Research and application of Radix Notoginseng

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Abstract

In Chinese traditional medicine, Radix Notoginseng, the dried root of Panax Notoginseng Burkill (Panax notoginseng (Burk.) F. H. Chen) (Araliaceae), is a well-known traditional Chinese medicine. The active constituents include saponin, dencichine, flavonoid, and polysaccharide. In this paper, some information on basic research and application, and introduce to the ethnopharmacology, chemistry, pharmacological actions and clinical application of Radix Notoginseng. Pharmacologically, the major functions of are (1) Invigorates blood circulation and reduces stasis of blood, stimulates the menstrual flow and activates venationcollaterals, dilates blood vessels, ameliorates blood circulation, prevents conglomeration of haematoblast and increases the blood flux to the brain. (2) It is used to treat apoplexy, hemiplegy, sequel of cerebrovascular diseases, ophthalmopathy, block of the centre vein of the retina, Eye Anterior chamber hemorrhage. (3) An injection of Total saponins can dilate blood vessels, ameliorate microcirculation, reduce obstruction in blood vessel. It has a good effect on treating Heart disease from lung disorders and heart exhaustion. (4) It has good effect on treating all kinds of hemorrhage diseases, such as, empyesis, ophthalmorrhagia, bleeding (all kinds of bleeding in general). It is also good for treating blood in stool, uterine bleeding, and excessive menstruation. (5) It is used for curing coronary heart disease. After taking it, patients’ condition were notably improved, and their cardiogram showed that when they rested or did sports, their condition was getting better. (6) When it is used to cure high blood fat, the high content of cholesotin or the total blood serum fat in blood is notably lowered. (7) Brain infarction: it has good effect on treating apoplexy caused by cerebral veins stasis. (8) It is used in curing toxic hepatitis, and the content of SGTP is notably reduced. It is also Anti-liver fibrosis, and can prevent hepatitis complicated by digestive path bleeding. (9) It can be used to cure skull flesh wound external wound of head, chronic kidney function failure, scar proliferation after burn and parodontitis. Clinically, Radix Notoginseng is one of the most important components of famous Chinese recipe and possesses a wide variety of applications in clinical practice. The herb is officially listed in the Chinese Pharmacopoeia. The medicinal use of the herb in different from that of ginseng. It is used mainly as a hemostatic drug in the treatment of different types of bleeding. Radix notoginseng had been showed to have satisfactory therapeutic effect on coronary disease, hemopetysis, hemoturia, head injury and inflantial acute nephritis.

Keywords Panax notoginseng; Radix Notoginseng; saponin; ethnoparmacology; chemistry; pharmacology; pharmacokinetics; toxicity, clinical application

Introduction

Chinese materia medica is an important part of traditional Chinese medicine and Chinese civilization. In the history, Chinese traditional medicine arose from mythical medicine to a system of Chinese drugs and herbal medicine. The first book on materia medica "Shen-nong Bencao Jing" known as "the canon of materia medica" was
compased in the second century BC by the folk under the pseudonym of Shenong, the Holy Farmer. Chinese medicinal plants are today playing an outstanding role within the framework of official health services. China is endowed with an abundant resource of medicinal plants, more than five thousand plants have been identified as medicinal plants. The 2005 edition of The Chinese Pharmacopoeia recorded about 700 items of Chinese drugs originating from medicinal plants.

In Chinese traditional medicine, *Radix Notoginseng*, the dried root of *Panax Notoginseng* Burkill (*Panax notoginseng*(Burk.) F. H. Chen) (*Araliaceae*), is a well-known traditional Chinese medicine. The active constituents include saponin, dencichine, flavonoid, and polysaccharide. In 2000, Hong Kong medical Publishers published “Modern Research on Chinese Medicinal Plants” edited by Professors Liu Changxiao, Xiao Peigen and Li Dapeng[1]. In this paper, some information on basic research and application, and introduce to the ethnopharmacology, chemistry, pharmacological actions and clinical application of *Radix Notoginseng* [2]. Searching Medline, we learn that the research and review papers were more than 2700 from 1968 to 2008. Based on above information, we selected part papers and finished this review paper.

**Ethnopharmacology**

The source of the earliest record of *Radix Notoginseng* was in *Bencao Gangmu* (*Compendium of Materia Medica*). The ethnopharmacology was listed in many books on traditional Chinese medicine.[2][5]

**Properties in Chinese material medica** The herb is sweet and slightly bitter in flavour, slightly warm in nature, and acts on the heart, liver and spleen channels. Being sweet for mildness, warm for clearing, it acts heart and liver channels and blood division for resolving blood stasis and improving blood circulation. When the stasis is resolved and the blood returned back to the vessels, the bleeding without retaining blood stasis, it is an important herb to stop bleeding and alleviate pain. The herb is often used to treat various kinds of bleeding and pains due to blood stasis. Effects for traditional Chinese medicine are resolving blood stasis, stopping bleeding, promoting blood circulation and alleviating.

**Indication for clinical therapy of traditional Chinese medicine** Indication for clinical therapy of traditional Chinese medicine are (1) The herb powder can be orally taken, 2-3 times a day, 3g each time, to treat haematemesis, hemafecia, metrorrhagia and metrostaxis and other kinds of bleeding, with a better effect for bleeding with blood stasis. To treat haematemesis, hemafecia caused by ulcer of the digestive tract, the herb can be used in combination with hyacinth bletilla and cuttle bone. (2) To treat traumatic ecchymosis and swelling pain, the herb can be orally taken or externally applied or used in combination with other herbs for removing blood stasis and alleviating pain. To treat obstruction of the heart channel by blood stasis and colic due to obstruction of Qi in the chest, the herb is often used in combination with ginseng for supplementing Qi, clearing the channels, removing blood stasis and alleviating pain.

**Plant studies**

*Radix Notoginseng* [Fig 1] is the dried root of *Panax Notoginseng* Burkill (*Panax notoginseng*(Burk.) F. H. Chen) (Fig2).

Fig 1. *Radix Notoginseng*


Fig 2. Plant of *Panax notoginseng* Burkill

The microscopic features of transverse section of *Radix Notoginseng* is showed in Fig 3.

**Chemical studies**

Early in 1960-1980s, Chinese researchers studied the chemical substances of *Radix Notoginseng*. The main constituents are saponins of protopanaxadiol and protopanaxatriol types. A number of ginsenosides such as Rb1, Rb2, Rb3, Re, Rd, Re, Rg1, Rg2, Rh etc were isolated from *Panax notoginseng*. In addition to the ginsenosides, a number of ginsenosides have been isolated. The major notoginsenosides are R1, R2, R3, R4 and R6A. Sachinoside B1 was isolated from the rootlets of the herb. From the data of chemical analysis of a herb's constituents and its external appearance, we can postulate not only the quality but also the origin of the herb.

The active constituents of *Radix Notoginseng* which is cultivated in Wenshan of Yunnan, China, include saponin, dencichine, flavonoid, and polysaccharide; however, the levels of these components vary in different geographical regions of growth and also show a seasonal variation. By using high-performance liquid chromatography and spectrophotometry, the contents of notoginsenoside R1, ginsenoside Rg1, Rb1, Rd, dencichine, flavonoid, and polysaccharide were determined and compared with *Radix Notoginseng* collected from different regions of growth in China, as well as from different seasons of harvest and market grades. Using the contents of these active constituents as markers, the best quality of *Radix Notoginseng* is found in the southwestern parts of Wenshan, and the best season for the harvest is September to October. In addition, the unseeded plants produced a better quality of *Radix Notoginseng*. The current results provide useful information for the quality control of *Radix Notoginseng* and its further development in establishing the good agriculture practice standard of *Panax notoginseng* in China. The fingerprint (Fig 4) and the types of chemical structures of ginsenosides is shown in Table 1.

A fingerprint (Fig 5, Table 2) of raw material, extracted and injections of *Radix Notoginseng* has been studied and provides the quality information. Polaris C18-A column was used, with mixtu res of acetonitrile and water as mobile phase in a gradient mode. The wavelength of measurement was 203nm. According to the selected chromatographic conditions, a good fingerprint of radix notoginseng and its extract, preparation has been described. The method is simple, accurate with good reproducibility.
It may be practical value for the quality control of sample for Radix Notoginseng and its preparation.[12]

Fig 4. Chromatography of reference compounds by 011 line ItPLC-UV-MS (a) HPLC chromatogram at 200 Bin (b) TIC chromatogram in positive ESI mode (c) TIC chromatogram in negative ESI mode

Table 1. Chemical structures of saponins in Panax notoginseng

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<th>RRT</th>
<th>Acceptable Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (marker 1, notoginsenoside R₁)</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>2 (marker 2, ginsenoside Rg₁)</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>3 (ginsenoside Re)</td>
<td>1.06 (vs Rg₁)</td>
<td>±0.04</td>
</tr>
<tr>
<td>4 (marker 3, ginsenoside Rb₁)</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>5 (ginsenoside Rd)</td>
<td>1.12 (vs Rb₁)</td>
<td>±0.03</td>
</tr>
<tr>
<td>6</td>
<td>1.17 (vs Rb₁)</td>
<td>±0.03</td>
</tr>
</tbody>
</table>

Fig 5. A reference fingerprint chromatogram of Radix Notoginseng extract

Chemical components of the root, stem and leaves of Panax japonicum var. major were compared with those of Radix ginseng and Radix Notoginseng by TLC. The results showed that the total saponin of the root Panax japonicum var. major was closer to that of Radix ginseng and the total saponin of its stem and leaves was similar to Radix notoginseng. A better extractive technology was obtained after isolating and purifying the whole herb of Panax japonicum var. major by ethyl alcohol at different concentrations. The components were compared by TLC. The results showed that with 60% ethyl alcohol the yield of the total extract was 17.15%.[14]

