Absorption of Ginsenosides of Ginseng Preparations in Rat Small Intestine

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Abstract **AIM** Since bioavailability of ginsenosides is small by oral administration, the absorption of ginsenosides in the small intestine was studied. **METHODS** The absorption action was investigated in an in situ perfusion model of rat small intestine. A ginseng (root of *Panax ginseng* C. A. Meyer) decoction and a ginsenosides liquor was used as perfusion solution. **RESULT AND CONCLUSION** A mean value for ginsenosides absorbed in 3 hours per rat was 21.79 mg and 18.41 mg, respectively. Absorption of ginsenosides in the ginsenosides liquor basically followed first-order reaction of kinetics. The absorption of ginsenosides in the decoction was delayed in the second hour. The results confirm that the small intestine has normal ability to absorb ginsenosides. It is suggested that the prepartions containing ginsenosides should be protected from acid hydrolysis in stomach and absorbed as completely as possible in small intestine.

Key words Ginsenoside; *Panax ginseng*; Acsorption

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1 Introduction

The root of *Panax ginseng* C. A. Meyer (Araliaceae) is a well-known tonic herbal drug commonly used in China and Korea, commercially available over the world. The biological activity of ginseng is mostly attributed to ginsenosides, a group of triterpenoid saponins. In last two decades biopharmaceutical research was carried out into the drug. Odani *et al* reported the absorption, distribution, excretion and metabolism of ginsenosides, in which ginsenoside Rg_1 and Rb_1, two major ginsenosides, were studied. It was estimated that only 1.9% ~ 20.0 % of a dose of ginsenoside Rg_1 administering orally was absorbed from the upper parts of the rat digestive tract[1]. The result was mainly based on two methods, including determination of the unabsorbed residue in the digestive tract and comparison of the excretion between the oral and veined administration of the ginsenoside. Moreover the absorption of ginsenoside Rb_1 was very poor, being 0.11% of a dose administered orally, which was determined by comparison of the urinary excretion between the oral and veined administration of the ginsenoside[2].

Considering that a main current route of ginseng administration is oral, its bioavailability appears very important to a ginseng preparation. The present study aims at evaluating the absorption of general ginsenosides in the small intestine directly, precluding the influence from degradation and metabolism.

2 Experimental

2.1 *Drugs and reagents*

Ginsenosides was extracted and isolated from the dry root of *Panax ginseng* C. A. Meyer purchased from a crude drug company in Nanjing. Ginsenoside Rg_1, supplied by the National Control Office of Pharmaceutical and Biological Products, Beijing, was used as the chemical reference for assay of ginsenosides in the circulating solution.

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2.1.1 *Preparation of ginsenosides liquor* Ginsenosides (252.3 mg) was dissolved in Kreb-Ringer's nutritional solution to form a perfusion solution, in which phenol red was added (about 50 μg/ml) for determination of solution volume. Ginsenosides concentration of the liquor was 1.20 mg/ml.

2.1.2 *Preparation of ginseng decoction* Air-dried and powdered ginseng roots (12 g) were boiled with 150 ml of distilled water and then simmered for 40 min. After filtration the residue was simmered with 80 ml of distilled water for 30 min and filtered. The extracting solution was combined and added with the gradients of Kreb-Ringer's nutrient solution and red phenol as described above. The decoction for perfusion contained 1.20 mg/ml of ginsenosides.

2.2 *Animals*

SD rats (Animal Center, China Pharmaceutical University), weighing approximately 200 g, were used in the experiment. The animals were deprived of food but given free access to water for one night prior to surgery.

2.3 *Intestinal perfusion*

The absorption test in the rat small intestine was performed as described by Prescott *et al*[3, 4]. Animals were anesthetized fully with pentobarbital sodium (40 mg/kg, i.p.) and after a surgical procedure a circulation was connected between the topside of duodenum and the downside of ileum cannulated with plastic tubes (id = 5 mm) through a peristaltic pump and a storing container in a bath at 37℃. The intestinal segment was rinsed with saline at 37℃, moistened and covered with gauze. 50 ml of the perfusing solution was added in the store container and flowed at a rate of 5 ml/min through the rat small intestine. After 15 min, 3.5 ml of the perfusion solution was removed for assay of ginsenosides (0.5 ml of the sample for assay of phenol red to determine the volume of the circulating solution). At the same time, 3.5 ml of a phenol red Kreb-Ringer's solution (23.3 μg/ml) was added in the circulating solution. Samples were taken at 30, 60, 120, and 180 min for assay with the same method.

