Progress in Chemical Compositions and Pharmacological Activities of *Althaea officinalis*

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Abstract *Althaea officinalis* (Malvaceae), mainly distributed in Europe and China, is an ornamental, edible and medicinal plant, which is effective in reducing cough and phlegm. To better develop and utilize *A. officinalis*, 46 kinds of compounds including flavonoids, phenolic acids, steroids, coumarins and other types isolated from this plant are summarized, and their pharmacological effects such as anti-tussive, anti-inflammatory, anti-oxidation, anti-bacterial and anti-fungal activities are discussed in this review.

Keywords *Althaea officinalis*, flavonoids, anti-tussive, anti-oxidation

Introduction

Althaea officinalis L. (Malvaceae), commonly known as marshmallow, is a perennial herb which is native throughout damp areas of Europe and Asia.^[1,2] The roots, leaves and flowers of this plant are usually used as food and medicine in many countries all over the world. For example, the root of *A. officinalis* is used traditionally for the treatment of irritation of oral and pharyngeal mucosa, dry cough, mild gastritis, skin burns, insect bites, catarrh, ulcers, abscesses, constipation and diarrhea.^[3] Modern pharmacological studies revealed that *A. officinalis* showed anti-tussive, anti-oxidant, anti-inflammatory, anti-estrogenic, anti-microbial, immunomodulatory, anti-urolithiasis and cytotoxic activities.^[1] It mainly contained mucilage, flavonoids, polysaccharides and phenolic acids.^[3] Until now, its chemical compositions and pharmacological effects have not been systematically sorted out. This review, containing 43 references related to traditional usage and modern research, provides a systematic overview of *A. officinalis*. Besides, the possible research directions in the future are discussed in the article.

Chemical Constituents

Researchers have isolated and identified 46 compounds from different parts of this plant, including flavonoids, phenolic acids, coumarins, steroids and amino acids, etc.

Flavonoids are the main ingredients of *A. officinalis*. At present, a total of 17 flavonoids were obtained from the plant, and they are tiliroside (1),^[4] kaempferol 3-glucoside (2),^[4] quercetin 3-glucoside (3),^[4] hypolaetin-8-glucoside (4),^[5] hypolaetin-8- β -gentiobioside (5),^[5] astragalin (6),^[6] kaempferol 7-O-glucoside (7),^[6] hypolaetin-8-O- β -D-(2"-O-sulfo)-glucopyranoside (8),^[7] 4'-O-methylhypolaetin-8-O- β -D-(2"-O-sulfo)-glucopyranoside (9),^[7] 4'-O-methylhypolaetin-8-O- β -D-(3"-O-sulfo)-glucuronopyranoside (10),^[7] 4'-O-methylisoscuteallarein-8-O- β -D-(3"-O-sulfo)-glucuronopyranoside (11),^[7] hypolaetin-8-O- β -D-(3"-O-sulfo)-glucuronopyranoside (theograndin II) (12),^[7]

hypolaetin-8-O- β -D-glucopyranosyl-(1" $\rightarrow$ 4")- β -D-glucuronopyranoside (13),^[7] quercetin (14),^[8] kaempferol (15),^[8] hypolaetin 8-O- β -D-glucoside (16),^[9] isoscuteallarein 4'-methyl ether 8-O- β -D-glucoside-2"-SO₃K (17).^[9] Among them, 8–11 are new compounds isolated from the roots of *A. officinalis* for the first time. The structures of these compounds were shown in Figure 1.

In addition, previous studies revealed that *A. officinalis* contained steroids, triterpenoids, coumarins, phenolic acids, tannins, amino acids and other compounds. Until now, 1 steroid and 1 triterpenoid were isolated from the roots and seeds, which were identified as β -sitosterol (18)^[10,11] and lanosterol (19),^[10] respectively. Three coumarins were separated from the roots and identified as 5,6-dihydroxycoumarin-5-dodecanoate-6 β -D-glucopyranoside (20),^[10] scopolin-6'-O- α -L-rhamnopyranoside (21)^[7] and scopoletin (22).^[3,9] The structures of these compounds were shown in Figure 2.

Other types of compounds were also isolated from *A. officinalis* and respectively identified as caffeic acid (23),^[6,9] 4-hydroxybenzoic acid (24),^[3,6,9] ferulic acid (25),^[6,9] 4-hydroxycinnamic acid (26),^[3,6,9] vanillic acid (27),^[6,9] chlorogenic acids (28),^[6] *N*-(*E*)-caffeoyl-L-dopa (29),^[7] *N*-(*E*)-caffeoyl-L-tyrosine (30),^[7] *N*-(*E*)-coumaroyl-L-dopa (31),^[7] *N*-(*E*)-coumaroyl-L-tyrosine (32),^[7] salicylic acid (33),^[3,9] *p*-hydroxyphenylacetic acid (34),^[3,9] lauric acid (35),^[10] *n*-hexacos-2-enyl-1,5-olide (36),^[10] 2 β -hydroxycalamene (37),^[10] *n*-triacontanoic acid (38),^[11] 3,4-dihydroxybenzyl octadecane (39),^[11] 24 β , 28 β -dihydroxy octa tetracont-36-en-1-oic-acid (40),^[11] *n*-tetracosane (41),^[11] 5 β ,13 β -dihydroxynonacosanyl godoleate (42),^[11] *n*-pentatriacontane (43),^[11] diglucosyl oleate (44),^[11] *N*-(*E*)-cinnamoyl-L-aspartate (45)^[7] and glycine betaine (46).^[7] Among them, 36, 37, 39, 40 and 42 are new natural products isolated from the seeds and roots of *A. officinalis*. The structures of these compounds were shown in Figure 3.