A sensitive method for quantitating the pharmacologically active polyacetylenes panaxydol and panaxylnol in Radix Ginseng was developed using a capillary gas chromatography-mass spectrometric (GC-MS) method. The detection mode of selected ion monitoring (SIM) allowed sensitive and selective quantitation of the two compounds in ginseng. Method validation showed that the GC-MS method has much lower detection and quantitation limits than the high-performance liquid chromatography HPLC-UV method. This indicates that GC-MS is particularly useful for the analysis of polyacetylene compounds, which have relatively low abundances compared with ginsenosides in ginseng. Based on the quantitative results of different types of ginseng herbs, it was found that the panaxydol and panaxylnol contents were higher in forest ginseng than in cultivated ginseng. This method was further applied to the quantitative analyses of panaxydol and panaxylnol in Radix Notoginseng and American ginseng. The ratio of panaxydol to panaxylnol can be utilized as a marker for differentiating ginseng, notoginseng, and American ginseng. This study introduces the first GC-MS method for the quantitative analysis of polyacetylenes in herbs of the Panax genus.[15]

An HPLC-DAD-ESI-MS³ method was developed for simultaneous analysis of major chemical constituents in "QI-SHEN-YI-QI" dropping pill, a traditional Chinese medicine (TCM) widely used for treating cardiovascular diseases. The chromatographic separation was performed on an Intersil ODS-3 C₁₈ column (4.6 mm x 250 mm, 5 microm), whilst water with 0.05% acetic acid and acetonitrile were used as mobile phase. On the basis of the characteristic UV absorption profile, the information of molecular weight, and structure provided by ESI-MS(n), 31 constituents derived from Astragalus membranaceus, Radix Salviae Miltiorrhizae, and Panax notoginseng, were detected and 20 of them were identified in this study. The proposed method contributes to the quality control of "QI-SHEN-YI-QI" dropping pill.[16]

A rapid ultra performance liquid chromatography coupled with photo diode array detection method (UPLC-PDA) was developed for the simultaneous determination of 11 saponins, namely notoginsenoside R₁, ginsenoside Rg₁, Re, Rf, Rb₁, Rg₂, Rc, Rb₂, Rb₃, Rd and Rg₃ in Panax notoginseng. The analysis was performed on...
Acquity UPLC system with Acquity UPLC BEH C18 column and gradient elution of water and acetonitrile in 12 min. The high correlation coefficient ($r^2=0.9968$) values indicated good correlations between the investigated compounds' concentrations and their peak areas within the test ranges. The LOQ and LOD were lower to 0.2-2.4 and 0.1-1.8 ng on column, respectively. The overall intra- and inter-day variations (RSD) of 11 saponins were lower than 3.1%. The developed method was successfully used for the analysis of saponins in Panax notoginseng with overall recovery of 93.0-101.6% for the analytes. The results show that UPLC is a powerful tool for analysis of components in Chinese medicines.[17]

**Pharmacological studies**

The major functions of are (1) Invigorates blood circulation and reduces stasis of blood, stimulates the menstrual flow and actives venationcollaterals, dilates blood vessels, ameliorates blood circulation, prevents congestion of haematoblast and increases the blood flux to the brain. (2) It is used to treat apoplexy, hemiplegy, sequela of cerebrovascular diseases, ophthalmopathy, block of the centre vein of the retina, Eye Anterior chamber hemorrhage. (3) An injection of Total Panax notoginseng saponins can dilate blood vessels, ameliorate microcirculation, reduce obstruction in blood vessel. It has a good effect on treating Heart disease from lung disorders and heart exhaustion. (4) It has good effect on treating all kinds of hemorrhage diseases, ophthalmomopathy, block of the centre vein of the retina, Eye Anterior chamber hemorrhage. (5) It is used for curing coronary heart disease. After taking it, patients’ condition were notably improved, and their cardiogram was getting better. (6) When it is used to cure high blood fat, the high content of cholesterol or the total blood serum fat in blood is notably lowered. (7) Brain infarction: it has good effect on treating apoplexy caused by cerebral veins stasis. (8) It is used in curing toxic hepatitis, and the content of SGTP is notably reduced. It is also Anti-liver fibrosis, and can prevent hepatitis complicated by digestive path bleeding. (9) It can be used to cure skull flesh wound external wound of head, chronic kidney function failure, scar proliferation after burn (an injury, like by fire) and parodontitis.

**Effect on central nervous system**

The saponins exhibited strong effect on inhibiting the spontaneous activities of mice. The action is enhanced by chlorpromazine or reserpine. It antagonized the central nervous stimulating action of amphetamine or caffeine and elevates the effect on hypotropics such as sodium pentobarbital and sodium pentothal. It also showed significant analgesia effect. The total saponin isolated from the leaves has similar effects.[18] The saponin showed analgesia activity in mice comparable to that of aminopyrine. The analgesia action time was shortened that of morphine and 1-terahyropalmatine. The total saponin induced sedative effect and inhibited caffeine-induced locomotive excitation.[19]

**Effects on cardiovascular system**

The saponin fraction of Panax notoginseng given intravenously to dogs decreased blood pressure and peripheral vascular resistance. The hypotensive effect of the saponins appeared to be due primarily to direct dilation of the blood vessel caused by inhibition on calcium-influx.[20-24] Heart rate was not affected.[25]

Antiarrhythmic effects of the total saponin and panaxatriol saponin were recorded on chlorom-induced ventricular fibrillation in mice, barium chloride or aconitine-induced arrhythmiz in rats, and epinephrine-induced arrhythmia in rabbits.[26, 27]

Experimental on animals showed that Rb, total saponins of the leaves and n-butylacoholic extracts of the roots of Panax notoginseng inhibited the maximum contractile effect on the calcium and shifted the concentration-response curves to the right in non-parallel manner in pig coronary strips. Relaxation induced by Rb was dependent on dose, the IC50 was 9.2 mg · ml⁻¹. Total saponins, Rg1, Rg2, and Ro did not have any effect on cumulative dose-response curves for calcium in pig coronary strip. Rb also reduced the maximum contractility response and shifted the concentration-response curves to the right in a non-parallel manner in puinea pig left atria.[28]

The extract of Panax notoginseng containing saponins and flavones decreased myocardial cAMP and cGMP, after oral administration for one week to mice. In rabbits with heart ischemia, the ST segment of T wave was normalized after treatment with the extract.[29] It was also found that the saponin was effective in protecting rabbits against hemorrhagic shock due to the improvement on heart function after intravenous injection of the saponin.[30]

In Root of Panax notoginseng, the active constituents include saponin, dencichine, flavonoid, and polysaccharide; however, the levels of these components vary in different geographical regions of growth and also show a seasonal variation. By using high-performance liquid chromatography and spectrophotometry, the contents of notoginsenoside R1, ginsenoside Rg1, Rg2, Rd, dencichine, flavonoid, and polysaccharide were determined and compared with Radix Notoginseng collected from different
regions of growth in China, as well as from different seasons of harvest and market grades. Using the contents of these active constituents as markers, the best quality of Radix notoginseng is found in the southwestern parts of Wenshan, and the best season for the harvest is September to October. In addition, the unseeded plants produced a better quality of Radix Notoginseng. The current results provide useful information for the quality control of Radix notoginseng and its further development in establishing the good agriculture practice standard of P. notoginseng in China.\[31\]

In order to explore the relationship between the active components and the functional links of Chinese herbs, the effect of Xuesaitong capsule, a preparation made of multi-component Panax notoginseng saponins (PNS) on platelet activating molecule expression and aggregation in patients with blood hyperviscosity syndrome (BHS) was observed, with aspirin (ASP) as a control. One hundred and twenty patients with BHS were divided, adopting randomized, double-blinded and double simulated principle into 2 groups, the PNS group and the ASP group, 60 in each group. Changes of the TCM clinical syndrome, platelet adhesion and aggregation, endothelin (ET), prostacyclin, thromboxane, CD62P and CD41 before treatment and after 28 days treatment was observed. Comparison between the therapeutic effects of the two groups on TCM clinical syndrome showed that the total effective rate in the PNS group was 86.67% and that in the ASP group 56.67%, showing significant difference (P < 0.05). Compared with before treatment, after treatment, levels of platelet adhesion and aggregation, endothelin, prostacyclin and thromboxane were significantly different in both groups (P < 0.05 or P < 0.01): levels of CD62P and CD41 in the PNS group were also significantly different, but the difference was insignificant in the ASP group: no significant difference was shown in both groups in levels of triglyceride, total cholesterol and very low density lipoprotein-cholesterol. PNS may inhibit activation of platelet through multiple components and multiple pathways, which is different from that of ASP, only through inhibition on arachidonic acid metabolism to suppress platelet aggregation. PNS has effects of decreasing platelet superficial activation, inhibiting platelet adhesion and aggregation, preventing thrombosis and improving microcirculation, and its therapeutic effect on clinical syndrome is better than that of ASR.\[32\]

