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Review Article

Pharmacological Properties of *Atractylodes macrocephala* Koidz.: A Comprehensive Review

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Abstract: *Atractylodes macrocephala* Koidz. (AMK), commonly known as Baizhu, is a medicinal and edible plant. Researchers have identified over 77 metabolites in AMK. Many studies have demonstrated the diverse pharmacological activities of AMK, including enhancing gastrointestinal function; modulating immune responses; regulating hormonal secretion; and exerting antitumor, anti-inflammatory, antiaging, antioxidant, antiosteoporotic, antibacterial, and neuroprotective effects.

Keywords: *Atractylodes macrocephala* Koidz.; pharmacological activities; active ingredients

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1 Introduction

AMK is a traditional medicinal plant in China that is classified under the *Atractylodes* genus in the Asteraceae family. This perennial medicinal plant predominantly grows in the southern Qinling Mountains in China and is widely distributed in Japan and Korea[1]. AMK is well known for its therapeutic functions, including promoting urination, stabilizing pregnancy, and reducing sweating. AMK has also been extensively used in Southeast Asia. For more than 2000 years, AMK has been employed to treat a variety of conditions, including spleen deficiency, poor appetite, abdominal distention, diarrhea, dizziness due to phlegm retention, edema, spontaneous sweating, gastrointestinal disorders, and restlessness during pregnancy[2-4].

AMK primarily contains triterpenoids, sesquiterpenoids, polyacetylenes, coumarins, phenylpropanoids, polysaccharides, steroids, and other metabolites. Among these, sesquiterpenoids, polyacetylenes, and polysaccharides are the most abundant. Extensive research has shown that AMK exhibits a wide range of biological activities, including enhancing gastrointestinal function, modulating immune responses, regulating hormone secretion, and exerting antitumor, anti-inflammatory, antioxidant, antiosteoporotic, antibacterial, and neuroprotective effects. AMK is one of the many traditional Chinese medicines that are both medicinal and edible and that play crucial roles in health and wellness[5-9].

The aim of this review is to provide a comprehensive overview of AMK, covering its botanical characteristics, phytochemistry, pharmacology, and pharmacokinetics. By consolidating the current research, we seek to offer a thorough reference for future studies and the development and utilization of AMK.

2 Chemicals and major active components

2.1 Triterpenoids and sesquiterpenoids

With advancements in isolation techniques, a substantial number of major active components in AMK, such as triterpenoids and sesquiterpenoids, have been extensively analyzed. These triterpenoids and sesquiterpenoids include taraxeryl acetate **1**[10], atractylenolide I **2**, atractylenolide II **3**, atractylenolide III **4**[11], atractylenolide IV **5**[12], atractylenolide V **6**[13], atractylenolide VI **7**, atractylenolide VII **8**[4], 3β-acetoxyl atractylenolide I **9**[14], 13-hydroxyl-atractylenolide II **10**, 4-ketone-atractylenolide III **11**, eudesm-4(15)-ene-7β,11-diol **12**, 8β-methoxyatractylenolide **13**, atractylenother **14**, 8-epiatractylenolide III **15**, 4(R),15-epoxy-8β-hydroxyatractylenolide II **16**[15] 3, 4(*R*),15-epoxy-atractylenolide II **17**[16], atractylenolactam **18**[17], 8β-ethoxyasterolid **19**, selina-4(15),7(11)-dien-8-one **20**, juniper camphor **21**, eudesm-4(15),7-diene-9α,11-diol **22**, atractylon **23**, atractylmacrols A **24**, atractylmacrols B **25**, atractylmacrols C **26**, atractylmacrols D **27**, atractylmacrols E **28**[18], biatractylenolide **29**[19], biatractylenolide II **30**[20], biepiasterolide **31**, isoasterolide A **32**[21], 8β, 9α-dihydroxy atractylenolide II **33**[22], 4,6-dihydroxy-3,3a-dihydro atractylenolide III **34**, 6,9-dihydroxy-3,3a-dihydro atractylenolide III **35**, and 6-hydroxy-3,3a-dihydro atractylenolide III **36**[23] (Fig. 1). Currently, research on the differences in the metabolites of AMK before and

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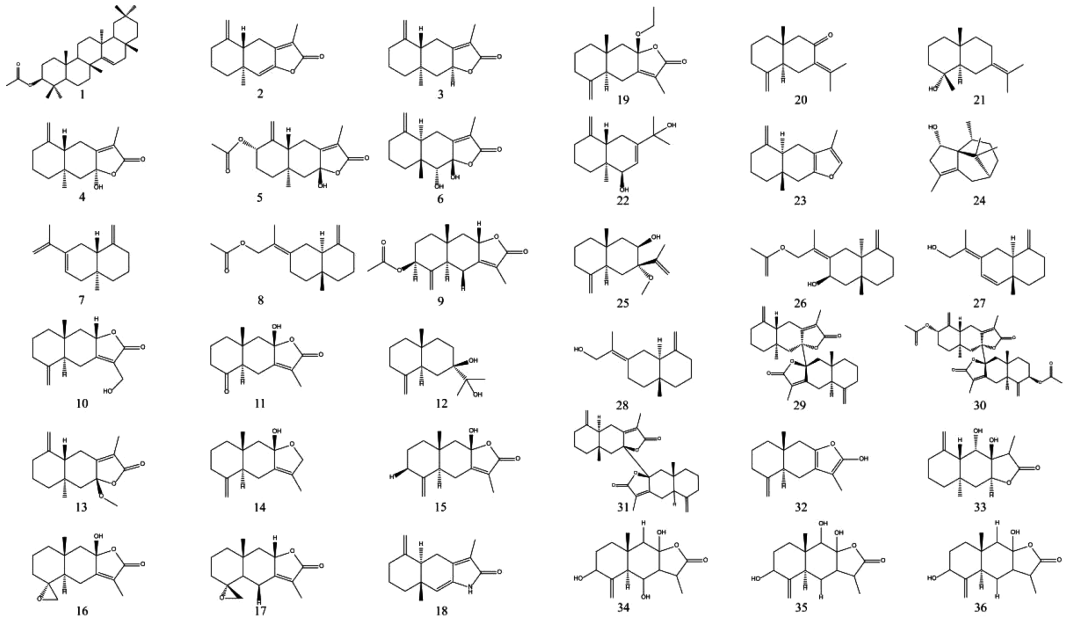


