

Research Progress on the Identification and Pharmacological Activity of the Active Components of the Rhododendron Species

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<http://dx.doi.org/10.13005/bbra/2939>

(Received: 14 June 2021; accepted: 20 September 2021)

Rhododendron is one of the plants with the broadest spectrum species, the most extended history of traditional medicine use, and the wide range of pharmacological properties. In 2013, a report was published to summarize the studies reported from 1898 to 2012. Many phytochemical compounds and their various treatment effects of over 40 Rhododendron species were mentioned in the present review. This review aims to evaluate the newly discovered and observed phytochemical compounds in recent years and their activities in some Rhododendron species.

Keywords: Compounds; Pharmaceutical Activity; Rhododendron species.

Traditional natural chemicals rely primarily on selection based on ethnic pharmacological or epidemiological knowledge, followed by plant extract screening and activity-induced fractions. The genus of *Rhododendron* has been chosen as a case study because rhododendron extracts are still used in large numbers of ethnic medical applications ¹. *Rhododendron* is found worldwide; at present, there are about 1024 species of this genus (excluding subspecies classification) worldwide, spanning multiple climatic zones from south to north, and mainly distributed in latitudes between 20 ° S and 65 ° N ². Rhododendrons are mainly distributed in Asia, North America, and Europe, especially in the eastern and western

Himalayas ³. Popescu *et al.* ¹ and Cai *et al.* ⁴ published a comprehensive report on *Rhododendron* species, including anti-inflammatory, anti-injury, antimicrobial, and antiprotozoal, antiviral activity, immunomodulatory activity, antioxidant activity, anti-diabetic activity, and cytotoxicity. In addition, Pandita *et al.* ⁵ presented various phytochemical compounds, including the *Rhododendron* plant, which has significant medicinal value. *Rhododendron micranthum* tastes bitter. It has the effect of ventilating, regulating pain, and coughing of sputum. For example, the branches are drugged for chronic tracheitis, rheumatism, lumbar pain, menorrhoea, postpartum joint pain ⁶. The dry leaves of *Rhododendron dauricum* are scented

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with hardness, hardness, and cold with cough and sputum, and are often used to treat acute, chronic bronchitis, asthma, and other conditions ⁷. This review aims to comprehensively discuss the newly discovered and observed effects of compounds and drugs in *Rhododendron* species after 2013 and the further development prospects for producing potent and effective drugs.

Individual *Rhododendron* Species

Rhododendron aganniphum

Polysaccharides have various biological activities such as antioxidants, immunomodulators, antipruritic agents, hypoglycemic properties, skin penetration enhancers, and thickener properties. Because of these ideal characteristics, they have been used in many industrial fields. However, to extract polysaccharides involved in plants, some problems are due to hydrolysis, ionization, or oxidation due to heating or longer extraction time. Moreover, it leads to a reduction in the added value of polysaccharides. Guo *et al.* ⁸ used Ultrasonic Assisted Extraction (UAE), cheap, environmentally friendly, less time-consuming, effective, and efficient. The optimization method they used was a Box-Behnken design (BBD)-like optimization procedure, which in turn investigated the antioxidant and rheological properties of polysaccharides. 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, hydroxyl radical scavenging activity, and superoxide free radical scavenging activity were used to analyze polysaccharides, and stable shear behavior and frequency scanning measurement were used to obtain a rheological characterization of polysaccharides. The optimized ultrasonic-assisted polysaccharide extraction method is extraction temperature 25°C, liquid-solid ratio 25:1, extraction time 2.2 h, ultrasonic treatment power 20W. The experimental yield of polysaccharides was 9.428%. In comparison, the traditional method based on in vitro antioxidant activity: The free radical scavenging activity of DPPH was about four times higher than the control, similar to the vitamin E (VE) at a concentration of 0.2 mg/ml. Under the concentration of 0.2 mg/ml, ultrasonic extraction, traditional hot water extraction, and VE scavenging rates were 84.139%, 52.671%, and 94.176%, respectively. The EC₅₀ and VE were 0.041, 0.194 and 0.02 mg/ml, respectively.

The hydroxyl radical scavenging activities are as follows: when the concentration is 0.2 mg/ml, methods 1, 2, and ascorbic acid (Vc) are 39.773%, 16.581%, and 61.283%, respectively. The EC₅₀ values and Vc were 0.529, 0.783 and 0.092 mg/ml, respectively. The superoxide radical scavenging activities are 84.871%, 80.296%, and 96.033%, respectively. The measurement results show that the ultrasonic-assisted extraction method affects the apparent viscosity and dynamic viscoelasticity.

Rhododendron album Blume

Rhododendron album Blume (R.A.) is mainly distributed in smaller and smaller high-altitude forests in West Java and Central Java, Indonesia. By Park *et al.* ⁹ and Park *et al.* ¹⁰, it was found that the methanol extract of R.A. showed anti-inflammatory activity, especially R. A. statistically inhibited the iNOS and COX-2 expression in lipopolysaccharide (LPS)-stimulated RAW267 cells. They proved that R.A. is a natural and powerful anti-inflammatory compound that can block the activation of NF- κ B and mitogen-activated protein kinase (MAPKs) pathways induced by LPS. The molecular mechanism is that the methanol extract of R.A. inhibits LPS-induced NF- κ B activation in RAW 264.7 macrophages by inhibiting the phosphorylation of NF- κ B and its subsequent inhibition of NF- κ B nuclear transfer. The methanol extract of R.A. significantly inhibited the phosphorylation of p38, extracellular signal-regulated kinase (ERK) 1/2, and c-Jun N-terminal kinase (JNK) in RAW 264.7 cells stimulated by LPS.

Rhododendron alutaceum

Rhododendron alutaceum only grows in the alpine forests of southwest China. According to Li *et al.* ¹¹, it is used in traditional Chinese medicine for relieving cough and resolving phlegm. In this regard, Li *et al.* ¹¹ tried to find compounds with pharmacological activity from the leaves of this *Rhododendron alutaceum*. Extraction was performed by using a 75% Me₂CO/H₂O solution and at room temperature. In addition, the filtrate was concentrated in a vacuum oven, and the resulting residue was extracted with petroleum ether and ethyl acetate, respectively. In this study, a new phenolic glycoside, 3'-keto rhododendrin (Fig. 1. 1), and a new sesquignan, alutaceuol (Fig. 1. 2), together with twelve known phenolic compounds like rhododendrin.

Rhododendron ambiguum

Rhododendron ambiguum and *Rhododendron cinnabarinum* belong to the subsection *Triflora* and *Cinnabaria*, respectively. Shrestha *et al.*¹² studied the polyphenolic properties of these two plants of different ages and used 80% methanol solution to extract polyphenol. They identified 59 polyphenol compounds from two *Rhododendron* species. However, 46 of these compounds have been established in these plants. It was found that there was no significant difference in polyphenols in different years, but the variety and concentration of these compounds were the highest.

Furthermore, they used the radius of the inhibition zone to measure the inhibitory activity of these compounds against Gram-positive bacteria. This measurement found that the compounds

in flowers have lower biological activity than leaves and fruits. The main biologically active compounds are as follows: Methyl gallate hexoside, Salicylic acid- *O* -hexoside, 4- *O* -Caffeoylquinic acid, Myricetin- *O* -rhamnoside, Myricetin- *O* -pentoxide, Quercetin- *O* -Pentoxide, Quercetin- *O* -rhamnoside, (Epi)gallocatechin-(epi) Gallocatechin, Procyanidin Trimer C, (Epi) Gallocatechin-(epi)catechin and (Epi)catechin- *O* -D-glucopyranoside.

Rhododendron anthopogonoides Maxim

Rhododendron anthopogonoides Maxim grows on high-altitude mountain slopes, especially in Tibet, China. It has been used as traditional medicine. Its therapeutic effects include clearing heat and warming the body, clearing heat and detoxification, relieving cough and phlegm, relieving swelling and pain, relieving phlegm

