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Traditional uses, phytochemistry, pharmacology, and toxicology of *Pterocephalus hookeri* (C. B. Clarke) Höeck: a review

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Pterocephalus hookeri (C. B. Clarke) Höeck is a member of the Dipsacaceae family and has been used in traditional Tibetan medicine for thousands of years. *P. hookeri* clears heat, detoxifies, stops dysentery, eliminates distemper, dispels wind, and relieves stagnation and is mainly prescribed for heat syndrome, dysentery, arthritis, and plague. Approximately 93 chemical compounds have been isolated and identified from *P. hookeri*, including iridoid glycosides, lignan and triterpenoids. Meanwhile, modern pharmacological studies have shown that *P. hookeri* has anti-inflammatory, anti-rheumatoid arthritis, analgesic, anticancer, and neuroprotection activities. However, studies on the *in vivo* pharmacokinetics and mechanism of action, discovery of quality markers, and qualitative and quantitative analysis are still insufficient. Hence, this paper provides a comprehensive review of the ethnic medicine, phytochemistry, pharmacology, and toxicology of *P. hookeri* to increase the understanding of the medicinal value of *P. hookeri*.

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1. Introduction

Pterocephalus hookeri (C. B. Clarke) Höeck is an herbaceous plant that belongs to the subfamily *Pterocephalus* in the Dipsacaceae family. The genus *Pterocephalus* currently includes 25 species which are mainly distributed in Europe, Asia, and Africa. Two species, *P. hookeri* and *Pterocephalus bretschneideri* (Batalin) E. Pritz. ex Diels, are found in China. *P. hookeri* is widely distributed in Sichuan, Yunnan, and Tibet (China)[1,2] and is one of the most popular Traditional Tibetan Medicines, known as "སྨན་རྩི་དོན་བུ". It is known as fairy grass and is recorded in

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many classic Tibetan medicine books, such as The Four Medical Tantras (late 8th century AD)[3] and Jing Zhu Materia Medica (19th century AD).[4] The formal Chinese name of *P. hookeri* is Yi-shou-cao (Chinese name: 翼首草), which was first adopted by the *Chinese Pharmacopoeia* in 1977.[5] *P. hookeri* is also known as Bang-zi-du-wu (Tibetan name: སྦང་རྫི་དུ་ཝ།) in traditional Tibetan medicine and is widely used to treat cold, pain, plagues, and arthritis. Since 1993, the phytochemical and pharmacological research of *P. hookeri* has attracted widespread attention.[6] To date, compounds isolated from *P. hookeri*, include: iridoids, triterpenoids, and phenylpropanoids. Modern pharmacological studies have demonstrated that *P. hookeri* possesses anti-inflammatory, anti-rheumatoid arthritis, analgesic, antitumor, immunomodulatory, neuroprotection, and antibacterial activities.

This review aims to summarize comprehensive information on the botanical characteristics, distribution, traditional use, ethnopharmacology, chemical composition, pharmacological activity, and toxicity characteristics of *P. hookeri*, referencing ancient books and modern documents, to lay the foundation for further research on the mechanism of action of this traditional medicinal plant and to guide the development of therapeutic drugs.

2. Botanical characterization and distribution

P. hookeri is a perennial herb with a height of 5–35 cm. Its roots are conical, thick, and fleshy, and the upper part of the root is densely covered with brown residual petioles. Their leaves are basal, spatulate to oblong-oblanceolate, 3–20 cm long, and 1–4 cm wide, have curved coarsely dentate or pinnately lobed tips, and are tapered into stalks at the base, and have conspicuous midribs. Both sides of their leaves have thick and short villi (hairs). The scape is single, rarely two or three, and densely shirred. The capitulum is spherical, with a diameter of 2–3 cm. The flowers are white or pink, and the bracts are like involucres, narrow. The epicalyx is tube-shaped, approximately 5 mm long, and pilose. The calyx is completely split into a pinnate crest. The corolla is funnel shaped, and 8–12 mm long. The apex has four or five lobes, and the crown tube is pubescent (fine short hairs) inside and outside. The stamens, usually four in number, are

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slightly protruding. The flowering and fruit period of *P. hookeri* is from July to September each year. The habitat, the whole plant, and the inflorescence of *P. hookeri* are shown in Fig. 1.

P. hookeri mainly grows on hillsides, grasslands, meadows, and forests at an altitude of 1800–5700 m. In China, it is mainly distributed in eastern Tibet, northwestern Yunnan, southern Qinghai, southern Gansu, and northwestern Sichuan. In addition, *P. hookeri* can also be found in Nepal, Sikkim, Bhutan, and northern India.[7]

3. Traditional medicinal uses

P. hookeri is mostly used in China and Tibet as a traditional Tibetan medicine, with a long history of its use as a drug. In traditional Tibetan medicine, the main effect of *P. hookeri* is to clear heat, detoxify, dispel wind, and relieve pain. It is mainly used to treat exogenous fever and rheumatoid arthritis.[4] In the early stages of preparing this paper, the research group referred to Tibetan medicine-related monographs, woodcut boards, and handwritten documents, which confirmed that the earliest record of the application of *P. hookeri* is the Dunhuang Tubo medical document "Chang Juan" (长卷),[8] which was written before the 7th century AD. Many other ancient Tibetan medical classics, such as "The Four Medical Tantras" (四部医典),[3] "Jing Zhu Materia Medica" (晶珠本草),[4] and "Lan Liu Li" (蓝琉璃),[9] also recorded the uses of *P. hookeri*. Moreover, the herb has been included in many standards, such as the *Chinese Pharmacopoeia*),[10] Pharmacopoeia standards of the Ministry of Health,[11] and Tibetan medicine standards[12] (Fig. 2). In a similar way to traditional Chinese medicine, *P. hookeri* is used to treat diseases in the form of prescriptions. According to the research team's preliminary statistics, 215 prepared preparations containing *P. hookeri* are available, which are mostly used in combination with *Corydalis hendersonii*, *Corydalis mucronifera*, *Gentiana straminea*, and *Terminalia chebula* for the treatment of plague, pneumonia, colds, measles, biliary fever, intestinal fever, and arthritis.[13] Some of them have withstood the test of time and are still used by the Chinese Tibetan hospitals, and some have even become mature medicines, occupying a certain place in the market (Table 1). In summary, *P. hookeri* and its prescriptions are mainly used to treat inflammatory and pain-related disease.

4. Phytochemistry

To date, 93 phytoconstituents have been isolated from the different parts of *P. hookeri*, including iridoids, triterpenes, fatty acids, lignans, flavonoids, steroids, saccharides, and amino acids (Table 2).

4.1 Iridoids

Iridoids are monoterpenoids composed of six-membered oxygen heterocycles and fused cyclo-pentane rings. Iridoids are usually subdivided into four groups: iridoid glycosides, bis-iridoids, seco-iridoids, and non-glycosidic iridoids.[38–40] The main compounds isolated from the different parts of *P. hookeri* are iridoids, and 33 iridoids (Table 2) have been isolated. According to their structures, they were divided into four groups, compounds **1–4** (four iridoids), compounds **5**, **6** (two secoiridoids), compounds **7–29** (23 bis-iridoids), and compounds **30–33** (four iridoid oligomers) iridoid glycosides. The structures of these compounds are shown in Fig. 3.

