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Ethnopharmacology, phytochemistry, bioactivities and quality control of the *Gnaphalium* genus: an updated review

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Abstract

The genus *Gnaphalium* (*Asteraceae*) is distributed across most regions of the world. Some of them are not only used as a food source, but has also been used for the treatment of various diseases including pain, rheumatism, chronic pharyngitis and arthritis in China since ancient times. In this review, we would like to summarize previous research on genus *Gnaphalium*, including traditional uses, phytochemistry, bioactivities and quality control. The data presented here on genus *Gnaphalium* was generated based on various scientific research databases, including SciFinder, PubMed, ScienceDirect, Wiley library, Web of Science, and CNKI. Analysis of these findings showed that plants in genus *Gnaphalium* have a capital power in various therapeutic uses, including pulmonary protection, antimicrobial activity, antioxidant activity, anti-inflammatory and anti-complementary activities, and antidiabetic effect. Consistent with this, the chemicals from the plant extracts revealed its richness in various chemicals, including flavonoids, phenolic acids, terpenoids, sterols, and others. In spite of its wide applicable value worldwide, the quality control of genus *Gnaphalium* is still based on local standards. Thus, we argue that a national standard is required for genus *Gnaphalium* in China, to validate its bioactivity and future clinical trials rigorously.

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Introduction

The genus *Gnaphalium* (family *Asteraceae*) contains ~200 species scattered throughout the world, including China, Mexico, Argentina, North Korea, Philippines, Indonesia, India, and Australia[1,2]. It is documented that several species have long been used for treating asthma, cough, phlegm, rheumatism, and other disorders. In addition, *Gnaphalium affine* and *Gnaphalium hypoleucum* are served as vegetables in southern China[3,4]. Although Zheng et al. reviewed several chemicals and pharmacological functions of *Gnaphalium* in 2013[5], many bioactive chemical compounds have been identified afterward in different *Gnaphalium* species to verify and validate their medicinal applications. Here, we summarize the recent achievements in investigation of the ethnopharmacological application, phytochemicals, pharmacological effect, and quality control study of genus *Gnaphalium*. Furthermore, the limitations of the existing studies and future directions of *Gnaphalium* research are discussed to provide ideas for future research and development.

Botanical diversity and traditional applications

Morphological description

Gnaphalium affine is an annual herb with a stem about 10–40 cm in length, covered with white thick cotton hairs. The leaf is oblanceolate or obovate, about 5–7 cm in length and 11–14 mm in width, usually with only one vein. The flower is capitulum that densely forms corymbs at the top of the branches, and is involucrally bell-shaped with 2–3 layers. The outer layer is obovate or spoon-shaped, the inner layer is long and spoon-shaped; the female flowers are very common, the corolla is tubular, the top of the corolla is enlarged with 3-tooth, and the lobes are glabrous.

Gnaphalium hypoleucum is an annual stout herb with an erect stem, about 10–40 cm in length. The leaf is linear, about 8 cm in length and 3 cm in width, usually with only one vein, which is obviously visible on the top but not on the bottom. The flower is capitulum that densely forms corymbs at the top of the branches, and is involucrally bell-shaped with four layers.

The outer layer is obovate, the back surface is covered with white cotton wool, the inner layer is linear, the top is pointed or acute, and the back surface is usually glabrous. The male flowers are very common, the corolla is filiform.

Gnaphalium japonicum is an annual delicate herb with a slightly erect stem, about 8–27 cm in length. The leaf is sword-shaped linear, about 3–9 cm in length and 3–7 in width, covered with sparse hairs above and thick white cotton hairs on the bottom. The flower is compound capitulum, and forms radial or astral leaflets. The total bract is nearly bell shaped, the outer layer is broadly elliptic, membranous, reddish brown. The middle layer is obovate oblong, and the upper part is reddish brown. The inner layer is linear, and the top is blunt and reddish brown.

Gnaphalium liebmannii, known as 'gordolobo' in Mexico, is an annual herb, about 10–150 cm in length. The leaf is narrowly elliptic or oblanceolate, about 2–9 cm in length and 0.5–1.5 cm in width, corolla, tomentose, margin smooth, and sessile. The flower is corymb and bell-shaped, and 3–9 mm in length, 2.5–7 mm diameter.

Traditional applications

In China, the edible history of *G. affine* has been going on for thousands of years. As early as the Jin Dynasty, *G. affine* had been used together with glutinous rice to make cakes for human consumption (Fig. 1). Not only Chinese, the Japanese also used it for cooking porridge, and gradually people found that *G. affine* has certain pharmacological effects. To date, hundreds of species in *Gnaphalium* are found across the worlds, several of them have been recorded as traditional medicine in Asia, including China, Japan, and Korean, as well as countries in America (Mexico and Argentina). Most of these reports are related to the management of rheumatism, cough, and asthma. Additionally, some species are also used to treat bacterial and fungal infections, diarrhea, cancer, respiratory infections, and several other conditions (Table 1). In China, several registered drugs have been developed from *Gnaphalium* species, such as 'Fufang Fuercao Heji (复方佛耳草合剂)', containing *G. affine* as the main component, and used for the management of chronic obstructive pulmonary diseases (COPDs)[6]. Recently, *G. affine* can also be used as a vegetable for making spices and functional yogurts[7]. Apart from the medical and edible values, *G. affine* is also used as natural dye for silk coloring in Yunnan, China.

Phytochemistry

There are multiple previous studies focusing on the chemicals in *Gnaphalium* species. To date, 257 compounds have been identified and characterized. The existing literature indicates the existence of multiple components, predominantly in flavonoids, phenolic acids, alkaloids, and terpenoids. Some of these components are directly or indirectly attributed to the pharmacological activities of plants in the genus *Gnaphalium*. According to previous research, the chemical studies of the genus *Gnaphalium* have mainly focused on *G. affine*, *G. hypoleucum*, *G. sylvaticum*, *G. undulatum*, *G. oligandrum*, *G. pellitum*, *G. oxyphyllum*, and *G. adnatum*. Here, the structures and other information of these identified compounds are summarized in Figs 2–12 and Table 2, respectively.

Fig. 1 The morphology of the *Gnaphalium affine* and its processed products. (a), (b) The overground part of *G. affine*. (c) The pastry of *G. affine*, called qingtuan, also known as Qingming food.

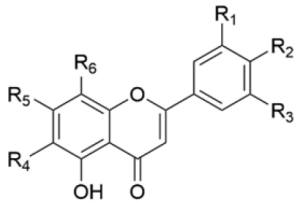
Table 1. Ethnopharmacological uses of reported *Gnaphalium* species.

Gnaphalium species	Country	Ethnopharmalogical uses	Reference
G. affine	China, Mexico, Latin America	Phlegm-removing, anemopyretic cold, antibacterial, bronchitis, chronic obstructive pulmonary diseases, antihypertensive, ulcer, antitussive, expectorant, antiasthmatic, bronchial asthma, respiratory disease, diuretics, antipyretics and antimalarials, wound, backache, coronarism.	[8–24]
G. hypoleucum	China	Inflammation, cough, gout, expectorant.	[25]
G. polycaulon	China	Clear heat and dampness.	[26]
G. japonicum	China	Promoting blood circulation to relieve pain, promoting dampness, treating acne, irregular menstruation, abdominal pain and dysentery during menstruation, clearing away heat and toxins.	[27,28]
G. adnatum	China	Treat *Helicobacter pylori*.	[29]
G. uliginoshisum	Russia, Bulgaria	Hypertension, thrombophlebitis, venous thrombosis, ulcer.	[30,31]
G. stramineum	Guatemala	Gastrointestinal diseases.	[32]
G. gaudichaudianum	Latin America, Argentina	Subcutaneous mycoses, expectorant, hemostasis.	[33,34]
G. liebmannii	Mexico	Asthma, cough, bronchitis.	[35]

Flavonoids

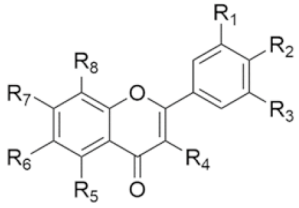
Flavonoids are very common compounds in the genus *Gnaphalium*. Several studies have described flavonoids as a chemical index for the quality study of the herbs in *Gnaphalium*, even though they are not included in the Chinese Pharmacopoeia. Nevertheless, the flavonoid content in *Gnaphalium* is not high and varies significantly in different regions[36,37].

To date, over 100 flavonoids have been authenticated in genus *Gnaphalium*, which are mainly classified as flavonol, dihydroflavone, chalcone, and others. In flavonol, quercetin is the most significant aglycone, while luteolin and apigenin are the main skeletons in other flavonoids. Among the flavone glycosides in *Gnaphalium*, glucose is the main substituted group, which are mostly located in C-7 of flavonoids, except for C-3-substituted glucose in isorhamnetin-3-*O*-*β*-*D*-galactopyranoside (**47**), patuletin-3-*O*-*β*-*D*–glucopyranoside (**48**), quercetin-3-*O*-*β*-*D*-galactopyranoside (**57**), kaempferol-3-*O*-*β*-*D*-glucopyranoside (**61**), 3,5,7,4'-tetrahydroxy-3'-methoxyflavonoid-3-O-*β*-D-glucopyranoside (**72**), and 3,5,7,3',4'-pentahydroxy-6-methoxyflavonoid-3-*O*-*β*-*D*-glucopyranoside (**73**). Interestingly, another type of flavone glycosides, including quercetin-4'-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**46**), apigenin-7-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**40**), apigenin-4'-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**1**), luteolin-