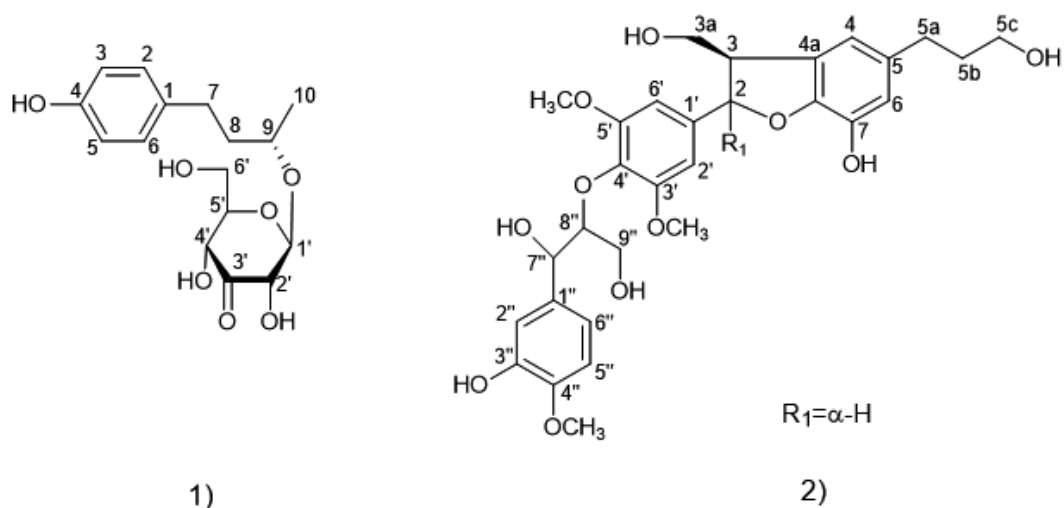


Fig. 1. Chemical structures extracted from *Rhododendron alutaceum*

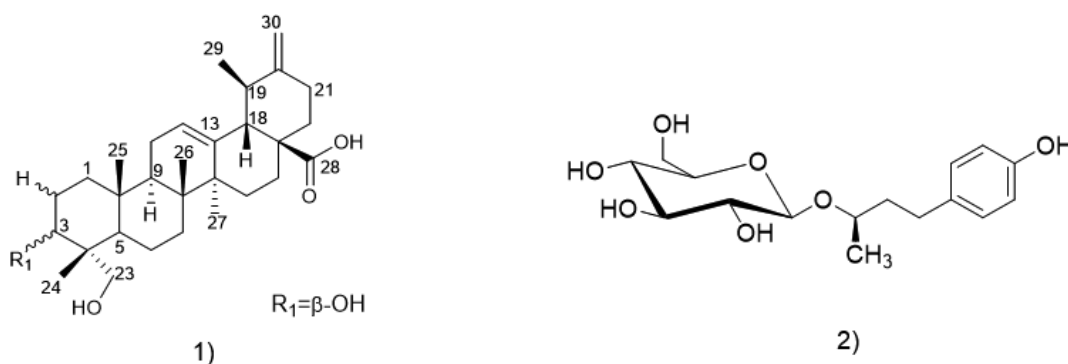


Fig. 2. Chemical structures extracted from *Rhododendron brachycarpum*

and relieving spasm, relieving inflammation, and relieving pain¹³. The correlation was also analyzed between the phenolic and flavonoid contents of the extracts and their antioxidant properties. *In vitro* antioxidant study¹⁴, the effect of the crude extract and solvent fractions on total antioxidant activity, reducing power, DPPH radical scavenging, 2,2'-azino-bis-(3-ethyl benzothiazoline-6-sulfonic acid) disodium salt (ABTS) radical scavenging, superoxide radical scavenging, hydroxyl radical scavenging, and nitric oxide radical scavenging was examined. In addition, Jing *et al.*¹⁴ studied how the extract affects the hypoxia-induced damage in PC12 cells through cell viability, lactate dehydrogenase release, malondialdehyde production, and antioxidant enzyme activity. According to the results of this study, among the extracts of hexane, ethyl acetate, n-butanol, and water, the highest yield was found in the ethyl acetate part, while the n-hexane part showed the lowest yield. In addition, the number of phenols and flavonoids in the above solvent extracts was found to be the highest in n-butanol and ethyl acetate. The hydroxyl scavenging activities of the above solvent extracts were n-butanol, crude extract, water, ethyl acetate, and hexane in turn. When the EC₅₀ of ascorbic acid was 50.73 ± 1.83 µg/ml, the EC₅₀ values were 145.87 ± 0.83 µg/ml, 204.65 ± 4.26 µg/ml, 232.95 ± 2.87 µg/ml, 240.39 ± 2.50 µg/ml, and 468.93 ± 16.17 µg/ml, respectively. Various solvent extracts' DPPH free radical scavenging activities are n-butanol, ethyl acetate, crude extract, hexane, and water. When the EC₅₀ of the ascorbic

acid control was 30.39 ± 0.23 µg/ml, the EC₅₀ values were 53.11 ± 0.12 µg/ml, 61.78 ± 0.11 µg/ml, 63.73 ± 0.95 µg/ml, 259.65 ± 13.04 µg/ml, and 273.35 ± 1.4 µg/ml, respectively. When the EC₅₀ value of ascorbic acid was 18.53 ± 10.13 mm/ml, these extracts' ABTS radical scavenging activity from various solvents decreased in the following order: ethyl acetate, n-butanol, crude extract, hexane, water. The different solvent extracts showed superoxide radical scavenging activity in n-butanol, ethyl acetate, crude extract, n-hexane, and water. When the EC₅₀ value of ascorbic acid is 450.32 ± 6.28 µg/ml, the EC₅₀ value is 270.67 ± 0.58 µg/ml, 433.33 ± 7.68 µg/ml, 483.00 ± 2.65 µg/ml, >1,000 µg/ml and >1,000 µg/ml. Various solvent extracts showed nitric oxide radical scavenging activity, followed by n-butanol, ethyl acetate, crude extracts, hexane, and water. When the EC₅₀ value of ascorbic acid is 126.72 ± 7.24 µg/ml, the EC₅₀ value is respectively 151.34 ± 3.67 µg/ml, 183.83 ± 2.34 µg/ml, 197.38 ± 4.25 µg/ml, >1,000 µg/ml and >1,000 µg/ml.

Rhododendron arboreum

Rhododendron arboreum is growing in the Seram Valley in the Hazara branch of Jammu and Kashmir, Pakistan, and it has a variety of pharmacological effects, such as spasmolysis and convergence diuresis, and sialagogic¹⁵. In order to study related compounds with the above effects, Nisar *et al.*¹⁶ first obtained methanol extracts of *Rhododendron arboreum* bark and then conducted activity-guided fractionation of n-hexane, n-butanol, and chloroform. The

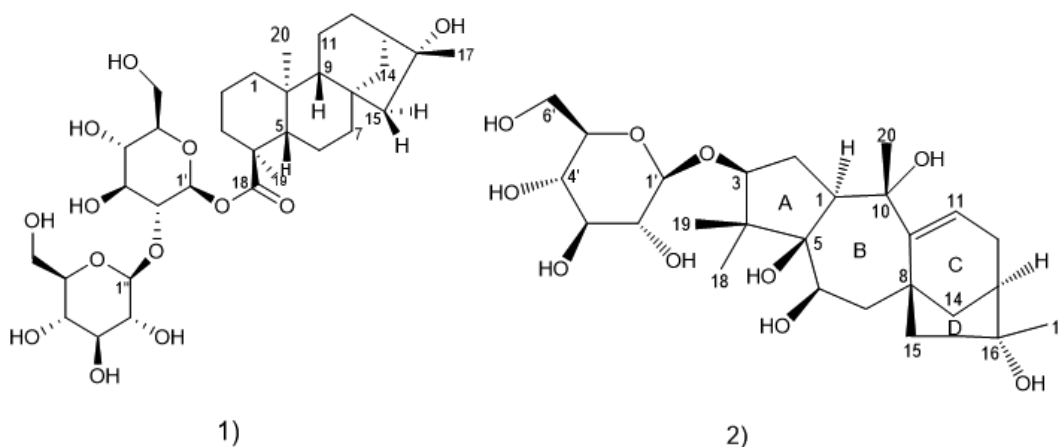


Fig. 3. Chemical structures extracted from *Rhododendron brachycarpum*

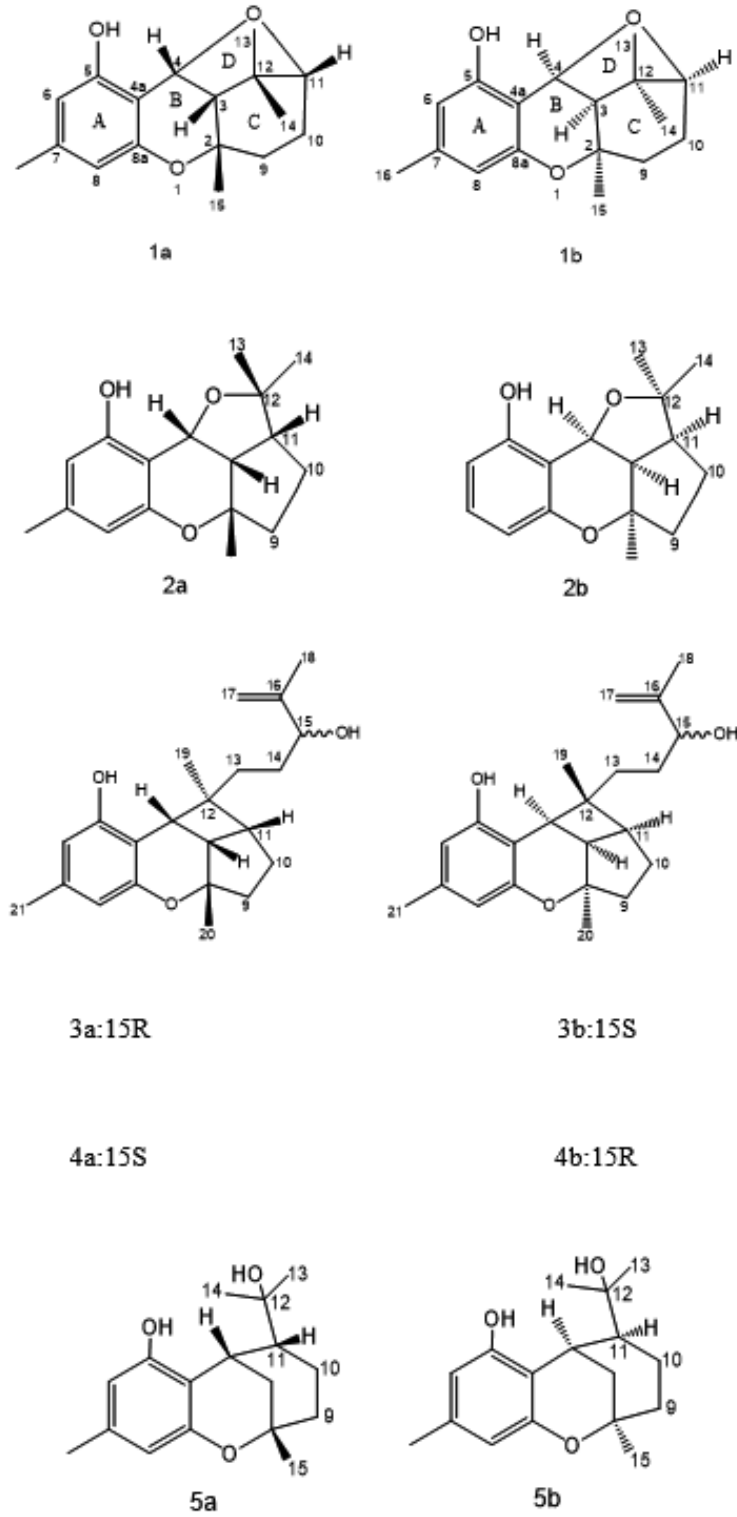


Fig. 4. Chemical structures extracted from *Rhododendron capitatum* Maxim.

