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The review on medicinal herbs in the treatment of gout through xanthine oxidase inhibitory activity: Call for more research strategy in the future

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ABSTRACT

Medicinal herbs, as their derivative phytocompounds are increasingly demonstrated as beneficial complementary treatments for gout. An extensive volume of *in vitro* and *in vivo* investigations has reported the beneficial effects of herbal medicines on xanthine oxidase inhibitory activity and reducing uric acid. Here, we briefly review studies that investigated herbs and their chemical components for gout management. In addition, we also discuss and recommend traditional medicine opinions on the research strategy for gout treatment. This review should provide insightful knowledge support for the evidence-based application of herbal medicines in gout treatment.

INTRODUCTION

Gout is a kind of inflammatory arthritis in which uric acid crystals accumulate in the joints, especially in the knee, ankle, wrist, finger, and elbow [1]. Xanthine oxidase (XO), a key enzyme in purine catabolism, catalyzes the oxidation of xanthine to uric acid in the body, but overformulation of uric acid may lead to hyperuricemia [2]. Late complications of long-term acute gout may induce poly-articular or oligo-articular gout, which is one of the most throbbing and painful conditions in humans [3]. Furthermore, gout patients have a higher risk of cardiovascular disorders as well [4,5]. One of the major strategies in the control of uric acid overproduction in gout treatment and its complications is that many new antihyperuricemic drugs have been synthesized and invented recently. However, some uric acid-lowering drugs have clinically toxic side effects. Hence, natural products have been considered to investigate their beneficial promotion. Bioactive natural chemical components are potential candidates with a safe, effective, and potential inhibitory effect on XO activity that stimulates uric acid production. Normally, there is a lack of systematic reviews about medicinal herbs and their chemical compounds with antihyperuricemic and anti-gout valuables. In this work, we attempted to review and summarize (1) the XO inhibitory capacity of herbal crude extracts, (2) the antihyperuricemic and antigout effects of purified chemical compounds *in vitro* and *vivo*, and (3) the molecular docking mechanism of the active chemical compounds and their derivatives focusing on XO inhibitory activities. Further research strategy for gout treatment therapy is still recommended.

MATERIALS AND METHODOLOGY

In this work, we used XO, uric acid, and gout as the keywords to collect information related to gout investigations from Web of Science, Science Direct, Springer, Google Scholar, PubMed, and other professional websites. This review summarizes and evaluates the gout treatment properties of medicinal herbs reported in the literature.

IN VITRO STUDIES

XO inhibitory capacity of herbal crude extracts

Investigations of medicinal plants have uncovered a number of anti-gouts. González *et al*. [6] reported the XO

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inhibitory activity of 34 crude extracts from species belonging to the Celastraceae and Lamiaceae. The 26 species from 18 families utilized for gout treatment in northeastern North America have been shown to have XO inhibitory capacity [7]. Over a hundred Chinese medicinal plants have been evaluated for antigout [8]. In other works, a number of herbal medicines have also been reported for XO inhibitory potency [9–23]. Interestingly, in all candidates, 46 herbs with outstanding XO inhibitory potency have been organized and listed in Table 1. However, many herbs in this group had not been investigated on pharmacological mechanisms, kinetics, *in vivo* and *in silico,* and clinically related to anti-gout activity.

XO inhibitory capacity of chemical compounds from herbal medicines

The chemical composition of herbal medicines for gout treatment has been studied for some recent decades. The phytochemical studies on XO inhibitory capacity have resulted in the isolation of hundreds of compounds. In all candidates, 85 chemical compounds with the lowest haft maximal inhibitory concentration (IC_{50}) of XO inhibitory activity from a series of studies have been displayed in Table 2. The chemical compound group exhibited the highest potency with an IC_{50} < 1 μM. It included 2′,4′-dimethoxy-4,5′,6′-trihydroxychalcone (IC_{50} 0.21 μM), neotaiwanensol B (IC_{50} 0.28 μM), eupatilin (IC_{50} 0.37 μM), chrysoeriol (IC_{50} 0.5 μM), hyprhombin C (IC_{50} 0.6 μM), apparicine (IC_{50} 0.65 μM), and luteolin (IC_{50} 1.2 μM). The isolated compound chemical structures are shown in Figure 1.

In serial other studies, XO inhibitory activity has also been evaluated. Baicalin and baicalein are the key XO inhibitory compounds of scutellariae radix [60]. The total alkaloids of *nelumbinis folium* inhibited XO with an IC_{50} of 3.313 μg/ml [61]. Flavonol glycosides of *Allium cepa* L. displayed XO inhibitory activity with an IC_{50} from 10.5 to 20.8 μg/ml [62]. Hoshani *et al*. [63] reported that leaf extracts of *Physalis alkekengi* at the green fruit stage exhibited higher XO inhibitory efficacy compared to the vegetative stage (86.86% and 45% at the concentration of 0.3 mg/ml, respectively). The underlying mechanisms of curcumin in preventing XO have been elucidated via studies on the molecular docking simulations [64]. The XO inhibitory effects of the main phenols of pickled radish have been characterized by molecular docking stimulated by hydrophobic interactions and hydrogen bonds and elucidated by molecular dynamics [65]. Betacyanin from *Hylocereus undatus* rind exhibited an XO inhibitory effect with an IC_{50} of 9 mM. Kinetics study and docking analysis for the XO inhibitory mechanism of betacyanin were also proved [66]. Du and Li [67] revealed that porphyra polysaccharide is capable of XO inhibitory activity through study on enzyme kinetics and molecular docking. The XO inhibitory mechanism of other natural products had also been evidenced revealed via fluorescence titration, molecular level interaction of chemical compounds with the amino acid residues, such as black rice anthocyanins [68]; chrysoerial [69]; monoterpenoids and flavonoid aglycones of *Chrysanthemum morifolium* [70]; flavonoids of *Gardenia oudiepe* [71]; *Chrysanthemum moriforlium* [72]; Quercetin-3-O-rhamnoside and chlorogenic acid obtained from *Smilax china* L. exhibited strong XO inhibitory capacity through kinetics and mechanism analysis [73]; luteolin [74]; Genistein from soybean [75]; atherospermidine and cyathocaline extracted from *Alphonsea cylindrica* and *Alphonsea elliptica* [76]; malic acid [77]; Eugenol, a marker component of clove [78]; benzofuran from *Viburnum grandiflorum* with an IC_{50} value of 0.59 μM) [79]; quercetin from *Erodium birandianum* [80]; catechin, epicatechin, gallic acid, and ellagic acid from acetone extract of *Vicia faba* L. seeds [81]; and 6-(3-methylbut-1-enyl)-5,7-dimethoxy-4′-hydroxy flavone from *Spilanthes calva* [82].