1:R_1=R_3=R_4=R_6=H,R_2=O-β-D-(6''-E-Caffeoyl)-Glu,R_5=OH
2:R_1=R_4=OCH_3,R_2=OH,R_3=R_6=H,R_5=O-β-D-(6''-E-Caffeoyl)-Glu
3:R_1=R_3=R_4=R_6=H,R_2=OH,R_5=O-β-D-Glu
4:R_1=OCH_3,R_2=OH,R_3=R_4=R_6=H,R_5=O-β-D-Glu
5:R_1=R_3=R_4=R_6=H,R_2=OH,R_5=O-glucuronic acid methylester
6:R_1=R_3=R_4=R_6=H,R_2=R_5=OH
7:R_1=R_5=OH,R_2=O-β-D-Glu,R_3=R_4=R_6=H
8:R_1=R_3=R_4=R_6=H,R_2=R_5=OCH_3
9:R_1=R_3=R_4=R_6=H,R_2=OCH_3,R_5=OH
10:R_1=R_2=R_5=OH,R_3=R_4=R_6=H
11:R_1=R_2=R_3=R_4=R_6=H,R_5=OH
12:R_1=R_2=R_4=R_5=OCH_3,R_3=R_6=H
13:R_1=R_2=OH,R_3=R_4=R_6=H,R_5=O-methyl glucuronate
14:R_1=R_2=R_4=OH,R_3=R_6=H,R_5=O-β-D-Glu
15:R_1=R_3=R_4=R_6=H,R_2=OCH_3,R_5=O-rutinoside
16:R_1=R_2=,R_3=R_6=H,R_4=OCH_3,R_5=O-β-D-Glu
17:R_1=R_4=OCH_3,R_2=R_5=OH,R_3=R_6=H
18:R_1=R_2=R_5=OH,R_3=R_6=H,R_4=OCH_3
19:R_1=R_2=OH,R_3=R_4=R_6=H,R_5=O-β-D-Glu
20:R_1=R_3=R_4=R_6=H,R_2=O-β-D-Glu,R_5=OH
21:R_1=R_3=OCH_3,R_2=R_5=OH,R_4=R_6=H
22:R_1=R_3=R_4=R_6=H,R_2=OCH_3,R_5=O-β-D-rutinoside
23:R_1=R_2=,R_3=R_4=R_6=H,R_5=O-glucuronate
24:R_1=R_3=R_4=R_6=H,R_2=OCH_3,R_5=O-β-D-xylopyranosyl-(1- 2)[a -L-rhamnopyranosyl-(1-6)]-β-D-glucopyranoside
25:R_1=R_5=OH,R_2=O-β-D-(6''-E-Caffeoyl)-Glu,R_3=R_4=R_6=H
26:R_1=R_2=OH,R_3=R_6=H,R_4=OCH_3,R_5=O-β-D-(6''-E-Caffeoyl)-Glu
27:R_1=R_2=OH,R_3=R_4=R_6=H,R_5=OCH_3
28:R_1=R_2=OH,R_3=R_6=H,R_4=OCH_3,R_5=O-β-D-Glu
29:R_1=R_2=R_3=R_4=H,R_5=R_6=OCH_3
30:R_1=R_3=R_6=H,R_2=R_5=OH,R_4=OCH_3
31:R_1=R_5=R_6=OCH_3,R_2=OH,R_3=R_4=H
32:R_1=R_2=R_3=H,R_6=OH,R_4=R_5=OCH_3
33:R_1=R_3=R_6=H,R_2=OH,R_4=OCH_3,R_5=O-β-D-Glu
34:R_1=R_4=OCH_3,R_2=R_5=OH,R_3=R_6=H
35:R_1=OCH_3,R_2=OH,R_3=R_4=R_6=H,R_5=O-β-D-Glu
36:R_1=R_2=R_3=R_4=H,R_5=OH,R_6=O-2-Methylbutyryl
37:R_1=R_2=R_3=R_4=H,R_5=OH,R_6=O-(z)-2-Methylbutenoyl
38:R_1=R_4=R_8=H,R_2=R_3=R_6=OCH_3,R_5=R_7=OH
39:R_1=R_4=OCH_3,R_2=OH,R_3=R_6=H,R_5=O-β-D-(6''-E-Caffeoyl)-Glu
40:R_1=R_3=R_4=R_6=H,R_2=OH,R_5=O-β-D-(6''-E-Caffeoyl)-Glu

Fig. 2 Structures of flavones in genus *Gnaphalium*.



41:R_1=R_3=R_6=H,R_2=R_4=R_8=OCH_3,R_5=R_7=OH
42:R_1=R_3=R_6=R_8=H,R_2=R_5=R_7=OH,R_4=O-β-D-(6''-E-caffeoyl)-glucopyranoside
43:R_1=R_2=R_4=R_6=R_7=R_8=OCH_3,R_3=H,R_5=OH
44:R_1=R_3=R_6=R_8=H,R_2=R_5=R_7=OH,R_4=O-β-D-(6''-O-coumarin)-glucopyranoside
45:R_1=OCH_3,R_2=R_4=R_5=OH,R_3=R_6=R_8=H,R_7=O-β-D-glucopyranoside
46:R_1=R_4=R_5=R_7=OH,R_3=R_6=R_8=H,R_2=O-β-D-(6''-E-caffeoyl)-glucopyranoside
47:R_1=OCH_3,R_3=R_6=R_8=H,R_2=R_4=R_7=OH,R_5=O-β-D-galactopyranoside
48:R_1=R_2=R_5=R_7=OH,R_6=OCH_3,R_3=R_8=H,R_4=O-β-D-glucopyranoside
49:R_1=R_2=R_5=R_7=OH,R_3=R_6=R_8=H,R_4=OCH_3
50:R_1=R_2=R_3=R_6=H,R_4=R_8=OCH_3,R_5=R_7=OH
51:R_1=R_2=R_5=R_7=OH,R_3=R_6=R_8=H,R_4=OCH_3
52:R_1=R_2=R_4=R_5=OH,R_3=R_6=R_8=H,R_7=OCH_3
53:R_1=R_3=H,R_2=R_4=R_6=R_7=OCH_3,R_5=R_8=OH
54:R_1=R_2=R_4=R_5=OH,R_3=R_6=R_8=H,R_7=O-β-D-glucopyranoside
55:R_1=R_2=R_3=R_6=H,R_4=OCH_3,R_5=R_7=OH,R_8=(2-Methylbutyric acid)
56:R_1=R_2=R_4=R_5=OH,R_3=R_6=R_8=H,R_7=O-β-D-glucopyranoside
57:R_1=R_2=R_5=R_7=OH,R_3=R_6=R_8=H,R_4=O-β-D-galactopyranoside
58:R_1=R_2=R_3=R_6=R_8=H,R_4=R_7=OCH_3,R_5=OH
59:R_1=R_2=R_4=R_5=OH,R_3=R_6=R_8=H,R_7=OCH_3
60:R_1=R_2=R_4=R_5=R_7=OH,R_3=R_6=R_8=H
61:R_1=R_3=R_6=R_8=H,R_2=R_5=R_7=OH,R_4=O-β-D-glucopyranoside
62:R_1=R_3=H,R_2=R_4=R_6=R_7=R_8=OCH_3,R_5=OH
63:R_1=R_2=R_3=R_8=H,R_4=R_7=OCH_3,R_5=R_6=OH
64:R_1=R_3=R_8=H,R_2=R_4=R_5=R_6=OH,R_7=O-β-D-glucopyranoside
65:R_1=R_3=R_6=R_8=H,R_2=R_5=R_7=OH,R_4=OCH_3
66:R_1=R_4=R_5=R_7=OH,R_2=O-β-D-glucopyranoside,R_3=R_6=R_8=H
67:R_1=R_2=R_5=R_7=OH,R_3=R_6=R_8=H,R_4=O-β-D-glucopyranoside
68:R_1=R_2=R_4=R_5=R_6=R_7=OH,R_3=R_8=H
69:R_1=R_5=R_7=OH,R_2=O-β-D-glucopyranoside,R_3=R_6=R_8=H,R_4=O-β-D-galactopyranoside
70:R_1=R_2=R_4=R_5=R_6=OH,R_3=R_8=H,R_7=O-β-D-glucopyranoside
71:R_1=OCH_3,R_2=R_4=R_5=R_7=OH,R_3=R_6=R_8=H
72:R_1=OCH_3,R_2=R_5=R_7=OH,R_3=R_6=R_8=H,R_4=O-β-D-glucopyranoside
73:R_1=R_2=R_5=R_7=OH,R_3=R_8=H,R_4=O-β-D-glucopyranoside,R_6=OCH_3
74:R_1=R_2=R_3=R_6=H,R_4=R_5=OH,R_7=R_8=OCH_3
75:R_1=R_2=R_3=H,R_4=R_5=OH,R_6=R_7=R_8=OCH_3
76:R_1=R_3=H,R_2=R_5=R_7=R_8=OCH_3,R_4=R_5=OH
77:R_1=R_2=R_3=R_6=H,R_4=R_7=R_8=OCH_3,R_5=OH
78:R_1=R_2=R_3=H,R_4=R_6=R_7=R_8=OCH_3,R_5=OH
79:R_1=R_2=R_3=R_6=H,R_4=R_8=OCH_3,R_5=R_7=OH
80:R_1=R_2=R_3=R_6=R_8=H,R_4=OCH_3,R_5=R_7=OH
81:R_1=R_2=R_3=R_6=H,R_4=OCH_3,R_5=R_7=OH,R_8=O-(2-Meyhyl-2-butenoyl)
82:R_1=R_2=R_3=R_8=H,R_4=R_6=OCH_3,R_5=R_7=OH
83:R_1=R_2=R_3=H,R_4=R_6=R_7=OCH_3,R_5=R_8=OH
84:R_1=R_2=R_3=H,R_4=R_6=R_8=OCH_3,R_5=R_7=OH
85:R_1=R_5=R_4=R_8=OCH_3,R_3=R_6=H,R_5=R_7=OH
86:R_1=R_2=R_3=H,R_4=R_5=R_7=OH,R_6=R_8=OCH
87:R_1=R_2=R_3=R_6=H,R_4=OCH_3,R_5=R_7=R_8=OH
88:R_1=R_2=R_5=OH,R_3=R_6=R_7=R_8=H,R_4=OCH_3

Fig. 3 Structures of flavonols in genus *Gnaphalium*.

4'-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**25**), 5,7,3',4'-Tetrahydroxy-6-methoxyflavonoid-7-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**26**), and naringenin-7-*O*-*β*-*D*-(6''-E-caffeoyl)-glucopyranoside (**97**), were isolated from *G. affine,* which contain an E-caffeoyl group in the flavone glycosides[57]. The information of the aforementioned flavonoids are presented in Figs 2–4 and Table 2, respectively.

Terpenoids

Terpenes and terpenoids are very common natural products in the world, and over 22,000 chemicals have been identified from various plants[58]. Because of the basic five-carbon isoprene units in terpenes and terpenoids, they were divided into monoterpenoids, sesquiterpenes, diterpenoids, and triterpenoids with distinct functional groups[59,60]. Due to its diverse structures, several activities, such as anti-inflammatory, antiparasitic, antioxidant, anticancer, antiviral, and antimicrobial properties, have been reported[61]. In this review, 50 terpenes and terpenoids were identified in genus *Gnaphalium* (Figs 5–8, Table 2). Here, we will focus on these compounds and provide an overview of terpenes and terpenoids in genus *Gnaphalium*.

Triterpenoids

Triterpenoids usually contain six five-carbon isoprene units. Normally, these units can be connected into different carbon ring and formed different types of triterpenoids. The major triterpenoids (**105**–**120**) isolated from genus *Gnaphalium* mainly use amyrin and ursolic acid as structural skeletons, and most of them are distributed in *G. affine*, except for squalene in *G. gaudichaudianum*. Among them, eight ursane triterpenes (**109–116**) are the most abundant, followed by four oleanane triterpenes (**105**–**108**). Also, three lupane triterpenes (**117–119**) and one chain triterpene (**120)** identified in *G. affine*. All information, including names, structures and source plants of triterpenoids, are listed in Table 2 and Fig. 5.

