Chapter 77
Chrysanthemum morifolium Ramat 菊花 (Juhua, Florists Chrysanthemum)

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77.1 Botanical Identification

Juhua is the dried flower head of chrysanthemum plant (*Chrysanthemum morifolium* Ramat). *Chrysanthemum morifolium* is a perennial herb covered with white villous hairs, cultivated in many areas in China for medicinal and food applications as well as for ornamental use. The *chrysanthemum morifolium* plant is about 60–100 cm high, densely covered with white villous hairs and has ovate or ovate-lanceolate shaped leaves (3.5–5 cm long, 3–4 cm wide), which are obtuse at the apex and subcordate at the base. Flower heads are at terminal or axillary of stem, with outer flower ligulate shaped petals in white or yellow color, withthe center of the flower being yellow and tubular in shape. The flowers are harvested during the blossoming season, followed by drying to produce Juhua herbal material which is characterized as a mixture of plain to sweet and bitter taste (Fig. 77.1).

Chinese Pharmacopoeia lists four major cultivars based on the areas where they are produced and post-harvest processing methods. These cultivars are known as Boju, Chuju, Gongju and Hangju. The edible chrysanthemum is widely cultivated and produced in Zhejiang, Anhui, Sichuan, Henan, Hebei and Shandong provinces in China. Flower heads are harvested from September to November when flowers are in blossom. Traditionally chrysanthemum flowers are naturally sun dried or dried in shade with or without pretreatment. Boju (traditionally produced in Bo Zhou area of Anhui province) flowers are cut with stems and dried in shade, flower heads are then collected after they are dry, with 1.5–3 cm (diameter) in off-white color; Chuju (1.5–2.5 cm diameter, off-white color, traditionally produced in Chu Zhou area of Anhui province) flowers are collected and fumigated with sulfur, followed by sun drying; Gongju (1.5–2.5 cm, white or off-white, traditionally produced in Xin county of Anhui province) flowers are dried to 90 % dryness at

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Y. Liu et al. (eds.), *Dietary Chinese Herbs*, DOI 10.1007/978-3-211-99448-1_77

Fig. 77.1 Representative flowering chrysanthemum (**a**) and chrysanthemum crude drug (**b**)

60 °C followed by sun drying; Hangju (2.5–4 cm diameter, white or yellow; white chrysanthemum is traditionally for food consumption as tea alternative and yellow chrysanthemum is for medicinal use, traditionally produced in the area around Hangzhou of Zhejiang province) flowers are steamed for 4–5 min followed by sun drying. Chinese Pharmacopeia requires that chrysanthemum commodity contain less than 15 % of moisture, no less than 0.20 % (dry weight) of chlorogenic acid, no less than 0.080 % (dry weight) of luteolin glycoside and no less than 0.70 % (dry weight) of 3,5-caffeoylquinic acid [1].

Chrysanthemum is used as traditional Chinese medicine for "expelling wind and clearing away heat", "clearing heat and eliminating toxic substances" and "brightening eyes" in many traditional Chinese medicine formulas and also for daily food consumption as tea alternative. Juhua has sweet and bitter tastes and a slightly cold property, acting on lung and liver meridians, with functions such as "Expelling wind and heat, used for upper respiratory infections", "subduing hyperactivity of the liver and improving acuity of vision, used for inflammation of the eyes and blurred vision" and "calming the liver, used for headache and dizziness". The typical daily dose is 5–10 g [1].

77.2 Chemical Constituents

Flavonoids have been identified from *Chrysanthemum morifolium* flower, including flavones (apigenin, acacetin, luteolin, diosmetin and eupatorin), flavanone (eriodictyol), flavonols (quercetin, isorhamnetin, kaempferol, kaempferide, chrysosphenol C and chrysosphenol D) as well as their glycosides and acetyl glycosides [1–6] (structures are shown in Fig. 77.2), of which, luteolin glycoside is also used as a quality control marker for this herb [1].