IN VIVO STUDIES

Moringa oleifera hydrolysate at doses of 200 and 500 mg/kg significantly reduced the serum uric acid level of hyperuricemic rats by regulating serum XO activity [83]. For *Paeonia suffruticosa* leaf extract, it effectively decreased increased serum uric acid in hyperuricemic mice. Insure evidence indicated the effects of protecting against renal damage and oxidative stress induced by hyperuricemia of apigenin 7-O-glucoside in mouse models [84]. It has been reported that extract of Rhizoma *Alpiniae officinarum* has hypouricemic and renal protective effects on hyperuricemic mice by XO inhibitory activity, down-regulating $URAT_1$ and $GLUT_9$, which is similar to the study on XO inhibitory activity of Saengmaeksan formulation including of *Panax ginseng* reported by Sung *et al*. [85]. Galangin, kaempferide, and 3-methoxyl-glangin are its marker XO inhibitors [86]. The mixture of methanol extracts of *Euonymus laxiflorus*, *Rubia lanceolata,* and *Gardenia jasminosides* reduced serum urate levels in hyperuricemic mice [87]. Interestingly, Huang *et al*. [88] reported that genistein, apigenin, quercetin, rutin, and astilbin exhibited insignificant effects on XO activity *in vitro,* but these compounds decreased serum uric acid levels in mice. The XO inhibitory effect of Lobetyolin, being a main bioactive chemical compound of *Codonopnis* plants, had been reported by Yoon and Cho [89]. It is revealed that lobetyolin exhibited weekly inhibitory XO capacity through a mixed-type mechanism, but it significantly decreased liver XO activity with a dose of 50 mg/kg in rats. The ethanol extract of *Campomanesia velutina* and its isolated myricitrin were demonstrated to be able to decrease serum uric acid levels and inhibit hepatic XO activity [90]. The *Christia vespertilionis* leaf aqueous extract induces a decrease in uric acid levels (31.95%) in mice at a dose of 200 mg/kg [22]. Many other studies on antigout activity in *in vivo* models of medicinal herbs and phytochemical compounds resulted in strong antigout benefits. All results indicated that evaluated herbal extracts exhibited no damage to the liver and kidney in hyperuricemic rats and inhibited excessive uric acid levels, which includes *Artemisia selengensis* leaf extracts [91]; theaflavin with an IC_{50} of 63.17 μM [92]; lemon-peel extract [93]; and green tea polyphenols [94], which may suggest an attractive strategy for antigout therapy.

SCIENCE OPINION AND RESEARCH STRATEGY

Former studies have shown that the pathogenesis of hyperuricemia in the blood is closely related to metabolism, immunity, and inflammation. Traditional medicine considers weaknesses in the liver, spleen, and kidneys as the principal causes of an increase in uric acid. In addition, the “military

Table 1. XO inhibitory capacity of herbal crude extracts.