Diterpenoids

Up to now, **37** diterpenoids are identified in genus *Gnaphalium*, and most of them possess (–)-pimara-8(14), 15-diene and

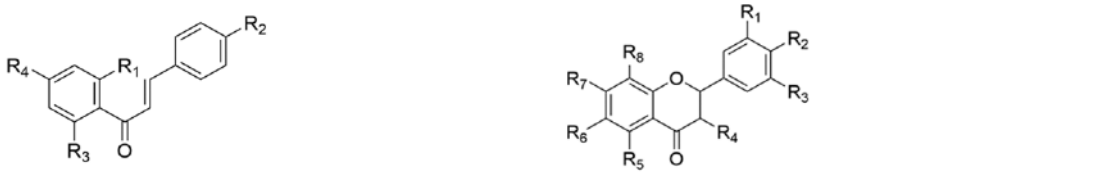


Fig. 4 Chalcones and flavanones isolated from the genus *Gnaphalium*.

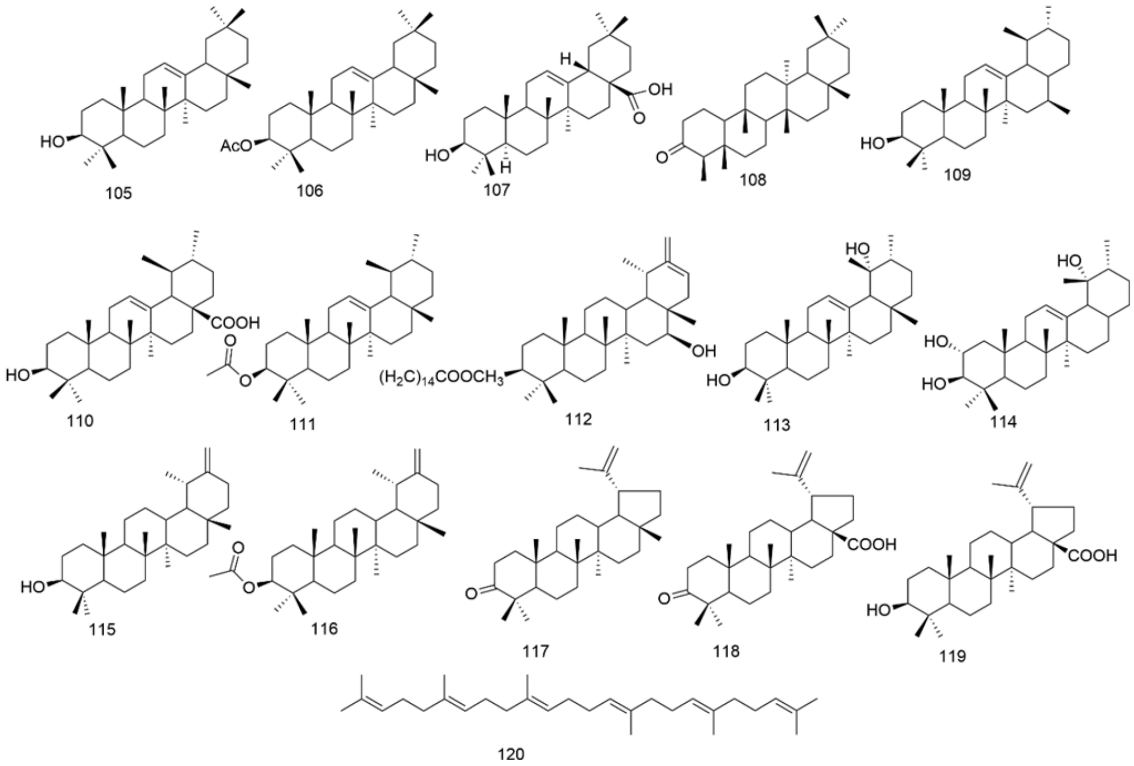


Fig. 5 Structures of triterpenoids in genus *Gnaphalium*.

(–) kaurene as chemical skeletons. In total, 22 kaurane diterpenes (**132–147, 151–156**), nine pimarane diterpenes (**121–127, 148, 140**), four labane diterpenes (**128–131**) were identified. In addition, there is one rare diterpene (**157**), which was a 15-hydroxy substituted wedeliaseccokaurenolide, from *G. undulatum*. The structures, names and source plants of diterpenes in genus *Gnaphalium* are presented in Fig. 6 and Table 2. By comparing the distribution of different compounds in genus *Gnaphalium*, it is found that diterpenes are the main component of *G. gaudichaudianum*, which can be regarded as a marker of *G. gaudichaudianum* to distinguish from other species.

Sesquiterpenoids

A total of 20 sesquiterpenoids were isolated from genus *Gnaphalium*. Among them, **185** and **186** are isolated from *G. oligandrum*, while **170, 172, 176**, and **177** are from *G. japonicum*. The specific information, including names and source plants of these compounds, are listed in Table 2.

Monoterpenoids

Five monoterpenoids were identified from *G. affine* (**178**–**182**).

Phenolic acids

Phenolic acids are normally considered as antioxidants because of the presence of phenol moiety and the ability to induce endogenous protective enzymes[62]. Also, phenolic acids have demonstrated anti-diabetic potential by inhibiting alpha-glucosidase and alpha-amylase, converting carbohydrates into glucose[63]. Furthermore, compared to methyl ester and butyl ester, the inhibitory effect of phenolic acid on microbial growth has been extensively investigated[64]. In genus *Gnaphalium*, 27 phenolic acids are isolated and identified, most of them are from *G. affine*. Additionally, caffeoyl substituted quinic acid is a special type of phenolic acids, in which quinic acid and caffeioyl groups are connected *via* the ester bond (Fig. 9, Table 2).

Steroids and sterols

Sterol compounds are structurally composed of four-cyclic compounds with a cyclopentanoperophenanthrene nucleus[65]. However, only seven steroids have been authenticated in the genus *Gnaphalium*. Among them, *β*-sitosterol **(212)** was confirmed to exist in *G. affine, G. hypoleucum, G. inornatum, G. pellitum, G. oxyphyllum, G. liebmannii,* and *G. viscosum*. Among the species, all the steroids were identified from *G. affine*. One

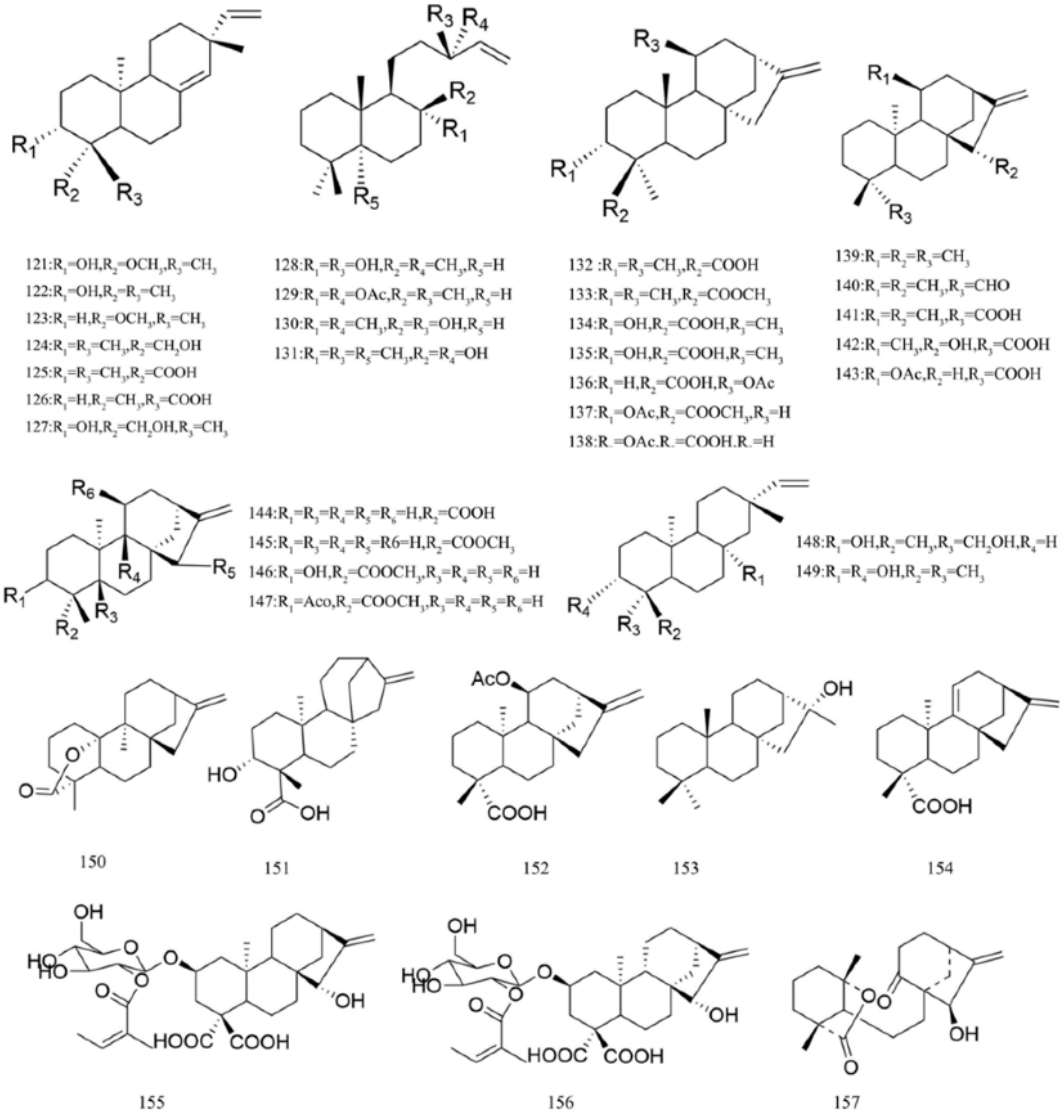


Fig. 6 Diterpenoids isolated from the genus *Gnaphalium*.

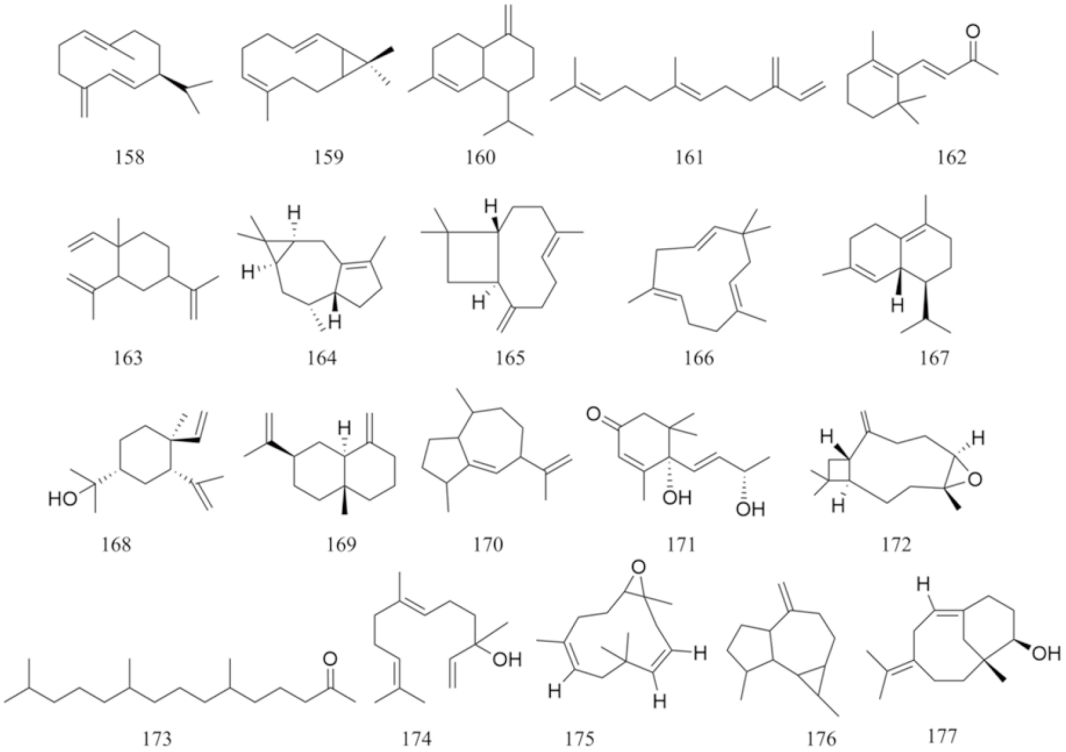


Fig. 7 Sesquiterpenoids isolated from the genus *Gnaphalium*.

