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Chemical constituents, health benefits, and applications of *Agastache rugosa*: A review

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ABSTRACT: *Agastache rugosa* (Fisch. & C.A. Mey.) Kuntze (*A. rugosa*), a perennial aromatic herb of the Lamiaceae family, has significant medicinal and culinary value. Its complex chemical profile includes terpenoids, flavonoids, phenylpropanoids, and sterols, which contribute to diverse pharmacological activities such as anti-inflammatory, antioxidant, antibacterial, and neuroprotective effects. This article systematically reviews the chemical components, health benefits, and application status of *A. rugosa*, with a focus on its dual role as a medicinal and edible plant. We also highlight its potential for further research and development in pharmaceuticals, functional foods, and cosmetics. By consolidating existing knowledge and identifying emerging trends, this review aims to facilitate further scientific exploration and commercial utilization of *A. rugosa*, highlighting its untapped potential in integrative medicine and nutraceutical industries.

Keywords: *Agastache rugosa*, Chemical constituents, Health benefits, Mechanisms, Application

1. Introduction

Agastache rugosa (Fisch. & C.A.Mey.) Kuntze (*A. rugosa*), commonly known as "Huoxiang" or Korean mint, is an aromatic perennial herb in the family Lamiaceae [1]. Characterized by erect stems reaching 50-150 cm in height, this species features ovate-lanceolate leaves with serrated margins that emit a distinct fragrance when crushed. Its aromatic quality can rival that of high-quality spices, such as agarwood and sandalwood [2]. Its terminal spike-shaped inflorescences bear pale purple to white bilabiate flowers. *A. rugosa* is a paradigm plant that is both edible and medicinal. The concept of "food and medicine homology" emphasizes its dual functionality as both a nutrient source and a therapeutic agent. The medicinal components within it have no harmful effects on the body and can be consumed over a prolonged period [3, 4]. The tender leaves of *A. rugosa* are nutritious edible parts and also a multi-functional flavoring agent. In Traditional Chinese Medicine (TCM), it is classified as a pungent, slightly warm herb that exerts therapeutic effects along the spleen, stomach, and lung meridians. Documented therapeutic applications include anti-emetic properties,

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management of summerheat syndrome, and treatment of gastrointestinal disorders such as anorexia, cholera, and epidemic pathogenic conditions (miasma) [5]. Modern pharmacological studies have shown that *A. rugosa* also possesses various activities such as anti-inflammatory [6, 7], antioxidant [8, 9], and antibacterial [10-12] properties, which are closely related to its rich chemical components.

In China, *A. rugosa* cultivation is primarily concentrated in Sichuan, Yunnan, Guangdong, and northeastern provinces. Internationally, it is grown on a limited scale as a medicinal-ornamental species in South Korea and Japan, while European and North American cultivation occurs sporadically for aromatic or horticultural purposes. At present, the applications of *A. rugosa* have expanded from traditional Chinese medicine to functional foods, cosmetics, biopesticides, and other fields. Although the existing reviews have focused on the genus *Agastache*, systematic analyses specifically targeting *A. rugosa* remain limited. This article, in combination with the latest research progress, reviews the studies on its chemical constituents, health benefits, and applications, aiming to promote the quality of this plant, optimize its therapeutic applications, and facilitate its development and utilization.

2. Chemical constituents of *A. rugosa*

2.1 Volatile oil components

The characteristic aroma of *A. rugosa* is predominantly derived from its volatile oil constituents. Monoterpenoids and sesquiterpenoids collectively constitute the major fraction of *A. rugosa* volatile oil. The components of monoterpenoids contain chain, monocyclic, and bicyclic structures. Sesquiterpenoids contain 15 carbon atoms (three isoprene units) and primarily exhibit cyclic structures. Additionally, *A. rugosa* volatile oil contains aromatic compounds, with estragole (**119**) as a characteristic component that contributes to the plant's distinctive pungent aroma, along with minor aliphatic constituents. **Table 1** and **Figure 1** summarize the volatile oil components identified in *A. rugosa*.

Table 1 Volatile oil components from *A. rugosa.*

Type	No.	Component	Refs.	No.	Component	Refs.
Monoterpenoid	**1**	Myrcene	[10]	**27**	(±)-Pulegone	[20]
	2	*trans*-Ocimene	[22]	**28**	Isopiperitenone	[20]
	3	Linalool	[25]	**29**	(-)-Limonene	[22]
	4	Artemisia triene	[13]	**30**	Dihydrocarveol	[17]
	5	Santolinatriene	[22]	**31**	Phellandrene	[17]
	6	(*E*)-*β*-Ocimene	[22]	**32**	*β*-Phellandrene	[41]
	7	Citronellal	[17]	**33**	Thymol	[25]
	8	Geranial	[17]	**34**	Carvacrol	[25]
	9	Neral	[17]	**35**	*p*-Cymenene	[10]
	10	(*Z*)-Myroxide	[22]	**36**	*trans*-Limonene oxide	[22]
	11	D-Limonene	[21]	**37**	Terpinen-4-ol	[17]
	12	Menthone	[20]	**38**	(±)-Nerol oxide	[17]
	13	Pulegone	[20]	**39**	Linalool oxide	[17]
	14	Limonene	[25]	**40**	(*S*)-Verbenone	[15]
	15	Isopulegone	[20]	**41**	Sabinen	[10]
	16	*p*-Menthan-3-one	[42]	**42**	*α*-Pinene	[25]
	17	(+)-Dihydrocarvone	[15]	**43**	*trans*-Chrysanthenol	[15]
	18	Carvone	[15]	**44**	(±)-Myrtenol	[17]
	19	(-)-*cis*-Carveol	[15]	**45**	Fenchol	[17]

Sesquiterpenoid	**20**	L-Carveol	[43]	**46**	*dl*-Borneol	[17]
	21	*trans*-*p*-Mentha-2,8-dienol	[10]	**47**	(±)-Camphor	[41]
	22	*p*-Mentha-2,8-dien-1-ol	[10]	**48**	*β*-Pinene	[17]
	23	*p*-Menthan-3-one, cis-	[10]	**49**	Dehydro-1,8-cineole	[25]
	24	Piperitone	[20]	**50**	1,8-Cineole	[22]
	25	*γ*-Terpinene	[25]	**51**	Cashmeran	[44]
	26	*α*-Terpineol	[25]	**52**	Nepetalactone	[20]
	53	*cis*-*α*-Farnesene	[25]	**84**	1,2,3,4,5,6,7,8-Octahydro-1,4-dimethyl -7-(1-methylethenyl) vazulene	[15]
	54	*α*-Farnesene	[25]	**85**	*γ*-Gurjunene	[44]
	55	Nerolidol	[22]	**86**	*α*-Guaiene	[44]
	56	Germacrene D	[45]	**87**	Guaia-6,9-diene	[44]
	57	*α*-Caryophyllene	[15]	**88**	Patchoulene	[44]
	58	(*Z*,*Z*,*Z*)-1,5,9,9-Tetramethyl-1,4,7-cycloundecatriene	[46]	**89**	*γ*-Cadinene	[20]
	59	Germacrene B	[25]	**90**	*γ*-Muurolene	[20]
	60	4,11,11-Trimethyl-8-methylenebicyclo [7.2.0] undec-4-ene	[25]	**91**	*δ*-Cadinene	[25]
	61	*β*-Caryophyllene	[21]	**92**	Cadina-4,9-diene	[25]
	62	Caryophyllene oxide	[15]	**93**	*cis*-Calamenene	[44]
	63	Bicyclogermacrene	[25]	**94**	*epi*-Bicyclosesquiphellandrene	[46]
	64	*α*-Humulene epoxide II	[44]	**95**	2-Isopropyl-5-methyl-9-methylene-bicyclo[4.4.0]dec-1-ene	[46]
	65	*γ*-Elemene	[20]	**96**	Cadinene	[17]
	66	Elixene	[25]	**97**	*β*-Cadinene	[20]
	67	*β*-Elemen	[20]	**98**	*τ*-Muurolol	[20]
	68	(-)-*β*-Elemenol	[22]	**99**	*epi*-*α*-Cadinol	[20]
	69	*trans*-*α*-Bergamotene	[46]	**100**	*α*-Cadinol	[20]
	70	*α*-(-)-Bisabolol	[13]	**101**	*α*-Isonootkatol	[44]
	71	*β*-Bisabolene	[13]	**102**	Neointermedeol	[44]
	72	Spathulenol	[15]	**103**	Eremophilene	[44]
	73	(±)-Ledene	[25]	**104**	Valencen	[44]
	74	Aromadendrene	[25]	**105**	Corymbolone	[44]
	75	Viridiflorol	[25]	**106**	*α*-Muurolene	[15]
	76	Isoledene	[25]	**107**	*cis*-(-)-Thujopsene	[15]
	77	*α*-Gurjunene	[44]	**108**	*α*-Copaene	[15]
	78	Alloaromadendrene	[44]	**109**	Seychellene	[15]
	79	Pogostol	[44]	**110**	(+)-*α*-Longipinene	[45]
	80	Rotundone	[44]	**111**	Patchoulol	[47]
	81	*β*-Patchoulene	[44]	**112**	Acorenone B	[15]
	82	*α*-Patchoulene	[44]	**113**	*β*-Bourbonene	[20]
	83	*δ*-Bulnesene	[44]	**114**	*β*-Cubebene	[20]
Aromatic	**115**	2-Phenyl-1-hexanol	[22]	**129**	*p*-Cymen-7-ol	[25]
	116	Eugenol	[21]	**130**	2-Methylbenzenemethanol	[22]
	117	2-Allylphenol	[15]	**131**	3-Ethylphenol	[44]
	118	Chavicol	[45]	**132**	2, 4, 6-Trihydroxybenzaldehyde	[15]
	119	Estragole	[20]	**133**	Methyl salicylate	[45]
	120	Benzyl isopentyl ether	[10]	**134**	Benzaldehyde	[45]
	121	Anethole	[44]	**135**	Anisaldehyde	[48]
	122	Asarone	[45]	**136**	Acetophenone	[25]
	123	Methyl eugenol	[21]	**137**	1,2-Diethylbenzene	[22]
	124	3-Methoxycinnamaldehyde	[46]	**138**	1,2,3,4-Tetramethylbenzene	[46]
	125	4-Methoxycinnamaldehyde	[49]	**139**	*α*-Damascenone	[22]
	126	*trans*-Cinnamaldehyde	[44]	**140**	*β*-Ionone	[17]
	127	4′-Methoxypropiophenone	[45]	**141**	Jasmone	[17]
	128	2-Phenylpropionaldehyde	[22]			
Aliphatic	**142**	Octane	[10]	**163**	4-Methyl-1-penten-3-ol	[22]
	143	Tridecane	[10]	**164**	3-Methyl-3-pentanol	[22]
	144	Pentadecane	[50]	**165**	2,5-Dimethyl-5-hexen-3-ol	[22]
	145	Heptadecane	[15]	**166**	(±)-7-Octen-4-ol	[50]
	146	Heneicosane	[50]	**167**	3-Octanone	[20]
	147	Heptacosane	[45]	**168**	Methyl hexadecanoate	[51]
	148	2,6-Dimethylheptane	[22]	**169**	(3*Z*,6*Z*,8*E*)-Dodeca-3,6,8-trien-1-ol	[22]
	149	Farnesane	[50]	**170**	Methyl linolenate	[45]
	150	Hexane,2,2,3-trimethyl	[10]	**171**	1-Octen-3-yl acetate	[22]

Other	**151**	Hexane,2,3,4-trimethyl	[10]	**172**	2-Propen-1-yl 3-methyl-2-butenoate	[22]
	152	*cis*-Salvene	[22]	**173**	Geranyl acetate	[17]
	153	1.8-nonadiyne	[22]	**174**	Citronellyl acetate	[17]
	154	2-Methyl-5,7-bis (methylene)-1,8-nonadiene	[22]	**175**	Linalyl acetate	[41]
	155	3-Hexen-1-ol	[10]	**176**	Octeny acetate	[50]
	156	1-Octen-3-ol	[10]	**177**	Decanal	[15]
	157	1-Hexanol	[13]	**178**	Pentadecanal	[15]
	158	Leaf alcohol	[45]	**179**	(*E*)-2-Hexenal	[10]
	159	3-Octanol	[20]	**180**	2-Phenyl propionaldehyde	[22]
	160	5-Methyl-2-hexanol	[22]	**181**	2, 2-Dimethylhexanal	[50]
	161	2-Heptanol	[22]	**182**	6,6,7-Trimethyl-2,5-octanedione	[10]
	162	2,3-Dimethyl-3-methoxybutan-1-ol	[22]	**183**	Perhydrofarnesyl acetone	[44]
	184	Phytol	[15]	**192**	(*Z*)-Cinerone	[10]
	185	Protocatechuic acid	[51]	**193**	Dehydroelsholtzia ketone	[28]
	186	4-Hydroxybenzoic acid	[52]	**194**	Pogostone	[44]
	187	4-Methoxybenzoic acid	[53]	**195**	Thymoquinone	[54]
	188	4-Aminosalicylic acid	[15]	**196**	Cyclopentanol, 2-methyl-	[15]
	189	Epishyobunol acetate	[50]	**197**	2-Ethenylbicyclo[2.1.1] hex-2-ene	[22]
	190	2-Heptylfuran	[15]	**198**	7-(1-(*E*)-Prop-1-enyl)cycloocta-1, 4-diene	[22]
	191	Cyclohexanone	[10]			

