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Rhizoma *Atractylodis macrocephalae*: a review of photochemistry, pharmacokinetics and pharmacology

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Rhizoma *Atractylodis macrocephalae* is commonly used in Traditional Chinese Medicine. Its traditional functions include treating hypofunction of the spleen with the loss of appetite, abdominal distension diarrhea, phlegm drink dizziness palpitation, edema, fetal movement restless. A literature search was conducted by systematic searching multiple electronic databases including Web of Science, PubMed, CNKI and Google Scholar. Chemical composition analysis of RAM showed that the main compositions were volatile oil, lactones, polysaccharides, amino acids, vitamins and resins. Pharmacological studies indicated that RAM possessed antitumor activities, neuroprotective effect, anti-hepatotoxicity, immune and anti-inflammatory activity, etc. This review gives a detailed description of the chemical constituents, pharmacology and pharmacokinetics of RAM and provides reliable basis for clinical development and application.

1. Introduction

Rhizoma Atractylodis macrocephalae (RAM) (Fig. 1A-C), frequently referred to as "Baizhu" in Chinese, is the dried root of *Atractylodes macrocephala*, a Compositae plant. It has been utilized for about 2000 years in Chinese history. About 7000 tons of RAM are used for medical consumption in China every year. (Chen et al. 2007). In the Chinese Pharmacopoeia (2015 version), RAM is mainly recommended for the treatment of spleen deficiency, inappetence, abdominal distension, diarrhea, dizziness, edema, spontaneous sweating, and other diseases (Chinese Pharmacopoeia 2015). RAM is mainly growing in the provinces of Zhejiang, Jiangsu, Jiangxi, Hunan and Anhui in China. It was first recorded in the Shennong's Classic of Materia Medica (Shennong-Ben-cao-Jing) written during the period of the Eastern Han Dynasty. In addition, this plant has also been described in other historical books of TCM, such as Collective Notes to the Canon of Materia medic (Ben-Cao-Jing-Ji-Zhu, CE 480-498), Plants as Herbal Medicine (Ben-Cao-Tu-Jing, Song dynasty, CE960-1279), and Compendium of Materia Medica (Ben-Cao-Gang-Mu, Ming Dynasty, CE 1368-1644). RAM is usually harvested in winter. Both crude RAM and its preparations stir-frying with wheat bran (Fig. 1D) were used to treat patients. Meanwhile, a proper processing methodology could significantly alter the pharmacological properties of crude RAM, the reduction of characteristic of dryness and the strengthen spleen. Phytochemical research revealed that RAM main contains three categories of compounds, volatile oil, lactones and polysaccharides (Duan et al. 2008). Meanwhile, various pharmacological activities of RAM have been reported, including immunomodulatory, antitumor activities and anti-inflammatory properties (Li et al.2007; Zhang et al.2006).

No concise review of RAM has been published so far and there is little information about pharmacokinetic studies. Therefore, in this review, we have made a detailed description of the RAM with reference to the various documents and websites. We are providing an overview of the phytochemistry and their corresponding pharmacological actions of RAM in view of its role in the development of new drugs and therapeutics for various diseases. The pharmacokinetics of main components are also included.

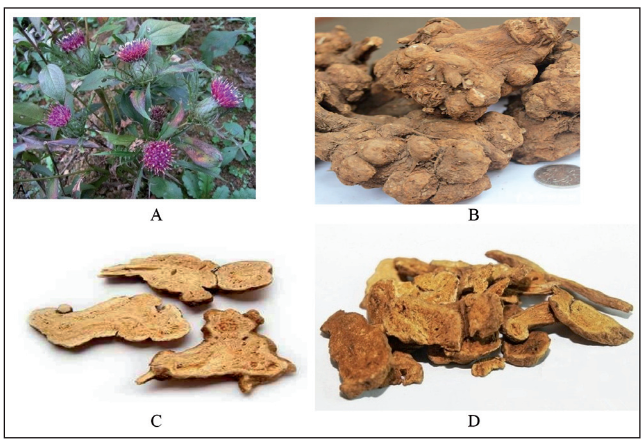

Fig. 1: A : Overground part from *Atractylodis macrocephalae* Koidz.; B: medicinal portion of *Rhizoma Atractylodis macrocephalae*; C: commercial herbal pieces of *Rhizoma Atractylodis macrocephalae*; D: Bran Fried atractylodes

2. Traditional uses

In TCM, there are severval formulas containing RAM used traditionally (Table 1), such as shenling baizhu powder, which contains RAM, Radix Codonopsis pilosulae, Poria, Radix Glycyrrhizae, Rhizoma Dioscorea, Semen Dolichoris Album, Semen Nelumbinis, Semen Coicis, Fructus Amomi and Radix Platycodi, has the clinical effect of liver protection and treatment of non-infectious intestinal diseases (Zhou 2011). Zhang et al. (2028) fed non-alcoholic fatty liver disease rats shenling baizhu powder, before and after treatment a significant difference was observed (Zhang et al.2018).

RAM usually was used to invigorate the spleen and eliminate dampness. For example, Sijunzi decoction was composed of four common drugs: RAM, Panax Ginseng, Poria cocos and *Glycyrrhiza uralensis* Fisch. It has been used to treat patients with nausea, vomiting, chronic gastritis or chronic atrophic gastritis and diarrhea (Liu et al. 2016; Li et al. 2015; Qu et al. 2018). Another classic herbal formula of TCM is Baizhu Shaoyao San (BSS), which comprises four medicinal herbs: RAM, Paeoniae Radix Alba, Saposhnikoviae Radix and Citri Reticulatae Pericarpium. It

Table 1: Traditional Chinese medicine formulas containing RAM used in traditional uses

Formulation name	Dosage form	Composition	Efficacy and application	Reference
Shenling Baizhu powder	powder	*Rhizoma Atractylodis macrocephalae*, *Radix Codonopsis pilosulae, Poria, Radix Glycyrrhizae, Rhizoma Dioscorea, Semen Dolichoris album, Semen Nelumbinis, Semen Coicis, Fructus Amomi* and *Radix Platycodi*	hepatoprotective properties and clinical efficacy in treating non-infectious intestinal disease	Welfare Pharmacy
Sijunzi decoction	decoction	*Radix Ginseng, Poria cocos, Rhizoma Atractylodis macrocephalae* and *Radix Glycyrrhizae.*	treat patients with chronic gastritis or chronic atrophic gastritis, nausea, vomiting and diarrhea	Taiping Huimin Heji Ju Fang
Baizhu Shaoyao San	powder	*Rhizoma Atractylodis macrocephalae*, *Paeoniae Radix alba*, *Citri Reticulatae pericarpium* and *Saposhnikoviae Radix*	tonifying spleen and softening liver as well as eliminating dampness and relieving diarrhea	Dan-Xi-Xin-Fa
Yu Ping Feng San	powder	*Radix Saposhnikoviae*, *Radix Astragali*, and *Rhizoma Atractylodis macrocephalae*	treatment of respiratory diseases, such as recurrent respiratory tract infections, chronic bronchitis, nosocomial pneumonia, and allergic rhinitis	Dan-Xi-Xin-Fa
Banxia Baizhu Tianma Decoction	decoction	*Pinellia ternata, Atractylodes macrocephala, Gastrodia elata,* tangerine peel*, Poria cocos, Glycyrrhiza*, ginger, and red jujube	Treatment of vertebrobasilar insufficiency vertigo in China	Medical Insights
Qiwei Baizhu Powder	Powder	*Panax ginseng* C.A.Mey, *Atractylodes macrocephala* Koidz, *Poria cocos* Wolf, *Pueraria lobata* Ohwi, *Agastache rugosa*, Costustroot, *Glycyrrhiza uralensis* Fisch.	treatment of infantile diarrhea, including the infantile diarrhea caused by Human Rota virus	Pediatric drug certificate
Lingguizhugan Decoction	decoction	*Poria*, *Ramulus Cinnamomi*, *Rhizoma Atractylodis macrocephalae*, and *Radix et Rhizoma Glycyrrhizae*	treating fullness and discomfort in chest and hypochondrium, phlegm and fluid retention, dizziness etc.	*Shang han za bing lun*
Shipi powder	powder	*Mangnolia officinalis*, *Rhizoma Atractylodis macrocephalae*, pawpaw, costusroot, Grass nuts, semen Arecae, *Radix Aconiti carmichaeli*, white poria, *Rhizoma zingiberis*, liquorice	Warming yang, strengthening spleen,promoting qi and water,and treating yang deficiency wate	Yi-Fang-Lei-Ju
Ginseng Powder	powder	Ginseng, *Rhizoma Atractylodis macrocephalae*, *Pinellia ternate, Rhizoma Zingiberis*, Old orange peel, the root bark of white mulberry, *Angelica sinensis*, liquorice, *Astragalus mongholicus*, Asarum,	Children vomiting, paediatric vomiting, abdominal pain	Taiping Holy Preions for Universal Relief
Jiawei Liujunzi decoction	decoction	Ginseng, R*hizoma Atractylodis macrocephalae*, *Poria cocos*, *Astragalus mongholicus*, Chinese yam, liquorice, fructus amomi, *Mangnolia officinalis*, *Myristica fragrans*	Invigorating Qi and invigorating spleen, removing dampness and stopping diarrhea	Criterion of proof and rule · class square
Zhenren yangzang decoction	decoction	Ginseng, *Angelica sinensis*, *Rhizoma Atractylodis macrocephalae*, *Myristica fragrans*, *Cinnamomum cassia*, liquorice, Chinese herbaceous peony, costusroot, myrobalan, *Pericarpium Papaveris*	Effect of astringent sausage and relieving diarrhea	Welfare Pharmacy
Fangji Huangqi decoction	decoction	*Saposhnikovia divaricata*, liquorice, *Rhizoma Atractylodis macrocephala*e, *Astragalus mongholicus*	Invigorate qi and dispel wind and invigorate spleen and water. Main treatment of feng shui or rheumatism, symptoms of sweating out of bad wind, heavy body swelling, unfavorable urination, pulse floating, limb joint pain	Synopsis of Golden Chamber
Zhishi daozhi pill	pill	*Rheum officinale*, *Fructus Aurantii immaturus*, massa medicate fermentata, *Poria cocos*, *Scutellaria baicalensis*, *Rhizoma coptidis*, *Rhizoma Atractylodis macrocephalae*, *Rhizoma Alismatis*	Eliminating food and guiding stagnation, clearing heat and dispelling dampness, treating gastrointestinal dysfunction, chronic dysentery, etc	Differentiation on endogenous
Soup in renal	decoction	Liquorice, *Rhizoma Atractylodis macrocephalae, Rhizoma Zingiberis, Poria cocos*	Dispelling cold and dehumidification	Synopsis of Golden Chamber
Dexfenfluramine Hudrochlorid	powder	*Radix saposhnikoviae*, szechwan lovage rhizome, *Angelica sinensis*, Chinese herbaceous peony, dried peppermint leaf, rheum officinale, mirabilite, *Ructus forsythia*, Ephedra, gypsum, *Radix Platycodons*, *Scutellaria baicalensis*, *Rhizoma Atractylodis macrocephalae*, jasmine, *Schizonepetae herba*, talc, liquorice	Clearing away heat and diarrhea	Xuanming Lun Fang, Clear Synopsis on Recipes
Ginseng Bolus	pill	Ginseng, prepared Rehmannia root, *Dens Draconis*, fushen, *Rhizoma Atractylodis macrocephalae*, liquorice, *Radix Ophiopogonis*, *Radix Saposhnikoviae*, goldleaf, silver foil	After the treatment of the heart wind deficiency, palpitations, or anxiety, there is a trance and uneasiness from time to time	Criterion of proof and rule · class square
Angelica Pain-Relieving Decotion	decoction	*Rhizoma Atractylodis macrocephalae*, ginseng, *Sophora flavescens*, *Rhizoma Cimicifugae*, *Radix Puerariae*, *Rhizoma Atractylodis*, *Radix Saposhnikoviae*, *Rhizoma anemarrhenae*, *Rhizoma alismatis*, *Scutellaria baicalensis*, *Polyporus umbellatus*, *Angelica sinensis*, *Radix Glycyrrhizae*, Preparataoriental wormwood, Notopterygium root	Clearing heat and dampness, sparing wind to relieve pain	yixueqiyuan
Add or subtract to supplement zhongyiqi soup	decoction	Ginseng, *Rhizoma Atractylodis macrocephalae*, Astragalus, *Angelica sinensis*, *Radix bupleuri*, liquorice, *Citri reticulatae pericarpium*, *Rhizoma cimicifugae*, *Poria cocos*	Pregnancy swelling	FuQingzhu's Obstetrics and Gynecology
Supplemented Center-Rectifying Decoction	decoction	Ginseng, *Rhizoma Atractylodis Macrocephalae*, *Radix Glycyrrhizae preparata*, *Rhizoma zingiberis*, szechwan lovage rhizome	It is used for treating excessive alcohol and excessive drinking , and it can be used for promoting blood circulation , and can be used for treating nasal hemorrhage	Treatise on Three Categories of Pathogenic Factors
Flavored buzhong yiqi soup	decoction	Ginseng, Astragalus, *Angelica sinensis*, *Rhizoma Atractylodis macrocephalae*, *Rhizoma cimicifugae*, *Radix Bupleuri*, Red orange, liquorice, Ephedra root, Blighted wheat, *Radix Paeoniae alba*, Cassia, *Semen Zizyphi spinosae*	spontaneous perspiration due to yang insufficiency	Yilinshengmo
Fetus-quieting beverage	decoction	Prepared rehmannia root, szechwan lovage rhizome, *Caulis perllae*, *Scutellaria baicalensis*, *Rhizoma Atractylodis macrocephalae*, *Fructus amomi*, liquorice	Nourishing serum fever, invigorating spleen and Fetal	Longevity and Life Preservation