The earliest reports on iridoids in *P. hookeri* were published in 2000. Tian *et al.* separated loganin (compound **1**) from the whole plant of *P. hookeri* for the first time, and the compound was considered the predominant compound.[15] Wu *et al.* reported 24 iridoids (compounds **4**, **5**, **7–9**, **10–28**). Compounds **7–11**, **19–20**, **27** were originally isolated from *P. hookeri*. The bis-iridoids may be the key ingredients which account for the anti-inflammatory effects of *P. hookeri*, and compounds **7**, **8**, **27** can inhibit TNF-α-induced NF-κB-dependent promoter activity.[22–25] Furthermore, Zhang *et al.* isolated three iridoid glycosides from the 95% ethanol extracts from the whole plant of *P. hookeri* in 2014, namely, loganetin (compound **2**), 5-[3-(1-hydroxyethyl) pyridine], 7-loganin ester (compound **29**), and dipsanoside A (compound **30**), using chemical methods and spectral analysis.[16] In addition, Huang *et al.* isolated two iridoid glycosides (compounds **31**, **32**) from the 95% ethanol extracts of

Fig. 1 Photographs of the original plant of *P. hookeri* in its natural habitat, the whole plant, and its flowers.

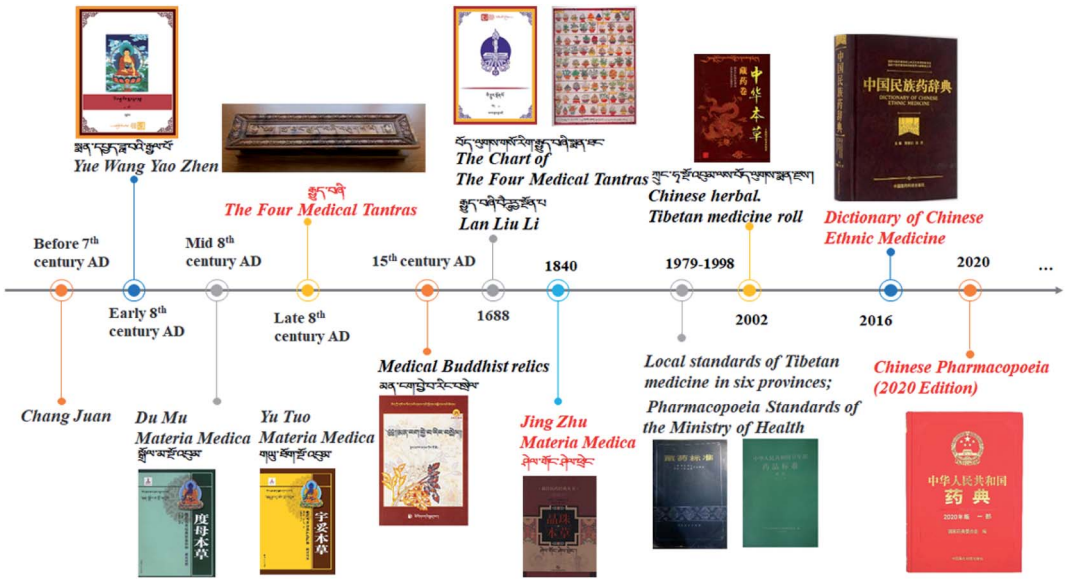

Fig. 2 The important records of *P. hookeri*.

the aerial parts of *P. hookeri*. Compound **32** is a novel iridoid oligomer. Huang *et al.* elucidated its structure using extensive spectroscopic analysis, including 1D-NMR and 2D-NMR experiments, and showed that it had no significant activity against MCF-7 (human breast cancer), HEPG2 (human liver carcinoma), and H460 (human large cell cancer of the lung) cancer cells (IC_{50} > 50 μM, $n = 3$).[17] Moreover, Tang *et al.* detected two iridoid glycosides (compounds **3**, **6**) from 70% methanol extracts

Table 1 Commercial drugs containing *P. hookeri* used in China

No	Preparation name	Composition	Traditional and clinical uses	Ref.
1	Shi'erwei Yishou San	*Pterocephali* herba, *Santali albi* lignum, *Carthami* flos, and so on	Treatment of plague, influenza, Japanese encephalitis, fever	10
2	Jiebai Wan	*Pterocephali* herba, *Carthami* flos, *Myristicae* semen, and so on	Treatment of indigestion, stomach pain, vomiting and diarrhea	10
3	Pomegranate Puan San	*Pterocephali* herba, *Cinnamomi* cortex, *Piperis longi* fructus, and so on	Treatment of indigestion, urination problems, stomach pain	11
4	Jiuwei QingPeng San	*Pterocephali* herba, Radix *Inulae racemosa*, *Chebulae* fructus, and so on	Treatment of pneumonia, fever, sore throat	11
5	Dasimabao Wan	*Pterocephali* herba, *Chebulae* fructus, *Aucklandiae* radix, and so on	Treatment of meningitis, colds, pharyngitis, pneumonia	11
6	Qingfei Zhike Wan	*Pterocephali* herba, *Arnebiae* radix, *Phyllanthi* fructus, and so on	Treatment of lung disease, colds, cough, chest pain	11
7	Ershiwuwei Yuganzi San	*Pterocephali* herba, *Dendrobii* caulis, *Adhatoda vasica* Nees, and so on	Treatment of high blood pressure, stomach ulcers, liver pain	11
8	Ershiwuwei Yuganzi Wan	*Pterocephali* herba, *Carthami* flos, *Aucklandiae* radix, and so on	Treatment of high blood pressure, liver pain, thirst, irregular menstruation	11
9	Shierwei Qixiao Tangsan	*Pterocephali* herba, *Gentianae macrophullae* flos, *Solms-laubachiae* radix, and so on	Treatment of cough, influenza	11
10	Jiedu capsule	*Pterocephali* herba, *Cistanches* herba, *Tsaoko* fructus, and so on	Treatment of dermatitis and other skin diseases	14

