New Progress on the Pharmacological and Pharmacokinetical Study of Ginsenoside Rg3
Chen Xin-Mei*, Zhou Chang-Zheng and Zhang Xiao-Ping
College of Pharmacy, Shandong University of Traditional Chinese Medicine, Ji′nan, 250355, China

Abstract
More than 40 kinds of ginsenosides have already been isolated from white or red ginseng. Recent years, a great interest has been focused on the effects of a single ginsenoside, ginsenoside Rg3, which is a minor ginsenoside in panax ginseng and is reported showing various medicinal effects. Ginsenoside Rg3 is now one of the most popular research projects of the world, and it provides a good material to overcome cancer. According to the reports of literature, this article summarized the origin, characterization, pharmacological activities, metabolism and the pharmacokinetic studies of ginsenoside Rg3. The brief summary on the progress of the research will provide the basis for the further development and utilization.

Keywords: Ginsenoside Rg3; Pharmacological activities; Metabolism; Pharmacokinetics

Introduction
Panax ginseng is a well-known medicinal herb commonly used worldwide for many years, which has been used medicinally for several millennia and is currently one of the most widely consumed herbal products all over the world. It has been applied to treat many disorders, such as debility, aging, stress, diabetes, insomnia and sexual inadequacy. The pharmacologically active components of ginseng are ginsenosides which have demonstrated various biological activities, including anti-inflammatory and anti-tumor effects and so on. Ginsenosides with a dammarane skeleton are classified into two categories: 20(S)-protopanaxadiol (ppd) and 20(S)-protopanaxatriol (ppt) compounds, has been regarded as the major active component of P. ginseng C.A. Meyer [1]. Ginsenoside Rg3, a minor ginsenoside from the panax ginseng, is ppd type compound which is an active component in Red Ginseng. Two new conversation ginsenosides having cyclic ether were isolated from dehydration products of 20(S)-ginsenoside Rg3, which confirmed the existence from red ginseng extract by liquid chromatography [2]. Developed as a promising new anti-cancer agent, ginsenoside Rg3 has a good chance to be used as the major active component in a Category-I drug of anti-tumor and anti-cancer in China.

Pharmacological Activities
Ginsenoside Rg3 has been proposed to be used as a chemotherapeutic agent. Recent reports have demonstrated ginsenoside Rg3 has anti-cancer and various pharmacological effects [3]. Ginsenoside Rg3 can suppress some kinds of tumor from growing, induces tumor cell apoptosis, selectively inhibits tumor cell adhesion and invasion, resists tumor metastasis and then regulates the immune function.

Anti-tumor and anti-cancer effects
Lung cancer: Chen et al. [4] used the method of in vitro cell culture, drug interferences and gene chip to observe Rg3 on relevant expressed genes for the different signal transduction of human lung cancer cell lines A594, which indicated Rg3 had a significance effect on the signal transduction of human lung cancer cell lines A594, then the effect of Rg3 is multi-target on genes to human lung cancer cell lines A594 rather than on one certain gene. The clinical observation hold that the treatment of Rg3 to lung cancer mixed with chemotherapy is more effective and significantly higher than chemotherapy alone. Liu et al. [5] studied that the combination of low-dose chemotherapy and anti-angiogenic inhibitors suppress growth of experimental tumors more efficiently than conventional therapy or anti-angiogenic agent alone. This may be an innovative and promising therapeutic strategy in the experimental treatment of human lung cancer. Sun et al. [6] reported that the Shenyi capsule (ginsenoside Rg3 capsule) had significantly inhibitory effect on B16-4A5 cell growth and induced the apoptosis.