**Action to experimental thrombosis**

To study the effect and the mechanism of Xuesaitong drop pills (total saponins in Radix Notoginseng; XDP) on experimental thrombosis, thrombolysis and blood theology. The rats were randomly divided into five groups: control, XDP (90, 30, 10 mg·kg\(^{-1}\)), Xuesaitong tablet (XP) 30 mg·kg\(^{-1}\). Then the effect of the drugs on thrombus and thrombosis was studied after the rats's thrombosis was induced by the arteriovenous shunt. Second, the rats were randomly divided into seven groups: model, XDP (90, 30, 10 mg ·kg\(^{-1}\)), XT (90, 30 mg·kg\(^{-1}\)), lumbrokinase capsule. Then the effect of the drugs on thrombus and thrombosis was studied after the rats thrombosis was induced by the electrical stimulation of common carotid artery. Third, the rats were randomly divided into six groups: control, model, XDP (80, 40, 20 mg·kg\(^{-1}\)), XT (40, 20 mg·kg\(^{-1}\)). Then the effect of the drugs on blood circulation promoting was observed after the rats' acute blood stasis induced by adrenalin and icy water. XDP 90, 30 mg·kg\(^{-1}\) could notably lighten the wet-weight and dry-weight of thrombus in the arteriovenous shunt model in rats in a dose-dependent manner (P< 0.01). XDP 90 mg·kg\(^{-1}\) with intragastric administration for 3 days had the satisfactory effect on thrombolysis after the rat's thrombosis was induced by the electrical stimulation of common carotid artery (P< 0.01). XDP 80, 40, 20 mg·kg\(^{-1}\) reduced significantly erythrocyte aggregation (P<0.01) and decreased the whole blood viscosity at low shear rate (P < 0.05). XDP 80, 40 mg·kg\(^{-1}\) reduced the whole blood viscosity at high shear rate and plasma viscosity (P< 0.05). XDP 80 mg·kg\(^{-1}\) decreased the whole blood viscosity at high shear rate (P< 0.05). XDP can significantly inhibit the thrombosis and has the satisfactory effect on thrombolysis. One kind of the mechanism is related to the effect on blood rheology.\[34\]

LC-ESI-MS methods were developed for the analysis of chemical and metabolic components in traditional Chinese medicinal combined prescription containing Radix Salvia miltiorrhiza and Radix Notoginseng (commonly known as Fufang Danshen prescription, FDP). The HPLC experiments used a reversed-phase Zorbax C18 column with the column temperature at 30 degrees C and a binary mobile phase system consisting of aqueous formic acid (0.1%) and acetonitrile using a gradient elution at the flow rate of 1.0 mL·min\(^{-1}\). The ESI-MS was operated with a single-quadrupole mass spectrometer in both negative and positive ion modes. 36 major chromatographic peaks of FDP, including 14 saponins, 13 phenolic acids and nine diterpenoid quinones were characterized by their MS spectra and in comparison with some of the reference standards. In addition, after oral administration of extraction of FDP, the rat's plasma, urine and feces were also analyzed; 53 metabolic components including 30 original components and 23 transformative components of FDP were detected, and possible metabolite pathways of some components in FDP were given. The analysis of chemical and metabolic components in FDP by HPLC-MS...
methods could be a useful means of identifying the multi-components of FDP and to hint at their possible metabolic mechanism of action in the body. [35]

Fufang Danshen (FFDS) is a famous typical Chinese complex prescription, which is mainly composed of Radix Salvia miltiorrhiza (SM) and Radix Notoginseng (PN). An HPLC method is developed to analyze SM, PN, and FFDS effectively; the effective analysis is achieved by using a gradient elution procedure with a mobile phase consisting of acetonitrile and 0.025% aqueous phosphoric acid (v/v). Through this method, 33 peaks in FFDS are clearly exhibited, and the components that make up the 33 peaks in FFDS are evaluated. Also, the chemical ingredients are compared between the single herbs (SM and PN) and the complex prescription (FFDS). The result indicate that the chemical ingredients in FFDS are not simply a combination of SM and PN. In addition, the HPLC method is suitable for the routine quality control of SM, PN, and FFDS, which could present a uniform quality control method for single medicines and one of the most commonly used Traditional Chinese Medicine-complex prescriptions. [36]

The nuclear 18S rRNA and chloroplast MATK genes of 18 samples of Panax notoginseng and its processed material (Radix Notoginseng) were analyzed. The two genes, regardless of cultivar origin, were found to be identical to genotype R1 and M1, respectively, of the published sequences (GenBank accession no. D85171 and AB027526). This phenomenon implies that the species is highly conserved, which is probably caused by the use of the same strain in cultivation and the lack of active mutation in these two genes. [37]

In Radix notoginseng, the main components, saponins, have been reported to have many pharmacological activities. To test the general assumption that herbs of a single species planted and harvested from a single location are uniform in chemical and genetic makeup, chemical analysis and DNA fingerprinting were carried out. High-performance TLC together with HPLC analysis were used to analyze 17 randomly sampled 3-year-old roots from a single farm for the presence of six saponins. Five roots showed distinct chemical profiles with changed ratios of ginsenosides Rd/Rg1, Re/Rg1, or Rb1/Rg1. The same samples, together with some 1- and 2-year-old samples, were also subjected to fluorescent amplified fragment length polymorphism (AFLP) analysis, and their internal transcribed spacer 2 (ITS 2) regions were sequenced. Fluorescent AFLP analysis was found to be much more polymorphic than the ITS 2 sequence and showed clear evidence of genetic diversity within the tested population. In conclusion, genetic diversity and variation of saponin contents between individual Panax notoginseng roots have been detected. We suggest that genetic diversity affects the contents of the six saponins. The saponin contents variation and genetic diversity were also found among Panax notoginseng root samples collected from China and Singapore markets. Since variable saponin contents may affect therapeutic efficacy, combining the use of genetic profiling with chemical profiling will help ensure greater uniformity in the quality of Panax notoginseng roots. The genetic and chemical diversity within a population also provides the opportunity for breeding new cultivars with more desirable chemical constituents. [38]

The root of Panax notoginseng is a commonly used traditional Chinese medicine, which is mainly cultivated in Yunnan China. The identified active constituents in Radix Notoginseng include saponin, ssavonoid and polysaccharide; however, the levels of these active constituents vary greatly with different extraction processes. This variation causes a serious problem in standardizing the herbal extract. By using HPLC and spectrophotometry, the contents of R1, Rg1, Rb1, Rd, and savonoids were determined in the extracts of Radix Notoginseng that were derived from different processes of extraction according to an orthogonal array experimental design having three variable parameters: nature of extraction solvent, extraction volume and extraction time. The nature of extraction solvent and extraction volume were two distinct factors in obtaining those active constituents, while the time of extraction was a subordinate factor. The optimized condition of extraction therefore is considered to be 20 volumes of water and extracted for 24 h. In good agreement with the amount of active constituents, the activity of anti-platelet aggregation was found to be the highest in the extract that contained a better yield of the active constituents. The current results provide an optimized extraction method for the quality control of Radix Notoginseng. [39]

The active constituents of Radix Notoginseng, include saponin, dencichine, flavonoid, and polysaccharide; however, the levels of these components vary in different geographical regions of growth and also show a seasonal variation. By using high-performance liquid chromatography and spectrophotometry, the contents of notoginsenoside R1, ginsenoside R(g1), R(b1), R(d), dencichine, flavonoid, and polysaccharide were determined and compared with Radix Notoginseng collected from different regions of growth in China, as well as from different seasons of harvest and market grades. Using the contents of these active constituents as markers, the best quality of Radix Notoginseng is found in the southwestern parts of Wenshan, and the best season for the harvest is September to October. In addition, the unseeded plants produced a better quality of Radix Notoginseng. The current results provide useful information for the quality
control of Radix Notoginseng and its further development in establishing the good agriculture practice standard of Panax notoginseng in China. [40]

A systematic evaluation on the levels of organochlorine pesticide residues (OCP) was conducted on four selected, authentic Chinese materia medica, namely: Radix Angelicae Sinensis, Radix Notoginseng, Radix Salviae Miltiorrhizae and Radix Ginseng. Altogether ten representative batches of samples were analysed for each herb. Six batches were collected in the major cultivation areas of the Mainland whilst the remaining four batches were procured in the Hong Kong herbal market. All except Radix Angelicae Sinensis have been identified as containing quintozene and hexachlorocyclohexane in various levels. Hexachloro-benzene and lindane were also reported in samples of Radix Ginseng. The banned pesticide, DDT and its derivatives, was also observed in one of the Radix Notoginseng samples. The investigation will be continued for a target list of common used herbs in Hong Kong. All the results will be gathered and analysed for setting up regulatory permissible limits of OCP residues in Chinese materia medica used in Hong Kong. [41]

It has been found that Sanqi of different size exhibits different curative effects. Such a phenomenon may be attributed to that the chemical constituent from shell region is different from that of core region. To prove the above-mentioned hypothesis, Ultraviolet-Visible (UV-Vis), FTIR, fluorescence spectroscopy, together with HPLC and electrospray ionization mass spectroscopy (ESI-MS) were utilized to study the variation of chemical compositions from shell and core regions of Sanqi. The results demonstrate that the chemical compositions of Sanqi from shell and core regions are different. In summary, differences in chemical composition between Sanqi shell and core were manifested from versatile aspects. Such differences shed a light on the different curative effects of Sanqi. [42]

To observe the effect of six common Chinese medicinal herbs for promoting blood circulation, including Radix Paeoniea rubra (I), Radix Salviae miltiorrhizae (II), Rhizoma Chuanxiong (III), Radix Notoginseng (IV), Semen Persicae (V) and wine steamed Radix et Rhizoma Rhei (VI), on blood lipids and inflammatory reaction of atherosclerotic plaques in ApoE gene deficiency mice. Ninety mice, 6 - 8 weeks old, were divided into 8 groups, the model group, the control group (treated with simvastatin) and the six treated groups treated with the above-mentioned 6 Chinese medicinal herbs respectively. All the mice were fed with the diet of western kind for 13 weeks until the mature atherosclerotic plaques formed in them. Then they were treated with respective drugs for another 13 weeks except those in the model group. All the mice were sacrificed at the end of experiment, their blood was collected for lipids determination, heart and aorta were taken out for determining the level of CD68 in root of aorta, as well as the expressions of monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) by immunohistochemistry staining. All the 6 Chinese herbs showed regulatory action on blood lipids. The positive expression of CD68 in the model group displayed the highest activity. As compared with the model group, the CD68 positive expressed cells in the control group and the groups treated with Chinese herbs II, III, and IV were lesser (P<0.05), and the expression of inflammatory factors (MCP-1 and TNF-α) in atherosclerotic plaques was significantly lower in the control group and the group treated with Chinese herb VI (P<0.05). Chinese medicinal herbs tested in this study can interfere the maturing progress of atherosclerotic plaques and stabilize the plaques in Apo E deficiency mice, the mechanisms may relate to its actions in regulating lipids metabolism and inhibiting inflammatory reaction. Different Chinese medicinal herbs for activating blood circulation of conventional dosage might show difference in potency and acting links. [43]

