ -eudesmol (50 or 100 mg/kg)	Atropine-, dopamine-, 5-hydroxytryptamine-treated mice	Inhibiting the dopamine D2 and 5-HT3 receptor	Kimura and Sumiyoshi (2012)
	Inhibiting of gastric ulcer	n-butanol extract 0.18 g/kg	Rats	Improving blood circulation in ulcer, promoting DNA, RNA and protein synthesis	Piao and Piao (1996)
	Anti-gastrointestinal mucosal injury	Atractylenolide I (ATL-I) 5 and 10 $\mu$ M	IEC-6 cell	Promoting IEC-6 cell proliferation and migration; increasing polyamines content, and enhancing TRPC1 and PLC- $\gamma$ 1 mRNA and protein expression	Song et al. (2017)
	Resisting gastric ulcer	Hinesol IC50: $5.8 \times 10^{-5}$ M	Porcine gastric membrane vesicles	Inhibiting H <sup>+</sup> , K <sup>+</sup> -ATPase and Mg <sup>2+</sup> -ATPase and Ca <sup>2+</sup> -ATPase activity	Satoh et al. (2000)
Immunomodulatory activity	Anti-gastric ulcer	<i>A. lancea</i> 2.5 g/kg	Acetic acid imitated rats	The gastroprotective effects were mediated by up-regulating trefoil factor 2 and epidermal growth factor	Yu et al. (2015)
	Immunostimulatory effects	The boiling water extract 1.0 mg/mL	Murine normal colonic epithelial MCE301 cells	Inducing secretion of granulocyte colony-stimulating factor	Shimato et al. (2018)
	Immunomodulatory activity	Acidic polysaccharide (ALP-3) 50, 100, 250, 500, 1000, 2000 $\mu$ g/mL	Murine RAW264.7 macrophage cell line	Stimulating macrophage proliferation, and stimulating phagocytic, NO and cytokines production on RAW264.7 cells	Qin et al. (2019)
	Intestinal immune system modulating activity	ALP-1 and ALP-3 50, 100, 250, 500, 1000, 2000 $\mu$ g/mL	Peyer's patch cells	Activating T cells in Peyer patch cells and promoting the production of CSF	Qin et al. (2019)
Anti-tumor activity	Intestinal immune system modulating activity	Polysaccharides 100 $\mu$ g/mL	Peyer's patch cells	Regulating intestinal immune system	Yu et al. (1998)
	Inhibitory effect on human gastric cancer cells	Water extract of the <i>A. lancea</i> 0.0625, 0.125, 0.25, 0.5, and 1 mg/mL	BGC-823 and SGC-7901 cells	Inhibiting the growth of BGC-823 and SGC-7901 cells	Zhao et al. (2014)
	Anti-leukemia	Atractylenolide I (ATL-I) 3.13–100 $\mu$ g/mL	Human K562 CML, U937 AML and Jurkat T lymphoma cells	Inducing apoptosis and differentiation of macrophage lineage	Huang et al. (2016)
	Anti-melanoma effects	Atractylenolide I (ATL-I) 40, 60, 80, 100, 120, 150 $\mu$ M	Human A375, Hs294T and SK-MEL-5 melanoma cells	Inhibiting phospho-janus kinase 2, phospho-signal transducer and activator of transcription 3, matrix metalloproteinase-2 and -9	Fu et al. (2018)
