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Basic Research Related to the Development of New Traditional Chinese Drugs

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Chinese traditional drugs have a long history to be used in clinics to treat various diseases and are confirmed to be effective approach through thousands of years of medical practice. Therefore, as a common understanding, the drug development from traditional Chinese medicines could be considered as a "shortcut" way with less blindness and more saving of time and money since development of new Chinese drugs has a different approach from that of western new drugs. Firstly, Chinese new drug development can be simplified as "from men to animal" process rather than "from animal to men" in western medicines. Hence the successful rate would be higher. Secondly, the original drugs or prescriptions from which the new drugs are planned to develop have been known what symptoms they are indicated for. Therefore, the developing procedure is actually a refine process with much less blindness than that of western drugs.

China has vast resources of medicinal plants utilized as traditional Chinese medicine or health-care products. The general survey of medicinal plant resources has shown that there are 11146 species used in Chinese medicine all over the China, majority of which have not been investigated either chemically or pharmacologically. Therefore, Chinese medicinal plants could be considered as the important resources for discovery and development of new drugs. Investigation over a number of herbs has resulted in the development of several new drugs, among which artemisinin is the most prominent one. From an overview of these new drugs' developing process, all of them were related to the detailed basic research on the plants from which they were derived. These basic studies include investigations on their chemical constituents, pharmacological studies, and quality evaluation and standardization. In the past several years, we studied the chemical constituents of several commonly used traditional Chinese drugs to some detail and we'd like to present some of them in the following section.

Gaultheria yunnanensis (Franch.) Rehd. is a plant from the family Ericaceae, its root called *DianBaiZhu* is widely used in southwest and southeast region of China for the treatment of rheumatoid arthritis, trauma, chronic tracheitis and Meniere's diseases. Pharmacological investigation showed that the EtOAc and n-butanol extracts possessed strong anti-inflammatory and analgesic activities. Studies on the chemical constituents and activities has not been reported before. The chemical constituents and activities of the title plant have, therefore, been investigated in detail. From the ethanol extract, thirty eight compounds including five new lignans and two new

diterpenoids have been isolated and identified. Based on their chemical and spectral properties (mp, 1HNMR, 13CNMR, COSY, NOESY, HETCOR, HMBC, etc.), their structures were elucidated and the five new lignans have been identified as 2,3-napthalenedimethanol-1β,2α,3,4-tetrahydro-7-hydroxy-1-(4-hydroxy-3,5-dimethoxy-phenyl)-6-methoxy-2α,3α-diacetate(I), 2,3-napthalenedimeth-anol-1α,2β,3α,4-tetra-hydro-7-hydroxyl-(4hydroxy-3,5-dimethoxy-phenyl)-6,8-dimethoxy-2a,3a-diacetate (II), anhydro-(+)-lyoniresinol (III), anhydro-(-)-5'-methoxyisolariciresinol (IV) and (+)-lyoniresional-2α-O-α-L-arabinopyranoside (V). They were named as gaultherin A (I), gaultherin B (II), gaultherin C (III), gaultherin D (IV) and gaultheroside A (V) respectively. The two new diterpenoids were identified as 13-acetyl-12-hydroxy-8,11,13-podocarptrien-18-oic acid (VI) and 13-acetyl-3,12-dihydroxy -10-methyl-Δ4(18)-1,2,3,5,6,7-hexahydrophenanthrene (VII), named gaultheric acid and gaulthero-noterpene. One new natural product was identified as (-)-5'-methoxyisolariciresinol (VIII). The other known compounds were elucidated as methyl salicylate (V1), ethyl salicylate (V2), phenyl salicylate (V3), 3β-acetylsitosterol (A1), 3β-acetyl-12,15-dien-dammarane (A2), 3β-acetyl-20(29)-lupen-28-aldehyde (A3), 3b-acetyloleanolic acid (A4), sitosterol (A5), ursolic acid (A6), stigmasterol (A7), 3b-hydroxy-20(29)-lupen-28-aldehyde(A10), scopoletin (B7), palmitic acid (B9), daucosterol (B12), (+)-lyoniresinol (B13), 3,4,5-trimethoxybenzoic acid (B16), acetylsyringic acid (B17), ferulic acid (C1), salicylic acid (C2), vanillic acid (C3), chlorogenic acid (C5), genticic acid (C7), protocatechuic acid (C8), (+)-catechin (C9), proanthocyanidin-A2 (C10), rutin (C11), quercetin (C12), (-)-5'-methoxyisolariciresinol-2a-O-β-D-xylopyranoside (D2), (-)-isolariciresinol-2a-O-β-D-xylopyranoside (D3), and (+)-lyoniresinol-2a-O-β-D-glucopyranoside (D4) respectively. Except for 1 and A6, the other compounds were isolated from the genus of Gaultheria for the first time.