To establish the quantitative method of notoginsenoside R1, ginsenoside Rg1 and Rb1 in Radix Notoginseng and its preparation Xuesaitong injection by HPLC-ELSD. The column was packed with 5 microm Diamonsil C18 stationary phase. The mobile phase consisted of acetonitrile-water, eluted in gradient mode. The temperature of drift tube was 105 degrees C and the nebulizer nitrogen flow rate was 2.9 L x min⁻¹. The linear ranges of the three components were 0.456-2.25 microg, 1.47-7.38 µg and 1.20-6.03 µg respectively. The average recoveries of the three components in Radix Notoginseng were 97.1% (RSD 1.9%), 96.8% (RSD 2.0%), 97.0% (RSD 2.2%) respectively; in Xuesaitong Injection were 98.7% (RSD 1.9%), 98.5% (RSD 1.8%), 98.1% (RSD 1.4%) respectively. It was proved that the method was reliable, simple, and precise, that could be used for quality control. [44]

To study the derivation, acetylation specifically, as well as the application of evaporative light-scattering detector (ELSD) detection of Panax notoginseng extract for a better understanding of its components, as well as to study the authentication of this herb. Acetonitrile-water gradient elution of the samples was used for the analysis and the ultraviolet (UV) detection used to observe the difference between the extract samples before and after acetylation. Mobile phases containing 30% and 85% acetonitrile, respectively, were used to observe the differences between chromatograms of the samples obtained using UV and ELSD detection. By acetylating the extract before analysis, differentiation of the
early-eluting components was observed, some of the derivatives were retained extremely strongly. Different eluting profiles were obtained from the extract samples using UV and ELSD. Using the latter technique, different patterns of change in the retention of peaks could be observed, uncovering more information relating to the composition of the extract. The decrease of polarities of a part of the hydrophilic components as a result of acetylation of the extract and the differentiation of these early-eluting, difficult-to-separate compounds in the chromatograms should be helpful for the characterization and authentication of the TCM. ELSD can be used to detect the carbohydrates, which are known to have pharmacological effects, and sensitize the detection of glycosides. This is also helpful for the above-mentioned aspects.[45]

To select the optimum extraction process of Zhanjin Ruji. To observe influence of extraction time upon the extraction rate of volatile oil, the orthogonal test was adopted to observe the extraction process by alcohol from the extraction rate and content of the total saponins in Radix Notoginseng. The three kinds of herbs including Radix Angelicae Sinensis, Resina Olibani and Myrrha were extracted with water for 3 hours, 95% of volatile oil can be distilled. The three kinds of herbs including Radix Notoginseng, Herba Lycopodi and Radix Gentianae Macrophyllae were extracted by alcohol. Four factors such as alcohol concentration (A), extraction times (B), extraction time (C), and solvent amount (D), had not significant effect on the content of total saponins in Radix Notoginseng in herbal extraction, but factor A and B had significant effect on the extraction rate. The optimum extraction process was as follows extracted with 5 times the amount of the solvent volum 60% alcohol for 3 times and with each time for 1 hour. Three times experiments showed that the extraction rate was 26.5% and the content of the total saponins in Radix Notoginseng was 17.28% mg·g⁻¹. The above experimental results can provide experimental basis for deciding the extraction process of Zhanjin Ruji.[46]

In the model rat with precancerous lesion of stomach induced by the combined method of insertion of a spring into the pylorus and high salt hot paste, effects of Radix Notoginseng on gastric secretion and protective factors of stomach were investigated. The results indicated that gastric secretion, gastric mucosal blood flow (GMBF) and aminohexose content lowered significantly, and malondialdehyde (MDA) increased significantly (P < 0.01) in the model group as compared with the normal group; after treatment with Radix Notoginseng Powder for 12 weeks, both gastric secretion and GMBF increased, and MDA content decreased as compared with the negative control group (P < 0.01), with no significant increase of aminohexose content. It is suggested that Radix Notoginseng may improve gastric secretion, and that increase of GMBF and antagonism against the lesion of oxygen free radicals are possibly one of its mechanisms.[47]

To assess the effects of different natural medicines on the growth and acid production of Actinomyces viscosus, thus making preparations for screening an effective agent to mediate the balance of oral microflora. Actinomyces viscosus ATCC 19246 was chosen as the experimental bacteria. 11 kinds of traditional Chinese medicine, such as Rhizoma Ligustici Chauanxiong, Sargentodoxa Cuneata and Galla Chinensis were extracted by means of maceration, percolation and reflux extraction. First, the values of MIC of various extracts were measured. Second, the experimental medium containing various extracts was prepared. The concentration of the extracts was lower than the MIC of the medicine, and the initial pH of the medium was 7.4. Then Actinomyces viscosus was cultured in the medium for 48 h, and finally the rest pH was measured. When the concentration of the medicines was lower than or equal to 8.000 mg·ml⁻¹, it was found that all kinds of medicine except Radix Notoginseng can inhibit the growth of Actinomyces viscosus effectively, especially Polistes mandarinus and Semen Arecae. Tea polyphenols, Radix Notoginseng, Radix et Rhizoma Rhei, Polistes mandarinus and Sargentodoxa cuneata can inhibit the acid production of Actinomyces viscosus effectively, but Radix Scutellariae, Rhizoma Ligustici Chauanxiong, Semen Arecae, Radix Angelicae Dahuricae, Galla Chinensis and Catachu have no preliminary effect on it. Tea polyphenols, Radix et Rhizoma Rhei, Polistes mandarinus and Sargentodoxa cuneata can inhibit the growth and the acid production of Actinomyces viscosus effectively.[48]

To study the antioxidant, activity of Qizhu decoction (QZT) both in vivo and in vitro. QZT consists of 4 herbal constituents (Rhizoma Atractylodis Macrocephalae, Poria cocos, Radix Notoginseng, and Radix Astragali), each of the components and their combinations were examined in vitro for 1, 1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radical scavenging activities, and for the inhibition of thiobarbituric acid-reactive substances (TBARS) formation in rat liver homogenate. At the same time, their in vivo protective effect on cerebral ischemia-reperfusion injury was determined in rats. RESULTS: Only the preparations having a higher antioxidant activity comparable to QZT in all three in vitro assays were relatively active in vivo both for TBARS inhibition and glutathione peroxidase preservation, although the activities were much lower than that of QZT as a whole. QZT formula is a good natural antioxidant having an effective preventive effect against cerebral ischemia reperfusion damage.[49]
Qizhu Tang (QZT) was studied for its in vitro antioxidant activity and the effect on cerebral oxidative damage after forebrain ischemia followed by reperfusion in rats. The QZT decoction was shown to have strong hydroxyl radical (.OH) scavenging activity (approx. 0.1 mM as Trolox equivalent) when determined by ESR using DMPO as a spin trap reagent and H2O2/UV as the .OH source. When the QZT decoction was injected into rats duodenum 2 h before cerebral ischemia, the oxidative brain damage after 45 min reperfusion was strongly inhibited in terms of two biochemical indications, thiobarbituric acid reactive substance formation and the loss of glutathione peroxidase. Since the QZT formula consists of 4 herbal constituents (Rhizoma atractyloids, Poria, Radix notoginseng and Radix astragali), each of the component herbs and their combinations were also examined for their protective effects on the cerebral ischemia/reperfusion injury and the effects were compared with their in vitro antioxidant potential. Although some of the incomplete formulas showed as strong antioxidant activities as complete QZT in vitro, only the complete QZT formula was effective in preventing cerebral oxidative injury in rats, and other preparations showed limited activity in vivo.[50]

HPLC methods were developed for the determination of glycyrrhizin in Radix Glycyrrhizae and Rb1, Rb2, Re, Rd, Re, Rf and Rg in Radix Notoginseng. These methods were used as reference methods for near-infrared (NIR) spectroscopy. Spectroscopic calibrations were developed for the determination of glycyrrhizin, the total content of ginsenosides and the individual major ginsenosides Rb1, Rd, Re and Rg1. Standard errors of cross validation (SECV) were 1.22 mg·g−1 for glycyrrhizin (concentration range 21.3-34.1 mg·g−1) and 0.99 mg·g−1 for the sum of ginsenosides (concentration range 55.3-71.1 mg·g−1). The corresponding coefficients of determination R2 were 0.94 and 0.98, respectively. The SECVs were generally less than a factor 2.5 of the repeatability standard deviation of the HPLC methods.[51]

Previously, 185 ribosomal RNA gene and matK gene sequences of Chinese herbal medicines, Ginseng Radix, Panacis japonici Rhizoma and Panacis quinquefolii were shown to correspond with those of the original plants, Panax ginseng, Panax japonicus and Panax quinquefolius, respectively, with the species-specific sequences especially for 18S rRNA gene sequences. In Panax notoginseng and its derivative, however, researchers found two genetic groups with respect to both gene sequences. Five base substitutions were detected on both gene sequences and the homology between two groups was 99.7% for the 18S rRNA gene and 99.6% for the matK gene, respectively. One genetic group was found to have the identical sequences as those of P. ginseng.[52]