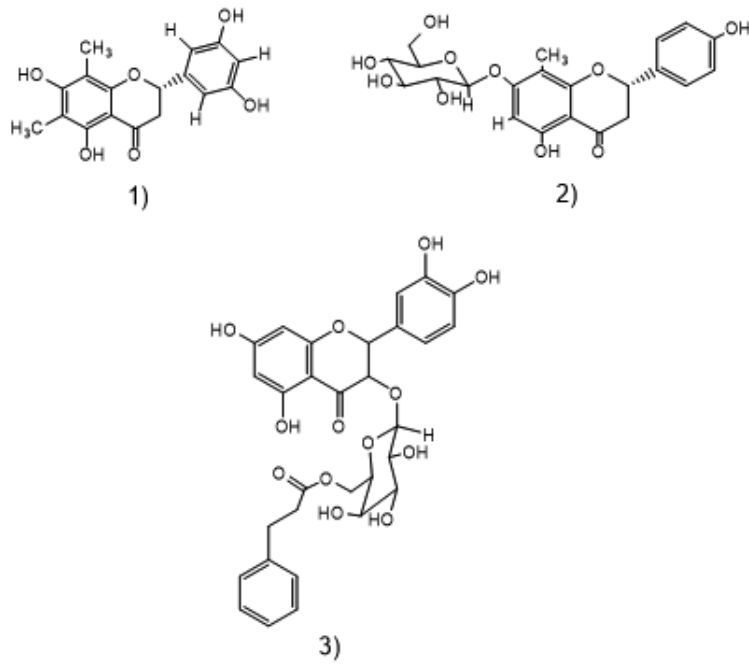


Fig. 5. Chemical structures extracted from *Rhododendron dauricum* L.

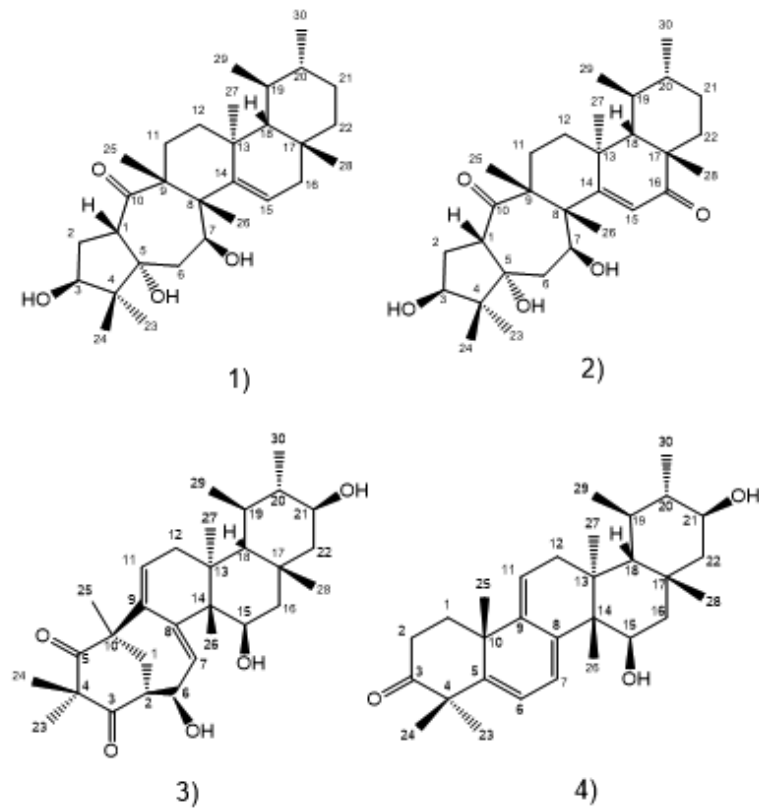


Fig. 6. Chemical structures extracted from *Rhododendron latoucheae*

identified compounds were ursolic acid, -sitosterol, pineal, dandelion, betulinol, acetic acid-induced torsion, carrageenan-induced mouse foot edema, and the possibility of anti-inflammatory drugs in

Rhododendron was investigated. The lipoxygenase activity associated with inhibiting the above two models was also measured. The results are as follows: The ethyl acetate fraction (200 mg/kg i.p.)

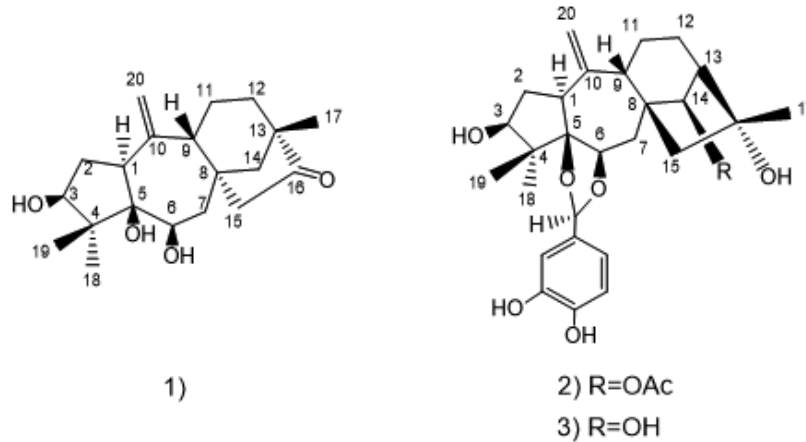


Fig. 7. Chemical structures extracted from *Rhododendron micranthum*

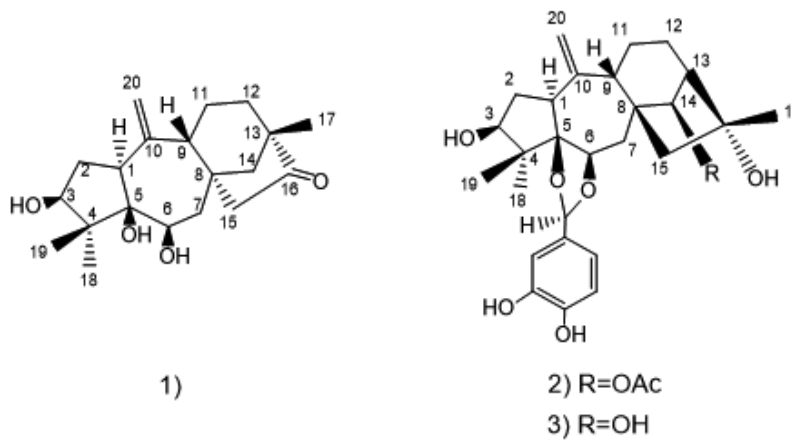


Fig. 8. Chemical structures extracted from *Rhododendron molle*

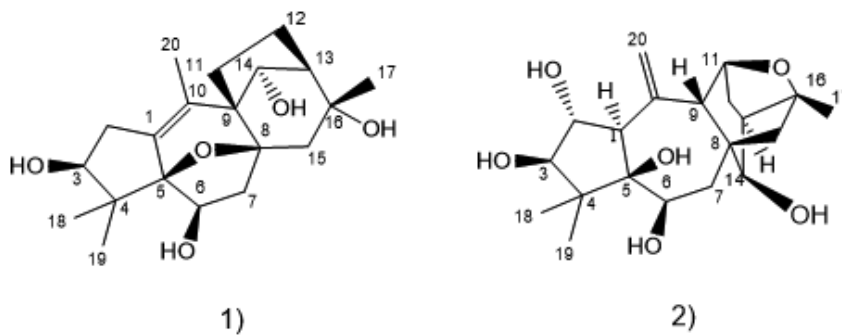


Fig. 9. Chemical structures extracted from the root of *Rhododendron molle*

indicated the maximum analgesic effect (82%) on acetic acid-induced writhing, followed by the crude extract and chloroform fractions, both at a dose of 200 mg/kg i.p. In addition, the n-butanol and water-containing fractions showed a reduction in pain irritation (33.77% and 48.88%, respectively),

while the n-hexane fraction (200 mg/kg i.p.) showed any analgesic effect. The lipoxygenase inhibitory activity of the crude methanol extract *in vitro* and solvent extract of *Rhododendron* are: while the standard value is $98.78 \pm 0.35\%$, the inhibitory rates of crude extract, n-hexane, chloroform, ethyl

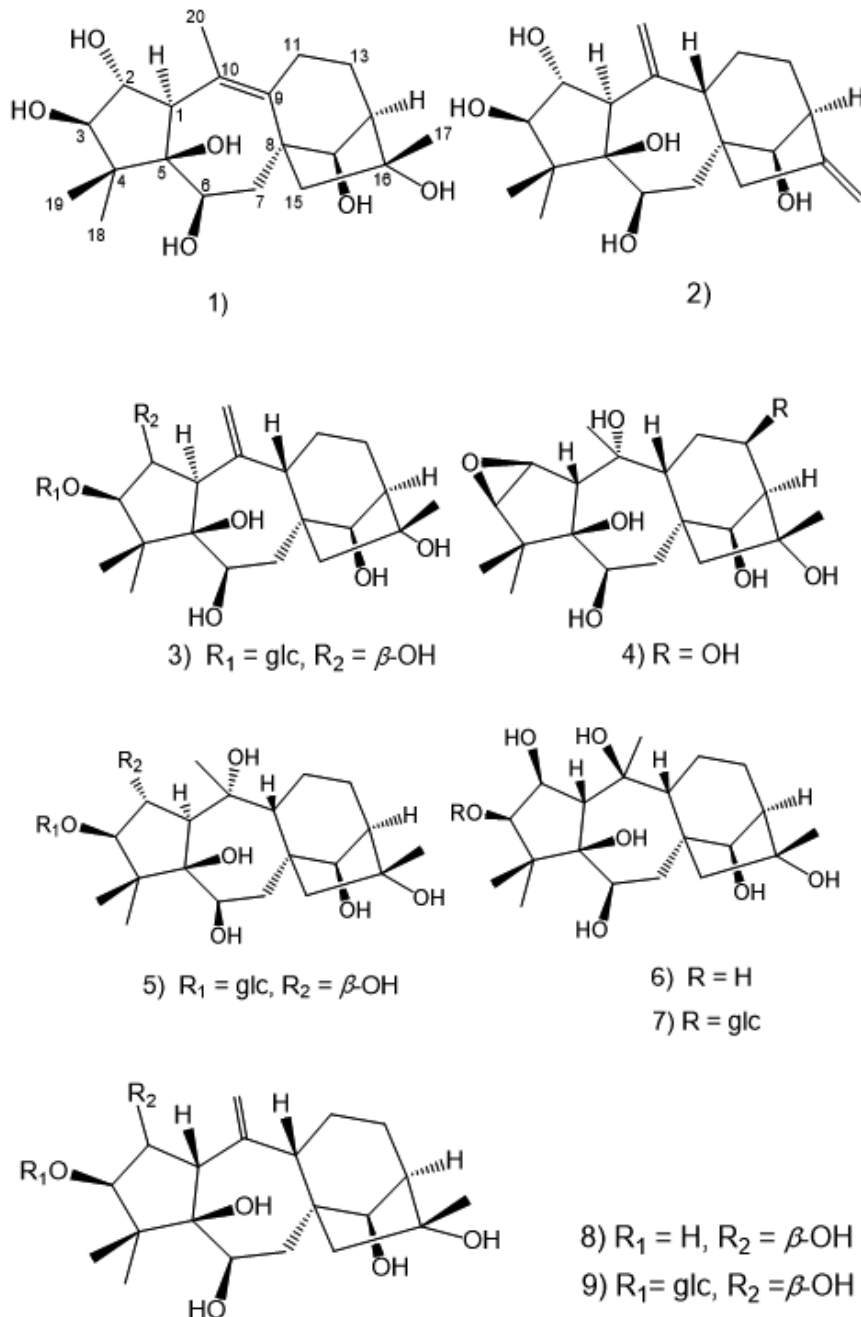


Fig. 10. Chemical structures extracted from the fruits of *Rhododendron molle*

acetate, butanol, and water are $50.44 \pm 0.92\%$, $8.23 \pm 0.30\%$, $68.47 \pm 1.45\%$, $90.58 \pm 1.02\%$, $22.11 \pm 0.85\%$, and $48.35 \pm 1.22\%$, respectively. In addition, the various results of the extracts as mentioned earlier/fractions on carrageenan-induced paw edema in mice are as follows: each sample shows a dose-dependent manner (1-5 hours) for all time courses (1-5 hour) anti-inflammatory activity 200 mg/kgi.p.), except for n-butanol.

