Pharmacological effects of *Picrasma quassioides* (D. Don) Benn for inflammation, cancer and neuroprotection (Review)

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Abstract. *Picrasma quassioides* (D. Don) Benn is an Asian shrub with a considerable history of traditional medicinal use. *P. quassioides* and its extracts exhibit good therapeutic properties against several diseases, including anti-inflammatory, antibacterial and anticancer effects. However, the composition of compounds contained in *P. quassioides* is complex; although various studies have examined mixtures or individual compounds extracted from it, studies on the application of *P. quassioides* extracts remain limited. In the present review, the structures and functions of the compounds identified from *P. quassioides* and their utility in anti-inflammatory, anticancer and neuroprotectant therapies was discussed. The present review provided up-to-date information on pharmacological activities and clinical applications for *P. quassioides* extracts.

Contents

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1. Introduction

Picrasma quassioides (D. Don) Benn is a perennial herbaceous plant of the Simaroubaceae DC family that grows in Korea, China, Japan and Nepal. *P. quassioides* is a widely used Asian traditional medicine and is officially recorded in the Korea and Chinese Pharmacopoeia (ed. 2020) (1). The dried branches and leaves of *P. quassioides* may be ingested or used as an externally applied medicine. According to concepts of Korean/Asian medicine, the *P. quassioides* flavor is bitter and cold with little poison, and the meridian tropism involves the lung and large intestine. The functions and indications for use include 'removing heat or dampness' (concepts of Korean/Asian medicine) and detoxification. Thus, this Asian traditional medicine may be used for wind-heat cold (treatments aimed at expelling out heat and cooling the body), sore throat, diarrhea and eczema (2). *P. quassioides* is also used to treat rabies and snake bite (3).

The stem of *P. quassioides* is a thick cylinder that may range from 4 to 30 cm in diameter. The surface is brown and has a fine longitudinal texture, and the lenticel is raised, light-brown and round or rhomboid in shape. The stem is pale yellow, dark toward the middle with clear rings in its cross-section and has a bitter taste. The branches are cylindrical with a diameter of 0.5-15 cm, with a dark brown or reddish-brown surface, longitudinal stripes, and spotty and slightly raised, light-brown lenticels. The cross-section is pale yellow, with myelination in the middle, and the taste is bitter. The roots are cylindrical with a diameter of 3-8 cm. Their surface is gray-brown with gray-brown longitudinal cracks and the pores are not obvious.

The cross-section is pale-yellow and the root has an overall bitter taste (4). Collectively, the entire *P. quassioides* plant is of substantial medicinal value. The root is removed in autumn and winter along with the young branches and the rough external skin is scraped off. The branches and trunks are dried, cleaned and sliced; the leaves may be washed with clean water and cut into pieces. The dried branches and leaves are stored and used for medicinal purposes (5,6).

2. Active components of *Picrasma quassioides* (D. Don) Benn

The chemical composition of *P. quassioides* is complex. Studies have identified the active components by separating and purifying the plant parts according to the structure and organic reaction characteristics following different extraction processes to obtain a variety of compounds. After nuclear magnetic resonance mass spectrometric analysis, experiments including cell-based assays, determination of GAPDH activity and others are used to test the properties of the extracted compounds. Previous studies separated and extracted the major components and confirmed that they are β-carboline alkaloids, carthinone alkaloids, bis-β-carboline alkaloids, quassinoids and triterpenoids (7-10).

β-carboline alkaloids. Although most β-carboline alkaloids are extracted from natural plants, a small number of them have been synthesized chemically. β-carboline alkaloids have a planar tricyclic ring system consisting of indolopyridine carboline rings. These β-carboline alkaloids are the most representative alkaloids in *P. quassioides*. This alkaloid type has various chemical structures and a wide range of biological activities. A total of 38 β-carboline alkaloids have been isolated from *P. quassioides* (compounds 1-38). The structures and names of these compounds are presented in Figs. 1-3 and Table I and Fig. S1.

Carthinone alkaloids. Similar to β-carboline alkaloids, carthinone alkaloids are polycyclic compounds containing a carboline ring. The entire molecule is a highly conjugated system. All carthinone types share a common canthin-6-one backbone, i.e., the basic structure is based on a canthin-6-one backbone. A total of 12 carthinone alkaloids were isolated from *P. quassioides* (compounds 39-50). The structures and names of these compounds are presented in Fig. 4 and Table II and Fig. S1.

Bis-β-carboline alkaloids. Bis-β-carboline alkaloids are bimolecular compounds formed by two indole alkaloids joined by chemical bonds. These compounds are important alkaloid components in Picrasma BL species and may have biological activities similar to those of β-carboline alkaloids. A total of 10 bis-β-carboline alkaloids have been isolated from *P. quassioides* (compounds 51-60). The structures and names of these compounds are presented in Figs. 5 and 6, Table III and Fig. S1.

Quassinoids. Quassinoids are characteristic components of Simaroubaceae DC species, and its parent nuclear structure is mainly composed of nigakihemiacetal and nigakilactone. A total of 45 quassinoids have been isolated from *P. quassioides* (compounds 61-105); their names structures are presented in Figs. 7-9 and Table IV and Fig. S1.

Triterpenoids. Although triterpenoids account for a small proportion of the active compounds in *P. quassioides*, these molecules have anti-inflammatory and anticancer effects. A total of eight triterpenoids have been isolated from *P. quassioides* (compounds 106-113). The structures of these compounds are presented in Fig. 10 and Table V and Fig. S1.

3. Anti-inflammatory role of *Picrasma quassioides* (D. Don) Benn

P. quassioides is a plant with effective anti-inflammatory action that has been used for numerous years in Asian traditional medicine. While previous studies have investigated the anti-inflammatory effects of *P. quassioides*, the underlying molecular mechanisms have remained elusive. Inflammation is a defensive response produced by local tissues to external stimulation (11). However, excessive, persistent inflammatory reactions lead to physical and pathological damage and may eventually lead to the development of several diseases such as asthma (12), diabetes (13), hypertension (14), rheumatoid arthritis (15) and arteriosclerosis (16). Lipopolysaccharide (LPS) is an inflammatory activator that binds to toll-like receptor 4 in macrophages (17), activating nuclear factor-κB (NF-κB) (18) and mitogen-activated protein kinase (MAPK) (19). These two signaling pathways cause the release of inflammatory factors (20), thereby regulating oxidative stress responses and accelerating inflammatory responses, which may cause changes in inflammatory proteins (21). In particular, inflammation induces the protein degradation of the recombinant inhibitory subunit of NF-κB α, MAPK-related protein phosphorylation, increased inducible nitric oxide (NO) synthase (iNOS) and cyclooxygenase-2 (COX-2) protein expression and release of inflammatory mediators such as NO, tumor necrosis factor α (TNF-α) and interleukin (IL)-6 (Table VI) (22).

NO is an important inflammatory factor. Therefore, inhibiting NO production is an effective method for treating and preventing inflammation-related diseases. TNF-α is a polypeptide cytokine that regulates other inflammatory factors and proteases, thereby regulating inflammation (23). IL-6 is another circulating cytokine that regulates immune cell activation, T and B cell proliferation and differentiation, as well as inflammatory responses (24). Of note, ILs are divided into proinflammatory (IL-1, -6 and -8) and anti-inflammatory (IL-4 and -10) factors. COX, also called prostaglandin G/H synthase, has two isoforms, COX-1 and COX-2, which have key roles in inflammation and are targeted by nonsteroidal anti-inflammatory drugs (25).

P. quassioides extracts effectively inhibited ovalbumin-induced allergic asthma in mice. *In vitro* experiments suggested that *P. quassioides* extracts have an anti-inflammatory role by reducing IL-4, IL-5, IL-13, immunoglobulin E and iNOS expression (26). Methanolic extracts of *P. quassioides* suppressed iNOS and COX-2 expression by inhibiting NF-κB activity and reducing ERK phosphorylation to achieve anti-inflammatory effects *in vitro* (27). Similarly,

