Progress in the Study of Chemical Composition and Pharmacological Effects of *Dipsaci Radix* and Predictive Analysis of Quality Markers

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Abstract: Dipsaci Radix, the dried root of Dipsacus asper Wall. ex Henry, is a traditional Chinese medicinal herb. Modern phytochemical research indicates that it predominantly contains triterpenoid saponins, iridoids, volatile oils, alkaloids, lignans, polysaccharides, and other chemical components. Clinically, it is widely used to treat conditions associated with liver and kidney deficiency, such as soreness and weakness of the lower back and knees, rheumatic arthralgia, traumatic injuries, bone fractures, metrorrhagia, and threatened miscarriage. This study presents a predictive analysis of potential quality markers (Q-Markers) for Dipsaci Radix based on multiple perspectives, including its botanical phylogenetic relationships, the measurability of its chemical components, its traditional properties according to Chinese medicine, the effects of different processing methods, and its geographical origins. The analysis has identified the following compounds as potential Q-Markers: asperosaponin VI, loganin, loganic acid, sylvestroside I, dipsanoside B, dipsanoside A, sweroside, asperosaponin X, asperosaponin XIII, α-hederin, 5-hydroxymethylfurfural (5-HMF), isochlorogenic acid A, chlorogenic acid, isochlorogenic acid B, isochlorogenic acid C, caffeic acid, ursolic acid, and hederagenin. This study provides a scientific reference for Q-Marker research and the refinement of the quality evaluation system for Dipsaci Radix.

Keywords: Dipsaci Radix; Chemical Composition; Pharmacological Action; Quality Marker

1. Introduction

Dipsaci Radix, the dried root of Dipsacus asper Wall. ex Henry(family Dipsacaceae)[1], is typically harvested in autumn. After harvesting, the root crown and fibrous roots are removed. The roots are then dried over low heat until partially dry, piled up to allow them to undergo a traditional "sweating" process until the interior turns greenish, and finally dried thoroughly. First documented in the Shennong Bencao Jing (The Divine Farmer's Materia Medica), Dipsaci Radix derives its Chinese name (Xu Duan) from its renowned ability to "heal fractures and mend bones." It is also known by other names such as "monk's head" and "drumstick herb." The plant is primarily distributed in China's Jiangxi, Hubei, Hunan, Guangxi, and Sichuan provinces [2]. Dipsaci Radix is slightly warm in nature, with bitter and pungent tastes, and acts on the Liver and Kidney meridians. Its therapeutic effects include tonifying the liver and kidneys, strengthening tendons and bones, repairing bone fractures, and stopping metrorrhagia. These properties make it clinically effective for a range of conditions arising from liver-kidney deficiency, including lumbago, weak knees, rheumatic arthralgia, tendon and bone injuries, as well as for uterine bleeding and threatened miscarriage.

This study provides a comprehensive review and analysis of the chemical constituents and pharmacological effects of Dipsaci Radix. Based on the "Five Principles" of Q-Marker concept in traditional Chinese medicine, we conduct a predictive analysis of its Q-Markers across several dimensions: botanical phylogenetic relationships, traditional medicinal properties, chemical component measurability, effects of

processing methods, and impact of geographical origins. The aim is to provide a scientific basis for the quality control of Dipsaci Radix, thereby enhancing its clinical application value and therapeutic potential.

2. Chemical Composition

Dipsaci Radix mainly contains triterpenoid saponins, iridoids, volatile oils, alkaloids, lignans, and polysaccharides, with triterpenoid saponins and iridoids being the most abundant components. In recent years, as research has progressed, phenylpropanoids, organic acids, and proteins have also been identified [3].