has been used as a representative mediative formula for tonifying spleen and softening liver as well as eliminating dampness and relieving diarrhea (Xu et al. 2018). At present, RAM has been widely used in the clinical treatments of acute and chronic intestinal inflammation, painful diarrhea, and diarrhea-type irritable bowel syndrome (Fan et al. 2005; Bian et al. 2006).

RAM was also used to treat abnormal fetal movement and prevent miscarriage. For example, Bu-Shen-Yi-Qi formula which consists of RAM, Dangshen, Tusizi et al. has played an important role in the treatment of recurrent spontaneous abortion (Yang et al.2018). Besides, RAM has a significant therapeutic effect for vertigo. Banxia Baizhu Tianma Decoction combined with RAM, *Pinellia ternata*, *Poria cocos*, *Gastrodia elata*, tangerine peel, Glycyrrhiza, red jujube, and ginger. This prescription was mainly used for the treatment of headaches, dizziness, and abnormal sensations (Guo et al. 2017).

In general, RAM is a common herbal medicine in Chinese patent medicines and clinical compounds. It has become one of the indispensable condiments of supplements and soups as well.

3. Phytochemistry of RAM

Up to now, about 170 compounds have been isolated and characterized from RAM, including volatile oil, polysaccharides, lactones, vitamins, amino acids, resins etc. Among them, the lactones were the primary bioactive components.

3.1. Volatile oil

The volatile oil fraction is rich in acetylenic and sesquiterpenes compounds, such as atractylol, atractylon, selina-4(14),7(11)-dien-8-one, aromadendrene and so on. Figure 2 shows the structure of the most important volatile oil component of the RAM. The content of volatile oil in the RAM was estimated as 1.4% (Li et al. 2007).

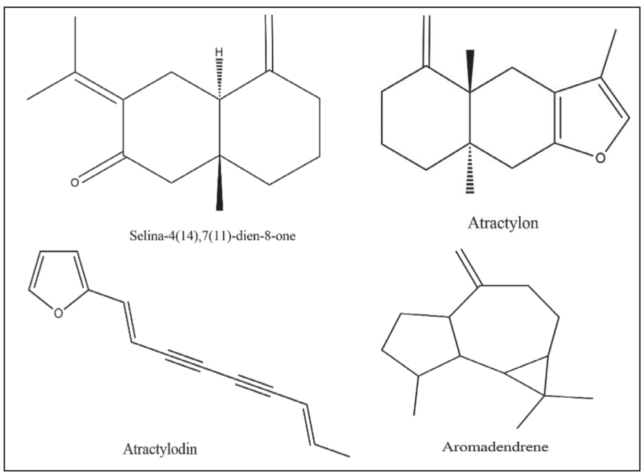

Fig. 2: Chemical structure of major compounds present in volatile oil

Wang et al. (2016) used steam distillation to extract the volatile oil of RAM, and then used GC-MS to analyse the constituents. They separated 37 substances with atractylone as the main component.

The content of volatile oil was greatly influenced by different extraction methods, but the composition was similar. The usual extraction methods are steam distillation, Soxhlet extraction and supercritical extraction. The results showed that atractylon content is highest when the volatile oil is extracted by steam distillation and supercritical extraction (Chen et al. 1996).

3.2. Sesquiterpene lactone compounds

Lactones are the key active constitutes in RAM (Chen et al. 2013). Figure 3 shows the structure of the main lactones of the RAM. Table 3 shows the Sesquiterpene lactone compounds isolated from RAM. The lactones isolated from RAM include atractylenolide I, II, III, IV, biatractylolide, 8,9 -epoxy atractylactone, 4,15-epoxy hydroxyl atractyllide and so on. The contents of atractylenoside I ranged from 0.0091% to 0.1034%, and the level of atractylenolide III ranged from 0.0155% to 0.2227% (Li et al. 2001).

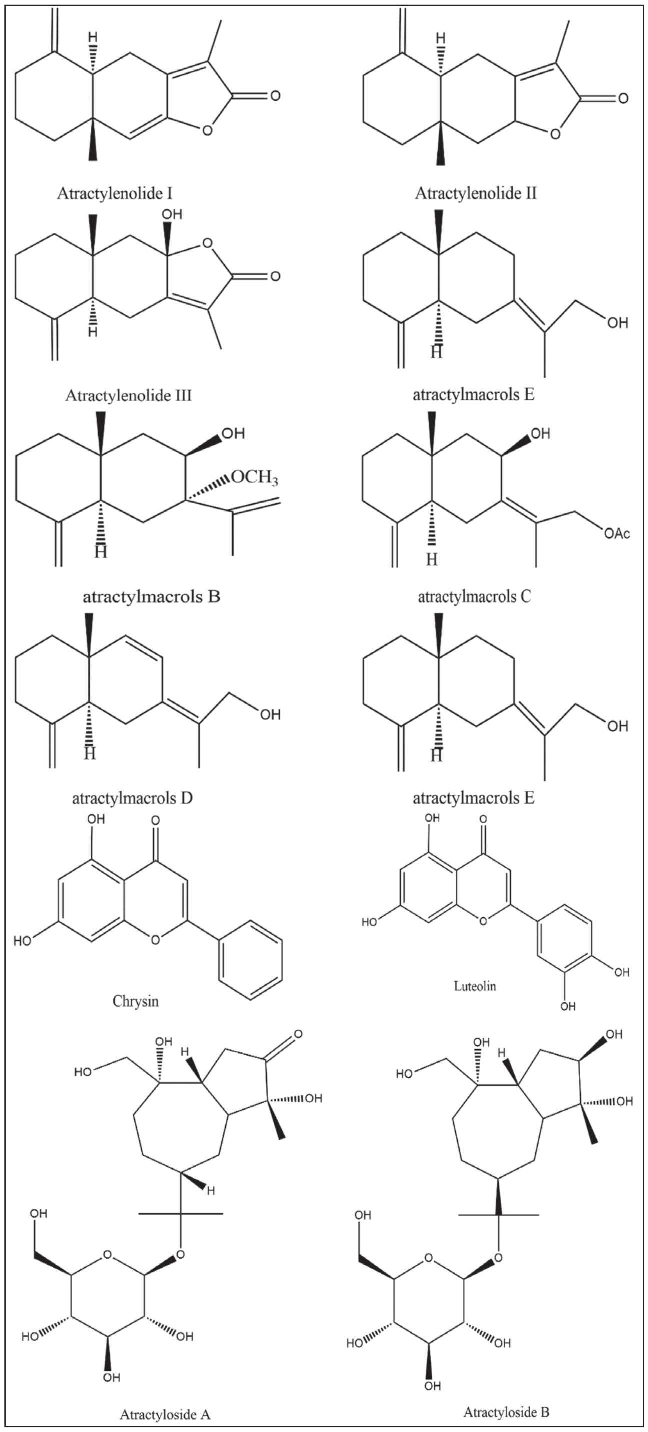

Fig. 3: The chemical structure of some lactones

RAM was extracted with 95% ethanol, and the extract was treated with ethyl acetate-water, separated by column chromatography to obtain atractylmacrols A-E, five new sesquiterpenes, as well as six known analogues, including atractylenolide I-III, 8β-methoxy-atractylenolide I, eudesma-7(11)-en-4-ol, eudesma-4(15),7(11)-dien-8-one (Wang et al. 2018).

With the help of UHPLC-FT-ICR-MS, Guan et al. (2018) found 11 sesquiterpenes of RAM in Sijunzi decoction: atractyloside A, atractyloside B, atractylenolide I-III, atractylentrid, chrysin, selina-4(14),7(11)-dien-8-one, dibutyl phthalate, luteolin, icarisside D1.

