REVIEW
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Research progress and quality markers prediction analysis of *Dysosma versipellis*

Yuan-Hui Guo[1], Peng Lu[2], Jia-Xing He[3], Bao-Nan Ma[3], Ebuka-Olisaemeka Nwafor[4], Wen-Xin Wang[5*], Chuan-Xin Liu[1*]

[1]Endocrine and Metabolic Disease Center, First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Medical Key Laboratory of Hereditary Rare Diseases of Henan, Luoyang Sub-center of National Clinical Research Center for Metabolic Diseases, Luoyang 471000, China. [2]Department of Pharmacy, Suzhou TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou 215009, China. [3]College of Traditional Chinese Medicine, Beijing University of Traditional Chinese Medicine, Beijing 100029, China. [4]School of Health & Biomedical Sciences, RMIT University – Bundoora Campus, Melbourne 3083, Australia. [5]School of Biological and Medical Engineering, Beihang Univesity, Beijing 100083, China.

[*]**Corresponding to:** Wen-Xin Wang, School of Biological and Medical Engineering, Beihang Univesity, No. 37, Xueyuan Road, Haidian District, Beijing 100083, China. E-mail: wwx15735178895@163.com. Chuan-Xin Liu, Endocrine and Metabolic Disease Center, First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Medical Key Laboratory of Hereditary Rare Diseases of Henan, Luoyang Sub- center of National Clinical Research Center for Metabolic Diseases, No. 24, Jinghua Road, Jianxi District, Luoyang 471000, China. E-mail: 15222003775@163.com.

Author contributions

Yuan-Hui Guo was responsible for writing the quality marker section and completed the English manuscript. Wen-Xin Wang, Peng Lu, Jia-Xing He, Bao-Nan Ma, Ebuka-Olisaemeka Nwafor consulted the data, completed the chemical composition and pharmacological activity part, and sorted out the relevant charts. Wen-Xin Wang and Chuan-Xin Liu strictly supervised and determined the final version. Chuan-Xin Liu is also responsible for all aspects of design review writing. All authors read and agreed to the final text.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

PPT, podophyllotoxin; PPTs, podophyllotoxin derivatives; KS, Kaposi sarcoma; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syn-drome; Q-Marker, Quality Marker.

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Abstract

Dysosma versipellis is the rhizome of Bajiaolian in Berberaceae. It is a unique medicinal plant in China and it was the first to be recorded in *Shennong's Classic of Materia Medica* (unknown author, 25–220 C.E.). It has complex chemical components as well as complex, pharmacological and toxicological effects are extensive. Based on the recent research progress, the chemical constituents, pharmacological activities and toxicological effects of *Dysosma versipellis* were summarized. Combined with the core concept of quality markers of traditional Chinese medicine, the prediction and analysis were carried out from the aspects of phytogenetics and the source pathway of specific chemical constituents, traditional medicinal properties, traditional efficacy, chemical composition measurability, blood components, and pharmacokinetics, in order to provide reference for further study of *Dysosma versipellis*.

Keywords: *Dysosma versipellis*; lignans; flavonoids; chemical composition; pharmacological activity; toxicological effect; quality marker; podophyllotoxin; kaempferol; quercetin

Highlights

Dysosma versipellis is a unique plant in China with diverse pharmacological activities and a long history of use. There has long been a huge demand for *Dysosma versipellis*. However, there are many kinds of *Dysosma versipellis* on the market, and the quality is uneven, which seriously affects the clinical efficacy of traditional Chinese medicine. The quality control of Chinese medicinal materials is the guarantee and basis for the effectiveness and safety of clinical use of Chinese medicine. In this study, the quality markers of *Dysosma versipellis* were predicted and analyzed to provide reference for the construction of *Dysosma versipellis* quality evaluation system.

Medical history of objective

Dysosma versipellis is a traditional Chinese folk medicine. It was first recorded in *Shennong's Classic of Materia Medica* (unknown author, 25–220 C.E.), mainly distributed in Guizhou, Sichuan, Yunnan, Guangxi and Hubei in China. It has been recorded in *Compendium of Materia Medica* (Shi-Zhen Li, 1368–1644 C.E.), etc. It is mostly used for the treatment of epidemic hemorrhagic fever, mumps, encephalitis B, sore throat, carbuncle boils, rheumatism, and bruises.

Background

Dysosma versipellis is a traditional Chinese herbal medicine. It is the rhizome of *Dysosma versipellis*, which belongs to Berberidaceae [1, 2]. It is also known as Jiangbianyiwanshui, Guijiu, Bajiaoqi, Dujiaolian, and Shanheye [3]. It is mainly distributed in Hubei, Hunan, Jiangxi, Guizhou, Guangxi, Anhui and other regions [4]. It was first recorded in *Shennong's Classic of Materia Medica* (unknown author, 25–220 C.E.). "It is cold, and bitter, moreover, it is toxic, and belongs to the lung as well as liver meridians. It has the effects of eliminating phlegm and resolving masses, clearing heat and detoxifying, removing blood stasis, and relieving pain." It is commonly used in the treatment of rheumatoid arthritis, snake venom bite, fall injury, carbuncle boils, hemiplegia, cough, and tracheitis [5, 6]. In recent years, the chemical constituents of *Dysosma versipellis* have been systematically studied by scholars, which mainly include lignans, flavonoids, anthraquinones, volatile oils, amino acids and trace elements [7, 8]. Modern pharmacological studies have shown that *Dysosma versipellis* anti-tumor, antiviral effect, especially for esophageal cancer and uterine cancer treatment effect is obvious [9]. However, in recent years, it has often been mistakenly taken or overdosed, resulting in serious toxic reactions to the liver, kidney, heart, nervous system and other systems even leading into death [10–12]. The quality of Chinese medicinal materials is closely related to their growth environment, planting conditions, processing methods, and many more. The evaluation system of traditional medicinal materials may no longer apply. As a commonly used traditional Chinese medicine, *Dysosma versipellis* has a huge market demand and wide clinical application. Therefore, there is an urgent need to establish a new quality evaluation system. Based on a systematic review of the chemical constituents, pharmacological activities, and toxicological effects of *Dysosma versipellis*, this study predicted and analyzed its quality markers to provide a basis for establishing a scientific and reasonable quality evaluation system of *Dysosma versipellis*.

Chemical Composition

Lignans

Lignans are the most abundant chemical components in *Dysosma versipellis*, mainly including podophyllotoxin (PPT), deoxypodophyllotoxin, 4'-Desmethylpodophyllotoxin, podophyll-otoxone, isopicropodophyllone, dehydropodophyllotoxin, picropodophyllin and other components, which have the effects of scavenging free radicals and anti-oxidation. PPT is not only the main effective medicinal component of *Dysosma versipellis*, but also the quality index of dysosma plants [1]. See Table 1 and Figure 1 for details.

Flavonoids

Flavonoids are a kind of high content components in *Dysosma versipellis*. At present, flavonoids isolated from *Dysosma versipellis* mainly include kaempferol, quercetin, kaempferol-3-O-*β*-D-glucopyranoside, quercetin-3-O-*β*-D-glucopyranoside and other components. See Table 2 and Figure 2 for details.

Anthraquinones

Dysosma versipellis contains anthraquinone compounds, mainly including physcion, dysoanthraquinone, 2-Deme-thyldysoanthraquinone, dysosmajol. Among them, 2-Deme-thyldysoanthraquinone exists in Guizhou *Dysosma versipellis*, physcion and dysoanthraquinone exist in Guizhou *Dysosma versipellis*, Yunnan *Dysosma versipellis* and Guangxi *Dysosma versipellis* [16, 18, 23]. See Table 3 and Figure 3 for details.

Amino acids and trace elements

There are also amino acid compounds in *Dysosma versipellis*. Free amino acids are the most abundant having the sum of arginine, glutamic acid and tyrosine accounts for about 56% of the total free amino acids, which has a useful detoxification effect on the liver [19]. *Dysosma versipellis* contains 10 essential trace elements, namely Fe, Cu, Zn, Mn, Sr, Se, I, Co, Mo, Ni [20]. See Table 4 and Figure 4 for details.