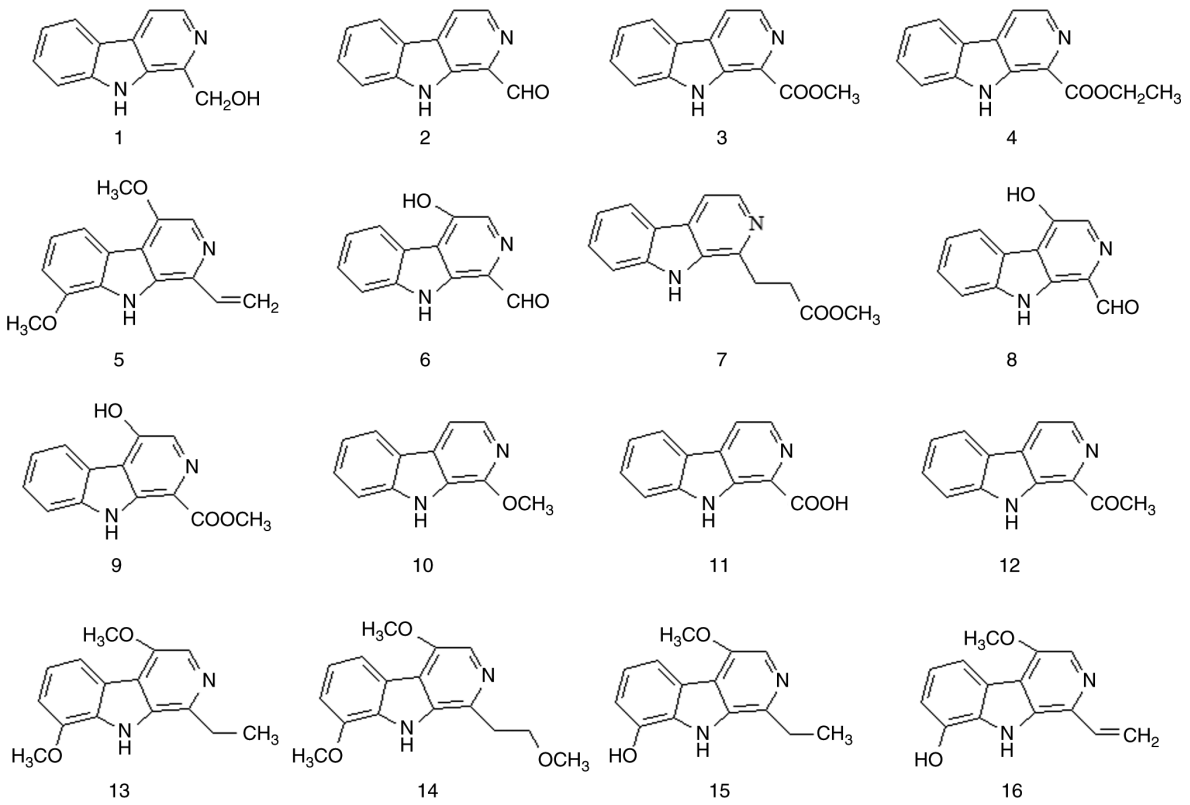

Figure 1. Structure of β-carboline alkaloids (1). Chemical formula of compounds 1-16 and the corresponding names: 1) 1-hydroxymethyl-β-carboline, 2) 1-formyl-β-carboline, 3) 1-methoxyformacyl-β-carboline, 4) 1-ethoxyformyl-β-carboline, 5) 1-vinyl-4,8-dimethoxy-β-carboline, 6) 1-formyl-4-methoxy-β-carboline, 7) 1-methoxypropionyl-β-carboline, 8) 1-formyl-4-hydroxy-β-carboline, 9) 1-methoxyformacyl-4-hydroxy-β-carboline, 10) 1-methoxyl-β-carboline, 11) β-carboline-1-methanoic acid, 12) 1-ethanoyl-β-carboline, 13) 1-ethyl-4,8-dimethoxy-β-carboline, 14) 1-(2-methoxyl)-ethyl-4,8-dimethoxyl-β-carboline, 15) 1-ethyl-4-methoxyl-8-hydroxy-β-carboline and 16) 1-vinyl-4-methoxyl-8-hydroxy-β-carboline.

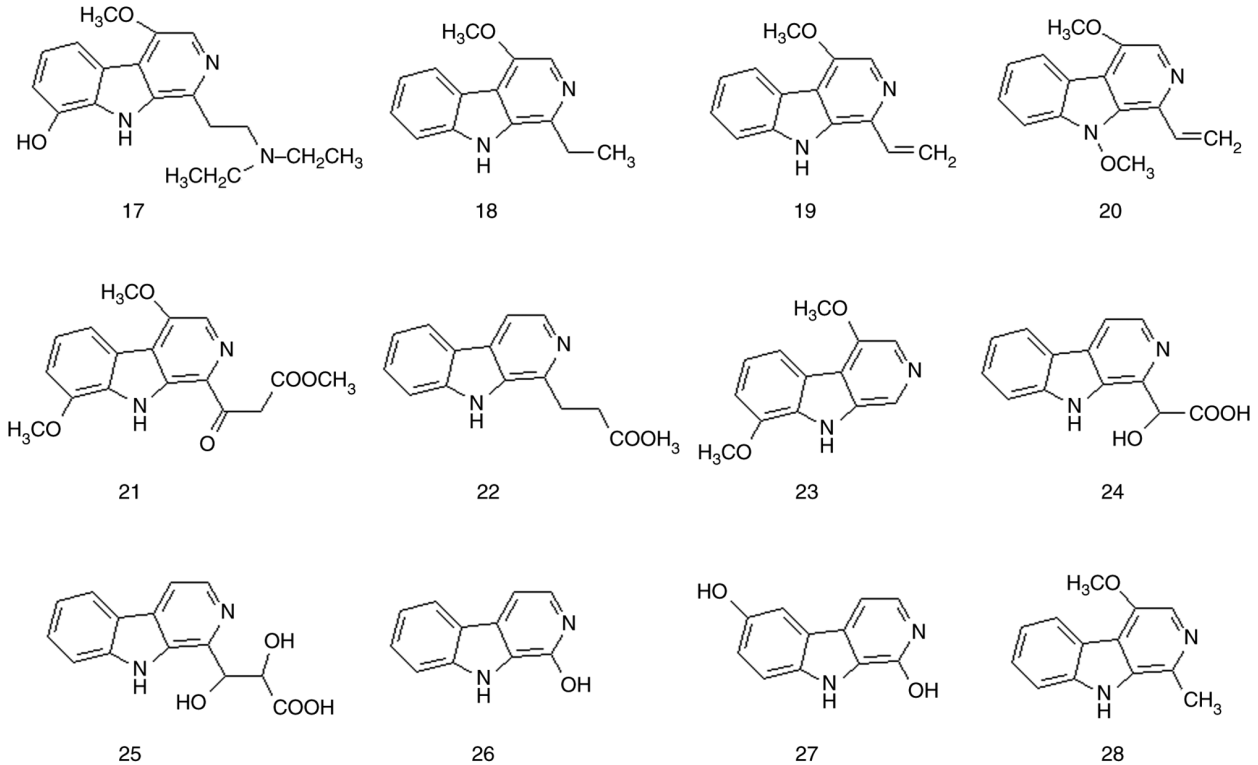

Figure 2. Structure of β-carboline alkaloids (2). Chemical formula of compounds 17-28 and the corresponding names: 17) 1-(2-ethylamino)-ethyl-4-methoxyl-8-hydroxy-β-carboline, 18) 1-ethyl-4-methoxyl-β-carboline, 19) 1-vinyl-4-methoxyl-β-carboline, 20) 1-vinyl-4,9-dimethoxy-β-carboline, 21) 1-(1-carbonyl-2-methoxybutyly)-4,8-dimethoxy-β-carboline, 22) 1-carboxypropyl-β-carboline, 23) 4,8-dimethoxy-β-carboline, 24) 1-(2-hydroxy)-carboxypropyl-β-carboline, 25) 1-(1,2-hydroxy)-carboxypropyl-β-carboline, 26) 1-hydroxy-β-carboline, 27) 1,6-dihydroxy-β-carboline and 28) 1-methyl-4-methoxyl-β-carboline.