Table 2 Chemical composition of *P. hookeri*

No.	Compounds	Molecular	Type	Plant part	Ref.
1	Loganin	$C_{17}H_{26}O_{10}$	Iridoid	Aerial regions, whole plant	15–20
2	Loganetin	$C_{11}H_{16}O_5$	Iridoid	Aerial regions	16
3	Loganic acid	$C_{16}H_{24}O_{10}$	Iridoid	Whole plant	18 and 20
4	Isoboonein	$C_9H_{14}O_3$	Iridoid	Root	21 and 22
5	Sweroside	$C_{16}H_{22}O_9$	Iridoid (seco-iridoid)	Root, whole plant	16–22
6	6′-Apiofuranosylsweroside	$C_{21}H_{30}O_{13}$	Iridoid (seco-iridoid)	Whole plant	20
7	Pterocenoid B	$C_{22}H_{30}O_{10}$	Iridoid (bis-iridoid)	Root	23
8	Pterocenoid C	$C_{22}H_{30}O_{10}$	Iridoid (bis-iridoid)	Root	20
9	Pterocenoid D	$C_{21}H_{28}O_{10}$	Iridoid (bis-iridoid)	Root	20
10	Pterocenoid E	$C_{23}H_{32}O_9$	Iridoid (bis-iridoid)	Root	22
11	Hookerinoid A	$C_{23}H_{32}O_9$	Iridoid (bis-iridoid)	Root	24
12	Laciniatoside I	$C_{28}H_{38}O_{14}$	Iridoid (bis-iridoid)	Root, whole plant	20, 25–28
13	Pteroceside D	$C_{36}H_{56}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	22 and 25
14	Triplostoside A	$C_{35}H_{52}O_{20}$	Iridoid (bis-iridoid)	Root, aerial regions, whole plant	16–20, 22, 29
15	Cantleyoside	$C_{33}H_{46}O_{19}$	Iridoid (bis-iridoid)	Root, aerial regions, whole plant	15–18, 20, 22, and 27
16	Sylvestroside I	$C_{33}H_{48}O_{19}$	Iridoid (bis-iridoid)	Root, whole plant	16, 19, 20, 22, 27, 29
17	Sylvestroside III dimethyl acetal	$C_{29}H_{42}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	22 and 27
18	Sylvestroside III	$C_{27}H_{36}O_{14}$	Iridoid (bis-iridoid)	Root, whole plant	20, 22, 27, 28
19	Hookerinoid B	$C_{23}H_{34}O_{11}$	Iridoid (bis-iridoid)	Root	25
20	Pterocenoid H	$C_{23}H_{34}O_{11}$	Iridoid (bis-iridoid)	Root	22 and 25
21	Pteroceside A	$C_{35}H_{54}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	22 and 25
22	Pteroceside B	$C_{33}H_{50}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	22 and 25
23	Pteroceside C	$C_{32}H_{48}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	22 and 25
24	Laciniatoside II	$C_{25}H_{34}O_{12}$	Iridoid (bis-iridoid)	Root, whole plant	20,22,26–28
25	Sylvestroside IV	$C_{27}H_{36}O_{14}$	Iridoid (bis-iridoid)	Root, whole plant	22,27,28
26	Sylvestroside IV dimethyl acetal	$C_{29}H_{42}O_{15}$	Iridoid (bis-iridoid)	Root, whole plant	19,22 and 29
27	Pterocenoid A	$C_{21}H_{23}NO_7$	Iridoid (bis-iridoid)	Root	23
28	Pterhookeroside	$C_{21}H_{34}O_{10}$	Iridoid (bis-iridoid)	Root	21
29	5-[3-(1-Hydroxyethyl) pyridine], 7-loganin ester	$C_{25}H_{33}NO_{12}$	Iridoid (bis-iridoid)	—	16
30	Dipsanoside A	$C_{66}H_{88}O_{38}$	Iridoid (oligomer)	Aerial regions, whole plant	16 and 17
31	Pterocephanoside	C57H74O30	Iridoid (oligomer)	Aerial regions	17
32	Dipsanoside B	$C_{66}H_{90}O_{37}$	Iridoid (oligomer)	Aerial regions, whole plant	17
33	Pterocephanoside A	$C_{58}H_{78}O_{30}$	Iridoid (oligomer)	Whole plant	30
34	Chlorogenic acid	$C_{16}H_{18}O_9$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	18, 20 and 31
35	3,4-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	20
36	3,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	20
37	4,5-Dicaffeoylquinic acid	$C_{25}H_{24}O_{12}$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	20
38	Isochlorogenic acid A	$C_{25}H_{24}O_{12}$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	18
39	Isochlorogenic acid C	$C_{25}H_{24}O_{12}$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	18
40	2,5-Dihydroxycinnamic acid methyl ester	$C_{10}H_{10}O_4$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	19
41	3,4-Dihydroxycinnamic acid methyl ester	$C_{10}H_{10}O_4$	Phenylpropanoid (simple phenylpropanoid)	Whole plant	29
42	(+)-1-Hydroxypinoresinol 4′-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{12}$	Phenylpropanoid (lignan)	Whole plant	21 and 29
43	(+)-1-Hydroxypinoresinol 4″-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{12}$	Phenylpropanoid (lignan)	Whole plant	21 and 29
44	(+)-Syringaresinol-β-D-glucoside	$C_{28}H_{36}O_{13}$	Phenylpropanoid (lignan)	Root	21
45	8-Hydroxypinoresionol-4′-*O*-β-D-glucoside	$C_{26}H_{32}O_{14}$	Phenylpropanoid (lignan)	Whole plant	32
46	8′-Hydroxylpinoresionol-4′-*O*-β-D-glucoside	$C_{26}H_{32}O_{14}$	Phenylpropanoid (lignan)	Whole plant	32

Table 2 (*Contd.*)