Other kinds

Dysosma versipellis also contains the chemical composition of steroids, such as sitosterol-3-O-glucoside, cleistanthin-B, β-sitosterol, 7β-hydroxysitosterol, followed by esters and acids, for instance, 2-hydroxymethyl-5-furan, ethyl, acrylate, Ethyl p-hydroxybenzoate, p-methoxybenzoic acid, P-hydroxybenzoic acid [8, 15, 21]. Besides anthrone, tannin, palmitic acid, vanillic acid, astragaloside, glucose, sucrose, fatty acid, *α*-aminobutyric acid and polysaccharide [7, 31]. See Table 5 and Figure 5 for details.

Pharmacological activity

Antiviral effect

In 1986, Dai et al. [17]. first used *Dysosma versipellis* injection to treat encephalitis b in China, which had a great antipyretic effect on patients with mild, moderate to severe fever, and significantly reduced the mortality of encephalitis b. Zhang et al. [13]. compared the anti-herpes simplex virus effects of methanol and dichloromethanol extracts from the rhizomes of *Dysosma versipellis*, *Dysosma delavayi*, *Dysosma furfuracea*, *Sinopodophyllum hexandrum* and *Diphylleia sinensis*. The results show, methanol extract, except for *Dysosma delavayi* could effectively inhibit herpes simplex virus, while dichloromethane extract, except for *Dysosma versipellis*, showed no anti-scar virus effect due to its high toxicity. Yao et al. found through antiviral experimental research that, kaempferol and podophyllotoxin isolated from *Dysosma versipellis* aqueous solution have obvious inhibitory effects on Coxsackie B virus and herpes simplex virus type I, quercetin-3-O-β-D-glucofuranoside only has inhibitory effect on herpes simplex virus type I [14]. In addition, PPT, deoxypodophyllotoxin, and peltatin have been identified as reliable antiviral compounds [24-26]. These compounds can either reduce the ability of infected cells to release the virus or inhibit the virus in the replication cycle at the necessary early stage after the virus is absorbed into the cell, thereby exerting antiviral effect. PPT can also be used for the treatment of condyloma acuminatum and other perianal and sexually transmitted diseases caused by human papillomavirus [27, 28]. At present, cocktail therapy is being used in combination with other chemotherapeutic, integrating new technologies for fighting cancer and viruses in order to achieve better therapeutic effects. PPT combined with interferon has shown a significant effect on human genital infection. In addition, PPT

association with cisplatin can be used to treat neuroblastoma. Molluscum contagiosum, a viral skin infection caused by mollusk provirus, is a susceptible population of children and has been reported to be treated with PPT [33]. Podophyllotoxin derivatives (PPTs) have been found to be inhibitors of herpes simplex virus, Sindbis virus, murine cytomegalovirus, and vesicular stomatitis virus [30]. Etoposide treatment for adult AIDS patients with mild to moderate Kaposi sarcoma (KS) can delay the progression of KS and shorten the initial reaction time of KS to obtain short-term clinical efficacy [29]. A recent study reported the research progress of PPTs etoposide in phase II clinical trials, which can be used to treat COVID-19 patients with cytokine storm complications [32].

Anti-tumor effect

The anti-tumor material basis of *Dysosma versipellis* is aryl tetrahydronaphthalene lactone lignan component-PPT [22]. PPT is the main active ingredient of *Dysosma versipellis*, which has a significant inhibitory effect on gastric cancer cells, human prostate cancer cells, human breast cancer cells and human gastric adenocarcinoma cells (poorly differentiated) and other tumor cells [34]. The mechanism of action is to inhibit the polymerization of microtubules and prevent cells from entering the division process from the pre-division stage, thereby inhibiting the growth of cancer cells and exerting anti-tumor efficacy [35]. However, due to its high toxicity and serious gastrointestinal adverse reactions, it is not suitable for direct clinical use [36]. PPTs have broad-spectrum pharmacological potential. Various experiments have confirmed that PPTs, such as etoposide, etoposide phosphate, teniposide, GL331, NK-611, TOP53 and Npf-etoposide can be used as anticancer drugs [37–42]. Many clinical studies have confirmed that these compounds work against lung cancer, various types of genital tumors, non-Hodgkin's lymphoma, glioblastoma multiforme lymphoma and non-lymphocytic leukemia [43]. However, the clinical application of PPTs in cancer treatment is limited due to their serious toxic side effects and poor water solubility. It has been reported that adverse events caused by PPTs may involve secondary neutropenia, myelodysplastic disorders and leukemia [44]. Due to the low free diffusion ability of PPT and etoposide, the addition of highly selective substituents to modify the molecular structure of PPT plays a crucial role in achieving the order of magnitude difference of half inhibitory concentration between tumor cells and normal cells. Li et al. proposed a new bifunctional PPTs-2-pyridyl aldehyde hydrazone dithiocarbamate S-propionate podophyllotoxin ester, which can simultaneously inhibit matrix metalloproteinases and topoisomerase II to exert anti-proliferation and anti-metastasis effects [45]. In the local expansion model of xenotransplantation animals, PtoxPdp is superior to etoposide in inhibiting tumor and has a wide application value in the field of antitumor drugs. Zi et al. designed and synthesized 14 new PPTs, and determined their cytotoxic activity

Table 1 Lignans in *Dysosma versipellis*

Number	Compound	Molecular formula	Molecular weight	Reference
1	Podophyllotoxin	$C_{22}H_{22}O_8$	414.40	[8, 13, 14]
2	Deoxypodophyllotoxin	$C_{22}H_{22}O_7$	398.40	[8, 9, 11]
3	Picropodophyllin	$C_{22}H_{22}O_8$	414.40	[8, 10, 15]
4	Podophyllotoxin glucoside	$C_{28}H_{32}O_{13}$	576.50	[8, 10]
5	4'-Desmethylpodophyllotoxin	$C_{21}H_{18}O_8$	398.00	[9]
6	β-Polyphyllin	$C_{44}H_{70}O_{16}$	855.00	[9]
7	4'-Desmethylisopodophyllotorone	N/A	398.00	[9]
8	(+)-Rosinol	N/A	381.00	[9]
9	α-Polyphyllin	$C_{44}H_{70}O_{16}$	855.00	[9]
10	4'-Desmethylpodophyllotoxin	N/A	400.00	[9, 10, 16]
11	4', 5'-Didemethylpodophyllotoxin	$C_{20}H_{18}O_8$	386.00	[10]
12	4'-Demethylpodophyllotoxin-4-O-β-D-glucoside	N/A	562.00	[10, 16]
13	Diphyllin	$C_{21}H_{16}O_7$	380.30	[10,11]
14	Diphyllin-4-O-β-D- glucoside	N/A	542.00	[10]
15	Dysosmarol	$C_{20}H_{24}O_7$	376.40	[10]
16	Podophyllotoxone	$C_{22}H_{20}O_8$	412.40	[10–12]
17	Dehydropodophyllotoxin	$C_{22}H_{18}O_8$	410.40	[11, 12]
18	β-Peltatin	$C_{22}H_{22}O_8$	414.40	[11]
19	Isopicropodophyllone	$C_{22}H_{20}O_8$	412.40	[11, 12, 17]
20	Picropodophyllin-1-ethyl ether	$C_{24}H_{26}O_8$	442.50	[12]
21	β-Peltatin	$C_{22}H_{22}O_8$	414.40	[18]
22	α-Peltatin	$C_{21}H_{20}O_8$	400.40	[18]
23	Picropodophyllotoxone	$C_{22}H_{20}O_8$	412.39	[18]
24	Picropodophillotoxin4-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside	N/A	N/A	[16]
25	Podophyllotoxin-4-O-β-D-glucoside	N/A	N/A	[19]
26	4'-Norpodophyllotoxin-4-O-β-D-glucoside	N/A	N/A	[19]
27	4'-Nor-deoxypodophyllotoxin	N/A	N/A	[19]
28	α-Podophyllin	N/A	N/A	[19]
29	α-Polyphyllin-5-O-glucoside	N/A	N/A	[19]
30	β-Polyphyllin-5-O-glucoside	N/A	N/A	[19]
31	4'-Norpodophyllotoxin	N/A	N/A	[19]
32	Isodopodophyllotoxin	N/A	N/A	[19]
33	Picropodophyllotoxin-4-O-β-D-glucoside	N/A	N/A	[20]
34	4'-Demethylisopodophyllotoxin	N/A	N/A	[21]
35	3', 4'-O, O-Didemethylpophyllotoxin	N/A	N/A	[22]