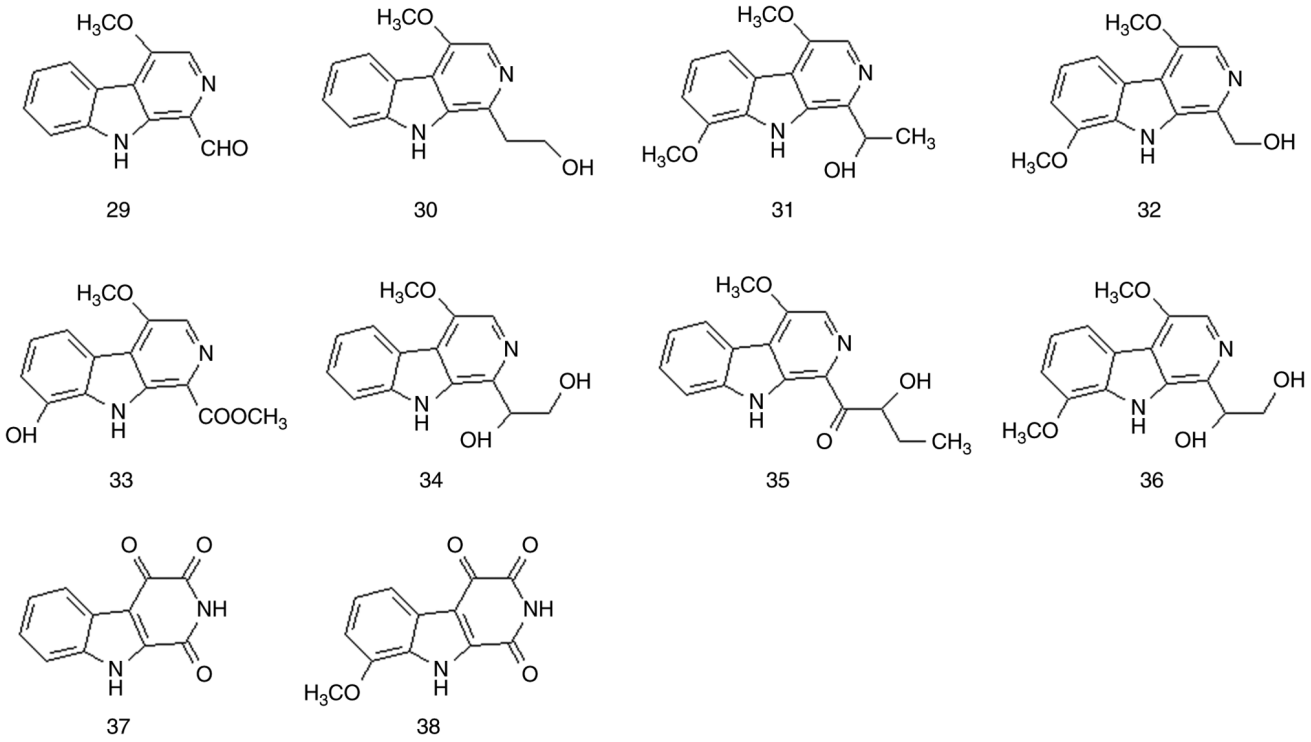

Figure 3. Structure of β-carboline alkaloids (3). Chemical formula of compounds 29-38 and the corresponding names: 29) 1-formyl-4-methoxyl-β-carboline, 30) 1-(2-dihydroxy)-ethyl-4-methoxyl-β-carboline, 31) 1-(1-hydroxy)-ethyl-4,8-dimethoxy-β-carboline, 32) 1-(2-hydroxy)-ethyl-4,8-dimethoxy-β-carboline, 33) 1-methoxyformacyl-4-methoxyl-8-hydroxy-β-carboline, 34) 1-(1,2-dihydroxy)-ethyl-4-methoxyl-β-carboline, 35) 1-(2-ethoxyethanol)-4-methoxyl-β-carboline, 36) 1-(1,2-dihydroxy)-ethyl-4,8-dimethoxy-β-carboline, 37) 1,2,3,4-tetrahydro-1,3,4,-trioxo-β-carboline and 38) 8-methoxyl-1,2,3,4-tetrahydro-1,3,4,-trioxo-β-carboline.

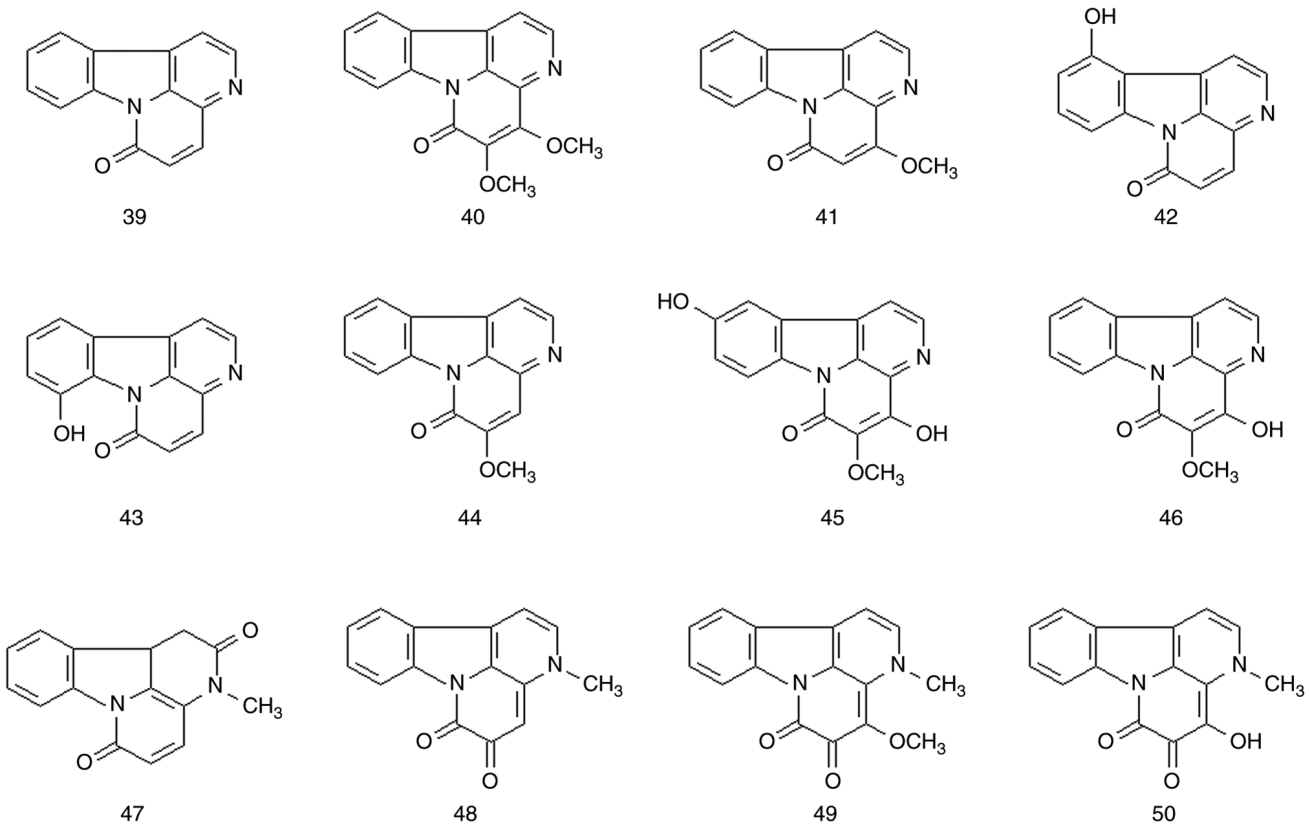

Figure 4. Structure of canthinone alkaloids. Chemical formula of compounds 39-50 and the corresponding names: 39) canthin-6-one, 40) 4,5-dimethyl-canthin-6-one, 41) 4-methoxy-5-hydroxy-canthin-6-one, 42) 11-hydroxy-canthin-6-one, 43) 8-hydroxy-canthin-6-one, 44) 5-methoxy-canthin-6-one, 45) 4,10-dyhydroxy-5-methoxy-canthin-6-one, 46) 4-hydroxy-5-methoxy-canthin-6-one 47) 3-methyl-canthin-2,6-dione, 48) 3-methyl-canthin-5,6-dione, 49) 3-methyl-4-methoxyl-canthine-5,6-dione and 50) 3-methyl-4-hydroxy-canthine-5,6-dione.

Table I. β-carboline alkaloids of *Picrasma quassioides* (D. Don) Benn.

No.	Name	Basic structure (Fig. S1)
1	1-hydroxymethyl-β-carboline	(1)
2	1-formyl-β-carboline	(1)
3	1-methoxyformacyl-β-carboline	(1)
4	1-ethoxyformyl-β-carboline	(1)
5	1-vinyl-4,8-dimethoxy-β-carboline	(1)
6	1-formyl-4-methoxy-β-carboline	(1)
7	1-methoxypropionyl-β-carboline	(1)
8	1-formyl-4-hydroxy-β-carboline	(1)
9	1-methoxyformacyl-4-hydroxy-β-carboline	(1)
10	1-methoxyl-β-carboline	(1)
11	β-carboline-1-methanoic acid	(1)
12	1-ethanoyl-β-carboline	(1)
13	1-ethyl-4,8-dimethoxy-β-carboline	(1)
14	1-(2-methoxyl)-ethyl-4,8-dimethoxyl-β-carboline	(1)
15	1-ethyl-4-methoxyl-8-hydroxy-β-carboline	(1)
16	1-vinyl-4-methoxyl-8-hydroxy-β-carboline	(1)
17	1-(2-ethylamino)-ethyl-4-methoxyl-8-hydroxy-β-carboline	(1)
18	1-ethyl-4-methoxyl-β-carboline	(1)
19	1-vinyl-4-methoxyl-β-carboline	(1)
20	1-vinyl-4,9-dimethoxy-β-carboline	(1)
21	1-(1-carbonyl-2-methoxybutyly)-4,8-dimethoxy-β-carboline	(1)
22	1-carboxypropyl-β-carboline	(1)
23	4,8-dimethoxy-β-carboline	(1)
24	1-(2-hydroxy)-carboxypropyl-β-carboline	(1)
25	1-(1,2-hydroxy)-carboxypropyl-β-carboline	(1)
26	1-hydroxy-β-carboline	(1)
27	1,6-dihydroxy-β-carboline	(1)
28	1-methyl-4-methoxyl-β-carboline	(1)
29	1-formyl-4-methoxyl-β-carboline	(1)
30	1-(2-dihydroxy)-ethyl-4-methoxyl-β-carboline	(1)
31	1-(1-hydroxy)-ethyl-4,8-dimethoxy-β-carboline	(1)
32	1-(2-hydroxy)-ethyl-4,8-dimethoxy-β-carboline	(1)
33	1-methoxyformacyl-4-methoxyl-8-hydroxy-β-carboline	(1)
34	1-(1,2-dihydroxy)-ethyl-4-methoxyl-β-carboline	(1)
35	1-(2-ethoxyethanol)-4-methoxyl-β-carboline	(1)
36	1-(1,2-dihydroxy)-ethyl-4,8-dimethoxy-β-carboline	(1)
37	1,2,3,4-tetrahydro-1,3,4-trioxo-β-carboline	(2)
38	8-methoxyl-1,2,3,4-tetrahydro-1,3,4-trioxo-β-carboline	(2)

P. quassioides extracts also inhibit TNF-α and IL-8 release in the colon of a trinitrobenzene sulfonic acid-induced colitis mouse model (28).