2.1 Triterpenoid Saponins

Triterpenoid saponins are not only the most abundant chemical constituents in Dipsaci Radix but also its primary active components[3].To date, 22 such compounds have been isolated and identified, including asperosaponin X, asperosaponin XII, asperosaponin C, asperosaponin V, asperosaponin IX, asperosaponin XI, and asperosaponin VI. Their chemical names, molecular formulas, and structural configurations are detailed in Table 1. Notably, 3β-hydroxy-24-nor-urs-4(23), 12-dien-28-oic acid is a new compound, while ursolic acid was isolated from the roots of Dipsacus asper for the first time in recent years.

Table 1. Triterpenoid saponins from Dipsacus asperoides

No.	Chemical Name	Molecular Formula	Chemical Constitution	Reference
1	Asperosaponin X	$C_{76}H_{124}O_{40}$	R_1=D－Xyl－D－glu－(1→4)－L－rha－(1→3)－D－glu－(1→3)－rha－1→2)－L－ara R_2=ester	[4]
2	Asperosaponin XII	$C_{71}H_{116}O_{36}$	R_1=L－rha－(1→3)－D－glu－(1→4)－D－glu－(1→3)－rha－(1→2)－L－ara R_2=ester	[5]
3	Asperosaponin XIII	$C_{76}H_{124}O_{39}$	R_1=D－xyl－(1→4)－D－glu－(1→4)－［－L－rha－(1→3)－D－glu－(1→3)－L－rha－(1→2)－L－ara R_2=H	[5]
4	3-O-α-L-rhamnopyranosyl(1→3)-β-D-glucopyranoside(1→3)-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranosyl hederagenin-28-β-D-glucopyranoside(1→6)-β-D-glucopyranoside	$C_{65}H_{106}O_{31}$	R_1=L－rha－(1→3)－D－glu－L－rha－(1→2)－L－ara R_2=D－glu－(1→6)－D－glu ester	[6]
5	Akebiasaponin D	$C_{47}H_{76}O_{18}$	R_1=－O－L－ara R_2=D－glu－(1→6)－D－glu ester	[7]
6	Akebiasaponin D 4'－acetate	$C_{49}H_{78}O_{19}$	R_1=4－O－acetyl－L－ara R_2=D－glu－(1→6)－D－glu ester	[8]
7	Asperosaponin A	$C_{42}H_{68}O_{14}$	R_1=H R_2=ester	[9]
8	Asperosaponin B	$C_{59}H_{96}O_{25}$	R_1=D－glu－(1→4)－［－L－rha－(1→6)－D－glu－(1→3)－L－rha－(1→2)－L－ara R_2=H	[8]
9	Asperosaponin C	$C_{64}H_{104}O_{30}$	R_1=D－glu－(1→4)－D－glu－(1→4)－D－glu－(1→3)－rha－(1→2)－rha－(1→4)－rha－(1→2)－L－ara R_2=H	[8]
10	Macranthoidin A	$C_{59}H_{96}O_{27}$	R_1=D－glu－(1→3)－L－rha－(1→2)－L－ara R_2=ester	[8]
11	Macranthoidin B	$C_{53}H_{86}O_{22}$	R_1=D－glu－(1→4)－D－glu－(1→3)－L－rha－(1→2)－L－ara R_2=H	[8]
12	Gigantaeside D	$C_{30}H_{48}O_4$	R_1=R_2=H	[8]
13	Cauloside A	$C_{35}H_{56}O_8$	R_1=L－Ara R_2=H	[8]
14	Kalopanaxsaponin A	$C_{41}H_{66}O_{12}$	R_1=L－rha－(1→2)－L－ara R_2=H	[8]

15	Asperosaponin F	$C_{41}H_{66}O_{13}$	R_1=L－ara R_2=D－glu ester	[10]
16	Dipsacobioside	$C_{41}H_{66}O_{12}$	R_1=L－rha－(1→4)－L－ara R_2=H	[8]
17	Akebiasaponin D	$C_{47}H_{76}O_{18}$	R_1=L－Ara R_2=ester	[11]
18	3β-Hydroxy-24-nor-urs-4(23),12-diene-28-oic acid	$C_{29}H_{44}O_3$	R_1= L-Rha-(1→4)-L-Ara,R_2= H	[6]
19	ursolic acid	$C_{30}H_{48}O_3$	R_1= D-Glc-(1→3)-L-Ara,R_2= L-Rha-(1→4)-L-Ara	[6]

2.2 Iridoids

To date, 22 iridoid compounds have been isolated from Dipsaci Radix, including loganic acid, sweroside, dipsanoside A, and sylvestroside III. The chemical names of these compounds are listed in Table 2.