Colon cancer: A certain concentration of Rg3 or tumor relevant apoptosis-inducing ligand (TRA IL) can effectively inhibit the growth of colon cancer cell lines HCE8693, but the former effect is slightly weaker and more dependent than the latter, when the two combine with each other, the inhibition and apoptosis to HCE8693, the effect was highly increased compared with the individual factors and had obvious synergistic effects. A research about the proteomic analysis of the anti-cancer effect of 20(S)-ginsenoside Rg3 in human colon cancer cell lines was studied for 20(S)-ginsenoside Rg3 can increase the anti-proliferative effects of chemotherapy [3]. The mechanism of the anti-proliferative effect of 20(S)-ginsenoside Rg3 at the protein level in HT-29 colon cancer cells was investigated using two-dimensional gel electrophoresis and MALDI-TOF/TOF MS, and also a database was used to identify protein changes in 20(S)-ginsenoside Rg3 treated HT-29 cells. The cytotoxicity of 20(S)-ginsenoside Rg3 in colon cancer is dependent on several mechanisms including apoptosis. Kim et al. [7] examined the susceptibility of colon cancer cells treated with Rg3 and the results indicated that ginsenoside Rg3 could induce activation of NF-xB and enhance the susceptibility of colon cancer cells and it could be useful as an anti-cancer agent.

*Corresponding author: Chen Xin-Mei, Vice Professor, College of Pharmacy, Shandong University of Traditional Chinese Medicine, Ji′nan, 250355, China, E-mail: xinmeichen@126.com

Received November 09, 2011; Accepted December 20, 2011; Published December 22, 2011


Copyright: © 2012 Xin-Mei C, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
**Ovarian cancer**: Xu et al. [8] investigated the synergism of ginsenoside Rg3 and cyclophosphamide (CTX) on growth and angiogenesis of human ovarian cancer [8]. They found that life quality, the number of living days and average tumor weights of each treated group of mice were more impressive than control. When used alone or combined with CTX ginsenoside Rg3 significantly inhibited the growth and angiogenesis of ovarian cancer. Ginsenoside Rg3 and CTX combined with enhanced the anti-tumor effect each other and improved the life quality and survival time of mice with tumor, which implied the positive interaction between the ginsenoside Rg3 and CTX.

**Anti-virus effects**

Li et al. [9] discovered that the concentration of Rg3 varied from 0.125~4.000 μg·ml⁻¹ could inhibit herpes simplex virus (HSV-1) in different ways and have weak effects on other viruses by observing the anti-virus activity of Rg3 [9]. Chang et al. [10] had also proved that Rg3 has the effect of anti-HSV-1 in vitro experiments.

**Interference in chronic obstructive pulmonary disease (COPD)**

Li et al. [11] observed that the capsule of Rg3 had effects on serum immunoglobulin and cytokines of patients. Then they used case-control and multivariate study. Ginsenoside Rg3 capsule has active effects on enhancing the immune system of COPD patients and provides the basis for the drug treatments for COPD and rehabilitation interference.

Qian et al. [12] hold the idea that getting the metabolism data of Rg3 is of great importance to understand pharmacological activities of the anti-tumor component and they proved the ginsenoside has a very short half-life in vivo. They believe that the metabolism of ginsenoside Rg3 could play an important part in the antitumor activity, and the protopanaxadiol obtained in ginseng extract could inhibit Helicobacter Pylori growth, but protopanaxadiol cannot be transformed from ginsenoside Rg3 in the stomach.

**Other effects**

Ginsenoside Rg3 is known for its protective effect against hyperglycemia, obesity and diabetes in vivo. Fatigue is a complex physiological and biochemical process. Similarly, immunity system is also a complex preventive mechanism for the body. Cheng et al. [13] summarized the various anti-fatigue effects and the improvement on immunity of the ginsenoside Rg3 in detail. It can easily enhance the Organism immunity system. In addition, ginsenosides had double effects on the regulation of the stimulation and inhibition of the central nervous system (CNS) and it could regulate the nerve transmits [14]. Kim Min et al. [15] examined the effect of Rg3 on insulin signaling and glucose uptake in cultured L6 myotubes and investigated the mechanism involved. They found that Rg3 could improve insulin signaling and glucose uptake primarily by stimulating the expression of the insulin receptor substrates (IRS-1) and GLUT4.