Table 2: The volatile oil isolated from RAM

No.	Phytochemicals	Chemical formula	Formula weight	Ref.
1	1,2,3,3a,8,8a-Hexahydro-2,2,8-trimethyl-5,6-azulenedicarboxaldehyde	$C_{15}H_{20}O_2$	232	(Wang et al. 2016)
2	1,4a-Dimethyl-7-(1-methylethylidene)-decahydro-1-naphthalenol	$C_{15}H_{26}O$	222	(Wang et al. 2016)
3	1,4-Dimethyl-7-(1-methylethenyl)-1,2,3,5,6,7,8,8a-octahydro-azulene	$C_{15}H_{24}$	204	(Wang et al. 2016)
4	1,5-Dimethyl-2,6-bis(methylene)-cyclooctane	$C_{12}H_{20}$	164	(Wang et al. 2016)
5	2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydro-naphthalene	$C_{15}H_{24}$	204	(Wang et al. 2016)
6	2-Nerolidol	$C_{15}H_{26}O$	222	(Wang et al. 2016)
7	2,3,8,8-Tetramethyltricyclo[5,2,2,0(1,6)]undec-2-ene	$C_{15}H_{24}$	204	(Wang et al. 2016)
8	3,6,8,8-Tetramethyl-2,3,4,7,8,8a-hexahydro-1H-3a,7-methanoazulene	$C_{16}H_{26}O$	234	(Wang et al. 2016)
9	3,8-Dimethyl-4-(1-methylethylidene)-2,4,6,7,8,8a-hexahydro-azulenone	$C_{15}H_{22}O$	218	(Wang et al. 2016)
10	4-(2,6,6-Trimethyl-2-cyclohexen-1-ylidene)- 2-butanone	$C_{13}H_{20}O$	192	(Wang et al. 2016)
11	4a,8-Dimethyl-2-(1-methylethenyl)-1,2,3,4,4a,5,6,8a-octahydro-naphthalene	$C_{15}H_{24}$	204	(Wang et al. 2016)
12	4a,8-Dimethyl-2-(propan-2-ylidene)-1,2,3,4,4a,5,6,8a-octahydronaphthalene	$C_{15}H_{24}$	204	(Wang et al. 2016)
13	4,5-Dehydro-isolongifolene	$C_{15}H_{24}$	204	(Wang et al. 2016)
14	4a,5-Dimethyl-3-(1-methylethylidene)-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone	$C_{15}H_{22}O$	218	(Wang et al. 2016)
15	6-Ethenyl-6-methyl-1-(1-methylethenyl)-3-(1-methylidene)-6-cyclohexene	$C_{15}H_{24}$	204	(Wang et al. 2016)
16	8,9-Dehydro-neoisolongifolene	$C_{15}H_{24}$	204	(Wang et al. 2016)
17	8-Hydroxy-4-isopropylidene-7-methylbicyclo[1,3,5] undec-1-ene	$C_{15}H_{20}O_2$	232	(Wang et al. 2016)
18	Aristolene	$C_{15}H_{20}$	200	(Wang et al. 2016)
19	Aromadendrene	$C_{15}H_{24}$	204	(Wang et al. 2016)
20	Atractylone	$C_{15}H_{22}O$	218	(Wang et al. 2016)
21	Calarene	$C_{15}H_{24}$	204	(Wang et al. 2016)
22	Cyperene	$C_{15}H_{24}$	204	(Wang et al. 2016)
23	Caryophyllene	$C_{15}H_{24}$	204	(Wang et al. 2016)
24	Eudesma-4(14),11-diene	$C_{15}H_{24}$	204	(Wang et al. 2016)
25	Ledene	$C_{15}H_{24}$	204	(Wang et al. 2016)
26	Ledene alcohol	$C_{15}H_{24}O$	220	(Wang et al. 2016)
27	Valencene	$C_{15}H_{24}$	204	(Wang et al. 2016)
28	Spathulenol	$C_{15}H_{24}O$	220	(Wang et al. 2016)
29	α-Caryophyllene	$C_{15}H_{24}$	204	(Wang et al. 2016)
30	β-Humulene	$C_{15}H_{24}$	204	(Wang et al. 2016)
31	β-Panasinsene	$C_{15}H_{24}$	204	(Wang et al. 2016)
32	β-Elemene	$C_{15}H_{24}$	204	(Wang et al. 2016)
33	β-Vatirenene	$C_{15}H_{24}$	204	(Wang et al. 2016)
34	γ-Neoclovene	$C_{15}H_{24}$	204	(Wang et al. 2016)
35	γ-Elemene	$C_{15}H_{24}$	204	(Wang et al. 2016)
36	γ-Himachalene	$C_{15}H_{24}$	204	(Wang et al. 2016)
37	γ-Neodovene	$C_{15}H_{24}$	204	(Wang et al. 2016)
38	1-Allyl-3,5-dimethylpyrazole	$C_8H_{12}N_2$	136.19	(Chen et al. 2016)
39	1-(4-Methoxyphenyl)-4,6-dimethyl-2(1h)-pyrimidinone	$C_{15}H_{18}N_4$	254.33	(Chen et al. 2016)

No.	Phytochemicals	Chemical formula	Formula weight	Ref.
40	2-Methylbutanoic acid	$C_5H_{10}O_2$	102.133	(Chen et al. 2016)
41	2,6-Dimethylpyrazine	$C_6H_8N_2$	108.14	(Chen et al. 2016)
42	2-Ethyl-3-methylpyrazine	$C_8H_{12}N_2$	136.19	(Chen et al. 2016)
43	(2Z,9E)-2,9-Heptadecadiene-4,6-diyn-8-ol	$C_{17}H_{24}O$	244.37186	(Chen et al. 2016)
44	3-Methylbutanoic acid	$C_5H_{11}NO_3$	133.15	(Chen et al. 2016)
45	3-Methylenecycloheptene	C_8H_{12}	108.184	(Chen et al. 2016)
46	5-Hydroxymethylfurfural	$C_6H_6O_3$	126.111	(Chen et al. 2016)
47	6-(1,1-Dimethylethyl)-3,4-dihydro-1(2H)-naphthalenone	$C_{10}H_{11}NO$	161.2	(Chen et al. 2016)
48	6-Isopropenyl-4,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-naphthalenol	$C_{15}H_{24}O$	220.35046	(Chen et al. 2016)
49	7-Ethinyl-1,4a-dimethyl-4a,5,6,7,8,8a-hexahydro-2 (1H)-naphthalenone	$C_{12}H_{18}O$	178.27072	(Chen et al. 2016)
50	8a-Methyl-3,4,4a,5,8,8a-hexahydro-1(2H)-naphthalenone	$C_{11}H_{16}O$	164.24414	(Chen et al. 2016)
51	Aromandendrene	$C_{15}H_{24}$	204.35	(Chen et al. 2016)
52	Alloaromadendrene	$C_{15}H_{24}$	204.35	(Chen et al. 2016)
53	Aristolone	$C_{15}H_{22}O$	218.335	(Chen et al. 2016)
54	Benzaldehyde	C_7H_6O	106.122	(Chen et al. 2016)
55	Benzeneacetaldehyde	$C_{10}H_{10}O$	146.19	(Chen et al.2016)
56	Caryophyllene oxide	$C_{15}H_{24}O$	220.35	(Chen et al. 2016)
57	Epizonarene	$C_{15}H_{24}$	204.35	(Chen et al. 2016)
58	Furaneol	$C_6H_8O_3$	128.13	(Chen et al. 2016)
59	Germacrene B	$C_{15}H_{24}$	204.35	(Chen et al.2016)
60	Humulene	$C_{15}H_{24}$	204.35	(Chen et al. 2016)
61	Limonene	$C_{10}H_{16}$	136.24	(Chen et al. 2016)
62	Ledene oxide-(II)	$C_{15}H_{24}O$	220.3505	(Chen et al. 2016)
63	Methylene cyclopropanecarboxylic acid	$C_5H_6O_2$	98.09994	(Chen et al. 2016)
64	Nandrolone	$C_{18}H_{26}O_2$	274.404	(Chen et al. 2016)
65	Patchoulane	$C_{15}H_{26}$	206.36694	(Chen et al. 2016)
66	Spathulenol	$C_{15}H_{24}O$	220.3505	(Chen et al. 2016)
67	Valencene	$C_{15}H_{24}$	204.36	(Chen et al. 2016)
68	(Z)-4-Hexadecen-6-yne	$C_{16}H_{28}$	220	(Chen et al. 2016)
69	α-Curcumene	C15H22	202	(Chen et al. 2016)
70	β-Selinene	$C_{15}H_{24}$	204.351	(Chen et al. 2016)
71	(-)-Aristolene	$C_{15}H_{24}$	204.352	(Chen et al. 2016)
72	(-)-γ-Elemene	$C_{15}H_{24}$	204.353	(Chen et al. 2016)
73	[s-(Z,Z)] 3,7-Cyclodecadiene-1-methanol,α,α,4,8-tetramethyl	$C_{15}H_{26}O$	222.3663	(Chen et al. 2016)
74	Hexahydrotoluene	C_7H_{14}	98	(Chen et al. 2016)
75	1-Cyclopentyl ethane	C_7H_{14}	98	(Chen et al. 2016)
76	1-Methoxy-2-propyl acetate	$C_6H_{12}O_3$	132	(Chen et al. 2016)
77	1R,4R,7R,11R-1,3,4,7-Tetramethyltricyclo [5. 3. 1. 0(4,11)] undec-2- ene	$C_{15}H_{24}$	204	(Chen et al. 2016)
78	1(10)-aristolene	$C_{15}H_{24}$	204	(Chen et al. 2016)
79	1-Ethenyl-1-methyl-2-(1-methylethenyl)-4-(1-methylethylidene)-cyclohexane	$C_{15}H_{24}$	204	(Chen et al. 2016)

No.	Phytochemicals	Chemical formula	Formula weight	Ref.
80	1α,4αH,10αH-Guaia-5,11-diene	$C_{15}H_{24}$	204	(Chen et al. 2016)
81	2,3,3a,4,5,9a-Hexahydro-3a,7,9,9a-tetramethyl-1H-cyclopenta cyclooctene	$C_{15}H_{24}$	204	(Chen et al. 2016)
82	2,3,3-Trimethyl-2-[(1E)-3-methyl-1,3-butadien-1- yl]-6-methylene- cyclohexanone	$C_{15}H_{22}O$	218	(Chen et al. 2016)
83	2,3,4,4a,5,6-Hexahydro-4a,8- dimethyl-β-methylene-2- naphthalneethanol	$C_{15}H_{22}O$	218	(Chen et al. 2016)
84	3-Methylenecycloheptene	C_8H_{12}	108	(Chen et al.2016)
85	4,5-Dehydroisolongifolene	$C_{15}H_{22}$	202	(Chen et al. 2016)
86	5-(2,2- Dimethylpropylidene)hexahydro-1(2H)-pentalenone	$C_{13}H_{20}O$	192	(Chen et al. 2016)
87	6-Isopropenyl-4,8a-dimethyl -1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-none	$C_{15}H_{22}O$	218	(Chen et al. 2016)
88	6-Isopropenyl-4,8a-dimethyl -1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-ol	$C_{15}H_{24}O$	220	(Chen et al. 2016)
89	10-Epicyperene	$C_{15}H_{24}$	204	(Li et al. 2013)
90	10-Methyl-1(9)octal -2-one	$C_{11}H_{16}O$	164	(Li et al. 2013)
91	Atractylenolide I	$C_{15}H_{18}O_2$	230	(Li et al. 2013)
92	Atractylenolide II	$C_{15}H_{20}O_2$	232	(Li et al. 2013)
93	Atractylenolide III	$C_{15}H_{20}O_3$	248	(Li et al. 2013)
94	Copaene	$C_{15}H_{24}$	204	(Li et al. 2013)
95	Curcumene	$C_{15}H_{22}$	202	(Li et al. 2013)
96	Dehydroaromadendrene	$C_{15}H_{22}$	202	(Li et al. 2013)
97	Dehydrocycloisolongifolene	$C_{15}H_{22}$	202	(Li et al. 2013)
98	Elixene	$C_{15}H_{24}$	204	(Li et al. 2013)
99	Guaia-5,11-diene	$C_{15}H_{24}$	204	(Li et al. 2013)
100	Guaiene	$C_{15}H_{24}$	204	(Li et al. 2013)
101	Hexahydrotoluene	C_7H_{14}	98	(Li et al. 2013)
102	Juniper camphor	$C_{15}H_{26}O$	222	(Li et al. 2013)
103	o-Xylol	C_8H_{10}	106	(Li et al. 2013)
104	Orthodene	$C_{10}H_{16}$	136	(Li et al. 2013)
105	Phenylmethane	C7H8	92	(Li et al. 2013)
106	Pyranton A	$C_6H_{12}O_6$	116	(Li et al. 2013)
107	Phenylethane	C_8H_{10}	106	(Li et al. 2013)
108	p-Xylene	C_8H_{10}	106	(Li et al. 2013)
109	p-Methylcumene	$C_{10}H_{14}$	134	(Li et al. 2013)
110	Schrenkianaone	$C_{20}H_{22}O_2$	294	(Li et al. 2013)
111	Selina-3,7(11)-diene	$C_{15}H_{24}$	204	(Li et al. 2013)
112	Spathulen	$C_{15}H_{24}O$	220	(Li et al. 2013)
113	Terpin-4-ol	$C_{10}H_{18}O$	154	(Li et al. 2013)
114	Tetradecane	$C_{14}H_{30}$	198	(Li et al. 2013)
115	Velleral	$C_{14}H_{20}O_2$	232	(Li et al. 2013)
116	Valencene	$C_{15}H_{24}$	204	(Li et al. 2013)
117	α-Gurjunene	$C_{15}H_{24}$	204	(Li et al. 2013)
118	α-Bergamotene	$C_{15}H_{24}$	204	(Li et al. 2013)
119	β-Maaliene	$C_{15}H_{24}$	204	(Li et al. 2013)