No	Herbal medicine	IC_{50}	Refereces
1	Ethanol extract of *Hyptis obtusiflora* Presl ex Benth aerial parts	1.4 µg/ml	[6]
2	Ethanol extract of *Hyptis lantanaefolia* Poit. aerial parts	2.1 µg/ml	[6]
3	*Larix laricina*	Inhibition of 86.33% at 100 µg/ml	[7]
4	Methanol extract of *Cinnamomum cassia* twig	18 µg/ml	[8]
5	Methanol extract of *Chrysanthemum indicum* flower	22 µg/ml	[8]
6	Methanol extract of *Lycopus europaeus* leaves	38 µg/ml	[8]
7	Water extract of *Polygonum cuspidatum* rhizome	38 µg/ml	[8]
8	Methanol extract of *Salvia spinosa* L	53.7 µg/ml	[9]
9	Methanol extract of *Anthemis palestina* Boiss	168.0 µg/ml	[9]
10	Methanol extract of *Chrysanthemum coronarium* L.	199.5 µg/ml	[9]
11	Methanol extract of *Achillea biebersteinii* Afansiev	360.0 µg/ml	[9]
12	Methanol extract of *Rosmarinus officinalis* L.	650.0 µg/ml	[9]
13	Methanol extract of *Ginkgo biloba* L	595.8 µg/ml	[9]
14	Methanol extract of *Artemisia vulgaris* L.	14.7 µg/ml	[10]
15	Methanol extract of *Blumea balsamifera*	6.0 µg/ml	[10]
16	Methanol-H2O extract of *Tetracera scandens*	15.6 µg/ml	[10]
17	Methanol extract of *Caesalpinia sappan*	14.2 µg/ml	[10]
18	Methanol extract of *Chrysanthemum sinense* flower	5.1 µg/ml	[10]
19	Ethanol extract of *Sida rhombifolia* L. stems	21.43 µg/ml	[11]
20	Ethanol extract of *Sonchus arvensis* L. leaves	23.64 µg/ml	[11]
21	Ethanol extract of *Clerodendrum floribundum* R. Br. leaves and branches	6.0 µg/ml	[12]
22	Ethanol extract of *Eremophila maculata* aerial parts	30.9 µg/ml	[12]
23	Ethanol extract of *Stemodia grossa* Benth aerial parts	37.4 µg/ml	[12]
24	Ethanol extract of *Lychnophora trichocarpha* aerial parts	6.16 µg/ml	[13]
25	Ethanol extract of *Lychnophora ericoides* aerial parts	8.28 µg/ml	[13]
26	Ethanol extract of *Lychnophora staavioides* aerial parts	33.97 µg/ml	[13]
27	Ethanol extract of *Lychnophoriopsis candelabrum* aerial parts	37.70 µg/ml	[13]
28	Hydroalcoholic extract of *Coccinia grandis* leaves	21.25 µg/ml	[14]
29	Methanol extract of *Strychnos nux-vomica* leaves	6.8 µg/ml	[14]
30	Chloroform fraction of *Erythrina stricta* Roxb	21.2 µg/ml	[14]
31	Methanol extract of *Populus nigra*	8.3 µg/ml	[15]
32	Methanol extract of *Betula pendula*	25.9 µg/ml	[15]
33	Ethanol extract of *Hypericum perforatum*	39.4 µg/ml	[15]
34	*Caryophyllus aromaticus*	46.7 µg/ml	[15]
35	Methanol extract of *Erythrina indica* bark	52.75 µg/ml	[16]
36	*Allium cepa* L	17.36 µg/ml	[17]
37	Methanol extract of *Saraca thaipingensis* leaves	33.0 µg/ml	[18]
38	Methanol extract of *Caesalpinia pulcherrima*	53.0 µg/ml	[18]
39	Methanol extract of *Archidendron clypearia*	15.6 µg/ml	[19]
40	*Smilax poilanei* Gagnep	20.0 µg/ml	[19]
41	*Linociera ramiflora* (Roxb.) Wall	25.4 µg/ml	[19]
42	*Passiflora foetida* L.	25.5 µg/ml	[19]
43	*Syzygium aromaticum*	39.58 µg/ml	[20]
44	Methanol extract of *Alcea glabrata*	370 µg/ml	[21]
45	Water extract of *Christia vespertilionis*	61.37 µg/ml	[22]
46	Ethyl acetate fraction of *Artemisia selengensis* Turcz *leaves*	1.67 mg/ml	[23]

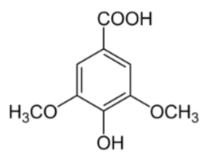
Table 2. XO inhibitory capacity of chemical compounds from herbal medicines.

No	Chemical compounds	Herbal medicines	IC_{50}	Refereces
1	Coniferyl ferulate	*Chuanxiong rhizome*	1.97 µM	[2]
2	Luteolin	*Chrysanthemum sinense*	1.2 µM	[10]
3	(−)-7-O-galloyltricetiflavan	*Archidendron clypearia*	25.5 µM	[19]
4	Apigenin	*Syzygium aromaticum*	3.27 µg/ml	[20]
5	Syringic acid	*Conyza bonariensis*	500 µM	[24]
6	Takakin 8-O-glucuronide	*Conyza bonariensis*	170 µM	[24]
7	Valoneic acid dilactone	*Lagerstroemia speciosa*	2.5 µM	[25]
8	Ellagic acid	*Lagerstroemia speciosa*	71.5 µM	[25]
9	Cinnamaldehyde	*Cinnamomum cassia*	7.8 µM	[26]
10	2-Methoxycinnamaldehyde	*Cinnamomum cassia*	13.8 µM	[26]
11	2-Hydroxycinnamaldehye	*Cinnamomum cassia*	14.6 µM	[26]
12	Cinnamic acid	*Cinnamomum cassia*	26.4 µM	[26]
13	Coniferaldehyde	*Cinnamomum cassia*	36.3 µM	[26]
14	O-Coumaric acid	*Cinnamomum cassia*	32.2 µM	[26]
15	Tsugaric acid D	*Ganoderma tsugae*	90.2 µM	[27]
16	Tsugaric acids A	*Ganoderma tsugae*	116.1 µM	[27]
17	3-oxo-5*α*-lanosta-8,24-diene-21-oic acid	*Ganoderma tsugae*	181.9 µM	[27]
18	4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde	*aloe-emodin derivatives*	2.79 µM	[28]
19	Eupatilin	*Gnaphalium affine*	0.37 µM	[29]
20	5-hydroxy-6,7,3',4′-tetramethoxyflavone	*Gnaphalium affine*	3.15 µM	[29]
21	Xanthoangelol	*Angelica keiskei*	8.5 µM	[30]
22	Luteolin-7-O-glucoside	*Flos Chrysanthemum*	23.61 µM	[31]
23	Apigenin-7-O-glucoside	*Flos Chrysanthemum*	38.80 µM	[31]
24	Hyprhombin C	*Hyptis rhomboides*	0.6 µM	[32]
25	Nudibaccatumin A	*Piper nudibaccatum*	62.94 µM	[33]
26	Nudibaccatumin B	*Piper nudibaccatum*	70.67 µM	[33]
27	Neotaiwanensol B	*Piper nudibaccatum*	0.28 µM	[33]
28	6-gingerol	*Zingiber officinale*	10.5 µM	[34]
29	6-shogaol	*Zingiber officinale*	15.2 µM	[34]
30	6-paradol	*Zingiber officinale*	12.4 µM	[34]
31	Isorhamnetin	*Berchemia lineata*	47.0 µM	[35]
32	Emodin	*Berchemia lineata*	45.0 µM	[35]
33	Physcion	*Berchemia lineata*	53.6 µM	[35]
34	Ranuncoside	*Ranunculus muricatus L.*	43.3 µM	[36]
35	3β, 20*α*, 24-trihydroxy-29-norolean12-en-28-oic acid 24-O-*β*-L-fucopyranosyl-(1→2)-6-O-acetyl-*β*-D-glucopyranoside	*Stauntonia brachyanthera*	5.22 µM	[37]
36	Isoquercitrin	*Stauntonia brachyanthera*	1.60 µM	[37]
37	Lycocernuasides B	*Palhinhaea cernua*	30.36 µM	[38]
38	Lycocernuasides C	*Palhinhaea cernua*	42.65 µM	[38]
39	Lycocernuasides D	*Palhinhaea cernua*	35.33 µM	[38]
40	Orcinosides I	*Curculigo orchioides*	250 µM	[39]
41	Orcinosides J	*Curculigo orchioides*	620 µM	[39]
42	5,7-dihydroxy-3-(3′-hydroxyphenyl)coumarin	*Coumarin derivatives*	2.13 µM	[40]
43	Baicalein	None	7.54 µM	[41]
44	Baicalin	None	1.23 µM	[41]
45	Isoacteoside	*Cistanche deserticola*	46.91 µM	[42]
46	Kankanoside G	*Cistanche deserticola*	85.31 µM	[42]