No.	Compounds	Molecular	Type	Plant part	Ref.
47	(7*R*,8*S*)-Erythro-7,9,9′- trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan-4-*O*-β-D-glucoside	$C_{26}H_{36}O_{12}$	Phenylpropanoid (lignan)	Root	21
48	Cedrusin-4-*O*-β-glucoside	$C_{26}H_{34}O_{11}$	Phenylpropanoid (lignan)	Root	21
49	Ptehoosine A	$C_{31}H_{32}O_9$	Phenylpropanoid (lignan)	Whole plant	33
50	Ptehoosine B	$C_{31}H_{32}O_9$	Phenylpropanoid (lignan)	Whole plant	33
51	Syringaresinol	$C_{22}H_{26}O_8$	Phenylpropanoid (lignan)	Whole plant	33
52	Pinoresinol	$C_{20}H_{22}O_6$	Phenylpropanoid (lignan)	Whole plant	33
53	Hookeroside A	$C_{52}H_{84}O_{20}$	Triterpenoid (oleanane-type)	Whole plant	6, 19, 20 and 29
54	Hookeroside B	$C_{57}H_{92}O_{24}$	Triterpenoid (oleanane-type)	Whole plant	6, 19, 20 and 29
55	Hookeroside C	$C_{83}H_{102}O_{28}$	Triterpenoid (oleanane-type)	Whole plant	6, 19, 20 and 29
56	Hookeroside D	$C_{71}H_{82}O_{18}$	Triterpenoid (oleanane-type)	Root, whole plant	6, 15, 19, 20 and 29
57	Songoroside A	$C_{35}H_{56}O_7$	Triterpenoid (oleanane-type)	Whole plant	6, 15, 19, 20 and 29
58	Oleanolic acid	$C_{30}H_{48}O_3$	Triterpenoid (oleanane-type)	Whole plant	6, 15, 19, 20 and 29
59	Rivularicin	$C_{62}H_{100}O_{27}$	Triterpenoid (oleanane-type)	Whole plant	19, 20 and 34
60	Oleanolic acid 3-*O*-β-D-xylopyranosyl(1→3)-α-L-rhammopyranosyl(1→2)-β-D-xylopyranoside	$C_{43}H_{56}O_{19}$	Triterpenoid (oleanane-type)	Whole plant	19 and 29
61	Oleanolic acid 3-*O*-β-D-xylopyranosyl(1→4)-β-D-glucopyranosyl (1→2)-β-D-xylopyranoside	$C_{47}H_{74}O_{30}$	Triterpenoid (oleanane-type)	Whole plant	19 and 29
62	Oleanolic acid 3-*O*-β-D-glucopyranosyl(1→4)-β-D-xylopyranosy(1→3)-α-L-rhamnopyanosyl(1→2)-β-D-xylopyranoside	$C_{42}H_{46}O_{25}$	Triterpenoid (oleanane-type)	Whole plant	19 and 29
63	Giganteaside D	$C_{31}H_{48}O_{15}$	Triterpenoid (oleanane-type)	Whole plant	19, 20 and 29
64	Prosapogenin Ax	$C_{42}H_{68}O_{24}$	Triterpenoid (oleanane-type)	Whole plant	6 and 29
65	Prosapogenin Bx	$C_{47}H_{75}O_{30}$	Triterpenoid (oleanane-type)	Whole plant	6 and 29
66	Pterocephin A	$C_{52}H_{84}O_{35}$	Triterpenoid (oleanane-type)	Whole plant	35
67	Oleanonic acid	$C_{30}H_{46}O_3$	Triterpenoid (oleanane-type)	Whole plant	36
68	Ursolic acid	$C_{30}H_{48}O_3$	Triterpenoid (ursane-type)	Whole plant	6, 15, 19 and 20
69	11,12-Epoxy-2,6-dihydroxy-24-norursa-1,4-dien-3-on-2-on-(28→13)-olide	$C_{28}H_{36}O_6$	Triterpenoid (ursane-type)	Root	24
70	Hookerinoid C	$C_{28}H_{40}O_5$	Triterpenoid (ursane-type)	Root	24
71	Palmitic acid	$C_{16}H_{32}O_2$	Fatty acid (saturated)	Whole plant	6 and 15
72	Heptadecanoic acid	$C_{17}H_{34}O_2$	Fatty acid (saturated)	Whole plant	37
73	Pentadecanoic acid	$C_{15}H_{30}O_2$	Fatty acid (saturated)	Whole plant	37
74	Myristic acid	$C_{14}H_{28}O_2$	Fatty acid (saturated)	Whole plant	37
75	Stearic acid	$C_{18}H_{36}O_2$	Fatty acid (saturated)	Whole plant	37
76	Arachidic acid	$C_{20}H_{40}O_2$	Fatty acid (saturated)	Whole plant	37
77	Behenic acid	$C_{22}H_{44}O_2$	Fatty acid (saturated)	Whole plant	37
78	Lignoceric acid	$C_{24}H_{48}O_2$	Fatty acid (saturated)	Whole plant	37
79	Lignoceric acid	$C_{23}H_{46}O_2$	Fatty acid (saturated)	Whole plant	37
80	Ginkgolic acid	$C_{22}H_{34}O_3$	Fatty acid (unsaturated)	Whole plant	37
81	Linoleic acid	$C_{18}H_{32}O_2$	Fatty acid (unsaturated)	Whole plant	37
82	Oleic acid	$C_{18}H_{34}O_2$	Fatty acid (unsaturated)	Whole plant	37
83	Palmitoleic acid	$C_{16}H_{30}O_2$	Fatty acid (unsaturated)	Whole plant	37
84	Eicosenoic acid	$C_{20}H_{38}O_2$	Fatty acid (unsaturated)	Whole plant	37
85	α-Linolenic acid	$C_{18}H_{30}O_2$	Fatty acid (unsaturated)	Whole plant	37
86	5,7,3′,4′,6′-Pentahydroxyflavanone	$C_{15}H_{12}O_7$	Flavonoid (flavanone)	Whole plant	36
87	Luteolin	$C_{15}H_{10}O_6$	Flavonoid (flavone)	Whole plant	8
88	L-Methionine	$C_5H_{11}NO_2S$	Amino acid	Whole plant	36
89	*p*-Hydroxy benzaldehyde	$C_7H_6O_2$	Phenolic acid	Whole plant	36
90	β-Gentiobiose	$C_{12}H_{22}O_{11}$	Carbohydrate	Whole plant	15
91	Twenty alkyl ethers	$C_{40}H_{82}O$	Ethers	Whole plant	36

Table 2 (*Contd.*)

No.	Compounds	Molecular	Type	Plant part	Ref.
92	Pentatriacontane	$C_{35}H_{72}$	Alkane	Whole plant	36
93	β-Sitosterol	$C_{29}H_{50}O$	Steroid	Whole plant	36

of *P. hookeri* using UPLC-Q-TOF/MS and identified them by using standard products.[20] Most recently, pterocephanoside A (compound **33**) was isolated from *P. hookeri*, and the compound mostly possessed *seco*-iridoid subtype and iridoid subtype skeletons and showed an inhibitory effect on LPS-induced NO production in RAW 264.7 cells (murine macrophages), but the activity was weak.[30]

4.2 Phenylpropanoids

The skeleton of phenylpropanoid is formed from C6–C3 units, however, some of the carbons in the side chain might have been lost during the biosynthesis. Phenylpropanoids are widely found in traditional Chinese medicine and have various physiological activities, such as antioxidation, anti-inflammatory, antibacterial, hemostasis, antitumor, and they can give cardiovascular protection.[41–43] To date, **19** phenylpropanoids have been detected this plant, and they are divided into two groups: simple phenylpropanoids (compounds **34–41**) and lignans (compounds **42–52**), according to their structures, and they are shown in Fig. 4.

Compounds (**42–44**, **47**, **48**) were isolated and purified from *P. hookeri* with silica gel chromatography using a Sephadex LH-20 column, semipreparative HPLC, NMR, and HR-ESIMS. It should be noted, that these compounds have never been found in the genus *Pterocephalus* before, and have the potential to become useful chemotaxonomic markers of *Pterocephalus*.[21] Li *et al.* established a UFLC-PDA fingerprint analysis method for use with *P. hookeri* from different producing areas, and identified five components with standards, including compound **34**.[31] Two phenylpropanoids (compounds **45**, **46**) were separated and identified in the *P. hookeri* 95% ethanol extracts by spectral analyses, including HR-ESIMS, NMR, and HPLC.[32] Compound **40** and **41** were originally isolated from *P. hookeri*.[19,29] Tang *et al.* using a standard comparison method, identified three