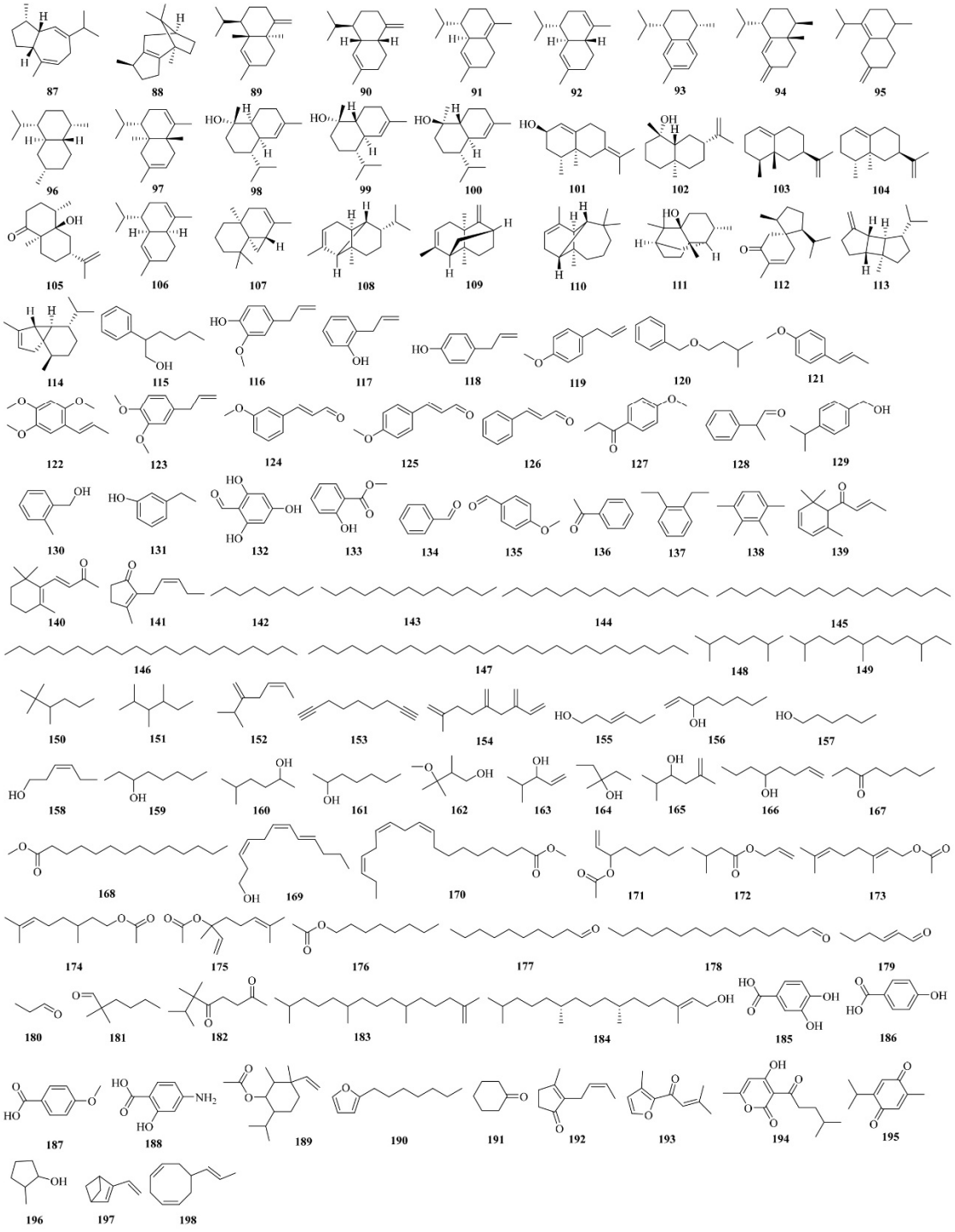


Figure 1 Volatile oil components from *A. rugosa.*

Multiple extraction methodologies have been employed to isolate volatile oils from *A. rugosa*, including steam distillation, supercritical fluid extraction, ultrasound-assisted extraction, molecular distillation, microwave-assisted extraction, headspace solid-phase microextraction, and supercritical carbon dioxide extraction [13]. In a novel approach, Wang et al. employed ultrafiltration (UF) and vapor permeation (VP) membrane technologies to extract and separate volatile oils. Their findings revealed that the UF method preferentially enriched oxygenated constituents such as alcohols and phenols, whereas the VP method exhibited selectivity toward alkene compounds. These results demonstrate that both UF and VP techniques are effective for enriching *A. rugosa* volatile oils while achieving favorable separation efficiency [14].

Comparative studies have further evaluated extraction methods such as CO_2 supercritical extraction, steam distillation, and ethanol reflux extraction. Ethanol reflux extraction demonstrated superior efficacy in isolating active components, offering advantages in process simplicity and solvent recyclability, thereby reducing operational costs.

A. rugosa is rich in terpenoids, primarily pulegone (**13**) [10, 15], menthone (**12**) [16], *p*-menthan-3-one (**16**) [10], and limonene (**14**) [17]. These terpenoids, being classified as menthane type monoterpenoids, serve as flavoring agents in food, perfumery, and herbal products [18, 19]. Additionally, numerous research studies have highlighted that the dominant constituent in the volatile oil extracted from *A. rugosa* is the phenylpropanoids known as estragole (**119**), which belongs to the aromatic family [13, 20-24] or methyl eugenol (**123**) [25]. This is due to the differences in origin, harvest period, plant age, etc., which cause variations in the composition of *A. rugosa* volatile oil. Scientists have identified six different chemotypes of *A. rugosa* based on the variation in major components. These chemotypes include estragole, pulegone, isopulegone, methyl eugenol, menthone, and nepetalactone [20]. The predominant volatile oils in Korean *A. rugosa* are characterized by high levels of estragole (**119**), accounting for 84.25% in leaves and 57.94% in flowers [22]. In Australian *A. rugosa*, its nectar exhibits the greatest concentration of estragole (**119**), with levels reaching 97.16%, followed by the flowers at 96.74% and the leaves at 94.35% [13]. The primary constituent of the volatile oil of *A. rugosa* from Heilongjiang and Liaoning is also estragole (**119**). The proportion of estragole (**119**) in the volatile oil of *A. rugosa* is much higher than that of other Lamiaceae plants. Estragole (**119**) endows *A. rugosa* with strong aromatic characteristics and has broad-spectrum antibacterial and anti-inflammatory activities [26, 27]. The primary constituent of the volatile oil of *A. rugosa* from Jilin is dehydroelsholtzia ketone (**193**) [28]. The primary constituent in the volatile oil of *A. rugosa* flowers obtained from Xinjiang is pulegone (**13**), and the primary constituent present in the volatile oil of *A. rugosa* leaves is *p*-menthan-3-one (**16**) [10].

The volatile oil content of *A. rugosa* is higher during the pre-flowering and flowering stages, and lower during the deciduous stage. Pulegone (**13**) levels are highest during the flowering stage, gradually declining as the plant matures. For menthone types, the best harvesting period is in full bloom, while those with high estragole (**119**) content are best harvested post-bloom [29]. The appropriate time for harvesting *A. rugosa* can be determined by analyzing the composition and content at different growth stages.

The age of the maternal parents of *A. rugosa* has an impact on the chemical quality of the offspring plants. Offspring plants from maternal parents that are two years or older can yield essential oils rich in estragole (**119**) [23]. Understanding the differences in the volatile oil of *A. rugosa* allows for selecting the appropriate origin, harvesting period, and plant part (leaves or flowers) to prepare volatile oil rich in the desired components. This serves as a useful reference for developing flavorings and medicines from *A. rugosa*.

2.2 Non-volatile components

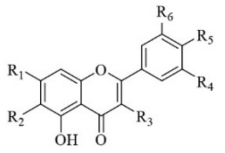
2.2.1 Polyphenols

Polyphenols are essential and abundant active components in *A. rugosa*. The total polyphenol content in the ethanol extract of *A. rugosa* was reported as (38.11 ± 0.88) mg/g [30], while that in the aqueous extract was (38.9 ± 1.7) mg/g [31]. Through phytochemical investigations, researchers have successfully isolated a variety of polyphenol compounds from *A. rugosa*. These compounds can be classified into several categories, including flavonoids, phenylpropanoids, and other phenols, as detailed in **Table 2** and **Figure 2**.

Table 2 Polyphenols from *A. rugosa.*

Type	No.	Component	Refs.	No.	Component	Refs.
Flavonoid	**199**	Apigenin	[15]	**215**	Acacetin 7-*O*-(6″-*O*-malonyl)-*β*-D-glucopyranoside	[55]
	200	Acacetin	[55]	**216**	Acacetin7-*O*-(2″-*O*-acetyl-6″-*O*-malonyl)-*β*-D-glucopyranoside	[55]
	201	Luteolin	[53]	**217**	Acacetin-7-*O*-(3″-*O*-acetyl-6″-*O*-malonyl)-*β*-D-glucopyranoside	[53]
	202	Diosmetin	[53]	**218**	Linarin	[32]
	203	Kaempferol	[52]	**219**	4-Hydroxy-2-(4-methoxyphenyl)-7-[[6-*O*-[(2*E*)-1-oxo-2-buten-1-yl]-*β*-D-glucopyranosyl]oxy]-4H-1-benzopyran-4-one	[56]
	204	Quercetin	[52]	**220**	Tilianin	[55]
	205	4',5-Dihydroxy-3,3',7-trimethoxyflavone	[32]	**221**	Acacetin 7-*O*-(3″-acetylglucopyranoside)	[53]
	206	Cirsimaritin	[15]	**222**	Kaempferol 3-*O*-rutinoside	[32]
	207	Genistein	[32]	**223**	Kaempferol 3-*O*-*β*-D-glucopyranoside	[34]
	208	Calycosin	[32]	**224**	Quercetin 3-glucuronide	[33]
	209	Calycosin 7-*O*-*β*-D-glucoside	[57]	**225**	Rutin	[52]
	210	Apigenin 7-*O*-glucoside	[15]	**226**	6,7-Dimethoxy-3′,4′,5-trihydroxyflavone-3-*O*-glucoside	[32]
	211	Luteolin 7-*O*-glucoside	[53]	**227**	Agastachin	[58]
	212	Diosmetin 7-*O*-*β*-D-glucoside	[53]	**228**	(-)-Epicatechin	[52]
	213	Isoagastachoside	[55]	**229**	Dihydrochalcone	[33]
	214	Agastachoside	[15]	**230**	Phlorizin	[15]
Phenylpropanoid	**231**	*trans*-Cinnamic acid	[52]	**247**	Salidroside	[59]
	232	*p*-Coumaric acid	[33]	**248**	Ferulic acid glucoside	[33]
	233	Caffeic acid	[52]	**249**	(*E*)-4-Hydroxycinnamyl alcohol 4-*O*-*β*-D-glucopyranoside	[56]
	234	Methyl caffeate	[53]	**250**	*p*-Coumaric acid glucoside	[33]
	235	Ethyl caffeate	[53]	**251**	3-Hydroxyestragole *β*-D-glucopyranoside	[56]
	236	Ferulic acid	[33]	**252**	3-*O*-Caffeoylquinic acid	[33]
	237	2, 5-Dihydroxycinnamic acid	[32]	**253**	3-*p*-Coumaroylquinic acid	[32]
	238	Rosmarinic acid	[55]	**254**	3-Feruloylquinic acid	[34]
	239	Methyl rosmarinate	[53]	**255**	4-Caffeoylquinic acid	[33]
	240	Ethyl rosmarinate	[53]	**256**	4-*p*-Coumaroylquinic acid	[34]
	241	Chavicol *β*-D-glucoside	[53]	**257**	5-*O*-Caffeoylshikimic acid	[34]
	242	1-*O*-*β*-D-Glucopyranosyloxy-2-hydroxy-4-allylbenzene	[53]	**258**	(3*R*,7*R*)-Tuberonic acid-12-*O*-[6′-*O*-(*E*)-feruloyl]-*β*-D-glucopyranoside	[53]
	243	Chavicol-1-*O*-(6′-*O*-acetyl)-*β*-D-glucopyranoside	[53]	**259**	Salicylic acid-2-*O*-[6′-*O*-(*E*)-feruloyl]-*β*-D-glucopyranoside	[53]
	244	Chavicol-1-*O*-(6′-*O*-methylmalonyl)-*β*-D-glucopyranoside	[53]	**260**	Nepetoidin B	[53]
	245	1-Hydroxy-2-*O*-*β*-D-glucopyranosyl-4-allylbenzene	[53]	**261**	Agastenol	[60]
	246	Cimidahurinine	[56]	**262**	Agastinol	[60]
Phenolic	**263**	Benzyl *β*-D-glucopyranoside	[59]	**266**	4,6*Z*-Megastigmadien-3-one 9-glucoside	[59]
	264	(6*R*,9*R*)-3-Oxo-*α*-ionol 9-*O*-*β*-D-glucopyranoside	[59]	**267**	4,6*E*-Megastigmadien-3-one 9-glucoside	[56]
	265	5*β*,6*α*-Dihydroxy-3*β*-(*β*-glucopyranosyloxy)-7-	[59]	**268**	(-)-Quinic acid	[33]

megastigmen-9-one



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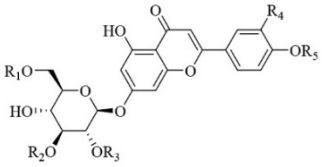