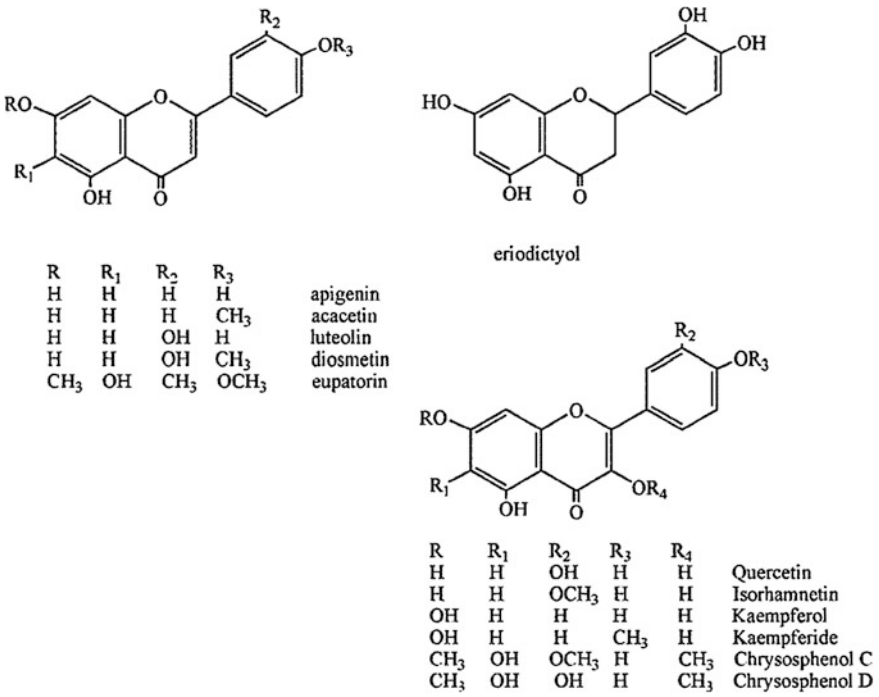

Fig. 77.2 Structure of flavonoid aglycones in *Chrysanthemum morifolium* ramat

Phenolic acids are another class of phytochemicals identified from chrysanthemum. Chlorogenic acid and 3,5-di-caffeoylquinic acid (Fig. 77.3) are known phenolic acids in *Chrysanthemum morifolium* flower, and serve as quality check markers for this herbal material in current China Pharmacopeia [1]. In addition, 1-caffeoylquinic acid, 3-caffeoylquinic acid, caffeic acid 4-glucoside, 4-caffeoylquinic acid, 5-sinapoylquinic acid, caffeic acid, 1,3-di-caffeoylquinic acid, 3,4-di-caffeoylquinic acid, 1,4-di-caffeoylquinic acid, 1,5-di-caffeoylquinic acid, 3-methyoxaloyl-1,5-di-caffeoylquinic acid, 4,5-di-caffeoylquinic acid, 4-caffeoyl-5-feruloylquinic acid, and 3,4,5-tricaffeoylquinic acidare also found in chrysanthemum flower [3] (Fig. 77.3). Caffeoylquinic acid content reaches its peak value when 50 % tubular florets and 70 % ray florets open, which is consistent with the traditional harvest practice [5].

Terpene, sesquiterpene and their oxidized derivatives are the primary volatile compounds from *Chrysanthemum morifolium* flowers. Terpene includes borneol, camphor, α-pinene, β-pinene and 1,8-cineole; sesquiterpene includes farnesene, farnesol, α-cubebene and muurolol, etc. Of the identified volatile compounds from Hangju (Chrysanthemum produced in Zhejiang region), volatile compounds with relative content greater than 1 % include 2-methyl-1-pentene, camphor, borneol, bornyl acetate, β-elemene, α-cubebene, curcumene, α-bergamotene, β-bisabolene,