Table 2. The Iridoid Compounds in Dipsacus Asper

No.	Chemical Name	Reference	No.	Chemical Name	Reference
1	loganic acid	[9]	12	Dipsacoside A	[13]
2	Linsheng dipsacoside I	[9]	13	Linsheng dipsacoside III	[13]
3	Dipsacoside B	[9]	14	Linsheng dipsacoside IV	[13]
4	sweroside	[12]	15	Dipsacoside C	[14]
5	loganin	[12]	16	Dipsacoside D	[14]
6	Dipsacoside H	[12]	17	Dipsacoside G	[14]
7	Dipsacoside F	[12]	18	Dipsacoside M	[14]
8	Dipsacoside E	[12]	19	Dipsacoside N	[14]
9	6′-O-β-D-apiofuranosyl-sweroside	[12]	20	lisianthioside	[14]
10	triplostoside A	[12]	21	Syringopicroside I	[15]
11	cantleyoside	[13]	22	dipasperoside A	[16]

2.3 Volatile oils

Li et al.[17] performed GC-MS analysis on the volatile oils extracted from Dipsaci Radix using ultrasound-assisted extraction. A total of 51 compounds were identified, with γ-sitosterol, stigmasterol, 24-methyl-5-cholesten-3-ol, and lanosterol being the most abundant.

2.4 Alkaloids

Yang et al. [18] isolated and purified two alkaloid compounds from Dipsaci Radix, identified as venoterpine and cantleyine via spectroscopic methods. Literature reports also indicate the presence of gentianine [19].

2.5 Lignans

Using techniques such as macroporous resin chromatography, preparative HPLC, and reversed-phase silica gel chromatography, Sun et al.[12] isolated six lignan compounds from Dipsaci Radix:
(7R,8S,7'R,8'S)-5-methoxyprinsepiol-4-O-β-D-glucopyranoside,
(7R,8S,7'R,8'S)-prinsepiol-4-O-β-D-glucopyranoside,
(7R,8S,7'R,8'S)-fraxiresinol-4'-O-β-D-glucopyranoside,
(7R,8S,7'R,8'S)-8-hydroxypinoresinol-4'-O-β-D-glucopyranoside,
(7R,8S,7'R,8'S)-8-hydroxypinoresinol-4-O-β-D-glucopyranoside, and acanthoside D.

2.6 Other Components

Polysaccharides have also been identified in Dipsaci Radix [20]. Furthermore, literature reports[13] indicate the presence of 15 organic acid compounds, including dipsaicin, 2,6-dihydroxycinnamic acid, vanillic acid, caffeic acid, 2′-O-caffeoyl-D-glucopyranoside ester, chlorogenic acid, isochlorogenic acids A, B, and C, and various caffeoylquinic acid esters and acids.

3. Pharmacological Effects

3.1 Anti-osteoporotic and Bone-Protective Effects

Osteoporosis is a major risk factor for fractures and can significantly delay the healing process. This delayed healing can lead to limb dysfunction, chronic pain, and an increased risk of re-fracture, creating a vicious cycle that severely impacts patients' quality of life. Recent research has focused on the potential of TCM in treating osteoporosis. Studies have shown that the saponins found in Dipsaci Radix are key components responsible for its anti-osteoporotic effects, promoting bone differentiation through multiple pathways.