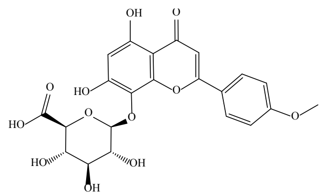
Continued

No	Chemical compounds	Herbal medicines	IC_{50}	Refereces
47	Cistanoside F	*Cistanche deserticola*	36.41 µM	[42]
48	(−) ethyl 1, 4-di-O-caffeoylquinate	*Gnaphalium affine*	11.94 µM	[43]
49	(−) methyl 1, 4-di-O-caffeoylquinate	*Gnaphalium affine*	15.04 µM	[43]
50	2′-hydroxygenistein	*Apios americana*	21.8 µg/ml	[44]
51	3′-methoxy-4′,5,7-trihydroxyisoflavone	*Apios americana*	31.6 µg/ml	[44]
52	Lupinalbin	*Apios americana*	38.8 µg/ml	[44]
53	Apparicine	*Tabernaemontana bufalina*	0.65 µM	[45]
54	Acetyl phenyl acetate	*Zanthoxylum armatum*	5.59 µM	[46]
55	Prudomestin	*Zanthoxylum armatum*	6.73 µM	[46]
56	Tambulin	*Zanthoxylum armatum*	5.62 µM	[46]
57	Icarisid E	*Cyclocarya paliurus*	31.81 µM	[47]
58	Icarisid J	*Cyclocarya paliurus*	29.71 µM	[47]
59	Paucatalinones L	*Paulownia catalpifolia*	29.6 µM	[48]
60	Paucatalinones N	*Paulownia catalpifolia*	20.3 µM	[48]
61	2′,4′-dimethoxy-4,5′,6′-trihydroxychalcone.	*Perilla frutescens*	0.21 µM	[49]
62	Neocucurbitacin D	*Herpetospermum pedunculosum*	15.27 µM	[50]
63	Cucurbitacin E	*Herpetospermum pedunculosum*	10.16 µM	[50]
64	Cucurbitacin B	*Herpetospermum pedunculosum*	18.41 µM	[50]
65	6-oxoisopimaric acid	*Cryptomeria japonica*	17.3% at concentration of 50 µM	[51]
66	6α-hydroxyisopimaric acid	*Cryptomeria japonica*	16.5% at concentration of 50 µM	[51]
67	Isopimaric acid	*Cryptomeria japonica*	2.6% at concentration of 50 µM	[51]
68	Isopimara-7,9(11),15-trien-18-oic acid	*Cryptomeria japonica*	30.5% at concentration of 50 µM	[51]
69	Chrysoeriol	*Alfalfa*	0.5 µM	[52]
70	Liquiritigenin	*Alfalfa*	1.0 µM	[52]
71	Mycotoxin alternariol	*Callicarpa kwangtungensis Chun*	0.23 µM	[53]
72	Quercetin	*Flos sophorae immaturus*	0.03 mg/ml	[54]
73	Kaempferol	*Flos sophorae immaturus*	0.11 mg/ml	[54]
74	Rutin	*Flos sophorae immaturus*	5.62 mg/ml	[54]
75	Hyperoside	*Flos sophorae immaturus*	11.48 mg/ml	[54]
76	Protocatechuic acid	*Flos sophorae immaturus*	22.13 mg/ml	[54]
77	Quercitrin	*Flos sophorae immaturus*	367.82 mg/ml	[54]
78	*β*,*β*-dimethylacrylshikonin	*Arnebia euchroma*	7.475 µg/ml	[55]
79	Deoxyshikonin	*Arnebia euchroma*	4.487 µg/ml	[55]
80	7,4′-dihydroxyflavone	*Glycyrrhiza glabra*	32.86 µM	[56]
81	3,3′,4,4′-tetrahydroxy-2-methoxychalcone	*Glycyrrhiza glabra*	28.29 µM	[56]
82	Osmundacetone	*Inonotus obliquus*	129.08 µM	[57]
83	Davallialactone	*Sanghuangporus vaninii*	90.07 mg/ml	[57]
84	Kaempferol-3-rhamnoside	*Pithecellobium dulce*	70.4 µg/ml	[58]
85	Sodium kaempferol-3’-sulfonate		0.338 µM	[59]