No.	Phytochemicals	Chemical formula	Formula weight	Ref.
120	β-Himachalene	$C_{15}H_{24}$	204	(Li et al. 2013)
121	β-Eudesmene	$C_{15}H_{24}$	204	(Li et al. 2013)
122	β-Sesquiphellandrene	$C_{15}H_{24}$	204	(Li et al. 2013)
123	β-Cedrene	$C_{15}H_{24}$	204	(Li et al. 2013)
124	β-Eudesmol	$C_{15}H_{26}O$	222	(Li et al. 2013)
125	γ-Terpinene	$C_{10}H_{16}$	136	(Li et al. 2013)
126	γ-Gurjunene	$C_{15}H_{24}$	204	(Li et al. 2013)
127	γ-Elemene	$C_{15}H_{24}$	204	(Li et al. 2013)
128	γ-Maaliene	$C_{15}H_{24}$	204	(Li et al. 2013)
129	δ-Terpinene	$C_{10}H_{16}$	136	(Li et al. 2013)
130	δ-Guaiene	$C_{15}H_{24}$	204	(Li et al. 2013)

Table 3: Sesquiterpene lactone compounds isolated from RAM

NO	Phytochemicals	Chemical formula	Molecular mass	References
1	Atractylmacrol A	$C_{15}H_{24}O$	220	(Wang et al.2017)
2	Atractylmacrol B	$C_{16}H_{26}O_2$	250	(Wang et al.2017)
3	Atractylmacrol C	$C_{17}H_{26}O_3$	278	(Wang et al.2017)
4	Atractylmacrol D	$C_{15}H_{22}O$	218	(Wang et al.2017)
5	Atractylmacrol E	$C_{15}H_{24}O$	220	(Wang et al.2017)
6	Z-Ligustilide	$C_{12}H_{14}O_2$	190	(Zhou et al.2012)
7	Atractylenolide I	$C_{15}H_{18}O_2$	230	(Zhou et al.2012)
8	Atractylenolide II	$C_{15}H_{20}O_2$	232	(Zhou et al.2012)
9	Atractylenolide III	$C_{15}H_{20}O_3$	248	(Kim et al. 2007)
10	Atractylenolide IV	$C_{17}H_{23}O_5$	307	(Kim et al. 2007)
11	AtractylenolideV	$C_{15}H_{20}O_4$	264	(Hoang et al.2016)
12	Atractylenolide VI	$C_{15}H_{20}$	200	(Yang et al. 2012)
13	Atractylenolide VII	$C_{17}H_{27}O_2$	263	(Yang et al. 2012)
14	8β-Ethoxy Atractylenolide III	$C_{18}H_{26}O_3$	290	(Jia et al. 2017)
15	Atractyline	$C_{15}H_{20}O$	216	(Jia et al. 2017)
16	Atractylodin	$C_{13}H_{10}O$	182	(Jia et al. 2017)
17	Erythrodiol 3-acetate	$C_{32}H_{52}O_2$	468	(Jia et al. 2017)
18	Beta-Sitosterol	$C_{29}H_{50}O$	414	(Jia et al. 2017)

Dong et al. (2008) used petroleum ether-ether (1:1) extract of RAM and then screened by cell membrane chromatography and subsequently separated by column chromatography, isolated atractylenolide I and atractylenolide III. These components have been shown to exert remarkable anti-inflammatory effects *in vivo* (Dong et al.2008). GC-MS was used to analysis the components of RAM, Zhou et al found that atractylenolide I and atractylenolide II from RAM (Zhou et al.2012).

3.3. Polysaccharides

Atractylodes macrocephala polysaccharides (AMP) are major medicinal components of RAM and have a variety of biological activities, such as anti-stress, enhancing immunity, regulating the enzyme activity, promoting the growth of probiotics, mitigating the virus caused by liver injury and so on (Xu et al. 2018; Guo et al. 2012; Xie et al. 2013; Duan et al. 2008).

Under the influence of geographical location, environmental conditions and extraction methods, the structure of polysaccharide is relatively difficult to analyze. Nevertheless, researchers have clarified several polysaccharides' composition or their structural backbones (Table 4). The AMP are mainly composed of galactose, glucose, mannose, arabinose, and rhamnose, etc. For example, three polysaccharides were isolated from RAM (BZ-3-1, BZ-3-2 and BZ-3-3). According to the retention time, the average molecular weight was estimated as $5.65×10^4$, $5.59×10^4$, $5.51×10^4$ Da. BZ-3-1 and BZ-3-2 contained the same types of monosaccharides (rhamnose, arabinose, mannose, glucose, and galactose), but the amount of glucose was higher in BZ-3-2. The monosaccharide composition of BZ-3-3 was different from the other two (BZ-3-1 and BZ-3-2). It only contains mannose and glucose (Ji et al. 2017). Xu et al. (2017) extracted AMP60, AMP70, AMP80 and AMPtp from the RAM. They found that AMPtp was homogeneous polysaccharide with Mn of $1.867×10^3$ by GPC analysis. AMPtp are composed of glucose, mannose, rhamnose, arabinose and galactose, with mass percentages of 60.67%, 14.99%, 10.61%, 8.83% and 4.90%, respectively by HPLC analysis, connected by 1, 3-linked β-D Galp and 1, 6-linked β-D Galp residues by NMR analysis and was amorphous in structure by SEM analysis(Xu et al. 2017).
Besides, Han et al. (2016) isolated and purified a homogeneous polysaccharide from RAM and named PRAM2. It has an average molecular weight of 19.6 $×10^3$ and consists of glucose, rhamnose, xylose, arabinose and mannose. The ratio is 1: 1.3: 1.5: 1.8: 2.1: 3.2.

Table 4: Polysaccharides composition or their structural backbones of RAM

Name	Source	Composition	Molecular Weight	Extraction method	Ref
BZ-3-1	RAM	Rha : Ara : Xyl : Man : Glc : Gal = 14.1 : 39.4 : 1.4 : 4.2 : 22.6 : 18.3	$5.65 × 10^4$ Da	hot water	(Ji et al. 2017)
BZ-3-2	RAM	Rha : Ara : Man : Glc : Gal = 2.6 : 7.6 : 21.1 : 62.6 : 6.1	$5.59 × 10^4$ Da	hot water	(Ji et al. 2017)
BZ-3-3	RAM	Man : Glc = 15.4 : 85.6	$5.51 × 10^4$ Da	hot water	(Ji et al. 2017)
AMPtp	RAM	glucose, mannose, rhamnose, arabinose and galactose with mass percentages of 60.67%, 14.99%, 10.61%, 8.83% and 4.90%,	$2.325×10^3$ Da	water extraction and ethanol precipitation	(Xu et al.2017)
PRAM2	RAM	rhamnose : xylose : arabinose : glucose : mannose : galactose = 1 : 1.3 : 1.5 : 1.8 : 2.1 : 3.2.	19.6 $×10^3$ Da	petroleum ether reflux extraction, 80% ethanol with reflux method, distilled water extract,	(Han et al.2016)
RAMPS	RAM	glucose, mannose, arabinose, galactose, xylose, d-Ribose and rhamnose, with mass percentages of 66.39%, 21.24%, 5.64%, 2.65%, 2.30%, 1.15% and 0.64%, respectively	RAMPS had two peaks, $2.20×10^5$, $2.15 × 10^3$	water	(Zhao et al.2016)
RAMPS	RAM	Rhamnose : arabinose : xylose : mannose : glucose : galactose = 1.00 : 2.49 : 2.07 : 4.94 : 11.33 : 1.35		Hot water	(Xie et al.2012)

3.4. Acetylenic compounds

Dong et al. (2008) used petroleum ether-ether (1:1) extract of RAM and then screened by CMC and subsequently separated by CC. Three compounds were isolated from RAM, including 14-acetoxy-12-senecioyloxytetradeca-2E,8E,10E-trien-4,6-diyn-1-ol, 14-acetoxy-12-α-methylbutyl-2E,8E,10E-trien-4,6-diyn-1-ol and 14-acetoxy-12-β-methylbutyl-2E,8E,10E-trien-4,6-diyn-1-ol (Dong et al.2008).

3.5. Other ingredients

In addition to the above mentioned components, RAM is rich in amino acids, such as aspartic acid, serine, glutamic acid, alanine, et al. Besides, many researchers have determined that RAM also contains vitamins, resins and others.

4. Pharmacological properties

RAM, as an important Chinese herbs, has a wide range of clinical applications. It has been recognized to possess antitumor activities, neuroprotective effect, anti-hepatotoxicity, immune, anti-inflammatory activity et al. The primary pharmacological actions of RAM are summarized in Table 5.

4.1. Antitumor activities

Many chemical components of RAM have antitumor activities. The constituents from the petroleum ether extracts of the RAM demonstrated antitumor activities (Wei et al. 2011) as did the volatile oil. Zhang et al. (2006) found that the volatile oil from RAM significantly inhibited the growth of Ehrlich ascites tumor and prolonged the lifespan of mice (Zhang et al. 2006). Furthermore, AMP has antitumor activity. AMP obviously restrained C6 cells multiplication by DNA fragmentation and inducing cell apoptosis. The mechanisms include the loss of mitochondrial membrane potential by AMP treatment and the release of cytochrome c to cytosol. Besides, the cleavage of capase-3, caspase-9 and poly (ADP-ribose) polymerase (PARP) was activated after AMP treatment in C6 cells (Li et al. 2014).
Atractylenolide I is a eudesmane-type sesquiterpenoid lactone (eudesman-type sesquiterpenoid lactone), which is one of the main natural compounds of RAM and has unique anti-tumor effects (Liu et al. 2006; Li et al. 2015; Qu et al. 2018; Xu et al. 2019; Fan et al. 2005; Bian et al. 2006). For example, a study stated clearly that atractylenolide I induced apoptosis of A549 lung cancer cells *via* a chondriosome-mediated apoptotic pathway (Liu et al. 2013). Atractylenolide I induces apoptosis of human promyelocyte HL-60 cells, and induces cytotoxicity by inhibiting oxidative activity and activities of copper and zinc superoxide dismutase (Wang et al. 2006). Besides, a study showed that atractylenolide I may play a role in the treatment of gastric cancer. The study demonstrated that atractylenolide I could potently inhibit cancer cell proliferation and induce apoptosis through inactivating Notch pathway (Ma et al. 2014). It is noteworthy that a clinical study has also shown that atractylenolide I treatment for cachexia during gastric cancer can improve appetite and Karnofsky performance with few side effects (Liu et al. 2008). In addition, atractylenolide I has therapeutic effects on both human bladder cancer cell lines *in vitro* and *in vivo*. Atractylenolide I inhibits xenograft growth, triggers G2/M cell cycle arrest, induces apoptosis through intrinsic pathway and blocks PI3K/Akt/mTOR signaling pathway (Yu et al. 2016). Furthermore, atractylenolide I could induce apoptosis and differentiation of leukemia cells (Huang et al. 2016).
Atractylenolide I, atractylenolide II, and atractylenolactam exerted anti-proliferative activities, induced cell differentiation and inhibited cell migration via Ras/extracellular regulated protein kinases and phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathways in B16 melanoma cells (Yan et al. 2011).