	Antimelanoma effects	Atractylenolide II (ATL-II) 12.5, 25 mg/kg	B16 xenograft mouse	Suppressing STAT3 activation and tumor growth	Fu et al. (2014)
	Antigastric carcinoma	ATL-II 50, 100, 200, 400 $\mu$ M	Human gastric carcinoma cell lines HGC-27 and AGS	Modulating Akt/ERK signaling pathway to inhibit cell proliferation, motility and inducing apoptosis	Tian and Yu (2017)
	Antitumor activity	Atractylenolide III (ATL-III) 1, 10, 100 $\mu$ M	HMC-1 cell	Inhibiting mast cell proliferation, phosphorylated signal transducer, IL-13, proinflammatory cytokines and activator of transcription	Yoo et al. (2017)
	Antitumor activity	ATL-III 100 $\mu$ M	LAD2 human mast cell	Inhibiting mast cell proliferation and the production of inflammatory cytokine	Yoo et al. (2017)
	Antitumor activity	Hinesol 5, 10, 25, 50, 100 $\mu$ M	Human leukemia HL-60 cells	Hinesol induced apoptosis through the JNK signaling pathway in HL-60 cells	Masuda et al. (2015)
	Anti-cholangiocarcinoma	$\beta$ -eudesmol IC50: 39.33 mg/mL	The CCA cell lines, and normal human cell line	Promoting cell cycle arrest at G1 phase, and inducing cell apoptosis through activation of caspase-3/7	Kotawong et al. (2018)
	Anti-hepatocellular carcinoma	$\beta$ -eudesmol IC50: $16.51 \pm 1.21$ – $24.57 \pm 2.75$ $\mu$ g/mL	B16-F10 and HepG2 cell lines	Inducing tumor cell death by caspase-mediated apoptosis pathways	Bomfim et al. (2013)
	Anti-multiple myeloma cells	$\beta$ -sitosterol 0, 6.25, 12.5, 25, 50, 100 mM	Human multiple myeloma U266 and MM1S cell	Increasing the sub-G1 apoptotic population, activating caspase-9 and -3	Sook et al. (2014)
	Anti-tumor activity	$\beta$ -eudesmol 10–100 mM	HeLa, SGC-7901, and BEL-7402	Inhibiting angiogenesis by suppressing CREB activation in the growth factor signaling pathway	Ma et al. (2008)
	Inhibiting of Cholangiocarcinoma	$\beta$ -eudesmol (0, 1, 10, 30, 100 $\mu$ M), dicoumarol (1 $\mu$ M), 5-FU (0, 3, 10, 30, 100 $\mu$ M), DOX (0, 0.1, 0.01, 1, 10 $\mu$ M)	Human CCA cell line, KKU-100	Enhancing chemotherapeutic effects of 5-fluorouracil and doxorubicin in the high NQO1-expressing human CCA cell line, NQO1-KKU-100	Srijwangsa et al. (2018)
	Inhibiting of lung and colon cancer	$\beta$ -eudesmol 5–100 $\mu$ M	Human lung (A549) cells, colon (HT29 and Caco-2) cells	Inhibiting proliferation of tumor cells and superoxide production; inhibiting adhesion and migration of A549 and HT29 cell	Sghaier et al. (2016)
	Anti-angiogenic mechanism and anti-tumor activity	$\beta$ -eudesmol (2.5–5 mg/kg)	Implanting H22 and S180 mice tumor cells into oxters of 7-week-old KM mice	Suppressing CREB activation in growth factor signaling pathway	Ma et al. (2008)