2.4 *Assay*

2.4.1 The volume of the circulating solution was calculated using concentration of phenol red, because this reagent is not absorbed by the small intestine. The concentration of phenol red in the circulating perfusion solution was determined by UV-VIS spectrophotometry[4].

2.4.2 Determination of total ginsenosides in the circulating perfusion solution was performed at 560 nm with UV-VIS spectrophotometry. Samples were extracted with ethyl ether (3 ml, 4 times), and then with water-saturated n-butanol (5 ml, 5 times). The n-butanol solution was evaporated on a water bath to dryness. The residue was dissolved in 2 ml of methanol. 100 μl of the solution was placed in a test-tube and then was evaporated to dryness for the assay of the total ginsenosides according the literature method[5]. Each sample was performed for three times. The linearity of the determination of ginsenoside Rg_1 was verified by regression analysis. The correlation coefficient was 0.99. Known amounts of ginsenoside Rg_1 were submitted to the sample preparation process and assayed. The average recovery was 100.06% ($s \pm 3.04\%$, $n=3$).

2.4.3 The absorbed ginsenosides were calculated by the following equations:

$$W_a = C_{n-1}V_{n-1} - C_nV_n \quad (1)$$

where W_a is the weight of ginsenosides absorbed in the small intestine; C is the concentration of ginsenosides in the circulating solution at the time of assay; V is the volume of the circulating perfusion solution at the same time; and n indicates the order of assay. $V_{1\text{-}5}$ is given by:

$$V_1 = \frac{C'_0V_0}{C'_1} \quad (2)$$

and

$$V_n = \frac{(V_{n-1} - 3.5)C'_{n-1} + 3.5C_p}{C'_n} \quad (3)$$

where C' is the concentration of phenol red in the circulating perfusion solution at the time of assay, and C_p is the concentration of the phenol red solution added in the circulating perfusion solution.

3 Results and discussion

The absorption of ginsenosides in the small intes-

tine of rats varies in the absorption rate and the ginsenosides concentration, according to the type of preparations of ginseng for the test. As shown in Table 1, while the small intestine was perfused with the ginsenosides liquor, the absorption rate of two third of the samples linearly declined as concentration of absorption decreased in the circulation solution, although in the starting (0～30 min) the absorption was not very consistent with the this relationship. The correlation coefficients were 0.9999, 0.9391 and 0.9894 for data of the three samples in Table 1, respectively. This basically belonged to the first order reaction of absorption kinetics. The absorption of ginsenosides in the ginseng decoction was more complex (Table 2). In the second hour, the absorption decreased to a great extent, but the tendency was changed in the third hour. Since there were many polysaccharides in the ginseng decoction and it was reported that viscous polysaccharides probably reduced absorption by resisting the convective effects of intestinal contractions[6], the influence of the ginseng polysaccharides on the absorption of ginsenosides should be considered.

Tab 1. Absorption of ginsenosides liquor in rat small intestine

Time (h)	1[a]		2[a]		3[a]		Mean (A)
	A[b] (mg)	C[c] (mg/ml)	A[b] (mg)	C[c] (mg/ml)	A[b] (mg)	C[c] (mg/ml)	
0～1	16.32	1.095	15.19	1.092	13.88	1.089	15.13
1～2	5.35	0.901	2.35	0.959	4.05	0.914	3.92
2～3	2.42	0.844	3.08	0.902	2.73	0.852	2.74
Total	24.09		20.62		20.66		21.79

[a]Rat numbers; [b]Ginsenosides absorbed; [c] Mean concentration during the period

Tab 2. Absorption of ginsenosides of ginseng decoction in rat small intestine

Time (h)	1[a]		2[a]		3[a]		Mean (A)
	A[b] (mg)	C[c] (mg/ml)	A[b] (mg)	C[c] (mg/ml)	A[b] (mg)	C[c] (mg/ml)	
0～1	10.87	1.087	11.24	1.081	11.15	1.083	11.09
1～2	1.35	0.929	0.75	0.912	1.70	0.912	1.27
2～3	6.69	0.857	6.81	0.855	4.64	0.868	6.05
Total	18.91		18.80		17.49		18.41