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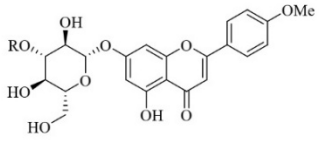
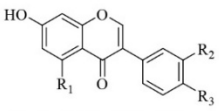
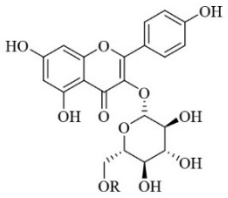
218 R_1=Rha,R_2=Acetyl,R_3=H,R_4=H,R_5=Me
219 R_1=,R_2=H,R_3=H,R_4=H,R_5=Me



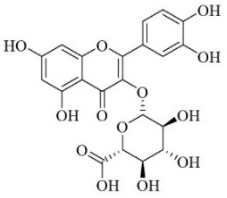
220 R=H
221 R=Acetyl



207 R_1=OH,R_2=H,R_3=OH
208 R_1=H,R_2=OH,R_3=OMe
209 R_1=Glu,R_2=OH,R_3=OMe



222 R=Rha
223 R=H



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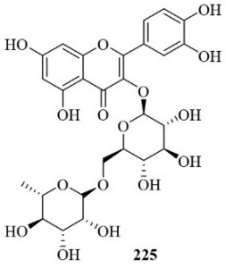

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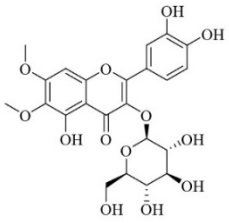

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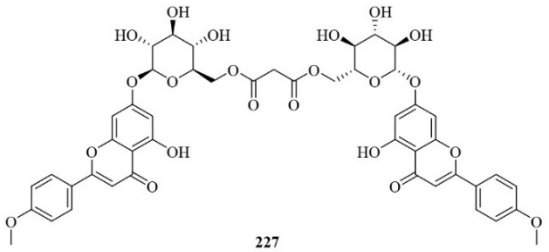

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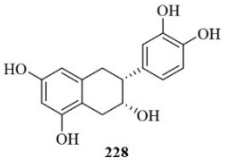

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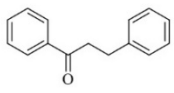

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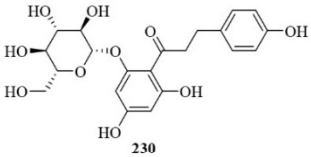

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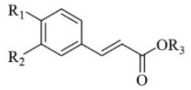
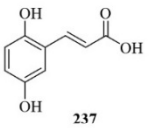


231 R_1=H,R_2=H,R_3=H
232 R_1=OH,R_2=H,R_3=H
233 R_1=OH,R_2=OH,R_3=H
234 R_1=OH,R_2=OH,R_3=Me
235 R_1=OH,R_2=OH,R_3=Et
236 R_1=OH,R_2=OMe,R_3=H



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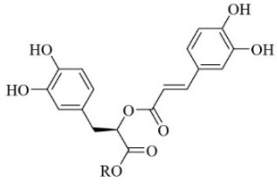
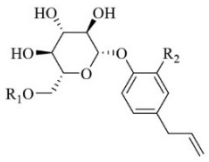
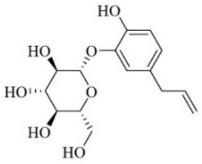


238 R=H
239 R=Me
240 R=Et



241 R_1=H,R_2=H
242 R_1=H,R_2=OH
243 R_1=Acetyl,R_2=H
244 R_1=Methylmalony,R_2=H



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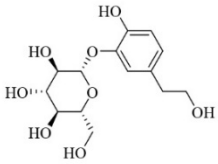

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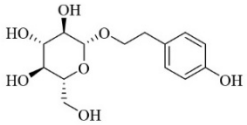

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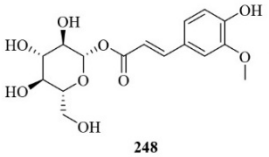

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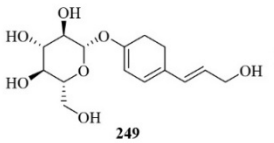

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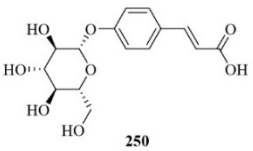

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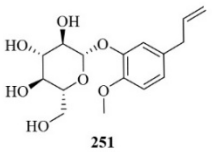

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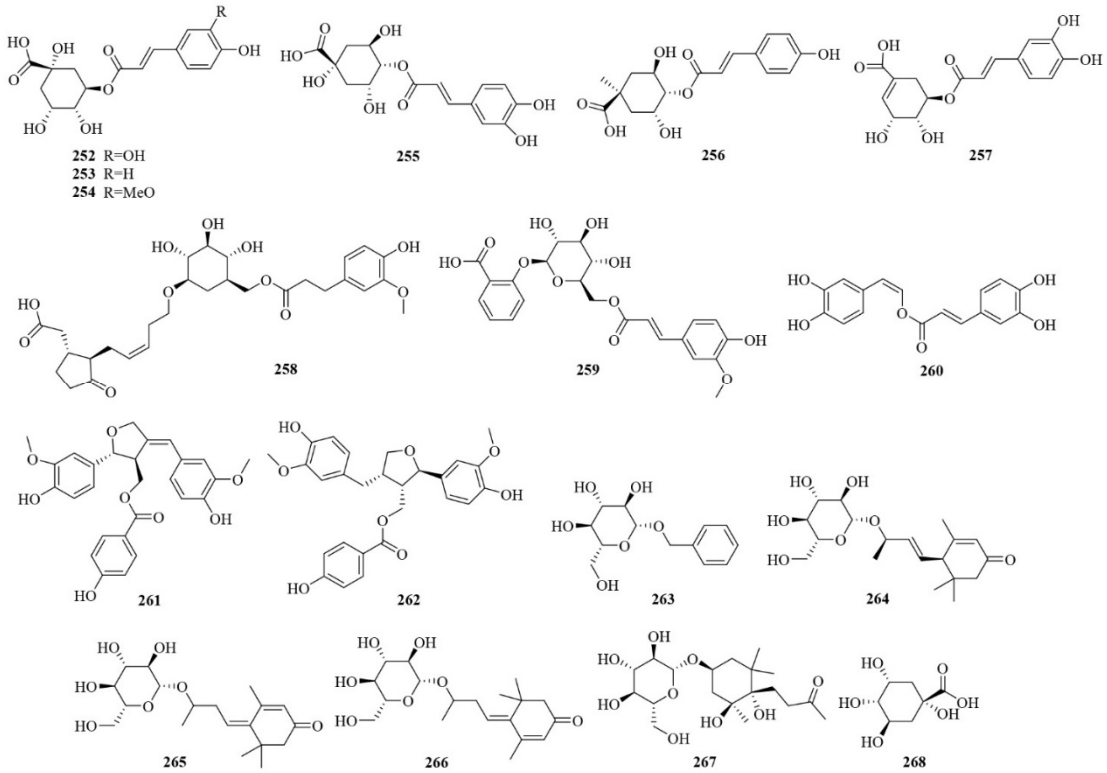

Figure 2 Polyphenols from *A. rugosa.*

A total of 32 distinct flavonoids (No. **199-230**) have been identified in *A. rugosa*, predominantly comprising flavones and flavonols, along with dihydroflavonoids and flavonoid glycosides. The aqueous extract contains total flavonoids at (22.8 ± 7.6) mg/g, dominated by 7-*O*-glycosylated flavones (e.g., acacetin derivatives) and 3-*O*-glycosylated flavonols (e.g., kaempferol and quercetin derivatives). Glucosides and rutinosides represent the predominant glycosidic forms, with certain compounds exhibiting acetylated or malonylated modifications [5]. These acylated derivatives are particularly important for phytochemical classification and investigations into biological activity. Functioning primarily as storage forms within plants, they can be hydrolyzed under specific conditions to release bioactive aglycones. In contrast, organic solvent extracts are enriched in free flavonoid aglycones, alongside methylated or prenylated flavonoids. These constituents display higher lipophilicity and potentially stronger direct bioactivity. The *A. rugosa* flower is the part with the highest overall concentration of flavonoids, especially tilianin (**220**) and acacetin (**200**), followed by leaves, stems, and roots [9, 32]. Tilianin (**220**) and acacetin (**200**) serve as the primary bioactive constituents of *A. rugosa*, including anti-inflammatory, antioxidant, anti-adipogenesis, and anticoagulant properties.

The leaves of *A. rugosa* are particularly rich in phenylpropanoids. Rosmarinic acid (**238**) is a common constituent in plants of the Lamiaceae family. Structurally, it consists of a catechol structure and a caffeic acyl group, which contributes to its antioxidant properties and tendency to undergo polymerization. In *A. rugosa*, rosmarinic acid (**238**) is recognized as the primary determinant of antioxidant activity. Research has demonstrated that its concentration rises substantially as the plant reaches maturity and progresses through the growing season. Notably, studies have revealed that two-year-old *A. rugosa* plants exhibit the highest levels of this bioactive compound [33, 34]. Additionally, varying lighting conditions (such as white fluorescent lamps

or a hybrid setup combining white and photosynthetically active radiation LEDs), along with the addition of amino acids, can significantly enhance the production of rosmarinic acid [35]. Furthermore, several rosmarinic acid derivatives were successfully isolated, including methyl rosmarinate (**239**) and ethyl rosmarinate (**240**). Caffeyl quinic acid components (**252**-**257**) are also important antioxidant component groups. The presence of agastenol (**261**) and agastinol (**262**) which are structurally complex phenylpropane dimers, serves as a distinctive chemical marker for species within the *Agastaceae* genus.

2.2.2 Terpenoids

In addition to its monoterpene and sesquiterpene constituents, *A. rugosa* also contains diterpenes and triterpenes. The diterpenoid profile of *A. rugosa* is predominantly composed of abietane-type compounds (**269-275**), clerodane-type diterpenoid (longikaurin D, **276**) and kaurane-type diterpenoid (methylagastanol, **277**). Triterpenoids are mainly characterized by oleanane-type (**278-283**) and structurally unique ursane-type structures (**284-288**). Notably, two novel ursane-type triterpenoids, agasursacid A (**287**) and agasursacid B (**288)**, were recently identified in this species, both characterized by unique acetyloxyaldehyde-modified structures [36]. For details, please refer to **Table 3** and **Figure 3**. These terpenoid components are mainly concentrated in the root system, while longikaurin D (**276**) is isolated from the aboveground parts (branches and leaves), and agasursacid A (**287**) and agasursacid B (**288**) are obtained from the whole plant [36-39]. Terpenoids exhibit diverse biological activities, and current research indicates that *A. rugosa* terpenoids demonstrate broad-spectrum nonspecific cytotoxicity. However, their therapeutic potential warrants further exploration [40].