(continued on next page)



Table 7 (continued)

Pharmacology	Pharmacological effects	Substances and dosages	Experimental model	Mechanisms	Ref.
Anti-inflammatory activity	Inhibiting angiogenesis	$\beta$ -eudesmol 10–100 $\mu$ M	Porcine brain microvascular endothelial cells, human dermal microvascular endothelial cells	The blockade of the ERK signaling pathway	<a href="#">Tsuneki et al. (2005)</a>
	Anti-inflammatory effects in vitro	AR methanol extract 100 $\mu$ g/mL	Murine macrophage-like cell line RAW264.7 cells	Inhibiting the production of NO	<a href="#">Shimato et al. (2018)</a>
	Anti-inflammatory effect	ATL-III 1–100 $\mu$ M, LPS 1 $\mu$ g/mL	The murine macrophage cell line RAW264.7	Suppressing the release of NO, PGE <sub>2</sub> , TNF- $\alpha$ and IL-6 related to the NF- $\kappa$ B- and MAPK signaling pathways	<a href="#">Ji et al. (2016)</a>
	Improving intestinal inflammation and cooccurring dysmotility	Atractylodin 10.0 mg/kg	Diarrheaprominent rats were established by acetic acid and restraint stress; constipation-prominent rats were established by cool water	Reducing pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in the plasma and inhibiting the expression of inflammatory mediators iNOS and NF- $\kappa$ B in jejunal segments in both CP and DP rats.	<a href="#">Yu et al. (2017)</a>
	Anti-inflammatory effects	Water extracts of <i>A. lancea</i> rhizomes 100, 200 mg/kg	Male C57BL/6 mice	Inducing the hepatic expression of CYP3A	<a href="#">Yuan et al. (2017)</a>
	Alleviating LPS-induced inflammatory responses	Atractylodin 40 or 80 mg/kg	Lipopolysaccharide (LPS)-induced inflammatory rates	Suppression of nucleotide-binding domain-like receptor protein 3 inflammasome and toll-like receptor 4 activation	<a href="#">Tang et al. (2018)</a>
Anti-bacterial activity	Ameliorate colitis	$\beta$ -sitosterol and stigmasterol 0.4%	Dextran sulfate sodium (DSS)-induced colitis in C57BL/6J male mice	Suppressing the activation of inflammatory master regulator NF- $\kappa$ B. Stigmasterol significantly lowered colonic inflammation score and the expression of cyclooxygenase-2 and colony stimulating factor-1	<a href="#">Feng et al. (2017)</a>
	Antimycotic effect	AR 0.5–10.0%	<i>Trichophyton tonsuraus</i> , <i>Microsporum gypseum</i> et al.	This drug had apparent fungi action	<a href="#">Yin et al. (2000)</a>
Other activities	Combating multidrug resistant strains	Stigmasterol 1 $\mu$ g/disc, or in combination (1 $\mu$ g/disc ampicillin + 1 $\mu$ g/disc stigmasterol)	2 g-positive bacteria and 2 g-negative bacteria	Synergistic effects of stigmasterol and ampicillin against $\beta$ -lactamase producing clinical isolates	<a href="#">Yenn et al. (2017)</a>
	Protective effects of acute lung injury	LPS + AO-I (5, 10 and 20 mg/kg), LPS + VGX-1027 (0.5 mg/mouse)	LPS-induced acute lung injury mouse model	Inhibiting of TLR4 expression and NF- $\kappa$ B activation	<a href="#">Zhang et al. (2015)</a>
	Antiasthmatic properties	Stigmasterol 10–100 mg/kg	Ovalbumin-induced Guinea pigs	Reducing the proliferation of eosinophils, lymphocytes, and monocytes while reducing peribronchiolar, perivascular, and alveolar infiltration of inflammatory cells	<a href="#">Antwi et al. (2017)</a>
	Treatment of hallucinations of dementia	Atractylenolide III 0.03, 0.15, 0.75 mg/kg; $\beta$ -eudesmol 0.4, 2.0, 10 mg/kg	1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head-twitch mice	Active constituents contributing to the anti-hallucination effects of Byaku- and So-jutsu against serotonin receptors	<a href="#">Murayama et al. (2014)</a>
	Neuroprotective activity	Atractylenolide III 0.6, 1.2 and 2.4 mg/kg/day	Chronic high-dose homocysteine administration induced learning and memory impairment in rats	Decreasing homocysteine-induced reactive oxygen species formation and restored homocysteine-induced decrease of phosphorylated protein kinase C expression level	<a href="#">Zhao et al. (2015)</a>
	Autonomic nerve activity	$\beta$ -eudesmol 1.6, 1.8, 2.3, 2.4 ng/mL	Male Wistar rats (300–350 g)	Suppressing ASNA, partly through TRPA1 and the afferent vagus nerve	<a href="#">Ohara et al. (2018)</a>
	Influenza A virus treatment	Atractylon treatment at doses of 10–40 mg/kg	Influenza a virus (IAV) caused pneumonia in mice	Upregulating the expression of Toll-like receptor 7, MyD88, tumor necrosis factor receptor-associated factor 6 and IFN- $\beta$ mRNA but downregulating NF- $\kappa$ B p65 protein expression in the lung tissues of IAV-infected mice	<a href="#">Cheng et al. (2016)</a>
	Anti-diabetic activity	Metformin 200 mg/kg, stigmasterol 50, 100 mg/kg	Rat L6 cells	Enhancing the GLUT4 expression in L6 cells, skeletal muscle and white adipose tissue	<a href="#">Wang et al. (2017)</a>
	Anti-obesity effect	the ethanol extract of <i>Atractylodes lancea</i> rhizome (250, 500 mg/kg)	A high-fat diet-induced obesity mice	Atractylodin showed the highest lipase inhibitory activity	<a href="#">Jiao et al. (2014)</a>
	Anti-allergic activities	AR ethanol extracts 200 mg/day	Male NC/Nga mice	Inhibiting 5-LOX from RBL-1 cells	<a href="#">Lim et al. (2012)</a>