Zhang et al. [21] employed network pharmacology to elucidate the mechanism of Dipsaci Radix in treating osteoporotic fractures. They identified five active components, with β-sitosterol, sylvestroside, and gentianine being the primary ones, and 28 potential therapeutic targets. GO enrichment analysis revealed key targets such as CASP3, CASP8, JUN, HSP90AA1, and PTGS2. KEGG pathway enrichment suggested that the anti-osteoporotic effect is mediated through key pathways like the estrogen, IL-17, and apoptosis signaling pathways, indicating a multi-pathway, multi-target mechanism.

Xu et al. [22] found that asperosaponins (ASA) from Dipsacus asper significantly promote the osteogenic differentiation of rat bone marrow stromal cells (rBMSCs) in an osteoporosis model. The mechanism was attributed to the activation of the PI3K/AKT signaling pathway. Sun et al. [23] isolated a polysaccharide (DAP) from the roots of Dipsacus asper. Further studies showed that DAP prevents postmenopausal osteoporosis by upregulating osteoprotegerin (OPG) and vascular endothelial growth factor (VEGF), while downregulating RANKL and RANK expression, thereby activating the PI3K/AKT/eNOS signaling pathway.

3.2 Neuroprotective Effect

Alzheimer's disease (AD) is a neurological disorder characterized by cognitive decline and memory loss [24]. Studies indicate that Dipsacus asper possesses neuroprotective properties, making it a potential therapeutic agent for AD.

YU et al. [25] demonstrated that asperosaponin VI significantly reduces inflammatory responses in an AD model by inhibiting the release of cytokines and inflammatory factors from glial cells. WANG et al. [26] showed that asperosaponin VI effectively ameliorates memory impairment and anxiety induced by amyloid beta 25-35 (Aβ25-35) in rats. This effect is mediated by downregulating the hypothalamic-pituitary-adrenal (HPA) axis and reducing systemic corticosterone levels. Zheng et al.[27] found that Total saponins of Dipsacus asper improve learning and memory abilities in a vascular dementia rat model by modulating the expression of key proteins, including downregulating pro-apoptotic proteins (Bax, PARP, CASP3) and upregulating the anti-apoptotic protein Bcl-2.

3.3 Prevention of Recurrent Spontaneous Abortion

Recurrent spontaneous abortion (RSA) is a common clinical condition with a complex pathogenesis. Dipsaci Radix is rich in sterol components that exhibit estrogen-like activity, which can inhibit uterine smooth muscle contraction and promote corpus luteum formation, supporting normal uterine and embryonic development. Data mining analysis identify Dipsaci Radix as a frequently used traditional Chinese medicine for preventing and treating RSA [28].GAO et al. [29] found that asperosaponin VI increases progesterone receptor (PR) expression by activating the PR promoter in decidual and HeLa cells. Concurrently, it activates the Notch signaling pathway to induce decidualization, promoting embryo implantation and effectively preventing RSA.

3.4 Antitumor Effect

Xie et al. [30] reported that an aqueous extract of Dipsaci Radix induces apoptosis in HeLa cells by damaging mitochondria and activating the intrinsic apoptotic pathway.Shi et al. [31] demonstrated that the triterpenoid saponin, HN Saponin F, exhibits androgen-like activity. It competitively binds to androgen receptors with dihydrotestosterone (DHT), inhibiting the proliferation of androgen-dependent prostate cancer (LNCaP) cells.Zhou et al. [32] found that Dipsaci Radix saponins inhibit the proliferation and induce apoptosis of human promyelocytic leukemia (HL-60) and acute leukemia (U937) cells by promoting nitric oxide (NO) production.