Table 3 Terpenoids from *A. rugosa.*

Type	No.	Component	Refs.	No.	Component	Refs.
Diterpenoid	**269**	10-Hydroxy-3-methoxy-8,8-dimethyl-2-(1-methylethyl)-1,4,7(8*H*)-phenanthrenetrione 7-oxime	[40]	**274**	15-Hydroxy-agastol	[61]
	270	Agastol	[37]	**275**	Agastanone	[37]
	271	Isoagastol	[38]	**276**	Longikaurin D	[39]
	272	Dehydroagastol	[37]	**277**	Methylagastanol	[37]
	273	Agastaquinone	[40]			
Triterpene	**278**	Oleanolic acid	[62]	**284**	Ursolic acid	[51]
	279	3-*O*-Acetyl oleanolic aldehyde	[62]	**285**	Euscaphic acid	[15]
	280	Maslinic acid	[62]	**286**	Corosolic acid	[63]
	281	3*β*-Acetoxyolean-12-en-28-aldehyde	[62]	**287**	Agasursacid A	[36]
	282	Erythrodiol 3-acetate	[64]	**288**	Agasursacid B	[36]
	283	Oleanolic acid acetate	[65]			

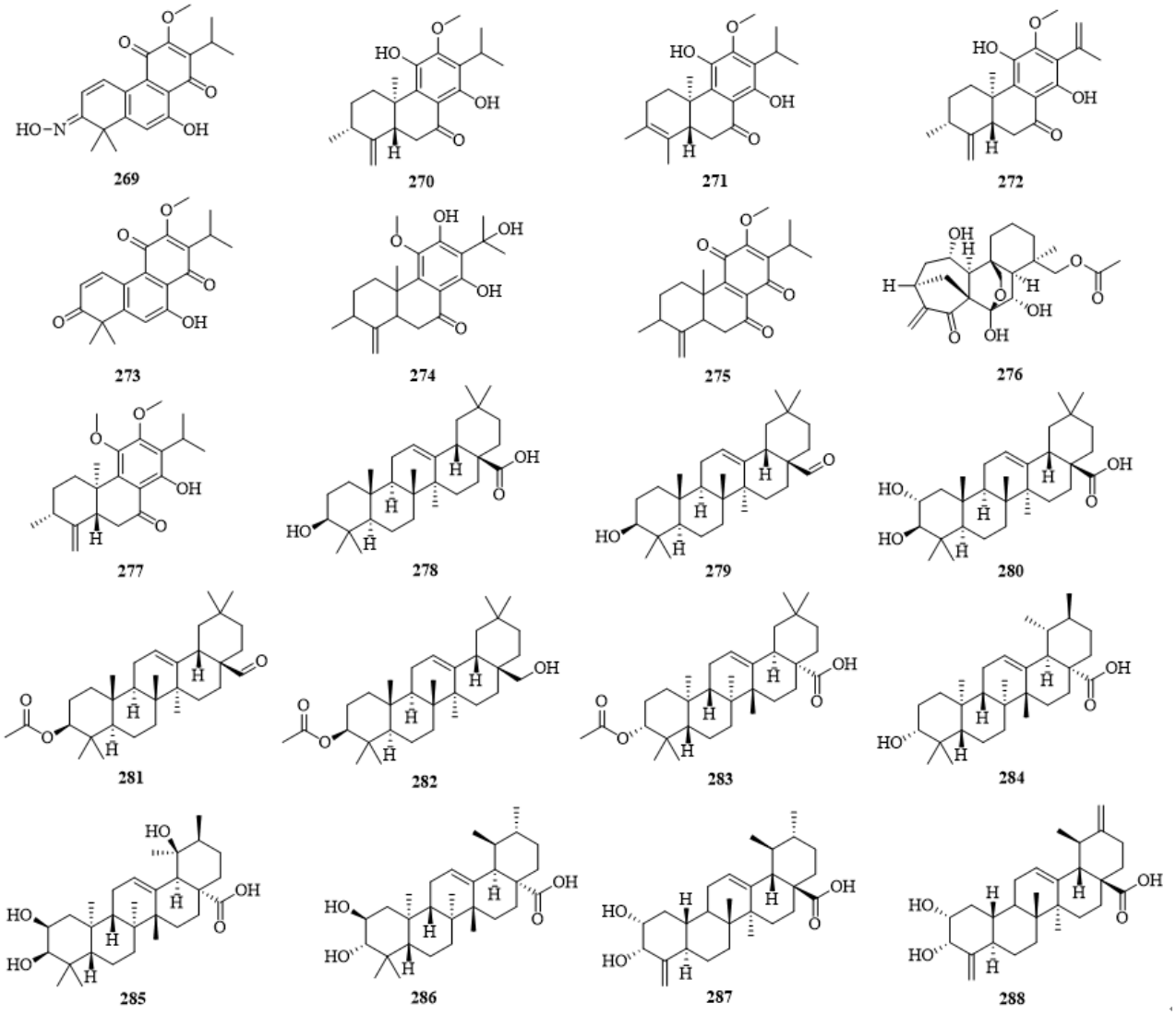

Figure 3 Terpenoids from *A. rugosa.*

2.3 Others

2.3.1 Steroids

A. rugosa contains steroid components including *β*-sitosterol (**289**) and daucosterol (**290**), both belonging to phytosterols with a basic cholesterane structure [51, 62]. The specific chemical structures are shown in **Figure 4**.

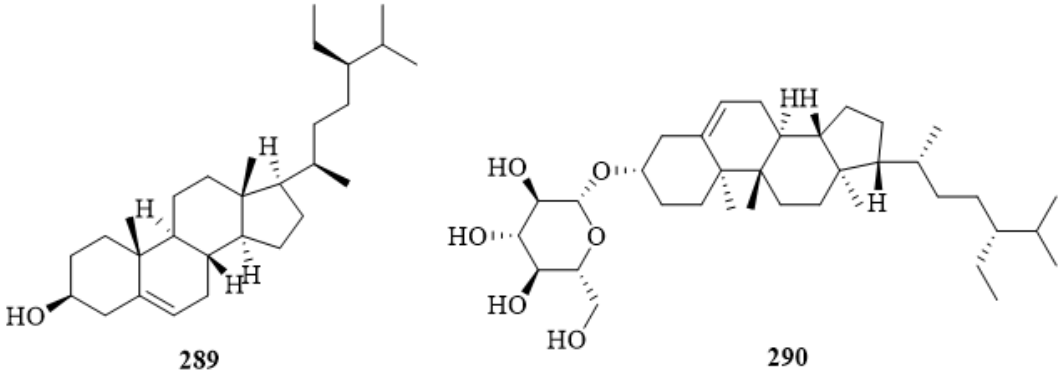

Figure 4 Steroid components from *A. rugosa.*

2.3.2 Carotenoids

Carotenoids, including violaxanthin (**291**), antheraxanthin (**292**), lutein (**293**), zeaxanthin (**294**), α-carotene (**295**), β-carotene (**296**), and β-cryptoxanthin (**297**), were extracted from *A. rugosa* plants, and their structures are shown in **Figure 5**[66, 67]. The concentration of carotenoids in the leaves of *A. rugosa* was found to be significantly higher than that in the stems, flowers, and roots [66].

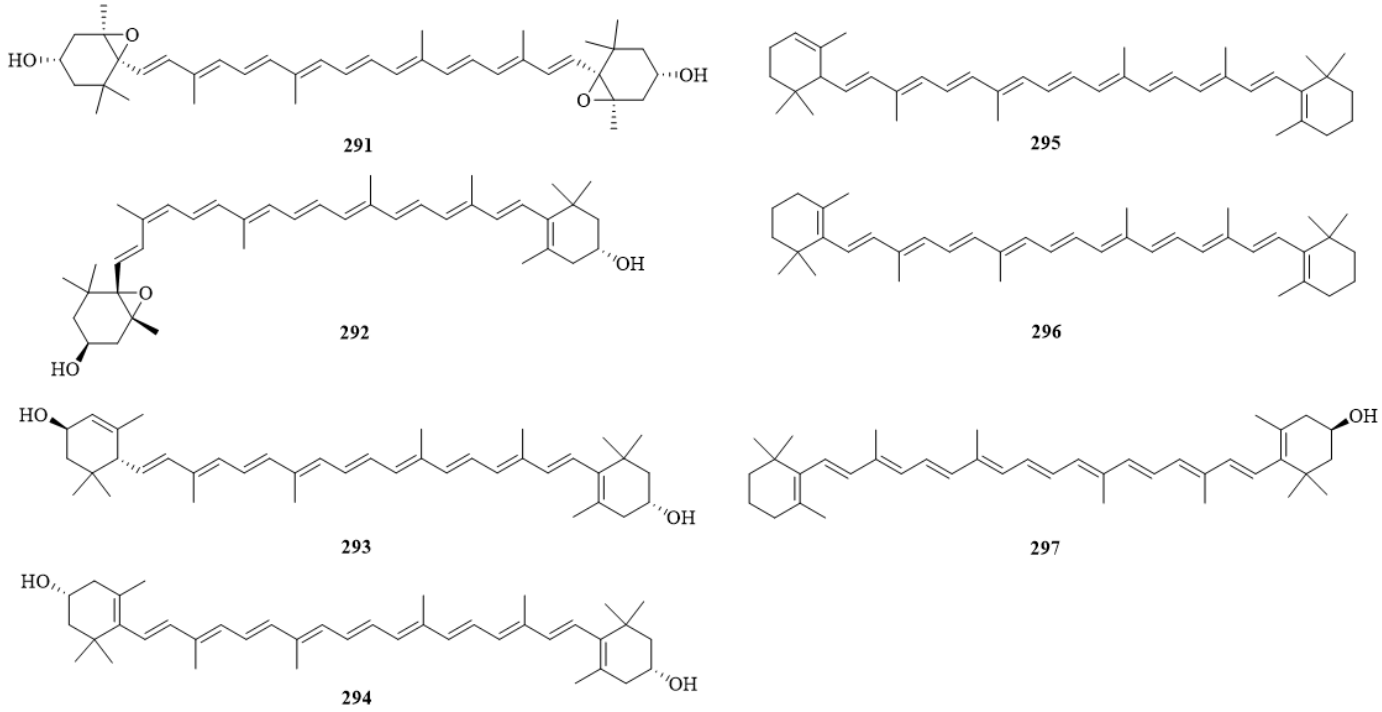

Figure 5 Carotenoids from *A. rugosa.*

3. Health benefits and mechanism of *A. rugosa*

3.1 Regulating gastrointestinal function

A. rugosa, a traditional herb with a long history of use, is commonly employed to treat gastrointestinal disorders. Traditional Chinese Medicine posits that it exerts its therapeutic effects by drying dampness and regulating qi movement [68]. To investigate the regulatory effect of *A. rugosa* on the gastrointestinal tract, researchers conducted experiments using various mouse models (**Table 4**).

Table 4 Effects of *A. rugosa* on gastrointestinal motility in different models.

Model	Administration	Results		Refs.
		Morphological & histological change	Blood & fluid	
ICR mice	*A. rugosa* aqueous extract (0.3 g/kg)	Gastric motility↑	—	[68]
Wistar rats	*A. rugosa* aqueous extract (2.5 g/kg)	Intestinal submucosa and myenteric nerve plexus of jejunum and ileum NOS1 expression↓	—	[69]
SPF grade KM mice	*A. rugosa* aqueous extract (4.5 g/kg, 2.25 g/kg)	Gastric emptying↑ Intestinal movement↓	D-Xylose↑	[70]
SPF grade KM mice	*A. rugosa* volatile oil extract (4.5 g/kg, 2.25 g/kg)	Gastric emptying↑ Intestinal movement↓	D-Xylose↑	[70]
SPF grade KM mice	*A. rugosa* non-volatile extract (2.248 g/kg, 1.124 g/kg)	Gastric emptying↑ Intestinal movement↓	D-Xylose↑	[70]

SPF grade KM mice with gastrointestinal motility disorders	*A. rugosa* aqueous extract (2.25g/kg)	Gastric emptying↑ Intestinal movement↑	D-Xylose↑ Gastrin↑ Motilin↑	[71]
ICR mice with intestinal motility suppression	*A. rugosa* aqueous extract (0.1 g/kg, 0.025 g/kg)	Intestinal movement↑	—	[72]
HCl/EtOH induced mucosal damage in C57BL6 mice	*A. rugosa* ethanol extract (0.1 g/kg)	Ulcers and bleeding erosion↓ Gastric mucous secretion↑	—	[55]
HCl/EtOH induced Gastric Mucosal Gastritis in C57BL6 mice	*A. rugosa* total extracts and volatile oil (0.2 g/kg, 0.1 g/kg)	Hemorrhagic bands and ulcer formation↓	COX-2↓	[73]

Comparative analysis across experimental models demonstrated the following: In healthy mice, *A. rugosa* significantly enhances gastrointestinal motility by accelerating gastric emptying and stimulating intestinal peristalsis [68-70]. Conversely, in pathological models, it ameliorates functional disorders. Specifically, in dysmotility models, bioactive extracts of *A. rugosa* promote gastric emptying and enhance intestinal motility. In gastritis-induced models, it exerts protective effects by upregulating gastric mucus secretion while suppressing key pro-inflammatory mediators, including cyclooxygenase-2 (COX-2), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). Additionally, it mitigates inflammatory cell infiltration, thereby preserving gastric mucosal integrity [55, 71-73]. Furthermore, a comparative analysis of various extracts revealed that the aqueous extract exerts a bidirectional regulatory effect on intestinal motility-lower concentrations enhance motility, whereas higher concentrations may exert an inhibitory effect. The ethanolic extract exhibited notably pronounced therapeutic potential in experimental gastritis models.