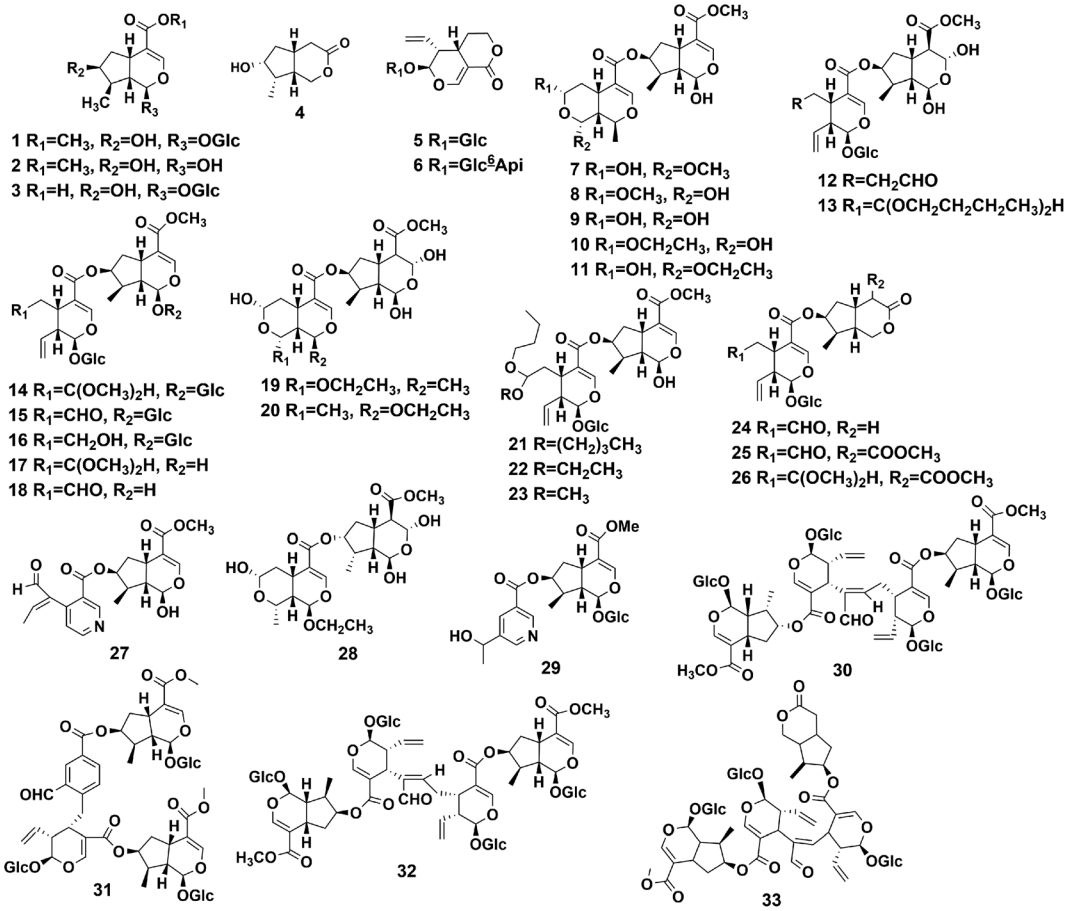

Fig. 3 The structures of the iridoids obtained from *P. hookeri*.

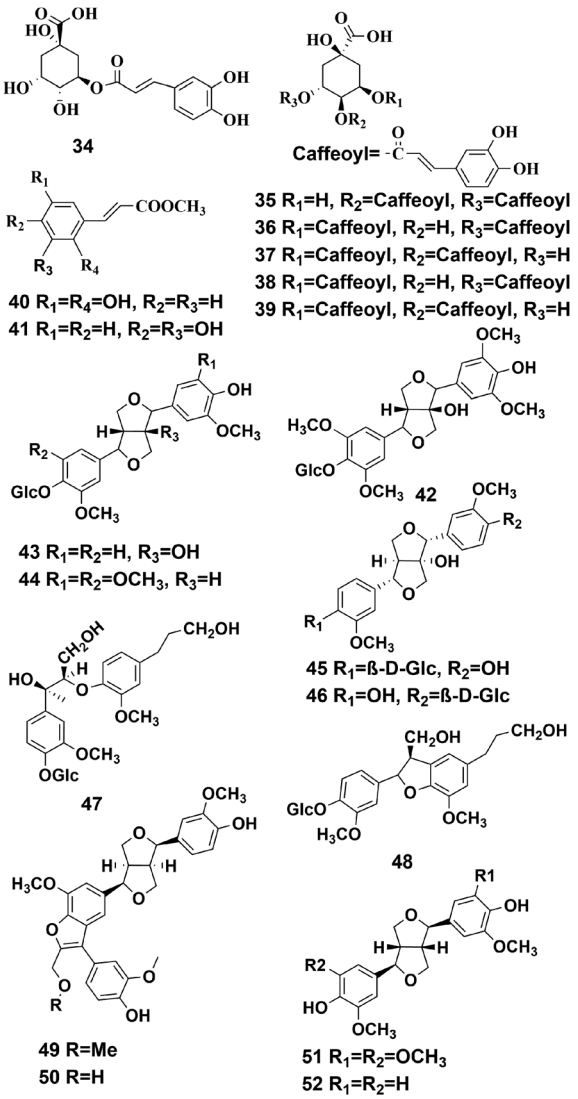

Fig. 4 The skeletal structures of phenylpropanoids obtained from *P. hookeri*.

phenylpropyl compounds (compounds **35–37**) from a 70% methanol extract of *P. hookeri* using UPLC-Q-TOF/MS.[20] Meanwhile, Wang *et al.* used UPLC-PDA to identify compounds **38, 39** from a methanol extract of *P. hookeri*, and proved that these compounds could be absorbed by rats using the everted intestinal sac model.[18] Two undescribed lignans (compounds **49, 50**) and two known lignans (compounds **51, 52**) were isolated by Dong *et al.*[33] Compound **49** was found to be effective in inhibiting angiogenesis.[32]

4.3 Triterpenoids

Terpenoids represent the largest and most diverse class of natural products produced by plants.[44] Terpenoids are abundant in *P. hookeri* and play an important role in many important physiological activities and biological functions. The main terpenoids in *P. hookeri* are two types of triterpenoids, including the oleanane type (compounds **53–67**) and the ursane type (compounds **68–70**). A total of 18 triterpenoids have been reported, and most of them share the same skeleton as the oleanane type. One of the characteristics of the oleanane type pentacyclic triterpenoids of *P. hookeri* is their aglycones, which are always replaced by glycosyl groups at the 3 or 28 sites. Their structures are shown in Fig. 5.

Using DA 201 resin, silica gel, and spectroscopic analysis methods, such as IR and NMR, Tian *et al.* separated and identified seven triterpenoids (compounds **53–58, 68**) from the 95% ethanol extracts of the whole plant of *P. hookeri*. This study was the first to isolate these compounds from *P. hookeri*.[6] In 2002, Zhang *et al.* isolated rivularicin (compound **59**) from *P. hookeri* for the first time.[34] They also separated oleanonic acid (compound **67**) from the 95% ethanol extracts of the whole plant of *P. hookeri*, and then established a quality control method for *P. hookeri* analysis using the oleanolic acid content. In addition, they verified that oleanonic acid exerts inhibitory effects on *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*.[36] Another two triterpenoids (compounds **69, 70**) were isolated and identified, and compound **69** was found to significantly inhibit the proliferation of Hep3B cells (human hepatocyte carcinoma), with an IC_{50} of 17.06 μm.[22] Yu *et al.* isolated and purified four triterpenoids (compounds **60–63**) with silica gel and Sephadex LH-20 columns and then determined their spectral data.[19] Zhang *et al.* studied the chemical components in the 90% ethanol extracts of *P. hookeri* using physical and chemical properties obtained by spectral data analysis and identified another two triterpenoids (compounds **64, 65**).[29] Wang *et al.* isolated pterocephin A (compound **66**) from *P. hookeri*. According to published pharmacological studies, the survival rates of L-02 cells (human fetal hepatocytes) decreased significantly when treated with pterocephin A at a concentration of 16 μmol L^{-1}, showing that the compound has obvious cytotoxicity.[35]