4.2. *Anti-inflammatory activity*

Inflammatory reactions include phospholipase A2 activation, NO production, ROS production, neutrophil, mast cells and macrophages histamine release. RAM has therapeutic effects on a variety of inflammatory diseases. The RAM extract has anti-inflammatory activity. Atractylenolide I and 14-acetoxy-12-senecioyloxytetradeca-2E, 8E, 10E-trien-4,6-diyn-1-ol of RAM were effective in acute and chronic inflammation models in mice (Li et al. 2007). Besides, five components from RAM were isolated and identified by routine spectrometric methods. The components contain not only atractylenolide I, 14-acetoxy-12-senecioyloxytetradeca-2E,8E,10E-trien-4,6-diyn-1-ol, but also atractylenolide III, 14-acetoxy-12-α-methylbutyl-2E, 8E, 10E-trien-4, 6-diyn-1-ol and 14-acetoxy-12-β-methylbutyl-2E, 8E, 10E-trien-4, 6-diyn-1-ol. The five components were found to exert potent anti-inflammatory actions *in vivo* (Dong et al. 2008). However, the anti-inflammatory mechanism could not be clarified.

Additionally, the study has shown that atractylenolide I and atractylenolide III are the two major compounds in RAM that contribute to its anti-inflammatory activities, by the inhibition of tumor necrosis factor-α (TNF-α) and nitric oxide (NO) production. Atractylenolide I showed more potent inhibition than atractylenolide III in the production of TNF-α and NO in lipopolysaccharide(LPS)-activated peritoneal macrophages (Li et al.2007). Meanwhile, Wang et al. (2009) also identified that atractylenolide I is the major component to anti-inflammatory. *In vitro* experiments revealed that atractylenolide I also was able to inhibit LPS-induction of TNF-α, and NO production in a dose-dependent manner. Besides, atractylenolide I can also inhibit interleukin-1β (IL-1β) production (Wang et al. 2009).

Atractylenolide I displayed a potent inhibitory effect on angiogenesis by a set of down-regulatory actions of NO, TNF-α, IL-1β, interleukine-6 (IL-6), vascular endothelial growth factor (VEGF), and placenta growth factor (PIGF) in chronic inflammation. The study shows that AO-I potently and dose-dependently reduced the level of TNF-α, IL-1β, VEGF, PIGF and NO in the exudates of FCA-stimulated mouse air pouches. Similarly, AO-I exhibited an inhibitory behavior *in vitro* that dose-dependently inhibited LPS-induced the peritoneal macrophages expression of TNF-α, IL-1β, VEGF, PIGF and NO (Wang et al. 2009).

Ji et al. (2014) found that atractylenolide I showed no inhibitory effect on cell viability at concentrations ranging from 1 to 100 mmol and markedly reduced the release of IL-6 and TNF-α in a concentration-dependent manner. In addition, atractylenolide I suppressed the activity of nuclear NF-kB and the phosphorylation of ERK1/2 and p38 in LPS-treated RAW264.7 cells. These data suggest that atractylenolide I shows an anti-inflammatory effect by inhibiting TNF-α and IL-6 production. Meanwhile, the anti-inflammatory effects of atractylenolide I may be associated with the inhibition of the NF-kB, ERK1/2 and p38 signaling pathways (Ji et al.2014).

4.3. *Neuroprotective effect*

RAM can be used for the treatment of diseases of the nervous system. Many active components or extracts of RAM have neuroprotective effects. In the process of screening for naturally occurring substances with neuroprotective effects *in vitro* against excitotoxicity, it was discovered that the ethanol extract from RAM exhibited significant neuroprotective activity against glutamate-induced excitotoxicity. It against excitotoxicity-induced neuronal apoptosis in primary cultured cerebral cortical neurons (Gao et al. 2012).

Furthermore, AMP play an important role in neuroprotection. Hu et al. (2014) found that AMP has a neuroprotective effect on hypoxia-induced apoptosis of cerebral cortical neurons. The mechanism may be due to a decrease in the levels of Bax and caspase-3 and an increase in the levels of Bcl-2 and the ratio of Bcl-2/Bax in hypoxic neurons (Hu et al. 2014).

Biatractylolide is an active ingredient existing in RAM and has shown pharmacological activities. It was isolated from the ethyl acetate extracts of RAM. Biatractylolide has a neuroprotective effect on glutamate-induced injury in rat adrenal pheochromocytoma cell and human bone marrow neuroblastoma cell line (SH-SY5Y) cells through a mechanism of the PI3K-Akt-GSK3β-dependent pathways (Zhu et al.2017).

Besides, atractylenolide III from RAM also has neuroprotective effects. Liu's experiment showed that atractylenolide III exerts a significantly neuroprotective effect against glutamate-induced neuronal apoptosis. Atractylenolide III inhibits glutamate-induced neuronal apoptosis in a concentration-dependent manner through inhibiting caspase signaling pathway. So, atractylenolide III may have a therapeutic potential in excitotoxicity-mediated neurological diseases (Liu et al. 2014). Meanwhile, Zhao et al. (2015) provided evidence that administration of atractylenolide III has significantly neuroprotective effects on meliorated learning and memory impairment induced by chronic high-dose homocysteine administration in rats. Atractylenolide III could decrease homocysteine-induced reactive oxygen species (ROS) formation and restored homocysteine-induced decrease of phosphorylated protein kinase C expression level. Moreover, atractylenolide III protected primary cultured neurons from apoptotic death induced by homocysteine treatment. Atractylenolide III may have therapeutic potential intreating Hcy-mediated cognitive impairment and neuronal injury (Zhao et al.2015).

4.4. *Immunomodulatory effects*

The studies have demonstrated that oral administration of a decoction made from RAM significantly increased the immune response induced by a foot-and-mouth disease (FMD) vaccine in mice (Li et al. 2009). AMP as well as many plant-derived polysaccharides, have been found to have immunomodulatory activities. Xie et al. (2012) verified that AMP contributes to the adjuvant activity against FMD vaccine in mice. After oral administration of AMP, a FMD vaccine induced significantly higher specific IgG (Xie et al. 2012).

The AMP has a backbone constructed by glucose, and the branches constituted by rhamnose and mannose (Liang et al. 2007). The polysaccharide structure has an influence on biological activity, so molecular structures of AMP may contribute to their immunomodulatory effects. Due to high molecular weight of AMP, it shows enteric mucosal immunity. The enteric mucosal system plays an important role in maintaining homeostasis. Recent research has shown that humoral and cellular immune responses enhanced significantly by injecting of AMP together with foot-and-mouth disease (FMD) vaccine. Xie et al. (2013) demonstrated that an increased serum IgG response to FMD vaccine was associated with the enhanced gut mucosal immunity by AMP.

Besides, immunomodulatory effects of AMP activity may derive from its ability to stimulate the proliferation of lymphocytes. AMP could stimulate macrophages to promote phagocytic activity and the production of NO, TNF-α, and IFN-γ. In addition, NF-kB was involved in the release of NO and TNF-α in AMP-activated macrophages. The RAM activates macrophages and has potent immunostimulating activity (Ji et al. 2015).

Furthermore, a recent study has reported that the polysaccharide extract of RAM enhanced immunity in aged rats. Results showed that thymus, spleen and cardiac indexes were significantly increased. It could be concluded that AMP displayed strong immunity in aged rats (Guo et al. 2012). Zhao et.al. (2016) also demonstrated that AMP has immunity-enhancing activity (Zhao et al.2016). AMP was found to induce proliferation of lymphocytes from bovine supramammary lymph node and research explained the lymphocyte-stimulating property of AMP (Xu et al. 2017).

4.5. *Anti-hepatotoxicity effects*

RAM is used in the treatment of liver disease in several countries. The principal bioactive component of RAM is AMP, which has been reported to prevent liver injuries caused by various chemicals or toxins. The hepatoprotective effects of AMP are ascribed to its antioxidant, anti-inflammatory and anti-fibrotic activities (Chi et al. 2001; Shan and Tian 2003).

Table 5: Primary pharmacological actions of RAM

Pharmacological effects	Compound name	Model	Dose range Tested	Minimal active concentration	Proposed mechanism	Ref.
Antitum or activites	Atractylodes macrocephala polysaccharide (AMPs)	Glioma C6 cells	50, 100, and 200 g/mL	50 g/mL	DNA fragmentation and apoptosis induction	(Li et al. 2014)
	Petroleum ether extracts	CEM cell, HepG2, MKN-45 cell line and Lovo cell line.	1,000 μg/ml	IC50 CEM cell 25.03, HepG2 78.39, MKN-45 cell 37.43; Lovo cell 32.18.	Cytotoxic activities	(Wei et al. 2011)
	Volatile oil	mice	50 , 100 mg/kg	50 mg/kg	Suppressing growth of Ehrlich ascites tumor	(Zhang et al. 2006)
	Atractylenolide I	human K562 chronic myeloblastic leukemia (CML), U937 acute myeloblastic leuATL-I in human K562 chronic myeloblastic leukemia (CML), U937 acute myeloblastic leukemia (AML) and Jurkat T lymphoma cells	3.13–100μg/mL	12.5 μg/mL	Induction of apoptosis and differentiation	(Huang et al. 2016)
	Atractylenolide I	A549 lung cancer cells	10, 20, and 40μm	10 μm	Induced apoptosis	(Liu et al. 2013)
	Atractylenolide I	human promyeloleukemic HL-60 cells	7.5, 15, and 30 μg/ml	15 μg/ml	Via Cu, Zn-SOD inhibition in HL-60 cells to induce apoptosis and bring about cytotoxicity	(Wang et al. 2006)
	Atractylenolide I	Human cell line MGC-803	0-100 μm	50 μm	Inhibit cancer cell proliferation and induce apoptosis through inactivating Notch pathway	(Ma et al. 2014)
	Atractylenolide I	B16 melanoma cells	100 μm	76.46 μm	Induced cell differentiation and inhibited cell migration	(Ye et al. 2011)
	Atractylenolide II (AT-II)			84.02 μm		
	Atractylenolactam (ATR)			54.88 μm		
Neuroprotective effect	Biatractylolide	rat adrenal pheochromocytoma cell (PC12) and human bone marrow neuroblastoma cell line (SH-SY5Y)	10,15, and 20 μM	10 μM	PI3K-Akt-GSK3β-dependent pathways; downregulate GSK3β protein expression and upregulate p-Akt protein expression,	(Li et al. 2017)
	Atractylenolide III	cells (cortical neurons from embryos of BALB/c mice)	10,20 and 40 μM	10 μM	Via inhibiting caspase signaling pathway;	(Liu et al. 2014)
	Atractylenolide III	rat	0.6, 1.2 and 2.4-mg/kg/day	0.6-mg/kg/day	Decreased homocysteine-induced reactive oxygen species (ROS) formation and restored homocysteine-induced decrease of phosphorylated protein kinase C expression level.	(Zhao et al. 2015)
	Atractylodis macrocephalae polysaccharides	cell (from neonatal rats)	0.00, 0.025, 0.05, 0.10, 0.25, 0.5, 1.00, 2.00, 4.00g/l	0.025 g/l	Reactive oxygen species (ROS) formation and restored	
	AtractylenolideII, atractylenolide I, biepiasterolid, isoatractylenolide I,atractylenolide III, 3β-acetoxyl atractylenolide I, (4E,6E,12E)-tetradeca-4,6,12-triene-8,10-diyne-13,14-triol, (3S,4E,6E,12E)-1-acetoxy-tetradeca-4,6,12-triene-8,10-diyne-3,14-diol	SH-SY5Y cells	0.1, 1.0, 10μM	0.1 μm	Homocysteine-induced decrease of phosphorylated protein	
	Ethanol extract from *Rhizoma Atractylodis macrocephalae*	Cerebral cortical neurons cell(from-BALB/c mice).	120,150,210,240μg/mL	120 μg/mL	Kinase C expression level.	(Gao et al .2012)
Anti-hepatotoxicity	*Atractylodes macrocephalae* polysaccharide	rats	0.4g/kg/d	0.4 g/kg/d	Antioxidant properties and inhibition of NF-κB activation	(Jin et al. 2011)
	A homogeneous polysaccharide was isolated and purified from *Rhizoma Atractylodis macrocephalae* (RAM) and named PRAM2.	mice	200, 100 and 50 mg/kg	50 mg/kg	The protective effect may be related to its anti-oxidation, its inhibition of NOS activity and NO level and its reduction of the production of free radicals.	(Han et al. 2016)
Immune	*Atractylodes macrocephalae* polysaccharide	ICR mice	0, 0.025, 0.05, 0.1 ,0.25 g	0.025g	Enhanced IgG titers, IgG subclasses, IFN-γ, IL-5 and the splenocyte proliferations stimulated by concanavalin A, lipopolysacharide, and FMDV	(Xie et al. 2011)