Molecular investigations have demonstrated that *A. rugosa* mediates gastroprotection through a multi-component, multi-pathway regulatory network. Network pharmacology analysis identified 99 of its constituents (e.g., acacetin, **200**; luteolin, **201**) associated with gastritis treatment. These active compounds function by suppressing the expression of pro-inflammatory mediators such as IL-1β, TNF-α, COX-2, and nitric oxide synthase (iNOS) [55, 73]. Collectively, *A. rugosa* achieves gastrointestinal homeostasis via multi-target regulation, simultaneously modulating neural pathways, hormonal pathways, and immune pathways.

3.2 Anti-photoaging activity

A. rugosa demonstrates significant efficacy in mitigating photoaging-induced skin damage, including wrinkles, epidermal thickening, erythema, pigmentation, and surface roughness. Additionally, it enhances skin hydration by reducing transepidermal water loss and improving moisture retention. The research finds that *A. rugosa* aqueous extract can participate in anti-photoaging by promoting the expression of antioxidant enzyme mRNAs and blocking NF-κB expression, thereby playing an antioxidant and anti-inflammatory role in the anti-photoaging effect [74]. It also inhibits UVB-induced activation of MAPK and activating protein 1 (AP-1) (c-fos), leading to the downregulation of proMMP-1, -2, and -9 expression, which are responsible for collagen degradation [75, 76]. By stimulating the TGF-β/Smad signaling pathway, *A. rugosa* aqueous extract increases the mRNA levels of upregulated hyaluronic acid synthase and collagen-related Col1a1, Col3a1, and Col4a1 genes, thus increasing hyaluronic acid and collagen expression, respectively [5, 31, 75, 77, 78]. In

addition, both aqueous and ethanol extracts of *A. rugosa* can decrease filaggrin and caspase-14 in HaCaT keratinocytes after UVB radiation and inhibit elastase and hyaluronidase related to the skin aging process [76, 79]. A comprehensive illustration of these pharmacological mechanisms is provided in **Figure 6**.

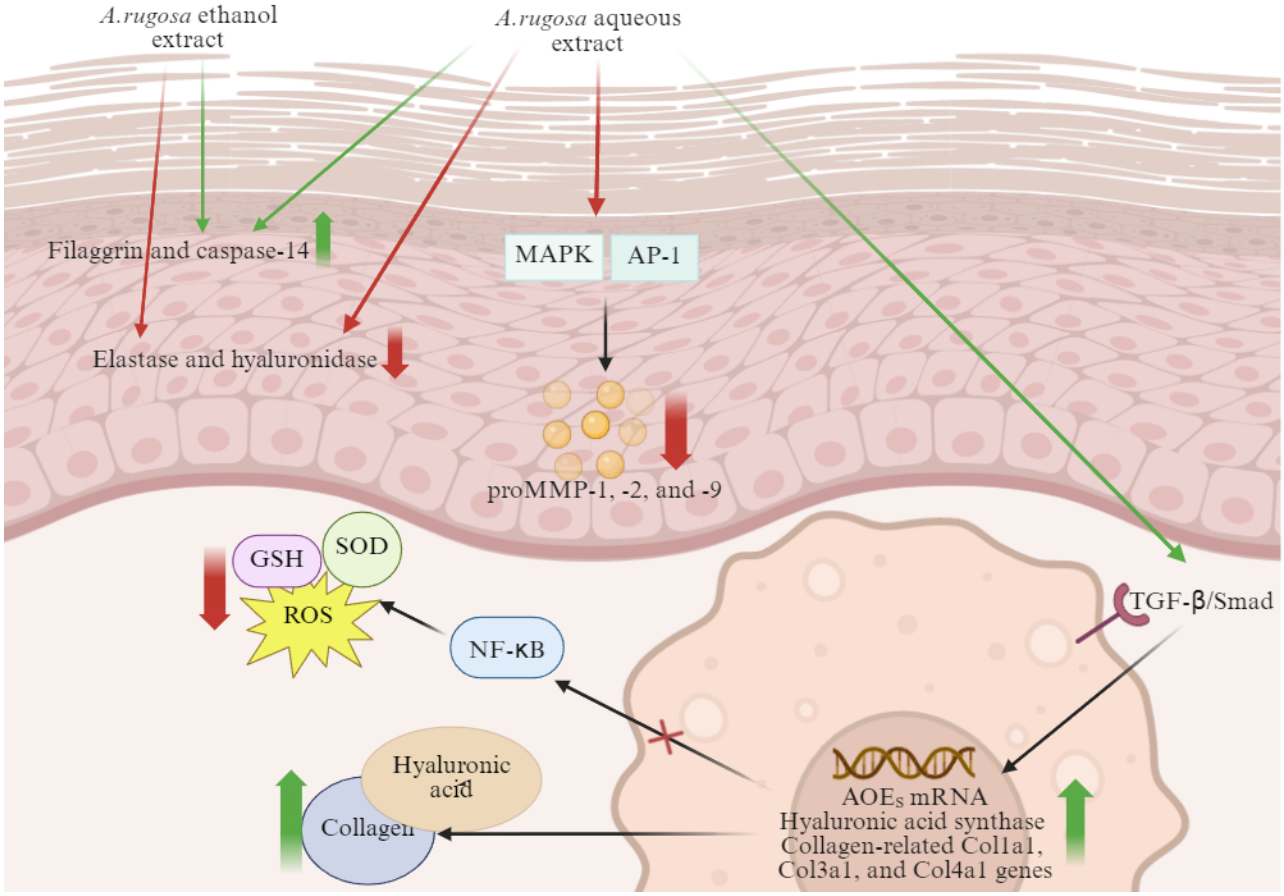

Figure 6 Anti-photoaging mechanism of *A. rugosa.*

These pharmacological characteristics position *A. rugosa* as a promising candidate for dermo-cosmetic applications. Probiotic bacterial fermentation plays a crucial role in cosmetic technologies, aiding in reducing the potential toxicities of cosmetic ingredients, promoting better absorption into the skin through modifications in their molecular compositions, and enhancing their beneficial pharmacological properties. Fermenting the leaves with probiotics further improved the activity levels of total glutathione (GSH) and superoxide dismutase (SOD), which were decreased by UVB, enhancing the anti-photoaging property and improving the therapeutic and cosmetic value of *A. rugosa* [76, 80]. Combining *A. rugosa* with other drugs can enhance its therapeutic effects. When combined with *Prunus persica* L., *Nelumbo nucifera*, *Hibiscus mutabilis* L., and *Wolfiporia extensa*, *A. rugosa* can boost collagen production and effectively reduce skin wrinkles [81]. The combination of *A. rugosa* and *Centella Asiatica* has a protective effect on UVB-damaged human skin fibroblasts (Hs68 cells) [79]. Nevertheless, further in-depth research is required to comprehensively analyze the anti-photoaging compounds present in *A. rugosa*. Identifying safe and efficacious bioactive agents will facilitate the development of sustainable, plant-derived cosmetic formulations, thereby aligning with the growing consumer demand for eco-friendly and natural skincare solutions.

3.3 Anti-inflammatory activity

Inflammation is characterized by redness, swelling, warmth, and pain at infection sites, representing a protective response to harmful stimuli. Research has established that *A. rugosa* extracts and their principal bioactive constituents exhibit pronounced and multifaceted anti-inflammatory properties, as summarized in **Table 5**. The volatile oil, aqueous extract, and ethanol extract significantly inhibit the expression of key pro-inflammatory cytokines, including TNF-α, interleukin-6 (IL-6), and interleukin-8 (IL-8), while downregulating the key inflammatory enzyme COX-2 and inhibiting inducible iNOS production, thereby reducing nitric oxide (NO) levels. The volatile oil, which is abundant in terpenoid compounds, exhibits high bioavailability and tissue permeability, enabling direct inhibition of COX-2 and IL-1β. This mechanism makes it particularly effective in managing localized inflammatory conditions like arthritis. The hydrophilic components (such as polysaccharides) in the aqueous extract repair the epidermal barrier, reduce IL-8, promote keratinocyte migration, and repair skin ultraviolet damage. Ethanol extract enriches multiple types of active ingredients and synergistically inhibits the NF-κB pathway, which can be used for systemic inflammation [44, 77, 82-84].

Table 5 Anti-inflammation activity of *A. rugosa.*

Tested substance/drug	Model	Type	Efficient doses and administration route	Results	Refs.
The volatile oil of *A. rugosa*	Male mice, subcutaneous injection of CFA induced arthritis	*In vivo*	100 mg/kg subcutaneous injection	COX-2↓, IL-1β↓, IL-6↓, TNF-α↓	[44]
A. rugosa ethanol extract	Flp-In 293 cells	*In vitro*	300 μg/mL	Selectively activated hTRPA1 and hTRPV1	[43]
A. rugosa ethanol extract	The RAW 264.7 mouse macrophage cells	*In vitro*	25, 50 and 100 μg/mL	NF-κB signaling pathway↓, NO↓, IL-1β↓, iNOS↓, COX-2↓	[84]
Compounds isolated from the ethanol extract of aerial parts of *A. rugosa*	The RAW 264.7 mouse macrophage cells	*In vitro*	—	PGE_2↓	[53]
Ethyl acetate fraction from ethanol extract of *A. rugosa*	LPS-stimulated BV-2 microglia	*In vitro*	25 μg/mL	iNOS↓, IL-6↓	[82]
A. rugosa aqueous extract	UVB-exposed HS68 cells	*In vitro*	10 and 20 μg/mL	IL-1β↓, IL-6↓, IL-8↓	[77]
Non-fermented and fermented aqueous extracts of *A. rugosa*	HaCaT keratinocyte cells	*In vitro*	5, 20 and 80 μg/mL	NO↓, ROS↓, iNOS↓	[83]

Genistein (**207**) and chavicol-1-*O*-(6′-*O*-methylmalonyl)-*β*-D-glucopyranoside (**244**), isolated from the ethanol extract of *A. rugosa*, inhibit LPS-induced PGE_2 synthesis with IC_{50} values of (16.8 ± 0.8) μmol/L and (14.3 ± 2.1) μmol/L, respectively [53]. Common compounds in *A. rugosa* include acacetin (**200**), L-carveol (**20**), *β*-caryophyllene (**61**), methyl eugenol (**123**), and rosmarinic acid (**238**), which can activate TRPA1/TRPV1 receptors *in vitro*. These receptors mediate pain and inflammation, and their agonists hold anti-inflammatory potential [43]. The anti-inflammatory intensity of these active ingredients is directly related to their characteristic functional groups: the 4'-methoxy group of flavonoids (such as acacetin, **200**) enhances membrane permeability and can reduce TNF-α by inhibiting the TLR4/NF-κB pathway. The bicyclic rigid

structure of terpenes (such as *β*-Caryophyllene, **61**) precisely binds to TLR4/RAGE, blocking inflammatory signal transduction. Phenylpropanin glycosides (such as chavicol-1-*O*-(6′-*O*-methylmalonyl)-*β*-D-glucopyranoside, **244**) increase the cellular uptake rate through malonate modification and target the inhibition of COX-2 active centers.

3.4 Antioxidant activity

Desta evaluated the antioxidant activity of various parts of *A. rugosa* using the DPPH free radical scavenging assay, 2, 2-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) free radical scavenging assay, reducing power assay, and Fe^{2+} chelating activity. The results showed that the stem of *A. rugosa* exhibited the highest antioxidant activity. Specifically, the antioxidant activity followed the order of stems > leaves > flowers > roots [32]. However, Park et al. demonstrated superior antioxidant activity in flowers compared to leaves and stems through superoxide and hydrogen peroxide radical scavenging assays [9]. Among them, the total phenol content in flowers is the highest. Phenolic substances are excellent donors of electrons or hydrogen atoms. Due to the low reactivity of the phenolic radical intermediates produced and the lack of molecular oxygen attack sites, they can act as effective antioxidants [85]. This explains why *A. rugosa* flowers have a greater antioxidant effect than leaves and stems. In addition, the dynamic analysis of the flowering period shows that the full flowering stage contains the peak level of anthocyanins, showing significantly higher antioxidant activity than that of the flower bud stage and partially open flowering stage [52]. The DPPH inhibition, ABTS, ORAC, and FRAP values of *A. rugosa* honey were found to be (9.85 ± 1.98) μmol TE/g, (26.88 ± 0.32) μmol TE/g, (19.78 ± 1.1) μmol TE/g, and (3.61 ± 0.02) μmol TE/g, respectively. Its significant antioxidant capacity was significantly positively correlated with the total phenol content [86]. The DPPH free radical scavenging activity of the volatile oil of *A. rugosa* (IC_{50} = 8.79 μg/mL) was superior to that of trolox C (IC_{50} = 13.80 μg/mL) [44], which might be attributed to the abundant phenylpropanoid structural components in *A. rugosa* contributing to the activity [87]. Molecular mechanism studies have shown that *A. rugosa* induces the high expression of heme oxygenase-1 (HO-1) by activating protein kinase G (PKG), thereby resisting oxidative stress damage caused by H_2O_2. This is one of the key pathways for the antioxidant effect of *A. rugosa* [6, 88].