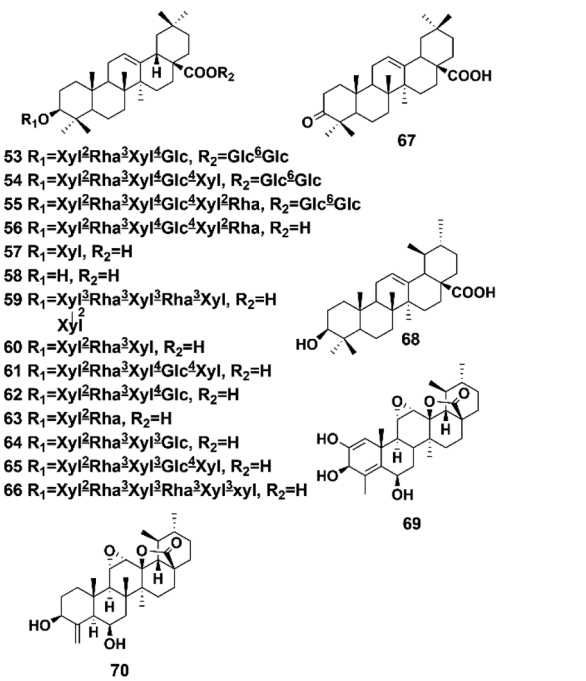

Fig. 5 The structures of triterpenoids obtained from *P. hookeri*.

4.4 Fatty acids

Fatty acids, used to be considered as only energy sources and structural components of the cell membrane, but they now show great potential for the treatment of several diseases, such as type II diabetes mellitus, nonalcoholic steatohepatitis, and chemically induced liver injury.[45–47] A total of **15** fatty acids have been isolated from *P. hookeri*, and these were divided into two group: saturated fatty acids (compounds **71–79**) and unsaturated fatty acid (compounds **79–85**), and their structures are shown in Fig. 6.

Palmitic acid (compound **71**) was the first reported fatty acid found in *P. hookeri*.[15] Then, by using GC-MS, Zhang *et al.* detected 14 fatty acid components (compounds **72–85**) from *P. hookeri* at the flowering and nonflowering stages. The compounds were identified by comparison with standards. Moreover, α-linolenic acid, a plant-derived n-3 polyunsaturated fatty acid, is a potential fatty acid biomarker because it is useful in distinguishing between the two groups.[36,37]

4.5 Other compounds

Some compounds do not belong to the previous classifications, such as flavonoids, carbohydrates, and steroids. Their structures are shown in Fig. 7.

In 2013, Zhang *et al.* isolated six compounds (compounds **86**, **88**, **89**, **91–93**) from a 95% ethanol extract of a whole *P. hookeri* plant and identified them with chemical methods and spectral analysis. Compound **86** was found to have a significant inhibitory effect on *Staphylococcus aureus*.[36] The only carbohydrate isolated from *P. hookeri* is β-gentiobiose (compound **90**).[15] In addition to compound **86**, another flavonoid, luteolin (compound **87**), was separated from the whole plant of *P. hookeri*.[29] It is a common ingredient with a wide range of

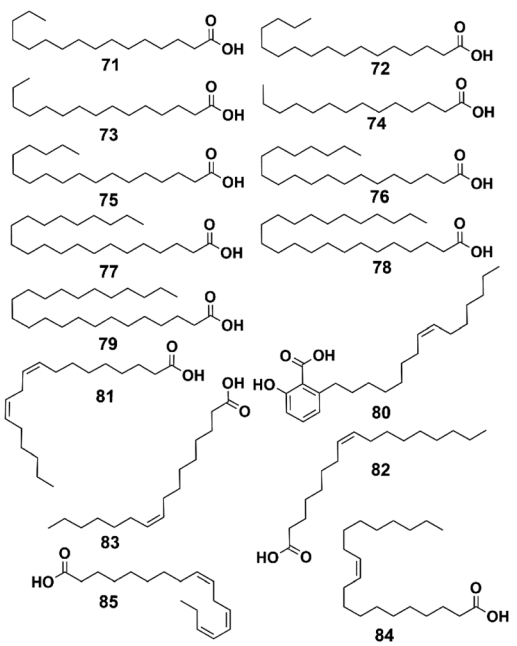

Fig. 6 The structures of fatty acids obtained from *P. hookeri*.

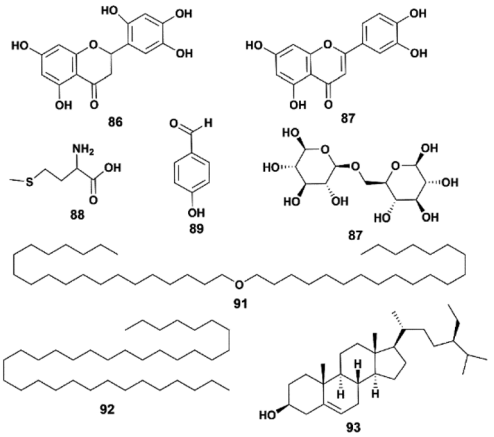

Fig. 7 The structures of compounds **86–93** obtained from *P. hookeri*.

pharmacological activities, such as antitumor, lipid lowering, anti-inflammatory and antioxidant activities.[48–50]

5. Pharmacological activities

P. hookeri is in widespread use, and its extracts and chemical components have been used in *in vitro* and *in vivo* experimental models. All its pharmacological activities are summarized in Fig. 8 and the following subsections will describe these in more detail.

5.1 Anti-inflammatory activity

The primary anti-inflammatory evaluation of *P. hookeri* was based mainly on the mouse models of xylene-induced ear edema and acetic acid-induced peritoneal capillary permeability, and rat models of carrageenan/fresh egg white-induced paw edema and cotton/agar pellet granuloma. In 2004, Guan *et al.* evaluated the anti-inflammatory activity of an *n*-butanol extract of *P. hookeri*, and the results showed that the extract had significant inhibitory effects on xylene-induced ear edema in mice and fresh egg white-induced paw edema in rats ($P < 0.05$) when the dose was 0.25–0.7 g kg^{-1}.[51] Interestingly, Zhang *et al.* (2009), Shen *et al.* (2017), and Chen *et al.* (2018) reported similar results.[27,52,53] Another model of acute inflammation is acetic acid-induced peritoneal capillary permeability. Acetic acid can increase the levels of prostaglandins, histamines, 5-hydroxytryptamine and other chemical mediators in the abdominal fluid, thus increasing vascular permeability. Using an ethanol extract of *P. hookeri* (2 g kg^{-1}), water extract (4 g kg^{-1}), and total glycosides (28–112 mg kg^{-1}, the main components found are compounds **1**, **5**, **15**, **16**) which can significantly inhibit the increase in vascular permeability induced by acetic acid in mice. The cotton/agar pellet granuloma model and dry weight of chronic inflammation correlated with the level of granulomatous tissue formation. An ethanol extract of *P. hookeri* (2 g kg^{-1}), *n*-butanol extract (0.25–0.5 g kg^{-1}), and total glycosides (28–112 mg kg^{-1}) could effectively inhibit cotton ball granuloma. Therefore, in addition to the acute stage of inflammation, the extracts of *P. hookeri* showed anti-inflammatory activity in the chronic stage of inflammation as well.[52,53] Bis-iridoids from *P.*