Anti-inflammatory effects of β-carboline alkaloids. 6-Methoxy-3-vinyl-β-carboline and 6,12-dimethoxy-3-vinyl-β-carboline were demonstrated to have inhibitory effects on NO, TNF-α and IL-6 secretion in LPS-induced RAW264.7 cells (27). 3-Methylcanthin-5,6-dione inhibited LPS-stimulated NO production in RAW264.7 cells and had antioxidant activity (29). Benzalharman, kumujian, 1-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and 1-acetophenone-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid inhibited excessive NO production and downregulated iNOS expression in RAW264.7 cells activated by LPS but had no evident inhibitory effect on COX-2 protein expression (30).

Anti-inflammatory effects of carthinone alkaloids. 4-Methoxy-5-hydroxycanthin-6-one significantly inhibited LPS-induced NO and TNF-α release and downregulated iNOS expression to achieve anti-inflammatory activity in RAW264.7 cells (31). Cathin-6-one and 9-methoxy-cathin-6-one inhibited NO production and downregulated iNOS and COX-2 expression in LPS-activated RAW264.7 cells. Furthermore,

Table II. Canthinone alkloids of *Picrasma quassioides* (D. Don) Benn.

No.	Name	Basic structure
39	Canthin-6-one	(3)
40	4,5-dimethyl-canthin-6-one	(3)
41	4-methoxy-5-hydroxy-canthin-6-one	(3)
42	11-hydroxy-canthin-6-one	(3)
43	8-hydroxy-canthin-6-one	(3)
44	5-methoxy-canthin-6-one	(3)
45	4,10-dyhydroxy-5-methoxy-canthin-6-one	(3)
46	4-hydroxy-5-methoxy-canthin-6-one	(3)
47	3-methyl-canthin-2,6-dione	(4)
48	3-methyl-canthin-5,6-dione	(5)
49	3-methyl-4-methoxyl-canthine-5,6-dione	(5)
50	3-methyl-4-hydroxy-canthine-5,6-dione	(5)

Table III. Bis-β-carboline alkaloids of *Picrasma quassioides* (D. Don) Benn.

No.	Name	Basic structure
51	Picrasidine A	(6)
52	Picrasidine C	(7)
53	Picrasidine F	(9)
54	Picrasidine G	(9)
55	Picrasidine H	(6)
56	Picrasidine M	(8)
57	Picrasidine N	(8)
58	Picrasidine U	(8)
59	Picrasidine S	(9)
60	Picrasidine R	(7)

this molecule downregulated prostaglandin E2 expression in a dose-dependent manner (30). *In vivo*, the antihypertensive effect of 1:4-methoxy-5-hyroxycanthin-6-one is probably associated with reduced superoxide dismutase activity and increased eNOS expression, which preserves endothelial function and directly relaxes the aorta in spontaneously hypertensive rats (32). 9-methoxy-cathin-6-one may also be used to treat dextran sulfate sodium-induced ulcerative colitis (33) and reduce Freund's adjuvant-induced chronic arthritis, while intragastric 4-methoxy-5-hydroxycanthin-6-one administration for 28 days ameliorated arthritis symptoms in rats (31). These studies indicated that 4-methoxy-5-hydroxy-canthin-6-one has good anti-inflammatory activity. Similarly, canthin-6-one or 4-methoxycanthin-6-one used alone or in conjunction demonstrated potent antiulcerogenic effects when evaluated in gastric lesion-induced mice (34). Meanwhile, in rat and mouse models of gastric ulcers, cathin-6-one reduced the myeloperoxidase and malonaldehyde production in the stomach and inhibited IL-8 and TNF-α release into the serum, which alleviated gastric ulceration (35). Picrasidine L promoted insulin signaling pathway activation and effectively inhibited protein tyrosine phosphatase (PTP) 1B (36), a non-transmembrane PTP that may be produced in large quantities in insulin-targeted tissues (37).

Anti-inflammatory effects of bis-β-carboline alkaloids. Quassidine A, a bis-β-carboline alkaloid, possesses a novel cyclobutane moiety; however, this molecule exhibited weak anti-inflammatory activity (38). By contrast, quassidine E and quassidine G inhibited NO, TNF-α and IL-6 release. In anti-inflammatory activity experiments *in vitro*, quassidine F isolated from *P. quassioides* had inhibitory effects on NO and IL-6 production, but not on TNF-α release (39). Furthermore, certain studies suggested that the anti-inflammatory mechanism of quassidine F is mediated by inhibiting the iNOS signaling pathway (27). Picrasidine C and picrasidine N are peroxisome proliferator-activated receptor (PPAR)α (2) and PPARβ/δ agonists (40). Indeed, picrasidine N selectively activates the PPARβ/δ target gene ANGPTL4 (41) to regulate various physiological functions such as facilitating skin wound healing (42) and reducing atherosclerosis development (43). Picrasmalignan A (quassinoids drug) reduced NO, TNF-α and IL-6 production in LPS-induced macrophages and upregulated iNOS and COX-2 expression *in vitro* (44).

4. Anticancer role of *Picrasma quassioides* (D. Don) Benn

Cancer is caused by the continuous proliferation and abnormal differentiation of cells. Worldwide, cancer is the second major cause of death in humans. Of note, cancer is a complex, multi-factorial disease, which makes treatment difficult and poses several challenges for survival (45,46). In recent years, cancer awareness has markedly improved, and treatments have also been developed. In spite of efforts regarding the early detection and timely treatment of cancer, cancer-associated mortality is at an all-time high (47). The currently available clinical treatments for cancer mainly include surgical treatment, radiotherapy and chemotherapy (48). Early cancer detection generally leads to surgical treatment, whereas chemotherapy is mainly used for advanced cancer. Commonly

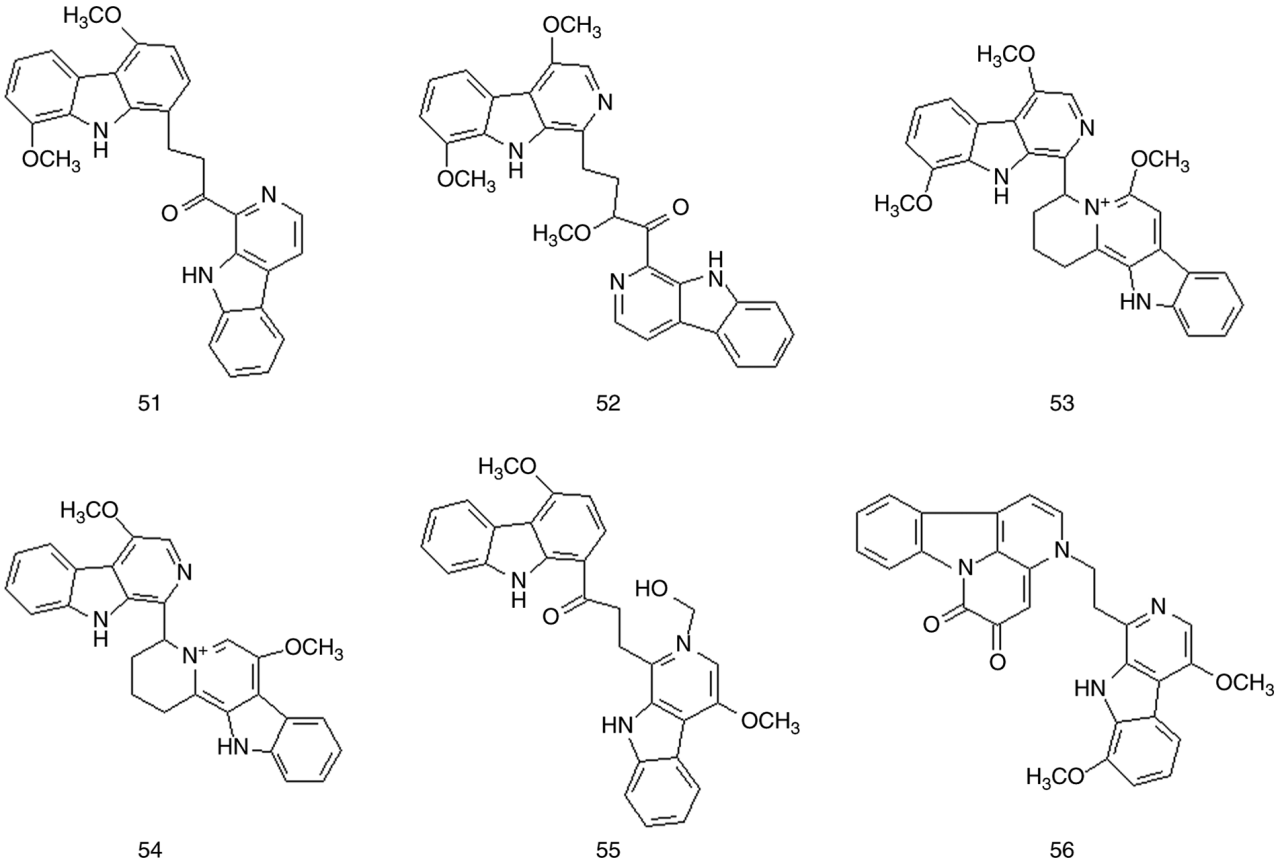

Figure 5. Structure of bis-β-carboline alkaloids (1). Chemical formula of compounds 51-56 and the corresponding names: 51) Picrasidine A, 52) picrasidine C, 53) picrasidine F, 54) picrasidine G, 55) picrasidine H and 56) picrasidine M.