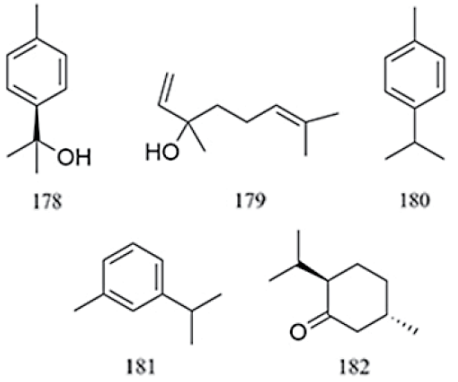


Fig. 8 Monoterpenoids isolated from the genus *Gnaphalium*.

glycosides, *β*-daucosterin (**210**), was isolated from *G.affine, G.adnatum,* and *G.hypoleucum*[38].

Alkaloids

Alkaloid compounds typically contain nitrogen atoms in their structures[66]. Currently, seven alkaloid (**217**–**223**) compounds have been found in the genus *Gnaphalium*.

Others

In addition to the previously reported compounds, other types of compounds, including sterols, amino acids, tannins, polysaccharides, etc., have also been isolated from genus *Gnaphalium*[48] (Fig. 12, Table 2) .

Pharmacology

Pulmonary protection

Most varieties of *Gnaphalium* are traditionally used to treat several respiratory diseases, such as asthma, cough, bronchitis, and bronchial infections. In the guinea pig tracheal experiment, the effect of methanol extract of *G. conoideum* on contractile agonist response was studied, and it was found that *G. conoideum* significantly reduced the contractile response to histamine by partially blocking Ca^{2+} channels[67]. Likewise, the tension change experiment of guinea pig tracheal segments was used to evaluate the anti-asthmatic effect of *G. liebmannii*, showing that the hexane extract can cause the concentration response curve of aminophenol to shift parallel to the right in a competitive manner, rather than causing the concentration response curve of histamine to shift parallel to the right, indicating that *G. liebmannii* can act as a phosphodiesterase inhibitor for tracheal muscle relax[68]. Additionally, *G. affine* is used as traditional medicine to treat expectorant and cough in China. Ye et al. evaluated the antitussive and expectorant activities of total flavonoids from *G. affine in vivo*, showing that macroporous resin-purified total flavonoids (purity: 40.13%) significantly decreased the number of cough times during 5 min and alleviated sputum secretion[69,70]. Similarly, the pretreatment of *G. affine* significantly decreased the inflammatory cytokines in alveolar lavage fluid of COPD (chronic obstructive pulmonary disease) rats[70]. Moreover, eight bioactive compounds were identified from *G. affine* extract through activity-guided fractionation, in which luteolin-4'-*O*-*β*-*D*-(6''-E-caffeoyl)-glucoside (**27**) displayed remarkable noncompetitive inhibition kinetics against human neutrophil elastase (HNE)[71].

Antimicrobial activity

The crude extracts and isolated plant compounds extracted from different species in *Gnaphalium* have antibacterial properties. For example, Caceres et al. investigated the antibacterial activity of the ethanolic extract from *G. stramineum* and *G.viscosum* against eight strains of bacteria including *Escherichia coli*,

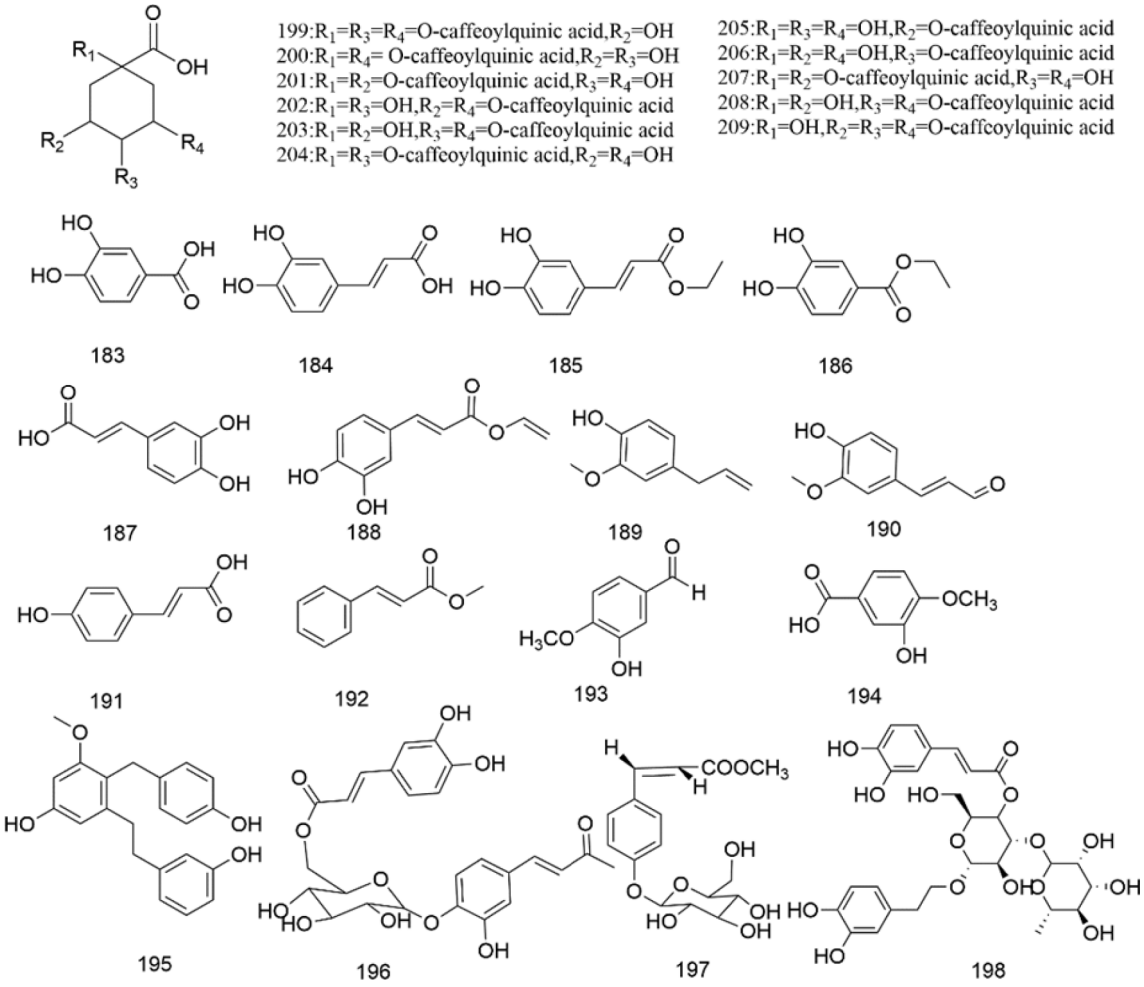


Fig. 9 Phenolic acids isolated from the genus *Gnaphalium*.

Salmonella enteritidis, *Salmonella typhi*, *Shigella dysenteriae*, *Shiegella flexneri*, *Staphylococcus aureus*, *Staphylococcus pneumonia*, and *Staphylococcus pyogenes*. Interestingly, extract from *G. stramineum* showed promising inhibitory effect against *S. typhi* and *S. dysenteriae* (≥ 9 mm), which are involved in gastrointestinal disorders; while extract from *G. viscosum* had a strong inhibitory effect against *S. pneumonias* and *S. pyogenes* that are associated with respiratory disease[32,72]. Additionally, *G. gaudichaudianum* methanol extract suppressed the growth of *Sporothrix schenckii* and *Fonsecaea pedrosoi* with MIC values of 50 and 12.5 μg/mL, respectively; and methanol, hexanic, and chloroformic extracts of *G. hirsutum* inhibited the growth of *Streptococcus pyogenes*[73]. The antimicrobial activity of extracts from different parts of *G. oxyphyllum* var. *oxyphyllum* hexanic was also evaluated, and demonstrated that the flower extract showed more broad-spectrum antimicrobial effect compared with the leaves extract[74].

Currently, it is believed that the antibacterial effect of *G. polycaulon* is related to its secondary metabolites. Previous study used *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* strains to test the antibacterial activity of chemicals in *G. polycaulon*, showing that the antibacterial activity of **255–257** with MIC values of 0.0077–44.85 μM[75]. Moreover, eugenol and linalool, the main essential oil in *G. affine* showed remarkable antimicrobial effect in food-borne microorganisms test[7]. In addition, eugenol could significantly reduce biofilm formation of *Vibrio parahaemolyticus* in Ashrafudoulla et al.'s research[76].

Antioxidant activity

The ethanol extract of *G. roseum*, which mainly contained flavonoids and phenols, exerted an antioxidant effect by the free radical scavenging test of α, α-diphenyl-β-picrylhydrazyl (DPPH), with a half-maximal inhibitory concentration (IC50) of ~72.9 ± 3.2 μg/mL. The antioxidant capacity of *G. affine* ethanol extract was demonstrated with the H_2O_2-induced oxidative stress, in which *G. affine* extract ameliorated oxidative reaction *via* the PI3K/AKT/GSK-3β signaling pathway in H9c2 cells, and 17 compounds including phenols and flavonoids, were identified in this extract by LC-MS analysis[77]. Moreover, 2,2'-Azino-bis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS), superoxide, and hydroxyl radical scavenging assays were used to bio-guided isolate the antioxidant compounds in *G. affine*, revealing quercetin (60) as the main antioxidant component[78]. In addition, flavonoids including apigenin (**6**), chrysin (**11**), wogonin (101), and luteolin (**10**) were well-represented in the ethanol extract of *G. affine*, and showed remarkable free radical scavenging capacity[38].