Furthermore, polysaccharides were also found from *A. officinalis* by researchers.^[12-17]

Figure 1 Flavonoids isolated from *Althaea officinalis*.

Figure 2 Steroid, triterpenoid and coumarins isolated from *Althaea officinalis*.

Figure 3 Other compounds isolated from *Althaea officinalis*.

Pharmacological Activities

A. officinalis has shown multiple pharmacological effects *in vitro* and *in vivo* such as anti-tussive, anti-inflammatory, anti-oxidation, anti-bacterial and anti-fungal activities, and so on.

Anti-tussive effects

A. officinalis has a long history as a traditional medicine for the treatment of cough and other respiratory problems. The German Standard License approved *A. officinalis* root tea for soothing irritation due to mucosal inflammation of the pharynx and upper respiratory tract,^[18] meanwhile, cough preparations containing aqueous extracts of *A. officinalis* roots also played an important role in cough treatment.

In a clinical trial, Fink *et al.*^[19] carried out an independently survey on patients ($n = 822$), who received oral administration of the aqueous extracts obtained from *A. officinalis* roots. The results of survey indicated that the aqueous extracts showed a good effect on the symptomatic treatment of oral or pharyngeal irritation with a very rapid onset of effects within 10 min in the

majority of cases.

Related researches showed the mucilage polysaccharide content of *A. officinalis* was 6.2%—11.6%.^[20] In order to investigate the effectiveness of the mucilage polysaccharides as an anti-tussive and anti-cough agent, the polysaccharides and rhamnogalacturonan isolated from *A. officinalis* roots and flowers were tested for anti-tussive activity in unanesthetized cats and guinea pigs of both sexes at oral doses of 50 to 100 mg/kg body weight,^[21-24] in a cough induced by mechanical stimulation, both polysaccharides and rhamnogalacturonan significantly reduced the intensity, the frequency and the number of cough efforts from laryngopharyngeal and tracheobronchial areas. The anti-tussive mechanism might be explained as mucilaginous herbs like *A. officinalis* roots could form a protective film on the respiratory mucosa thereby to prevent it from being stimulated by foreign antigens.^[18]

Anti-inflammatory effects

Bonaterre *et al.*^[25] studied the anti-inflammatory effects of root extracts of *A. officinalis* on Macrophages (Mφ) *in vitro* using the THP-1 (human acute monocytic leukemia) cell line. The

enzyme-linked immunosorbent assay results displayed that the extracts possessed potent inhibitory effects on LPS-induced release of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). The extracts were also found to protect human M ϕ against H₂O₂-induced cytotoxicity and cellular reactive oxygen species production, additionally improving the migratory capacity of the cells.

Anti-oxidation effects

Regarding the anti-oxidant activity of *A. officinalis*, many studies have been carried out *in vitro*. Benbassat *et al.*^[26] and Zaghlool *et al.*^[27] evaluated the anti-oxidant activity of roots extracts prepared with different extraction solvents applying ABTS, DPPH, hypochlorous acid scavenging and iron-induced lipid peroxidation assays. They found the water extracts possessed weak anti-oxidant activity, whereas the ethanol extracts showed well pronounced anti-oxidant activity. Moreover, the anti-oxidant properties of *A. officinalis* flowers ethanolic extracts were evaluated using different anti-oxidant tests *in vitro*,^[28] at the concentration of 50, 100, and 250 mg/mL. The extracts showed 85.5%, 91.2%, and 96.4% inhibition on peroxidation of linoleic acid emulsion, respectively. Furthermore, the extracts had effective reducing power, free radical scavenging, superoxide anion radical scavenging, and metal chelating activities at same concentration (50, 100, and 250 mg/mL).

The polysaccharides (1.0–5.0 mg/mL) obtained from ethanolic extracts of *A. officinalis* flowers were further investigated for anti-oxidant activity by Tabarsa *et al.*^[29] The IC₅₀ values of DPPH assay and ferric iron reducing assay were 4.77 and 3.10 mg/mL, respectively. A recent study^[30] showed the polysaccharides isolated from *A. officinalis* leaves illustrated a high degree of hydroxyl radical scavenging capacity with an IC₅₀ of 9.7 mg/mL. It was also found that the scavenging effect of polysaccharides on DPPH radicals increased linearly with increased concentration (0–20 mg/mL), showing 93.4% inhibition at a concentration of 20 mg/mL.

In addition, Sadighara *et al.*^[31] discovered that the anti-oxidant capacities of *A. officinalis* varied from strong to weak according to the plant colors (reddish-pink, pink, white) by CUPRAC and ferric iron-reducing assays.