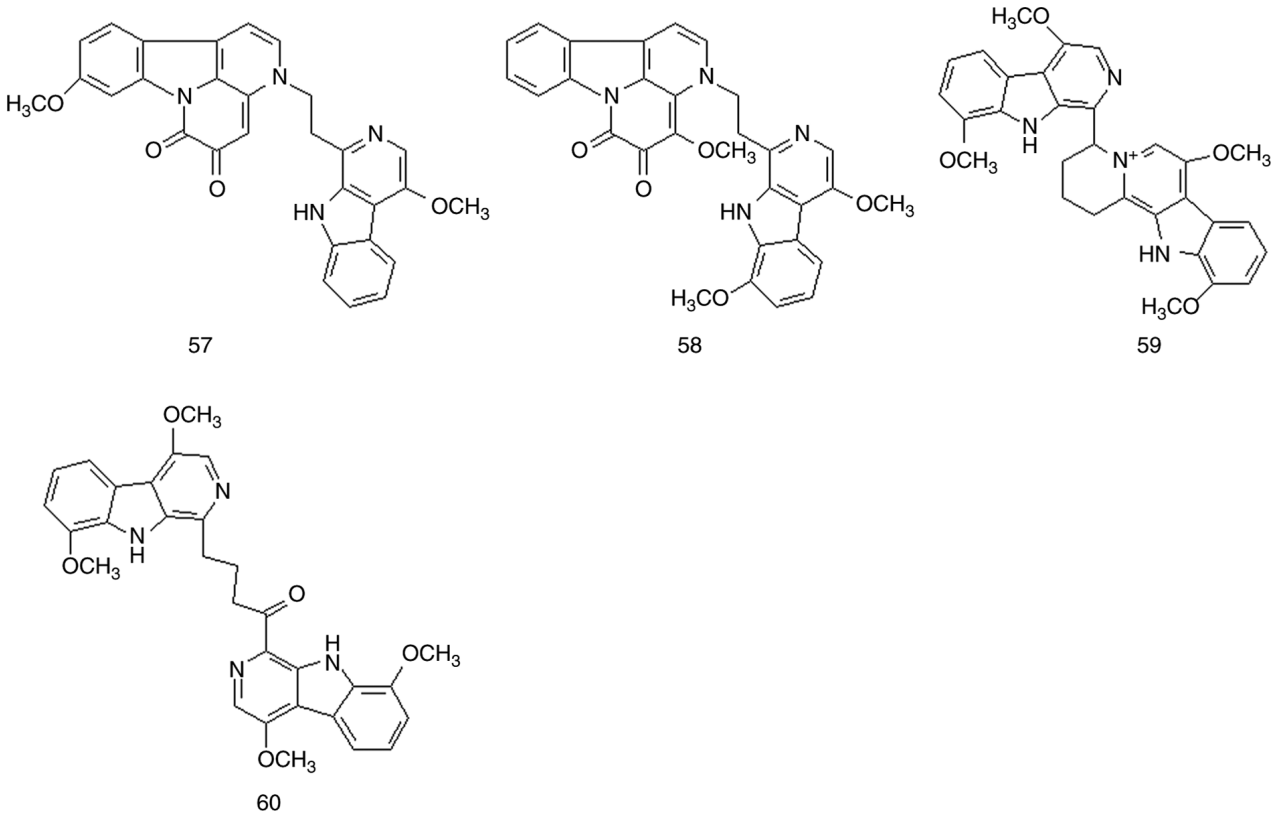

Figure 6. Structure of bis-β-carboline alkaloids (2). Chemical formula of compounds 57-60 and the corresponding names: 57) Picrasidine N, 58) picrasidine U, 59) picrasidine S and 60) picrasidine R.

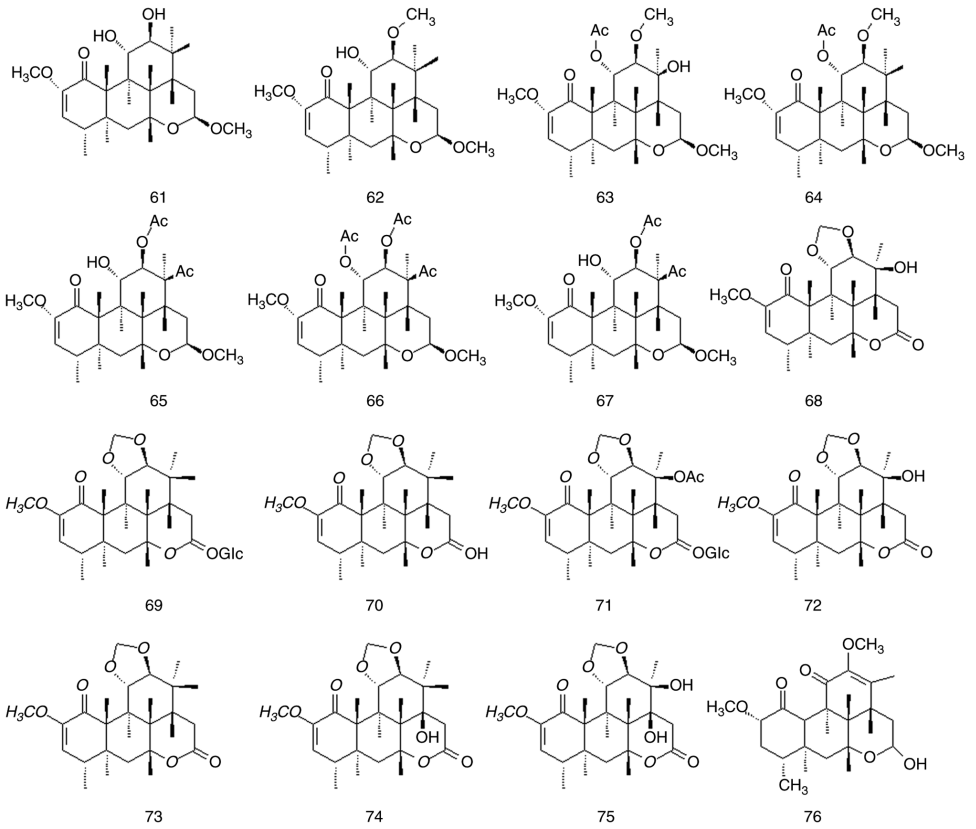

Figure 7. Structure of quassinoids (1). Chemical formula of compounds 61-76 and the corresponding names: 61) nigakilacetone A, 62) nigakilacetone B, 63) nigakilacetone C, 64) nigakilacetone E, 65) nigakilacetone F, 66) nigakihihemiacetal D, 67) kumulactone, 68) nigakilacetone L, 69) picrasinoside C, 70) picrasion B, 71) nigakilactone H, 72) picrasin D, 73) picrasin C, 74) picrasin D, 75) picrasin E and 76) nigakihihemiacetal B.