Anti-inflammatory and anti-complementary activities

Carrageenan-induced paw edema and collagen-induced arthritis models were used test the anti-inflammatory activity of

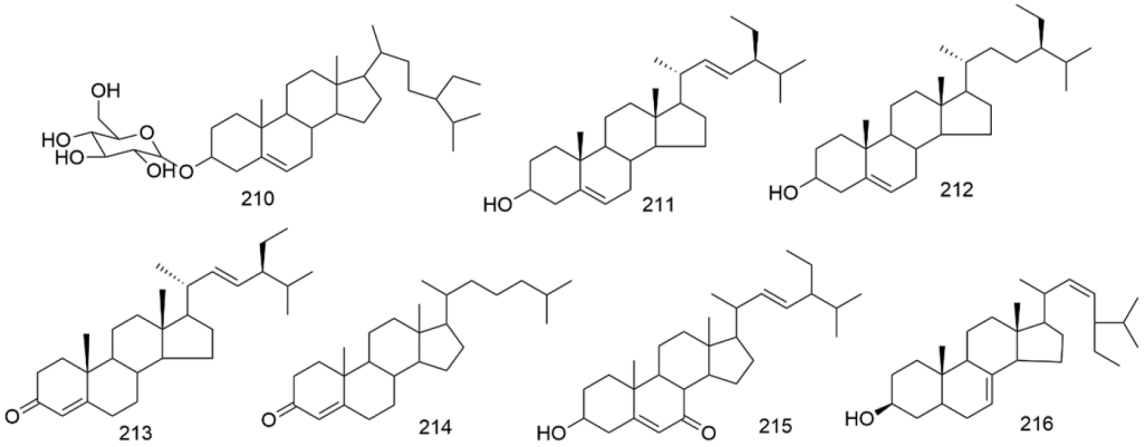


Fig. 10 Steroids and sterols isolated from the genus *Gnaphalium*.

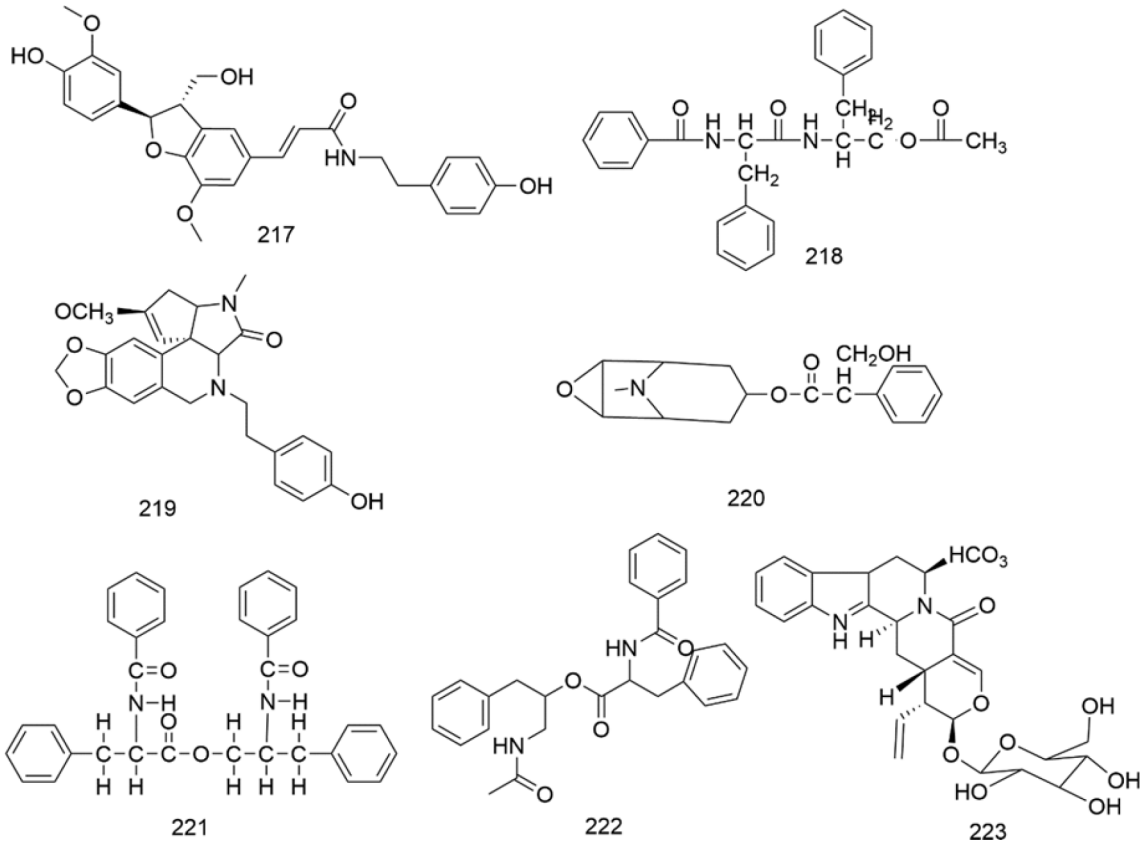


Fig. 11 Alkaloids isolated from the genus *Gnaphalium*.

G. affine ethanol extract, showing that the swelling caused by carrageenan and the inflammation caused by collagen were inhibited or reduced by 600 and 300 mg/kg extracts, respectively[79]. Another study showed that the methanol extract of *G. affine* decreased the expressions of *iNOS* and *COX*-2 in LPS-stimulated RAW264.7 cells by inhibiting the activation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways[80]. Apart from *G. affine*, different polar solvent extracts of *G. stramineum* demonstrated that the methanol extract suppressed the carrageenan-induced edema in rats[81]. Bioassay-guided fractionation of the methanol extract of *G. affine* resulted in the isolation of four anti-inflammatory compounds, quercetin (**60**), luteolin (**10**), quercetin-4'-O-β-D-(6''-E-caffeoyl)-glucoside(**46**) and luteolin-4'-O-β-D-(6''-E-caffeoyl)-glucoside (**25**), according to NO expression in LPS-stimulated RAW264.7 cells. Furthermore, luteolin-4'-O-β-D-(6''-E-caffeoyl)-glucoside (**25**) was confirmed to exert anti-inflammatory effect *via* suppressing the expression of *COX*-2[71].

The complement system is an essential part of the innate immunity and plays an important role in inflammatory reaction[82]. The anti-complementary activity of *G. hypoleucum* ethanol extract and its fractions were assayed based on the classical pathway of the complement system *in vitro*, revealing that the total ethanol extract possessed a more potent anti-complementary effect (CH_{50} = 0.165 ± 0.025)[83]. Through a systematic chemical study of *G. hypoleucum*, ursolic acid and

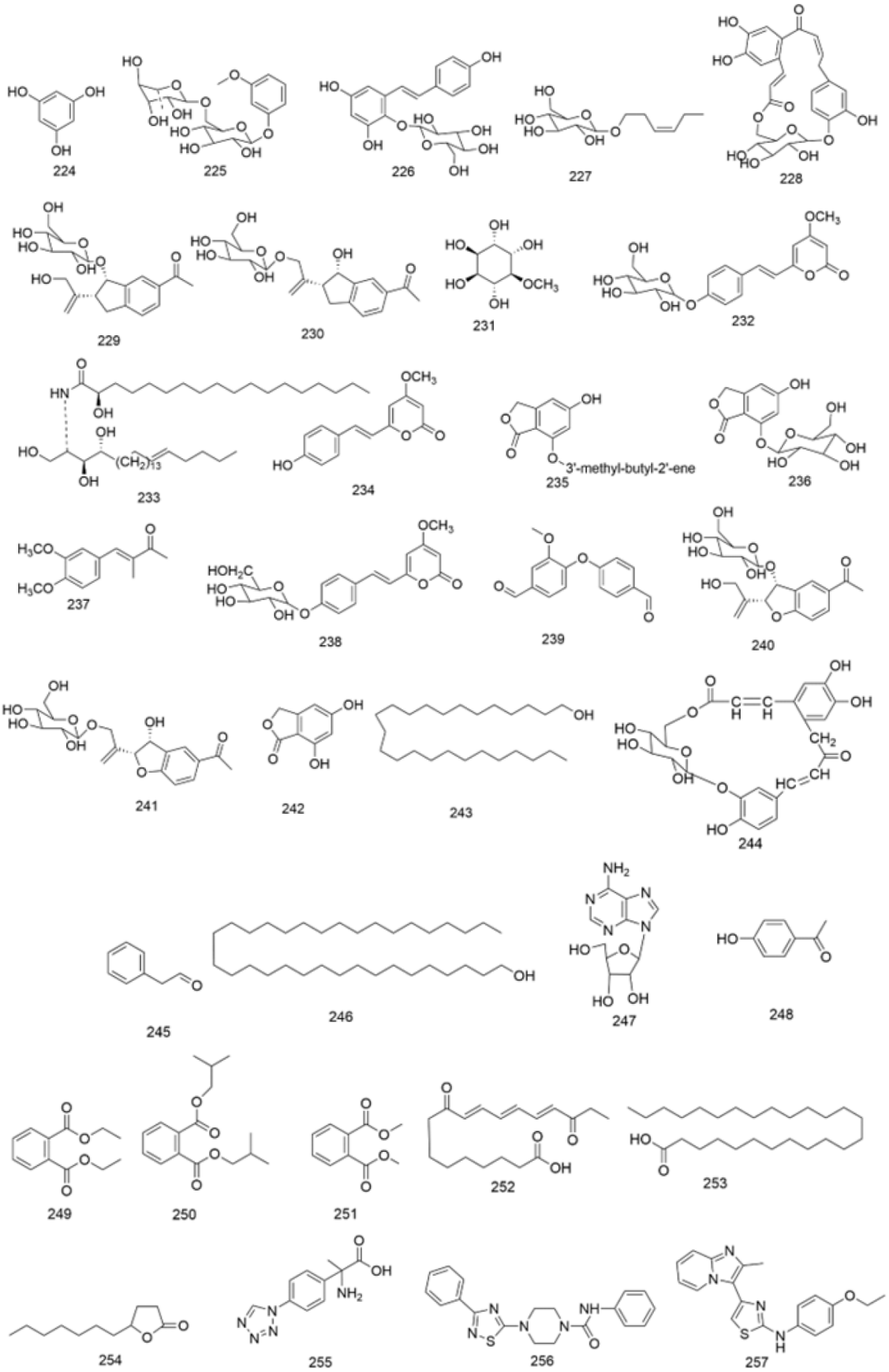


Fig. 12 Other compounds isolated from the genus *Gnaphalium*.

Table 2. Compounds isolated and identified from the *Gnaphalium* L.