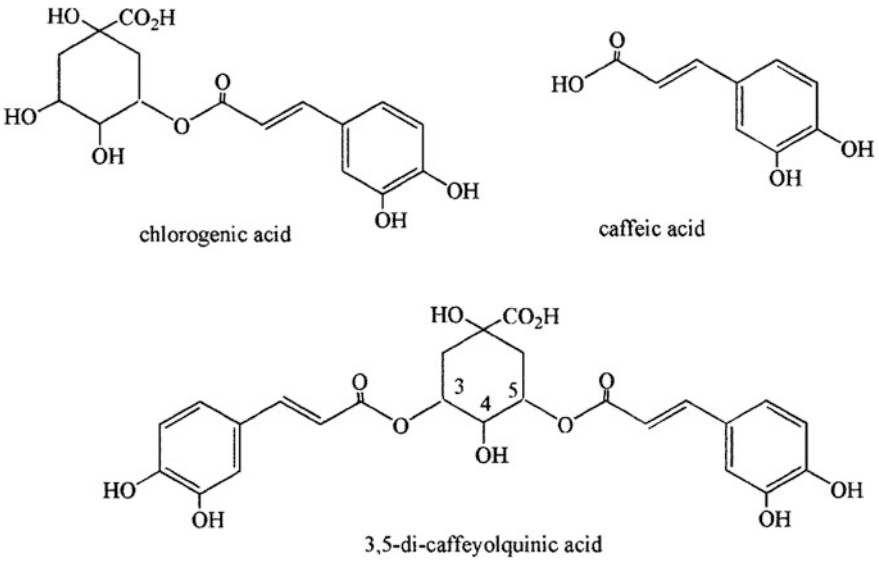

Fig. 77.3 Structures of caffeic acid and its derivatives found in *Chrysanthemum morifolium* ramat

β-cadinene, caryophyllene oxide, β-maaliene, alloaromadendrene, α-costol, hexadecanoic acid, hexadecanoic acid, heneicosane, 9,12-octadecadienoic acid, tricosane, tetracosane and pentacosane according to their retention time on GC/MS [7]. Similarly, another group of researchers identified 58 volatile compounds from *chrysanthemum morifolium,* with β-humulene as the most abundant compound, other significant compounds including ledene oxide, *cis*-Z-α-bisaboleneepoxide, 3,4-dihydro-,2,2-dimethyl-2H-1-benzopryan, *trans*-limonene oxide, 2-methyl-5-(1-methylethenyl)-cyclohexanone, 2,6-dimethyl-1,3,6-heptatriene, 1,6-dibromo-hexane, β-elemene, bromo-cyclohexane, 1-(1,5-dimethyl-4-hexenyl-4-methylbenzene, 3,3,6,6-tetraethyl-tricylco[3.1.0.0(2,4)]hexane, 3-cyclohexene-1-methanol,6-isopropenyl-4,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydro-naphthalen-2-ol, caryophyllene, 1-tert-butyl-1,5,-cyclooctadiene, α-farnesol, α-farnesene, limonene, α-pinene, 2-methyl-1-pentene, camphor, borneol, bornyl acetate, β-elemene, α-cubebene, curcumene, α-bergamotene, β-bisabolene, β-cadinene, caryophyllene oxide, β-maaliene, alloaromadendrene, α-costol, hexadecanoic acid, heneicosane, 9,12-octadecadienoic acid, tricosane, tetracosane, astaured hydrocarbons (n-nonadecane, n-eicosane, n-heneicosane, n-docosane, n-pentoacosane, n-hexacosane, n-heptacosane, n-octacosane, n-nonacosane, n-triaceontrane, n-hentriacontane, and n-tritriacontane) [4]. It seems that the volatile compounds vary with the growing area, harvest season, post-harvest process as well as the freshness of the chrysanthemum materials.

Phytosterols, such as campesterol, stigmasterol, β-sitosterol, α-amyrin and β-amyrin, are identified from *Chrysanthemum morifolium*. Ukiya et al. identified and

characterized 24 triperpenediols and triols from n-hexane extraction fraction of *Chrysanthemum morifolium* flower, including arnidiol [taraxast-20(30)-ene-3β,16β-diol]; brein (urs-12-ene-3β,16β-diol); calenduladiol [lup-20(29)-ene-3β,16β-diol]; (24R)-cycloart-25-en-3β,24-diol; dammarenediol II [(20S)-dammar-24-ene-3β,20-diol]; 3-epicabraleadiol [(20S, 24S)-20,24-epoxydammarane-3β,25-diol]; erythrodiol (olean-12-ene-3β, 28-diol); faradiol (taraxast-20-ene-3β,16β-diol); maniladiol (olean-12-ene-3β,16β-diol); (24S)-25-methoxycycloartane-3β,24-diol; (24R)-saringosterol [(24R)-stigmasta-5,24^1(24^2)-diene-3β,24-diol]; (24S)-saringosterol [(24S)-stigmasta-5,24^1(24^2)-diene-3β,24-diol]; (24R)-cycloartane-3β,24,25-triol; (24S)-cycloartane-3β,24,25-triol; faradiol α-epoxide [(20R,21S)-20,21-epoxytaraxastane-3β,16β-diol]; heliantriol A1 [olean-olean-13(18)-ene-3β,16β,28-triol]; heliantriol B2 [lup-20(29)-ene-3β,16β,28-triol]; heliantriol C (taraxast-20-ene-3β,16β,28-triol); (24S)-lanost-9(11)-ene-3β,24,25-triol; longispinogenin (olean-12-ene-3β,16β,28-triol); (24S)-25-methoxycycloartane-3β,24, 28-triol; 22α-methoxyfaradiol (22α-methoxytaraxast-20-ene-3β,16β-diol); (24S)-29-norcycloartane-3β, 24,25-triol [8]. In addition, endoperoxysequitepene lactone and 10α-hydroxy-1α,4α-endoperoxy-guaia-2-en-12,6α-olide have also been identified from chrysanthemum [6].