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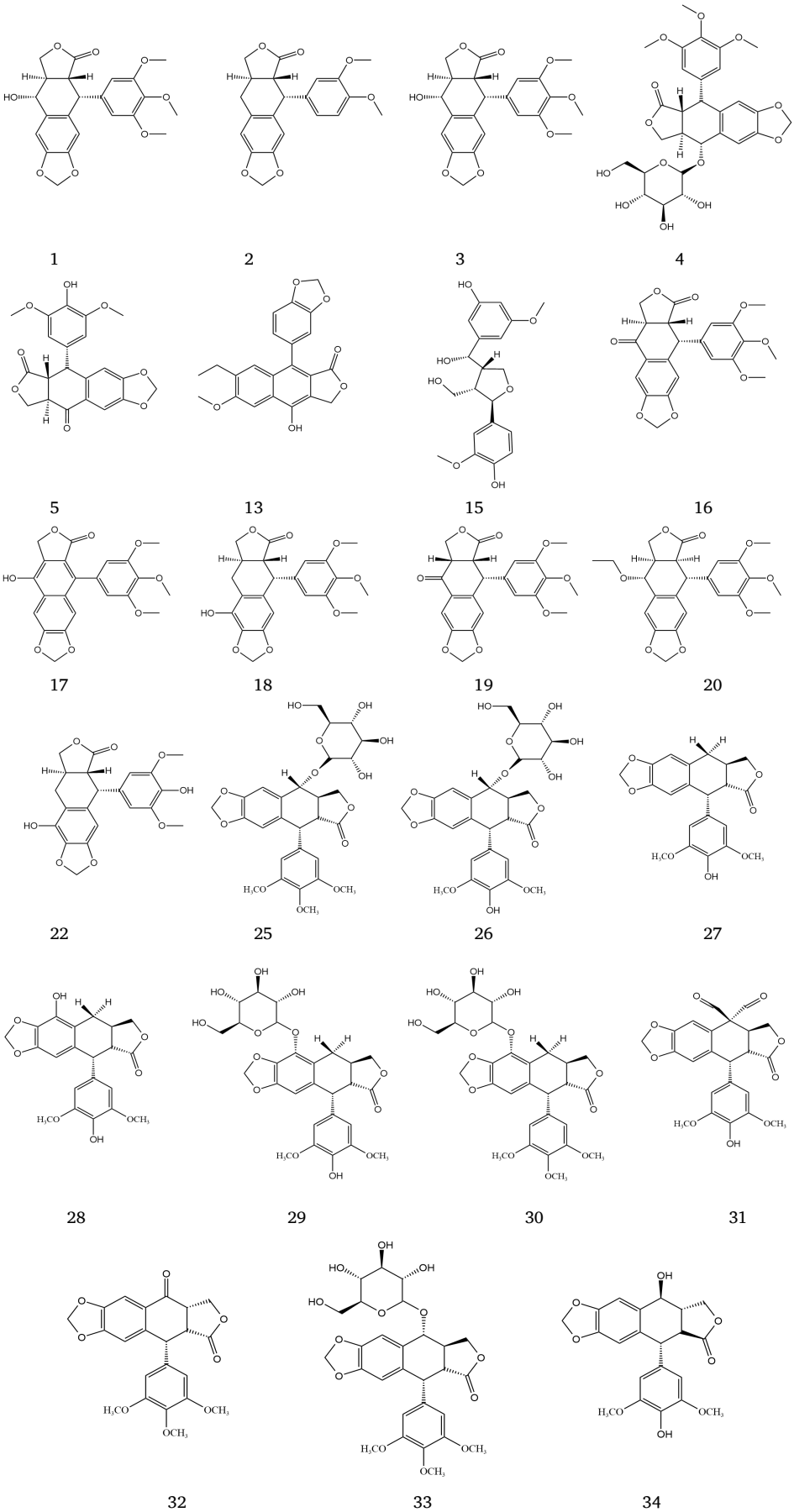

Figure 1 Structure skeleton of lignan compounds in *Dysosma versipellis*

Table 2 Flavonoids in *Dysosma versipellis*

Number	Compound	Molecular formula	Molecular weight	Reference
1	Kaempferol	$C_{15}H10O_6$	286.24	[8, 10, 11, 16 , 18]
2	Quercetin	$C_{15}H_{10}O_7$	302.23	[8, 10]
3	Kaempferol-3-O-β-D-glucoside	$C_{21}H_{19}O11$-	447.40	[10]
4	Rutin	$C_{27}H_{30}O_{16}$	610.50	[18]
5	Quercetin-3-O-β-D-glucofuranoside	$C_{21}H_{20}O_{12}$	464.40	[23]
6	Quercetin-3-O-β-D-glucopyranoside	$C_{21}H_{20}O_{12}$	464.40	[16]
7	Kaempferol-3-O-β-D-glucopyranoside	N/A	448.00	[16, 24]
8	Kaempferol-3-O-[6”-(3-methoxy)-malonyl] -β-D-glucopyranoside	N/A	548.00	[24]
9	Kaempferol-3-O-(6”-O-acetyl)-β-D-glucopyranoside	N/A	490.00	[24]
10	Kaempferol-3-O-β-D-glucopyranoside	N/A	462.00	[24]
12	Quercetin-4’-O-β-D-glucopyranoside	N/A	464.00	[24]
13	Kaempferol-3-O-(6”-O-malonyl monoacyl) -β-D-glucopyranoside	N/A	534.00	[24]
14	Hyperin	$C_{21}H_{20}O_{12}$	464.40	[25]
15	Astragalin	$C_{21}H_{20}O_{11}$	448.40	[25]

Table 3 Sterols in *Dysosma versipellis*

Number	Compound	Molecular formula	Molecular weight	Reference
1	Physcion	$C_{16}H_{12}O_5$	284.26	[26–28]
2	Dysoanthraquinone	$C_{18}H_{14}O_7$	342.00	[26, 28]
3	2-Deme-thyldysoanthraquinone	N/A	N/A	[26]
4	Dysosmajol	N/A	N/A	[29]

N/A, indicates that this item is not available.

Figure 2 The skeleton of flavonoids in *Dysosma versipellis*

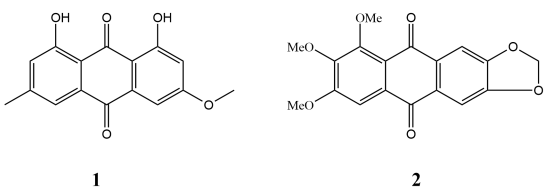

Figure 3 The skeleton of anthraquinone compounds in *Dysosma versipellis*

Table 4 Amino acids in *Dysosma versipellis*

Number	Compound	Molecular formula	Molecular weight	Reference
1	Aspartic acid	$C_4H_7NO_4$	133.10	[30]
2	Serine	$C_3H_7NO_3$	105.09	[30]
3	Glutamic acid	$C_5H_9NO_4$	147.13	[30]
4	Glycine	$C_2H_5NO_2$	75.07	[30]
5	Valine	$C_5H_{11}NO_2$	117.15	[30]
6	Isoleucine	$C_6H_{13}NO_2$	131.17	[30]
7	Phenylalanine	$C_9H_{11}NO_2$	165.19	[30]
8	Lysine	$C_6H_{14}N_2O_2$	146.19	[30]
9	Alanine	$C_3H_7NO_2$	89.09	[30]
10	Histidine	$C_6H_9N_3O_2$	155.15	[30]
11	Threonine	$C_4H_9NO_3$	119.12	[30]
12	α-Aminobutyric acid	$C_4H_9NO_2$	103.12	[30]
13	Cysteine	$C_3H_7NO_2S$	121.16	[30]
14	Tyrosine	$C_9H_{11}NO_3$	181.19	[30]
15	γ-Aminobutyric acid	$C_4H_9NO_2$	103.12	[30]
16	Ornithine	$C_5H_{12}N_2O_2$	132.16	[30]
17	Arginine	$C_6H_{14}N_4O_2$	174.2	[30]
18	Methionine	$C_5H_{11}NO_2S$	149.21	[30]
19	Hydroxyproline	$C_5H_9NO_3$	131.13	[30]
20	Proline	$C_5H_9NO_2$	115.13	[30]
21	Glutamine	$C_5H_{10}N_2O_3$	146.14	[30]
22	Leucine	$C_6H_{13}NO_2$	131.17	[30]

