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Review article

Pharmacokinetic profile of phytoconstituent(s) isolated from medicinal plants—A comprehensive review

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ABSTRACT

Herbal medicine, the backbone of traditional medicine, has played an important role in human health and welfare for a long period. Traditional therapeutic approaches of regional significance are found in Africa, South and Central America, China, India, Tibet, Indonesia, and the Pacific Islands. The considerable scientific significance and commercial potential of traditional medicines have resulted in increased international attention and global market demands for herbal medicines, especially Chinese herbal medicines. Herbal medicines currently are the primary form of health care for the poor in the developing countries, and also are widely used as a supplement or substitute for conventional drugs in developed countries. These traditional medicines have a pivotal role in the treatment of various ailments and more than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modifications of chemicals found in plants. Herbal medicines usually contain a complex mixture of various bioactive molecules, which make its standardization complicated, and there is little information about all compounds responsible for pharmacological activity. Several research papers have been published that claim pharmacological activity of herbal medicines but few are discussing the role of the exact phytoconstituent. Understanding the pharmacokinetic profile of such phytoconstituents is essential. Although there are research papers that deal with pharmacokinetic properties of phytoconstituents, there are a number of phytoconstituents yet to be explored for their kinetic properties. This article reviews the pharmacokinetic profile of 50 different therapeutically effective traditional medicinal plants from the year 2003 onward.

1. Introduction

Herbal medicines are known to have a strong reputation throughout history and within every culture to provide first-line and basic health services for patients with numerous disease conditions. The roots of herbal medicine are at the very beginning of human history. These are the oldest form of medicine for welfare of mankind, and they play a paramount role in culture-specific traditional medicinal systems (TMS), i.e., Ayurveda (India) and traditional Chinese medicine (China). Herbal medicine is an umbrella term that encompasses an array of treatment options to supplement conventional and nonconventional therapies. Herbal medicine approaches are completely different from modern orthodox medicines. The historical background of herbal medicine begins with ethnopharmacology, a term introduced in 1967, which mainly deals with the scientific study of the traditional medicinal plants. It can be defined as 'the scientific study of materials used by ethnic and cultural groups as medicines' and in most instances this is synonymous with the study of traditional medicine.[1] Phytochemicals, phytomedicine, natural remedies, natural products and their chemistry, and various other subjects are present in the realm of herbal medicines and are beyond the scope of this article. Basically, medicinal plants are a huge source of chemical compounds, including primary and secondary metabolites, alkaloids, flavonoids, and lignin. These medicinal plants and their extracts

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yield promising leads (active principals) to further strengthen the medicinal system. These natural bioactive compounds play a central role in combating many human diseases. More than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modification of phytoconstituents.[2] Recent studies have stated that 75–90% (developing world) and 80% (less developed/developing countries) of the current world population relies on the use of herbal medicines for their primary health care and other needs, which signifies the scope of TMS, where 85% of medicinal plants of TMS involve the use of plant extracts.[3,4] These phytochemicals show a more complex pharmacokinetic profile (the study of the time course of phytochemicals, absorption, distribution, metabolism, and excretion). This pharmacokinetic profile helps to elaborate the relationship between intensity and time course of pharmacology, the toxicological effects of phytochemicals in the human body, and extends the scope of the use and acceptance by different regulatory bodies. As pointed out by the World Health Organization, there is very limited knowledge about the chemical compositions, pharmacokinetics, pharmacodynamics, and metabolomics of TCM plants; the data about authentication, efficacy, and safety of TCM are known and are far from satisfactory to meet the required criteria for worldwide use.[5] To provide satisfactory data about safety and efficacy of these medicinal plants and for pharmacokinetic profile, we have gathered information from various search engines and other possible sources from 2003 onward to provide a detailed picture on ADME parameters (absorption, distribution, metabolism, and excretion) of some phytoconstituents. The review elaborates pharmacokinetic profile of 50 medicinally important phytoconstituents from different medicinal plants.