Figure 1 Triterpenoids and sesquiterpenoids are isolated from AMK. taraxeryl acetate 1, atractylenolide I 2, atractylenolide II 3, atractylenolide III 4, atractylenolide IV 5, atractylenolide V 6, atractylenolide VI 7, atractylenolide VII 8, 3*β*-acetoxyl atractylenolide I 9, 13-hydroxyl-atractylenolide II 10, 4-ketone-atractylenolide III 11, eudesm-4(15)-ene-7*β*,11-diol 12, 8*β*-methoxyatractylenolide 13, atractylenother 14, 8-epiatractylenolide III 15, 4(*R*),15-epoxy-8*β*-hydroxyatractylenolide II 16, 3,4(*R*),15-epoxy-atractylenolide II 17, atractylenolide 18, 8*β*-ethoxyasterolid 19, selina-4(15),7(11)-dien-8-one 20, juniper camphor 21, eudesm-4(15),7-diene-9*α*,11-diol 22, atractylon 23, atractylmacrols A 24, atractylmacrols B 25, atractylmacrols C 26, atractylmacrols D 27, atractylmacrols E 28, biatractylenolide 29, biatractylenolide II 30[20], biepiasterolide 31, isoasterolide A 32, 8*β*, 9*α*-dihydroxy atractylenolide II 33, 4,6-dihydroxy-3,3a-dihydro atractylenolide III 34, 6,9-dihydroxy-3,3a-dihydro atractylenolide III 35, and 6-hydroxy-3,3a-dihydro atractylenolide III 36

after processing has focused primarily on sesquiterpenes. Studies have shown that during bran-roasted AMK processing, the levels of atractylenolides I, II, and III decrease gradually with prolonged heating; this decrease is attributed to the thermal instability of these metabolites, which leads to their transformation[24]. However, some researchers have differing opinions. Studies comparing various processed forms of AMK indicate that the levels of sesquiterpenes show minimal variation among raw AMK, bran-roasted AMK, and soil-roasted AMK. In contrast, rice wash-bleached AMK contains higher levels of sesquiterpenes than raw AMK does[25]. Interestingly, other studies have suggested that extended heating can actually increase the levels of atractylenolides I and III[26, 27]. These conflicting findings highlight the need for further investigation into the processing mechanisms of AMK to fully understand their effects.

2.2 Polyacetylenes

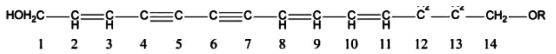
Currently, 21 polyacetylene metabolites have been isolated from AMK, including 14-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol **37**, 14*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol **38**, 12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1,14-diacetate **39**, 12*α*-methylbutyryltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1,14-diacetate **40**, 12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1,14-diacetate **41**, 14-acetoxy-12-methylpropionyltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol **42**, 14-acetoxy-12-methylpropionyltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **43**[28], 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol **44**, 14-acetoxy-12*α*-methylbutyryltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol **45**, 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **46**, 14-acetoxy-12*α*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **47**, 14-acetoxy-12*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **48**[29], 14*α*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **49**, 14*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **50**, 12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol **51**, 12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol **52**, 12-hydroxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol **53**, 12-hydroxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol **54**, 14-acetoxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol **55**, 1-acetoxyl-6*E*,12*E*-diene-8,10-diyne-3-ol **56**, and 3-acetoxyl-6*E*,12*E*-diene-8,10-diyne-1-ol **57**[30] (Fig. 2). Polyacetylenes exhibit significant anti-inflammatory activity, with 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol showing the most potent inhibitory activity among this class; it has an IC_{50} value of 19 μmol/L, which is significantly greater than that of the positive control iNOS inhibitor (L-NIL) used in experiments.

2.3 Coumarins and phenylpropanoids

Four coumarin and phenylpropanoid metabolites have been isolated from AMK rhizomes: ferulic acid **58**[31], *Z*-5-hydroxy ferulic acid **59,** 2-hydroxy ferulic acid **60**, and *Z*-methyl caffeate **61** (Fig. 3).

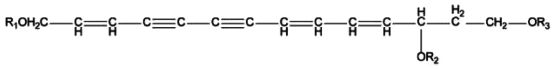
2.4 Polysaccharides

A newly identified polysaccharide, YY13008 **62**, was recently isolated from AMK via water extraction and alcohol precipitation methods[32]. Analysis revealed that this polysaccharide has a homogeneous and coil-like structure with an absolute molecular weight of 6546. The specific structure of YY13008 consists of numerous fructose units forming a fructan, starting with *β* (2→1) fructosyl linkages and ending with *α* (1→2) glucosyl linkages. Various polysaccharides, including the purified polysaccharide PAM **63**[33], the water-soluble homogeneous polysaccharide WAM **64**[34], two heteropolysaccharides PSAM-1 **65** and PSAM-2 **66**[35], and the AMK polysaccharide AMP **67**[36], have been obtained via water extraction, alcohol precipitation, and column



37. 2E,8Z,10E, R=Sen

38. 2E,8E,10E, R=β-MeB



39. 2E,8Z,10E, R_1=Ac, R_2=Sen, R_3=Ac

40. 2E,8Z,10E, R_1=Ac, R_2=α-MeB, R_3=Ac

41. 2E,8E,10E, R_1=Ac, R_2=Sen, R_3=Ac

42. 2E,8Z,10E, R_1=H, R_2=MeP, R_3=Ac

43. 2E,8E,10E, R_1=H, R_2=MeP, R_3=Ac

44. 2E,8Z,10E, R_1=H, R_2=Sen, R_3=Ac

45. 2E,8Z,10E, R_1=H, R_2=α-MeB, R_3=Ac

46. 2E,8E,10E, R_1=H, R_2=Sen, R_3=Ac

47. 2E,8E,10E, R_1=H, R_2=α-MeB, R_3=Ac

48. 2E,8E,10E, R_1=H, R_2=β-MeB, R_3=Ac

49. 2E,8E,10E, R_1=H, R_2=H, R_3=α-MeB

50. 2E,8E,10E, R_1=H, R_2=H, R_3=β-MeB

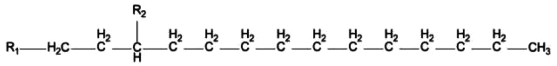
51. 2E,8E,10E, R_1=H, R_2=Sen, R_3=H

52. 2E,8Z,10E, R_1=H, R_2=Sen, R_3=H

53. 2E,8Z,10E, R_1=H, R_2=H, R_3=H

54. 2E,8E,10E, R_1=H, R_2=H, R_3=H

55. 2E,8E,10E, R_1=H, R_2=H, R_3=Ac



56. 6E,12E R_1=AcO, R_2=OH

57. 6E,12E R_1=OH, R_2=AcO

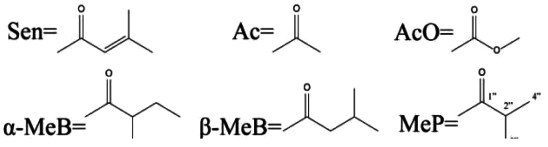
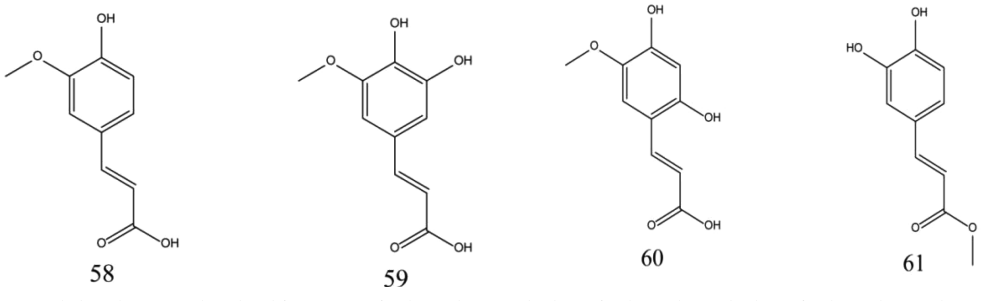