**Metabolism**

When ginsenoside Rg3 was anaerobically incubated with human fecal microflora, all specimens metabolized ginsenoside Rg3 to ginsenoside Rh2 and protopanaxadiol, and the main metabolite was ginsenoside Rg2. The properties of a novel α-glucosidase from *Fusarium proliferatum* ECU2042 that converts ginsenoside Rg3 into Rh2 was studied by Su et al. [16]. Most herbal medicines are usually administrated by oral way and the components of which come into contact with intestinal microflora in the alimentary tract inevitably. In order to measure Rg3 and its metabolites selectively and precisely Xie et al. [17] used the method HPLC-MS determination of ginsenoside Rg3 and its metabolites in rat plasma by solid-phase extraction (SPE). This is a novel and sensitive method for simultaneous determination of ginsenoside Rg3 and its metabolites in rat plasma by HPLC-MS. Compared with liquid-liquid extraction, SPE is an appropriate extraction procedure. Qian et al. [12] studied in vivo rat metabolism and pharmacokinetic studies of ginsenoside Rg3 and found that six metabolites of Rg3 were detected in rat feces samples after oral administration. The identification of metabolite and the proved metabolic pathway may provide important information to the bioactive form of this ginsenoside. Wang et al. [18] studied the metabolomics on the effects of the Ginsenoside Rg3 in a β-cyclodextrin-based formulation on tumor-bearing rats by a fully automatic hydrophilic interaction reversed-phase column-switching HPLC-ESI-MS approach. For this analysis of body fluids urine is the most favorable sample material. Because it can be collected noninvasively, which is more convenient. Moreover, urine contains many metabolites indicating the metabolic state of the organism [19] and reflecting specific traits to perturbations [20]. The ginsenoside Rg3 in human plasma and urine was also determined by high performance liquid chromatography–tandem mass spectrometry [21].

**Pharmacokinetic study**

To support pharmacokinetic studies of ginsenosides, Xie et al. [17] studied a novel method of quantitative analysis on ginsenoside Rg3. They separated the gradient of Rg3 using HPLC with ESI-MS in negative ionmode and the mobile phase additive is ammonium chloride. Pharmacokinetic studies suggest that ginsenosides are very poorly absorbed following oral administration. Qian et al. [12] also got the averaged results obtained from three rats and used this result to investigate the pharmacokinetics of Rg3. It showed the plasma profiles of Rg3 concentration changed with sample collection time after the intravenous administration and there was no Rg3 detected in the plasma samples collected after 1.5h. Nevertheless, both studies of Qian et al. and Cai et al. [22] have demonstrated short half-life of Rg3 after the intravenous administration, which again indicated that ginsenoside Rg3 was probably metabolized quickly in rat and this also agreed with the results of metabolism studies in recent literatures. Also, evaporative light-scattering inspection was applied to the study of the rat on the pharmacokinetic study of ginsenoside Rg3 in vivo, and Duan et al. [23] studied the corellelative references of recent years, summarized the research progress of ginsenoside Rg3 in pharmacodynamics and pharmacokinetics, probe into the antineoplastic mechanisms and the vivo distribution. Recent study [24] proved that Rg3 affected phosphorylation and expression of endothelial nitric oxide synthase (eNOS), besides the present results provide a mechanism for Rg3-stimulated endothelial NO production.

**Summary**

Above all, may be the difference between the rat groups or Rg3 solubility in dosing solutions can result in a slightly longer half-life. For oral administration, ginsenosides may be easily metabolized under the acidic conditions by the stomach and intestinal flora. The intestinal metabolites of Rg3 are Rh2 and protopanaxadiol. Investigation of the pharmacokinetic and metabolic profile of Rg3 in vivo is essential to clarify its mechanisms of action. Besides, many methods have been used for determination of Rg3 and its metabolites, such as HPLC, HPLC-UV, HPLC-MS and SPE etc., and those strategies are promising tools for metabolomics and pharmacokinetics studies as global analysis.
Great achievements have been made and it has a wider clinical application of the traditional Chinese medicine. Obviously, ginsenosides Rg3 is an important biological activity compound of great medical value, we hope that further study of its biological activity will be made so that its resources can be fully utilized and then it can make great contributions for the protection of human health.

References