To evaluate the effects of four herbal medicine extracts on a rat model of inflammatory hyperalgesia. Inflammation was induced by injecting complete Freund's adjuvant (CFA) into one hindpaw of each rat. Four herbs that are routinely prescribed in Traditional Chinese Medicine for treatment of pain were used: (Radix Angelicae Pubescentis (Duhuo), Patriniae Herba cum Radice (Bai jiang cao), Rhizoma Corydalis (Yanhusuo) and Panax Notoginseng. The crude water extracts of the herbs were injected intraperitoneally following a repeated treatment profile. Thermal hyperalgesia was assessed by testing each rat's paw withdrawal response to a noxious thermal stimulus. The magnitude of edema was determined by measuring the maximal thickness of the paw with a caliper. The effect of herb extracts on motor performance was assessed by using an accelerating rotarod test. Duhuo, Bai jiang cao, and Yan hu su significantly attenuated CFA-induced hyperalgesia at 2 h and facilitated the recovery from hyperalgesia (P<0.05), when compared to saline-treated rats. The CFA-induced edema was reduced by Duhuo at 24, 72 and 168 h; Bai jiang cao at 24 h, and Yan hu su at 24 hours and 168 hours. Sanqi did not produce any significant effect on inflammation and hyperalgesia. The rotarod performance was slightly reduced by Bai jiang cao, Yan hu su, and Sanqi (P<0.05) but not by Duhuo treatment. The present study identified Duhuo as a selective and effective herbal agent in attenuating persistent hind paw inflammation and hyperalgesia in rats. These results indicate that some herbal agents may provide an alternative approach to the treatment of persistent inflammatory pain and hyperalgesia.[53]

To study the effect and the mechanism of Xuesaitong drop pills TPNS on experimental thrombosis, thrombolysis and blood theology. First, the rats were randomly divided into five groups: control, TPNS (90, 30, 10 mg · kg−1), Xuesaitong tablet (XT) 30 mg · kg−1. Then the effect of the drugs on thrombus and thrombosis was studied after the rats thrombosis was induced by the arteriogenous shunt. Second, the rats were randomly divided into seven groups: model, TPNS (90, 30, 10 mg · kg−1), XT (90, 30 mg · kg−1), lumbrukinase capsule. Then the effect of the drugs on thrombus and thrombosis was studied after the rats/thrombosis was induced by the electrical stimulation of common carotid artery. Third, the rats were randomly divided into six groups: control, model, TPNS (80, 40 mg· kg−1), XT (40, 20 mg· kg−1). Then the effect of the drugs on blood circulation promoting was observed after the rats'acute blood stasis induced by adrenalin and icy water. XDP 90, 30 mg· kg−1 could notably lighten the wet-weight and dry-weight of thrombus in the
arteriovenous shunt model in rats in a dose-dependent manner \((P<0.01)\). TPNS 90 mg·kg\(^{-1}\) with intragastric administration for 3 days had the satisfactory effect on thrombolysis after the rat's thrombosis was induced by the electrical stimulation of common carotid artery \((P<0.01)\). XDP 80, 40, 20 mg·kg\(^{-1}\) reduced significantly erythrocyte aggregation \((P<0.01)\) and decreased the whole blood viscosity at low shear rate \((P<0.05)\). TPNS 80, 40 mg·kg\(^{-1}\) reduced the whole blood viscosity at high shear rate and plasma viscosity \((P<0.05)\). TPNS 80 mg·kg\(^{-1}\) decreased the whole blood viscosity at high shear rate \((P<0.05)\). TPNS can significantly inhibit the thrombosis and has the satisfactory effect on thrombolytic. One kind of the mechanism is related to the effect on blood rheology.\(^{[54]}\)

High-performance liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) methods were developed for the analysis of chemical and metabolic components in traditional Chinese medicinal combined prescription containing Radix Salvia miltiorrhiza and Radix notoginseng (commonly known as Fufang Danshen prescription, FDP). The HPLC experiments used a reversed-phase Zorbax C18 column with the column temperature at 30 degrees C and a binary mobile phase system consisting of aqueous formic acid \((0.1\%, \text{v/v})\) and acetonitrile using a gradient elution at the flow rate of 1.0 mL·min\(^{-1}\). The ESI-MS was operated with a single-quadrupole mass spectrometer in both negative and positive ion modes. 36 major chromatographic peaks of FDP, including 14 saponins, 13 phenolic acids and nine diterpenoid quinones were characterized by their MS spectra and in comparison with some of the reference standards. In addition, after oral administration of extraction of FDP, the rat's plasma, urine and feces were also analyzed; 53 metabolic components including 30 original components and 23 transformative components of FDP were detected, and possible metabolic pathways of some components in FDP were given. The analysis of chemical and metabolic components in FDP by HPLC-MS methods could be a useful means of identifying the multi-components of FDP and to hint at their possible metabolic mechanism of action in the body.\(^{[55]}\)

Fufang Danshen (FFDS) is a famous typical Chinese complex prescription, which is mainly composed of Root of Salvia miltiorrhiza Bunge (SM) and Root of Panax notoginseng (PN) and the complex prescription (FFDS). The result indicate that the chemical ingredients in FFDS are not simply a combination of SM and PN. In addition, the HPLC method is suitable for the routine quality control of SM, PN, and FFDS, which could present a uniform quality control method for single medicines and one of the most commonly used Traditional Chinese Medicine-complex prescriptions.\(^{[56]}\)

The nuclear 18S rRNA and chloroplast MATK genes of 18 samples of Panax notoginseng and its processed material Radix Notoginseng were analyzed. The two genes, regardless of cultivar origin, were found to be identical to genotype R1 and M1, respectively, of the published sequences (GenBank accession no. D85171 and AB027526). This phenomenon implies that the species is highly conserved, which is probably caused by the use of the same strain in cultivation and the lack of active mutation in these two genes.\(^{[57]}\)

In Radix Notoginseng, the main components, saponins, have been reported to have many pharmacological activities. To test the general assumption that herbs of a single species planted and harvested from a single location are uniform in chemical and genetic makeup, chemical analysis and DNA fingerprinting were carried out. High-performance TLC together with HPLC analysis were used to analyze 17 randomly sampled 3-year-old roots from a single farm for the presence of six saponins. Five roots showed distinct chemical profiles with changed ratios of ginsenosides Rd/Rg1, Re/Rg1, or Rb1/Rg1. The same samples, together with some 1- and 2-year-old samples, were also subjected to fluorescent amplified fragment length polymorphism (AFLP) analysis, and their internal transcribed spacer 2 (ITS 2) regions were sequenced. Fluorescent AFLP analysis was found to be much more polymorphic than the ITS 2 sequence and showed clear evidence of genetic diversity within the tested population. In conclusion, genetic diversity and variation of saponin contents between individual P. notoginseng roots have been detected. We suggest that genetic diversity affects the contents of the six saponins. The saponin contents variation and genetic diversity were also found among Panax notoginseng root samples collected from China and Singapore markets. Since variable saponin contents may affect therapeutic efficacy, combining the use of genetic profiling with chemical profiling will help ensure greater uniformity in the quality of Panax notoginseng roots. The genetic and chemical diversity within a population also provides the opportunity for breeding new cultivars with more desirable chemical constituents.\(^{[58]}\)