3.5 Anti-inflammatory and Analgesic Effects

Suh et al. [33] reported that asperosaponin VI exerts significant analgesic effects in mice in a dose-dependent manner. Studies by Gong et al. [34] and Luo et al. [35] identified asperosaponin VI as the primary active component responsible for the analgesic and anti-inflammatory effects of Dipsaci Radix. Its anti-inflammatory mechanism involves inhibiting the IL-6/STAT3 signaling pathway, downregulating DNMT3b expression, and activating the Nrf2 pathway in LPS-stimulated RAW264.7 macrophages, which also modulates macrophage polarization and reduces inflammation.

3.6 Other Pharmacological Effects

Feng et al. [36] found that asperosaponin VI

protects H9c2 rat cardiomyocytes from H2O2-induced oxidative stress and apoptosis by activating the ATF6 pathway. Li et al. [37] reported that a decoction of Dipsaci Radix increases serum immunoglobulin levels and Th1 cytokine levels while decreasing Th2 cytokine levels in mice, suggesting it enhances non-specific immune function. Additionally, Dipsaci Radix has demonstrated anti-aging and hepatoprotective effects [38].

4. Predictive Analysis of Q-Markers for Dipsaci Radix

4.1 Prediction Based on Botanical Phylogenetic Relationships

Dipsaci Radix is derived from a perennial herb of the genus Dipsacus (family Dipsacaceae). This family comprises approximately 12 genera and 300 species, primarily distributed across the Mediterranean, Asia, and southern Africa. In China, the Dipsacaceae family includes 5 genera (Dipsacus, Morina, Scabiosa L., Pterocephalus Adans, and Triplostegia) encompassing 25 species and 5 varieties, mainly found in the northeastern, northern, northwestern, and southwestern regions of China [39].

Plants of the Dipsacus genus are rich in triterpenoid saponins, iridoid glycosides, and alkaloids [40]. Triterpenoid saponins are both the most abundant and the principal active constituents. To date, 22 such saponins have been reported, with asperosaponin VI being the most predominant. Notably, no similar compounds have been reported in the other four genera. Therefore, asperosaponin VI can be identified as a candidate Q-Marker for Dipsaci Radix.

4.2 Prediction Based on Measurability of Chemical Constituents

The measurability of chemical components is a fundamental principle of Q-Marker prediction. The 2020 edition of the Chinese Pharmacopoeia uses the content of asperosaponin VI as a quantitative indicator for the quality control of Dipsaci Radix[1].Yang et al.[41] developed a stable and reliable HPLC method to simultaneously determine the content of seven components in Dipsaci Radix: asperosaponin VI, loganin, loganic acid, sylvestroside I, dipsanoside B, dipsanoside A, and sweroside.Feng Liang[42] employed HPLC to simultaneously determine the content of four components from different producing regions: asperosaponin VI, asperosaponin X, asperosaponin XIII, and α-hederin, demonstrating high sensitivity and accuracy. In summary, asperosaponin VI, loganin, loganic acid, sylvestroside I, dipsanoside B, dipsanoside A, sweroside, asperosaponin X, asperosaponin XIII, and α-hederin are quantifiable and can serve as candidate Q-Markers.

4.3 Prediction Based on Traditional Chinese Medicine Properties

Dipsaci Radix is slightly warm in naturewith bitter and pungent tastes, and acts on the Liver and Kidney meridians. In TCM theory, bitter substances (alkaloids, glycosides, and bitter principles) are considered the pharmacologically active constituents in bitter-tasting herbs [43], and they are primarily associated with the Liver Meridian [44]. Pungent-tasting herbs are believed to have moving and dispersing properties, with terpenes and volatile oils as their main chemical constituents [45]. Therefore, alkaloids, terpenoids, and volatile oil components are primary candidates for the Q-Markers of Dipsaci Radix.