No.	Compound	Source	Reference
Flavones			
1	Apigenin 4'-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. affine*	[3,5]
2	Gnaphaloside A	*G. tranzschelii*	[5]
3	Apigenin-7-O-β-D-glucopyranoside	*G. tranzschelii, G. luteoalbum*	[3,5]
4	Chrysoeriol-7-O-β-D -glucopyranoside	*G. uliginosum*	[3]
5	Apigenin-7-O-β-D-glucuronic acid methylester	*G. affine, G. hypoleucum*	[5,38]
6	Apigenin	*G. affine, G. hypoleucum*	[36–38]
7	Luteolin-4'-O-β-D-glucopyranoside	*G. affine, G. cheiranthifolium, G. hypoleucum, G. luteoalbum*	[37,38]
8	5-hydroxy-4',7-dimethoxyflavonoid	*G. affine*	[38]
9	Acacetin	*G. affine*	[38]
10	Luteolin	*G. affine, G. hypoleucum, H. polycaulon, G. luteoalbum, G. rufescens, G. sylvaticum, G. oxyphyllum*	[36–38]
11	Chrysin	*G. affine*	[38]
12	5-hydroxy-6,7,3',4'-tetramethoxyflavone	*G. affine*	[39]
13	Luteolin-7-O-β-D-glucuronide methyl ester	*G. hypoleucum*	[3]
14	6-Hydroxyluteolin-7-O-β-D-glucopyranoside	*G. hypoleucum, G. affine, G. tranzschelii*	[5,40]
15	Acacetin-7-O-rutinoside	*G. affine*	[3]
16	Eupafolin-7-O-β-D-glucopyranoside	*G. affine*	[3]
17	5,7,4'-trihydroxy-6,3'-dimethoxyflavone	*G. luteoalbum*	[3]
18	6-MethoxyLuteolin	*G. uliginosum, G. tranzschelii*	[3,5]
19	Luteolin-7-O-β-D-glucopyranoside	*G. luteoalbum, G. hypoleucum*	[3,5]
20	Apigenin-4'-O-β-D-glucopyranoside	*G. affine*	[3]
21	5,7,4'-trihydroxy-3',5'-dimethoxyflavone	*G. sylvaticum*	[3]
22	Linarin	*G. hypoleucum*	[3]
23	Luteolin-7-O-β-D-glucuronide	*G. hypoleucum*	[3]
24	Acacetin-7-O-β-D-xylopyranosyl-[α-L- rhamnopyranosyl]-β-D-glucopyranoside	*G. hypoleucum*	[3]
25	Luteolin 4'-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. hypoleucum, G. affine*	[3,5]
26	5,7,3',4'-Tetrahydroxy-6-methoxyflavonoid-7-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. tranzschelii*	[5]
27	Luteolin 7-O-methyl ether	*G. rufescens*	[5]
28	5,7,3',4'-tetrahydroxy-6-methoxyflavonoid-7-O-β-D-glucopyranoside	*G. tranzschelii*	[5]
29	5-hydroxy-7,8-dimethoxyflavone	*G. pellitum*	[5]
30	Hispidulin	*G. antennarioides*	[5]
31	Velutin	*G. gaudichaudianum*	[5]
32	5,8-dihydroxy-6,7-dimethoxyflavone	*G. gaudichaudianum*	[5]
33	Hispidulin 7-O-β-D-glucopyranoside	*G. antennarioides*	[5]
34	Jaceosidin	*G.luteoalbum, G.tranzschelii*	[5]
35	3,5,7,4'-tetrahydroxy-3'-methoxyflavonoid-7-O-β-D-glucopyranoside	*G. tranzschelii*	[5]
36	8-O-(2-methylbutyryl)-5,7,8-trihydroxyflavone	*G. robuscum*	[5]
37	8-O-[(Z)-2-methyl-2-butenyl]-5,7,8-trihydroxyflavone	*G. robuscum*	[5]
38	Eupatilin	*G. affine*	[39]
39	5,7,4'-Trihydroxy-3'-methoxyflavonoid-7-O-β-D-(6''-O-caffeoyloxy)-glucopyranoside	*G. affine, G. uliginosum*	[38]
40	Apigenin 7-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. affine*	[3,5]
Flavonols			
41	5,7-dihydroxy-3,8,4'-trimethoxyflavonoid	*G. hypoleucum, G. affine*	[38,40]
42	Tiliroside	*G. adnatum*	[41]
43	5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone	*G. affine, G. hypoleucum*	[2]
44	Kaempferol 3-O-β-D-(6''-O-coumarin)-glucopyranoside	*G. affine*	[42]
45	Isorhamnetin-7-O-β-D-glucopyranoside	*G. affine*	[38]
46	Quercetin 4'-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. hypoleucum, G. affine*	[3,5]
47	Isorhamnetin-3-O-β-D-galactopyranoside	*G. uliginosum*	[3]
48	Patuletin-3-O-β-D -glucopyranoside	*G. uliginosum*	[3]
49	5,7,3',4'-Tetrahydroxy-3-methoxyflavonoid	*G. indicum*	[3]
50	5,7-dihydrox-3,8-dimethoxyflavone	*G. gracile*	[3]
51	3-Methoxyquercetin	*G. gracile*	[3]
52	7-Methoxyquercetin	*G. pellitum*	[3]
53	5,8-Dihydroxy-3,6,7,4'-tetramethoxyflavonoid	*G. affine*	[42]
54	Quercitrin	*G. affine, G. sylvaticum*	[5]
55	8-O-(2-methylbutyrate)-5,7-dihydroxy 3-methoxyflavonoid	*G. robustum*	[3]
56	Quercimeritrin	*G. hypoleucum*	[43]

(to be continued)

Table 2. (continued)

No.	Compound	Source	Reference
57	Quercetin-3-O-β-D-galactopyranoside	*G. hypoleucum*	[43]
58	5-hydroxy-3,7-dimethoxyflavone	*G. uiscosum*	[42]
59	Rhamnetin	*G. pellitum, G. affine*	[5,38]
60	Quercetin	*G. affine, G. gracile, G. hypoleucum, G. polycaulon, H. pellitum, G. sylvaticum, l. G. uniflorum*	[36–38]
61	Kaempferol-3-O-β-D-glucopyranoside	*G. affine, G. uniflorum*	[5,38]
62	5-Hydroxy-3,6,7,8,4'-pentamethoxyflavone	*G. affine, G. hypoleucum*	[38]
63	5,6-dihydroxy-3,7-dimethoxyflavone	*G. affine*	[38]
64	Baicalein-7-O-β-D-glucopyranoside	*G. tranzschelii*	[5]
65	Isokaempferol	*G. dioicum*	[5]
66	Quercetin 4'-O-β-D-glucopyranoside	*G. affine, G. hypoleucum*	[5,40]
67	Isoquercitrin	*G. stramineu, G. sylvaticum, G. tranzschelii, G.uniflorum*	[5]
68	Quercetagetin	*G. affine*	[5]
69	Quercetin 3-O-β-D-galactopyranoside-4'-O-β-D-glucopyranoside	*G. uniflorum, G. affine*	[5]
70	Quercetagetin 7-O-β-D-glucopyranoside	*G. affine*	[5]
71	Isorhamnetin	*G. affine, G. hypoleucum*	[5]
72	3,5,7,4'-tetrahydroxy-3'-methoxyflavone-3-O-β-D-glucopyranoside	*G. tranzschelii*	[5]
73	3,5,7,3',4'-Pentahydroxy-6-methoxyflavone-3-O-β-D-glucopyranoside	*G. tranzschelii*	[5]
74	Gnaphaliin B	*G. affine, G. liebmannii*	[5]
75	3,5-dihydroxy-6,7,8-trimethoxyflavone	*G. chilense, G. microecephalum, G. robustum*	[5]
76	3,5-Dihydroxy-6,7,8,4'-tetramethoxyflavone	*G. affine*	[5]
77	5-Hydroxy-3,7,8-trimethoxyflavone	*G. affine, G. robustum, G. obtusifolium*	[5]
78	5-hydroxy-3,6,7,8-tetramethoxyflavonoid	*G. affine, G. hypoleucum,G. undulatum*	[5]
79	Gnaphaliin A	*G. affine, G. gracile, G. lanuginosum, G. liebmannii, G. obtusifolium, G. robustum*	[5]
80	5,7-Dihydroxy-3-methoxyflavonoid	*G. gracile, G. robustum*	[5]
81	8-O-(2-methyl-2-butenyl)-5,7-dihydroxy-3-methoxyflavonoid	*G. robustum*	[5]
82	5,7-dihydroxy-3,6-dimethoxyflavone	*G. wrightii*	[5]
83	5,8-dihydroxy-3,6,7-trimethoxyflavone	*G. affine, G. gaudichaudianum*	[5]
84	5,7-Dihydroxy-3,6,8-trimethoxyflavone	*G. affine, G. elegans*	[5]
85	5,7-Dihydroxy-3,8,3',4'-tetramethoxyflavone	*G. affine*	[5]
86	3,5,7-trihydroxy-6,8-dimethoxyflavone	*G. obtusifolium*	[5]
87	5,7,8-Trihydroxy-3-methoxyflavonoid	*G. robuscum*	[5]
88	Quercetin 3-methyl ether	*G. gracile, G. indicum*	[5]
Chalcones			
89	2',4',4-Trimethoxy-6'-methoxychalcone	*G. affine*	[5]
90	Gnaphalin	*G. affine, G. cheiranthifolium, G. multiceps, G. purpurascens, G. luteoalbum, G. hypoleucum*	[5]
91	2',4,4'-trihydroxy-6'-methoxychalcone	*G. affine*	[38]
92	4,4'，6'-Trimethoxy-2'-methoxychalcone	*G. affine*	[38]
93	2',4'-dihydroxy-4,6'-dimethoxychalcone	*G. affine*	[38]
94	2'-hydroxy-4,4',6'-trimethoxychalcone	*G. affine*	[38]
95	4,2',4',6'-Tetramethoxychalcone	*G. affine*	[38]
96	2',4,4'-trihydroxy-6'-methoxychalcone-4-glucopyranoside	*G. affine*	[3]
Flavanones			
97	Naringenin-7-O-β-D-(6''-E-caffeoyl)-glucopyranoside	*G. affine*	[42]
98	Taxifolin	*G. affine*	[42]
99	Dihydroapigenin	*G. affine*	[38]
100	Pinocembrin	*G. purpurascens*	[5]
101	Wogonin	*G. affine*	[38]
102	4'-Hydroxy-5-methoxy-7-O-β-D-glucopyranosyl-dihydroflavanone	*G. hypoleucum*	[43]
103	7,4'-Dihydroxy-5-Methoxydihydroflavonoids	*G. hypoleucum*	[43]
104	5,7,3',4'-tetrahydroxyflavone	*G. affine*	[42]
Triterpenoids			
105	β-Amyrin	*G. affine*	[5,38]
106	β-amyrin acetate	*G. affine*	[38]
107	Oleanolic acid	*G. affine, G. hypoleucum*	[38]
108	Friedelin	*G. affine*	[38]
109	α-Amyrin	*G. affine*	[5,38]
110	Ursolic acid	*G. affine, G. hypoleucum*	[38]
111	α-amyrin acetate	*G. affine*	[38]
112	Faradiol 3-O-palmitate	*G. affine*	[44]

(to be continued)

Table 2. (continued)