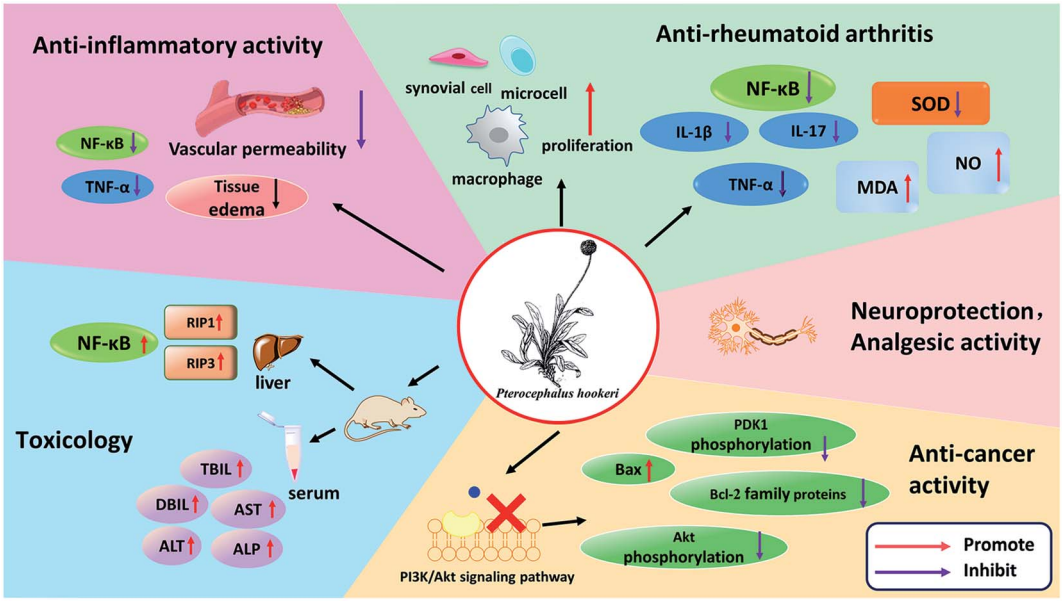

Fig. 8 Overview of the pharmacological activities of *P. hookeri*.

hookeri (25 and 50 μM, the main components were compounds **11** and **19**) significantly reduced TNF-α- and LPS-induced NF-κB activation in HEK293 cells (human embryonic kidney), and the main components, compounds **12**, **15–18**, **24–26**, reduced the production of inflammatory cytokines in a dose-dependent manner.[24,27]

5.2 Anti-rheumatoid arthritis

Rheumatoid arthritis (RA) is chronic auto-immune disorder, its main characteristics are swelling and pain in joints, and in synovial membranes. The main treatment is to suppress inflammation and relieve pain.[54] In Tibetan medicine, RA is known as "zhen bu" disease, and the clinical efficacy of Tibetan medicine on RA is as high as 94.6%.[55] *P. hookeri* is commonly used as a treatment for RA in Tibet. The animal adjuvant arthritis (AA) model is a contraindicated animal model mediated by T-cell immunity.[56–59] It is a commonly used animal model of RA in clinics because of its simplicity in modeling and consistency with clinical manifestations, pathomorphology, and immunological changes in patients with RA.[60] This model has been adopted in studies on the anti-arthritis effects of *P. hookeri*. Shen *et al.*[53] and Yang *et al.*[56] investigated the efficacy and mechanism of using the total glucosides of *P. hookeri* on AA rats and found that the total glycosides of *P. hookeri* (28, 56, 116, and 232 mg kg^{-1}) significantly reduced primary paw swelling, secondary paw swelling, and arthritis scores in the later stages of AA. In addition, the total glucosides of *P. hookeri* not only improved the proliferation of synovial cells, macrophages, and microcells, and induced inflammatory cell infiltration but it also significantly reduced the levels of IL-1β, TNF-α, and IL-17. However, these effects were not dose-dependent. Notably, the total glycosides of *P. hookeri* not only significantly increased MDA and NO levels but also significantly decreased the SOD level and the expression of NF-κB p65 in the synovial tissues of the joints. This result suggested that the anti-RA effect of total glycosides of *P. hookeri* may be related to the antioxidant effect and the inhibition of the NF-κB signaling pathway.[53,56]

5.3 Analgesic activity

The analgesic effects of *P. hookeri* were studied using several types of pain models, including acetic acid-induced abdominal writhing reflex (peripheral pain) and pain caused by a hot plate in mice (central pain). In 2017, the analgesic abilities of total glycosides from *P. hookeri* were evaluated by Shen *et al.*[53] At doses of 56 and 112 mg kg^{-1}, obvious analgesic effects on pain induced by acetic acid were observed. However, in a hot-plate test, the pain threshold only increased 30 min after treatment with 112 mg kg^{-1} dose. The total glycosides from *P. hookeri* showed a good peripheral analgesic effect, but the central analgesic effect was not obvious. The peripheral analgesic effect may be related to *P. hookeri*'s good anti-inflammatory effect.[53] Moreover, Chen *et al.*[27] showed that the bis-iridoid constituents from *P. hookeri* (50 and 100 mg kg^{-1}) significantly increased the hot-plate pain threshold and reduced the acetic acid-induced writhing response in mice ($P < 0.01$), and the efficacy of high-dose bis-iridoid constituents from *P. hookeri* (100 mg kg^{-1}) was superior to that of the positive control (rotundine, 20 mg kg^{-1}). The results are similar to those of Zhang's[52] previous experiment. These results indicated that iridoids possess analgesic effects.[27,52]

5.4 Anti-cancer activity

Cancer is not only a serious threat to people's health but also a difficult and hot topic of research. *P. hookeri* has antitumor effects. The total saponins of *P. hookeri* have inhibitory effects on a variety of cancer cells, such as SGC-7901 (human gastric cancer cells), HepG2, AGS gastric adenocarcinoma cells from a human stomach, and MBA-MD-231 (human breast cancer cells).[61] In 2015, Guo *et al.* conducted an in-depth study on the

antitumor effect of an *n*-butanol extract of *P. hookeri* (the main components were compounds **15**, **16**, **18**, **24**, **25**) on Hep3B cancer cells and found that the extract can selectively inhibit the proliferation of Hep3B cells *in vitro*, induce apoptosis, block the PI3K pathway, and regulate the protein level of the Bcl-2 family. In addition, the extract inhibited tumor growth by regulating the expression of Bcl-2 family proteins in xenografted tumor mouse models.[28,62]