3.5 Antimicrobial activity

The volatile oils extracted from *A. rugosa* flowers and leaves demonstrate significant biofilm-inhibitory effects. Specifically, the volatile oil from *A. rugosa* flowers exhibits strong antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (*E. coli*), while the volatile oil from *A. rugosa* leaves shows antibacterial activity against *E. coli* [10, 42]. Furthermore, the strong inhibitory effect of *A. rugosa* volatile oil on *Staphylococcus aureus* sub. aures, *E. coli*, *Salmonella enteritidis*, and *Pseudomonas aeruginosa* are associated with estragole (**119**), and a few terpenoids, including limonene (**14**), linalool (**3**), *β*-caryophyllene (**61**), and germacrene D (**56)** [24]. Shin et al. found that estragole (**119**) had antifungal activity against *Aspergillus and Candida* species (with MICs ranging from 2.5 to 10 mg/mL) [89]. *A. rugosa* volatile oil and

its major constituent estragole (**119**) also exhibited antifungal activity against *Blastoschizomyces capitatus*, *Trichophyton* species, and showed synergistic antibacterial effects with ketoconazole [26, 27].

Polyphenolic compounds represent one of the primary contributors to the antioxidant activity observed in *A. rugosa*. Studies have shown that plants with higher levels of rosmarinic acid (**238**) and total phenolics have superior antimicrobial activity [90]. A comparative analysis of methanol extracts obtained from *A. rugosa* demonstrated that floral-derived extracts exhibit superior antimicrobial activity compared to those extracted from the stems and leaves. This enhanced efficacy correlates with the higher phenolic content present in the flower extracts. Among the tested bacterial strains, the floral extracts displayed the strongest inhibitory effect against *E. coli*, followed by *Aeromonas hydrophila*, *Staphylococcus haemolyticus*, and *Aeromonas salmonicida* [9].

Aside from the *A. rugosa* plant itself, *A. rugosa* honey also possesses antimicrobial activity. *A. rugosa* honey shows strong antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *E. coli* [91, 92]. *A. rugosa* honey also demonstrated antifungal activity against skin fungi (*T. mentagrophytes* and *T. rubrum*) and *C. albicans* in Agar Well Diffusion (AWD) and Micro Dilution (MD) assays. This suggests that *A. rugosa* honey could be developed for preventing skin infections from bacteria and wound care, but further *in vivo* and clinical studies are needed to confirm this supposition [12, 92].

3.6 Cytotoxic activity

A. rugosa volatile oil exhibits cytotoxic effects on various cancer cell lines. The volatile oil of *A. rugosa* has been shown to be cytotoxic against human prostate cancer cells (LNCaP) and mouse B16 melanoma cells (B16), with patchoulol (**111**) identified as a key anticancer component [47]. Studies have demonstrated that the volatile oil derived from *A. rugosa* leaves and flowers displays dose- and time-dependent cytotoxicity against the gastric cancer cell line SGC-7901, with the major components, estragole (**119**) and pulegone (**13**), exhibiting better inhibitory effects compared to 5-FU [42]. Additionally, *A. rugosa* volatile oil and its major components, including estragole (**119**), limonene (**14**), and anisaldehyde, have been found to inhibit the proliferation of various cancer cell lines such as human lung carcinoma cells (A549), human hepatocellular carcinoma cells (Hep3B), human gastric carcinoma cells (KATO 111), and human breast adenocarcinoma cells (MCF7), while also demonstrating anti-mutagenic effects [48]. Lashkari et al. suggest that the cytotoxicity of estragole (**119**) may be attributed to its ability to induce apoptosis, characterized by nuclear fragmentation, chromatin condensation, and disruption of cell membrane integrity [93]. Moreover, the volatile oil has shown significant cytotoxic activity against MDA-MB-231 and HEPG2 tumor cell lines, indicating a synergistic effect between the compounds [48].

Non-volatile components of *A. rugosa* have also demonstrated cytotoxic properties. The diterpene agastaquinone (**273**), isolated from *A. rugosa* roots, exhibited non-specific cytotoxic activity against human cancer cell lines, including ovarian cancer (SK OV-3), melanoma (SKMEL-2), central nervous system carcinoma (XF498), and colon cancer (HCT15) [40]. Additionally, the lignans agastenol (**261**) and agastinol (**262**) inhibited apoptosis in U937 leukemia cells, with IC_{50} values of 11.4 and 15.2 mg/mL, respectively [94].

3.7 Anti-osteoporotic activity

Various extracts derived from *A. rugosa* demonstrated significant potential in combating osteoporosis, with the underlying mechanism illustrated in **Figure 7**. The ethanol extract of *A. rugosa* has been shown to have therapeutic effects on postmenopausal osteoporosis by activating the bone morphogenetic protein, TGF-β, and the Wnt signaling pathway. Recent research suggested a connection between gut microbiota and bone health, indicating that alterations in gut microbiota could play a role in enhancing bone health in individuals with estrogen-deficient osteoporosis [32]. Hong et al. found that *A. rugosa* ethanol extract could inhibit bone loss by improving the diversity of gut microbiota [95]. *A. rugosa* extract can mitigate OVX-induced bone loss and bone marrow fat accumulation, interfere with the early RANK signaling pathway of osteoclast precursors, suppress the expression of c-Fos and NFATc1, and thus hinder the formation of osteoclasts. These effects are attributed to the bioactive components in *A. rugosa*, such as rosmarinic acid (**238**), tilianin (**220**), luteolin (**201**), and apigenin (**199**), which possess anti-osteoclast activity [1]. NO may play a role in mediating cytokine-induced bone turnover and is considered a key factor in bone remodeling, including osteoblast apoptosis in arthritic joints. The methanol extract of *A. rugosa* leaves has been shown to significantly and dose-dependently reduce the expression of iNOS activated by a TNF-α and IL-1β mixture, inhibit the activation and translocation of NF-κB from cytoplasmic components to the nucleus, and markedly decrease the production of NO [96].

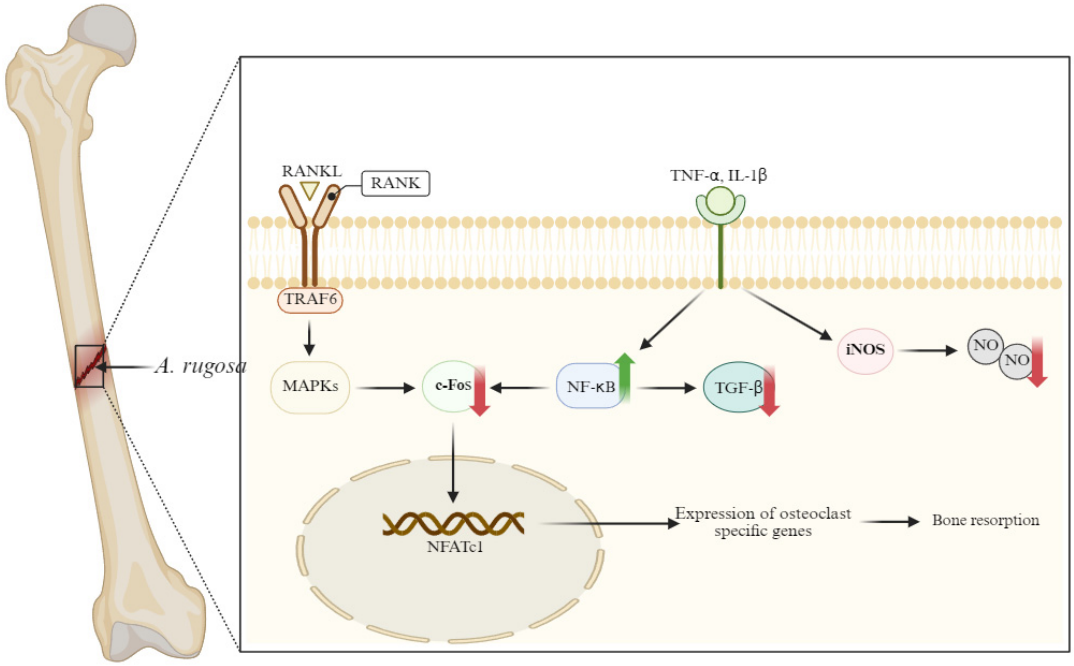

Figure 7 Anti-osteoporotic mechanism of *A. rugosa.*

3.8 Anti-obesity activity

Research indicates that some dietary herbs may aid in weight loss and exhibit potential therapeutic benefits for managing obesity [97]. *A. rugosa* contributes to obesity management through multiple mechanisms, including blood sugar regulation, inhibition of adipogenesis (fat cell formation), and suppression of appetite, thereby reducing overall food intake. Within *A. rugosa*, acacetin (**200**) plays a crucial role in

raising intracellular calcium levels, thus activating the CaMKII-AMPK pathway and facilitating the translocation of GLUT4 to enhance glucose absorption [98]. Rosmarinic acid (**238**), tilianin (**220**), agastachoside (**214**), and acacetin (**200**) may also be hypoglycemic components of *A. rugosa.* These hypoglycemic components involve target proteins associated with hypoglycemia, including PPAR-γ, DPP IV, glucokinase, *α*-glucosidase, SGLT2, aldose reductase, and corticosteroid 11-*β*-dehydrogenase [99]. The hypoglycemic effect of *A. rugosa* suggests that it has potential as a valuable candidate for an anti-diabetic medication (**Figure 8**).

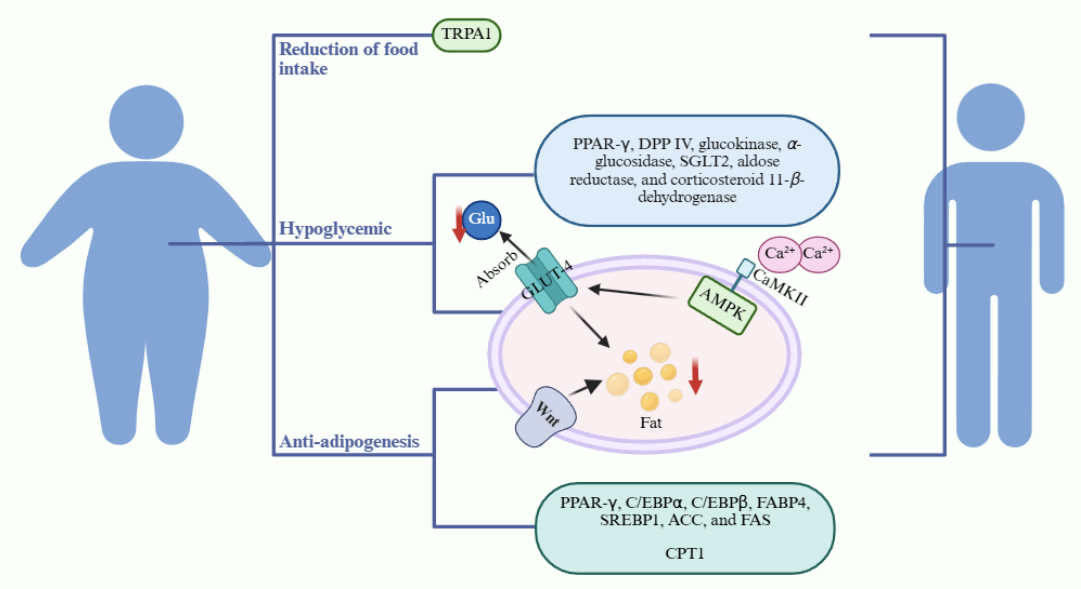

Figure 8 Anti-obesity mechanism of *A. rugosa.*

A. rugosa extract exhibits anti-lipogenic effects on 3T3-L1 adipocytes, primarily by downregulating genes related to fat production: PPAR-γ, C/EBPα, C/EBPβ, FABP4, SREBP1, Acetyl-CoA carboxylase (ACC), and FAS, while also increasing levels of the lipolytic factor carnitine palmitoyltransferase 1 (CPT1) [30, 100, 101]. Park et al. found that *A. rugosa* extract inhibited adipogenesis in 3T3-L1 adipocytes by activating the Wnt signaling pathway [100]. Kwon conducted research that revealed acacetin's (**200**) ability to activate AMP-activated protein kinase (AMPK), triggering the translocation of GLUT4 and effectively inhibiting the accumulation of lipids [98].

Research conducted by Kim et al. on obese mice induced by a high-fat diet demonstrated that administration of *A. rugosa* resulted in a decrease in food intake, inhibiting the increase in visceral fat weight and fat cell hypertrophy [101]. The pharmacological mechanism may involve the active ingredients in *A. rugosa* controlling gastrointestinal motility by activating TRPA1, enhancing secretion and peristaltic reflexes, and mediating the release of cholecystokinin from endocrine cells to delay gastric emptying and reduce food intake, ultimately contributing to the suppression of body weight [43, 102].