Immune	Polysaccharides extract of *Rhizoma Atractylodis macrocephalae*	Aged rats	0.4–0.6 %	0.40%	Increased the thymus, spleen and cardiac indexes and reduced the caspase-3 activity ratio, Smac/DIABLO and HtrA2/Omi protein expression, Smac/DIABLO and HtrA2/Omi mRNA expression levels	(Guo et al. 2012)
	Polysaccharides from *Atractylodis macrocephalae*	chickens (male)	0.5 mL RAMPS 60c (6 mg mL −1)	0.5 mL RAMPS 60c (6 mg mL^{-1})	Significantly enhanced-lymphocyte proliferation , increased anti-body titers, improved the percentages of $CD4^+$ and $CD8^+$ T cells influence cell cycle distribution	(Zhao et al .2016)
	Atractylodis macrocephalae Koidz. polysaccharides (RAMPS)	mice	0.25 ml (0.05 g)	0.25 ml (0.05g)	Increased both serum specific IgG response and intestinal mucosal immunity as shown by elevated total sIgA, mRNA expression of TGF-β, IL-6, TNF-α, IgA + cells and intestinal intraepithelial lymphocytes in duodenum.	(Xie et al. 2013)
	Polysaccharide fraction of *Atractylodis macrocephalae* Koidz.	cow	16,32,48mg	16 mg	By potentiating mRNA expression of proinflammatory cytokines (IL-1α, IL-1β and TNF-α)	(Xu et al. 2015)
	Atractylodes macrocephala on polysaccharides	lines-RAW264.7 cells	25, 50, 100, and 200lg/mL	25 g/ml	Stimulated macro-phages to promote phagocytic activity and the production of NO, TNF-a, and IFN-c.	(Ji et al. 2014)
	Atractylodes macrocephala polysaccharide	White Roman chicks (male) and cells	0.391,0.781,1.562, 3.125,6.250µg/ml	0.391 µg/ml	Promoted lymphocyte proliferation and elevate the antibody titers and content of IFN-γ, IL-2 and IL-6.	(Liu et al. 2015)
	Atractylodis macrocephala polysaccharide	cows	12.5, 25, 50, 100µg/ml	12.5 µg/ml	Increased level of $[Ca^{2+}]$, ratios of G2/M and S phase cells, upregulated mRNA expression of IFN-γ and IL-17A, and downregulated IL-4 mRNA expression	(Xu et al. 2017)
Anti-inflammatory activity	Atractylenolide I	Thioglycolate-elicited peritoneal exudate cells	1–1000 µm	200 µm	By the inhibition of TNF-α and NO Production	(Li et al. 2007)
	Atractylenolide III		1–1000µm	200 µm		
	polyacetylenes	cell line, RAW264.7	3.75–120µM 3.75–60 µM	3.75 µM	inhibitor of NO production	(Yao et al. 2014)
	Atractylenolide I	cell and mice	5,10,20mg/kg 1,5,10µg/ml	5 mg/kg 1 µg/ml	Down-regulatory action of the most potent angiogenic factor VEGF, PlGF and NO significantly inhibited the proinflammatory cytokines such as TNF-α, IL-1β, IL-6	(Wang et al. 2009)
	Essential oil	cell(from BALB/c mice (25–30g))	1,5,10µg/ml	1 µg/ml	Inhibited LPS-induction of TNF-α, IL-1β and NO production	(Wang et al. 2009)
	Atractylenolide I (ATL-I)	cell line RAW264.9	25, 50 and 100 mM	25 µM	Inhibition of the NF-kB, ERK1/2 and p38 signaling pathways	(Ji et al. 2014)
	13-hydroxyl-atractylenolide II (1), 4-ketone-atractylenolide III (2), and eudesm-4(15)-ene-7β,11-diol (3), along with eleven known compounds (4–14),	cell line (RAW264.7	3-100 µM	3 µM		(Hoang et al. 2016)
	Fermented Preparations of RhizomaAtractylodis Macrocephalae	RAW264.7 cell	50,100 µl/ml	50 µl/ml	Inhibition of NF-κβ activation	(Bose et al. 2013)
	Atractylenolide I (ATL-I)	cell line RAW264.7	0,25,100 µM	25 µM	Inhibition of the NF-kB, ERK1/2 and p38 signaling pathways	(Ji et al. 2014)
	atractylenolide III 1, atractylenolide I 2, 14-acetoxy-12-senecioyloxytetradeca-2E,8E,10E-trien-4,6-diyn-1-ol 3, 14-acetoxy-12-α-methylbutyl-2E,8E,10E-trien-4,6-diyn-1-ol 4 and 14-acetoxy-12-β-methylbutyl-2E,8E,10E-trien-4,6-diyn-1-ol	mice	Compound 1 (10,25 mg/kg), compound 2 (25, 50,100 mg/kg), compound 3 (50, 100, 200 mg/kg), compounds 4 and 5 (25, 50, 100 mg/kg)	10 mg/kg 25 mg/kg 50 mg/kg 25 mg/kg		(Dong et al. 2008)
	Atractylenolide I and 14-acetoxy-12-senecioyloxytetradeca-2E,8E,10E-trien-4,6-diyn-1-ol	mice	30 mg/kg, 100 mg/kg and 300 mg/kg	30 mg/kg		(Li et al. 2007)
	Fermented preparations of *Rhizoma Atractylodis macrocephalae*	RAW264.7 cell	50,100 µl/ml	50 µl/ml	Suppression of nuclear factor-Kβ(NF-Kβ) activity	(Bose et al. 2013)

Jin et al. found that AMP had marked beneficial effects in an experimental model of hepatic ischemia–reperfusion injury (IRI). AMP significantly reduced the elevated expression of markers of liver dysfunction and the hepatic morphologic changes induced by hepatic IRI in rats. AMP also markedly inhibited IRI-induced lipid peroxidation and altered the activities of the antioxidant enzyme superoxide dismutase and malondialdehyde levels. Moreover, pretreatment with AMP suppressed the expression of interleukin-1β and NF-κB in IRI-treated rats. These results suggest that AMP exerts protective and therapeutic effects against hepatic IRI in rats, which might be associated with its antioxidant properties and inhibition of NF-κB activation (Jin et al. 2011). A homogeneous polysaccharide named PRAM2 isolated and purified from RAM has a certain protective effect on the CCl_4-induced liver injury in mice and a significant *in vitro* antioxidant activity. The mechanism may be related to its anti-oxidant effect, inhibition of NOS activity and NO level, and its reduction in the production of free radicals (Han et al. 2016).

4.6. Gastrointestinal tract protection activities

RAM, as a traditional Chinese herbal medicine, has been widely used in the treatment of many digestive and gastrointestinal disorders. It has been shown that RAM prevents viral gastroenteritis *via* the protection of intestinal mucosal cells against injury and improvement in the absorptive function (He et al. 2001). The enteric mucosal system is a physical barrier to prevent microbial infections. RAM decoction has a strong excitatory effect on gastric fundus muscle strips. It can promote gastrointestinal propulsive movement, and can obviously promote gastric emptying and small intestinal propulsion in mice (Bose et al. 2013).

AMP, one of the main ingredients of RAM, could enhance local mucosal immunity (Xie et al. 2013). AMP can promote the differentiation of IEC-6 cells by upregulating the expression and distribution of chorionic villi, thus promoting the repair of gastrointestinal mucosa (Wang et al. 2010). In addition, some studies have shown that macrocephalic lactone I has a strong effect on enhancing salivary amylase activity, promoting intestinal absorption and regulating intestinal function (Li et al.2007).

4.7. Other activities

RAM exhibited marked anti-adipogenic, and anti-obesity activities, and modulation of the gut microbial distribution. Plamitic acid, one component of RAM, has a peculiar position with respect to the biochemical characterization of major depression (Cocchi et al. 2010). Research reported that RAM has been to possess antioxidant activities (Wang et al. 2011; Wang et al. 2006).

5. Pharmacokinetics studies

Pharmacokinetic studies of the active ingredients in herbal medicine will contribute substantially to elucidation of their mechanisms of action and development of the quality of herbal medicine. The major ingredients of RAM are atractylon, atractylenolides I, II, and III (Duan et al. 2008). So, the pharmacokinetic studies focused on these compounds due to their high content and clear pharmacological activity.

Atractylon is the main active ingredient of RAM (Zhou et al. 2008; Wu et al. 2007). This compound exhibits various pharmacological activities including anti-inflammation, anti-tumor, cytotoxicity against various human cancer cell lines and inhibition of Na^+, K^+-ATPase activity (Wang et al. 2007, 2002; Kim et al. 2007; Satoh et al. 1996).Yan et al. developed a sensitive and selective GC-MS method for the determination of atractylon in rat plasma after intragastric administration of 10 mL/kg of RAM extract (equivalent to 565 mg/kg atractylon). The main pharmacokinetic parameters including half-time ($t_{1/2}$), 7.64±3.42 h, average dwell time (MRT(0–t), 6.42±0.69 h and MRT(0-∞), 9.79±3.83 h), maximum plasma concentration is 257.1±125.1 ng/mL, time to reach the maximum concentrations is 1.83±0.41 h, and area under the plasma concentration–time curve (AUC_{0-t}, 1386.6±525.0 ng h/mL and $AUC_{0-\infty,}$ 1533.7±477.0 ng h/mL). These data indicate that low levels of atractylon were seen after a relatively high oral dose (Yan et al. 2015).