77.3 Pharmacological Studies

77.3.1 Antioxidant Activity

The antioxidant potential of chrysanthemum extract has been demonstrated in oil emulsion [9], liposome model system with radical scavenging activity [10] and protecting erythrocyte membrane from superoxide radical induced damage [11]. Many phenolic phytochemicals found in *Chrysanthemum morifolium* are known to exhibit antioxidant activity and free radical scavenging capacity in various in vitro models. For example, luteolin and its glycoside suppress free radicals and inhibit lipid oxidation and nitric oxide production [12, 13]. Phenolic acid, 3,5-di-caffeoylquinic acid and 1,3-di-caffeoylquinic acid isolated from *Chrysanthemum morifolium* inhibited superoxide radical (IC_{50} = 2.0 ± 0.1 μg/ml and 2.6 ± 0.4 μg/ml, respectively) in xanthine/xanthine oxidase system [14]. Using hot water extract of *Chrysanthemum morifolium* Ramat, Lii et al. found that chrysanthemum extract and phytochemical associated with chrysanthemum (apigenin and luteolin) suppressed the reactive oxygen species, ICAM-1 and E-selectinin human umbilical vein endothelia cells induced by oxidized LDL (low-density lipoprotein) in a dose-dependent fashion [15].

A flavonoid enriched chrysanthemum extract was found to support oxidative stress status in a cerebral ischemia/reperfusion rats model, and improve neurological deficit score, percentage of infraction and brain edema and maintain superoxide dismutase activity, suggesting that the antioxidant activity of chrysanthemum played an

important role in protecting the animal from cerebral ischemia/reperfusion injury [16]. Similarly, after five days of gauge feeding with flavonoid rich chrysanthemum extract, the myocardial ischemia reperfusion injury in rat model was attenuated, which was attributed to the improvement of antioxidant defense mechanism [17]. Chrysanthemum extract feeding reduced the lipid peroxidation and improved antioxidant enzyme levels in a lead-induced mice oxidative model, and significantly lowered the lead level in blood, brain and other organs [9].

77.3.2 Anti-Inflammatory Activity

Chrysanthemum extract suppressed, bacterial lipopolysaccharide (LPS) induced production of prostaglandin E_2 (PGE_2) in mouse macrophage RAW264.7 at IC_{50} of 0.6 mg/ml [18]. Luteolin and its glycoside inhibited the production of PGE_2 and suppressed the expression of cyclooxygenase-2 (COX-2) in the same cell model [12]. Chrysanthemum methanolic extract was found to significantly inhibit 12-O-tetradecanoylphorbol-13-acetate induced edema in mice [19].

Lipid fraction of chrysanthemum flower extract was shown to contain triterpene diols and triols in their 3-O-fatty acid esters forms, and many of these triterpene diols and triols exhibited anti-inflammatory activity against 12-*O*-tetradecanoylphorbol-13-acetate induced inflammation in mice in the range of IC_{50} between 0.03 and 1.0 mg per ear [8].

77.3.3 Antibacterial and Antiviral Activity

Essential oil obtained from whole herb exhibited strong inhibition on *Streptococcus aureus* and *E. coli* [20]. The minimal inhibition concentration of chrysanthemum extract against oral pathogens *Streptococcus mutans, S. sanguinis* and *S. sobrinus* was greater than 8 mg/ml [21]. Flavonols (quercetin and kaempferol) and flavone (luteolin) exhibited inhibitory activity against methicillin-resistant *Staphylococcus aureus* [22]. In addition, 3-hydroxyl triterpenoids from non-saponifiable lipid fraction of chrysanthemum flower extract exhibited anti-tubercular activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$ [23]. Hu et al. found acetin-7-galatoyranoside from *Chrysanthemum morifolium* was the most effective HIV inhibitor among eight flavonoids isolated from this plant in H0 cell model and the structure-activity relationship showed that a structure with hydroxyl groups at C-5 and C-7 with C2-C3 double bond was more effective in inhibiting HIV growth [24].