Figure 2 Polyacetylenes isolated from AMK. 14-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol 37, 14*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol 38, 12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1,14-diacetate 39, 12*α*-methylbutyryltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1,14-diacetate 40, 12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1,14-diacetate 41, 14-acetoxy-12-methylpropionyltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol 42, 14-acetoxy-12-methylpropionyltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 43, 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol 44, 14-acetoxy-12*α*-methylbutyryltetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyn-1-ol 45, 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 46, 14-acetoxy-12*α*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 47, 14-acetoxy-12*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 48, 14*α*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 49, 14*β*-methylbutyryltetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 50, 12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol 51, 12-senecioyloxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol 52, 12-hydroxytetradeca-2*E*,8*Z*,10*E*-trien-4,6-diyne-1-ol 53, 12-hydroxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyne-1-ol 54, 14-acetoxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol 55, 1-acetoxyl-6*E*,12*E*-diene-8,10-diyne-3-ol 56, and 3-acetoxyl-6*E*,12*E*-diene-8,10-diyne-1-ol 57



58 59 60 61

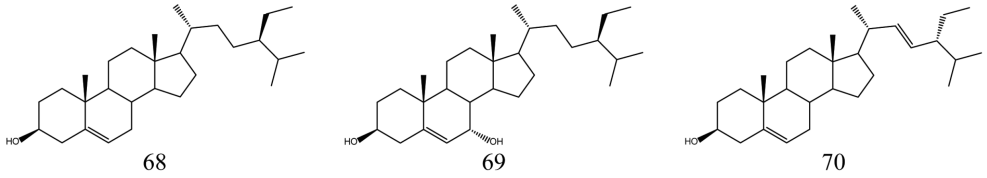
Figure 3 Coumarins and phenylpropanoids isolated from AMK. ferulic acid 58, *Z*-5-hydroxy ferulic acid 59, 2-hydroxy ferulic acid 60, and *Z*-methyl caffeate 61.

chromatography. AMK polysaccharides significantly stimulate NO production in RAW264.7 macrophages, with production increasing in a dose-dependent manner and peaking at a concentration of 200 μg/mL. Additionally, AMK polysaccharides increase the production of TNF-α and IFN-γ, induce the degradation of IκB, and activate NF-κB, thereby increasing macrophage phagocytosis[37]. When administered orally to mice, AMK polysaccharides increase the levels of IFN-γ and IL-4, directly stimulate antigen-specific antibody titters related to B lymphocytes, and ultimately enhance both cellular and humoral immune responses in mice[38].

2.5 Other metabolites

Three steroid metabolites have been isolated from the rhizomes of AMK: *β*-sitosterol **68**[12], 7-*α*-hydroxy-*β*-sitosterol **69**[29], and stigmasterol **70**[10] (Fig. 4).

AMK also contains other metabolites, including uridine **71**[31], atractyloside A **72**[10], palmitic acid **73**[12], 2-vinylaniline **74**, 4-



68 69 70

Figure 4 Steroids isolated from AMK. *β*-sitosterol 68, 7-*α*-hydroxy-*β*-sitosterol 69, and stigmasterol 70.

methoxycarbonyl benzoic acid **75**, ethylcoumarate **76**, and cucumariaxanthin B **77**[23] (Fig. 5).

3 Pharmacological activities

AMK is known to have diverse pharmacological properties. These properties include anti-inflammatory activity, immunomodulatory activity, antitumor effects, regulatory effects on energy metabolism, regulatory effects on gastrointestinal function, neuroprotective effects, regulatory effects on sex hormones and anti-uterine contraction effects, antioxidant and antiaging effects, antiosteoporotic effects, and antibacterial effects. These effects are summarized in Table 1, and the details are further discussed below.

3.1 Anti-inflammatory effects

Numerous studies have substantiated the potent anti-inflammatory effects of AMK[39,40]. Ethanol extract of the rhizome of AMK contains atractylenolide-1 and atractylenolide-2. Gastric tissue damage (induced by HCl ethanol) was significantly decreased in SD rats following the intragastric application of 35 mg/kg ethanol extract of the rhizome of AMK. These findings are distinct from the anti-inflammatory effects of 35 mg/kg ranitidine (gastric medication)[41]. Direct evidence of the anti-inflammatory effects of atractylenolide I against chronic inflammation was demonstrated using mouse air pouch models induced by Freund's complete adjuvant and coculture models of mouse aortic rings and peritoneal macrophages. Atractylenolide I inhibited the

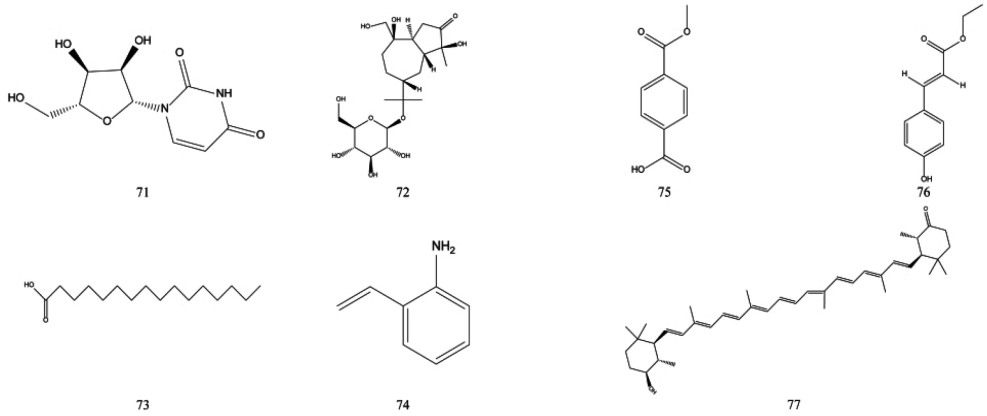


Figure 5 Other metabolites isolated from AMK. uridine 71, atractyloside A 72, palmitic acid 73, 2-vinylaniline 74, 4-methoxycarbonyl benzoic acid 75, ethylcoumarate 76, and cucumariaxanthin B 77.