The root of Panax notoginseng is a commonly used traditional Chinese medicine, which is mainly cultivated in Wenshan of Yunnan China. The identified active
Astragali
Quinquefolii
Chinese medical herbs under common names
herbs in any market outside of China. In this report,
there is no study on the gene tic heterogeneity of medical
common names in different regions in China. However,
in the extracts of spectrophotometry, the contents of notoginsenoside R1,
ginsenoside Rg1, Rb1, Rd, and sasavonoids were determined
in the extracts of Radix Notoginseng that were derived from
different processes of extraction according to an orthogonal
array experimental design having three variable parameters:
nature of extraction solvent, extraction volume and
extraction time. The nature of extraction solvent and
extraction volume were two distinct factors in obtaining
those active constituents, while the time of extraction was a
subordinate factor. The optimized condition of extraction
therefore is considered to be 20 volumes of water and
extracted for 24 h. In good agreement with the amount of
active constituents, the activity of anti-platelet aggregation
was found to be the highest in the extract that contained a
better yield of the active constituents. The current results
provide an optimized extraction method for the quality
control of Radix Notoginseng.[59]
A systematic evaluation on the levels of organochlorine
pesticide residues (OCP) was conducted on four selected,
authentic Chinese materia medica, namely: Radix
Angelicae Sinensis, Radix Notoginseng, Radix Salviae
miltiorrhizae and Radix Ginseng. Altogether ten
representative batches of samples were analysed for each
herb. Six batches were collected in the major cultivation
areas of the Mainland whilst the remaining four batches
were procured in the Hong Kong herbal market. All except
Radix Angelicae sinensis have been identified as containing
quintozene and hexachlorocyclohexane in various levels.
Hexachloro- benzene and lindane were also reported in
samples of Radix Ginseng. The banned pesticide, DDT and
its derivatives, was also observed in one of the Radix
Notoginseng samples. The investigation will be continued
for a target list of common used herbs in Hong Kong. All
the results will be gathered and analysed for setting up
regulatory permissible limits of OCP residues in Chinese
materia medica.[60] The different plant materials are used under the same
common names in different regions in China. However,
there is no study on the genetic heterogeneity of medical
herbs in any market outside of China. In this report,
Chinese medical herbs under common names Radix
Quinquefolii (American Ginseng or Xiyangshen), Radix
Astragali (Huangqi), Radix Notoginseng, Coptis
Cinnamomum, Radix Isatidis, Radix Codonopsis and
Radix Rehmannia were collected from three independent
herbal shops in Singapore and their DNAs were isolated
and subjected to fluorescence Amplified Fragment Length
Polymorphism (AFLP) analysis. While samples for Radix
Quinquefolii and Radix Astragali were homogenous
genetically [similarity index (SI) = 0.85-1.00] across the
three shops, genetic heterogeneity was found for the other
herbs (SI < 0.7). For example, four samples of Radix
Codonopsis were of three distinct patterns (SI < 0.6). Our
results highlight the situation that genetically distinct herbal
materials are labeled and marketed under the same common
names in an international market of Chinese medical herbs,
which may contribute to inconsistency in quality and
efficacy.[61] A water extract of Panax notoginseng is
being used as a therapeutic agent to stop haemorrhages and
as a tonic to promote health in Korean and Chinese
medicine. The pharmacokinetic profiles of PN have not
been accurately investigated. The preliminary aim was to
elucidate the pharmacokinetic features of PN. First, the
prevention of neutrophil functions was assessed. PN
inhibited neutrophil functions, including degranulation,
superoxide generation and leukotriene B4 production,
without any effect on 5-lipoxgenase activity. PN reduced
nitric oxide (NO) and prostaglandin (PGE2) production in
mouse peritoneal macrophages stimulated with
lipopolysaccharide (LPS) while no influence on the activity
of inducible NO synthase (iNOS), cyclo-oxygenase-2
(COX-2) or cyclo- oxygenase-1 (COX-1) was observed.
PN significantly reduced mouse paw oedema induced by
carrageenan. The results indicate that PN exerts
antiinflammatory effects related to the inhibition of
neutrophil functions and NO and PGE2 production, which
could be due to a decreased expression of iNOS and
COX-2.[62]
In the model rat with precancerous lesion of stomach
induced by the combined method of insertion of a spring
into the pylorus and high salt hot paste, effects of Radix
Notoginseng on gastric secretion and protective factors of
stomach were investigated. The results indicated that
gastric secretion, gastric mucosal blood flow (GMBF) and
aminohexose content lowered significantly, and
malondialdehyde (MDA) increased significantly (P < 0.01)
in the model group as compared with the normal group;
after treatment with Powder of Radix Notoginseng for 12
weeks, both gastric secession and GMBF increased, and
MDA content decreased as compared with the negative
control group (P < 0.01), with no significant increase of
aminohexose content. It is suggested that Radix
Notoginseng may improve gastric secretion, and that
increase of GMBF and antagonism against the lesion of
oxygen free radicals are possibly one of its mechanisms.[63]
Anti-inflammatory effects
Total saponins extracted from the flows of Panax
notoginseng 50-100 mg·kg-1 inhibited significantly the
edemas of the rat paws and the inflammation of the mouse auricles induced by many agents. This action of the saponins did not depend on the existence of the adrenals.\textsuperscript{22} The saponins decreased the anti-inflammatory effect may be direct action, the saponins may act indirectly via the pituitary adrenocortical system\textsuperscript{20,64}.

The pharmacological findings of the \textit{Panax notoginseng} have been based on the saponins or sterol glycosides, although polysaccharides with immuno-potentiating activity, proteins with antifungal, ribonuclease and xylanase activity, and a triacylglycerol (trilinolein) with antioxidant activity have been reported. Protective actions against cerebral ischaemia, beneficial effects on the cardiovascular system, and haemostatic, antioxidant, hypolipidaemic, hepatoprotective, renoprotective and estrogen-like activities have been described. Various methods for authentication of \textit{Panax notoginseng} are available.\textsuperscript{65}

Although there has been some success with protein-based anti-tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) therapeutics, the problems associated with protein-based drugs demand alternative approaches. Researchers screened various herbal extracts for their ability to inhibit TNF-\(\alpha\) secretions and found that BT-201, an n-butanol extract of \textit{Panax notoginseng} has such an ability. The purpose of this study has been to evaluate the anti-inflammatory and anti-rheumatic effects of BT-201. The anti-inflammatory effects were evaluated by measuring the effects of BT-201 on the production of TNF-\(\alpha\), IL-1\(\beta\), inducible nitric oxide (iNO), and matrix metalloproteinase-13 (MMP-13), \textit{in vitro}. The anti-rheumatic effects were evaluated by treating mice with collagen-induced arthritis (CIA) using a daily oral administration of BT-201 at 15 mg kg\(^{-1}\)d\(^{-1}\). In addition, the effects on NF-kB and mitogen-activated protein kinase (MAPK) pathways were evaluated by Western blotting using phospho-specific antibodies. BT-201 significantly inhibited all the inflammatory parameters evaluated in vitro and delayed the onset and progression of CIA. BT-201 inhibited the activation of NF-kB, ERK, p38, and JNK pathways. The results demonstrated that BT-201 can modulate various aspects of inflammation in vitro and that it has disease-modifying, anti-rheumatic effects in vivo, suggesting that it can be a potential alternative to the current anti-TNF-alpha therapeutics for rheumatoid arthritis and other inflammatory disease.\textsuperscript{66}

Immunological adjuvant effect

Ginsenoside Rh4, a saponin isolated from the roots of \textit{Panax notoginseng}, was evaluated for its haemolytic activity and adjuvant potential on specific antibody and cellular response to ovalbumin (OVA) in mice. Compound 1 showed a slight haemolytic effect, its concentration inducing 50\% of the maximum haemolysis (HD(50) value) being 407±12 microg/ml using a 0.5\% suspension of red blood cells. Compound 1 significantly increased the concanavalin A (Con A)-, lipopolysaccharide (LPS)-, and OVA-induced splenocyte proliferation in OVA-immunized mice especially at a dose of 25 microg (\(P<0.05\), \(P<0.01\), or \(P<0.001\)). The OVA-specific IgG1, IgG2a, and IgG2b antibody levels were also significantly enhanced by 1 at a dose of 25 microg compared to the OVA control group (\(P<0.05\) or \(P<0.01\)). Moreover, the enhancing effect of 1 on the OVA-specific IgG2b antibody responses to OVA in mice was more significant than that of Alum (Al(OH)(3) gel; \(P<0.01\)). These results suggest that 1 could be safely used as adjuvant with low or non-haemolytic effect.\textsuperscript{67}

Hepaprotective action

The increase in the SGPT induced by tetrachloride carbon in mice was significantly inhibited by sc injection of total saponins.\textsuperscript{29} In liver, kidney and testis of mice, the protein and DNA synthesis was also significantly increased by oral administration of total saponins.\textsuperscript{29}

Studies on Drug Metabolism and Pharmacokinetics

Structure-similar ginsenosides have different or even totally opposite biological activities, and manipulation of ginsenoside heterogeneity is interesting and significant to biotechnological application. In this work, addition of 1 mM phenobarbital to cell cultures of Panax notoginseng at a relatively high inoculation size of 7.6 g dry cell weight (DW)/L enhanced the production of protopanaxatriol-type (Rg1+Re) ginsenosides in both shake flask and airlift bioreactor (ALR, 1 L working volume). The content of Rg1+Re in the ALR was increased from 42.5 ± 4.0 mg per gram DW in untreated cell cultures (control) to 56.4 ± 4.6 mg per gram DW with addition of 1.0 mMol phenobarbital. The maximum productivity of Rg1+Re in the ALR reached 5.66 ± 0.38 mg L\(^{-1}\) d\(^{-1}\), which was almost 3.3-fold that of control. The maximum ratio of the detectable ginsenosides protopanaxatriol:protopanaxadiol (Rb1) was 7.6, which was about two fold that of control. The response of protopanaxadiol 6-hydroxylase (P6H) activity to phenobarbital addition coincided with the above-mentioned change of ginsenoside heterogeneity (distribution). Phenobarbital addition is considered as a useful strategy for manipulating the ginsenoside heterogeneity in bioreactor with enhanced biosynthesis of protopanaxatriol by \textit{Panax notoginseng} cells.\textsuperscript{68}

The efficient manipulation of ginsenoside heterogeneity of Panax notoginseng cells using a recently synthesized
elicitor, 2-hydroxyethyl jasmonate (HEJ, at 200 microM), has been reported. In this work, the activities of two enzymes related to ginsenoside heterogeneity (distribution), propanaxadiol 6-hydroxylase (P6H) and UDPG-ginsenoside Rd glucosyltransferase (UGRdGT), were examined in cell cultures of Panax notoginseng elicited by HEJ. P6H and UGRdGT activities were increased by HEJ with corresponding changes in Rb/Rg ratio and Rb1/Rd ratio. Endogenous jasmonic acid (JA) seemed to mediate the induction of UGRdGT activation, but was not involved in P6H activation. The results suggest that JA, as a signal transducer, may play an important role in the alteration of ginsenoside heterogeneity in elicited Panax notoginseng cells.