No.	Compound	Source	Reference
113	19α-hydroxy ursolic acid	*G. affine*, *G. hypoleucum*	[38]
114	2α,3α,19α-trihydroxy-28-norurs-12-ene	*G. affine*	[38]
115	Taraxasterol	*G. affine*	[38]
116	Taraxasterol acetate	*G. affine*	[5,38]
117	Lupeone	*G. affine*	[38]
118	Betulonic acid	*G. affine*	[44]
119	Betulinic acid	*G. affine*	[5]
120	Squalene	*G. gaudichaudianum*	[5]
Diterpenoids			
121	Ent-pimara-8(14),15-dien-3a,19-diol	*G. affine*	[45]
122	Ent-pimara-8(14),15-dien-3α-ol	*G.affine*	[38]
123	Ent-pimara-8(14),15-dien-19-ol	*G. affine*	[38]
124	Ent-Pimara-8(14),15-diene-19-ol	*G. gaudichaudianum*	[5]
125	Ent-pimara-8(14),15-dien-19-oic acid	*G. gaudichaudianum*	[5]
126	Ent-pimara-8(14),15-dien-18-oic acid	*G.gaudichaudianum*	[5]
127	Ent-Pimara-8(14),15-diene-3α,19-diol	*G. gaudichaudianum*	[5]
128	Sclareol	*G. gaudichaudianum*	[5]
129	8α,13α-Diacetoxycinnamyl alcohol	*G. gaudichaudianum*	[5]
130	8-epi-Sclareol	*G. undulatum*	[5]
131	8-epi-Eni-sclareol	*G. gaudichaudianum*	[3]
132	Kaur-16-en-19-oic acid	*G. gaudichaudianum*, *G. inornatum*, *G. rufescens*	[5]
133	Methyl kaur-16-en-19-oate	*G. gaudichaudianum*	[5]
134	3α-hydroxykaur-16-en-19-oic acid	*G. gaudichaudianum*	[3,5]
135	Methyl 3α-hydroxykaurl-16-en-19-oate	*G. gaudichaudianum*	[5]
136	11β-Acetoxycoel-16-ene-19-oleic acid	*G. rufescens*	[5]
137	Methyl 3α-acetoxycol-16-ene-19-oate	*G. gaudichaudianum*	[5]
138	3α-Acetoxycol-16-ene-19-oleic acid	*G. gaudichaudianum*	[5]
139	Ent-Kauran-16-ene	*G. undulatum*	[5]
140	Ent-Kaur-16-en-19-al	*G. undulatum*	[5]
141	Ent-Kaur-16-en-19-oic acid	*G. affine*, *G. graveolens*, *G. oligandrum*, *G. pellitum*, *G. undulatum*, *G. oxyphyllum*, *G. liebmannii*	[5]
142	15α-hydroxy-ent-kaur-16-en-19-oleic acid	*G. undulatum*, *G. viscosum*	[5]
143	11β-acetoxy-ent-kaur-16-en-19-oleic acid	*G. pellitum*	[5]
144	(–)-16-Kaurene-19-oic acid	*G. affine*	[3]
145	(–)-Methyl kaur-16-en-19-oate	*G.gaudichaudianum*	[3]
146	(3α,4α)-Kaur-16-en-18-oic acid-3-hydroxy-methyl ester	*G. gaudichaudianum*	[3]
147	3α-acetoxykaur-16-en-19-oic acid Me ester	*G. gaudichaudianum*	[3]
148	Ent-pimar-15-ene-8α,19-diol	*G. gaudichaudianum*	[5]
140	Ent-pimar-15-ene-3α,8α-diol	*G. gaudichaudianum*	[5]
150	Zoapatlin	*G. hypoleucum*, *G. affine*, *G. oxyphyllum*, *G. liebmannii*, *G. viscosum*	[40]
151	Ent-3β-hydroxykaur-16-en-19-oic acid	*G. affine*, *G. viscosum*	[38]
152	(–)-11β-Acetoxy-16-kaurene-19-oic acid	*G. affine*	[3]
153	Kauranol	*G. rufescens*	[5]
154	Ent-Kaur-9(11),16-en-19-oic acid	*G. oligandrum*, *G. undulatum*	[5]
155	Sylviside	*G. sylvaticum*	[5]
156	Carnoside	*G. sylvaticum*	[3]
157	15β-hydroxy-Wedeliaseccokaurenolide	*G. undulatum*	[5]
Sesquiterpenoids			
158	Gemamane D	*G. oligandrum*	[5]
159	(2*E*,6*Z*)-7,11,11-trimethylbicyclo[8,1,0]undec-2,6-diene diterpene	*G. oligandrum*	[5]
160	γ-Cadinene	*G. affine*	[46]
161	(E)-β-Farnesene	*G. pensylvanicum*	[36]
162	Irisone	*G. pensylvanicum*	[36]
163	(–)-β-Elemene	*G. affine*	[48]
164	α-Gurjunene	*G. affine*	[48]
165	Trans-Caryophyllene	*G. affine*	[21]
166	α-Humulene	*G. affine*	[48,49]
167	δ-Cadinene	*G. affine*	[48]
168	α-elemol	*G. affine*	[48]
169	β-selinene	*G. affine*	[8]
170	γ-Gurjunene	*G. japonicum*, *G. affine*	[49]
171	Corchoionol C	*G. affine*	[38, 50]

(to be continued)

Table 2. (continued)

No.	Compound	Source	Reference
172	Caryophyllene oxide	*G. affine*, *G. japonicum*	[51]
173	6,10,14-trimethyl-2-Pentadecanone	*G. affine*	[52]
174	Nerolidol	*G. affine*	[51]
175	1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene	*G. affine*	[51]
176	Aromadendrene	*G. affine*, *G. japonicum*, *G. pensylvanicum*	[8]
177	7R,8R-8-hydroxy-4-isopropylidene-7-methylbicyclo[5,3,1] undec-1-ene	*G. japonicum*	[46]
Monoterpenoids			
178	α-Terpineol	*G. affine*	[21]
179	Linalool	*G. affine*	[21]
180	*p*-cymene	*G. affine*	[21]
181	*m*-cymene	*G. affine*	[48]
182	Pulegone	*G. affine*	[52]
Phenolic acids			
183	Protocatechuic acid	*G. affine*	[46]
184	Caffeic acid	*G. affine*	[46]
185	Ethyl Caffeate	*G.affine*	[38]
186	Ethyl protocate	*G.affine*	[38]
187	Trans caffeic acid	*G. tranzschelii*	[5]
188	Caffeic acid ethylene ester	*G. hypoleucum*	[40]
189	Eugenol	*G. affine*	[36, 21]
190	Coniferylaldehyde	*G. affine*	[38]
191	*P*-hydroxycinnamic acid	*G. affine*	[38]
192	Methyl cinnaminate	*G. hypoleucum*	[47]
193	Isovanillin	*G. affine*	[38]
194	Isovanillic acid	*G. affine*	[38]
195	3',5-dihydroxy-2- (4-hydroxybenzyl) -3-methoxybibenzyl	*G. affine*	[44]
196	Everlastoside L	*G. affine*	[38]
197	Methyl *p*-hydroxycinolinate glucoside	*G. affine*	[38]
198	Acteoside	*G. affine*	[44]
199	1,4,5-tri-O-caffeoylquinic acid	*G. affine*	[38]
200	1,5-di-O-caffeoylquinic acid	*G. affine*	[38]
201	1,5-dicaffeoylquinic acid methyl ester	*G. affine*	[38]
202	1,3-di-O-caffeoylquinic acid	*G. affine*	[38]
203	3,5-di-O-caffeoylquinic acid	*G. affine*	[20]
204	3,4-di-O-caffeoylquinic acid	*G. affine*	[20]
205	1,4-di-O-caffeoylquinic acid	*G. affine*	[42]
206	Chlorogenic acid	*G. affine*	[46]
207	4-O-caffeoylquinic acid	*G. stramineum*	[5]
208	4,5-di-O-caffeoylquinic acid	*G. stramineum*	[5]
209	3,4,5-tri-O-caffeoylquinic acid	*G. stramineum*	[5]
Steroids and sterols			
210	Daucosterol	*G. affine*, *G. adnatum*, *G. hypoleucum*	[50]
211	Stigmasterol	*G. affine*, *G. adnatum*, *G. gaudichaudianum*, *G. viscosum*, *G. oxyphyllum*, *G. liebmannii*	[38]
212	β-sitosterol	*G. affine*, *G. hypoleucum*, *G. inornatum*, *G. pellitum*, *G. oxyphyllum*, *G. liebmannii*, *G. viscosum*	[38]
213	Stigmasta-4,22-dien-3-one	*G. affine*, *G. adnatum*	[38]
214	4-Cholesten-3-one	*G. affine*	[5]
215	3β-hydroxy-stigmasta-5,22-dien-7-one	*G. affine*	[5]
216	α-spinasterol	*G. affine*	[38]
Alkaloids			
217	Grossamiade K	*G. affine*	[44,38]
218	Aurantiamide acetate	*G. hypoleucum*	[3]
219	Matrine	*G. sphacelatum*	[5]
220	Scopolamine	*G. affine*	[5]
221	Anabellamide	*G. affine*	[38]
222	Patriscabratine	*G. affine*	[38]
223	Longumoside A	*G. affine*	[44]
Others			
224	Phloroglucinol	*G. affine*	[53]
225	3-methoxyphenol1-O-α-L-rhamnopyranosyl-4-(1→6)-O-β-D-glucopyranoside	*G. affine*	[38]
226	2,3,5,4'-tetrahydtoxysilbene-2-O-β-D-glucopyranoside	*G. affine*	[50]

(to be continued)

Table 2. (continued)

No.	Compound	Source	Reference
227	(Z)-3-hexenyl O-β-D-glucopyranoside	*G. polycaulon*	[5]
228	Gnaphalium A	*G. affine*	[54]
229	Gnaphaliol 3-O-β-D-glucopyranoside	*G. polycaulon*	[5]
230	Gnafaliol 9-O-β-D-glucopyranoside	*G. polycaulon*	[5]
231	(+)-Pinenutol	*G. pellitum*	[5]
232	Panamin	*G. hypoleucum*	[40]
233	Tithoniamide B	*G. affine*	[50]
234	4'-Hydroxydehydrogenase	*G. hypoleucum*	[3]
235	Anaphatol	*G. affine, G. adnatum*	[38,41]
236	7-O-(β-D-glucopyranosyl)-5-hydroxyisobenzofuran-1(3H)-one	*G. affine, G. adnatum*	[38,41]
237	4-(3',4'-dimethoxyphenyl)-3-methyl-butyl-3-ene-2-one	*G. affine, G.adnatum*	[38]
238	Desmethylyangonine-4'-glucopyranoside	*G. affine*	[38]
239	3-(4'-formylphenoxy)-4-methoxybenzaldehyde	*G. affine*	[38]
240	3-Hydroxydihydrobenzofuranose	*G. polycaulon*	[55]
241	Gnaphaliol 9-O-β-D-glucopyranoside	*G. polycaulon*	[55]
242	5,7-dihydroxyl-isobenzofuran-1(3H)-one	*G. affine, G. adnatum*	[41]
243	1-Hexacosanol	*G. affine*	[38]
244	Gnaohaliin C	*G. hypoleucum*	[3]
245	Benzeneacetaldehyde	*G. affine*	[48]
246	1-Tetratriacontanol	*G. affine*	[50]
247	Adenosine	*G. polycaulon*	[5]
248	4-hydroxyacetophenone	*G. affine*	[56]
249	Diethyl phthalate	*G. affine*	[38]
250	Diisobutyl phthalate	*G. pensylvanicum*	[36]
251	Dimethyl phthalate	*G. japonicum*	[46]
252	9,16-dixo-10,12,14-octadeca-trienoic acid	*G. affine*	[56]
253	*N*-hexacosanic acid	*G. affine*	[5]
254	Myristicin aldehyde	*G. affine, G. japonicum*	[46]
255	N-butyl-isobutyl terephthalate	*G. adnatum, G. affine*	[41,48]
256	1-Palmitoyl-rac-glycerol	*G. affine*	[50]
257	4'-hydroxydehydrokawain	*G. affine*	[38]

luteolin-4'-O-β-D-(6''-E-caffeoyl)-glucopyranoside (**25**) were showed to have a strong inhibitory effect on the complement activation, with CH_{50} values of 0.014 and 0.045 mg/mL, respectively. Additionally, 27 flavonoids were isolated from *G. affine*, providing a basis for exploring the structure-activity relationship of flavonoids in *G. affine*. By investigating the anti-complementary effect of each flavonoid, the flavonol–sugar–aromatic side chain and the hydroxy group in C-4' in flavonoids played an important role in anti-complementary activity[57].