[a]Rat numbers; [b]Ginsenosides absorbed; [c] Mean concentration during the period

In the stomach, some of ginsenosides could be decomposed, due to hydrolysis under acidic conditions[7]. Several kinds of intestinal bacteria, which exist in large intestine, could hydrolyze ginsenosides[8]. Since there is lysozyme, few bacteria exist in small intestine. Therefore the main place in which ginsenosides can be decomposed is stomach and large intestine. The results confirm that the small intestine has normal ability to absorb ginsenosides. We suggest that the preparations containing ginsenosides should be protected from acid hydrolysis in stomach and absorbed as completely as possible in small intestine.

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人参制剂中人参皂甙在大鼠小肠中的吸收

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摘 要 目的 由于口服人参皂甙的生物利用度较小，本文研究了小肠对人参皂甙的吸收功能。**方法** 采用在体大鼠小肠吸收模型，以人参煎剂和人参总皂甙溶液剂作为灌流液。**结果与讨论** 在3小时中每只大鼠吸收的人参皂甙平均值分别为21.79 mg 和18.41 mg。大鼠小肠对人参总皂甙溶液中人参皂甙的吸收基本遵循动力学一级反应；对人参煎剂中人参皂甙的吸收在第二小时时受到阻滞。该结果显示大鼠小肠对人参皂甙具有正常的吸收功能，建议含人参制剂应能避免胃酸水解，并尽可能在小肠得到完全的吸收。

关键词 人参皂甙；人参；吸收

21世纪我国医药发展的十大趋势

1. 市场竞争的国际化 我国庞大的医药市场将诱使外国大公司巨资投入，入世后中国可能会成为全球的主要医药原料及制剂生产基地；药品进出口贸易将急剧增长；药品价格中外悬殊的现象将荡然无存，本土医药市场竞争更趋激烈。

2. 企业发展规模化 中国医药企业整体规模较小，随着深化企业改革和行业结构调整，5年后一批以上市公司为主体的大公司、大集团可望脱颖而出，他们将通过联合、购并、重组、实现超常规的资源汇聚、资产增值和资本扩张，形成足以与外国大公司同台竞争的实力，并在国内外两个市场上大显身手。

3. 医药企业经营多元化 医药企业在发展和巩固医药业的同时，向多元化经营拓展。将以医药经营为主，多种经营为辅。

4. 企业经营年轻化 一批作风正派、观念新、懂经营、善管理的高文化层次的中青年技术骨干将路身于企业管理阶层。

5. 政府管理市场化 根据 WTO 规划，政府的职能主要在制定经济规划、市场监管和社会服务诸方面。相信未来5年政府职能转变将会逐步到位，一个符合经济运行规律的政府宏观经济管理体系将逐步建立。

6. 传统与现代相结合的医药现代化 医药行业借助于现代化信息技术和网络技术实现跨越式发展。

7. 企业数量大幅缩减 加入 WTO 后，伴随着市场竞争的加剧，中国医药市场版图将重新划分。5年后中国医药企业数量可能减少1/3左右。

8. 具有自主知识产权的新药快速增长 许多有实力的医药企业开始关注于技术创新和产品创新，加紧建立企业自主知积产权体系。从中国国情、加紧建立企业自主知识产权体系。从中国国情、民族传统及医药发展现状分析，5年后中国最有可能形成在民族医药自主知识产权的领域是：

(1)中成药；(2)中西结合药；(3)生化药；(4)生物工程药；(5)基因芯片；(6)保健滋补品；(7)药用新材料等。

9. 药品价格向价值回归 未来5年，药品价格整体虚高的现象将根本扭转。这主要是因为同类品种生产相对集中，具有相对规模优势，生产经营的成本下降，药品价格趋合理水平也顺理成章。由于新药审批制度的改革，新药同类品种会减少。那些具有自主知识产权的新药将受到专利保护。其价格等于一般普通药应属正常。

10. 西部成为医药原料的生产基地 入世后由于东部医药企业面临生产成本等因素的压力，不得不把部分医药原料生产迁往西部省份。此外，西部丰富的中草药资源、生物多样性资源、劳动力资源以及市场等，都将积极地吸引东部医药企业去开发利用。

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