The purpose of this research is to evaluate the effect of self-micelle formation and incorporation of lipid in the formulation on absorption of Rg1 and Rb1 from intestinal tract in rats. Rg1 and Rb1 were extracted from PNS. The critical micellar concentration (CMC) of PNS in deionized water was determined to be 0.339 mg·mL⁻¹. At normal physiological ionic strengths, PNS was salted out from the solution above the CMC. The particle size of the micelle grows as PNS concentration increases. By in situ injection to a closed loop of the rat jejunum, AUC(0-6h) obtained after administration of low concentration solution (12mg·mL⁻¹) was 3.61 times for g Rg1 and 3.84-folds for ginsenoside Rb1 compared with high concentration solution (120 mg·mL⁻¹). The release rate of ginsenosides in aqueous medium was too slow to complete in 24h, especially for Rb1. The data suggested that the self-micelle formation tendency in ginsenosides might prevent them from permeation or absorption through the cell membrane of gastrointestinal (GI) tract. To inhibit the formation of micelles, lipid was incorporated in the PNS formulation. The intraduodenal bioavailability in rats showed that the bioavailability was enhanced remarkably relative to the aqueous solution. AUC(0-inf) of ginsenoside Rg1 and Rb1 in the lipid-based formulation were 207.52±53.95 and 148.58±36.73 mug ml⁻¹h, respectively from its aqueous solution above the CMC. The particle size of the micelle grows as PNS concentration increases. By in situ injection to a closed loop of the rat jejunum, AUC(0-6h) obtained after administration of low concentration solution (12mg·mL⁻¹) was 3.61 times for g Rg1 and 3.84-folds for ginsenoside Rb1 compared with high concentration solution (120 mg·mL⁻¹). The release rate of ginsenosides in aqueous medium was too slow to complete in 24h, especially for Rb1. The data suggested that the self-micelle formation tendency in ginsenosides might prevent them from permeation or absorption through the cell membrane of gastrointestinal (GI) tract. To inhibit the formation of micelles, lipid was incorporated in the PNS formulation. The intraduodenal bioavailability in rats showed that the bioavailability was enhanced remarkably relative to the aqueous solution. AUC(0-inf) of ginsenoside Rg1 and Rb1 in the lipid-based formulation were 207.52±53.95 and 148.58±36.73 mug ml⁻¹h, respectively from its aqueous solution. These findings suggested a new strategy to increase the absorption of amphiphilic saponins.

LC-ESI-MS methods were developed for the analysis of chemical and metabolic components in traditional Chinese medicinal combined prescription containing Radix Salvia miltiorrhiza and Radix Notoginseng (commonly known as Fufang Danshen prescription, FDP). The HPLC experiments used a reversed-phase Zorbax C18 column with the column temperature at 30 degrees C and a binary mobile phase system consisting of aqueous formic acid (0.1%, v/v) and acetonitrile using a gradient elution at the flow rate of 1.0 mL·min⁻¹. The ESI-MS was operated with a single-quadrupole mass spectrometer in both negative and positive ion modes. 36 major chromatographic peaks of FDP, including 14 saponins, 13 phenolic acids and nine diterpenoid quinones were characterized by their MS spectra and in comparison with some of the reference standards. In addition, after oral administration of extraction of FDP, the rat's plasma, urine and feces were also analyzed; 53 metabolic components including 30 original components and 23 transformative components of FDP were detected, and possible metabolic pathways of some components in FDP were given. The analysis of chemical and metabolic components in FDP by HPLC-MS methods could be a useful means of identifying the multi-components of FDP and to hint at their possible metabolic mechanism of action in the body.

LC-ESI/MS method was employed for the pharmacokinetic evaluation of total PNS (TPNS) in rats. After oral or intravenous administration of TPNS at the dosage of 300.0 or 10.0 mg·kg⁻¹ to rats respectively, R1, Rg1, Rd, Re and Rb1 were simultaneously determined in rat plasma. Pharmacokinetic parameters and absolute bioavailability of R1, Rg1, Rd, Re and Rb1 were obtained by the Drug And Statistics for windows (DAS) pharmacokinetic software. The pharmacokinetic parameters of all analytes were different form each other. T½ was changed from 0.72 to 22.16 h and AUC was changed from 1.03 to 98.94 mg·L⁻¹·h after oral or intravenous administration TPNS or TPNS injection. The absolute bioavailability of R1, Rg1, Rd, Re and Rb1 were of 9.29%, 6.06%, 2.36%, 7.06% and 1.18%, respectively.

To clarify the cause of poor oral absorption of Rg1, the active ingredient in PNS used for treating hemorrhage. Caco-2 cell monolayers were used as an in vitro model to study the transport mechanism of Rg1 across the intestinal mucosa. Moreover, the serum concentration-time profiles after peroral (po), intraduodenal (id), portal venous (pv) and tail venous (iv) administration of Rg1 in rats were compared to evaluate the first-pass effects in the stomach, intestine, and liver. Uptake of Rg1 by Caco-2 cell monolayers was temperature-dependent, but was not influenced by cyclosporin A. The change in the apical pH produced no obvious effect on the uptake of Rg1. The uptake and transport of Rg1 was non-saturable; whereas the flux from the apical compartment to the basolateral compartment (A-B) increased in a linear manner with the increase in concentration, indicating passive transport. An apparent permeability coefficient of (2.59±0.17)·10⁻⁷ cm·s⁻¹ (C0=1 mg·mL⁻¹) predicted incomplete absorption. A significant difference was observed between the po (F(po) was 3.29% at a dose of 1500 mg·kg⁻¹), id (F(id) was 6.60% at a dose of 1200 mg·kg⁻¹) and pv (F(pv) was 50.56%)
administration methods, and the barrier function of the intestine was more significant than those of the stomach and liver in the absorption process. Elimination in the stomach, large intestine and liver contributed to the low oral bioavailability of Rg1, but low membrane permeability might be a more important factor in determining the extent of absorption.[73]

To study the mechanism of absorption after oral administration of PNS, Caco-2 cells and rat models were applied to evaluate the degradation of both Rb1 and Rg1 in PNS in gastrointestinal lumen, and the transport mechanism of PNS across the intestinal mucosa, and the barrier function of stomach, intestine and liver involved in absorption process. Rb1 and Rg1 proved to be readily eliminated in stomach, but stable in relatively neutral circumstance. Both Rb1 and Rg1 in PNS, especially for Rb1, degraded significantly in the contents of large intestine. However, both of them kept mainly intact in the contents of small intestine. Uptake of both Rb1 and Rg1 by Caco-2 cell monolayer was inhibited at low temperature, but not by cyclosporine A, and the change in the apical pH showed no pronounced effect. Uptake and transport were non-saturable and increased linearly with increasing of concentrations of Rb1 and Rg1 over the range of concentration tested, which indicated a passive transport. There was no significant difference of absorption characteristic between monomer (Rb1 and Rg1) and mixture (PNS). Uptake amount of Rg1 (1.07 ± 0.16 µg·mg⁻¹ protein (C0 = 1 mg·mL⁻¹) in Caco-2 cells was a little higher than that of Rb1 (0.77 ± 0.03) µg·mg⁻¹ protein (C0 = 1 mg·mL⁻¹). Meanwhile, apparent permeability coefficient of (5.90±1.02) ·10⁻⁸ cm·s⁻¹ (C0 = 1 mg·mL⁻¹) predicted an incomplete absorption. The investigation on the pharmacokinetic behavior of Rb1 after different routes of administration to rats showed a significant difference between PO (F(PO) was 0.64%), ID (F(ID) was 2.46%) and PV (F(PV) was 59.49%) administration, and the first-pass effect of the intestine is more significant than that of the stomach and liver in the absorption process. In summary, elimination in the stomach, large intestine and liver contributed to the poor absorption of Rb1, but the low membrane permeability might be a more important factor dominating the extent of absorption.[73]

Metabolomics study

Metabolite profiling of five medicinal Panax herbs including Panax ginseng, Panax notoginseng, Panax japonicus (Rhizoma Panaxis Majoris), and Panax quinquefolium were performed using ultra-performance LC-quadrupole TOF-MS (UPLC-QTOFMS) and multivariate statistical analysis technique. Principal component analysis (PCA) of the analytical data showed that the five Panax herbs could be separated into five different groups of phytochemicals. The chemical markers such as ginsenoside Rf, 20(S)-pseudoginsenoside F11, malonyl gisenoside Rb1, and gisenoside Rb2 accountable for such variations were identified through the loadings plot of PCA, and were identified tentatively by the accurate mass of TOFMS and partially verified by the available reference standards. Results from this study indicate that the proposed method is reliable for the rapid analysis of a group of metabolites present in herbal medicines and other natural products and applicable in the differentiation of complex samples that share similar chemical ingredients.[76]

In another paper, the metabolite profiling of different parts of Panax notoginseng was carried out using rapid UPLC-ESI-MS and multivariate statistical analysis.
Principal component analysis (PCA) of the UPLC-ESI-MS data showed a clear separation of compositions among the flower buds, roots and rhizomes of Panax notoginseng. The saponins accounting for such variations were identified through the corresponding loadings weights and were further verified by accurate mass, tandem mass and retention times of available standard saponins using UPLC-QTOFMS. Finally, the influential factors of different metabolic phenotypes of Panax notoginseng was elucidated. The currently proposed UPLC-ESI-MS/MS analytical method coupled with multivariate statistical analysis can be further utilized to evaluate chemical components obtained from different parts of the plant and/or the plant of different geographical locations, thereby classifying the medicinal plant resources and potentially elucidating the mechanism of inherent phytochemical diversity.[77]