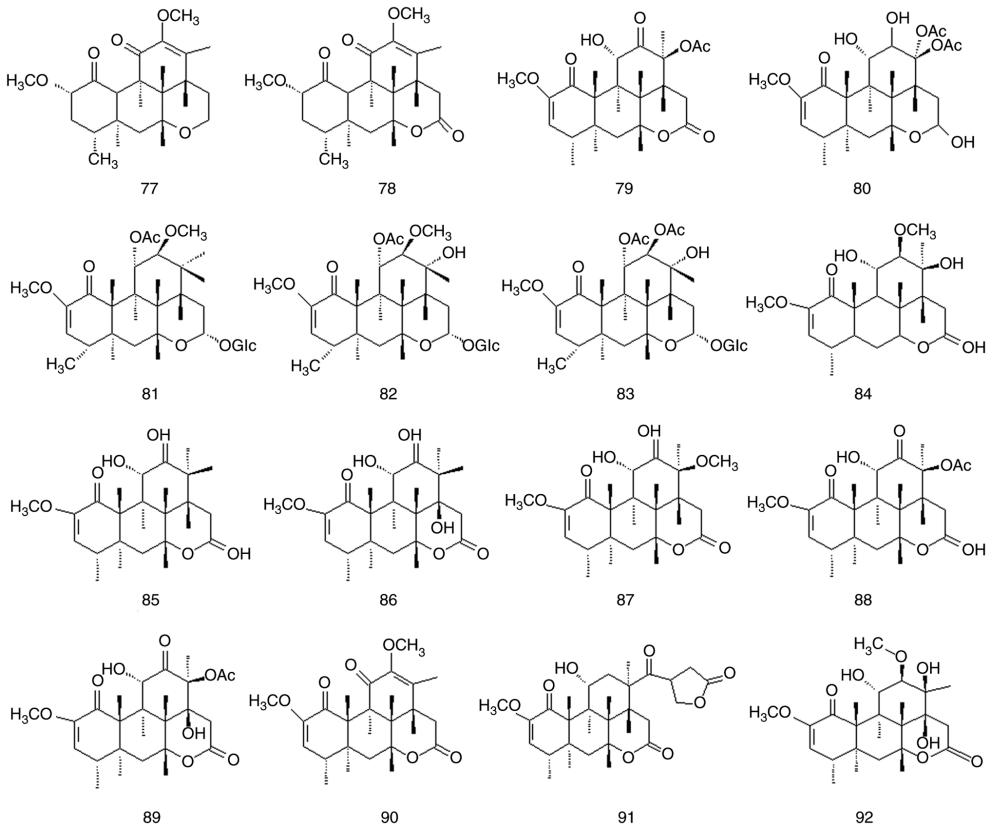

Figure 8. Structure of quassinoids (2). Chemical formula of compounds 77-92 and the corresponding names: 77) picrasinoside B, 78) quassin, 79) Picraqualide D, 80) picraqualide E, 81) Picrasinoside D, 82) picrasinoside E, 83) picrasinoside G, 84) nigakihihemiacetal A, 85) nigakihihemiacetal C, 86) nigakilactone M, 87) nigakilactone N, 88) picraqualide A, 89) picraqualide C, 90) nigakilactone D, 91) nigakilactone G and 92) nigakilactone H.

Table IV. β-carboline alkloids of *Picrasma quassioides* (D. Don) Benn.

No.	Name	Basic structure
61	Nigakilacetone A	(10)
62	Nigakilacetone B	(10)
63	Nigakilacetone C	(10)
64	Nigakilacetone E	(10)
65	Nigakilacetone F	(10)
66	Nigakihihemiacetal D	(12)
67	Kumulactone	(10)
68	Nigakilacetone L	(10)
69	Picrasinoside C	(12)
70	Picrasionol B	(12)
71	Nigakilacetone H	(10)
72	Picrasinol D	(12)
73	Picrasin C	(10)
74	Picrasin D	(10)
75	Picrasin E	(10)
76	Nigakihihemiacetal B	(12)
77	Picrasinoside B	(12)
78	Quassin	(12)
79	Picraqualide D	(10)
80	Picraqualide E	(12)
81	Picrasinoside D	(12)
82	Picrasinoside E	(12)
83	Picrasinoside G	(12)
84	Nigakihihemiacetal A	(12)
85	Nigakihihemiacetal C	(12)
86	Nigakilacetone M	(10)
87	Nigakilacetone N	(10)
88	Picraqualide A	(12)
89	Picraqualide C	(10)
90	Nigakilacetone D	(10)
91	Nigakilacetone G	(10)
92	Nigakilacetone H	(10)
93	Picrasin G	(10)
94	Nigakilacetone J	(10)
95	Nigakilacetone K	(10)
96	Nigakihihemiacetal E	(12)
97	Nigakihihemiacetal F	(12)
98	Picrasinoside A	(12)
99	Picrasinol A	(12)
100	Nigakilacetone O	(10)
101	Picrasinol C	(12)
102	Picrasin A	(11)
103	Picrasin B	(10)
104	Picraqualide B	(10)
105	Picrasin F	(10)

used chemotherapy drugs include 5-fluorouracil, cisplatin, paclitaxel and doxorubicin (49). However, the toxic side effects of chemotherapy drugs affect patient health (50). Natural Chinese herbal medicine has become a hot topic in anticancer research in recent years due to low toxicity and reduced side effects of various herbal formulations (51).

Several studies indicated that the crude extracts or compounds derived from Chinese herbal medicines effectively inhibited the proliferation of liver, gastric, lung, breast and colon cancer cells and induced cancer cell apoptosis (50-54). The pathways that induce cell death include the intrinsic pathway, extrinsic pathway and the endoplasmic reticulum (ER) stress pathway (47). The intrinsic pathway is also called the mitochondrial pathway. During apoptosis, various mitochondrial components integrate cell death signals and mediate the progression of apoptosis (55). The extrinsic pathway is activated by cell surface death receptors, such as Fas and TNF receptor (56). ER stress causes caspase-12 activation and induces apoptosis (57). ER stress may also promote DNA damage and autophagy-induced cell death (58). It is possible that chemotherapy drugs directly act on genes or proteins to stimulate the activation of downstream signaling pathways, involving B-cell lymphoma-2, MAPK, phosphatidylinositol 3-kinase/protein kinase B and recombinant glycogen synthase kinase 3 beta, to induce cell death (59-62).

P. quassioides extracts may induce cervical cancer cell apoptosis by upregulating the expression of the pro-apoptotic proteins Bad and t-Bad (63). In addition, these extracts may activate the reactive oxygen species (ROS)-mitochondria axis to cause death of SiHa human cervical cancer cells (64). Ethanolic extracts of *P. quassioides* also induced H-Ras^{G12V} liver cancer cell apoptosis (65), whereas the n-butanol extract induced HT-29 colon and NCI-N87 gastric cancer cell apoptosis. Importantly, these extracts exhibited no cytotoxicity to 293T normal human cells (66).

Anticancer effects of β-carboline alkaloids. 4-Methoxy-1-vinyl-β-carboline and 1-methoxy-β-carboline are cytotoxic to A2780 and SKOV3 human ovarian cancer cells and exhibited excellent antitumor activity (67). β-carboline-1-carboxylic acid, isolated from the stem of *P. quassioides*, demonstrated moderate inhibitory activities against K562 leukemia cancer cells and SGC-7901 human gastric cancer cells (68) (Table VII).

Anticancer effects of carthinone alkaloids. In vitro, 9-methoxy-canthin-6-one and canthin-6-one isolated from *P. quassioides* demonstrated significant cytotoxic activity against A549 lung cancer and MCF-7 breast cancer cells (69). Furthermore, 4,5-dimethoxy-10-hydroxy-canthin-6-one, canthin-6-one alkaloids, 8-hydroxy-canthin-6-one, 4,5-dimethoxy-canthin-6-one and 5-hydroxy-4-methoxycanthin-6-one exhibited significant cytotoxic activity against CNE2 nasopharyngeal carcinoma cells. Thus, carthinone alkaloids may be used to effectively treat various cancer types (70).

Anticancer effects of bis-β-carboline alkaloids. A novel bimolecular compound (B-9-3), synthesized from two β-carboline alkaloids, promoted cell death by causing necrotic apoptosis and reducing proliferation of NCI-H460 human non-small-cell lung cancer cells, T47D breast cancer cells and HCT-116 colon cancer cells (71). Two novel bis-β-carboline alkaloids, quassidines I and J, had cytotoxicity in HeLa human cervical cancer