Ali *et al.*¹⁷ studied the effects of plant compounds in *Rhododendron arboreum* bark on renal cell carcinoma (A498), non-small cell lung cancer (NCl-H226), squamous cell carcinoma (H157), and human ovarian cancer (MDR). -2780AD). For MDR2780AD, HepG2, H157, and NCl-H226, the isolated compound 15-tallow acid showed potential anticancer activity with IC₅₀ values of $2.3 \pm 0.1\mu\text{M}$, $4.9 \pm 0.2\mu\text{M}$, $9.2 \pm 0.2\mu\text{M}$, and $10.3 \pm 0.1\mu\text{M}$, respectively. The value of A498 is $32.8 \pm 1.2\mu\text{M}$.

***Rhododendron brachycarpum* G. Don**

Rhododendron brachycarpum G. Don mainly grows in the central and northern regions of PRK, the Kuril Islands, and Japan's northern and central regions. These days, due to radical climate changes, the number of short-fruited *Rhododendrons* continues to decrease, so it is considered a rare endangered species¹⁸. This plant, especially the leaves, has been used to treat diabetes (D.M.), high blood pressure, headaches, and rheumatoid arthritis. In addition, phytochemical compounds in these treatments have been studied, such as flavonoids, diterpenoids (grey toxin I), and triterpenoids. Choi *et al.*¹⁹ purified seven potential PTP1B inhibitors and a new triterpene compound (Fig. 2.1) and determined the potential inhibitory effects of these compounds on PTP1B. According to the results of the present study, the isolated compounds of neo triterpene and haptenic acid A (Fig. 2.1) showed significant inhibitory effects with IC₅₀ values of $3.1 \pm 0.3\mu\text{M}$ and $6.3 \pm 0.6\mu\text{M}$, respectively, compared with $4.0 \pm 0.3\mu\text{M}$ using RK-682 as a positive control. Jeon *et al.*²⁰ isolated a new phytochemical component (Fig. 2.2) from the *Rhododendron* leaves and determined that its chemical structure contains phenylpropanol and glucopyranoside. In addition, they investigated the effect of this *Rhododendron* against inflammation. They proved that it has intracellular ROS (reactive oxygen species) scavenging activity and inhibits

nuclear factor- κ B (NF- κ B) nuclear transcription. The mechanism is as follows: the process is through Inhibit the phosphorylation of NF- κ B, inhibit NF- κ B (I κ B α) and I κ B α kinase (IKK α).

According to their results, *Rhododendron* reduced the expression of pro-inflammatory mediators in TNF α /TFN- α -stimulated keratinocytes, involving cyclooxygenase-2, intracellular adhesion molecule-1, interleukin ligand 1, and Chemokine (CC motif) ligand 17. In addition, they observed that *Rhododendron* has a promising candidate molecule for the treatment of inflammatory skin diseases such as psoriasis.

Zhou *et al.*²¹ discovered 22 compounds in *Rhododendron azalea* for the first time, such as highly oxidized diterpenoids. They emphasized that the compounds contained in the plant have good resources due to their remarkable homogeneity in chemical molecules. They isolated a new compound, *rhododendron* A (Fig. 3.1), from *Rhododendron breviflora* and determined its structure (3S, 5S, 6R)-1,1,5,9-tetramethyl-3- β -D-pyridine Glucopyranoxy-2,3,4,5-tetrahydro-7H-chromene-6-ol. This study demonstrated that compounds with megaglycosides, including *Rhododendron* A migrate HMGB1-induced pro-inflammatory vascular stimulation, ultimately alleviate the lethality of sepsis.

Tuan *et al.*²² isolated the derivative (Fig. 3.2) of *Candida griseo-9(11)-ene* and five known *Grifola frondosa* toxins (Grinidae B, rhodomoside A, piersformoside, grayanotoxin III, and grayanotoxin I) for the first time. Topical treatment of *Rhododendron* isolated from *Rhododendron* shows potential skin inflammation. According to their results, the reasons are as follows: first, *rhododendron* treatment reduces the signs and symptoms of imiquimod-induced psoriasis-like skin inflammation. In addition, *Rhododendron* reduces the levels of IMQ-induced TLR-7 downstream targets and MAP kinase signaling in normal human epidermal keratinocytes. Finally, *Rhododendron* may inhibit IMQ-induced interaction between IRAK1 and TRAF6 in cultured primary keratinocytes and retain the expression of dimple-1 in IMQ-treated keratinocytes. Liquid chromatography-quadrupole time Mass spectrometry (LC-QTOF-MS) combined with liquid chromatography-tandem mass spectrometry (LC-MS/MS) to

identify grayanotoxins from *rhododendrons*. The grayanotoxins I and grayanotoxins III in dietary supplements and homemade wine.

***Rhododendron capitatum* Maxim**

Rhododendron capitatum is a small

deciduous shrub in China's rich resources. Liao *et al.*²³ separated two enantiomeric carotenoids, (-)- and (+)-carotenoids A (Fig. 4. 1a and 2a) and B (Fig. 4. 2a and ab). They identified these compounds by using spectral data, X-ray crystallography, and

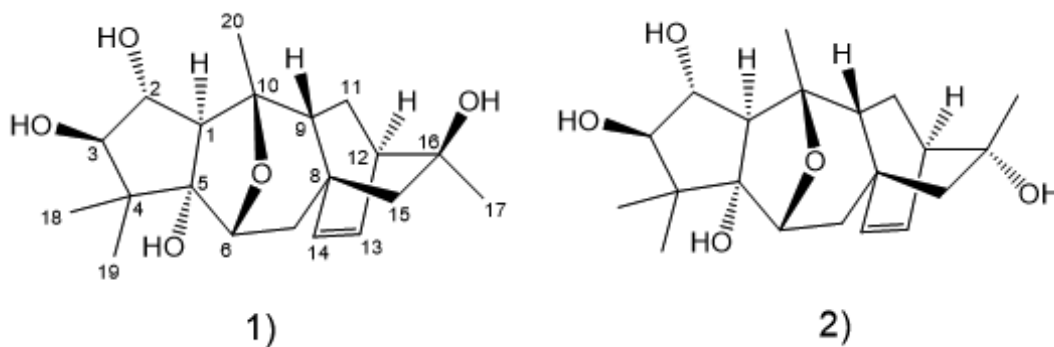


Fig. 11. Chemical structures extracted from the leaves of *Rhododendron mole*

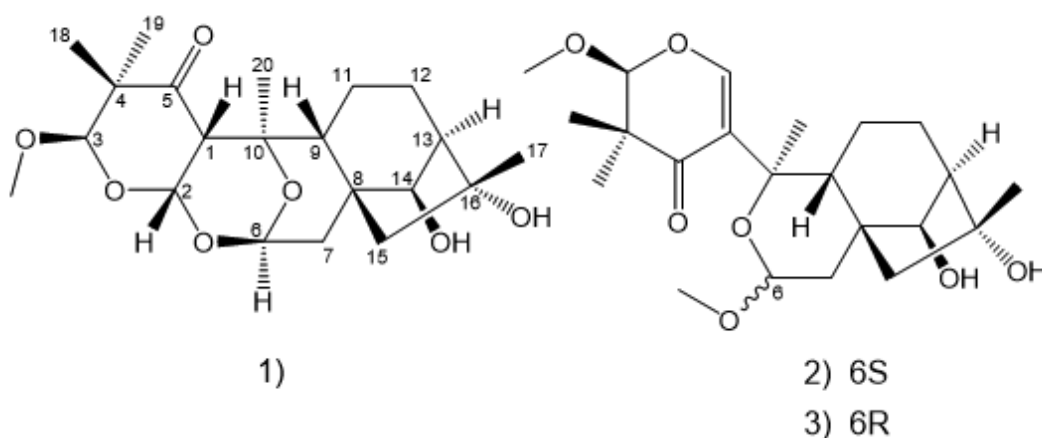


Fig. 12. Chemical structures extracted from the leaves of *Rhododendron mole*

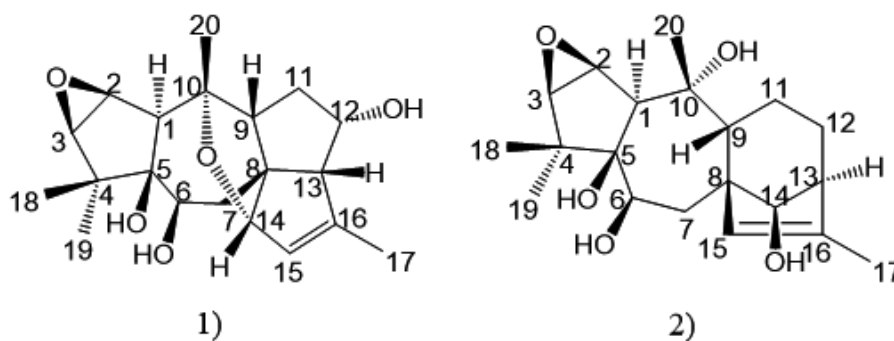


Fig. 13. Chemical structures extracted from the leaves of *Rhododendron mole*

electronic circular dichroism systems. Carotenoid A (Fig. 4. 1a and 1b) has a unique 6/6/6/4 ring. In addition, determine whether these compounds (Fig. 4. 1a, 1b, 2a, and 2b) also inhibit PTP1B. According to their research results, compounds 2a and 2b showed inhibitory effects, and the IC_{50} values were $43.56 \pm 8.53 \mu M$ and $30.38 \pm 13.41 \mu M$, respectively, when oleanolic acid (a potent natural PTP1B inhibitor) was used in the assay. The positive control is $2.46 \pm 0.18 \mu M$. They also isolated five new enantiomers (+)-/(-)-carotenoids C (Fig. 4. 1a and 1b), E (Fig. 4. 3a and 3b), F (Fig. 4. 4a and 4b), (-)-/ (+)-carotenoids D (Fig. 4. 2a and 2b) and G (Fig. 4. 5a and 5b). Therefore, 1a and 1b are the first pair of mero monoterpenes containing an unprecedented 6/6/6/5 ring system among these compounds. 1a has antiviral activity against herpes simplex virus type 1 (HSV1) in vitro, with an IC_{50} value of $80.6 \pm 4.7 \mu M$. However, none of these compounds 1a to 5a showed an inhibitory effect on PTP1B.