Atractylenolide I, II and III of RAM are the major ingredients. They have attracted more and more attention because of their multiple therapeutic effects. They exhibited activities in anti-inflammatory and anticancer (Liu et al. 2008; Li et al. 2007; Wang et al. 2006; Yan et al. 2011; Wang et al. 2002).Therefore, it is important to investigate the pharmacokinetics of atractylenolide I, II and III .

Li et al. (2012) used an HPLC-MS/MS method to perform a pharmacokinetic study of atractylenolide I in the plasma of rats administered with 20g/kg RAM extract. The main pharmacokinetic parameters T_{max} (the time to peak), C_{max} (the concentration to peak), $T_{0.5}$ (the biological half time), K_e (the elimination rate constant) and area under curve (AUC_{0-T}) were 0.81±0.11 h, 7.99±1.2 ng/ml, 1.94±0.27 h, 0.365±0.06/h, and 22.21±1.9μg·h/l, respectively.

The oral bioavailability of atractylenolide II was detected by a rapid, simple and reproducible UPLC-QqQ-MS method in rat plasma with relatively low concentrations. Single oral administration of 100 mg/kg of atractylenolide II led to C_{max} 8.4±2.4 ng/mL, T_{max} 0.1±0.1 h, $T_{1/2}$ 0.04±0.01 h and $AUC_{0-\infty}$ 17.9 ± 4.9 ng h/mL (Jia et al. 2017).

Yan et al. (2015) performed simultaneous determination and pharmacokinetic study of atractylenolide I, II and III in rat plasma after intragastric administration of RAM extract (containing 7.8 mg/kg atractylenolide I, 2.1 mg/kg atractylenolide II, and 4.1 mg/kg of atractylenolide III) by UPLC–MS/MS. The pharmacokinetic parameters of atractylenolide I, II and III were: Atractylenolide I: C_{max} 2.18±0.23 ng/mL; T_{max}, 1.2± 0.27 h; atractylenolide II: C_{max} 2.47±0.43 ng/mL; T_{max} 0.8±0.27 h; atractylenolide III: C_{max} 135.26±33.75 ng/mL; T_{max} 0.80±0.45 h; $T_{1/2}$ 9.81±1.85 h; $AUC_{0-\infty}$,1258.06± 265.79 ng·h /mL, respectively. $T_{1/2}$ and $AUC_{0-\infty}$ of atractylenolide I and II were not detected under the chromatographic conditions reported.

6. Discussion and future perspectives

RAM as a warm-toning medicine, most widely used in Traditional Chinese Medicine. In this review, we summarized the literature about RAM, including its traditional uses, phytochemistry, pharmacological properties, and pharmacokinetics. The significance of summarizing the traditional uses of RAM is that the plant has a wide range of pharmacological activities and can lay a foundation for further scientific research. In recent years, RAM has been proven to have a variety of pharmacological activities, for instance antitumor activities, anti-inflammatory activity, immunomodulatory effects, anti-hepatotoxicity, gastrointestinal tract protection activities and so on. At present, more than 170 compounds have been isolated. Among them lactones are the primary bioactive constituents, the volatile oil composition is unstable, we need to further study, using UPLC fingerprint to establish a scientific quality standard of RAM.

In clinical practice, RAM is usually prescribed in the form of a recipe. But the literature search revealed that there are some studies about the active ingredients and the mechanism of action of prescriptions. We hope this review will provide a new reference for future researchers. Further investigations should focus on the mechanism of action behind the pharmacological effects of RAM. In addition, we should clarify the mechanism of action and synergy between RAM and different compounds. This could not only scientifically explain the principle of compatibility, but also promote the development of a modern generation of Traditional Chinese Medicines.

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References

Bian ZX, Wu TX, Liu L, Miao JX, Wong H, Song L, Sung JJY (2006) Effectiveness of the Chinese herbal formula TongXieYaoFang for irritable bowel syndrome: a systematic review. J Altern Complement Med 12: 401-407.

Bose S, Kim H (2013) Evaluation of in vitro anti-inflammatory activities and protective effect of fermented preparations of Rhizoma Atractylodis macrocephalae on intestinal barrier function against lipopolysaccharide insult. Evid Based Complement Alternat Med 2013: 363076.

Chen LR, Shao Q, Lu Y (1996) The content of atractylodes was determined by ultraviolet spectrophotometry. J Zhejiang Med Univ 25: 270.

Chen Qinhua, He Hongsheng, Li Peng, Zhu Jun, Xiong Min (2013) Identification and quantification of atractylenolide I and atractylenolide III in Rhizoma Atractylodes macrocephala by liquid chromatography–ion trap mass spectrometry. Biomed Chromatogr 27: 699–707.

Chen W, He GF, Jiang MH (2007) Advances of the rhizome of Atractylodis macrocephalae Koidz, during the recent decades. Lishizhen Med Met Med Res 18: 338–340.

Chen HP, Pan HH, Zhang X (2016) GC-MS combined with AMDIS and retention index was used to study the dynamic variation of volatile components in radix atractylodes sauteed with bran at different processing temperatures. China J Chin Materia Medica 41: 2646-2651.

Chi Y, Li W, Wen H, Cui X, Cai H, Bi X (2001) Studies on separation, purification and chemical structure of polysaccharide from Atractylodes macrocephala. Zhong Yao Cai 24: 647–648.

Chinese Pharmacopoeia Commission, Pharmacopoeia of the People’s Republic of China (China Medical Science and Technology Press, Beijing, (2015), Vol. I, p. 103.

Cocchi M, Tonello L (2010) Biomolecular considerations in major depression and ischemic cardiovascular disease. Cent Nerv Syst Agents Med Chem 10: 97-107.

Dong H, He L, Huang M, Dong Y (2008) Anti-inflammatory components isolated from Atractylodes macrocephala Koidz. Nat Prod Res 22: 1418-27.

Duan Q, Xu DJ, Liu CX, Li CL (2008) Advances of the rhizome of Atractylodis macrocephalae Koidz. Chin Trad Herbal Drugs 39: 4–6.

Fan H, Qiu MY, Mei JJ, Shen GX, Liu SL, Chen R (2005) Effects of four regulating-intestine prescriptions on pathology and ultrastructure of colon tissue in rats with ulcerative colitis. World J Gastroenterol 11: 4800–4806.

Gao Q, Ji ZH, Yang Y, Cheng R, Yu XY (2012) Neuroprotective effect of Rhizoma Atractylodis macrocephalae against excitotoxicity-induced apoptosis in cultured cerebral cortical neurons. Phytother Res 26: 557-561.

Guan Z, Wang M, Cai Y, Yang H, Zhao M, Zhao C (2018) Rapid characterization of the chemical constituents of Sijunzi decoction by UHPLC coupled with Fourier transform ion cyclotron resonance mass spectrum etry. J Chromatogr B 1086:11-22.

Guo Ling , Sun Yong Le, Wang Ai Hong, Chong En Xu, Meng Yuan Zhang (2012) Effect of polysaccharides extract of rhizoma atractylodis macrocephalae on thymus, spleen and cardiac indexes, caspase-3 activity ratio, Smac/DIABLO and HtrA2/Omi protein and mRNA expression levels in aged rats. Mol Biol Rep 39: 9285–9290.

Guo Z, Su Z, Wang Z, Luo X, Lai R (2017)The effect of Chinese herbal medicine Banxia Baizhu Tianma decoction for the treatment of vertebrobasilar insufficiency vertigo: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 31: 27-38.

Han B, Gao Y, Wang Y, Wang L, Shang Z, Wang S, Pei J (2016) Protective effect of a polysaccharide from Rhizoma Atractylodis macrocephalae on acute liver injury in mice. Int J Biol Macromol 87: 85-91.

He ST, He FZ, Wu CR, Li SX, Liu WX, Yang YF, Jiang SS, He G (2001) Treatment of rotaviral gastroenteritis with Qiwei Baizhu powder, World J Gastroenterol 7: 735–740.

Hu WX, Xiang Q, Wen Z, He D, Wu XM, Hu GZ (2014) Neuroprotective effect of Atractylodes macrocephalaon polysaccharides in vitro on neuronal apoptosis induced by hypoxia. Mol Med Rep 9: 2573-2581.

Huang HL, Lin TW, Huang YL, Huang RL (2016) Induction of apoptosis and differentiation by atractylenolide-1 isolated from Atractylodes macrocephala in human leukemia cells. Bioorg Med Chem Lett 26: 1905-1909.

Hoang le S, Tran MH, Lee JS, Ngo QM, Woo MH, Min BS (2016) Inflammatory inhibitory activity of sesquiterpenoids from Atractylodes macrocephala rhizomes. Chem Pharm Bull 64: 507–511.

Ji G, Chen R, Zheng J (2014) Atractylenolide I inhibits lipopolysaccharide-induced inflammatory responses via mitogen-activated protein kinase pathways in RAW264.7 cells. Immunopharmacol Immunotoxicol 36: 420-425.

Ji GQ, Chen RQ, Zheng JX (2015) Macrophage activation by polysaccharides from Atractylodes macrocephala Koidz through the nuclear factor-kB pathway. Pharm Biol 53: 512-517.

Ji Y, Wang R, Peng Y, Peng C, Li X (2017) Purification, preliminary characterization, and immunological activity of polysaccharides from crude drugs of Sijunzi formula. Evid Based Complement Alternat Med 2017: 2170258.

Jia MQ, Xiong YJ, Xue Y, Wang Y, Yan C (2017) Using UPLC-MS/MS for characterization of active components in extracts of Yupingfeng and application to a comparative pharmacokinetic study in rat plasma after oral administration. Molecules 22: E810.

Jin C, Zhang PJ, Bao CQ, Gu YL, Xu BH, Li CW, Li JP, Bo P, Liu XN (2011) Protective effects of Atractylodes macrocephala polysaccharide on liver ischemia–reperfusion injury and its possible mechanism in rats. Am J Chin Med 39: 489-502.

Kim HK, Yun YK, Ahn YJ (2007) Toxicity of atractylon and atractylenolide III identified in Atractylodes ovata rhizome to Dermatophagoides farina and Dermatophagoides pteronyssinus. J Agric Food Chem 55: 6027–6031.

Satoh K, Nagai F, Ushiyama K, Kano I (1996) Specific inhibition of Na+, K(+) –ATPase activity by atractylon, a major component of Byaku-jutsu, by interaction with enzyme in the E2 state. Biochem Pharmacol 51: 339–343.

Li CQ, He LC, Dong HY, Jin JQ (2007) Screening for the anti-inflammatory activity of fractions and compounds from Atractylodes macrocephala Koidz. J Ethnopharmacol 114: 212–217.

Li CQ, He LC, Jin JQ (2007) Atractylenolide I and atractylenolide III inhibit Lipopolysaccharide-induced TNF–alpha and NO production in macrophages. Phytother Res 21: 347–353.

Li R, Sakwiwatkul K, Yutao L, Hu S (2009) Enhancement of the immune responses to vaccination against foot-and-mouth disease in mice by oral administration of an extract made from Rhizoma Atractylodis Macrocephalae (RAM).Vaccine 27: 2094–2098.

Li W, Wen HM, Cui XB, Zhang F C, Dong J (2007) Chemical constituents of Rhizoma Atractylodis macrocephalae. Chin Trad Herbal Drugs 38:1460–1462.