Table 1 Pharmacological activities of AMK

Tested substance	Model	Tissue	Dose	Time	Results	Reference
Anti-inflammatory effects						
Atractylenolide I	Freund's complete adjuvant-induced air pouch mice model	Blood; fluid from air pouches; granuloma tissues	5, 10, 20 mg/kg; i.p.	11 days	↓NO, TNF-α, IL-1β, IL-6, VEGF, PlGF	[42]
	Aortic ring cocultured with peritoneal macrophages (mouse model)	/	1, 5, 10 μg/ml	12 h	↓NO, TNF-α, IL-1β, IL-6, VEGF, PlGF	
Atractylenolide I	LPS-treated inflammatory RAW264.7 cells	/	20, 40, 60 μM	24 h	↓IL-6, IL-1β	[43]
Supercritical CO_2 fluid extracts of AMK	Acetic acid-induced vascular permeability mouse mode	Pigment in the abdominal cavity	125, 250, 500 mg/kg (extracts), p.o.;	30 min	↓increased vascular permeability	[44]
atractylenolide I			30, 100, 300 mg/kg; p.o.			
14-acetoxy-12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol	Carrageenan-induced paw edema mouse model	Paw volume	100, 200, 400 mg/kg; i.p.	3 days	↑inhibition of edema	
	Cotton-pellet granuloma mouse model	Granuloma tissues	30, 100, 300 mg/kg; p.o.	7 days	↑the percentage of inhibition of inflammation	
Atractylenolide I	LPS-treated inflammatory RAW264.7 cells	/	1-100 μM	24 h	↓IL-6, TNF-α, activity of nuclear NF-κB and phosphorylation of ERK1/2 and p38, MD-2, CD14, SR-A, TLR4, MyD88	[45]
Immunomodulatory effects						
Polysaccharide extracts of AMK	Immune responses to foot-and-mouth vaccine (FMDV) (mouse model)	Blood, spleen tissue	0, 0.025, 0.05, 0.1, 0.25 g; oral	7 weeks	↑IgG titers, IgG subclasses, IFN-γ, IL-5 and splenocyte proliferation stimulated by concanavalin A, lipopolysaccharide, and FMDV	[48]
Polysaccharide extracts of AMK	FMDV mouse model	Blood, intestinal mucosa	0.05 g; oral	1 week and 2 weeks	↑total sIgA, TGF-β, IL-6, TNF-α, IgA^+ cells, intestinal intraepithelial lymphocytes in duodenum	[50]

(Continued)

Tested substance	Model	Tissue	Dose	Time	Results	Reference
Water extracts of AMK	FMDV mouse model	Serum, spleen tissue	0, 0.0625, 0.125, 0.25, 0.5 g; oral	7 weeks	↑IgG titers, IgG subclasses, IL-5, IFN-γ	[51]
Pure AMK polysaccharides Crude AMK polysaccharides	Piglets	Blood, contents from ileum, cecum and colon	0.3%; oral	14 days	↑peripheral blood lymphocyte transformation rates and mRNA abundances of interleukin-6, TNF-α, IFN-γ, and nuclear factor of activated T cells transcription factor	[52]
AMK powder	Piglets	Blood, spleen tissue	1 g/kg; oral	30 days	↑IgG, IgA, IL-1, IL-2	[53]
Polysaccharide extracts of AMK	Heat stress chicken model	Spleen tissue	200 mg/kg; oral	6 weeks	↑IL-2, IFN-γ, CAT activity, T-AOC, -OH inhibition, activities of mitochondrial complexes I, II and V, Mg^{2+}-ATPase, Na^{+}-K^{+}-ATPase, Ca^{2+}-ATPase, Drp1, Mfn1, Mfn2, Mff, Opa1, Bcl-xl ↓IL-1β, TNF-α, Cyt-c, p53, Bak, Bax	[54]
Antitumor effects						
Ethanol extracts of AMK	Head and neck cancer KB cell line	/	1, 2, 3, 4 mg/mL	24 h	↑Bax/Bcl-2, LC3II, ATG5 ↓PARP1, p-AKT/AKT, mTOR	[59]
Methanol extracts of AMK	Human lymphoma Jurkat T cells, leukemia U937 and HL-60 cells	/	75, 100, 125 μg/mL	24 h	↑apoptosis, ROS	[60]
Atractylenolide I	Human K562 CML, U937 AML and Jurkat T leukemia cells	/	3.13-100 μg/mL	12-72 h	↑apoptosis ↓caspase-3, caspase-9, CD14, CD68	[61]
Polysaccharide extracts of AMK	Glioma C6 cells	/	10, 50, 100, 250, 500, 1,000 g/mL	24, 48, and 72 h	↑PARP, caspase-3, caspase-9, cytosol ↓mitochondria	[62]
Atractylenolide II	MCF 10A cells	/	1-1,000 μM	24, 48, and 72 h	↑Nrf2, GSH/GSSG ratio ↓IL-6, IL-1β, MDA, 8-OHdG	[63]
	N-nitroso-*N*-methylurea-induced breast cancer rat model	Mammary glands	100, 200 mg/kg; i.p.	3, 5, 9 weeks	↑GSH/GSSG ratio, Nrf2, Ho-1, Nqo1, p-JNK/JNK, p-Erk1/2/Erk1/2 ↓IL-6, TNF-α, 8-OHdG, MDA, TNF-α, IL-6	
Regulator effects on energy metabolism						
Water extracts of AMK	3T3-L1 cells	/	1, 5, 10, 25 g/mL	8 days	↓adipogenesis, adipocyte differentiation, p-AKT/AKT	[64]
	High fat diet-fed rats	Plasma	0.5 g/kg; oral	6 weeks	↓final body weight, triglyceride	
Water extracts of AMK	C2C12 cells	/	0.2, 0.5, 1.0 mg/mL	25 h	↑PGC1α, NRF1, TFAM, total ATP, UCP3, p-AMK/AMK, p-ACC/ACC, SIRT1, GLUT-4, glucose uptake, CPT-1β ↓FFA	[65]
Water extracts of AMK	High fat diet-fed mice	Serum and liver, brown adipose tissue, pancreas, gastrocnemius muscle tissue	100, 300 mg/kg	16 weeks	↑PGC1α, UCP1, p-AMPK/AMPK, HO-1, CAT, NRF1, TFAM ↓body weight, fasting serum glucose, serum insulin levels, glucose intolerance, serum total cholesterol	[66]
Regulatory effects on gastrointestinal function						
Polysaccharide extracts of AMK	Intestinal flora rat model	Feces	0.035, 0.105 g/kg; oral	10 days	↑body weights, Shannon's diversity index ↓ecological balance of intestinal flora, flora species	[33]
Methanol extracts of AMK	IEC-6 cell injury model	/	50, 100, 200 μg/mL	24 h	↑polyamine content, membrane hyperpolarization, elevation of $[Ca^{2+}]$cyt, acceleration of cell migration, Kv1.1	[67]

(Continued)