Rhododendron colletianum

Said *et al.*²⁴ used a 90% methanol aqueous solution to extract the crude leaf extract. Using liquid chromatography-electrospray ionization-time-of-flight mass spectrometry (LC-ESI-micro TOF-MS) and NMR, cannabis dichromatic tannin was characterized. They determined the antimicrobial effect of the compound against Gram-positive (*Staphylococcus epidermidis*, *Micrococcus leuteus*, *Bacillus aquimarius*, *Bacillus subtilis*, *Bacillus thiopterus*, *Bacillus thuringiensis*, *Rhodococcus corynebacterioides*, and *Clavibacter michiganensis*) and Gram-negative bacterium, and

Escherichia coli strains DH5 α and TG1. Compared with the other thirteen *Rhododendron* species, the crude extract of *Rhododendron* showed the most potent inhibitory effect. Therefore, they studied the effect of the diploid isochromic acid of *Rhododendron* on the inhibition of the above bacteria. According to their measurement, cannabis chromogenic acid shows a substantial inhibitory value for all Gram-positive bacteria, and the MIC (Minimum Inhibitory Concentration) value is in the range of 0.9 to 15.6 mm/ml. MIC is for Gram-negative bacterium *Escherichia coli* (TG1) reaches 1,000 $\mu g/ml$.

Rhododendron dauricum L.

Studies have found that farrerol, a known flavonoid compound isolated from *Rhododendron dauricum* L., can inhibit the apoptosis of cancer cells²⁵. This experiment studied the cytotoxic and apoptosis effects of farrerol on human gastric cancer SGC-7901 cells through a mitochondrial-mediated pathway. According to MTT analysis and Annexin-V FTTC/PI double staining method, farrerol's IC_{50} value for SGC-7901 cells is 40.4 $\mu mol/l$ for 24 h.

Lou *et al.*²⁶ discovered two new C-methyl flavanones, 5, 7, 3', 5' -tetrahydroxy-6, 8-di-C-methyl flavanone, and 5, 4'-dihydroxy-8-C-methylflavanone-7-O- β -D-glucopyranoside and one new flavonoid glycoside, quercetin-3-O- β -D-(6-O-cinnamoyl)-galactoside. (See Fig. 5.) Therefore, seven known compounds were isolated, syzalterin, poriolin, farrerol-7-O- β -D-glucopyranoside, myrciacetin, quercetin-3-O- β -D-(6-p-hydroxy-benzoyl)-galactoside, quercetin-

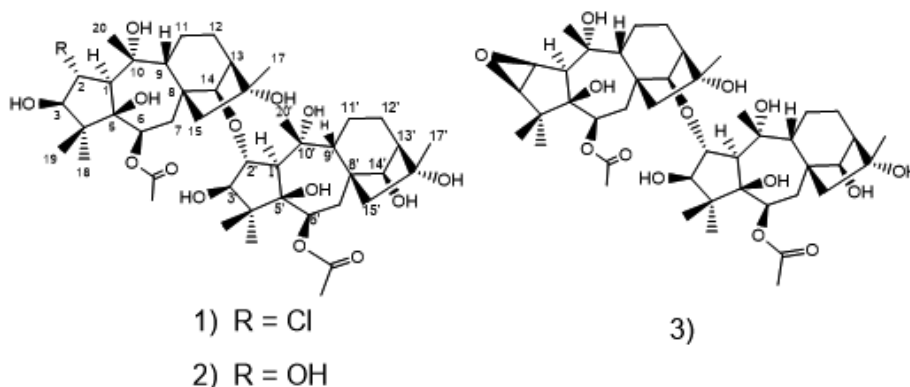


Fig. 14. Chemical structures extracted from the leaves of *Rhododendron mole*

3-O-2-D-(6-p-coumaroyl)-galactoside, and 5, 7, 3', 5'-tetrahydroxyl flavanones.

Using high-performance liquid chromatography and quadrupole time of flight tandem mass spectrometry, Wang *et al.*⁷ identified

24 types of flavonoids, six types of phenolic acids, two coumarins, and 1 type of terpene.

From their perspective, among these compounds, poriolin, farrerol-7-O- β -D-(6-p-hydroxy benzoyl)-galactoside, quercetin-3-O- β -D-(6-p-coumaroyl)-

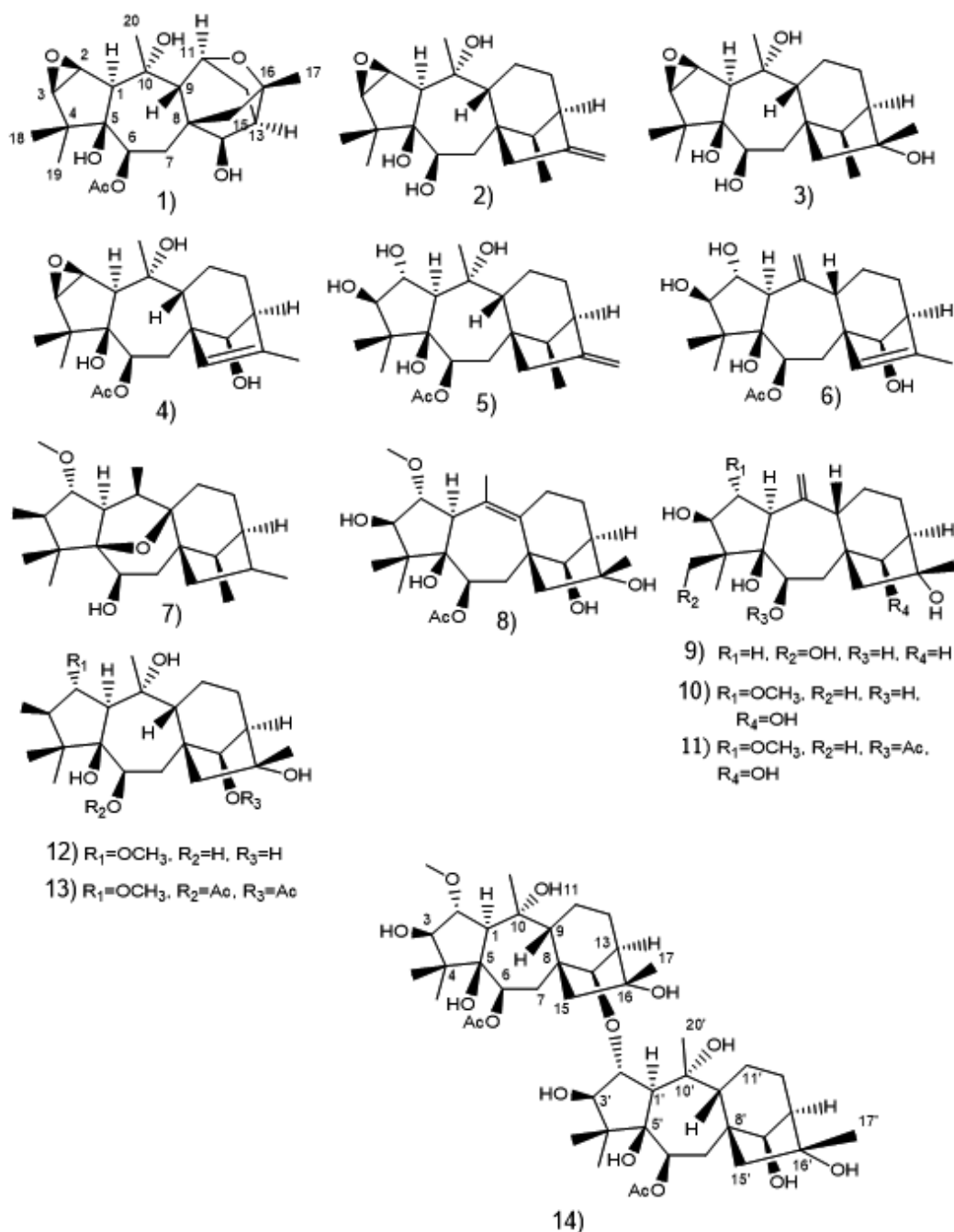


Fig. 15. Chemical structures extracted from the fruits of *Rhododendron mole*

galactoside and myriciacetin were identified for the first time from this genus, respectively. In addition to these compounds, seven biologically active ingredients were also identified, gallic acid, scopoletin, dihydroquercetin, quercetin, kaempferol, 8 desmethyl farrerol, and farrerol. Daurichromenic acid (DSA) is isolated from the leaves of *Rhododendron dauricum* and has anti-HIV solid activity. However, the designation of this plant as a protected species makes this compound unrestricted to find new resource applications for drugs. For this reason, 20 heterologous expressions from *Stachybotrys bisbyi* and grifolic acid synthase and daurichromenic acid synthase from *Rhododendron dauricum* in *Aspergillus oryzae* through enantioselective 6-endo-tricyclization-mediated three-step combinatorial biosynthesis (+)-lauric acid. Moreover, it introduces a halogenase derived from *Fusarium*. Enter the DCA production strain and complete the synthesis of new (+)-5-chloromeroterpenoids. In addition, it was studied that two chlorinated derivatives showed significant antibacterial activity compared to non-chlorinated compounds. There are several studies on this daurichromenic acid.²⁷⁻²⁹