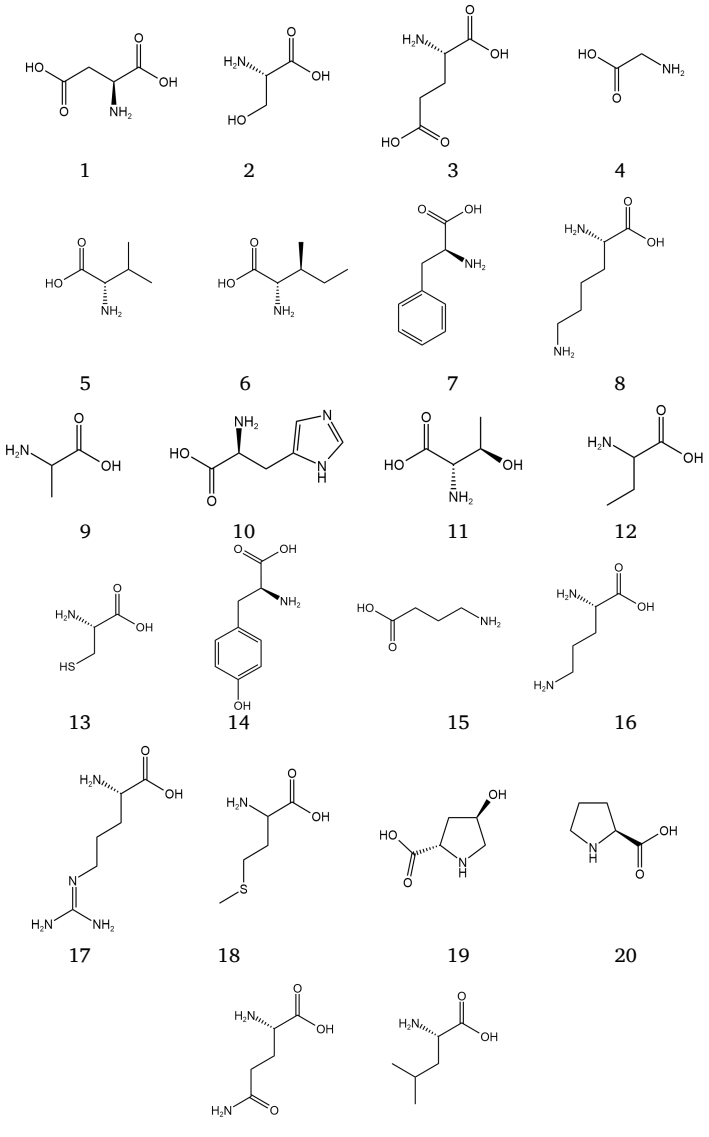

Figure 4 Structure skeleton of amino acid compounds in *Dysosma versipellis*

Table 5 Other compounds in *Dysosma versipellis*

Number	Compound	Molecular formula	Molecular weight	Reference
1	Vanillic acid	$C_8H_8O_4$	168.15	[8]
2	Sitosterol-3-O-glucoside	$C_{35}H_{60}O_6$	576.85	[8]
3	*β*-Sitosterol	$C_{29}H_{50}O$	414.70	[10, 16]
4	7*β*-Hydroxysitosterol	$C_{29}H_{58}O_2$	438.00	[12]
5	Cleistanthin-B	$C_{27}H_{26}O_{12}$	542.50	[16]
6	2-Hydroxymethyl-5-furan ethyl acrylate	$C_{10}H_{14}O_3$	122.00	[12]
7	Ethyl p-hydroxybenzoate	$C_9H_{10}O_3$	166.17	[12]
8	P-Methoxybenzoic acid	$C_8H_8O_3$	152.15	[12]
9	P-Hydroxybenzoic acid	$C_7H_6O_3$	138.12	[12]
10	Astragalin	$C_{21}H_{20}O_{11}$	448.40	[32]

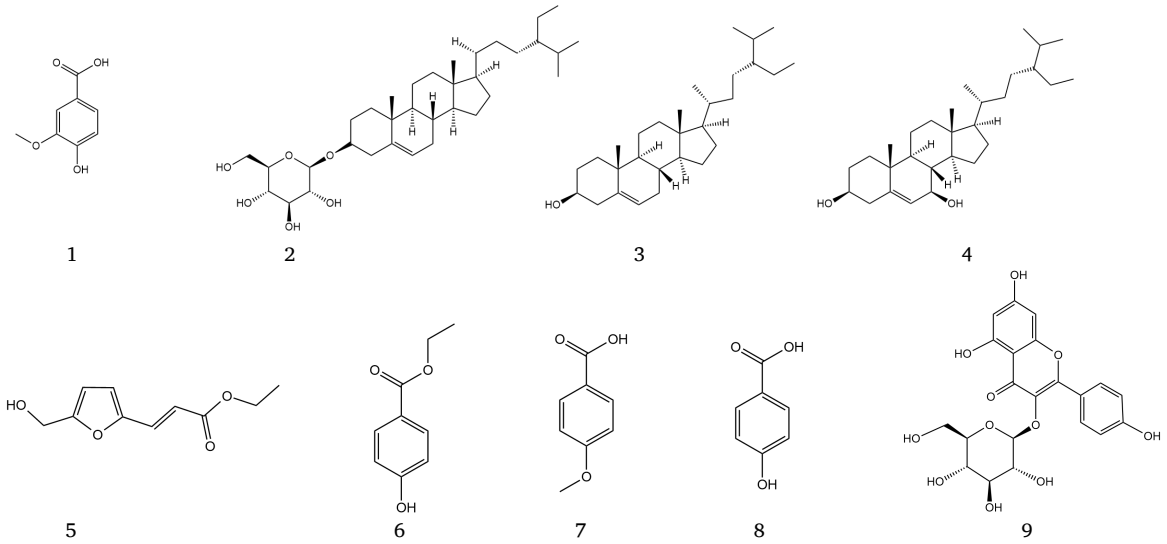

Figure 5 Structure skeleton of other compounds in *Dysosma versipellis*

against human colon cancer cells, human breast cancer cells, human non-small cell lung cancer cells, human liver cancer cells and human myeloid leukemia cells by MTT assay [46]. Among them, 4β-(biotin)-4-deoxypodophyllotoxin has the strongest cytotoxic activity, which can significantly down-regulate the expression levels of marker proteins caspase 3 and DNA repair enzymes in human non-small cell lung cancer cells and human lung adenocarcinoma cells, activate the transcription of inositol-dependent kinase 1α, increase the expression of endoplasmic reticulum stress-related factors glucose-regulated protein 78 and transcription factor splicing X-box binding protein 1, and induce apoptosis of human non-small cell lung cancer cells. In vivo studies showed that the compound could significantly inhibit the growth of transplanted ascites tumor in Institute of Cancer Research mice at the dose of 20 mg/kg; further molecular docking results showed that the compound binds well to the ATPase domain of topoisomerase II. These data suggest that the compound is a promising tumor therapeutic agent, worthy of further study. Wu et al. designed and synthesized 22 PPTs, and evaluated the cytotoxicity of these compounds in human non-small cell lung cancer cells, human breast cancer cells, human liver cancer cells and human normal liver cell lines [47]. The results showed that the efficacy of most compounds was better than that of clinical antitumor drug etoposide, especially compound 2 (sarcosine derivative of Boc group). It has high selectivity to cancer cells and normal cells and low toxicity to human normal hepatocytes, and it can induce apoptosis of human lung cancer cells through nuclear division. Apoptosis detection and cell cycle analysis showed that compound 2 induced apoptosis of human lung cancer cells and prevented them from changing from S phase to G phase, while there was no significant change in human normal liver cells. These PPTs have broad-spectrum, efficient anticancer activity, improved drug targeting and lower toxicity. At present, understanding the serious adverse reactions of new PPTs and actively exploring their related mechanisms in tumor therapy have become a research hotspot for the development of new anticancer drugs [48].