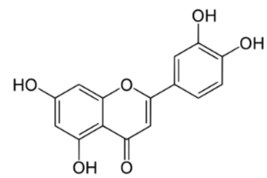
prieshood theory” is the primary principle of the control composition, which is modeled following the rule of the ancient monarchy system. In traditional medicine, this principle is applied, and each ingredient plays a particular role in treating the whole harmony and balance. The use of medicinal herbs, herbal extracts, and chemical compounds may contribute to the lower incidence of hyperuricemia. However, the fundamental principle in the treatment therapy of gout is to improve and restore liver, renal, and spleen function. Although kinetic studies and molecular docking analysis have been evidenced, there have not



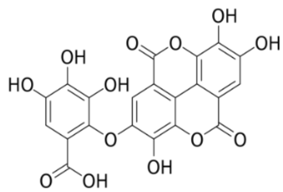
syringic acid



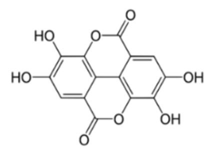
takakin 8-O-glucuronide



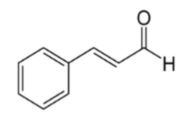
luteolin



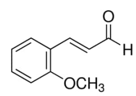
valoneic acid dilactone



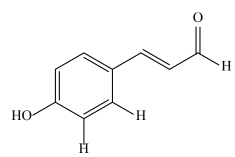
ellagic acid



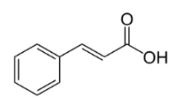
6. cinnamaldehyde



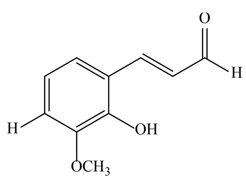
7. 2-methoxycinnamaldehyde



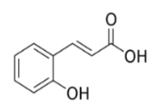
8. 2-Hydroxycinnamaldehye



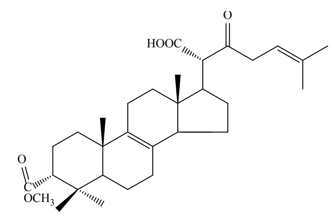
9. cinnamic acid



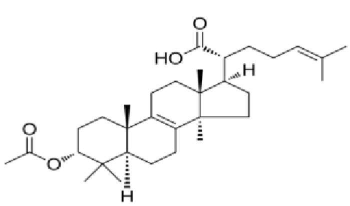
10. coniferaldehyde



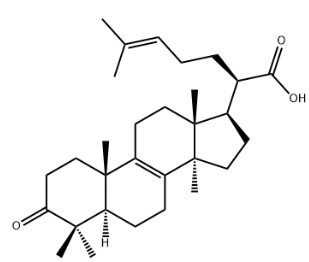
11. o-Coumaric acid



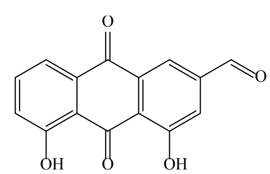
12. tsugaric acid D



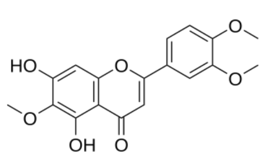
13. tsugaric acids A



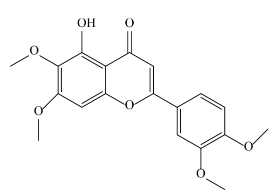
14. 3-oxo-5α-lanosta-8,24-diene-21-oic acid



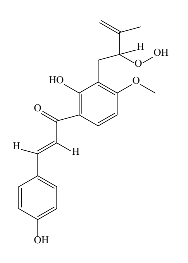
15. 4,5-dihydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde



16. eupatilin

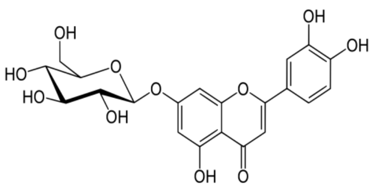


17. 5-hydroxy-6,7,3',4′-tetramethoxyflavone

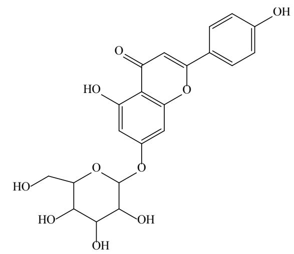


18. xanthoangelol

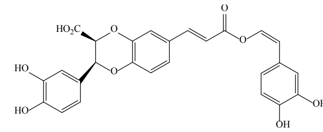
Continued



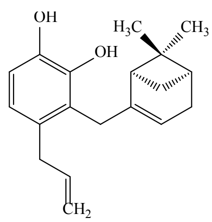
19. luteolin-7-O-glucoside



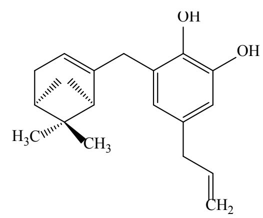
20. apigenin-7-O-glucoside



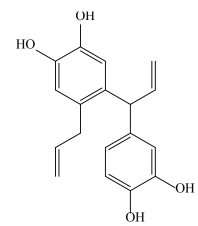
21. hyprhombin C



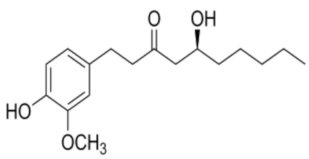
22. nudibaccatumin A



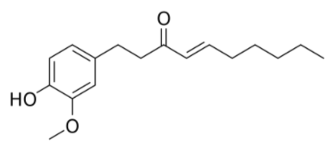
23. nudibaccatumin B



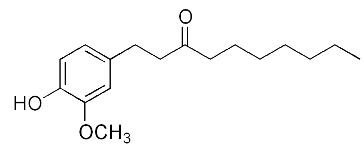
24. neotaiwanensol B



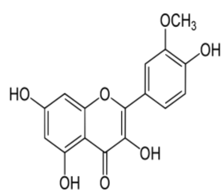
25. 6-gingerol



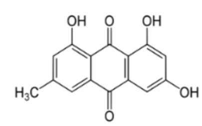
26. 6-shogaol



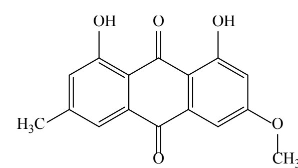
27. 6-paradol



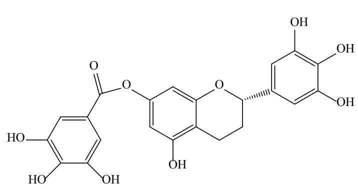
28. isorhamnetin



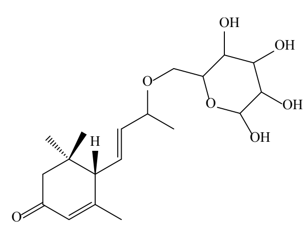
29. emodin



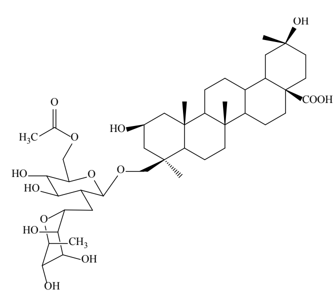
30. physcion



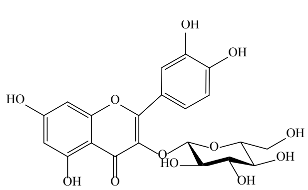
31. (−)-7-O-galloyltricetiflavan



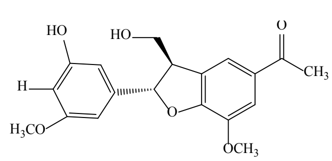
32. ranuncoside



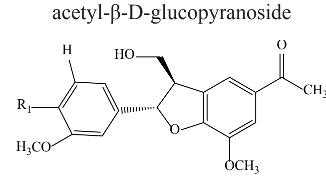
33. 3β, 20α, 24-trihydroxy-29-norolean12-en-28-oic acid 24-O-β-L-fucopyranosyl-(1→2)-6-O-acetyl-β-D-glucopyranoside



34. isoquercitrin



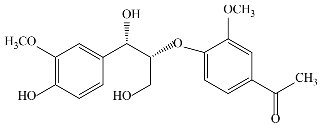
35. lycocernuasides B



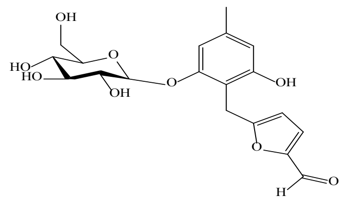
R1=OGlc

36. lycocernuasides C

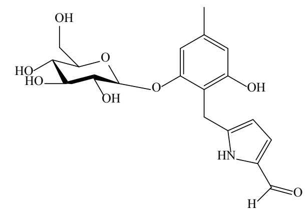
Continued



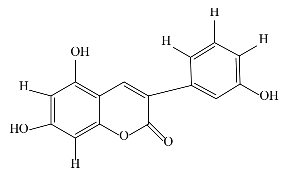
37. lycocernuasides D



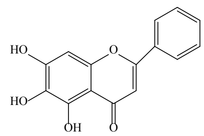
38. orcinosides I



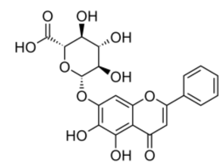
39. orcinosides J



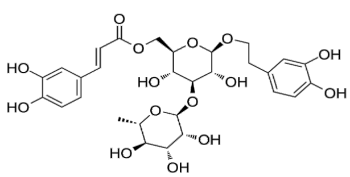
40. 5,7-dihydroxy-3-(3′-hydroxyphenyl) coumarin



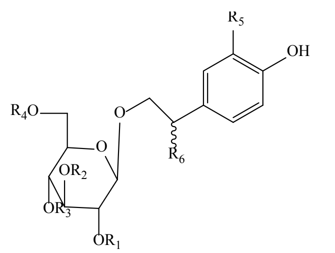
41. baicalein



42. baicalin



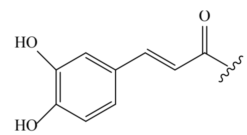
43. Isoacteoside



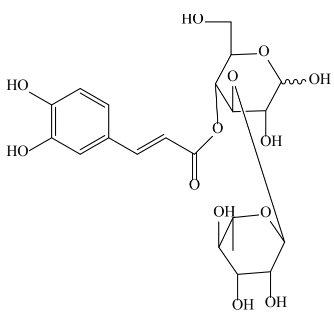
R1, R3, R5, R6(H); R2(Rha); R4(Cf)