Anti-bacterial and anti-fungal activities

The extracts of *A. officinalis* from different parts showed good anti-microbial activity. The 70% ethanolic extracts of *A. officinalis* roots were found to be against *Streptococcus mutans* and *Lactobacillus acidophilus*. The minimum inhibitory concentration (MIC) for *S. mutans* and *L. acidophilus* were 102.0 and 212.5 mg/mL, respectively.^[32] Moreover, the ethanolic extracts also showed an inhibitory effect on *Pseudomonas aeruginosa* by an agar well plate test,^[33] and the MIC and minimum bactericidal concentration (MBC) was 62.5 mg/L.^[33]

Jafari-Sales *et al.*^[34] explored the anti-bacterial effect of ethanolic extracts extracted from *A. officinalis* stems and leaves on antibiotic-resistant strains of *Staphylococcus aureus*. The obtained MIC and MBC were 3.2 and 6.5 mg/mL by agar dilution method, respectively. Additionally, the hydroalcoholic extracts of leaves of *A. officinalis* were efficacious against gram-positive bacteria, while they were not effective on gram-negative bacteria at the tested concentrations.^[35] The extracts of *A. officinalis* can be a great candidate for the treatment of gram-positive infections, which are worthy of further study.

Khamees *et al.*^[36] investigated aqueous extracts (300–400 mg/mL) and methanol extracts (100–400 mg/mL) of flowers of *A. officinalis*, and the results exhibited valuable antibacterial

effects against gastrointestinal pathogens (*S. aureus*, *Escherichia coli*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Plasmodium vulgaris* and *Streptococcus dysenteriae*) *in vitro*. Especially, the methanol extracts were found to possess more potent inhibition effects on the growth of bacteria species. In addition, Valiei *et al.*^[37] discovered that the hexane extracts of *A. officinalis* from flowers and roots exhibited good anti-microbial activities against *E. coli*, *Pseudomonas aeruginosa*, *K. pneumoniae*, *Bacillus subtilis*, *Enterococcus faecalis*, *S. aureus* and *Staphylococcus epidermidis* *in vitro* by the disc diffusion method (DDM).

The *A. officinalis* seed extracts and essential oil were screened for anti-microbial activity by Gautam *et al.*^[38] The essential oil possessed significant inhibition activities against *Streptococcus pyogenes* (21.3 $\pm$ 0.28 mm) and *Haemophilus influenzae* (19.0 $\pm$ 0.50 mm) at 200 mg/mL. Meanwhile, the essential oil and the aqueous extracts showed higher anti-fungal activities on *Aspergillus niger* with inhibition rates of 41.28% and 36.27%.

Anti-ulcer effects

In order to investigate the protective effects of extracts of *A. officinalis* on pyloric ligation-induced gastric ulcer in rats, the gastric juice and blood samples of rats in different administration groups were analyzed by Zaghlool *et al.*^[39,40] They found that oral administration with *A. officinalis* (100 mg/kg/day) for 14 d could significantly decrease ulcer number and ulcer index. Meanwhile, all blood and tissue parameters were significantly corrected by varying degrees.

Wound healing effects

The wound healing effects of *A. officinalis* was reported in previous studies. Rezaei *et al.*^[35] found the topical administration of hydroalcoholic extracts of *A. officinalis* leaves could accelerate the wound healing processes and increase the wound healing percent on excision wound model in rats. An investigation on flower mucilage ointment of *A. officinalis* displayed that the 15% flower mucilage significantly enhanced wound healing and reduced the days needed for complete healing compared with the non-treated groups in rabbits.^[41] Moreover, the *A. officinalis* aqueous extracts incorporated into a nanofibrous scaffold prepared by electrospinning the blend of poly (ϵ -caprolactone) and gelatin could better exert the healing effects.^[42]

Other pharmacological effects

A. officinalis extracts administration exhibited neuroprotective effects against 6-hydroxydopamine (6-OHDA)-induced hemi-Parkinsonism in rats.^[43] 10 mg/kg aqueous extracts of *A. officinalis* leaves might attenuate rotational behavior in the 6-OHDA administered group and protect the neurons of substantia nigra pars compacta.

Conclusion and Perspective

In summary, as a traditional folk medicinal plant, *A. officinalis* is widely distributed and easy to obtain. With the efforts made by researchers in recent years, many chemical components of *A. officinalis*, including flavonoids, polysaccharides, phenolic acids, coumarins and steroids, have been identified by various chromatographic methods. The diversity of the chemical constituents of the plant helps to explain the diverse pharmacological properties such as anti-tussive, anti-inflammatory, anti-oxidant, anti-bacterial and anti-fungal effects, etc. However, the current researches on the mechanism of the bioactive components and the active ingredients related to the therapeutic effects of *A. officinalis* are very limited, which greatly hinders its application in health care

products. To better utilize the resources of *A. officinalis*, it is necessary to further study the active compositions and its molecular mechanism in detail.

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Conflict of Interest

The authors declare no conflict of interest.

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