4.4 Prediction Based on Different Processing Methods

Clinically, Dipsaci Radix is often used in larger doses and is commonly administered in the form of raw slices, or processed with salt or wine [46].Guo et al. [47] found that after processing with salt, the contents of asperosaponin VI, loganic acid, and sweroside increased significantly, while the contents of dipsanoside A, dipsanoside B, 5-hydroxymethylfurfural (5-HMF), sylvestroside I, isochlorogenic acids A, B, C, chlorogenic acid, and caffeic acid decreased to varying degrees. Fan et al.[48] reported that compared to the raw herb, both salt- and wine-processed products showed increased levels of asperosaponin VI (with a greater increase in the wine-processed product), while levels of asperosaponin X decreased. Wang et al. [49] observed an increase in ursolic acid content after processing. Consequently, the following are candidate Q-Markers: asperosaponin VI, 5-HMF, dipsanoside B, loganic acid, sweroside, dipsanoside A, sylvestroside I, isochlorogenic acid A, chlorogenic acid, isochlorogenic acid B, isochlorogenic acid C, caffeic acid, asperosaponin X, and ursolic acid.

4.5 Prediction Based on Different Geographical Origins

Dipsaci Radix is mainly produced in Hubei, Sichuan, Yunnan, Chongqing, and Guizhou provinces [50], It is renowned for the distinctive "center of a Prunus mume flower" characteristic of its cross-section and is considered a genuine (Dao-di) medicinal material from Enshi Prefecture, Hubei Province [51]. Feng Liang [42] used HPLC to determine the content of asperosaponins VI, XIII, X, and α-hederin in samples from Sichuan, Hubei, Yunnan, and Guizhou. Comprehensive analysis indicated that the samples from Fuling (Sichuan) and Hefeng (Hubei) were of the highest quality. Li et al. [52] determined the content of hederagenin in samples from five regions (Yunnan, Hubei, Sichuan, Guangxi, and Guizhou) and found significant regional variation, with the content in samples from Hubei and Sichuan being significantly higher than in others. Therefore, asperosaponin VI, asperosaponin XIII, asperosaponin X, α-hederin, and hederagenin can serve as crucial reference markers for the selection of Q-Markers.

5. Conclusions and Future Perspectives

Dipsaci Radix is a widely-used medicinal herb with abundant resources. As summarized in this review, its chemical composition includes triterpenoid saponins, iridoids, volatile oils, alkaloids, lignans, polysaccharides, and organic acids. Its pharmacological effects are extensive, encompassing anti-osteoporosis, neuroprotection, prevention of recurrent spontaneous abortion (RSA), antitumor, anti-inflammatory, analgesic, myocardial protection, immunomodulation, anti-aging, and hepatoprotective activities.

Current research on Dipsaci Radix appears to focus primarily on crude extracts, with relatively limited investigation into its individual components. Future efforts may benefit from chemical modification of its active components and in-depth exploration of the pharmacological activities of different compound classes. In addition, the absorption, distribution, metabolism, and excretion (ADME) of its bioactive components in vivo remain to be characterized, which would provide a solid foundation for understanding its pharmacodynamics and for quality evaluation.

Regarding quality control, a single indicator—such as the current reliance on asperosaponin VI content—may not be sufficient to comprehensively assess the overall quality of Dipsaci Radix. This review therefore systematically summarizes the chemical constituents and pharmacological effects of Dipsaci Radix. Guided by the Q-Marker concept, this study predicts and analyzes potential Q-Markers from multiple dimensions, including botanical phylogeny, chemical measurability, traditional properties, processing methods, and geographical origins. The following 18 compounds are identified as potential Q-Markers: asperosaponin VI, loganin, loganic acid, sylvestroside I, dipsanoside B, dipsanoside A, sweroside, asperosaponin X, asperosaponin XIII, α-hederin, 5-HMF, isochlorogenic acid A, chlorogenic acid, isochlorogenic acid B, isochlorogenic acid C, caffeic acid, ursolic acid, and hederagenin. These compounds provide a theoretical basis for establishing a comprehensive quality evaluation system and lay the groundwork for future research on the mechanisms of action of Dipsaci Radix.

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