44. kankanoside G

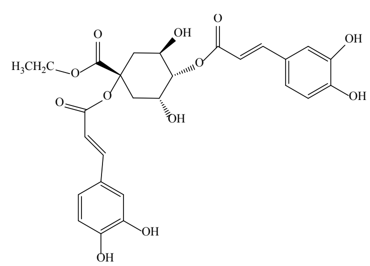
Cf=trans-caffeoyl



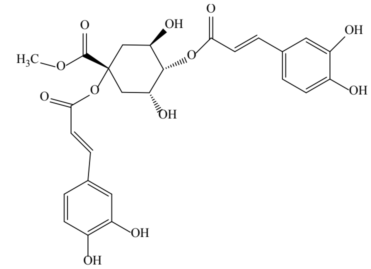
Rha=α-L-rhamnopranose



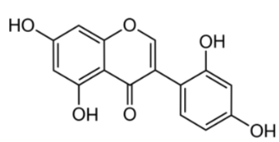
45. cistanoside F



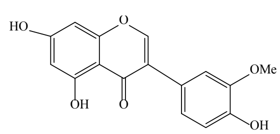
46. (−) ethyl 1, 4-di-O-caffeoylquinate



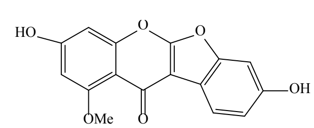
47. (−) methyl 1, 4-di-O-caffeoylquinate



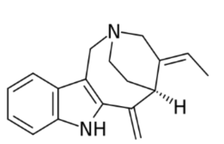
48. 2'-hydroxygenistein



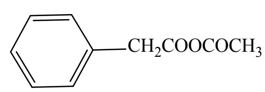
49. 3'-methoxy-4',5,7-trihydroxyisoflavone



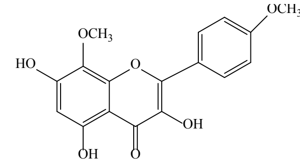
50. lupinalbin



51. apparicine

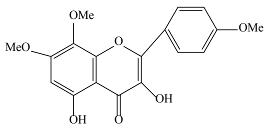


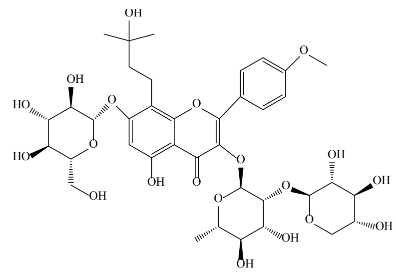
52. acetyl phenyl acetate

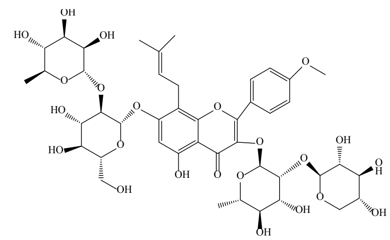


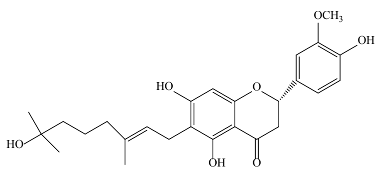
53. prudomestin

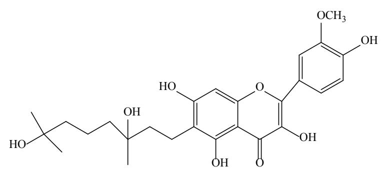
Continued

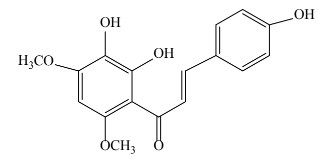

54. tambulin

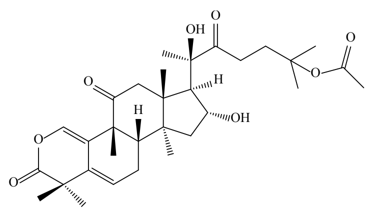

55. icarisid E

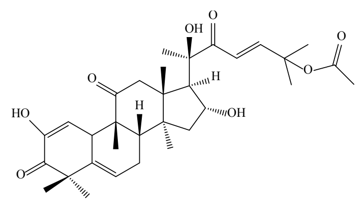

56. icarisid J

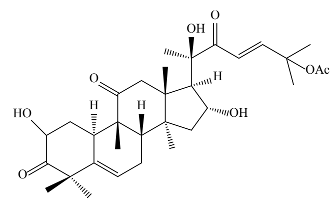

57. paucatalinones L

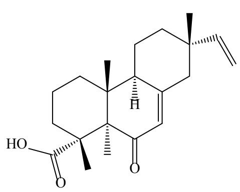

58. paucatalinones N

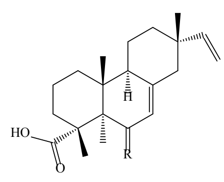

59. 2’,4’-dimethoxy-4,5’,6’-trihydroxychalcone.