77.3.4 Cardiovascular Health

Vasorelaxant effect was found when chrysanthemum extract was incubated with rat thoracic aorta in vitro. Chrysanthemum extract induced both endothelium dependent and independent relaxation using rat thoracic aorta, attributed to the its regulation on the nitric oxide as well as Ca^{2+}-channel and K^{+}-channel [25]. Chrysanthemum extract attenuated the reduction of contraction of isolated rat heart and cardiomyocytes induced byischemia/reperfusion by improving superoxide dismutase activity [26].

77.3.5 Antiglycation and Diabetic Benefit

The non-enzymatic browning reaction between amino acid and carbonyl group (reducing sugar) leads to the accumulation of the advanced glycation end products (AGEs). The glycation process occurs not only in food processing (Mallard reaction in thermal process) but also in biological systems, resulting in the modification of macromolecules with biological importance. Therefore prevention of overly occurred glycation is critical in preventing diabetic complications and the aging process. In a bovine serum albumin/glucose model, chrysanthemum flower effectively inhibited the formation of AGEs (measured by pentosidine) and N^{ϵ}-(carboxymethyl) lysine (CML), attributing to antioxidant and antiglycation activities of phenolic components such as chlorogenic acid and flavonoids in the extract [27, 28]. Though chrysanthemum extract inhibited glycation in an in vitro model, the measurement of skin elasticity improvement after eight weeks of daily oral intake of up to 150 mg chrysanthemum extract failed to show efficacy in a randomized controlled clinical trial, which the author speculated it was possibly due to post-translation modification of collagen [29].

Endoperoxysequiterpene lactone (10α-hydroxyl-1α,4α-endoperoxyl-guaia-2-en-12,6α-olide) showed strong inhibitory effect against α-glucosidase and lipase activity at IC_{50} of 229.3 and 161.0 μM level. While acacetin-7-glucsoide and rhamnoside inhibited both α-glucosidase and α-amylase, eriodictyol only effectively inhibited α-glucosidase [6]. This suggests that chrysanthemum may possess potential health benefits for diabetics.

77.3.6 Other Effects

Being used in Korea for the treatment of insomnia, chrysanthemum extract was found to extend the sleep time in mice induced by pentobarbital by increasing glutamic acid decarboxylase expression. However there was no effect on expression of $GABA_A$ receptor in the hippocampus of the mouse's brain, which was attributed to the Cl^{-} channel activation [30].

77.4 TCM Applications and Dietary Usage

77.4.1 TCM Application

Chrysanthemum is used with Sangye (leaf of *Morus alba*), Bohe (herb of *Mentha haplocalyx*) and Lianqiao (fruit of *Forsythia suspensa*) as *Sangjuyin* decoction to treat exogenous disease due to wind and heat or early stage of seasonal febrile disease manifested such as fever, headache and cough. Chrysanthemum is used with Sangye (leaf of *Morus alba*), Juemingzi (seed of *Cassia obtusifolia*) and Longdan (root and rhizome of *Gentiana manshurica*) to treat red and painful eyes due to wind and heat attacking liver meridian or flaming-up the exuberant liver-fire. Qi Ju Dihuang pill formulated with Gouqizi (fruit of *Lycium barbarum*), Shudihuang (prepared root tuber of *Rehmannia glutinosa*) and Shanzhuyu (pulp of *Cornus officinalis*) is used to treat blurred vision due to weakness of liver and kidney. Chrysanthemum is formulated with Shijueming (shell of *Haliotis Diversicolor*), Baishao (root of *Paeonia lactiflora*) and Chinese cat's claw (*Amulusuncarriae cum uuncis*) to treat dizziness and headache resulted from overly expressed liver-*Yang*. Fresh chrysanthemum flower juice can be used orally and residual used externally to treat furuncle and furunculosis, and this can also be achieved in combination with Zihuadiding (herb of *Viola yedoensis* Makino) and Pugongying (herb of *Taraxacum mongolicum* L).