Tested substance	Model	Tissue	Dose	Time	Results	Reference
Ethanol extracts of AMK	IEC-6 cell injury model	/	50, 100, 200 mg/L	12 h	↑cellular polyamine content, RhoA, nonmuscle myosin II, formation of nonmuscle myosin II stress fibers, acceleration of cell migration, Rac1 ↓CDC42	[68]
Water extracts of raw AMK, bran-roasted AMK and charred AMK	Alcohol-induced gastric ulcer mouse model	Stomach tissue	1.5 g/kg; oral	5 days	↓Percentage of ulcer area, ulcer index	[69]
Charred AMK nanocomponents	Alcohol-induced gastric ulcer mouse model	Blood, stomach tissue	0.4, 1.3, 5.1 g/kg	5 days	↑IL-10, PGE2, MUC5AC ↓Percentage of ulcer area, ulcer index, IL-6, MDA, H^+, K^+ ATPase, Pepsin, IL-1β, TNF-α	
Neuroprotective effects						
Ethanol extracts of AMK	Excitotoxicity induced by glutamate in cortical neurons	Cortical neurons	120-240 μg/mL	24 h	↑cell viability ↓apoptosis, DNA laddering ↑p-Akt	[73]
Biatractylolide	PC12 and SH-SY5Y Cells	/	10, 15, 20 μM	24 h	↓GSK3 β, apoptosis, LDH release, ROS	[74]
Atractylenolide III	Learning and memory impairment rat model	Hippocampus	0.6, 1.2, 2.4 mg/kg; oral	6 weeks	↑p-PKC ↓ROS, Casp-3	[76]
Atractylenolide III	Glutamate-induced neuronal apoptosis model	Cortical neurons	10, 20, 40 μM	24 h	↓apoptosis, DNA laddering, Casp-3	[77]
Polysaccharide extracts of AMK	Neuronal apoptosis induced by hypoxia	Cortical neurons	0.025, 0.05, 0.10, 0.25, 0.50, 1.0, 2.0, 4.0 g/L	48 h	↑Bcl-2, Bcl-2/Bax ↓apoptosis, Casp-3, Bax	[78]
Regulatory effects on sex hormones and anti-uterine contraction effects						
Ethanol extracts of AMK	Hyperandrogenic rat model of PCOS	Blood, uterus and ovaries	0.1, 0.3, 0.9 g/kg; oral	8 weeks	↑follicle stimulating hormone, follicle stimulating hormone receptor, aquaporin-9 ↓total testosterone, free androgen index, androstenedione, luteinizing hormone/follicle stimulating hormone, antimüllerian hormone	[80]
Soluble AMK extract (powder)	IL-6-stimulated human pregnant myometrial smooth muscle cell model	Human pregnant myometrial smooth muscle cells	1, 2, 4 mg/mL	/	↑BK_{ca}	[81]
Ethanol extracts of AMK	Bilaterally ovariectomized rat model	Serum	0.3 g/kg; oral	8 weeks	↑E2, osteocalcin ↓FSH, IL-6	[82]
Antioxidant and antiaging effects						
Polysaccharide extracts of AMK	Ischemia-reperfusion injury rat model	Liver	0.4 g/kg; oral	7 days	↑↓ALT, AST, TBIL, DBIL, MDA, NF-κB, IL-1β	[83]
Polysaccharide extracts of AMK	D-galactose-treated rat model	Blood, brain	100, 200 mg/kg; oral	6 weeks	↑GSH-Px, CAT, T-AOC, SOD ↓MDA, MAO, Lipo	[84]
Antiosteoporotic effects						
Ethanol extracts of AMK	RANKL-induced bone loss mouse model	Bone marrow-derived macrophages	10-200 μg/mL	48 h	↓c-Fos, NFATc1, p-ERK/ERK, p-JNK/JNK, p-P38/P38	[85]
	RANKL-induced bone loss mouse model	Right femur	0.25, 0.75 g/kg; oral	5 days	↓bone loss	
Atractylenolide I, atractylenolide III	Mesenchymal stem cells	/	1-300 μg/mL	7 days	↑collagen II, aggrecan, SOX9, Shh, Gli-1	[86]
Antibiotic effects						
Ethanol extracts of AMK	*Staphylococcus aureus*, *Escherichia coli*, *Bacillus, subtilis*, *Shigella flexneri*	/	5-40 mg/mL	24 h	↑inhibited growth	[88]
Water extracts of AMK	*Staphylococcus aureus*, *Escherichia coli*	/		24 h	↑inhibited growth	[89]

production of NO, TNF-α, IL-1β, IL-6, VEGF, and PlGF in a dose-dependent manner[42]. In inflammation models induced by leukocyte peritoneal lavage and lipopolysaccharide-stimulated RAW264.7 macrophages, both atractylenolide I and III exerted anti-inflammatory effects by inhibiting TNF-α expression and reducing NO production *via* the TLR4 signaling pathway.

Systemic pharmacology methods predicted and confirmed that atractylenolide I inhibits inflammation by regulating the expression of IL-6 and IL-1β, which may be one of the mechanisms by which AMK affects chronic gastritis[43]. Additionally, both atractylenolide I and 14-acetoxy-12-senecioyloxytetradeca-2*E*,8*E*,10*E*-trien-4,6-diyn-1-ol exhibited significant anti-inflammatory effects in mouse models of acute and chronic inflammation[44]. However, future studies should focus on elucidating the anti-inflammatory mechanism of action of atractylenolide I.

Despite the established anti-inflammatory effects of atractylenolide I and some of its mechanisms, the complexity of inflammation necessitates further investigation. In-depth studies revealed that atractylenolide I, at concentrations ranging from 1 mmol/L to 100 mmol/L, did not decrease the viability of RAW264.7 macrophages but significantly reduced the release of IL-6 and TNF-α in a concentration-dependent manner[45]. Furthermore, atractylenolide I inhibited the expression of MD-2, CD14, SR-A, TLR4, and MyD88 without affecting CR3 expression. Mechanistic studies indicated that atractylenolide I inhibited not only the TLR4 signaling pathway but also the NF-κB, ERK1/2, and p38 signaling pathways. However, these studies are based only on preliminary investigations with lower levels of evidence and lack further exploration of the specific anti-inflammatory mechanisms involved.

3.2 Immunomodulatory effects

The spleen is not only a central organ in anti-inflammatory responses but also the largest immune organ, containing numerous lymphocytes that play an irreplaceable role in maintaining a favorable environment within the body[46,47]. The polysaccharides in AMK contribute significantly to its immunomodulatory effects[48]. As an oral adjuvant, AMK can effectively enhances the immune response to foot-and-mouth disease (FMD) vaccines in mice. AMK polysaccharides significantly increased the titers of IgG and the levels of IgG, IFN-γ, and IL-5 and increased the degree of spleen cell proliferation induced by concanavalin A, lipopolysaccharide, and FMD vaccination[49]. Furthermore, the oral administration of AMK polysaccharides to FMD-vaccinated mice increased specific serum IgG responses and intestinal mucosal immune parameters[50]; this was evidenced by increased $SIgA^+$ and IgA^+ cell numbers and increased TGF-β, IL-6, and TNF-α levels. These results suggest that the enhanced serum IgG response may be associated with increased local mucosal immunity following the oral administration of AMK polysaccharides. These results support the findings that AMK enhances the preventive immune response to FMD in mice. Specifically, the oral administration of AMK water extract significantly increased the titters of specific IgG and IgG subclasses in the serum of model mice and the response of spleen cells to concanavalin A and lipopolysaccharide through the increased production of IL-5 and IFN-γ[51]. However, those authors did not include a positive control for comparing the efficacy of AMK polysaccharide supplementation.