Antidiabetic effect

Persistent hyperglycemia is generally considered to be related to insufficient insulin secretion and islet dysfunction or insulin resistance, which can cause a variety of complications, including diabetes nephropathy and diabetes eye disease. For now, treatment for hyperglycemia is mainly through the promoting glycolysis (dimethylbiguanide) and lowering postprandial blood sugar (acarbose). Several studies showed that various species in genus *Gnaphalium* can exert antidiabetic effect. Sun et al. evaluated the antidiabetic activity of total flavonoid extract of *G. hypoleucum* in both *in vivo* and *in vitro* models, and isolated the relevant compounds that may function in this process[84]. Total flavonoid extract of *G. hypoleucum* showed a significant α-glucosidase inhibitory activity (IC_{50} = 20.30 ± 3.45 μM) *in vitro*, and total flavonoids at 150 mg/kg significantly decreased the levels of fasting blood glucose (FBG) after 10 d ($p < 0.05$) *in vivo* in streptozotocin (STZ)-induced diabetic mice. Moreover, components including oleanolic acid (**107**), ursolic acid (**110**), 19α-hydroxyl ursolic acid (**113**), and luteolin-4'-O-β-D-(6''-E-caffeoyl)-glucopyranoside (**25**) showed significant α-glucosidase inhibitory activities, more effective than acarbose. In another study, Lu et al. isolated three compounds, including 3,5-di-O-caffeoylquinic acid (**203**), 3,4-di-O-caffeoylquinic acid (**204**), and 2',4,4'-trihydroxy-6'-methoxychalcone-4'-O-β-D-glucopyranoside (**96**) from *G. affine*, which can inhibit α-amylase activity[85].

Anti-hyperuricemia and gouty effect

Hyperuricemia is often associated with excessive production or insufficient excretion of uric acid (UA) in the body. When the serum uric acid concentration exceeds the solubility of uric acid, uric acid crystals will form in tissues such as the kidneys and joints, leading to kidney disease and gout[86]. Previous literature has reported several renal organic anion transporters, such as glucose transporter 9 (GLUT9) and uric acid transporter 1 (URAT1), involved in mediating uric acid excretion. Moreover, xanthine oxidase (XO) is a key enzyme that catalyzes the oxidation of hypoxanthine to xanthine and further to uric acid. Thus, mediating uric acid excretion and xanthine oxidase activity is the most effective way to treat gout and hyperuricemia. Several species in *Gnaphalium* have been used as a folk medicine for the relief of anti-inflammatory, antitussive, gout and expectorant activities, etc. Therefore, the anti-hyperuricemia and acute gouty effects of *G. affine* and *G. pensylvanicum* were investigated by determining the uric acid content in potassium oxonate induced hyperuricemic mice, revealing the significant anti-hyperuricemia and acute gouty effects of *G. affine* and *G. pensylvanicum* ethanol extracts *via* inhibiting xanthine oxidase activity in a concentration dependent manner (100, 200, and

400 mg/kg)[87,88]. Notably, the expressions of GLUT9 and URAT1 were also increased in mice treated with *G. affine* and *G. pensylvanicum* extracts for seven days compared with that in the control group. These studies suggest that the mechanism of anti-hyperuricemia and acute gouty effects by *G. affine* and *G. pensylvanicum* might be involved in both xanthine oxidase inhibition and uric acid excretion.

In order to verify the functional chemicals produced by *G. hypoleucum* in this process, the anti-gouty chemicals were screened in *G. hypoleucum via* xanthine oxidase inhibition assay. Luteolin-4'-O-glucoside (**7**) and luteolin (**10**) were identified, showing strong xanthine oxidase inhibition activities with IC50 values of 0.26 and 0.43 μg/mL, respectively. Moreover, their significant anti-hyperuricemia and acute gouty effects were further confirmed *in vivo via* inhibiting the xanthine oxidase activity in a concentration dependent manner (20, 40, and 100 mg/kg). In addition, the expressions of GLUT9 and URAT1 were increased in mice treated with luteolin-4'-O-glucoside (**7**) and luteolin (**10**) for six days compared with that in the control group. The paw swelling was also decreased by luteolin (**10**) and luteolin-4'-O-glucoside (**7**) in a dose-dependent manner in monosodium urate (MSU) crystal-induced mice[89].

Other activities

Apart from the above pharmacological effects, other activities of *Gnaphalium* have been reported recently. The water extract of *G. affine* exhibited a protective effect for carbon tetrachloride-induced acute liver injury[90]. A polysaccharide of *G. affine* could enhance the expression of *ALPase* expression synergistically with ascorbate from the early differentiation stage of MC3T3-E1 cells[91]. Two flavone isomers from *G. elegans* exibited remarkable anti-tumor effects, and four flavonoids **78**, **62**, **63**, and **92** isolated from the root of *G. affine* have antifeedant activity, and studies have suggested that the introduction of a methyl ether on the B-ring of the flavonoid decreased antifeedant activity in insect[92,93].

Quality control

At present, there is no national standard for *Gnaphalium* in China, and its quality control is mainly based on local standards. Therefore, it is necessary and urgent to strengthen research on the quality control of *Gnaphalium*. Regarding the quality standards of *Gnaphalium*, literature reports mostly focus on the qualitative and quantitative analysis of flavonoids and phenolic components. The content of quercetin (**60**) in *G. affine*, *G. pensylvanicum*, *G. japonicum*, and *G. adnatum* was basically determined by thin-layer chromatography (TLC) and ultraviolet–visible spectrophotometry (UV–vis)[94]. Additionally, Tian used high performance liquid chromatography (HPLC) to determine the contents of quercetin (**60**), luteolin (**10**), and luteolin-4'-O-β-D-glucose (**7**) in *G. affine*[37], as well as several phenols including protocatechuic acid (**183**), chlorogenic acid (**206**), caffeic acid (**184**), and 1,5-di-O-caffeoylquinic acid (**200**)[95]. HPLC-tandem mass spectrometry (MS/MS) were also used to determine and compare the contents of 3,5-dicaffeoylquinic acid (**203**), chlorogenic acid (**206**), kaempferol-3-O-β-D-glucoside (**61**), apigenin-7-O-β-D-glucoside (**3**), quercetin (**60**) and luteolin (**10**) in *G. affine*[96]. Quantitative analysis of multi-components by single marker (QAMS) method was recently established to determine the contents of chlorogenic acid (**206**), caffeic acid (**184**) and eupatilin (**38**) in *G. affine*, using chlorogenic acid (**206**) as the reference substance[97,98]. In addition, pharmacokinetic studies have shown that caffeic acid and caffeioylquinic acids in *G. affine* have a significant accumulation effect in uric acid nephropathy (UAN) rats, suggesting caffeic acid and caffeioylquinic acids might be the active components to treat UAN[99]. The above detection methods provide a certain basis for the quality evaluation research of *Gnaphalium*, but more detection technologies are still needed, such as gene sequencing and fingerprint chromatography, to verify confused varieties and establish a scientific quality control system.

Conclusions and perspectives

As a medical plant used worldwide, *Gnaphalium* plants are traditionally used to treat cough, phlegm, asthma, rheumatism, and other disorders. Flavonoids, terpenoids, and phenolic acids are the main chemical components and pharmacological ingredients in *Gnaphalium*. The pharmacological effects of *Gnaphalium* are mainly manifested in pulmonary protection, antimicrobial activity, anti-inflammatory and anti-complementary activities, antioxidant activity, antidiabetic effect, anti-hyperuricemia and gout effect, etc. There are also traditional Chinese medicine preparations with *G. affine* as tea on the market, which are mainly used for the treatment of hyperuricemia and gout. This review summarized previous research on genus *Gnaphalium*, including traditional uses, phytochemistry, bioactivities and quality control. However, there are several key issues worth pondering to further develop the medicinal potential of *Gnaphalium*.

First, more than 200 species in *Gnaphalium* have been found worldwide and over 200 compounds have been isolated and identified from *Gnaphalium* including flavonoids, terpenoids, phenolic acids, steroids, sterols, and other components. However, there are still disputes about the classification of *Gnaphalium*. Recently, Nie et al. divided *Gnaphalium* into two clades, *Gnaphalium* and *Pseudognaphalium*, using ITS and ETS sequencing[100]. Therefore, more comprehensive detection methods, including botanical phenotype, chemical interpretation and gene sequencing of each species, are still needed to describe the *Gnaphalium* taxonomy precisely.

Second, the present toxicological research of genus *Gnaphalium* needs to be further strengthened. As we know, some species in *Gnaphalium* are used as vegetable and food ingredients, with relatively low toxicity. However, further toxicological research is still required, especially for the long-term uses with large doses of poor extracts. The toxicity of each species of *Gnaphalium* should be comprehensively evaluated, including heavy metals and contaminations of pesticide residues, to provide a scientific basis for the safe use as both drug and food.

Third, at present, there is no unified national quality standard for genus *Gnaphalium*, and most of them are based on local standards. Moreover, only TLC or HPLC methods were used in some local standards, which might not reflect the comprehensive quality of *Gnaphalium*. Therefore, it is necessary to further strengthen the basic research on quality control, such as HPLC fingerprint, multiple component determination, and Q-marker establishment in *Gnaphalium* as soon as possible.

Author contributions

The authors confirm contribution to the paper as follows: conceptualization and supervision: Xiao Y, Sun L; draft

manuscript and figure preparation: Wang X, Yang Y; manuscript review and editing: Liu D, Xiong L, Dunzhu B, Zhang L, Chen W. All authors reviewed and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article.

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Conflict of interest

The authors declare that they have no conflict of interest. Wansheng Chen, Lianna Sun and Ying xiao are the Editorial Board members of *Medicinal Plant Biology* who were blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer-review handled independently of these Editorial Board members and their research groups.

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