(most of which are volatile oil) housed various biological activities. However, the in-depth molecular mechanism remains elusive. Many reports are available on sesquiterpenes, alkynes, and glycosides in AR, which are common in Compositae plants, and alkynes in safflower. They are important secondary metabolites formed by the long-term coevolution of plants and insects. Most of the main components could produce

cytotoxic effects on cancer cells, especially melanoma. However, a certain gap still exists between the current pharmacological activities and its clinical uses. For instance, the role of AR in the treatment of eyesight and flaccidity-syndrome has not been explored. In addition, the existing pharmacological activity studies were mainly based on cell models and supplemented by animal models. The dosage of AR

compounds with AR extracts considerably varies. Although no potential safety hazards were shown by the existing evidence using in clinical settings remain underdeveloped. In some studies, the type, weight, sex, and other factors of the animal models are not clear, and the reference value of drug doses ignoring the actual factors of experimental animals is of little value. Meanwhile, AR is traditionally used in decoction clinically, and previous studies showed that the activity of water solution and volatile oil in AR are basically the same in terms of strengthening spleen and stomach (Liu et al., 2012), anti-inflammatory activities, liver protection (Ta et al., 2011), and other pharmacological aspects (Xu et al., 2015). Therefore, the water-soluble material basis of AR must be studied for enhanced guidance on the application of AR in Chinese patent medicine. In addition, the pharmacological activity and mechanism of compound AR and the interaction of effective components need to be further studied.

## 6. Toxicity

According to TCM, the adverse reactions of AR are mainly manifested in “dryness”. The “dryness” of AR is not only a pharmacological action for treating diseases but also a factor causing adverse reactions. Unprocessed AR has strong “dryness” and is easy to consume Yin fluid. The adverse reactions include impairment of spleen Yin, dysfunction of spleen in transportation, distress in the epigastrium, mouth parching and tongue scorching, and constipation. Therefore, Yixue Rumen indicated AR to “mistakenly take blood consumption, yin fail to nourish the body, hyperactive the fire due to yin deficiency”. After processing, the “dryness” of AR is slowed down, and it could eliminate dampness and activate spleen and stomach by entering the middle Jiao. Taking AR orally does not cause swelling and could eliminate dampness blocking and abdominal distention. In the case of Yin deficiency and heat injury to the body, the “dryness” of AR is particularly prominent. Therefore, Bencao Jingshu recorded that “AR should not be taken for diseases that belong to Yin deficiency, blood deficiency, essence deficiency, tidal fever, dry mouth and lips, cough and spit, spitting blood, sore nose and throat, and constipation, stagnation and Qi deficiency in the liver and kidney.” Bencao Zheng also recorded that “those who have a deficiency of internal heat and Yin and loose sweating on the surface should not take AR.” The “dryness” of AR is related to its volatile oil. The Compendium of Materia Medica (Bencao Gangmu) recorded, “because of the dryness of AR, processing would be taken that its oil is soaked in glutinous rice swill, and it is used for slicing and baking.” The results showed that the volatile oil content of AR decreased after being fried with bran and rice swill (Zhao, 2009). Whether AR should be processed to reduce the content of the essential oil in clinical medication should be based on the needs of the disease. For instance, raw AR is suitable for cold syndrome and cold dampness arthralgia, while processed AR is suitable for dampness resistance and middle Jiao and flaccidity syndrome. In addition, the deficiency of the element body Yin should be used with caution. Studies on modern toxicology and pharmacology of AR verified the safety profiles in different animal models. Following administration of ethanolic *A. lancea* extract at the high dose level (5000 mg/kg body weight) in rats and mice, no significant toxicity was observed except for gastric stimulation and central nervous system inhibition symptoms (diminished response to touch and balance and decreased alertness and motor ability) (Plengsuriyakarn et al., 2012). It is important however for the knowledge of potential deleterious effects of *A. lancea* on cardiovascular system. The antiplatelet aggregation of *A. lancea* is possibly mediated through suppression of collagen-induced signaling pathway which is upstream of the release of thromboxane A2 from platelets (Nasu et al., 2009). Care should be taken when using *A. lancea* extract or its active constituents in patients with platelet disorders or coagulopathy. The results of acute and subacute toxicity tests in rats and mice indicated that *A. lancea* was safe at a wide range of dose levels (1000–5000 mg/kg body weight) (Koonrungsesomboon et al., 2014). An observational study conducted in China showed a safety