After the administration of AMK polysaccharides, the metabolic state and immune function of early-weaned piglets significantly improved, with notable increases in the serum concentrations of IgG, TNF-α, IFN-γ, and NF-AT[52]. Additionally, AMK increased the serum levels of IgG, IL-1, and IL-2, indicating that AMK supplementation is beneficial for growth and is more effective than antibiotics[53]. Studies on chicken spleen tissue models revealed that heat stress increased the expression of IL-1, TNF-α, and other proapoptotic genes while decreasing the expression of IL-2, IFN-γ, mitochondrial genes, and other antiapoptotic genes. Heat stress also inhibited the activity of mitochondrial complexes and ATPases[54]. However, some of these results did not demonstrate a dose–response relationship, and some studies lacked positive controls. More importantly, the researchers only conducted analyses of general indicators without further exploring the underlying mechanisms behind the effects.

3.3 Antitumor effects

In recent years, numerous studies have demonstrated that many components of AMK possess antitumor properties[55]. AMK polysaccharides, which are composed of arabinose and glucose (molar ratio, 1.00 : 4.57) with pyranose rings and α-type and β-type glycosidic linkages, have shown potential for the therapeutic treatment of esophageal cancer. In Eca109 cells treated with 2 mg/mL polysaccharide, the rate of inhibition of proliferation was 74.63%; it accelerated the apoptosis of Eca109 cells via the mitochondrial pathway and blocked cells in the S phase[56]. In a randomized study investigating the effects of AMK on cancer cachexia in gastric cancer patients, researchers reported that treatment with AMK led to a decrease in IL-1 levels and an increase in TNF-α levels in patient serum, an effect that was attributed to atractylenolide I present in AMK[57]. The results of that study suggested that atractylenolide I may help alleviate the symptoms of cancer cachexia in patients with gastric cancer, improve appetite, and mitigate weight loss, although it cannot completely reverse weight loss. The most likely mechanism involves the regulation of cytokine production and the inhibition of PIF hydrolysis. Additionally, a study involving 64 patients with advanced gastric cancer supported those findings[58]. However, the limitations of that study included the lack of a standard double-blind randomized controlled trial, the absence of tests for potential side effects, and the lack of direct evidence showing that AMK can inhibit tumor growth and prolong patient survival. Therefore, the evidence remains weak; no double-blind trials on atractylenolide I supplementation have been conducted, and there is no direct evidence, such as evidence of tumor growth inhibition or life extension. Moreover, in the two studies, the doses differed by a factor of ten, leading to somewhat inconsistent results.

AMK extracts also have a certain effect on cervical squamous cell carcinoma[59]. The specific mechanism involves the induction of apoptosis and autophagy in human oral epithelial cancer cells, with cancer cell viability significantly decreasing in a dose-dependent manner. Additionally, AMK induces the activation of PARP, CASP-3, and CASP-8 prior to apoptosis and promotes the upregulation of Bax expression and downregulation of Bcl-2 expression, thereby facilitating apoptosis. Furthermore, the action of AMK may be related to both the extrinsic death receptor pathway and the intrinsic mitochondrial pathway. In human leukemia cells, such as Jurkat T, K562, U937, and HL-60 cells, the antitumor mechanism of AMK extract primarily involves the induction of apoptosis via the promotion of ROS generation[60]. Interestingly, when K562 and U937 leukemia cells were treated with atractylenolide I, apoptosis was induced, and the expression of the surface markers CD14 and CD68 was increased, increasing the phagocytic ability and inducing the differentiation of the cells[61]. Nevertheless, no current explanations exist for the mechanism of action of AMK extracts, and the effectiveness of AMK has not been assessed in animal models in any of the studies reviewed.

AMK polysaccharides have also been shown to have antitumor

effects. AMK polysaccharides significantly inhibited the proliferation of C6 glioma cells by activating CASP-3, CASP-9, and PARP and by inducing apoptosis via the mitochondrial pathway in a dose-dependent manner through DNA fragmentation[62].

Intervention with atractylenolide II in N-nitroso-N-methylurea-induced mammary tumors in rats revealed that atractylenolide II can reduce the levels of proinflammatory cytokines (TNF-α and IL-6), decrease the levels of oxidative markers (MDA and 8-OH-dG), and increase the GSH/GSSG ratio, thereby alleviating inflammation and oxidative stress in model rats. Additionally, atractylenolide II was found to increase the mRNA expression and protein levels of Nrf2 and its downstream detoxifying enzymes. *In vitro* experiments further demonstrated that atractylenolide II upregulated Nrf2 expression and increased Nrf2 nuclear accumulation. Moreover, atractylenolide II activated JNK and Erk1/2 in MCF-10A cells, with increased phosphorylation in a time-dependent manner, thereby activating Nrf2. These results indicate that atractylenolide II exerts its antitumor effects by participating in the JNK/ERK signaling pathway and activating the Nrf2-ARE signaling pathway[63]. However, future research should aim to verify this antitumor effect in clinical settings, using lower doses appropriate for human use.

3.4 Regulatory effects on energy metabolism

In high-fat diet-induced obese mice, treatment with AMK water extract inhibited the Akt/PI3K pathway, thereby significantly reducing lipid accumulation in 3T3-L1 adipocytes and obesity[64]. AMK regulated the mitochondrial stimulation of glucose and lipid metabolism in C2C12 myotubes. AMK extract significantly increased the expression of PGC1α while downregulating NRF-1, TFAM, and total ATP content in C2C12 myotubes; it also increased the expression of PGC1α activators and metabolic sensors. Additionally, AMK extract significantly enhanced glucose uptake by promoting glucose consumption, reducing free fatty acid levels, and increasing the expression of carnitine palmitoyltransferase 1B (CPT1B)[65], indicating its potential for treating obesity, type 2 diabetes, and insulin resistance. Moreover, in high-fat diet-induced obese mice, AMK treatment resulted in a reduction in weight gain, liver lipid levels, and total serum cholesterol levels without altering food intake[66]; the treatment group also showed improvements in fasting blood glucose levels, serum insulin levels, and glucose intolerance. These findings suggest that the antiobesity mechanism of AMK may be related to its ability to promote energy metabolism in skeletal muscle and brown adipose tissue. However, those studies did not determine the specific metabolites in AMK water extracts that were responsible for reducing obesity and enhancing energy metabolism.

3.5 Regulatory effects on gastrointestinal function

AMK polysaccharides significantly improved rat vitality and increased body weight while promoting the digestion of reducing sugars by gut bacteria[33]. That study indicated that AMK polysaccharides can activate spleen and significantly alleviate gut microbiota dysbiosis, indicating that AMK polysaccharides have potential as a treatment for regulating the gut microbiota. When used to treat intestinal mucosal injury, AMK significantly increased polyamine content, membrane hyperpolarization, and cytosolic Ca^{2+} levels while also increasing Kv1.1 mRNA and protein expression, thereby promoting the accelerated migration of IEC-6 cells[67]. The results of that study suggested that AMK extract can significantly stimulate intestinal epithelial cell migration via the polyamine-Kv1.1 channel signaling pathway. Further research by the team indicated that AMK significantly increased the polyamine content and Rho mRNA and protein expression levels and stimulated IEC-6 cell migration through a polyamine-dependent mechanism, thus promoting the healing of injured intestines[68]. Those findings collectively suggest that AMK has great potential in treating intestinal diseases characterized by injury and ineffective mucosal repair. However, the underlying mechanism through which AMK extracts enhance gastrointestinal function remains unclear.