3.9 Neuroprotective activity

In aromatherapy, it has been shown that inhaling volatile oil from *A. rugosa* can stimulate the central nervous system, increase alertness and attention, enhance mental relaxation, and reduce stress and tension.

Exposure to the volatile oil of *A. rugosa* has been found to result in significant changes in EEG activity, with a decrease in absolute theta (AT) and relative theta (RT) power spectra, and an increase in relative alpha (RA), relative slow alpha (RSA), and alpha 50% spectral edge frequency (SEF50) power spectral values. Theta waves are associated with emotional processing, while alpha waves reflect brain inactivity and relaxation [103]. These findings suggest that *A. rugosa* volatile oil may have potential in the treatment of various psychophysiological disorders such as depression, anxiety, insomnia, and tension [21, 104].

The active compound acacetin (**200**) found in *A. rugosa* also demonstrated significant neuroprotective activity (shown in **Figure 9**). Acacetin (**200**) acts as a dual inhibitor of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), may restore the balance of monoamine neurotransmitters in the central nervous system by regulating their decomposition, which is beneficial for the treatment of depression, Parkinson's disease, Alzheimer's disease and anxiety disorders [105, 106]. Additionally, acacetin (**200**) has been shown to enhance the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK), activate the classical Ras/MAPK pathway, and induce neuronal genesis and differentiation. Acacetin (**200**) can also interfere with Beta-secretase 1 (BACE-1) activity and amyloid precursor protein (APP) synthesis, leading to a reduction in Aβ production and the number of APP [107].

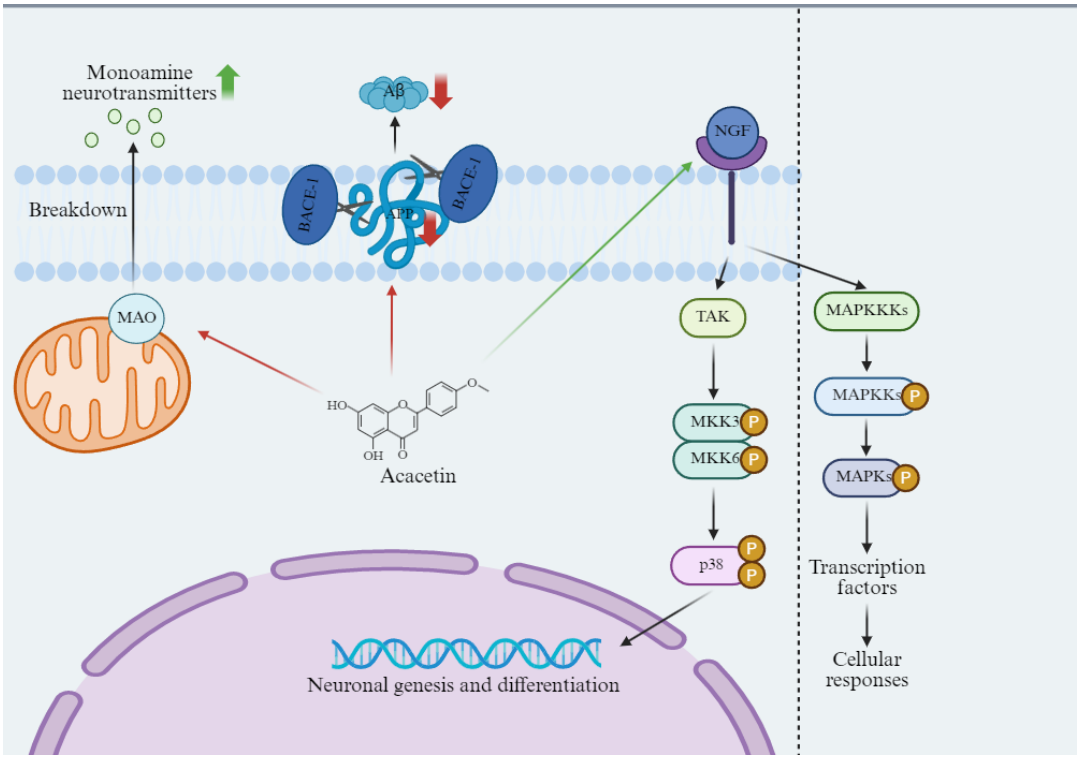

Figure 9 Neuroprotective activity of acacetin.

3.10 Liver protective activity

The various active components in *A. rugosa* exhibit liver protective effects, as shown in **Figure 10**. Cho utilized GalN/LPS-induced fulminant hepatic failure (FHF) mouse models to confirm the liver protective activity of acacetin (**200**) and *β*-caryophyllene (**61**). Acacetin (**200**) mitigated liver injury by reducing the production of the inflammatory cytokine TNF-α and promoting IL-6 levels to maintain hepatic homeostasis.

This protective mechanism involved inhibiting TLR4 signaling and enhancing autophagy flux. *β*-caryophyllene (**61**) protected against GalN/LPS-induced liver injury by down-regulating TLR4 and RAGE signaling pathways [47, 108]. Thymoquinone (**195**) can interfere with CYP2E1 activity, reduce alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and increase liver glutathione and glutathione peroxidase activity. Thymoquinone (**195**) can also inhibit the apoptosis of hepatocytes by suppressing MAPK phosphorylation and activating AMPK, thereby inhibiting the PI3K/mTOR signaling pathway. [54]. Tilianin (**220**) has an anti-lipogenesis effect, which could reduce lipid degeneration, improve the activity of antioxidant enzymes, inhibit the occurrence of inflammation, such as oxidative stress, and treat non-alcoholic fatty liver disease [30].

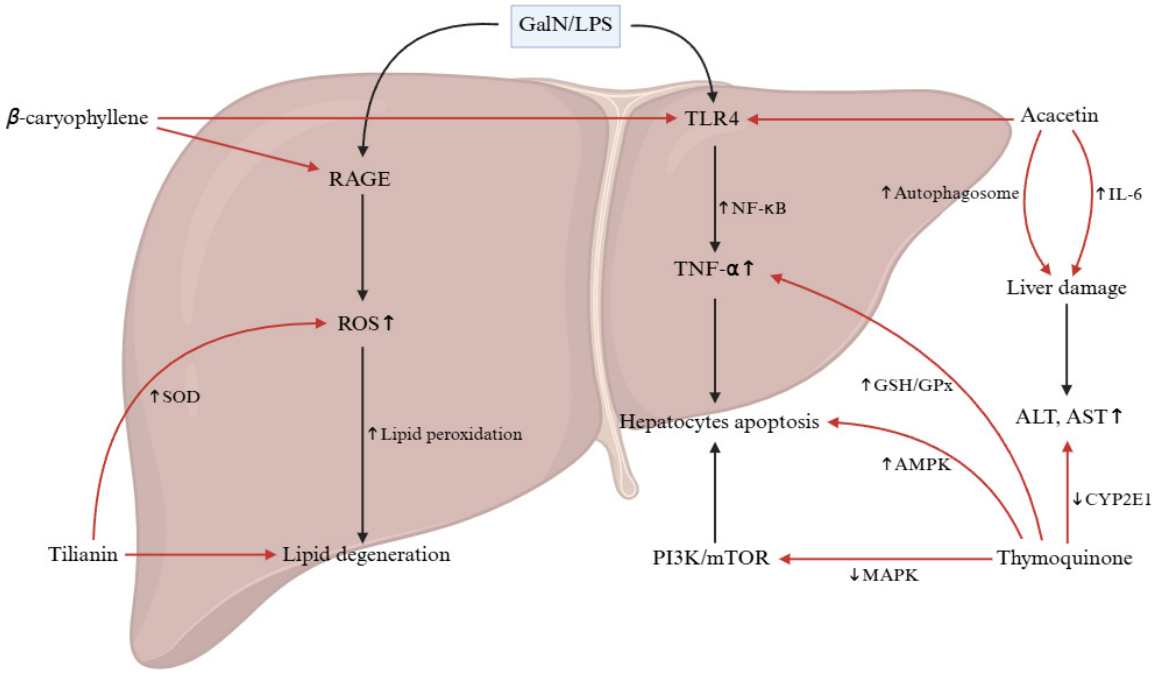

Figure 10 Liver protective activity of active components in *A. rugosa*.

3.11 Anti-atherosclerosis activity

The researchers observed a significant decrease in plasma cholesterol and triglyceride levels in mice following administration of *A. rugosa* extract, suggesting its promising role in atherosclerosis prevention. The potential molecular mechanism for the anti-atherosclerotic effects of *A. rugosa* involved up-regulation of the expression of $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ by the extract, leading to cell cycle arrest at the G0/G1 transition stage. This can inhibit the proliferation of aortic vascular smooth muscle cells (VSMC) and play an anti-atherosclerotic role *in vitro* [57]. One of the active ingredients in *A. rugosa* extract, tilianin (**220**), was found to inhibit TNF-α-induced VCAM-1 expression and NF-κB activation [109]. Additionally, *A. rugosa* volatile oil was shown to prevent atherosclerosis by inhibiting low density lipoprotein (LDL) oxidation, down-regulating the expression of SREBF-1, SREBF-2 and HMG-CoA reductase, and up-regulating the expression of the LDL receptor [17]. The mechanism of *A. rugosa* against atherosclerosis is shown below (**Figure 11**).

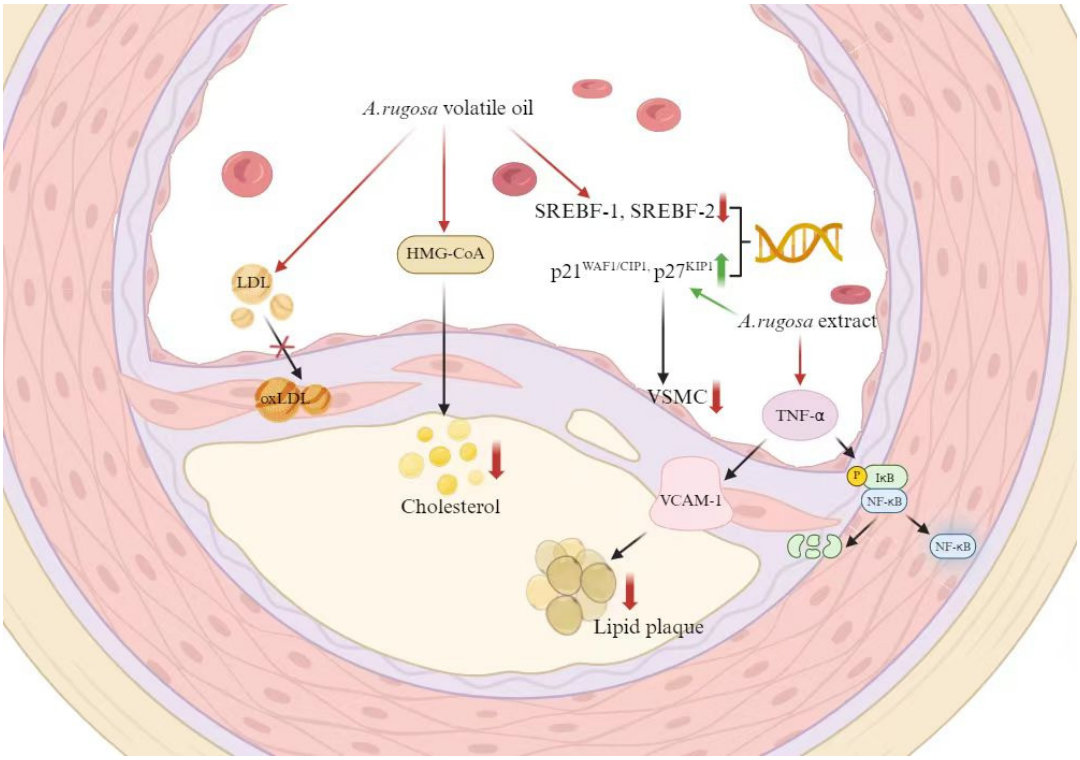

Figure 11 Liver protective mechanism of *A. rugosa.*

3.12 Impact on respiratory system

In a mouse model of asthma induced by house dust mites (HDM), tilianin (**220**) down-regulated IRF4 expression in dendritic cells to inhibit the Th2-immune response and reduce allergic inflammation. These findings will contribute to the development of tilianin (**220**) as a novel anti-asthma drug [110]. 4-methoxycinnamaldehyde (**125**) inhibited the entry of human respiratory syncytial virus (RSV) by interfering with viral attachment and internalization and may be helpful in the treatment of viral bronchiolitis [49]. Acacetin (**200**) and kaempferol (**203**) have shown good inhibition against coronavirus, making them potential candidates for the fight against COVID-19 [111]. By blocking the IL-17/STAT3 pathway and regulating the expression of inflammatory cytokines and CXCL-2, the Chinese herbal compounds *Glycyrrhiza glabra* and *A. rugosa* can effectively inhibit neutrophil airway inflammation and can be used in the treatment of chronic obstructive pulmonary disease (COPD) [112].