5.5 Neuroprotection

Parkinson's disease, also known as 'wobbly paralysis' in China, is a chronic neurodegenerative disease caused by extrapyramidal dysfunction. The disease usually occurs in middle age or later. The main cause of Parkinson's disease is the damage of dopaminergic neurons in the substantia nigra of the brain, and a decrease in dopamine biosynthesis in the striatum, which results in a significant reduction in dopamine transmitters and hypercholinergic nerve function, and these result in movement disorders. The neuroprotective effects of a *n*-butanol extract of *P. hookeri* (the main components are compounds **13–18**, **24**, **25**) have been demonstrated in transgenic zebrafish models. The DAT-GFP fertilized eggs treated with 100 μg mL^{-1} *n*-butanol extract were able to resist damage from to H_2O_2, and the number of dopamine neurons in the fertilized eggs was the same as that in the control group.[26]

6. Toxicology

Although *P. hookeri* has been used as a traditional Tibetan medicine for a long time, its potential toxicity has not been systematically elucidated. According to the records from the classical ancient books, *P. hookeri* has always been considered as a drug with a low toxicity, but reports about its toxicity are few. In early toxicity tests, mice received an oral water extract of *P. hookeri* 3000 times the clinical dose. The mice ate less and showed considerable weight loss. These results indicated that *P. hookeri* had some level of toxicity, but the study was not thorough.[51]

In view of the previous research results, Wang *et al.* evaluated the hepatotoxicity of an *n*-butanol extract of *P. hookeri* in 2019 and found that the serum levels of ALP, ALT, AST, DBIL, and TBIL were significantly increased ($P < 0.05$, $P < 0.01$) in the mice in the group which had received an *n*-butanol extract of *P. hookeri*. The results showed that the extract caused a certain degree of liver damage in the mice. The expression levels of NF-κB, RIP1, and RIP3 in the liver tissues and L-02 cells were upregulated after treatment with the extract and the L-02 hepatocytes. These results indicated that the extract can induce liver toxicity *in vivo* and *in vitro*, which can induce the development of inflammation and subsequent necrosis.[63]

7. Qualitative and quantitative analysis

The most recent quality control standard for *P. hookeri* is in the 2020 edition of the Chinese Pharmacopoeia, in which microscopic and TLC identification is mainly used for qualitative analysis, and quantitative analysis mainly uses HPLC.[10] Before 2013, a large number of studies showed that *P. hookeri* mainly contains triterpenoid saponins, and oleanolic acid and ursolic acid were considered to be the main quality control components of *P. hookeri*. Therefore, a variety of methods for the determination of oleanolic acid and ursolic acid were established, such as HPLC-evaporative light-scattering detection, HPLC with a photodiode array, and capillary zone electrophoresis.[37,64–66] In 2018, a UPLC-Q-TOF/MS method was established for the analysis of the chemical constituents of *P. hookeri*. A total of 17 iridoid glycosides, 7 phenolic acids, 13 triterpenes, and 3 other components were identified or preliminarily deduced. The 10 main components found were dipsanoside B, sweroside, cantleyoside, chlorogenic acid, loganic acid, loganin, sylvestroside I, dipsanoside A, isochlorogenic acid A, and isochlorogenic acid C, which were quantified using UPLC-PDA. Notably, iridoid glycosides and phenolic acids were found to be the main active components of the 40 compounds identified using molecular docking. The current quality control standard of *P. hookeri* uses oleanolic acid and ursolic acid as quality control indices, which cannot effectively control the quality of the medicinal material, lack direct correlation with biological activity, and are insufficient in evaluating the quality of *P. hookeri*. Therefore, a more suitable and feasible method is needed to comprehensively evaluate the quality of *P. hookeri*.[20,67]

8. Conclusion and perspectives

P. hookeri is not only a typical plateau herbaceous plant but also one of the commonly used Tibetan medicines for clearing heat, stopping dysentery, detoxification, eliminating distemper, dispelling wind, and relieving stagnation. This paper reviews the progress of research on *P. hookeri* from the aspects of traditional use, phytochemistry, pharmacology, and toxicology. Because of limited resources and investment, the study of *P. hookeri* and its decoctions have not received enough attention, and the study of its pharmacological activities and related molecular mechanisms is insufficient.

The chemical structures of the compounds found in *P. hookeri* plants are structurally diverse, and mainly include triterpenes, iridoid glycosides, phenolic acids, flavonoids, and other compounds. The crude extract and chemical components of monomers isolated from the plants are still in the preliminary stage, but they do show certain anti-inflammatory, antitumor, neuroprotective, and anti-rheumatoid arthritis activities. However, the identity of the pharmacodynamic substance is still unclear. Modern phytochemical and pharmacological studies have provided some evidence of some of the mechanisms of the action of *P. hookeri* and demonstrate its further development potential as an anti-inflammatory and antitumor agent.

In addition, quality markers from *P. hookeri* are necessary for the study of the mechanisms of action and quality control of medicinal materials. Currently, only oleanolic acid and ursolic acid have been selected as the quality indicators of *P. hookeri* in

the *Chinese Pharmacopoeia* in 2020. However, these compounds cannot effectively control the quality of *P. hookeri*. Therefore, chemicals and biomarkers that can better reflect the quality of *P. hookeri* are needed.

In conclusion, long-term clinical practice has proven the safety and efficacy of *P. hookeri*. To fully explore the medicinal value of *P. hookeri*, modern advanced research techniques (mass spectroscopy imaging technology and patch clamp technology) should be used to systematically study its absorption, distribution, metabolism, excretion, tissue distribution, mechanism of action, and quality evaluation, for the development of the use of *P. hookeri*.

Abbreviations

TNF-α	Tumor necrosis factor-α
NF-κB	Nuclear factor kappa-B
NMR	Nuclear magnetic resonance
UPLC-Q-TOF/MS	Ultra-performance liquid chromatography coupled with time-of-flight mass spectrometry
LPS	Lipopolysaccharide
NO	Nitric oxide
HPLC	High-performance liquid chromatography
HR-ESIMS	High resolution-electrospray ionization mass spectrometry
UFLC-PDA	Ultra-flow liquid chromatography-photo diode array
IR	Infrared spectroscopy
IC_{50}	50% inhibition concentration
GC-MS	Gas chromatography-mass spectrometry
RA	Rheumatoid arthritis
AA	Adjuvant arthritis
IL-1β	Interleukin-1β
IL-17	Interleukin-17
MDA	Malonaldehyde
SOD	Superoxide dismutase
Bcl-2	B-cell lymphocytoma-2
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
DBIL	Direct bilirubin
TBIL	Total bilirubin
TLC	Thin layer chromatography
Glc	Glucose
Xyl	Xylose
Rha	Rhamnose
Api	Apidside

Author contributions

Zhiqiang Gan – resources, supervision, visualization, writing – original draft, writing – review and editing. Juan Jiang – writing – original draft, writing – review and editing. Honglin Tao – resources, writing – original draft. Shiying Luo – resources. Xianli Meng – supervision. Jia Yu – supervision, writing – review and editing, funding acquisition. Yi Zhang – supervision, funding acquisition. Ce Tang – resources, supervision, writing – original draft, writing – review and editing, funding acquisition.

Conflicts of interest

The authors declare no conflict of interest.

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