Rhododendron ferrugineum

Rhododendron ferrugineum, a subalpine shrub, is known to be found throughout the Pyrenees and European Alps. Various phytochemical compounds have also been identified in the leaves of this species: triterpenoids, furans A to C, short-chain organic acids, volatile oils, flavonoids, flavan-3-ols, oligomeric proanthocyanidins, cinnamin B1, Original green acid, monosaccharide, oligosaccharide, fructan, arbutin. However, there are no reports of toxic diterpenoid maleimide derivatives. They first discovered the GT-1 quantitative detection method to determine the puerarin methylmercury compounds using Gas chromatography-mass spectrometry (GC-MS) to determine the *rhododendron* gray mold virus³⁰. *Porphyromonas gingivalis* is known to cause periodontitis and systemic chronic diseases, such as rheumatoid arthritis, cardiovascular disease, diabetes, and different oral tumors. Lohr *et al.*³¹ investigated the effects of azalea water extract and water-soluble raw polysaccharides on the adhesion, virulence, and biofilm formation of *Porphyromonas gingivalis*. According to their research results, this aqueous extract involves 2R, 3R-taxifolin-3-O- β -L-

arabinopyranoside, hyperoside, isoquercitrin, and chlorogenic acid, respectively. They are 12.1%, 1.6%, 0.9% and 1.6%. In addition, the tannin content value is 8.7% (w/w), and the tannin is mainly oligomeric proanthocyanidins. Moreover, in this study, the following ideal mechanism was observed: the original polysaccharides from the alpine rose *Rhododendron* and interact in a dose-dependent manner (each 1 mg/ml drop by up to 25%) and the adhesion of *Porphyromonas gingivalis* Attached by affecting Arg, this plant inhibits the gene expression of arginine-specific gingipainrgp A and IL-1 β , IL-6, IL-8 and TNF α in KB cells.

***Rhododendron formosanum* Hemsl.**

This plant is an endemic species distributed in the mountains of central Taiwan. It is previously known to have various biological activities, such as antimicrobial activity, anti-proliferation, enzyme inhibition, free radical scavenging properties, separate hydrophobic compounds, and two isomeric epoxy sterols. A study using 2D-NMR, CD spectrum, and MS separation and identification of 5 kinds of proanthocyanidins in *Rhododendron* leaf extract studied the biological effects of these compounds. According to their research results, all five compounds showed potential antioxidant activity, and when the MIC value was 4 μ g/ml, the new compound 3 showed intense antibacterial activity against *Staphylococcus aureus*. Other studies³² have found that type A proanthocyanidin trimer ursolic acid extracted from *rhododendron* leaves has potential antitumor activity, especially the cytoprotective function of cinnatanninD1 treated non-small cell lung cancer (NSCLC) cell autophagy. In addition, they observed that the compound inhibits the Akt/mammalian target of the rapamycin (mTOR) pathway and activates the extracellular signal-regulated kinase 1/2 pathway, leading to the induction of autophagy.

Rhododendron groenlandicum

Rhododendron groenlandicum is known as Labrador tea, and it is also one of the most promising anti-diabetic plants traditionally used by James Bay Cree in the east. This plant extract has shown significant effects in restoring the mechanism of glucose homeostasis in high-fat diet (HFD) mice. Li *et al.*³³ studied the ability of this plant extract to significantly increase blood sugar, insulinemia, and glucose tolerance in vivo,

and the test was used in HFD-induced obesity, immunohistochemistry (IHC), and biochemical parameters were used to evaluate the renal protective potential of *Rhododendron* treatment for another eight weeks. After all, this plant extract

reduced renal steatosis by about half, while the expression of Bcl-2 modifiers decreased from 13.96 AU to 9.43 AU. Ouchfoun *et al.*³⁴ conducted a similar investigation on *Rhododendron*. It was emphasized that Labrador tea showed promising

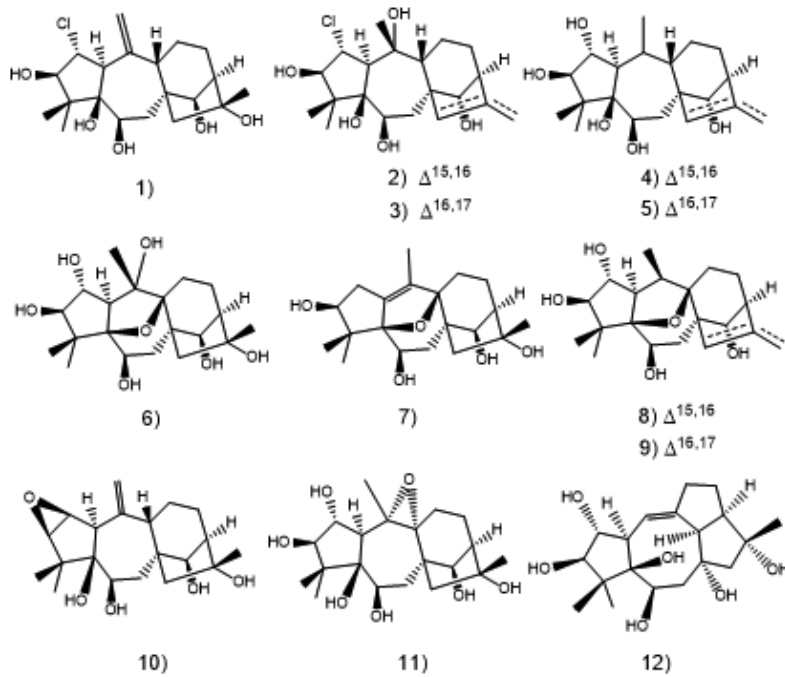


Fig. 16. Chemical structures extracted from the *Rhododendron pumilum* Hook. f.

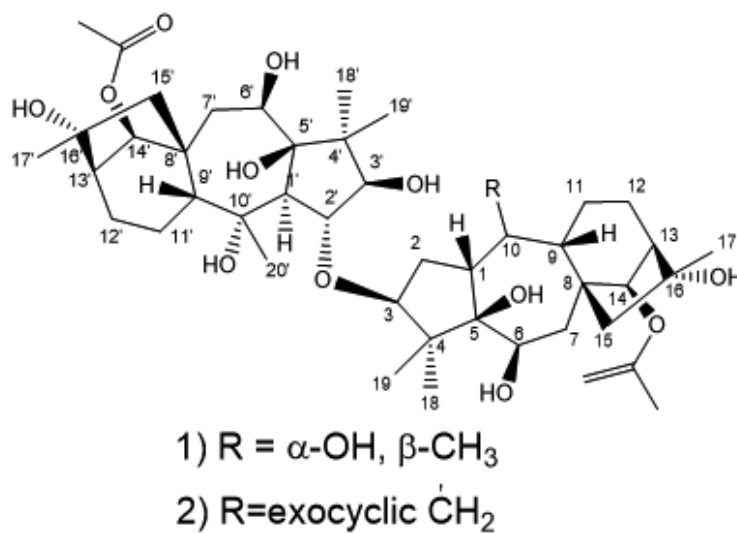


Fig. 17. Chemical structures extracted from the *Rhododendron seniavinii* Maxim.

anti-diabetic effects through research results to improve insulin sensitivity.

Rhododendron hainanense

Studies³⁵ have shown that the compound isolated from the aerial part of *Rhododendron* has good pharmacological activity on human leukemia cells (HL-60) and human liver cancer cells (SMMC-7721), and the preliminary structure-effect of the sulforhodamine B method relationship. According to these results, the compound isolated and identified here shows the solid inhibitory activity as 2,3 dihydro-5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-6,8-di Methyl-4H-benzopyran-4-one and 5-hydroxy-7,4'-dimethoxy-6,8-dimethylflavan have IC₅₀ values of 15.2 μ M and 13.2 μ M, respectively. To HL-60.

Rhododendron japonicum

Koda *et al.*³⁶ investigated a 61-year-old man who developed dizziness, severe nausea, and abdominal discomfort after taking 50 grams of azalea. In addition, there is significant hypotension and sinus bradycardia. The results show that this symptom is caused by the toxicity of some azalea species, namely the action of grayanotoxin.

Rhododendron latoucheae

The plant is distributed in mainland China's southern and southwestern parts and has historically been used for expectorating, relieving cough, promoting blood circulation, and removing stasis.

Liu *et al.*³⁷ identified four red terpenoids (Fig. 6) by high-performance liquid chromatography-mass spectrometry-solid phase extraction-nuclear magnetic resonance separation, among which 3 are newly rearranged triterpenoids (A, B, and C) and *rhododendron* Red steroid D resonance (HPLC-SPE-NMR) and extensive spectroscopic methods and electronic circular dichroism (ECD) analysis in flowers. In addition, they found that these compounds A and D showed potential activity against herpes simplex virus 1 (HSV-1) with IC₅₀ values of 8.62 and 6.87 μ M, respectively.

Rhododendron liqueur

Choi *et al.*³⁸ used liquid chromatography-tandem mass spectrometry to study the levels of grayanotoxin ('a' and 'b') in the blood of patients with grayanotoxin poisoning after taking cuckoo alcohol. According to their findings, the initial blood concentration of these patients ranged from

2.9 to 58.0 ng/ml, and the patients' mean arterial pressure was 36.7 to 76.7 mmHg. However, after 20 hours, the content of grayanotoxin in the blood dropped from the lower limit of quantification (LLOQ) to 17.8 and 2.52 ng/ml, while the average arterial pressure was 76.7 mmHg and 93.3 mmHg. More specifically, toxin III in the blood causes hypotension when the minimum value of the blood is 17.83-27.3 ng/ml, and the symptom is caused when the minimum value of the grayanotoxin I am 2.52 to 4.55 ng/ml.

Rhododendron luteum

Demir *et al.*³⁹ had quantified the contents of total polyphenols and flavonoids in the extract of dimethyl sulfoxide from *Rhododendron* and evaluated their effects on three kinds of cancer and human prepuce fibroblasts. According to their findings, polyphenols and flavonoids showed potent cytotoxicity to colon and liver cancer cells but no significant cytotoxicity to breast cancer.