Antibacterial, insecticidal effect

Kaempferol in *Dysosma versipellis* has inhibitory effects on *Staphylococcus aureus*, *Salmonella typhi*, *Shigella Castellani* and *Pseudomonas aeruginosa* [49]. Zhou et al. screened out 8 strains of endophytic fungi with strong resistance to integrase and lens epithelial growth factor p75 protein from 53 strains of endophytic fungi isolated from *Dysosma versipellis* with different morphotypes, and these active fungi were mainly derived from the roots and rhizomes of *Dysosma versipellis*, which was consistent with their medicinal parts [50]. Zheng et al. used broth microdilution method to screen antibacterial activity of 6 new flavonoids and 3 known flavonoids [8]. The six new flavonoids showed antibacterial activity against *Riemerella anatipestifer*, *Bacillus subtilis*, *Enterococcus faecali-s*, *pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Streptococcus agalactiae*, *Streptococcus suis*. Tan et al. obtained 19 strains of fungi from the roots, stems and leaves of *Dysosma versipellis* [51]. Among them, DV04 strain showed strong antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, which can be further studied. The median antifeeding concentration of deoxypodophyllotoxin to three-month-old *Clostera anastomosis* larvae was 0.217 mg/mL, the lethal concentration 50% was 0.0176 mg/mL, and the inhibition rate of growth and development was 46.13% [52]. When the concentration of deoxypodophyllotoxin was 4 g/L, the 48 h antifeedant rate of *Plutella xylostella* was 76.3%, and the final mortality rate was 4.9%. However, it only showed antifeedant activity against armyworm, and the antifeedant rate was 46.3% [53]. The lethal concentration 50% of deoxypodophyllotoxin to *Culex pipiens pallens* and *Pieris rapae* were 0.00148 g/L and 0.0454 g/L,

respectively, and the median antifeeding concentration to *Pieris rapae* was 0.0161 g/L [54].

Anti-inflammatory and immunosuppressive ability

Inflammation is the protective response of body tissues to stimuli such as pathogens, damaged cells and supposedly harmful stimulators. Hyperoside was intraperitoneally injected at 20 mg/kg/d for 7 days after implantation of woolen balls in rats, which significantly inhibited the development of inflammatory response [55]. Dai et al. used *Dysosma versipellis* injection in the treatment of encephalitis b [17]. Adult intravenous infusion of 40 mL plus 250 mL 10% glucose, 5–7 days played a significant antipyretic effect. Shi et al. studied the *Dysosma versipellis* injection in the treatment of epidemic parotitis, the control group using three drugs combination of moroxydine hydrochloride, *IsatisindigoticaFortune* injection and prednisone, for the treatment group using *Dysosma versipellis* injection, the results showed that the parotid gland swelling subsided faster, and shorter course of treatment the treatment group [56]. Studies have shown that PPTs can improve the clinical symptoms of rheumatoid arthritis patients [57].

The immune effect of *Dysosma versipellis* is less used in clinical practice, but in animal experiments found that PPTs can reduce the production of specific antibodies in mouse spleen cells and serum hemolysin level, hinder the occurrence of delayed type hypersensitivity in mice, reduce the weight of mouse spleen and thymus [58]. In addition, the immunosuppressive effect of PPTs can be used to prevent acute rejection of organ transplantation [59]. Hemophagocytic lymphohistiocytosis (HLH), it is a congenital or secondary immunomodulatory disorder that can be rapidly fatal due to inefficient control of T cells and subsequent macrophage activation. Macrophage activation syn-drome (MAS) is closely related to HLH. It has been found that etoposide and teniposide can alleviate the clinical symptoms of HLH and MAS [60]. COVID-19, which is currently ravaging the world, has been found to be highly heterogeneous in host response, ranging from asymptomatic to severe. Harmful self-sustaining circulation due to excessive inflammation and extreme immune responses after SARS-Cov-2 infection can cause severe COVID-19 [61]. In these cases, etoposide can be used to treat COVID-19-induced acute respiratory distress syndrome and cytokine storm-related severe inflammation [62].

Anti-snake venom action

Dysosma versipellis decoction has detoxification effect on various snakebites. He et al. found that *Dysosma versipellis* can effectively improve the plasma thrombin time, clotting time, and has a certain inhibitory effect on snake venom [63]. Related pharmacological mechanisms of podophyllotoxin and its derivatives See Figure 6.