Compared with raw AMK, high-temperature processing methods such as bran-roasted AMK and charred AMK exhibited enhanced anti-gastric ulcer effects that were proportional to the processing temperature and duration[69]. Aqueous solutions of charred AMK were shown to contain nanosized components, referred to as charred AMK nanocomponents (CAM-NCs), which modulated the diversity and structural composition of the intestinal microbiota in rats with alcohol-induced and stress-induced gastric ulcers. However, those studies did not explore the specific mechanisms through which CAM-NCs alleviated alcohol-induced ulcers.

3.6 Neuroprotective effects

Glutamate is cytotoxic, and the neurotoxicity induced by glutamate might result from oxidative damage caused by glutamate and NMDA receptors, leading to cell apoptosis. Therefore, glutamate-induced excitotoxicity plays a crucial role in neurological diseases[70]. Oxidative stress refers to the negative effect caused by an imbalance between the production and elimination of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the body, leading to oxidative damage. Oxidative stress is considered one of the pathogenic factors that can cause aging. Numerous studies have shown that ROS levels increase in neurodegenerative diseases and are associated with glutamate-induced neurotoxicity and Alzheimer's disease progression[71,72]. AMK ethanol extract reduced excitotoxicity-induced apoptosis in primary cultured cortical neurons, showing significant neuroprotective activity against glutamate-induced excitotoxicity[73]. Intervention with biatractylenolide in glutamate-induced damage in rat pheochromocytoma (PC12) cells and human neuroblastoma (SH-SY5Y) cell lines revealed that cell apoptosis was effectively inhibited, GSK3β protein expression was downregulated, and *p*-Akt protein expression was upregulated. Different concentrations of biatractylenolide significantly increased the survival of PC12 and SH-SY5Y cells in a dose-dependent manner. Biatractylenolide significantly elevated ROS levels, indicating that it can substantially reduce glutamate-induced ROS production[74]. Therefore, biatractylenolide may exert neuroprotective effects against glutamate-induced damage in PC12 and SH-SY5Y cells via the PI3K-Akt-GSK3β signaling pathway[75]. Atractylenolide III inhibited the formation of ROS induced by homocysteine and increased the expression levels of p-PKC, significantly reversing learning and memory impairments caused by chronic high-dose homocysteine administration and protecting neurons from homocysteine-induced apoptosis[76]. Additionally, atractylenolide III had a marked inhibitory effect on glutamate-induced neuronal apoptosis, likely through the dose-dependent inhibition of the caspase signaling pathway[77]. AMK polysaccharides effectively prevented hypoxia-induced neuronal growth inhibition, mitochondrial damage, and apoptosis. These

compounds significantly downgraded the mRNA and protein levels of Casp-3 and Bax while increasing the protein level of Bcl-2. Moreover, AMK polysaccharides increased Bcl-2 levels and the Bcl-2/Bax ratio in hypoxic neurons[78]. However, those studies lacked positive controls to substantiate the true efficacy of the experimental materials. Additionally, the selection of outcome measures was limited, with a lack of more robust indicators to further substantiate the neuroprotective effects.

3.7 Regulatory effects on sex hormones and anti-uterine contraction effects

Research has shown that AMK can regulate sex hormone levels in the body and can be used to treat polycystic ovary syndrome (PCOS). Excess androgens in the ovaries inhibit follicular development and significantly impact this disease. Total testosterone, the free androgen index, androstenedione are the hyperandrogenic indicators most strongly associated with PCOS[79]. AMK ethanol extract significantly reduced plasma total testosterone and androstenedione levels in PCOS model rats while also markedly lowering luteinizing hormone (LH) levels and increasing follicle-stimulating hormone (FSH) levels. Additionally, AMK ethanol extract decreased the expression of FSH receptors in the ovaries and increased the expression of aquaporin-9 (AQP-9) in a dose-dependent manner, thereby serving as a treatment for PCOS[80]. However, that study had significant limitations, including the absence of positive controls and the reliance on only basic hormonal assays. Additionally, the potential mechanisms underlying the effects of the ethanol extract were not elucidated.

Additionally, AMK helps maintain the membrane potential and resting state of myometrial smooth muscle cells during pregnancy. AMK water extract inhibited IL-6-induced contractions of pregnant human myometrial smooth muscle cells and enhanced Ca^{2+}-activated K^+ currents, indicating its potential to inhibit uterine contractions[81]. However, it is puzzling that the authors did not specify the source of the extract used or the duration of its effect on the cells. Moreover, the conclusion was based on a single, rather simplistic measure, making it difficult to fully trust the findings. Those results should be approached with caution and skepticism. The treatment of ovariectomized female rats with AMK ethanol extract and transcutaneous electrical acupoint stimulation resulted in increased serum estradiol and osteocalcin levels, suggesting that AMK may help alleviate menopausal symptoms in women[82]. Similarly, that study focused primarily on a few basic hormonal indicators in the serum and lacked an analysis of dose–response relationships. Future research should employ more reliable indicators for further investigation.

3.8 Antioxidant and antiaging effects

AMK polysaccharides significantly reduced the expression of liver dysfunction markers and the associated histological changes in a rat model of hepatic ischemia–reperfusion injury. Additionally, AMK polysaccharides markedly inhibited lipid peroxidation induced by hepatic ischemia–reperfusion injury; altered the activity of antioxidant enzymes, superoxide dismutase, and malondialdehyde; and suppressed the expression of interleukin-1 and NF-κB. The protective and therapeutic effects of AMK polysaccharides on hepatic ischemia–reperfusion injury in rats may be related to their antioxidant properties and the inhibition of NF-κB activation[83]. In a study on D-galactose-induced aging model mice, treatment with AMK polysaccharides significantly reduced the levels of oxidative markers such as malondialdehyde, monoamine oxidase, and lipofuscin; concurrently, the levels of superoxide dismutase, catalase, and glutathione peroxidase in the serum and superoxide dismutase and total antioxidant capacity in brain tissue significantly increased[84]. Those findings suggest that AMK polysaccharides possess antioxidant capabilities and potential antiaging effects. However, those studies have notable limitations, as they employed only one or two doses of AM polysaccharide supplements, resulting in limited data on dose-dependent effects.