profile of Fufang Cangzhu Tang, a Chinese herbal formula containing 15 g of AR decocted into 300 mL of liquor and separately administered orally two times a day for 8 weeks in 32 senile patients with obesity or overweight complicated with impaired glucose tolerance (Shi et al., 2006). In addition, animal experiments showed that the volatile oil of AR has a sedative effect in small dose, hyperreflexia in spinal cord, and inhibition effect in large dose, which eventually leads to respiratory paralysis and death (Wu, 1999). Its main inhibitory components are  $\beta$ -eucalyptol and atractylol, thus, it is harmful to organisms. Therefore, AR should be used with caution in patients with nervous system diseases because of its various effects on the nervous system. Meanwhile, it can discharge sodium and potassium; thus, electrolyte balance should be given attention in long-term applications. Several clinical studies of AR have been conducted in patients with different diseases/symptoms by using AR in various formulations (Liu et al., 2008). Atractyloside (ATR) is a diterpenoid glycoside and occurs naturally in Asteraceae plants (*A. macrocephala*, *A. lancea* and *Xanthium sibiricum*), many of which are used in foods and ethnomedicines. The toxicity of ATR has caused fatal renal proximal tubule necrosis and/or centrilobular hepatic necrosis in man and farm animals. And the degradation of ATR is a way to increase pharmaceutical safety for the Chinese medicinal industries (Zhu, 2012). However, no clinical study using AR extract or its main components alone has been conducted, signifying the need for further clinical trials to prove its clinical efficacy and safety for the human body. Although clinical research directly supporting its safety in the human body is lacking, the available information showed no serious adverse event.

## 7. Quality control

There is evidence that the sesquiterpenoids found in AR have pharmacological properties of improving gastrointestinal function, anti-tumor and anti-inflammatory, so the presence of these compounds may be a key indicator of the quality of the extract (Yang et al., 2012). The processing of AR also influenced the physicochemical properties and absorption of polyacetylenes. The extraction efficiencies of atractylodin and (4E, 6E, 12E)-tetradecatriene-8, 10-diyne-1, 3-diyl diacetate from AR were decreased when the rhizomes were stir-fried with bran compared to crude rhizomes (Liu et al., 2013). However, the processing of AR could increase the absorption of atractylodin. Stirfrying of AR with wheat bran could promote and accelerate the absorption of (4E, 6E, 12E)-tetradecatriene-8,10-diyne-1, 3-diyl diacetate and its concentration was highest in the spleen, possibly increasing the spleen-tonifying effect according to the traditional theory (Kim, 2016). Stability is another concerning issue as the occurrences of bioactive polyacetylenes can be changed under certain circumstances, like drying of the rhizomes under the sun. Atractylodin, atractylodinol, and acetylactylodinol were reported to have 1-cis isomers, (1Z)-atractylodin, (1Z)-atractylodinol, and (1Z)-acetylactylodinol. The proportions of those cis isomers were less than trans isomers as the cis isomers could be formed during the drying process of the AR under the sun. For example, (1E)-acetylactylodinol is rapidly isomerized to (1Z)-acetylactylodinol. On the one hand, the stabilities of 1-cis isomers were weaker than those of 1-trans isomers: (1Z)-acetylactylodinol more expeditiously disappeared in n-hexane solution compared to (1E)-acetylactylodinol dissolved in same solvent in the freezer. On the other hand, 1-cis isomer of atractylodin was relatively increased up to a similar ratio with its parent compound, atractylodin, in freezer storage, indicating that atractylodin was considerably unstable than its isomer and different from those two polyacetylenes, (1E)-atractylodinol and (1Z)-atractylodinol, which showed the same degree of instability (Resch et al., 2001).

According to the TCM theory, genuine (Dao-di) herb is a high-quality medicine produced from specific areas, with a long history of traditional use and excellent efficacy (Wang et al., 2018). Mao Cangzhu is considered a fine-quality good beginning from Hongjing Tao in the Northern and Southern Dynasties (386–589 A.D.). It has been used for more than