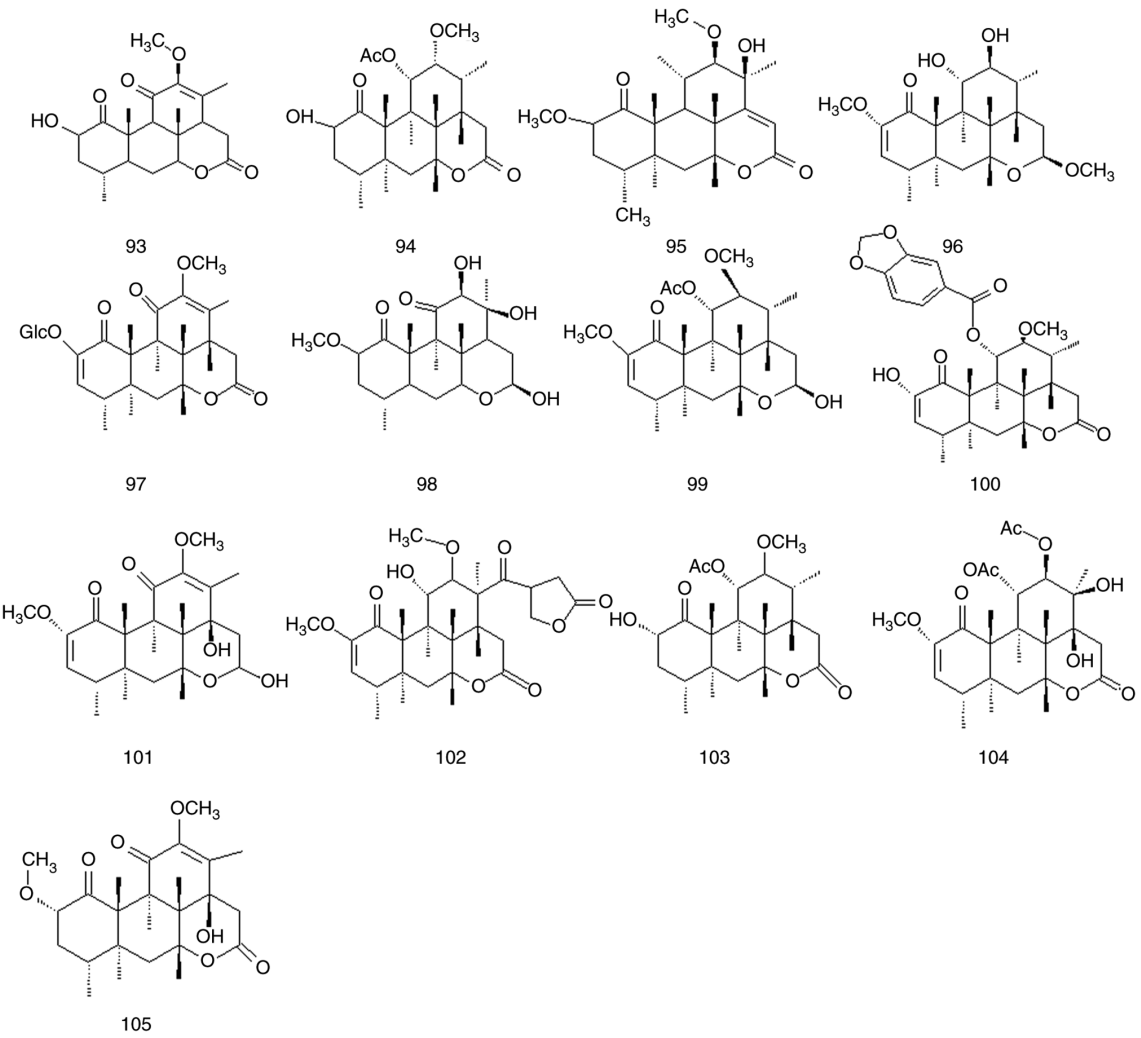

Figure 9. Structure of quassinoids (3). Chemical formula of compounds 93-105 and the corresponding names: 93) Picrasin G, 94) nigakilactone J, 95) nigakilactone K, 96) nigakihihemiacetal E, 97) nigakihihemiacetal F, 98) picrasinoside A, 99) picrasinoside A, 100) nigakilactone O, 101) picrasinol C, 102) picrasin A, 103) picrasin B, 104) picraqualide B and 105) picrasin F.

cells, MKN-28 gastric cancer cells and mouse melanoma B-16 cancer cells (72). In MDA-MB 468 human breast cancer cells, picrasidine G treatment increased the expression of apoptosis markers and inhibited the EGFR/STAT3 signaling pathway (73).

Anticancer effects of triterpenoids. The novel tirucallane-type triterpenoid kumuquassin C, isolated from the stem of *P. quassioides*, had excellent cytotoxic effects and blocked cell cycle progression in G1 phase in HepG2 liver cancer cells, thereby inducing cell apoptosis (74).

5. Neuroinflammatory role of *Picrasma quassioides* (D. Don) Benn

Neurological diseases cause physical damage to the nervous system, impairing human health and well-being. Such diseases include Alzheimer's disease (75). Through the isolation and extraction of plants and the ELISA test, it was determined that the drug resistance of certain bitter wood extracts was related to the deposition of neuroinhibitors and reduction of Aβ142. Further exploration of the structure-activity relationship of alkaloids and molecular docking experiments suggested that certain active components of *P. quassioides* (D. Don) Benn extracts may have efficacy for treating neurodegenerative diseases. In addition, the β-carboline alkaloids of sorrel wood extracts as benzodiazepine antagonists are able to effectively control social anxiety, convulsions and other types of behavior in mouse models (76,77). As major diseases in humans, neurological diseases are accompanied by changes in the corresponding enzymes monoamine oxidase (MAO)-A and MAO-B (78,79); furthermore, the levels of ROS increased in cells and damage to mitochondria occurred (80-82).

β-carboline alkaloids and neuroinflammation. 7-(4,4,4-Triflu orobutoxy)-1-methyl-β-carboline and 7-(cyclohexylmethoxy)-1-methyl-β-carboline exert inhibitory effects on MAO-A and MAO-B. These enzymes are important targets for intervention and treatment of diseases, such as clinical depression, anxiety and Parkinson's disease (83).

Canthinone alkaloids and neuroinflammation. It has been observed that picrasidine O improves learning and memory performance while reducing neurotransmitter-induced nerve

Table V. Triterpenoids of *Picrasma quassioides* (D. Don) Benn.

No.	Name	Basic structure
106	(24Z)-3α-oxahomo-27-hydroxy-7,24-triucalladien-3-one	(13)
107	(24Z)-27-hydroxy-3-oxo-7,24-triucalladien-21-al	(14)
108	(24Z)-27-hydroxy-3-oxo-7,24-triucalladien-3-one	(14)
109	(24Z)-27-hydroxy-3-oxo-7,24-triucalladien-21-diol	(14)
110	(24Z)-7,24-triucalladien-ene-3β,27-diol	(14)
111	(24Z)-3β,27-dihydroxy-7,24-triucalladien-ene-21-al	(14)
112	Hiapidol A	(14)
113	Lanosta-7,24-dien-3-one	(14)

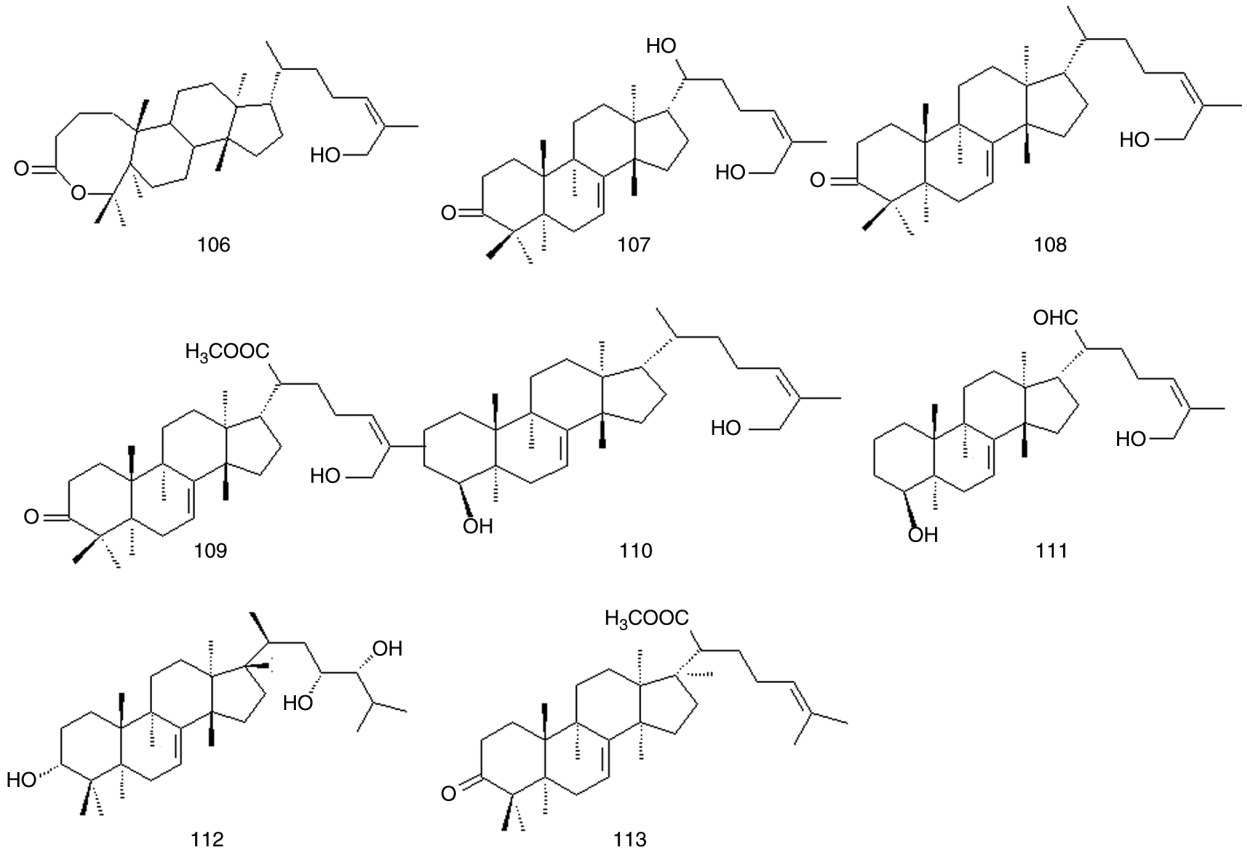

Figure 10. Structure of triterpenoids. Chemical formula of compounds 106-113 and the corresponding names: 106) (24Z)-3α-oxahomo-27-hydroxy-7,24-triucalladien-3-one, 107) (24Z)-27-hydroxy-3-oxo-7,24-triucalladien-21-al, 108) (24Z)-27-hydroxy-3-oxo-7,24-triucalladien-3-one, 109) (24Z)-27-hydroxy-3-oxo-7,24-triucalladien-21-diol, 110) (24Z)-7,24-triucalladien-ene-3β,27-diol, 111) (24Z)-3β,27-dihydroxy-7,24-triucalladien-ene-21-al, 112) hiapidol A and 113) lanosta-7,24-dien-3-one.

cell death and injury. In addition a, picrasidine O has no side effects on the heart rate and blood pressure (84). Furthermore, two classical canthin alkaloids, canthin-6-one and 5-methoxy-canthin-6-one, have good antioxidant capacity and may be used to prevent degenerative diseases and aging (85).