Toxicity and safety studies

The LD₅₀ of the total saponins of Panax notoginseng in mice was 1667 mg·kg⁻¹.[78] The dried rhizome of Panax notoginseng is a traditional Chinese herb extensively used for treatment of cardiovascular diseases and other ailments. PNS are known as the major pharmacologically active constituents. The purpose of this study was to investigate the cardioprotective effects of PNS against doxorubicin-induced cardiotoxicity and its possible influence on the anti-tumor activity of doxorubicin. Five groups of ICR mice were treated with saline (control group), doxorubicin alone (20 mg·kg⁻¹ I. P.), PNS alone, doxorubicin pretreated with PNS (100 mg·kg⁻¹ I. G. for 5 consecutive days) or amifostine (single dose of 200 mg·kg⁻¹ I. V., used as positive control). After 72 h of doxorubicin treatment, cardiac function, serum levels of lactate dehydrogenase (LDH), creatine kinase (CK) and creatine kinase isoenzyme (CK-MB) and activities of antioxidant enzymes in heart tissue were measured. Pretreatment with PNS significantly protected the mice from DOX-induced cardiotoxicity as evidenced from improved ventricular contractile function, lower levels of serum LDH, CK and CK-MB, minimal morphological changes in hearts, and normalization of myocardial superoxide dismutase, glutathione peroxidase and catalase activities. Additionally, in vitro cytotoxic studies demonstrated that PNS did not compromise the inhibitory effect of doxorubicin on the proliferation of cancer cells. These results imply the potentially clinical application of PNS to overcome the negative side effects of doxorubicin.[79]

The study was aimed to investigate the inhibitory effect of Panax notoginseng saponins (PNS) on the leukocyte adhesion and the expression of adhesion molecules in rat mesentery venules. Male Sprague-Dawley rats were anesthetized with urethane. These were divided into control, LPS (perfused with lipopolysaccharide), and PNS group (perfused with PNS). The mesenteric microcirculation was observed under a videomicroscope. The number of adherent leukocytes, which attached to the vascular wall during more than 10 seconds, was counted along single venules (30-50 μm in diameter, 200 μm in length). The expression of adhesion molecules was examined using flow-cytometry in blood which was taken from the abdominal aorta and incubated with FITC-labeled CD11b (or CD18) antibodies. The results showed that different changes in the leukocyte adhesion and the expression of adhesion molecules among three groups. In LPS group, the leukocyte adhesion increased significantly after 20 minutes during the observation time, while it was reduced markedly in PNS group. The expression of CD11b and CD18 on the neutrophils was induced in LPS group, while it was reduced significantly in PNS group. It was suggested that PNS could reduce leukocyte adhesion in venules under the inhibitory effect on the expression of adhesion molecules (CD11b and CD18) on neutrophils.[80]

Clinical pharmacology and application

Radix notoginseng is one of the most important components of famous Chinese recipe (Yunan Baiyao) and possesses a wide variety of applications in clinical practice. The herb is officially listed in the Chinese Pharmacopoeia. The medicinal use of the herb in different from that of ginseng. It is used mainly as a hemostatic drug in the treatment of different types of bleeding. Radix notoginseng had been showed to have satisfactory therapeutic effect on coronary disease, hemoptysis, hematuria, head injury and infieltal acute nephritis.

Clinical pharmacological studies exhibited that oral administration of 1-1.5 g Panax notoginseng did not produce any side effects, but a few patients complained nausea, repeated vomiting tendency of hemorrhagic as blood-tinged sputum, epistaxis, ingival bleeding, and menenorrhage. These simoons usually abated or disappeared, spontaneously without discontinuing the treatment.[81]

A single dose of 5 g by mouth may cause II degree atrioventricular block indicating the influence of large dose of the herb on the conduction system of heart.[81]

116 cases of coronary angina pectoris were treated with a powder composed of Radix Ginseng, Radix Notoginseng and Succinum, which was an empirical prescription of Dr. Yue Meizhong and compared with patients treated Fufang Danshen Tablet (a compound prescription of Radix Salviae Miltiorrhizae) as the control
group. Results indicated that the curative effects and ECG in the treated group were better than that in the control group \( (P < 0.01) \), so were improvement of general symptoms, physical strength as well as changes of lipid metabolism and microcirculation of nail fold.\[82\]

In order to explore the relationship between the active components and the functional links of Chinese herbs, the effect of Xuesaitong capsule, a preparation made of multi-component PNS on platelet activating molecule expression and aggregation in patients with blood hyperviscosity syndrome (BHS) was observed, with aspirin (ASP) as a control. Researchers had this study in 120 patients with BHS. The patients were divided, adopting randomized, double-blinded and double simulated principle into 2 groups, the PNS group and the ASP group, 60 in each group. Changes of the TCM clinical syndrome, platelet adhesion and aggregation, endothelin (ET), prostacyclin, thromboxane, CD62P and CD41 before treatment and after 28 days treatment were observed. The results indicated that comparison between the therapeutic effects of the two groups on TCM clinical syndrome showed that the total effective rate in the PNS group was 86.67\% and that in the ASP group 56.67\%, showing significant difference \( (P < 0.05) \). Compared with before treatment, after treatment, levels of platelet adhesion and aggregation, endothelin, prostacyclin and thromboxane were significantly different in both groups \( (P < 0.05 \text{ or } P < 0.01) \); levels of CD62P and CD41 in the PNS group were also significantly different, but the difference was insignificant in the ASP group; no significant difference was shown in both groups in levels of triglyceride, total cholesterol and very low density lipoprotein-cholesterol. PNS may inhibit activation of platelet through multiple components and multiple pathways, which is different from that of ASP, only through inhibition on arachidonic acid metabolism to suppress platelet aggregation. PNS has effects of decreasing platelet superficial activation, inhibiting platelet adhesion and aggregation, preventing thrombosis and improving microcirculation, and its therapeutic effect on clinical syndrome is better than that of ASP.\[83\]

To study the therapeutic effect and possible mechanism of total notoginseng saponins (PNS) for treatment of rheumatoid arthritis (RA), and to observe its safety and influence on RA immune related inner environment. Eighty-four patients were randomly assigned to two groups. All were treated with the routine therapy with diclofenac sodium, Leflunomide and prednisone, but for the 43 patients in the treatment group PNS was given additionally. The therapeutic course was 28 days for both groups. Clinical efficacy and change of indexes including platelet counts, immunoglobulins (IgG, IgA, IgM), complement (C3, rheumatoid factor (RF), C-reactive protein (CRP), ceruloplasmin (CER), haptoglobin (HPT), and alpha1-acid glycoprotein (AAG) were observed. RESULTS: Significant improvement of clinical symptoms, including the joint swelling index, joint tenderness index, joint pain index, time of morning stiffness and VAS revealed in both groups after treatment, and the effect in the treatment group was better \( (P < 0.05 \text{ or } P < 0.01) \). PLT, CER, AAG, HPT, CRP, IgG, IgA, IgM, C3 and RF were lowered in both groups \( (P < 0.01) \), but the lowering in PLT, CER, AAG and CRP in the treatment group was more significant than that in the control group respectively \( (P < 0.05 \text{ or } P < 0.01) \). PNS can significantly improve the condition of patients, enhance the therapeutic effect in treating RA, through regulating the disordered immunity and improving the effect of anti-inflammatory and analgesia.\[84\]

For clinical application, a traditional Chinese medicine compound recipe (TCMCR) Shuxiong sustained-release capsules (SXSRC) were prepared by multiparticulate time-controlled explosion technology. First, Shuxiong pellets were prepared with the refined medicinal materials containing in the recipe of Shuxiong tablets. Then, the pellets were coated sequentially with an inner swelling layer containing low-substituted hydroxypropyl- cellulose as the swelling agent and an outer rupturable layer of ethylcellulose. Finally, SXSRC were developed by encapsulating five kinds of pellets whose respective coating level of outer layer was 0\%, 9\%, 15\%, 18\% and 20\% at equivalent ratio in hard gelatin capsules. Under the simulated gastrointestinal pH conditions, the \textit{in vitro} release test of SXSRC was carried out. The value of similarity factor \( (f2) \) of hydroxysafflor yellow A and Panax
notoginseng saponins, hydroxysafflor yellow A and ferulic acid, Panax notoginseng saponins and ferulic acid was 90.1, 77.3, 87.0, respectively. The release profiles of these three compositions from SXSRC showed a characteristic of obvious sustained-release and no significant difference between them. The results indicated that using multiparticulate time-controlled explosion technology various components in TCMCR with vastly different physicochemical properties could be released synchronously while sustained-releasing. That complies with the organic whole conception of compound compatibility of TCMCR.[85]

Panax notoginseng is a commonly used Chinese herb. Although a few studies have found that notoginseng shows anti-tumor effects, the effect of this herb on colorectal cancer cells has not been investigated. 5-Fluorouracil (5-FU) is a chemotherapeutic agent for the treatment of colorectal cancer that interferes with the growth of cancer cells. However, this compound has serious side effects at high doses. In this study, using HCT-116 human colorectal cancer cell line, we investigated the possible synergistic anti-cancer effects between notoginseng flower extract (NGF) and 5-FU on colon cancer cells. The anti-proliferation activity of these modes of treatment was evaluated by MTS cell proliferation assay. Apoptotic effects were analyzed by using Hoechst 33258 staining and Annexin-V/PI staining assays. The anti-proliferation effects of four major single compounds from NGF, ginsenosides Rb1, Rb3, Rc and Rg3 were also analyzed. Both 5-FU and NGF inhibited proliferation of HCT-116 cells. With increasing doses of 5-FU, the anti-proliferation effect was slowly increased. The combined usage of 5-FU 5 µMol and NGF 0.25 mg/ml, significantly increased the anti-proliferation effect (59.4 ± 3.3%) compared with using 5-FU 5 µMol, 31.1 ± 0.4%; NGF 0.25 mg·ml⁻¹, 25.3 ± 3.6%). Apoptotic analysis showed that at this concentration, 5-FU did not exert an apoptotic effect, while apoptotic cells induced by NGF were observed, suggesting that the anti-proliferation target of NGF may be different from that of 5-FU, which is known to inhibit thymidilate synthase. This study demonstrates that NGF can enhance the anti-proliferation effect of 5-FU on HCT-116 human colorectal cancer cells and may decrease the dosage of 5-FU needed for colorectal cancer treatment.[86]

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