Li W, Wen HM, Zhang AH (2001) Study on quality standard of atractylodes atractylodes. J Pharm Anal 21: 170.

Li X, Peng Y, Peng C, Wang M, Hou J, Huang W (2015) Qualitative and quantitative analysis of constituents in Si-jun-zi Tang decoction by HPLC-DAD-ELSD and HPLC-ESI-MS. Curr Pharm Anal 11: 115-123.

Li X, Liu F, Li Z, Ye N, Huang C, Yuan X (2014) Atractylodes macrocephala polysaccharides induces mitochondrial-mediated apoptosis in glioma C6 cells. Int J Biol Macromol 66: 108-112.

Li Y, Zhang Y, Wang Z, Zhu J, Tian Y, Chen B (2012) Quantitative analysis of atractylenolide I in rat plasma by LC–MS/MS method and its application to pharmacokinetic study. J Pharm Biomed Anal 58: 172-176.

Li Y, Tao HY, Yang XW (2013) GC-MS analysis of volatile oils from rhizoma atractylodes and rhizoma atractylodes. Chin J Pharm Anal 33: 1210-1217.

Liang ZH, Guo ZX, Zhang LP (2007) Structure aspects of water soluble polysaccharide isolated from Atractylodes macrocephala Koidz. J Mol Sci 23: 185-188.

Liu C, Zhao H, Ji ZH, Yu XY (2014) Neuroprotection of atractylenolide III from Atractylodis macrocephalae against glutamate-induced neuronal apoptosis via inhibiting caspase signaling pathway. Neurochem Res 39: 1753-1758.

Liu H, Zhu Y, Zhang T, Zhao Z, Zhao Y, Cheng P, Li H, Gao H, Su X (2013) Anti-tumor effects of atractylenolide I isolated from Atractylodes macrocephala in human lung carcinoma cell lines. Molecules 18: 13357–13368.

Liu Y, Yang J, Cai Z (2006) Chemical investigation on Sijunzi decoction and its two major herbs Panax ginseng and Glycyrrhiza uralensis by LC/MS/MS. J Pharm Biomed 41: 1642-1647.

Liu Y, Jia Z, Dong L, Wang R, Qiu G(2008) A randomized pilot study of atractylenolide I on gastric cancer cachexia patients. Evid Based Complement Alternat Med 5: 337–344.

Ma L, Mao R, Shen K, Zheng Y, Li Y, Liu J, Ni L (2014) Atractylenolide I-mediated Notch pathway inhibition attenuates gastriccancer stem cell traits. Biochem Biophys Res Commun 450: 353-359.

Qu G, Qi X, Shao S, Li C, Wang C, Wang C, Gou Q (2018) Pharmacokinetics of Sijunzi decoction in rats’ plasma after oral administration using ultra high-performance liquid chromatography electrospray ionization quadrupole-time of flight mass spectrometry. Biomed Chromatogr 32: e4334.

Shan JJ, Tian GY (2003) Studies on physico-chemical properties and hypoglycemic activity of complex polysaccharide AMP-B from Atractylodes macrocephala Koidz. Yao Xue Xue Bao 38: 438–441.

Wang C, Duan H, He L (2009) Inhibitory effect of atractylenolide I on angiogenesis in chronic inflammation in vivo and in vitro. Eur J Pharmacol 612: 143–152.

Wang C, He L, Wang N, Liu F (2009) Screening anti-inflammatory components from Chinese traditional medicines using a peritoneal macrophage/cell membrane chromatography offline-GC/MS method. J Chromatogr B 27: 3019–3024.

Wang CC, Lin SY, Cheng HC, Hou WC (2006) Pro-oxidant and cytotoxic activities of atractylenolide I in human promyeloleukemic HL-60 cells. Food Chem Toxicol 44: 1308–1315.

Wang CC, Chen LG, Yang LL (2002) Cytotoxic activity of sesquiterpenoids from Atractylodes ovata on leukemia cell lines. Planta Med 68: 204–208.

Wang JH, Bose S, Kim HG, Han KS, Kim H (2015) Fermented Rhizoma Atractylodis macrocephalae alleviates high fat diet-induced obesity in association with regulation of intestinal permeability and microbiota in rats. Sci Rep 5: 8391.

Wang KT, Chen LG, Yang LL, Ke WM, Chang HC, Wang CC (2007) Analysis of the sesquiterpenoids in processed Atractylodis Rhizoma. Chem Pharm Bull 55: 50–56.

Wang KT, Chen LG, Chou DS, Liang WL, Wang CC(2011)Anti-oxidative abilities of essential oils from Atractylodes ovata Rhizome. Evid-Based Complement Alt Med 2011: 204892.

Wang ShuangYan, Ding LinFen, Su Jia, Peng LiYan, Song LiuDong, Xing-DeWu (2018) Atractylmacrols A-E, sesquiterpenes from the rhizomes of Atractylodes macrocephala. Phytochem Lett 23: 127-131.

Wang X, Li L, Ran X, Dou D, Li B, Yang B, Li W, Koike K, Kuang H (2016) What caused the changes in the usage of Atractylodis Macrocephalae rhizoma from ancient to current times? J Nat Med 70: 36-44.

Wang ZH, Li RL, Xu SF (2010) Effects of Atractylodes macrocephala sugar complex on differentiation and Chorionic villi protein expression of IEC-6 cells. Zhongyaocai 33: 938-944.

Wei Peng, Ting Han, Xin Wen-Bo, Zhang Xiao-Gang, Zhang Qiao-Yan, Jia Min, Qin Lu-Ping (2011) Comparative research of chemical constituents and bioactivities between petroleum ether extracts of the aerial part and the rhizome of Atractylodes macrocephala. Med Chem Res 20: 146–151.

Wu J, Zhou RB, Tong QZ, Chen Y, Wang GB (2007) Optimizing of the parameters in SFE-CO2 about volatile oil from Atractylodes macrocephala Koidz and studying on its constituents. Modern Chin Med 9: 14–18.

Xie F, Li YT, Su F, Hu SH (2012) Adjuvant effect of Atractylodis macrocephalae Koidz. polysaccharides on the immune response to foot-and-mouth disease vaccine. Carbohydrate Polymers 87: 1713–1719.

Xie F, Sakwiwatkul K, Zhang C, Wang Y, Zhai L, Hu S (2013) Atractylodis macrocephalae Koidz. polysaccharides enhance both serum IgG response and gut mucosal immunity. Carbohyd Polym 91: 68–73.

Xu W, Guan R, Shi F, Du A, Hu S (2017) Structural analysis and immunomodulatory effect of polysaccharide from Atractylodis macrocephalae Koidz. on bovine lymphocytes. Carbohydr Polym 174: 1213-1223.

Xu W, Guan R, Lu Y, Su X, Xu Y, Du A, Hu S (2015) Therapeutic effect of polysaccharide fraction of *Atractylodis macrocephalae* Koidz. in bovine subclinical mastitis. BMC Vet Res 11: 165.

Xu Wei, Du Aifang, Hu Songhua (2018) Transcriptome analysis of bovine lymphocytes stimulated by Atractylodis macrocephalae Koidz. polysaccharides in vitro. Vet Immunol Immunopathol 196: 30-34.

Xu Y, Cai H, Cao G, Duan Y, Pei K, Tu S, Zhou J, Xie L, Sun D, Zhao J, Liu J, Wang X, Shen L (2019) Profiling and analysis of multiple constituents in Baizhu Shaoyao San before and after processing by stir-frying using UHPLC/Q-TOF-MS/MS coupled with multivariate statistical analysis. Molecules 24: E940.

Yan H, Sun Y, Ma Y, Ji B, Hou X, Yu Z, Zhao Y (2015) Determination of atractylon in rat plasma by a GC–MS method and its application to a pharmacokinetic study. J Pharm Anal 5: 327-331.

Yan H, Sun Y, Zhang Q, Yang M, Wang X, Wang Y, Yu Z, Zhao Y (2015) Simultaneous determination and pharmacokinetic study of Atractylenolide I, II and III in rat plasma after intragastric administration of Baizhufuling extract and Atractylodis extract by UPLC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 993-994: 86-92.

Yan Ye, Chou GX, Hui Wang, Chu JH, Fong WF, Yu ZL (2011) Effects of sesquiterpenes isolated from largehead atractylodes rhizome on growth, migration, and differentiation of B16 melanoma cells. Integr Cancer Ther 10: 92-100.

Yao CM, Yang XW (2014) Bioactivity-guided isolation of polyacetylenes with inhibitory activity against NO production in LPS-activated RAW264.7 macrophages from the rhizomes of Atractylodes macrocephala. J Ethnopharmacol 151: 791-799.

Yang SL, Niu TT, Li XL, Li DJ, Li MQ, Wang HY (2018) Bu–Shen–Yi–Qi formula impairs cytotoxicity of NK cells by up-regulating IDO expression in trophoblasts. Gynecol Endocrinol 34: 675-679.

Yang E, Zhong YM, Feng YF (2012) Advance on the chemical constituents and pharmacological effects of Atractylodes macrocephala Koidz. J Guangdong Pharm Univ 28: 218–221.

Yu R, Yu BX, Chen JF, Lv XY, Yan ZJ, Cheng Y, Ma Q (2016) Anti-tumor effects of Atractylenolide I on bladder cancer cells. J Exp Clin Cancer Res 35: 40.

Zhang Y, Tang K, Deng Y, Chen R, Liang S, Xie H, He Y, Chen Y, Yang Q (2018) Effects of shenling baizhu powder herbal formula on intestinal microbiota in high-fat diet-induced NAFLD rats. Biomed Pharmacother 102: 1025-1036.

Zhang Z, Zhang HX, Shi TL, Liu YY(2006)Research about the antitumor function of Atractylodis macrocephala Koidz. volatile oil. Cancer Res Clinic18: 799–800.

Zhang Z, Zhang H X, Shi TL, Liu YY (2006) Research about the antitumor function of Atractylodis Macrocephala Koidz. volatile oil. Cancer Res Clinic 18: 799–800.

Zhao H, Ji ZH, Liu C, Yu XY (2015) Neuroprotection and mechanisms of atractylenolide III in preventing learning and memory impairment induced by chronic high-dose homocysteine administration in rats. Neuroscience 290: 485-491.

Zhao X, Sun W, Zhang S, Meng G, Qi C, Fan W, Wang Y, Liu J (2016) The immune adjuvant response of polysaccharides from Atractylodis macrocephalae Koidz in chickens vaccinated against Newcastle disease (ND). Carbohydr Polym 141: 190–196.

Zhou MY (2001) Shen Ling Bai Zhu San in treatment of 125 cases with infections in the upper respiratory tract. Sci Technol Chin Mater Medica 8: 68.

Zhou RB, Wu J, Tong QZ, Liu YM, Liu XD (2008) Studies on volatile oil from Atractylodes macrocephala with different distill methods. Zhong Yao Cai 31: 229–232.

Zhou Y, Ren Y, Ma Z, Jia G, Gao X, Zhang L, Qin X (2012) Identification and quantification of the major volatile constituents in antidepressant active fraction of xiaoyaosan by gas chromatography–mass spectrometry. J Ethnopharmacol 141: 187-92.

Zhu L, Ning N, Li Y, Zhang QF, Xie YC, Irshad M, Feng X, Tao XJ (2017) Biatractylolide modulates PI3K-Akt-GSK3β-dependent pathways to protect against glutamate-induced cell damage in PC12 and SH-SY5Y Cells. Evid Based Complement Alternat Med 2017: 1291458.