3.13 Other activities

Xanthine oxidase (XO) inhibitors, which block uric acid synthesis, can play an important role in the prevention of hyperuricemia [113]. The ethanol extract of *A. rugosa* demonstrated a strong inhibitory effect on XO (IC_{50} = 32.4 μg/mL), while acacetin (**200**) exhibited a potent inhibitory effect (IC_{50} = 0.58 μM), which may serve as a potential XO inhibitor [114]. Extraction of *A. rugosa* with hot water can enhance the immune response by promoting macrophage polarization, indicating that *A. rugosa* could be utilized as a natural immune booster or dietary supplement [115].

A. rugosa has been found to exhibit significant activity against human immunodeficiency virus (HIV) integrase, with its active component rosmarinic acid (**238**) demonstrating an IC_{50} against HIV integrase of

approximately 10 μg/mL. Acacetin (**200**) and tilianin (**220**) displayed notable anticoagulant activity by prolonging the activated partial thrombin time (APTT), prothrombin time (PT), and thrombin time (TT), as well as reducing the content of fibrinogen (FIB) [51].

4. Applications of *A. rugosa*

4.1 Edible value

As a versatile edible plant, the tender stems, leaves, and inflorescences of *A. rugosa* are rich in volatile oils, have a strong fragrance and are rich in nutrients, which can be directly used for cooking. *A. rugosa* can also be used for seasoning. As a seasoning in traditional dishes and an ingredient in soups, it can add aroma and flavor to various delicacies, and play a role in stimulating appetite, aiding digestion and enhancing appetite. *A. rugosa* can also effectively remove fishy smell, and in spicy and numbing spice formulas, it quietly plays an important role.

In the development of functional foods, *A. rugosa* oil serves as a viable substitute for artificial flavorings, functioning as a natural flavor enhancer in low-sodium health-conscious products. *A. rugosa*, along with dried tangerine peel, licorice liquid, peppermint oil, ginger juice, and other ingredients, can be made into a functional drink that integrates functions such as antibacterial, bad breath removal, stomach strengthening, and brain awakening [2]. In addition, the leaves of *A. rugosa* possess medicinal properties, making them suitable for herbal tea preparations that aid in fever reduction and heatstroke prevention. By utilizing the tender leaves of *A. rugosa* as raw materials and incorporating traditional Chinese medicinal herbs like *Atractylodes macrocephala* and *Pinellia ternata*, along with natural sweeteners such as honey and rock sugar dissolved in purified water, a functional *A. rugosa*-based drink can be formulated. This beverage offers therapeutic benefits, including heat clearance, thirst alleviation, throat hydration, summer heat relief, and detoxification [2]. *A. rugosa* honey is also a highly nutritious health product [12].

4.2 Medicinal value

A. rugosa was first recorded in the *Bencao Chengyabanjie* written by Lu Zhiyi during the Ming Dynasty. The *Diannan Bencao*, written by Lan Mao in the Ming Dynasty and later carved in the Qing Dynasty, also documented the use of *A. rugosa*. In addition, *A. rugosa* was mentioned in Ye Xiangyan's *Waiganwenrepian*, *Sanshifuqiwaiganpian*, Chen Pingbo's *Waiganwenbingpian*, Xue Shengbai's *Shirebingpian*, Lei Feng's *Shibinglun* and other works on febrile diseases [116]. These classic and renowned Chinese medicine texts describe *A. rugosa* as "tangy and lukewarm", and it was traditionally utilized in the treatment of cholera, vomiting, and miasma. For instance, *Zhiwuming Shitukao* mentioned that *A. rugosa*, as a summer medicine, is beneficial for conditions such as spleen and stomach vomiting, and cholera. In China, the utilization of *A. rugosa* is prevalent both on its own and in conjunction with other traditional Chinese medications. **Table 6** showcases typical traditional and contemporary formulas incorporating this herb. In the regions of north central and northern North America, indigenous people from various tribes traditionally used *A. rugosa* as a natural treatment for ailments such as coughs, fevers, wounds, and diarrhea [66]. Moreover, *A. rugosa* is listed

in the Korean Herbal Pharmacopoeia as a longstanding medicinal herb employed to alleviate conditions like anorexia, anxiety, bacterial infections, cholera, diarrhea, malaria, nausea, and vomiting [21, 52].

Table 6 The traditional and modern prescriptions of *A. rugosa* in China.

Name of the formula	Drug preparations details	Indications	Refs.
Huoxiang Zuojin Soup	*A. rugosa*, *Euodiae fructus*, *Citri reticulatae pericarpium*, *Poria*, *Akebiae caulis*, *Alismatis rhizoma*, *Aurantii fructus*, *Talcum*, *Polyporus*.	Infantile diarrhea	[116]
Qiwei Baizhu Powder	*A. rugosa*, *Panax ginseng*, *Atractylodes macrocephala*, *Poria cocos*, *Pueraria lobata*, *Costustroot*, *Glycyrrhiza uralensis*.	Seasonal epidemic	[119]
Xianghe Zhixie Decoction	*A. rugosa*, *Chebulae fructus*, *Puerariae lobatae*, *Poria*, *Crataegi fructus* and other traditional Chinese medicine.	Functional dyspepsia	[120]
Huo Pu Xia Ling Soup	*A. rugosa*, *Sojae semen*, *Magnoliae officinalis*, *Pinelliae rhizoma*, *Poria*, *Armeniacae semen amarum*, *Polyporus*, *Coicis semen*, *Alismatis rhizoma*, *Amomi fructus rotundus*.	Gastricism	[121]
Huashi Baidu prescription	*A. rugosa*, *Ephedrae herba*, *Armeniacae semen amarum*, *Gypsum fibrosum*, *Glycyrrhizae radix*, *Magnoliae officinalis*, *Atractylodis rhizoma*, *Tsaoko fructus*, *Pinelliae rhizoma praeparatum*, *Poria*, *Rhei radix*, *Astragali radix*, *Descurainiae semen*, *Paeoniae radix rubra*.	COVID-19	[122]
Qingfei Paidu Decoction	*A. rugosa*, *Ephedrae herba*, *Glycyrrhizae radix*, *Armeniacae semen amarum*, and so on. A total of 21 traditional Chinese medicines were included.	COVID-19	[123]
Ganghuo Kanggan Decoction	*A. rugosa*, *Carthami flos*, *Schizonepetae herba*, *Lonicerae Japonicae flos*.	Pneumonia	[124]

In the development of modern drugs, *A. rugosa* has demonstrated significant efficacy in regulating gastrointestinal functions and alleviating symptoms such as abdominal distension and vomiting. When combined with *Pinelliae rhizoma* and *Eupatorii herba*, its antiemetic properties are enhanced, making it a valuable component in clinical studies addressing chemotherapy-induced nausea. The volatile oil of *A. rugosa* has been purified for the development of antibacterial and anti-inflammatory drugs, including topical skin preparations and oral care products. By leveraging the volatility of the *A. rugose* volatile oil, sustained-release patches can also be designed for anxiety disorders or localized analgesia. *A. rugosa* exhibits diverse pharmacological properties and shows broad potential in both traditional and modern drug development. Future research should focus on bridging the gap between its historical use in "food and medicine homology" and modern "precision medicine" through technological innovation and rigorous clinical validation. This approach could offer natural, evidence-based solutions for chronic disease management, preventive healthcare, and overall wellness.

4.3 Other applications

A. rugosa exhibits anti-corrosion and antibacterial properties and is naturally non-toxic. The food industry can utilize it for the development and research of natural preservatives. The anti-inflammatory components in *A. rugosa* can be used as additives in face creams, eye creams, and the development of anti-wrinkle and anti-aging cosmetics that improve skin inflammation and fine lines [5, 31]. *A. rugosa* is rich in volatile oil, which holds potential application value in the extraction of aromatic oils and spices. It can be commercially cultivated and used in perfumery [9]. Due to its high insecticidal activity and minimal harm to the environment, *A. rugosa* essential oil can serve as an effective and safe plant insecticide [117].

Additionally, *A. rugosa* exhibits allelopathic properties and may be developed as a new environmentally friendly biological herbicide [118].

5. Conclusion and future perspectives

A. rugosa, recognized as a prime example of "food and medicine homology," serves not only as a nutritional resource but also demonstrates diverse therapeutic properties, highlighting its significant clinical potential in managing various diseases (**Figure 12**). In investigations regarding pharmacological activity, it has been discovered by researchers that the effectiveness of *A. rugosa* is closely linked to its volatile oil, polyphenols, and other chemical constituents. Essential volatile oil compounds, including estragole (**119**) and pulegone (**13**), exhibit significant antioxidant, anti-inflammatory, antibacterial, and anticancer properties. Among polyphenolic constituents, tilianin (**220**) demonstrates a range of pharmacological benefits, including cardioprotective, hepatoprotective, respiratory regulatory, and anticoagulant effects. Additionally, acacetin (**200**) plays a crucial role in metabolic regulation, demonstrating promising therapeutic applications in diabetes and obesity management, as well as in combating depression and Alzheimer's disease. Furthermore, acacetin (**200**) possesses anti-inflammatory, antioxidant, and antiviral characteristics. Similarly, rosmarinic acid (**238**) exhibits anti-inflammatory, antioxidant, and antiviral properties, along with potential therapeutic benefits in the treatment of osteoporosis. The treatment of conditions such as anti-photoaging, liver protection, and respiratory diseases often involves mitigating oxidative stress and suppressing inflammation. Molecular mechanism research has identified multiple key signaling pathways related to the therapeutic effects of *A. rugosa*, including the inhibition of the NF-κB pathway, the PI3K/mTOR pathway, inactivation of the MAPK/AP-1 signaling pathway, and stimulation of the TGF-β/Smad signaling pathway.

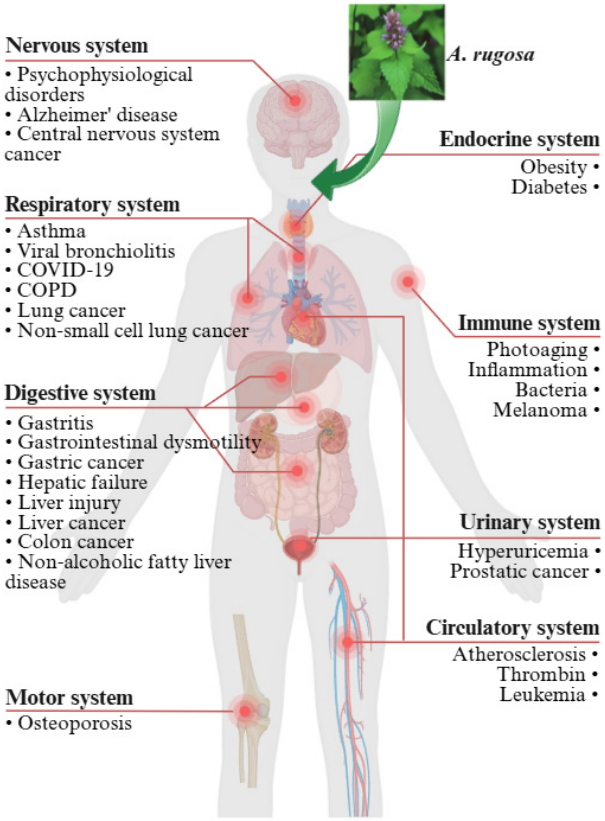

Figure 12 The health benefits of *A. rugosa*.

Furthermore, amid rising global health consciousness, consumer demands for food have shown a multi-dimensional trend: beyond ensuring safety and nutrition, they increasingly pursue health benefits, ecological sustainability, and economic accessibility. Within this context, *A. rugosa*, which possesses both medicinal value and edible properties, demonstrates unique developmental potential. Its application can extend to various fields such as functional food research, innovative dietary supplements, and cosmeceutical production. Integrating this traditional herb into modern lifestyles reflects an innovation in traditional Chinese medicine culture.

Although the value of *A. rugosa* has been recognized by both the academic community and industry, its further development still faces several key bottlenecks. First, most current pharmacological studies focus on crude extracts, and the molecular mechanisms of the active ingredients have not been systematically analyzed. Secondly, most studies are still at the *in vitro* stage, and there is relatively scarce data from *in vivo* experiments and clinical research. Thirdly, the quality control standard system for patchouli products needs to be improved. Finally, industry regulatory policies and commercial promotion strategies must also be optimized. In response to these challenges, future research should focus on the following aspects. Utilizing metabolomics and molecular docking techniques to clarify the key active ingredients and their mechanisms of action. Advancing *in vivo* experiments and conducting rigorous clinical trials to verify efficacy. Establishing scientific usage guidelines and supporting the development of industry standards, thereby fostering sustainable growth in the industry chain. The in-depth development of *A. rugosa* will not only expand the application scenarios in medical and health fields but also provide a practical blueprint for the innovative utilization of food and medicine resources.Declaration of Competing Interest

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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