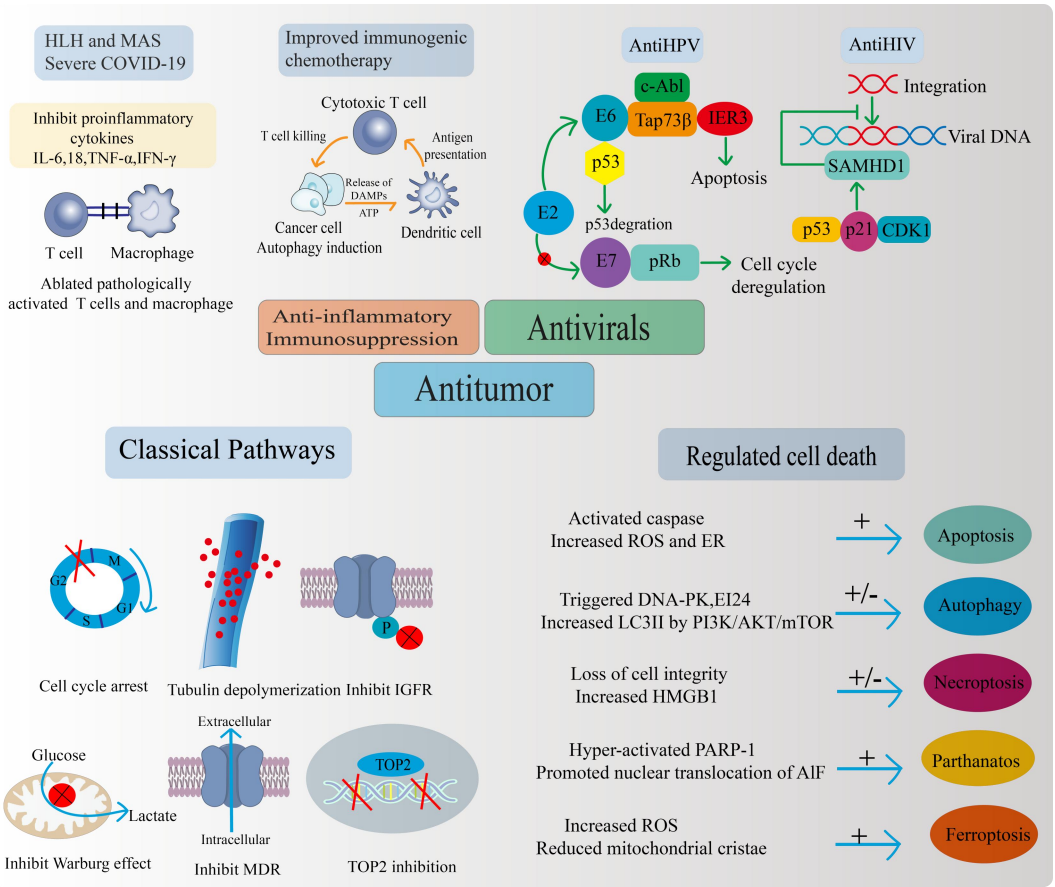

Figure 6 Related pharmacological mechanisms of podophyllotoxin and its derivatives. PPT and PPTs can treat HLH, MAS and severe COVID-19 by reducing proinflammatory cycle protein and inhibiting the proliferation of overactive T cells and macrophages. In addition, autophagy-mediated immunogenic cell death was found to be promoted in the tumor microenvironment after PPTs treatment. DAMPs can activate dendritic cells, and then induce specific anticancer immune killing effect. In antiviral aspect, Tap73β, the isomer of tumor suppressor gene p53, is resistant to oncoprotein E6, so the c-Abl/Tap73β/IER3 axis plays a role in the chemosensitivity of etoposide. PPT can inhibit the interaction between oncoprotein E2 and E7, thereby reducing the cell cycle disorder mediated by pRb affected by E7. In addition, PPTs can also down-regulate SAMHD1, thereby blocking human immunodeficiency virus integration in macrophages. The anti-tumor mechanisms of PPT and PPTs include induction of cell cycle arrest while inhibiting tubulin dimerization, TOP2, IGF-1R, Warburg effect and MDR1. Several regulatory cell death like apoptosis, parthanatos and ferroptosis could be induced by PPT and PPTs, but autophagy and necroptosis were regulated positively or negatively to maintain the dynamic balance in cancer cells death. PPT, podophyllotoxin; PPTs, podophyllotoxin derivatives; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syn- drome; HIV, human immunodeficiency virus; HPV, human papilloma virus; DAMPs, damage associated molecular patterns; pRb, retinoblastoma protein; MDR, multi drug resistance1; IGF-1R, insulin-like growth factor 1; SAMHD1, sterile alpha motif do- main and HD domain 1; TOP2, Topoisomerase II.

Toxicological effect

Effect on cardiovascular system

Dysosma versipellis has serious damage to the cardiovascular system, mostly toxic myocarditis, showing chest pain, palpitations, tachycardia or elevated myocardial enzymes and other symptoms [3]. Research report, the crystalline components extracted from *Dysosma versipellis* act on animals, and the results show that the crystalline components have an excitatory effect on the isolated frog heart; it has expansion effect on rabbit ear blood vessels; it has a slight contraction effect on the blood vessels of the hind limbs of frogs, the small intestine and renal vessels of rabbits [64]. Chen reported a death case of atrial fibrillation and coagulation disorder caused by *Dysosma versipellis* poisoning [12]. Among the clinical features of the patient, cardiotoxicity was the most obvious, first showing rapid atrial fibrillation, acute left heart failure, followed by cardiac arrest and death.

Effect on gastrointestinal tract

Dysosma versipellis poisoning can cause severe gastrointestinal reactions, and the early manifestations are increased gastrointestinal motility and weakened absorption [65]. Feng reported a case of *Dysosma versipellis* poisoning death [66]. After poisoning, the patient first showed paroxysmal upper abdominal pain, accompanied by persistent nausea, vomiting and diarrhea leading to multiple organ failure and death.

Effects on central nervous system

Dysosma versipellis has the effect of first excitation and then inhibition on the central nervous system. Podophyllotoxin injected into the animal body, showing convulsions, and then lethargy, coma, mydriasis, respiratory paralysis and other phenomena, then ultimately cardiac arrest and death [67]. Gong et al. summarized the specific characteristics of nervous system damage after *Dysosma versipellis* poisoning, which included the central nervous system and peripheral nervous system damage [68]. The central nervous system was severely damaged in the cerebral cortex, basal ganglia and spinal cord. In addition, damage to the peripheral nervous system was more significant in 17 patients with *Dysosma versipellis* poisoning in this study and consequently all of them presented with neurological sequelae.

Toxicity of viscera

Fang et al. reported that one patient had symptoms such as periumbilical pain, headache and convulsion after oral administration of *Dysosma versipellis* decoction [69]. Although active treatment was given after admission, it eventually led to multiple organ failure. Cao et al. reported that one patient was hospitalized in a coma after oral administration of self-made *Dysosma versipellis* medicinal liquor [70]. Due to excessive dosage, multiple organ failure such as liver function injury, myocardial injury, respiratory failure and bone marrow suppression occurred. Xu et al. observed the pathological changes of various organs after acute *Dysosma versipellis* poisoning in rats [71]. The results showed that acute *Dysosma versipellis* poisoning could cause pathological changes in heart, liver, kidney and brain (neurons), and its toxic effect positively correlated with the dose. Liu et al. found that podophyllotoxin-4-O-D-glucoside, PPT, podophyllotoxone and 3',4'-O,O-dimethyl-podophyllotoxin, by regulating PAH, SOD1, SOD2 and other related targets, affect glycerophospholipid metabolism, energy metabolism, phenylalanine metabolism and other related pathways, thereby inducing apoptosis, oxidative stress, inflammatory response, eventually leading to liver injury [72]. PPT can cause abnormal changes in tryptophan metabolism, glycerylphosphorylcholine metabolism and arachidonic acid metabolism in rats, resulting in dose-dependent renal injury. Changes in potential metabolites lipids and sulfate can be used as potential markers of PPT-induced renal injury [73].

Existing problems and potential of bioactive compounds from Dysosma versipellis

Dysosma versipellis is a rare and precious species in China. It is of great significance to identify its effective components for the rational use of *Dysosma versipellis*. PPT is the main component of *Dysosma versipellis*, which is very important in the pharmacological and toxicological effects of *Dysosma versipellis*. As the most important compound derived from *Dysosma versipellis*, further study on the pharmacological and toxicological mechanisms of PPT and PPTs is particularly critical for the development of new drugs derived from *Dysosma versipellis*. Although anti-cancer propertyis the most prominent feature in the development of new drugs, the biological activity of PPT and PPTs is quite diverse, and the potential of PPT as a lead compound for new drug development is far beyond its use in anti-cancer drug development. The emergence of large databases of omics and algorithms based on artificial intelligence and machine learning provides a means for the study of PPT and PPTs in multi-target diseases [74, 75]. With the advancement of computational methods, the molecular mechanisms of PPT and PPTs will be more clearly explained in the future, and repositioned PPT and PPTs may find new clinical applications. In addition, a large number of studies have focused on regulatory cell death targeting non-apoptotic pathways based on emerging nanobiotechnology. It is believed that this PPT and PPTs or synergistic targeted therapy with other natural drugs will provide ideas for the treatment of various incurable diseases [76]. In today's global COVID-19, etoposide has been redeveloped for the treatment of patients with cytokine storm complications in COVID-19. This discovery opens up new potential for the exploration of PPT and PPTs.

With the growing demand for PPT, plant sources have proven to be unreliable choices, and effective strategies need to be developed to expand the sources of podophyllotoxin to meet the creation of podophyllotoxin drugs. Microbial biotransformation as an important method may play an important role in PPT synthesis in the future [77]. Although some studies have explored the mechanism of *Dysosma versipellis* extract in esophageal cancer and apoptosis, its induction in malignant tumors or regulatory cell death has not been systematically and comprehensively studied. Other than that, etoposide and teniposide in PPTs are well known as anti-tumor drugs, but their drug resistance and bioavailability are low, and their side effects are large, which are severely limited in clinical treatment. Therefore, it is urgent to develop new podophyllotoxin drugs.

Predictive analysis of quality markers

In order to scientifically and objectively evaluate the quality of *Dysosma versipellis*, based on the concept of Quality Marker (Q-Marker) proposed by academician Chang-Xiao Liu in 2016, combined with the research status of *Dysosma versipellis*, a new quality evaluation system was established [78].