Quassinoids and neuroinflammation. In vitro experiments with quassin, picrasin B and nigakilactone F (86) demonstrated excellent neuroprotective effects against H_2O_2-induced oxidative stress in SH-SY5Y human neuroblastoma cells. Of note, these compounds had potent activity that was equal to the effects of trolox, but none of them had any cytotoxic activity towards HeLa or A549 cells. These results suggested that quassinoid compounds may have specific protective effects on neurons (87).

6. Clinical applications and developmental prospects of *Picrasma quassioides* (D. Don) Benn

Since the 1970s, numerous researchers have investigated *P. quassioides,* including its chemical components and pharmacological effects. However, as an Asian traditional medicine, *P. quassioides* exerts its effects via individual chemical components and through synergistic effects of several compounds.

Table VI. Anti-inflammatory effects of components of *Picrasma quassioides* (D. Don) Benn.

A, β-carboline alkaloids

Compound	Mechanism	(Refs.)
6-methoxy-3-vinyl-β-carboline	Inhibit the secretion of NO, TNF-α and IL-6	(27)
6,12-dimethoxy-3-vinyl-β-carboline	Inhibit the secretion of NO, TNF-α and IL-6	(27)
3-methylcanthin-5,6-dione	Inhibit the production of NO	(29)
Benzalharman	Inhibit the production of NO	(30)
Kumujian	Inhibit the production of NO	(30)
1-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid	Inhibit the production of NO	(30)
1-acetophenone-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid	Inhibit the production of NO	(30)

B, Carthinone alkaloids

Compound	Mechanism	(Refs.)
4-methoxy-5-hydroxycanthin-6-one	Inhibit NO and TNF-α release and down-regulation iNOS expression	(31)
Cathin-6-one	Inhibit NO production and down-regulation iNOS, COX-2 and PGE2 expression. Reduce MPO and MDA production and inhibit IL-8 and TNF-α release	(30,35)
9-methoxy-cathin-6-one	Inhibit NO production and down-regulation iNOS, COX-2 and PGE2 expression	(30)
1:4-methoxy-5-hyroxycanthin-6-one	Reduce SOD activity and increase eNOS expression	(32)
Picrasidine L inhibit PTP-1B	Promote insulin signaling pathway activation;	(36)

C, Bis-β-carboline alkaloids

Compound	Mechanism	(Refs.)
Quassidine E	Inhibit NO, TNF-α and IL-6 release	(39)
Quassidine G	Inhibit NO, TNF-α and IL-6 release	(39)
Quassidine F	Only inhibit the secretion of NO and IL-6 and the iNOS signaling pathway	(39,27)
Picrasidine C	PPARα and PPARβ/δ agonists	(40)
Picrasidine N	PPARα, PPARβ/δ agonist and selectively activate the PPARβ/δ target gene ANGPTL4	(40,41)
Picrasmalignan A	Reduce NO, TNF-α and IL-6 production and up-regulation iNOS and COX-2 expression	(44)

NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX, cyclooxygenase; PGE2, prostaglandin E2; SOD, superoxide dismutase; PTP, protein tyrosine phosphatase; PPAR, peroxisome proliferator-activated receptor.

Modern clinical research indicated that *P. quassioides* has a significant effect on hypertension (32), pneumonia (67,88), dysentery (89) and other disease symptoms (90,91). Previous studies have also developed various preparations and drugs using *P. quassioides*, such as Kumu injection, Xiaoyan Lidan tablet (92), Fufang Kumu Xiaoyan capsule (93) and Fufang Kumu Xiaoyan tablet (94). Thus, use of *P. quassioides* in clinical settings has been gaining considerable attention.

P. quassioides also has an antivenom effect. *P. quassioides* is recorded for the treatment of snake venom poisoning in the Chinese Pharmacopoeia. Furthermore, clinical experiments suggested that Kumu injections impart a strong protective effect on mice and dogs poisoned by silver ring snake venom. In addition, Kumu injections had a protective effect against five-step snake (*Hydrophis platurus*) and cobra (*Ophiophagus hannah*) venom in canines, but not in poisoned

Table VII. Role of active components of *P. quassioides*.

Active component	Anti-inflammatory	Anti-cancer	Neuroinflammatory
β-carboline alkaloids	6-methoxy-3-vinyl-β-carboline (27), 6,12-dimethoxy-3-vinyl-β-carboline (27), 3-methylcanthin-5,6-dione (29), 1-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (30), 1-acetophenone-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (30)	4-methoxy-1-vinyl-β-carboline (67), 1-methoxy-β-carboline (67), β-carboline-1-carboxylic acid (68)	7-(4,4,4-trifluorobutoxy)-1-methyl- β-carboline (77), 7-(cyclohexylmethoxy)-1-methyl-β-carboline (83)
Arthinone alkaloids	4-methoxy-5-hydroxycanthin-6-one (31), cathin-6-one (30,34,35), 9-methoxy-cathin-6-one (30, 33), 1:4-methoxy-5-hyroxycanthin-6-one (32), 4-methoxy-5-hydroxycanthin 6-one (31), 4-methoxycanthin-6-one (34), picrasidine L (36),	9-methoxy-canthin-6-one (69) canthin-6-one (69), 4,5-dimethoxy-10-hydroxy-canthin-6-one (70), canthin-6-one alkaloids (70), 8-hydroxy-canthin-6-one (70), 4,5-dimethoxy-canthin-6-one (70), 5-hydroxy-4-methoxycanthin-6-one (70)	Picrasidine O (84), canthin-6-one (85), 5-methoxycanthin-6-one (85)
Bis-β-carboline alkaloids	Quassidine A (38), quassidine E (39), quassidine G (39), quassidine F (39,27), picrasidine C (40), picrasidine N (40,41), picrasmalignan A (44)	B-9-3 (a new bimolecular compound) (71),quassidines I (72), quassidines J (72), picrasidine G (73)	-
Triterpenoids	-	Kumuquassin C (74)	
Quassinoids	-	-	Picrasin B (86), nigakilactone F (86)

mice (3). Furthermore, the effect of Kumu injections on other snake venoms remains to be studied.

P. quassioides has antimalarial effects; 6-hydroxy-4-methoxyl-1-vinyl-β-carboline extracted from the *P. quassioides* stem and bark inhibited the proliferation of the drug-resistant *Fusarium* protozoan. The cyclohexane extract of *P. quassioides* has strong antimalarial activity (95), which may be due to the antimalarial effect of nigakilactone in *P. quassioides* (96).

Quassinoids extracted from the *P. quassioides* stem may also be used as a stomachic agent and promote appetite when ingested in small amounts. However, excessive use may cause nausea. Nigakinone and methylnigakinone isolated from the methanolic extract of *P. quassioides* prevents the secretion of gastric juice in a dose-dependent manner and protects the gastric mucosa from potential side effects. Canthinone alkaloids and β-carboline alkaloids inhibited cAMP phosphodiesterase activity by accelerating blood flow in the gastrointestinal tract of rabbits. Thus, *P. quassioides* extracts have potential for treating stomach-related diseases (97,98).

However, *P. quassioides* compounds have a certain degree of cytotoxicity due to their the cold property of drug (according to the concepts of Korean/Asian medicine). Overdose of these compounds may cause coldness in the spleen and stomach. In more serious cases, vomiting, diarrhea, dizziness, convulsions and other symptoms may occur and may even cause death (99). Therefore, it is necessary to monitor the dosing of these compounds and they should be ingested only after proper consultation with a doctor.

7. Conclusions

Chemical studies on plants of the Picrasma BL family indicated that alkaloids and quassinoids may be the major components contained in *P. quassioides*. Most of these alkaloids have parent β-carboline and canthin rings. Quassin may be a tetracyclic diterpene lactone component. In general, *P. quassioides* extracts and isolated compounds have good anti-inflammatory, antibacterial, antitumor and neuroprotective activities, while also having beneficial effects on the digestive system, heat removal and detoxification.

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Availability of data and materials

Not applicable.

Authors' contributions

JL, YXG, HNS and TK conceptualized the study, performed the literature search, collected and analyzed data and wrote the manuscript. HJ, HS and DPX performed the literature search and analyzed data. HNS and TK performed the literature review and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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