1500 years and it is found in Maoshan in Jiangsu Province. Cangzhu always takes Maoshan as geo-authentic habitats. The volatile oil components of AR vary considerably and are distributed continuously. According to the composition of the volatile oil of AR, it can be divided into two chemical types. One is represented by “Hubei Cangzhu”, which is mainly found in Hubei, Anhui, Shaanxi, Southern Henan and other places. The total amount of the volatile oil in Hubei type (HBA) is high, and mainly composed of hinesol and  $\beta$ -cineole, with or without very small amounts of atractylone and atractylodin. The other type, Maoshan type (MA), is mainly represented in Maoshan, Jiangsu Province, including Jiangsu, Shandong, Hebei and northern Henan. Its total volatile oil is low, and mainly composed of atractylone and atractylodin. In the volatile oil, atractylone, hinesol,  $\beta$ -eudesmol, atractylodin showed a specific ratio. In MA, their ratio is 0.70–2.00: 0.04–0.35: 0.09–0.40: 1 (Guo et al., 2008). These results showed that 91% of the measured values are in this range. The clustering results of HPLC fingerprint of the water extract of AR were similar to those of the volatile components. The main components of “white frost” in AR are citronellol and  $\beta$ -cineole. The content of these two components in Mao Cangzhu is much higher than that in unfamous-region AR. The content of atractylone, which is the main component of the cinnabar point of Mao Cangzhu, is 25.92% of the total volatile oil of AR. The average content of atractylone in other production areas is only 0.69% of the total volatile oil, but this component was detected in some samples (Guo et al., 2002). Thus, atractylone is essential in reflecting the genuine characteristics of AR, suggesting that the efficacy of AR is more similar to that of AM. The strong ability of AR in drying dampness and strengthening the spleen is the reason why it has become a genuine medicine compared with the AR from other places of origin. Generally, phenotypic variation is a product of both genetic and environmental variation (O'Reilly-Wapstra et al., 2013). The qualities of AR samples are closely associated with their habitat, and the contents of curative components in AR vary considerably based on geographical factors. However, it remains unclear whether the geographical variations are based on genetic or environmental factors. At the colony levels, as a genuine medicinal material of AR, the phenotype (volatile oil) of AR has obvious differentiation, but at the same time, its genetic differentiation is not significant. It can be seen that the larger phenotypic variation and the smaller genetic variation of AR are inconsistent, and the correlation between them is poor. All of these suggest that in addition to genetic factors, the environment is even a very important factor in the formation of herbal medicine of AR. Japanese scholars also confirmed this point by transplanting AR. Takeda et al. (1996) found that the volatile oil composition of *A. lancea*, *A. chinensis* and *A. koreana* was closer to that of 2–3 years after it was transplanted to Nanjing Institute of Botany. The climate of Maoshan area is characterized by high temperatures, short dry season and sufficient rainfall. The unique ratio of volatile oil of AR may be the result of the specific metabolism of AR caused by a specific environment. The meteorological conditions in October have the greatest impact on the volatile oil components. The annual average and the meteorological conditions in February and September have a greater impact on the volatile oil components. High temperature is the limiting factor for the growth and development of AR, while several meteorological factors related to temperature in Maoshan area are the highest in the whole distribution area (Guo, 2005). The formation of AR has an obvious adverse effect. Some studies have reported that the activation of phytohormones such as jasmonic acid and abscisic acid through symbiosis with several endophytes induces the production of the essential oil compounds in *A. lancea* (Wang et al., 2015). Yuan et al. (2009) found that soil acidity stimulated the accumulation of essential oils in *A. lancea*, particularly  $\beta$ -eudesmol, by influencing the concentrations of phytohormones such as abscisic acid. These results suggested that the contents of essential oil compounds in *A. lancea* could vary depending on environmental factors such as biological and abiotic stresses. In contrast, Takeda et al. (1996) suggested that the contents of essential oil compounds are influenced largely by genetic factors based on a comparative

study of the essential oil compounds between wild and cultivated *A. lancea*. To examine genotype-environment ( $G \times E$ ) interaction and the effects of environmental factors, Tsusaka et al. (2019) cultivated six clones in different years and different locations (Hokkaido, Ibaraki), and determined contents of  $\beta$ -eudesmol, hinesol, atractylon, and atractylodin in the clones. Subsequently, genetic variances, environmental variances, and  $G \times E$  interaction variance based on the compound contents were evaluated. It is demonstrated that the contents of  $\beta$ -eudesmol, hinesol, atractylon, and atractylodin in *A. lancea* are influenced mainly by genetic factors. In addition, these essential oil compounds could be selected regardless of rhizome yields in the course of *A. lancea* cultivar development. Consequently, *A. lancea* cultivars with high yields and high contents of the essential oil compounds could be developed and a further investigation on the effects of environment factors on the compound contents is a must.