60. neocucurbitacin D

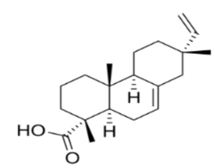

61. cucurbitacin E

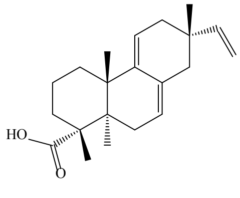

62. cucurbitacin B

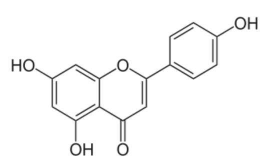

63. 6-oxoisopimaric acid

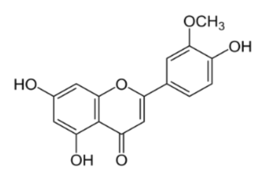

R=α-OH, β-H

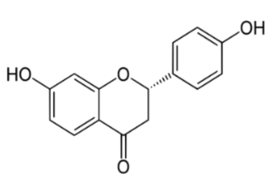
64. 6α-hydroxyisopimaric acid

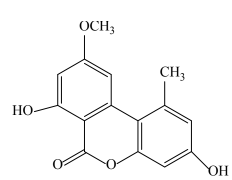

65. isopimaric acid

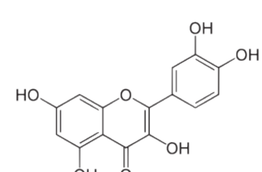

66. isopimara-7,9(11),15-trien-18-oic acid


67. apigenin

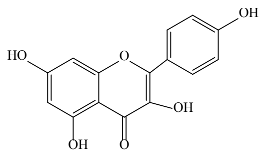

68.chrysoeriol

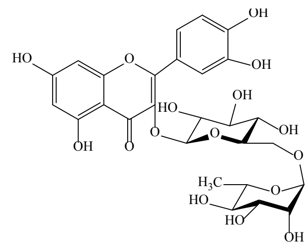

69. liquiritigenin

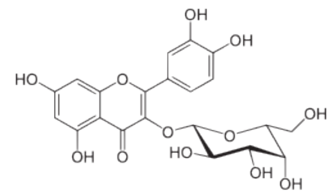

70. mycotoxin alternariol

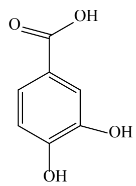

71. quercetin

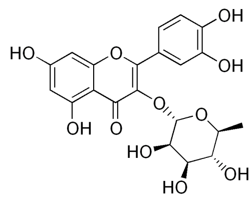
Continued

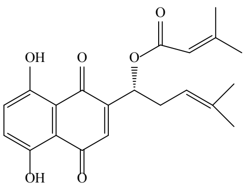

72. kaempferol

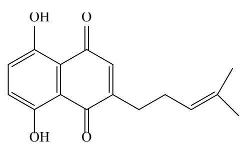

73. rutin

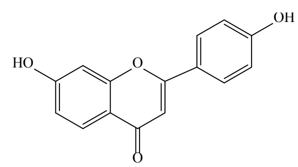

74. hyperoside

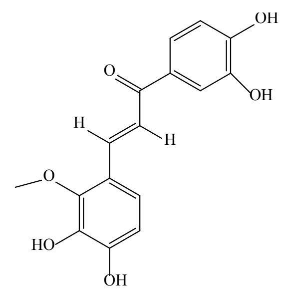

75. protocatechuic acid

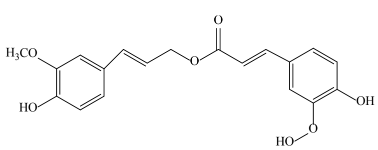

76. quercitrin

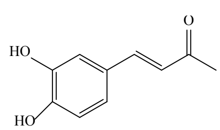

77. β,β-dimethylacrylshikonin

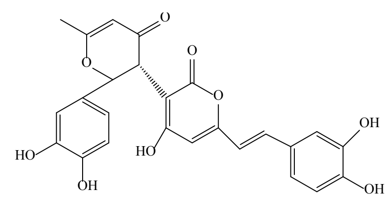

78. deoxyshikonin

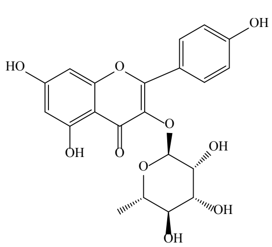

79. 7,4′-dihydroxyflavone


80. 3,3′,4,4′-tetrahydroxy-2-methoxychalcone


81. coniferyl ferulate


82. osmundacetone


83. davallialactone


84. kaempferol-3-rhamnoside

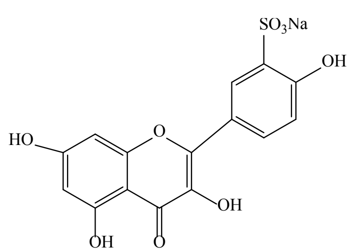

85. sodium kaempferol-3’-sulfonate

Figure 1. Chemical structures of compounds.

been any investigations *in vivo* on pharmacokinetics or internal metabolism in humans in a long time. Based on the above arguments, there is an urgent need to establish a comprehensive strategy for preventing and treating gout disease, which includes additional clinical trials with longer study periods on humans to certify the anti-gout potential of herbal medicine and case studies are also encouraged and called for in the future.

CONCLUSION

Gout has attracted considerable attention because it causes serious health damage and affects human life quality. Serial pharmacological studies have been investigated *in vitro* and also developed *in vivo* in rat models. Though several pharmacological mechanisms and kinetics-related XO inhibitory activities of independent herbal derivative extracts and chemical compounds have already been achieved as emerging evidence, the more comprehensive pharmacological mechanisms of synergistic combinations of herbs and chemical components with each other need to be elucidated. Moreover, we are concerned that the medical resistance phenomenon is very likely when used for a long time; therefore, firm evidence for more clinical studies and applications needs to be elucidated in order to form an effective gout therapeutic formula of herbal medicine.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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