Q-Marker prediction analysis based on pharmaphylogeny and biosynthetic pathways of specific chemical components

Dysosma versipellis is a plant of genus *Dysosma* of family Berberidaceae. It is a unique third-class endangered plant in China. It is mainly located at an altitude of 300–1500 m, southeastern Tibet-western Sichuan-Qinling-southern area of Huaihe River, Henan, Jiangxi, Hunan, Hubei, Sichuan, Zhejiang, Guangdong, Guangxi, Anhui, Shanxi, Guizhou, Yunnan are distributed [79, 80]. *Dysosma* plants contain 9 kinds and 1 variety, including 8 kinds of which can be used as medicine, Chinese herbal medicine *Dysosma versipellis* mainly its roots and rhizomes, can clear heat and detoxify, remove blood stasis and detumescence [7]. The genus *Dysosma* includes, *Dysosma versipellis*, *Dysosma diormis*, *Dysosma guangxiensis*, *Dysosma furfuracea*, *Dysosma aurantiocaulis*, *Dysosma pleiantha*, *Dysosma maiorensis*, *Dysosma tsayuensis*, *Dysosma lic huanensis*, *Dysosma veitchii* [81, 82]. The main active components of *Dysosma versipellis* are PPT and PPTs in lignans, quercetin and kaempferol in flavonoids [83]. *Dysosma veitchii* contains the most trace elements and *Dysosma diormis* the least;

Dysosma versipellis has the highest free amino acid content and the most varieties [84]. *Dysosma maiorensis* had the lowest content of lignans; high flavonoid content in *Dysosma tsayuensis*, *Dysosma versipellis* and *Dysosma pleiantha*; the content of total polyphenols in *Dysosma versipellis* was higher, followed by *Dysosma veitchii* and *Dysosma diormis*, and *Dysosma tsayuensis* was the least; *Dysosma versipellis* has high content of flavonoids and total phenols [85]. The content distribution of total flavonoids from high to low is root, leaf and stem [86]. The content of components in *Dysosma versipellis* samples is quite different, which may be closely related to its region, growth environment and harvest period [87]. PPT content is most closely related to the region, the PPT content in the central and eastern region is 5–35 times worse than the western region; Chen found that the characteristic absorption peaks of infrared spectroscopy spectra of *Dysosma versipellis* from different habitats may be related to esters and carboxylic acids in *Dysosma versipellis* from different habitats [4].

The secondary metabolites in plants are the results of their long-term genetic reproduction and environmental adaptation, showing the specificity of species, growth period and organ tissue. PPT is the main active substance and quality index of *Dysosma versipellis*. The analysis of its biological origin is conducive to the study of its unique chemical composition [88]. In the early stages of PPT biosynthesis, coniferyl alcohol as a synthetic precursor is synthesized from phenylalanine in nine steps, followed by site-selective and unusual enantiodimerization to form (+)-coniferyl alcohol, which is converted to PPT after a series of reactions such as reduction, catalysis, and methylation [89]. The specific synthesis pathway is shown in Figure 7. PPT, kaempferol and quercetin in flavonoids, total polyphenols, free amino acids and other components can be used as reference for Q-Marker.

Q-Marker prediction analysis based on traditional drug properties

The theory of drug property of traditional Chinese medicine originates from clinical practice. It is the main basis for exploring the mechanism of action of traditional Chinese medicine and guiding clinical medication, and also an important link between traditional Chinese medicine and traditional Chinese medicine, which can be used as the basis for studying Q-Marker [90]. *Dysosma versipellis* tastes bitter, pungent, and cool. It is also a lung, liver meridian. Bitter taste medicines mostly have the effect of lowering Qi (In traditional Chinese medicine, it refers to the most fundamental and subtle substances that constitute the human body and maintain life activities. At the same time, it also has the meaning of physiological function. In terms of traditional Chinese medicine, Qi and different words are used together to express different meanings.), drying dampness, strengthening Yin (The negative side of something or movement, such as inner, downward, restrained, heavy, qualitative, etc.), purging, purging fire, etc., belonging to the stomach, liver, lung meridian, the main chemical composition of flavonoids, volatile oil, sugars, quinones, alkaloids and glycosides, etc. [91]. The main efficacy of pungent herbs is divergent, Qi and blood, lung, liver, spleen and stomach meridian. The main chemical components are volatile oil, glycosides and alkaloids [92]. Cool medicine belongs to Yin. According to the theory of Yin and Yang (The outward, upward, exuberant, light, and functional aspects of things and movements.) opposition, it can be attributed to yang, liver, lung, heart and stomach meridians, containing flavonoids, tannins, organic acids, carbohydrates, esters, proteins, etc.[90]. Although the volatile oils and carbohydrates in *Dysosma versipellis* have certain biological activities, but the volatile oils are easy to volatilize and the stability of content determination is not good. Most of the carbohydrates in the organism exist in the form of polysaccharides, however their complex structure is not easy to separate and purify. These two are not suitable for Q-Marker. Thus, flavonoids, esters, quinones, etc. can be used as a reference for Q-Marker.

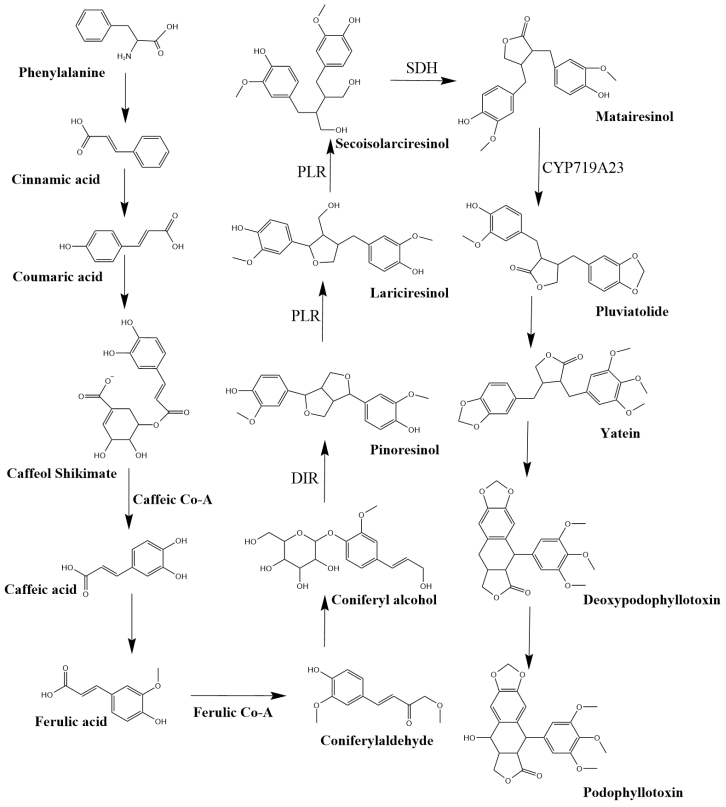

Figure 7 The biosynthesis pathway of podophyllotoxin. DIR, dirigent; PLR, pinoresinol lariciresinol reductase; SDH, secoisolariciresinol dehydrogenase; CYP719A23, the member of cytochrome P450 proteins.

Q-Marker prediction analysis based on traditional efficacy

Traditional efficacy is the embodiment of the effectiveness of Chinese medicine. Also Chinese medicine clinical medication basis. "*Guizhou Folk Prescription Collection*" (Ji-qiu Yang, Ji-zhong Yang, 1958–) recorded: "treatment of weak anal prolapse; external detumescence, and treatment of snakebites, furuncles". "*Fujian Folk Herbal Medicine*" (Fujian Institute of Traditional Chinese Medicine Herbal Research Office, 1958–1960) contained: "scattered knot live stasis, eliminate gall detoxification". "*Guangxi Traditional Chinese Medicine Annals*" (Guangxi Zhuang Autonomous Region Health Department, 1959–) contained: "clear heat and phlegm, detoxify snakes and insects. Cure lung heat phlegm cough, insect snake bite, single and double moth throat pain". "*Jiangxi Herbal Medicine*" (Jiangxi Provincial Health Bureau Revolutionary Committee, 1970–) recorded: "treating kidney deficiency, fatigue, heat stroke, stomach pain". "*Sichuan Chinese Medicine Records*" (Sichuan Collaborative Writing Group of Chinese Materia Medica, 1979–) recorded: "treatment of labor injury vomiting blood, low back pain, scabies white bald". Guangzhou army "*Common Herbal Medicine Manual*" (Guangzhou army logistics department health department, 1969–) recorded: "clear heat and detoxify, dryness and dampness purge fire. Cure lymphadenitis, mumps, carbuncle sore". It can be seen that *Dysosma versipellis* is mainly used for resolving phlegm, removing blood stasis and relieving pain, clearing heat and detoxifying, swelling and pain of throat, scrofula, gall tumor, carbuncle swelling and furuncle, snake bite and injury [87]. Modern pharmacological studies have found that PPT and PPTs have good therapeutic effects on tumors, cardiovascular diseases, leukemia, inhibition of central nervous system and anti-immunity; Kaempferol has anti-cancer, anti-epilepsy, anti-ulcer, anti-oxidation, anti-inflammatory, cough, cholagogue and other effects; quercetin can antioxidant and scavenging oxygen free radicals, can reduce blood pressure, enhance immune system function [83]. anti-inflammatory, anti-oxidation, enhance immune function corresponding to "resolving phlegm, clearing heat and detoxification, sore throat, scrofula, carbuncle, furuncle, traumatic injury"; anticancer corresponds to "gall tumor"; inhibition of the central nervous system corresponding to "snake bite"; the treatment of cardiovascular disease corresponds to the effect of "removing blood stasis and relieving pain". Therefore, PPT, kaempferol and quercetin can be used as Q-Marker reference.