Rhododendron micranthum

Zhang *et al.*⁴⁰ used high-performance liquid chromatography, proton nuclear magnetic resonance spectroscopy, and electron paramagnetic resonance to separate and identify some new compounds from *Rhododendron* leaves, including new diterpenes, mica ketone A (Fig. 7. 1), and two new ash Neem diterpenoids, red melanin A (Fig. 7. 2) and B (Fig. 7. 3) and three known diterpenoids of fennel. According to their results, micrathanone A exhibited a new tetracyclic diterpene carbon skeleton, and rhodomicroanols A and B have a 5,6-(3,4-dihydroxybenzylidene acetal) theme. In addition, 11 new diterpenoids of gray fennel and one new diterpenoid of resveratrol were identified, including 1-epifenneltoxin Xf!, 6-deoxymagnolin Xf!, 16-acetyl gray-blue Toxin II, 3-Oxypicline Toxin IX, 14-Deoxymagnolia Toxin VIII, 14-Acetyl Isosugar Toxin II, rhodomicroanols C, D, E, and F.⁴¹ In addition, known diterpenoids have been isolated. However, according to these researchers, these compounds have been identified from rhododendrons for the first time.

Rhododendron molle

Rhododendron molle is widely distributed throughout China and is a poisonous plant, especially flowers with anesthetic and insecticidal activities.

Zhou *et al.*⁴² isolated and identified eight compounds. Namely, cleaved myristicone

(1,5-opening Kalman-type skeleton), taxol XXI, 6-O-acetylgrubin XXI, 6,14-Di-O used high-performance liquid chromatography (HPLC), infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and single-crystal X-ray diffraction analysis methods to study the acetyl progestin XXI, rutin XXII, 2-O-methyl Glycoside XI, Oryzaol XXII and Eucalyptus XXIV. Among these compounds, ionaldehyde XXI, 6-O-acetylerythromycin XXI, 6,14-di-O-acetylerythromycin XXI, viburnum XXII, and 2-O-methylerythromycin X⁴¹ are respectively named New gray alkane diterpenes. In addition, they also identified seven known diterpenoids, such as Rhodomolleins XI and XI and Rhodojaponins I, II, III, VI, and VII.

Li *et al.*⁴³ isolated two new ash descending bodies from *Rhododendron* fruit, namely, mollanol A (Fig. 8. 1) and rhodomolleinn XXd! (Fig. 8. 2). In addition, they confirmed that in different cell types (such as IEC-6,293T and RAW264.7 cells), mollanolA exhibited transcriptional activation of the xbp1 upstream promoter and activation at 10 μ M was 112,148, and 207%, respectively. Handle comparison of photos. They also identified nine new ash drops from the roots of *Rhododendron molle* by using spectral analysis, high-resolution electrospray ionization mass spectroscopy (HRESIMS), and 1D and 2D NMR data. (See Fig. 9) The acetic acid-induced writhing test, hot plate test, formalin test, diabetic neuropathological model, and acute cerebral ischemia model found Jerusalem artichoke saponins b!, e!, and grayanotoxin b! showed high anti-inflammatory and anti-diabetic activities compared with morphine and gabapentin, respectively.

As a result of continued efforts, Li *et al.*⁴⁴ identified two new gray matter subclasses, rhodomollin A (Fig. 10. 1) and B (Fig. 10. 2) from *rhododendron* fruits. Furthermore, they found that using HPLC, spectroscopy, and X-ray crystallography to study these gray tartaric acids have a new skeleton (characterized by a 5-hand-7-pound-6-pound dense ring system). In addition, by using MDCK cells infected with influenza A/95-359 virus in vitro, rhodomollin B showed moderate activity against influenza virus A/95-359, and the measured IC₅₀ value was 19.24 μ M.

Zhou *et al.*⁴⁵ used high-performance liquid chromatography, spectroscopy, and single-

crystal X-ray diffraction technology to separate and identify three new diterpenoids from *Rhododendron* leaves Rhodiola A, B, and C. (See Fig. 11). They found that red bean alcohol acetal A revealed a novel cis/cis/cis/cis 6/6/6/6/5 pentacyclic ring system (features 11,13,18troxa-pentacyclo [8.7.1.15,8.02,8.012,17] nonadecane scaffold) and red bean alcohol acetal B and C show a pair of C-6 epimers with a rare 4-oxa Tricyclic [7.2.1.01,6] dodecane moiety and 2,3-dihydro-4H-pyran-4-one unit. This study confirmed that these taxol compounds (A, B, and C) showed PTP1B inhibitory activity, and the IC₅₀ values were 42.42 \pm 1.40 μ M, respectively. According to these researchers, 4-oxatricyclo [7.2.1.01,6] dodecane and 2-methoxy-2,3-dihydro-4H-pyran-4-one units may inhibit the activity of PTP1B related. This opinion is estimated through a preliminary structure-activity relationship study.

Zhou *et al.*⁴⁶ used spectroscopy and single-crystal X-ray diffraction techniques to isolate and identify rhodomollanol A (Fig. 12. 11) and a new grayanane diterpenoid, rhodomollein XXXI (Fig. 12. 2) from *Rhododendron* leaves. rhodomollacetal A shows a unique cis/trans/trans/cis/cis fused 3/5/7/5/5/5 six-ring system, consisting of the rare 7-oxa two Ring [4.2.1] nonane core and three cyclopentane units. Rhodomollein XXXI is estimated to be 2 α ,3 α -epoxy-5 α ,6 α ,10 α ,14 α -tetrahydroxy gray yellow-15(16)-ene. Among these compounds, rhodomollanol A showed potent PTP 1B inhibitory activity in vitro, and when oleanolic acid was used as a control, IC₅₀ value was 24.32 \pm 0.56 μ M, IC₅₀ value was 4.54 \pm 0.25 μ M, and Rhodomollein XXXI showed Weak PTP 1B inhibitory activity (IC₅₀ value > 200 μ M).

Three new dimer diterpenes, birhodomollein A, B, and C (Fig. 13), were isolated and identified from *rhododendron* flowers by HPLC, 1D, and 2D NMR, IR, and ESIMS.⁴⁷ As a result, it is estimated that dihydroanthraphenols A, B, and C are α -chloro-14' α -hydroxy-14 α , 2' α -oxo-bis-(6 α -acetoxy-3 α , 5 α , 10 α , 16 α - Tetrahydroxyglarane), 2 α ,14' α -dihydroxy-14 α , 2' α -oxo-di- (6 α -acetoxy-3 α , 5 α , 10 α , 16 α -tetrahydroxypueraran) and 2 α , 3 α -epoxy-3' α , 14' α -dihydroxy-14 α , 2' α -oxo-bis (6 α -acetoxy-5 α , 10 α , 16 α -trihydroxyglalan).

Zhou *et al.*⁴⁸ used high-performance liquid chromatography (HRESIMS) to separate 13 new fennel diterpenoids from *rhododendron* leaves and discovered a fennel diterpene compound

with anti-inflammatory effects, NMR, and single-crystal X-ray diffraction. These compounds are shown in Figure 14. In addition, they used mouse macrophages and cell viability assays to study the anti-inflammatory activity of 29 such compounds against LPS-induced NO production in RAW 264.7.

Li *et al.*⁴⁹ isolated and identified 12 new diterpenoids (Fig. 15) from the fruits of *Rhododendron*. In addition, they studied the antinociceptive activity of these compounds through a writhing test induced by acetic acid. Among them, 2, 3, 12, 13, and 15 showed significant analgesic effects at shallow doses (0.4 mg/kg), while 1, 4, 9, 16, and 18 at high doses (2 mg/kg) showed significant analgesic effect. Moreover, others are inactive at a dose of 2mg/kg.

Rhododendron mucronulatum for. albiflorum

Rhododendron mucronulatum for. albiflorum is distributed in mountainous areas and belongs to sunny areas in DPR Korea, China, and Japan. It is traditionally called a drug with high efficacy, such as tonic, diuretic, and stomachic.

Flavonoids were isolated and identified from *Rhododendron* by Mok *et al.*⁵⁰. The compounds isolated and purified from the flowers of *Rhododendron mucronulatum for. albiflorum* are as follows: kaempferol, afzelin, quercetin, quercetin, myricetin, and myricetin. These compounds have also been studied for AR inhibitory activity. The results showed that amaranth, quercetin, and quercetin had higher AR inhibitory activities, with IC_{50} values of 0.31, 0.4, and 0.13 µg/ml, respectively, and stronger than the control (tetramethyleneglutaric acid, IC_{50} value of 0.96 µg/ml/ml). They emphasized that the flavonoid rhamnosides (quercetin and quercetin) had a more substantial inhibitory effect on AR than flavonoid aglycones (afzelin and kaempferol) the dihydroxyflavonoids in the B ring showed better than trihydroxyflavonoids. Compounds have higher inhibition of AR activity.

***Rhododendron nivale* Hook. f.**

Guo *et al.*⁵¹ focused on the leaves and essential oils of *Rhododendron* and studied the oil composition and acaricidal activity of essential oils compared with the extracts of 70% ethanol, ethyl acetate, chloroform, and petroleum ether. As a result, in vivo and in vitro, the main compound of

essential oil, α -cadinene, showed the most vigorous acaricidal activity against *P. moth*.

***Rhododendron oldhamii* Maxim**

Tung *et al.*⁵² studied the antioxidant phytochemical components of *Rhododendron*. The leaf was measured by the HPLC-DPPH method, and the anti-hyperuricemia effects were tested using acute hyperuricemia induced by potassium oxazone (PO). Among these ingredients ((2R,3R)-epicatechin, (2R,3R)-taxifolin, (2R,3R)-astilbin, hyposide, guaijaverin, and quercitrin) ((2R, 3R)-astilbin, hyposide, guaijaverin, and quercitrin) showed pronounced reduction in renal damage. In addition, these significant phytochemicals significantly inhibited the concentration of serum uric acid, which was 5.41, 35.1, 56.3, 56.3, and 53.2% compared with the PO group. They found that rhododendron leaf extract (ethyl acetate part) improved fatty liver syndrome for the first time.⁵³ The results showed that this leaf extract could inhibit free fatty acid (FFA)-induced fat accumulation in HepG2 cells and improve fatty liver syndrome in nonalcoholic fatty liver disease (NAFLD) mice induced by HFD. Among these phytochemicals in the ethyl acetate portion of *rhododendron* leaf extract ((2R)-Pasteurella Vulgaris, Pasteurella guaijavirin and quercitrin), (2R-Pasteur 3R)-Pasteurium and Pasteurella showed vigorous fat accumulation inhibitory activity.

