



## Review

# Systematic review of recent advances in pharmacokinetics of four classical Chinese medicines used for the treatment of cerebrovascular disease



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## ABSTRACT

Recent studies have focused more on Chinese medicine used for the treatment of cerebrovascular disease. The current review covers researches on the pharmacokinetics of Chinese medicine, providing a convenient reference for researchers to increase efficiency of drug discovery, by compiling and discussing the pharmacokinetics of four classical Chinese medicines for therapy of cerebrovascular disease containing: *Panax notoginseng*, *Salvia miltiorrhiza*, *Ligusticum Chuanxiong* and *Gardenia*. It also helps to eliminate side effect as far as possible from inappropriate Chinese medicine usage. Current integrative and comprehensive review of Chinese medicine for cerebrovascular disease including 1) the absorption of some constituents is limited such as ginsenosides Rg1 and Rb1. It may be affected by gastric juice, first-pass effect, etc. 2) The interactions between Chinese medicine and prescription can occur. Borneol and carbomer would enhance the absorption of R1 and Rg1 in vivo by increasing adjacent cell transport ability. 3) The distribution of active constituents in brain is important for cerebrovascular disease. BBB protects brain from xenobiotic. Intranasal, intra-tympanic administration is a promising alternative to conventional administration to reach brain for ligustrazine. 4) Renal excretion is the uppermost route of these Chinese medicines. But biliary, fecal and urinary excretion are the other major routes. Theoretical and practical aspects are described with pharmacokinetic examples. In the end, this paper also discusses recent development of bio-analysis of Chinese medicine.

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**Abbreviations:** BBB, blood–brain barrier; CAD, Charged Aerosol Detector; CM, chitosan–microsphere; CP, compritol; CTS, cryptotanshinone; DGLC, Double gradient liquid chromatograph; DH-Ppt, dehydrogenated protopanaxatriol; DSS, danshensu; F, bioavailability; FA, ferulic acid; GMS, glyceryl monostearate; HLJDT, Huang-Lian-Jie-Du-Tang HP, cortex *Magnoliae officinalis*; i.d., intra-duodenal; i.g., intragastric; LICM, liposome-in-chitosan-microspheres; i.n., intranasal; i.m., intramuscular; i.t., intra-tympanic; i.v., intravenous; LLOQ, lower limit of quantification; MS, Mass Spectrometry; NA, no avail; ND, no detected; n.s., nasal; PA, protocatechuic aldehyde; PD, pharmacodynamics; PK, pharmacokinetics; PNS, panax notoginsenoside; p.o., peroral; Ppt, protopanaxatriol; p.v., portal venous; RA, rosmarinic acid; SAA, salvianolic acid A; SAB, salvianolic acid B; SLNs, solid lipid nanoparticles; TLC, Thin layer chromatography; TMPP, tetramethylpyrazine phosphate; TPA, total phenolic acids; TSIIA, tanshinone IIA; TSIIIB, tanshinone IIB; UPLC, Ultra performance liquid chromatography; ZZHPD, Zhi-Zi-Hou-Pu decoction; ZS, fructus *Aurantii immaturus*; ZZ, *Gardenia jasminoides* Ellis

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## 1. Introduction

Cerebrovascular disease is a considerable medicinal problem worldwide. It is a major cause of disability and death in Europe. More than one million people die of the consequences of cerebrovascular disease each year and more people have suffered sequelae of cerebrovascular disease [1]. Chinese medicines have been used for the remedy of cerebrovascular disease for thousands of years in China and other Asian countries. A variety of modern researches have helped to clarify its application in cerebrovascular disease. Indeed, based on the phytochemical constituents, molecular targets, and Chinese medicine prescription, these Chinese medicines are effective. Moreover, Chinese medicine can be applied as a complementary or alternative medical system. There are many therapeutic applications which are indicated by modern research [2]. Especially Chinese medicine has played an important role in the treatment studies of cerebrovascular disease since the combination with modern pharmaceutical industry.

The mechanism of prevention and therapy of cerebrovascular disease is strongly influenced by factors such as controlling hypertension, hypercholesterolemia, anticoagulation, dissolving clots, restoring blood flow, reducing inter-cerebral bleeding and improving brain blood circulation. The clinical application of Chinese medicine in cerebrovascular disease has been published in recent years. Some papers have summarized the pharmacology, pharmacokinetics, toxicology and biological analysis of Chinese medicine [3–6]. These reviews give us a good reference of Chinese medicine application. Nevertheless, there is a problematic issue in Chinese medicine pharmacology which concerns the concentrations of different compounds within each herb. These reviews are short of sufficient, detailed information of pharmacokinetics. As it is well-known, the investigation of pharmacokinetic characteristics is imperative.

And herb–herb interactions are similar to drug–drug interactions. This will affect the efficacy of Chinese medicine.

Pharmacokinetics is deemed the foundation of new drug discovery. Pharmacokinetics encompasses a broad spectrum of experiment and connotation. The four aspects of pharmacokinetics includes: absorption, distribution, metabolism and excretion. With the development of pharmacy, more and more attention has been paid to the pharmacokinetics in drug discovery. Generally, a typical pharmaceutical research aims to discover and identify potential active targets. It should have specific positive effects, enough dwell time and safety in vivo. Just like the synergistic and inhibitory researches associated with important phytochemicals from herbs and Chinese medicine formulations. The pharmacokinetic reviews could provide key information for researchers; it is indispensable for drug discovery [7,8]. The side effect of Chinese medicine profile related to inappropriate usage has gone down along with pharmacokinetic study.

We briefly introduce the characteristic of pharmacokinetics including the introduction of absorption, distribution, metabolism and excretion. It is the first review which focuses on the pharmacokinetics of Chinese medicine used for cerebrovascular disease and sums up the obstacles to the development of bio-analysis of Chinese medicine. Then we review recent pharmacokinetic advance of four typical brain protective Chinese medicines: *Panax notoginseng*, *Salvia miltiorrhiza*, *Ligusticum chuanxiong* and *Gardenia* (Fig. 1) and their major components. The complexity of Chinese medicine causes diverse pharmacokinetics.

We have to explain why we select these four Chinese medicines for review? As we know, promoting the circulation of blood and removing stasis are the principal mechanisms of Chinese medicine to remedy cerebrovascular disease, especially for ischemic stroke [5]. According to this principle, focus is on these four specific plants, while wide spread

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