The quality evaluation of AR is obviously based on the chemical composition and relative content of volatile oil as evaluation indicators. However, the lack of non-volatile parts limited this study. From Shen-nong Bencao Jing, who recorded that AR is used for “long-term use of AR would get longevity” to Bencao Gangmu, who recorded that “people often burn AR to avoid evil spirits in this disease and New Year’s day”. “Decocting baits” mainly used non-volatile parts, while “avoid poisonous gas” mainly used volatile oil parts. Enhancing the understanding on the quality evaluation of AR demands taking the volatile components as the index while regarding the non-volatile components. In the case of the unclear material basis of TCM, the overall effect of fingerprint is better than that of individual index components in terms of quality control. In addition, biomacromolecules play considerable roles in Chinese medicine, as their biological activities are related to TCM efficacy and their biological functions of the relationship between primary metabolism and the quality formation of TCM (Zhang et al., 2020). Understanding the functional properties and mechanisms of biological macromolecules could help demystify the drug properties and health benefits of TCM.

Further, The blood concentrations of the pharmacodynamic substances (mainly the active ingredients) of TCMs are usually very low. How can they exert pharmacological actions, in which forms (original form, metabolite or the both) do they exert the actions? The total chemical components of multi-sources TCMs from different plants are roughly the same, but the types and contents of chemical components are often obviously different (Kim et al., 2018). Is it reasonable for plants from different origins to be used as the same traditional Chinese medicine clinically? A new concept includes that the aggregate or summation of “effective forms” of pharmacodynamic substances of TCM is the core material base of the efficacy of TCM, and the “additive effect” of the blood concentrations of different “effective forms” is one part of the action mechanism (Xu et al., 2014). The “additive effect” of the different “effective forms” of a TCM means an “additive effect” of numerous constituents or/and metabolites on a same target, and therefore the efficacy brought by the addition of the concentrations of all these compounds, which differ from the “synergy effect” of multi-constituents on multi-targets and is a beneficial complement. Some constituents can be converted to each other in vivo and some metabolites are bioactive. These compounds having the similar structure are likely to have the same pharmacological effects on the same target, which could provide experimental evidence for the concept of “effective forms” and the hypothesis of “additive effect”.

## 8. Conclusions and future perspectives

The botany, traditional uses, phytochemistry, pharmacology, toxicity, and quality control of AR have been summarized in the present review. More than 200 compounds have been isolated and identified from the herb. Among them, sesquiterpenoids, and alkynes are the major active ingredients. And improving gastrointestinal activity supported the traditional use of AR. Nevertheless, there is still a lack of sufficient

research and further investigations need to be done in AR in the future. The related researches on Genus *Atractylodes* are mainly focused on *A. lancea* and *A. macrocephala*. As far as their active chemical components are concerned, other species also have important value, which is also a beneficial supplement for resource utilization of *Atractylodes*. The traditional uses of AR need to be further studied in the prevention and treatment of plague and night blindness and should be subjected to modern pharmacology to verify this idea and/or clarify its potential mechanism. The effective components, pharmacological activities, and mechanisms of TCM should be fully considered in the “effective forms”, “additive effect” and synergistic effect. We suggested that the “effective forms” and “additive effects” of the pharmacodynamic substances based on the same pharmacophore of TCM should be extensively investigated to further understand the pharmacodynamic substances and action mechanism of TCM. *A. lancea* is expected to be one of the candidate drugs for the treatment of cholangiocarcinoma. Further study on its biological activities in vivo and in vitro should be combined with toxicity study, and the appropriate dosages, models, and medication cycles should be selected according to the actual application. We should follow the quality control characteristics of TCM (integrity, processing, genuine) and combine with the clinical application, and a deep analysis of volatile oil and water-soluble components and their relationship is a must.

### Author's contributions

Wen-jin Zhang and Zhen-yu Zhao collated documents and wrote the manuscript; Li-kun Chang and Ye Cao helped perform the arrangement of tables and figures; Sheng Wang, Chuan-zhi Kang and Li Zhou contributed significantly to analysis and manuscript preparation; Hong-yang Wang assistance to the revision of the manuscript; Lu-qi Huang provided valuable idea; Lan-ping Guo provided financial supports and valuable discussion. All authors read and approved the final manuscript.

### Declaration of competing interest

The authors declare that they do not have any conflict of interest.

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