Rhododendron ponticum nectar

Kurtoglu *et al.*⁵⁴ tried to find changes in grayanotoxins I and III concentration during the 6-month storage period. However, there is no significant difference. In addition, various effects of azalea nectar on human health were investigated.⁵⁵⁻⁵⁷

Rhododendron pulchrum

Chai *et al.*⁵⁸ used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) mass spectrometry to study the structure anti-tyrosinase activity and mechanism of proanthocyanidins obtained from *Rhododendron* and high-performance liquid chromatography -Electrospray ionization mass spectrometry (HPLC-ESI-MS). Procyanidins are a complex mixture of procyanidins, prodelphinidins, protoveratrine, and their derivatives, and procyanidins are the main compound. Their

research results on the anti-tyrosinase analysis of the above compounds show reversible and mixed competitive tyrosinase inhibitors. Observe these results through their molecular docking analysis.

***Rhododendron pumilum* Hook. f.**

Zhang *et al.*⁵⁹ used HR-EIMS, NMR, IR, and other methods to isolate and identify two new dimers of gray alkane diterpenoids D (Fig. 16. 1) from azalea fruits with 3-O-2' linkages. And E (Fig. 16. 2) and ultraviolet light. The name birhodomollein D reveals that the dimer grayanane-type diterpene processes these two compounds' (C (3)-O-C (2') linkage.

***Rhododendron seniavinii* Maxim.**

Wang *et al.*⁶⁰ identified phytochemical components from *Eucommia ulmoides* leaves. Among them, the compound revealed a new flavonoid glycoside 5,7,3'-trimethoxy-quercetin 3-O- β -D-glucopyranoside (Fig. 17). It was confirmed by UV, FTIR, and NMR analysis.

***Rhododendron simsii* Planch.**

Rhododendron simsii Planch. is well known for treating bronchitis, pain, and coronary heart disease.

Cheng *et al.*⁶¹ studied whether the total flavonoids of *Rhododendron* contain total flavonoids. The flower comprises hyperoside, rutin, quercetin, and other flavonoids, inhibiting ventricular remodeling after coronary artery ligation-induced myocardial infarction. It indicates that the urotensin-II receptor (UTR)-RhoA-Rho-kinase (ROCK) pathway may involve the use of echocardiography, Morphological, histological and immunochemical analysis, Picrosirius red staining, Western blot analysis.

Rhododendron tomentosum

Koudelkova *et al.*⁶² had identified the most common leaf endophytes in *Rhododendron* leaves. They found that essential oils selected from *Rhododendrons* have different effects on oils isolated from *Rhododendrons*, which are different from those isolated from other substrates. Compared to corresponding strains of the same fungal species. This study investigated fungal species such as *Apiosporamontagnei*, *Chaetomium globosum*, *Desmazierella acicula*, *Hypoxylon howeanum*, and *Khuskiaoryzae*. They used headspace solid-phase microextraction (HP-SPME) and GC-MS to separate the volatile compounds in the essential oil of *Rhododendron*. They confirmed that the three

volatile compounds mentioned above, p-cymene, myrene alcohol, and Alpha-terpinene, potentially affect endophytic bacteria growth.

Synthesis and synchronization of *Rhododendron* species

Recently, many researchers have conducted comprehensive and simultaneous studies on *Rhododendron* species. Jaiswal *et al.*⁶³ studied whether proanthocyanidins were found in 16 species of *Rhododendrons* and confirmed that these compounds were based on the proanthocyanidin of (epi) catechin and (epi) Gallocatechin and used the negative ion mode tandem mass spectrometry. Lin *et al.*⁶⁴ studied the antioxidant activity of methanol extract from 10 leaves of *Rhododendron* in Taiwan: *Rhododendron breviperulatum* Hayata, *Rhododendron ellipticum* Maxim., *Rhododendron formosanum* Hemsl., *Rhododendron Kanehirai* Wilson, *Rhododendron mariesii* Hemsl. And Wilson, *Rhododendron oldhamii* Maxim., *Rhododendron pseudochrysanthum* Hayata, *Rhododendron rubropilosum* Hayata var. *rubropilosum*, *Rhododendron rubropilosum* Hayata var. *taiwanalpinum* and *Rhododendron simsii* Planch. Four antioxidant activity methods were used, involving DPPH free radical scavenging activity, superoxide free radical scavenging determination, ferrous ion chelation determination, and reducing power determination. According to their research results, the n-butanol part of the *Rhododendron* leaf extract of the *Rhododendron* species showed the most potent antioxidant activity. (2R, 3S)-Catechin, (2R, 3R)-Epicatechin, (2R, 3R)-Dihydromyricetin 3-O- β -L-arabinopyranoside (1), (2S, (2R, 3R)-paclitaxel 3-O- β -1-arabinofuranoside (2), myricetin 3-O- β -D-glucopyranoside, rutin, hyperoside and quercetin, and It was confirmed that among these compounds, 1 and 2 were the main compounds.

Rezk *et al.*⁶⁵ conducted a phylogenetic study on the antibacterial effects of 120 leaf extracts of *Rhododendron* plants against 26 bacteria (Gram-positive and Gram-negative bacteria). They conducted an agar diffusion test on 80% methanol extracts, *Rhododendron* species and confirmed that 17 species showed potential antibacterial activity against Gram-positive bacteria. However, they showed a small amount of leaf extract against Gram-negative bacteria. These species are as follows: *Rhododendron ferrugineum* L., *Rhododendron*

ambiguum Hemsley, *Rhododendron anthopogon* Don ssp. *anthopogon* Betty Graham, *Rhododendron hirsutum* L., *Rhododendron anthopogon* ssp. *Hypanthium* Bale. F. & Cullen, *Rhododendron concinnum* Hemsley, *Rhododendron sichotense* Pojarkova, *Rhododendron cinnabarinum* Hooker, *Rhododendron racemosum* Franchet, *Rhododendron ledebourii* Pojarkova, *Rhododendron rubiginosum* Franchet, *Rhododendron xanthostephanum* Merrill, *Rhododendron myrtifolium* Schott & Kotschy, *Rhododendron minus* Michaux, *Rhododendron polycladum* Franchet, *Rhododendron spinuliferum* Franchet and *Rhododendron hippophaeoides* var. *hippophaeoides* Hutchinson. According to these results, common genetic characteristics are responsible for producing biologically active secondary metabolites that mainly act on Gram-positive organisms, which may affect Gram-negative bacteria, depending on the activity of the multidrug efflux pump in the outer cell membrane.

Someone⁶⁶ has studied the cytotoxicity of 12 leaf extracts with potential antibacterial activity against epidermal keratinocytes (human HaCaT cell line) and intestinal epithelial cells (rat IEC6 cell line). To this end, five quantitative methods are used, such as plasma membrane integrity, cell viability, proliferation rate, cell metabolism, cytoskeletal structure, and determining the initiation of the cell death pathway through morphological and biochemical means. According to the results of total cell number and dead cell percentage of IEC6 and HaCaT cell cultures treated with azalea leaf extract, azalea extract is non-toxic to IEC6 cells, and azalea and azalea extracts did not affect HaCaT cells. Thus, this research provides robust data to produce effective and promising antibacterial agents suitable for human medicine. Furthermore, low cytotoxicity is significant for safe human antibiotic application.

Grimbs *et al.*⁶⁷ studied the relationship between the antibacterial activity and cytotoxic activity of 87 *Rhododendron* species. To this end, they first assessed the abnormal diversity of *Rhododendron* based on DNA regions, *trnK*, *trnLF*, and ITS. In addition, they determined the antimicrobial (against *Bacillus subtilis*) and cytotoxicity (against IEC-6 and HaCaT cells) of *Rhododendron* species. They detected more than 48,000 LC-MS peaks in their phytochemical fingerprints, and for each peak from the mass-

to-charge ratio (*m/z*), statistical evaluation methods such as principal component analysis and classification analysis are used. Based on these data, they explored the relationship between their respective biological activity classifications and phytochemical maps, identified secondary metabolites, and detected LC-MS peaks. Finally, they discovered and confirmed seven non-cytotoxic compounds (caffeoylquinic acid) from *Rhododendron* subgenus with potential antimicrobial activity.

Shrestha *et al.*⁶⁸ used a high-performance liquid chromatography-ion trap and time-of-flight mass spectrometer to separate and identify 69 kinds of hydroxycinnamic acid and its chlorogenic acid derivatives in the leaves of 69 species of *Rhododendron*. Among these compounds, the five most abundant hydroxycinnamates are *p*-coumarin-*O*-hexosidic isomer, 3-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid, 3-*Op*-coumarinic acid, and *cis*-5-*Op*-coumarinic acid. They emphasized that NMR studies must further analyze the more precise and perfect derivatives obtained from this study.

PROSPECTS AND CONCLUSION

From ancient times, plants represent the primary source of drugs and alternative medicine to combat disease: Plants are a rich source of valuable⁶⁹ sites such as alkaloids, quinones, tannins, terpenoids, flavonoids, and polyphenols⁶⁹. *Rhododendron* species have long been used in traditional medicine and animal studies, and *in vitro* studies have identified anti-inflammatory and liver-protective activities due to antioxidant effects of flavonoids or other phenolic compounds and saponins contained by plants^{70,71}. This review involves an investigation of 29 individual *Rhododendron* species and a comprehensive and simultaneous study of *Rhododendron*. In the study of antibacterial activity⁷², it was found that the study on gram-positive bacteria and its activity against gram-positive bacteria were significant, but no visible components were found for gram-negative bacteria. The highly effective substances mentioned in this review will continue to increase in value as pioneers in drug development. In the future, research on substances that have a strong inhibitory effect on gram-negative bacteria

should be strengthened, and specific research on the relationship between the structure and pharmacological properties of the compounds of the genus *Rhododendron* is needed.

ACKNOWLEDGMENT

This work was financially supported by the National Natural Science Foundation of China(21372049).

Conflict of Interest

The author declares no conflict of Interest.

Funding source

National Natural Science Foundation of China (NSFC) 21372049.

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