77.4.2 Dietary Usage

In China, chrysanthemum has been considered as ingredient used as both food and traditional Chinese medicine material by the Ministry of Health, therefore chrysanthemum has been widely used in food and beverages in China. Chrysanthemum is used alone or with other traditional Chinese herbs as a tea alternative and is widely consumed in summer to relieve damp hot. Chrysanthemum tea beverage, sweetened or non-sweetened, is widely available in China as ready-to-drink herbal tea. *Sang Ju Yin* (herbal tea drink formulated with mulberry leaf and chrysanthemum) is also popular in summer and such drinks are commercially available in both aseptic package (ready-to-drink) or as a drink granule. Fresh or dried chrysanthemum flower are sometime used in Chinese cooking too.

Chrysanthemum is also used widely in China in health foods applications with a functional claim. About 220 health foods containing chrysanthemum or its extract have been approved by State Administration of Food and Drug by middle of 2013. About 20 % of products carry a claim for "relieving vision fatigue", and are typically formulated with Sangye, Juemingzi and Gouqizi. Some of these products are formulated with bilberry extract and lutein, which is well aligned with traditional Chinese medicine principles of the usage of chrysanthemum.

77.5 Clinical Evidence

Published double-blind placebo-controlled studies using only *chrysanthemum morifolium* Ramat alone is limited. In a randomized controlled clinical trial, eight week oral administration of 50 and 150 mg chrysanthemum extract per day was proven to be safe, though the primary clinical outcome (improving skin condition) was not demonstrated [29]. In China, Juhua formulated with other traditional Chinese medicines have been clinically studied. In a non-placebo controlled study, granule containing extracts of fleecewood, Gouqizi, Juemingzi, Shanzha (fruit of *Crataegus pinnatifida*), Juhua and Jiaogulan (herb of *Gynostemm apentaphyllum*) (30 g raw material equivalency, twice per day) for stage 1 and 2 hypertensive patients resulted in the reduction of systolic pressure from 159.2 ± 13.5 mmHg to 136.9 ± 8.4 mmHg and diastolic pressure from 100.2 ± 8.4 mmHg to 86.2 ± 5.2 mmHg over 30 days [31].

77.6 Safety Evaluation and Toxicity Data

Chrysanthemum is considered to be safe and of low toxicity, the Ministry of Health of China listed chrysanthemum as one of 80 botanical ingredients used in "both food and medicine". Very few adverse events have been reported from consumption of chrysanthemum. Oral administration of 15 g/kg body weight chrysanthemum extract (containing 7.0 % luteolin and 5.19 % apigenin) did not lead to any observable toxicity in SD rats, and a daily gavage of up to 1280 mg/kg body weight of the same chrysanthemum extract did not lead to any toxicological change in body weight, food and water consumption, or hematologic and histopathologic changes, confirming the high tolerance to chrysanthemum [32]. Using an oral dose of 6.09 g/kg body weight chrysanthemum extract to feed pregnant rats (equivalent to 300 times the recommended human dose in China Pharmacopeia) for 10 days, no significant differences ($p > 0.05$)were found between the treatment group and the placebo group in term of body weight gain of the pregnant rats, average live fetus, absorptive fetus ratio, or body weight and length of fetus, indicating that chrysanthemum had no apparent teratogenicity and embryotoxicity [8]. The high tolerance to chrysanthemum was also confirmed in an eight-week oral administration of 150 mg/day chrysanthemum extract [29]. The primary flavone (luteolin 85.56 mg and apigenin 65.04 mg through administration of 12 *chrysanthemum morifolium* tablets per day) was excluded in urine in the forms of aglycone, sulfurate and glucuronate within 12 h of administration, the mean ($n = 8$) concentration of luteolin and apigenin in urine 6 h after administration were 1.239 ± 0.90 and 1.337 ± 0.91 μg/ml respectively [33]. On the other hand, contact dermatitis was reported from chrysanthemum plant, and the intensity to chrysanthemum is flower > leaf > whole plant > stems [34].

In summary, C*hrysanthemum morifolium* flower contains flavonoids, phenolic acids and volatile compounds, possessing antioxidant, anti-inflammatory, antibacterial and antiviral properties, and exhibits cardiovascular benefits mainly attributed to the phytochemical profiles. Chrysanthemum is safe and has been widely used in food and traditional Chinese medicine. Though chrysanthemum has been formulated and applied in traditional Chinese medicine, well-designed clinical trials are needed to demonstrate efficacy of chrysanthemum.

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