Q-Marker predictive analysis based on chemical composition measurability

The quantitative or qualitative analysis of chemical components of traditional Chinese medicine is one of the important references for the prediction and analysis of quality markers, and its analysis needs to rely on mature and reliable detection methods. Cui et al. established high performance liquid chromatography fingerprint of *Dysosma versipellis* to quantitatively analyze kaempferol, PPT, quercetin, (+)-tanegool-7'-methylether and 4'-demethylpodophyllotoxin [87]. The method is simple, reliable and stable. Zhang et al. used a new ultra performance liquid chromatography tandem mass spectrometry method to quantitatively analyze the lignans in *Dysosma versipellis* [93]. The results showed that podophyllotoxin-4-O-glucoside (5.87%), PPT (7.44%), 4'-demethylpodophyllotoxin (1.14%), 4-deoxypodophyllotoxin (0.06%). Jiang et al. isolated and purified *Dysosma versipellis* by silica gel column chromatography and gel purification, and isolated kaempferol, kaempferol-3-O-β-D-glucopyranoside and quercetin by reversed-phase high performance liquid chromatogra (RP-HPLC) [94]. Chen et al. used Sephadex-LH-20 gel column chromatography, preparative high performance liquid chromatogra and preparative thin layer chromatography to isolate and purify the histochemical components of the callus of *Dysosma versipellis* [95]. Kaempferol-3-O-(6"-O-malonyl)-β-D-glucopyranoside, kaempferol-3-O-(6"-O-acetyl)-β-D-glucopyranoside, kaempferol-3-O-(6"-(3"-methoxy)-malonyl)-β-D-glucopyranoside, kaempferol-3-O-β-D-glucopyranoside, quercetin-4'-O-β-D-glucopyranoside, isoquercetin, etc. Extraction, separation and identification technology of lignans and flavonoids in *Dysosma versipellis* has been mature, providing reliable technical support for the quality control of *Dysosma versipellis*. From the above analysis, PPT, 4'-demethylpodophyllotoxin, 4-deoxypodophyllotoxin, podophyllotoxin-4-O-glucoside, kaempferol, kaempferol-3-*O*-*β*-D-glucopyranoside, quercetin and isoquercetin can be used as Q-Marker reference.

Q-Marker predictive analysis based on blood components and pharmacokinetics

Kong et al. found that there were more transitional components in the blood of rats administered for 45 min by analyzing the chromatograms of Dysosma versipellis drug-containing serum, blank serum, alcohol extract and mixed reference substance, and 11 prototype components were detected in the blood, such as vanillic acid, rutin, dysosmarol, 4'-demethylpodophyllotoxin, podophyllotoxin-4-O-glucoside, PPT, 6-methoxypodophyllotoxin, deoxypodophyllotoxin, podophyllotoxone and β-sitosterol [96]. The concentration of PPT, podophyllotoxin, podophyllotoxin, deoxypodophyllotoxin etc. six lignans in the blood increased rapidly after entering the blood, and reached the peak at about 30 minutes. In addition, the rats were poisoned within 24 hours after intragastric administration, showing neurological poisoning and severe diarrhea, which may be related to the multiple poisoning reactions caused by these six highly toxic lignans [97]. Liu et al. studied the pharmacokinetic parameters of deoxypodophyllotoxin and its main metabolites in rat plasma and found that for metabolites M1 and M7, except for a few points, most of their concentrations were lower than 1.973 ng/mL. M2 was detected as the main metabolite in rat plasma due to its high concentration level [98]. After intravenous injection of 1, 2 or 4 mg/kg deoxypodophyllotoxin in rats, the $AUC_{0\rightarrow t}$ of M2 and the percentage of deoxypodophyllotoxin were 38.61 ± 6.46, 20.53 ± 8.77 and 26.85 ± 9.43%, respectively. Within the dose range studied, the pharmacokinetic properties of deoxypodophyllotoxin and metabolite M2 showed a linear relationship in rats. The structures of the main metabolites M1, M2 and M7 are shown in Figure 8. Therefore, dysosmarol, podophyllotoxin-4-O-glucoside, 4'-demethylpodophyllotoxin, picropodophyllin, podophyllotoxone, deoxypodophyllotoxin, 6-methoxypodophyllotoxin, etc. can be used as Q-Marker reference.

Conclusion

As a unique traditional Chinese medicine, *Dysosma versipellis* has a long history of use, rich pharmacological activity and definite curative effect. It is an important resource of traditional Chinese medicine. At

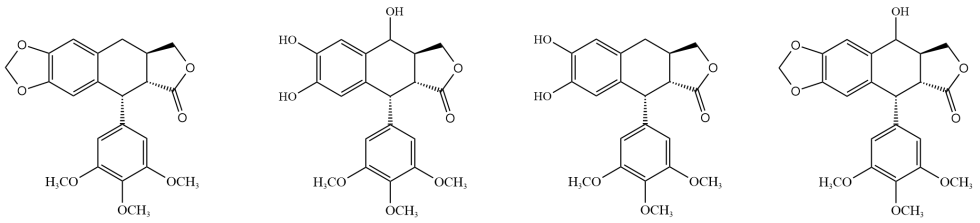

Figure 8 Deoxypodophyllotoxin and its main metabolites structure

this stage, domestic and foreign researchers have made remarkable achievements in the chemical composition, pharmacological activity and toxicological effect of *Dysosma versipellis*, but their research still has shortcomings. For instance, the current research on the toxic material basis of *Dysosma versipellis* is relatively weak, the toxic mechanism is relatively scarce, and the network pharmacology research on *Dysosma versipellis* is currently vacant. In addition, due to the complex composition of *Dysosma versipellis*, the lack of specificity of quality control standards, the low correlation with efficacy, and the imperfect quality control system are not conducive to the further development and utilization of *Dysosma versipellis*. In this study, based on the research status of chemical constituents, pharmacological activities and toxicological effects of *Dysosma versipellis*, according to the core concept of Q-Marker, the Q-Marker of *Dysosma versipellis* was predicted and analyzed from the aspects of pharmaphylogeny and biosynthetic pathways of specific chemical components, traditional drug properties, traditional efficacy, chemical composition measurability, blood components and pharmacokinetics. It is suggested that lignans, flavonoids, esters and quinones should be selected as the main components of Q-Marker of *Dysosma versipellis*; PPT, podophyllotoxin-4-O-glucoside, 4'-demethylpodophyllotoxin, 4-deoxypodophyllotoxin, kaempferol and quercetin were recommended as the main targets for single component selection. Total polyphenols, free amino acids, podophyllotoxone, picropodophyllin, kaempferol-3-O-β-D-glucopyranoside, isoquercetin, and dysosmarol were recommended as alternative components. This result is only based on the existing research results, the Q-Marker of *Dysosma versipellis* and the specific mechanism of action need to be further studied. The in-depth study in Q-Marker of *Dysosma versipellis* and the establishment of a reasonable scientific quality evaluation system are conducive to the systematic, objective and accurate evaluation of its quality and help to guide the rational use of its resources, which is of great benefit to the optimization and healthy development of *Dysosma versipellis* industry.

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