3.9 Antiosteoporotic effects

Studies exploring the inhibitory effects of AMK ethanol extracts on osteoclast differentiation have shown that atractylenolide I and atractylenolide II play key roles in this process[85]; they function primarily by sequentially inhibiting the activation of the transcription factors NF-κB, c-Fos, and nuclear factor of activated T cells C1 (NFATC1) in osteoclast precursors, thereby suppressing osteoclast differentiation. *In vitro* experiments validated that conclusion, suggesting that AMK has the potential to be developed into a drug for the prevention and treatment of osteoporosis. Moreover, the lactone components in AMK significantly increase chondrocyte differentiation efficiency. Both atractylenolide I and III significantly increased the activity of the Gli promoter, a target gene of the Sonic Hedgehog pathway, thereby inducing the differentiation of mesenchymal stem cells into chondrocytes[86]. *In vitro* experiments also showed that atractylenolide components significantly upregulated the expression of the chondrocyte-related transcription factor Sox9, which is essential for the activation of cartilage markers such as collagen II gene expression[87]. However, further randomized controlled trials are needed to clarify additional mechanisms potentially contributing to the antiosteoporotic effects and to assess the impact of other active metabolites found in AMK extracts.

3.10 Antibacterial effects

AMK extract exhibits notable antibacterial activity. AMK ethanol extracts, at concentrations ranging from 5 to 40 mg/mL, effectively inhibited *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and Shigella flexneri[88]. Notably, at a concentration of 5 mg/mL, AMK extract effectively inhibited the growth of *E. coli*. Additionally, extract from the aerial parts of AMK had stronger antibacterial activity than did extract from the rhizome. Furthermore, the polysaccharides and flavonoids in AMK water extracts, after plasma and acrylic acid regrafting treatment, well grafted onto polyethylene terephthalate (PET) nonwoven fabric, exhibiting strong antibacterial activity against both *S. aureus* and *E. coli*[89]. Interestingly, AMK was one of the few traditional medicines with stronger antibacterial activity against gram-negative bacteria than gram-positive bacteria, especially when the water extract was grafted onto PET nonwoven fabric following plasma treatment. Nevertheless, further research is needed to identify the active components of these extracts and to elucidate the specific mechanisms underlying their antibacterial effects.

3.11 Other effects

AMK has diuretic effects. AMK water extract was used to pretreat mouse inner medullary collecting duct-3 (MIMCD-3) cells under hyperosmotic stress for 30 min, and the results indicated that the hyperosmotic-induced increase in aquaporin 2

(AQP2) expression and its translocation to the apical plasma membrane were attenuated[90]. Immunoblot analysis also revealed that the protein and mRNA expression levels of tonicity-responsive enhancer binding protein (TonEBP) decreased following treatment with AMK water extract. The results of that study suggested that AMK may exert its diuretic effect by decreasing and inhibiting water reabsorption via the TonEBP-AQP2 signaling pathway. AMK also has antidepressant effects. Atractylenolide I was shown to alleviate depression induced by chronic unpredictable mild stress, likely through the inhibition of NLRP3 inflammasome activation and a reduction in IL-1β production[91]. Furthermore, AMK has antidiabetic effects. After treating alloxan-induced diabetic rats with AMK for 10 days, a significant reduction in blood glucose levels, water, and food consumption was observed, in addition to reduced pancreatic damage, suggesting the hypoglycemic potential of AMK[92].

Additionally, AMK has antidepressant effects and can alleviate anxiety disorders[93]. *In vitro* experiments revealed fewer γH2AX foci after atractylenolide II treatment. *In vivo* experiments demonstrated that the administration of atractylenolide II at a concentration of 60 mg/kg effectively prevented radiation-induced skin ulcers and edema and provided some protection to the intestines. Further research indicated that atractylenolide II promoted the expression of the antioxidant factors HO-1 and NAD(P)H quinone oxidoreductase-1 (NQO-1) via the Nrf2 signaling pathway, thereby significantly inhibiting ionizing radiation-induced damage. Moreover, atractylenolide II significantly upgraded the expression of mitogen-activated protein kinase p38 (MAPK p38). However, MAPK p38 inhibitors markedly downregulated the expression of Nrf2 and its downstream target genes HO-1 and NQO-1, resulting in the loss of the antiradiation effects of atractylenolide II[94]. Those findings suggest that atractylenolide II exerts its antiradiation effects through the MAPK p38/Nrf2 signaling pathway.

4 Pharmacokinetics

A study utilizing capillary gas chromatography coupled with selected ion monitoring mass spectrometry revealed the following primary pharmacokinetic parameters of atractylenolide I *in vivo*: time to peak concentration (T_{max}), 0.37 ± 0.19 h; peak concentration (C_{max}), 0.26 ± 0.05 μg/mL; area under the curve (AUC), 1.95 ± 0.30 μg·h/mL; and absorption rate constant (K_a), 10.08 ± 5.60 h^{-1}. The study also revealed that after the oral administration of atractylenolide I (50.0 mg/kg) to rats, the concentration of atractylenolide I in the body decreased over time. The distribution of atractylenolide I in the tissues followed the order liver > kidneys > spleen > cerebellum > heart > brain > lungs. Additionally, the protein binding rates of atractylenolide I in rat plasma, human plasma, and bovine serum albumin were 80.8% ± 3.9%, 90.6% ± 3.1%, and 60.9% ± 5.1%, respectively[95]. The pharmacokinetic parameters of atractylenolide I in rat plasma were quantified via high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with butyl acetone as the internal standard. The results revealed that the main pharmacokinetic parameters were a T_{max} of 0.81 ± 0.11 h, C_{max} of 7.99 ± 1.2 ng/mL, $T_{1/2}$ of 1.94 ± 0.27 h, and K_a of 0.365 ± 0.06 h^{-1}[96]. Despite differences in animal species, drug dosages, and sex between the two studies, the results provided reliable pharmacokinetic parameters for atractylenolide I, demonstrating that it is readily absorbed and slowly eliminated following oral administration. The pharmacokinetics of atractylenolide II and atractylenolide III in rats were studied using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with ryegrass lactone as the internal standard. The results indicated that the Tmax values for atractylenolides II and III were 0.67 ± 0.39 h and 0.67 ± 0.13 h, respectively; the C_{max} values were 7.99 ± 0.90 ng/mL and 9.79 ± 1.79 ng/mL, respectively; the AUC values were 28.46 ± 7.71 ng·h/mL and 37.43 ± 7.86 ng·h/mL, respectively; the CL values were 0.043 ± 0.015 L·h/kg and 0.029 ± 0.006, L·h/kg, respectively; and the $T_{1/2}$ values were 2.63 ± 1.08 h and 4 ±1.94 h, respectively[97]. To date, extensive pharmacokinetic studies have been conducted on atractylenolides I, II, and III. However, there is a relative scarcity of pharmacokinetic research on other active components in AMK, such as atractylenone and atractylenolide IV, necessitating further investigation.

5 Conclusion

This review summarizes the botanical characteristics, phytochemistry, pharmacology, and pharmacokinetics of AMK. Researchers have isolated and identified over 77 metabolites from AMK. Among these, sesquiterpenoids, polyacetylenes, and polysaccharides are considered the primary active metabolites. Despite significant progress in the phytochemistry and pharmacological studies of AMK, many areas remain to be explored. It is essential to bridge animal research with clinical studies. Specifically, investigating processed AMK via isolated methods may not be entirely appropriate. Future research should adopt a comprehensive approach to explore this traditional medicine effectively. Such an approach would be more conducive to investigating AMK as medicine and food, increasing the practical application value of study results.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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