Gleditsia sinensis Lam. (family Leguminosae) is widely distributed in China. Its small fruit produced by the decrepit or injured plant, called "Zhuyazao" in Chinese, was used as apoplexy, expectorant and pesticide. However, there is no report on the chemical constituents of this drug. We conducted a detailed investigation on the chemical constituents of the title plant. So far fifteen triterpenoidal saponins have been isolated and among which the nine identified saponins seven are new structures by using modern NMR techniques including DQF-COSY, HETCOR, HOHAHA, HMBC, etc. and other methods. The structures of seven new saponins were elucidated as 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl oleanolic acid-28-O-β-D-xylopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-[(6s),(2E)-2-trans-6-hydroxy-2,6-dimethyl-2,7-octadienosyl-(1→6)]-β-D-glucopyranosyl ester(**1**); 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopy-ranosyl oleanolic acid-28-O-β-D-xylopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-[(2E)-2-trans-2-hydroxymethyl-6-hydroxy-6-methyl-2,7-octadienosyl-(1→6)]- β-D-glucopyranosyl ester(**2**); 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl echinocystic acid-28-O-β-D-xylopy-ranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-[β-D-galactopyra-nosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-[(2E)-2-trans-2-hydroxylmethyl-6-hydroxy-6-methyl-2,7-octadieno-syl-(1→6)]- β-D-

glucopyranosyl ester(**3**), 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabino-pyranosyl-(1→6)-β-D-glucopyranosyl echinocystic acid-28-O-β-D-xylopy-ranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-[β-D-galactopy-ranosyl-(1→2)-α-L-rhamnopyrano-syl-(1→2)-[(6s),(2E)-2-trans-6-hydroxy2,6-dimethyl-2,7-octadienosyl-(1→6)]- β-D-glucopyranosyl ester (**4**), 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl echinocystic acid-28-O-β-D-xylopy-ranosyl-(1→3)-β-D-xylopy-ranosyl-(1→4)- α-L-rhamnopyra-nosyl-(1→2)-[(2E)-2-hydroxymethyl-6-hydroxyl-6-methyl-2,7-octadienosyl-(1→2) and (6S),(2E)-6-hydroxy-2,6-dimethyl-2,7-octadieno-syl- (1→3)- α-L- rhamnopyranosyl-(1→6)]- β-D-glucopyranosyl ester (**5**), 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl echinocystic acid-28-O-β-D-xylopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)- α-L-rhamnopyrano-syl-(1→2)-[(6S),(2E)-6-hydroxy-2,6-dimethyl- 2,7-octadienosyl-(1→2) and (6S), (2E)-6-hydroxy-2,6-dimethyl-2,7-octadienosyl- (1→3)- α-L- rhamnopyranosyl-(1→ 6)]- β-D-glucopyranosyl ester (**6**) and 3-O-β-D-xylopyanosyl-(1→2)-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranosyl echinocystic acid-28-O-β-D-xylopyra-nosyl-(1→3)-β-D-xylopyranosyl-(1→4)- α-L-rhamnopyranosyl-(1→2)-[(6S),(2E)-6-hydroxy-2,6-dimethyl- 2,7-octadienosyl-(1→2) and (2E)-2-hydroxymethyl-6-hydroxy-6-methyl-2,7-octadienosyl- (1→3)- α-L-rhamnopyranosyl-(1→6)]- β-D-glucopyra-nosyl ester (**7**) respectively.

Conyza blinii Levl. (Compositae) is distributed in southwestern districts of China. Its aerial parts are used in Chinese folk medicine for the treatment of chronic bronchitis and other inflammatory diseases. Preliminary pharmacological and clinical tests showed that it possessed expectorant, antitussive, antiinflammatory and antibacterial effects. Its crude extract has been developed into class 4 new Chinese drug and used in clinics for a period of time. However systematic chemical study on this plant has not been carried out. In order to shed light on the chemical entities responsible for its medical actions, we conducted chemical investigation on the title plant. A new trans-clerodane diterpenoid and six known compounds isolated and they were identified as conyzalactone, α-spinasterol, 5,8-dihydroxy-7,3',4'-trimethoxy-flavone, caffeic acid, syringic acid, friedelinol and n-triacontanol respectively. Studies on saponins from the plant are under investigation. And process to develop this medicinal plant into the class II new Chinese drug is under way.

Echinops grijisii is a composite plants, the roots of which were used as Yuzhou Loulu in Thaditional Chinese medicine. It is mainly used as antifebrile, antitoxicant and antiphlogistic agent. The chemical constituents were studied in order to shed light on the responsible principles. From the roots of Echinops grijisii fourteen compounds were isolated and their structures were identified. There are three new compounds identified and for the time being they are tentively named grijithioside, grijilignanside and grijisithiophene [5-(4-O-isopentanoyl-butynyl-1)-2,2'-bithiophene]. The other eleven compounds were identified as a-terthienyl, isocardopatine, cardopartine, 5-(3-buten-1-ynyl)-2,2'-bithiophene, 5-(3,4-dihydroxy-1-butynyl)-2,2'-bithiophene, ziyu-glycoside I, taraxerol acetate, triacontanoic acid, ursolic acid, daucosterol and sitosterol.

Cistanche deserticola L. (Orobanchaceae) is a famous traditional Chinese medicine and used for the treatment of male sexual impotence, female infertility, and

constipation etc. The pharmacological tests showed that its extract has very good Yang-strenthening, anti-aging, immunological, memory-improving, blood lipid lowering effects. Recent studies with several pure compounds isolated from the plant and total glycosides in our department verified that it is very promising to develop it into a drug to treat Alzheimer disease. Collaborative effort to lead to the objective is under way.