2. Pharmacokinetic profile of drugs

2.1. *Ammi visnaga L.* (阿密茴香 *ē mì huí xiāng*)

Visnagin is a furanocoumarins derivative and one of the major constituents in *Ammi visnaga* L. (Apiaceae). It is commonly known as Khella. It was used by ancient Egyptians as a treatment for kidney stone disease. Visnagin has cardiovascular effects due to calcium channel blocking actions. Visnagin also has negative chronotropic and inotropic effects and reduces peripheral vascular resistance. Its extract prevents urolithiasis (kidney stone formation) by decreasing calcium oxalate crystal growth in the stone-forming rat model.

A sensitive and highly selective liquid chromatography-tandem mass spectrometry (LC-MS) method was used to determine visnagin in rat plasma. Chromatography was performed on a Phenomenex Synergi Max RP, (75 × 2.0 mm internal diameter [i.d.], 4 μm, Torrance, CA, USA) analytical column at ambient temperature. The mobile phase used for analysis was 0.1% formic acid, 5mM ammonium acetate in deionized water and methanol (15:85, v/v) delivered at a flow rate of 0.2 mL/min. For quantitative determination of visnagin in a rat plasma, a 50-μL sample is required. Pharmacokinetic parameters after oral administration of visnagin are provided in Table 1.[6]

2.2. *Apium graveolens, Ligusticum sinensis, and Ligusticum wallichii* (芹菜 *qín cài*), *Ligusticum sinensis* (藁本 *gǎo běn*) and *Ligusticum wallichii* (川芎 *chuān xiōng*)

3-*n*-Butylphthalide is a volatile chemical present in several plants including *Apium graveolens*, *Ligusticum sinensis,* and *Ligusticum wallichii*. In China 3-*n*-butylphthalide [(±)-NBP] may be a promising new drug for the treatment of ischemic cerebral diseases, such as stroke.

Table 1
Pharmacokinetic parameters after oral administration of visnagin.

Parameters	Values
Peak plasma concentration (C_{max}) (ng/mL)	2969
Time of peak plasma concentration (T_{max}) (h)	0.33
Area under the concentration-time curve) (trapezoidal rule) (h × mg/L)	11.9
Apparent clearance (CL/F) (L/kg)	0.84
The terminal elimination half-life (h)	2.3

A high-performance liquid chromatography (HPLC)-mass spectrometry (MS)/MS with positive ionization mode was adopted to determine 3-*n*-butylphthalide in rat plasma. The system was equipped with an ACQUITY UPLCTM BEH C18 (50 × 2.1 mm i.d., 1.7 μm) column. Gradient mobile phase composed of acetonitrile (ACN) and water containing 0.1% formic acid was used. The separated compounds were detected by a Waters Tandem Quadrupole (TQ) Detector (Waters, Milford, MA). The column temperature, flow rate, and chromatographic run time per sample used was 35°C, 0.2 mL/min, and 3.0 minutes, respectively. The lower limit of quantification (LLOQ) value was 5.57 ng/mL. Pharmacokinetic parameters after intravenous administration of 3-*n*-butylphthalide (5 mg/kg) are provided in Table 2.[7] 3-n-Butylphthalide followed extensive metabolism in humans and produced four metabolites, i.e., 10-keto-NBP, 3-hydroxy-NBP, 10-hydroxy-NBP, and NBP-11-oic acid.[8]

2.3. *Atractylodes macrocephala Koidz* (白朮 *bái zhú*)

Atractylodes macrocephala Koidz is one of the TCMs listed in Chinese pharmacopoeia. It exhibits antitumor, anti-inflammatory, and antibacterial properties. The anticancer effect of atractylenolide I has been proved in different cancer cells.

The HPLC-MS/MS method was reported for quantification of atractylenolide I in Wistar rat plasma after oral administration of the ethanolic (95%) extract of atractylodis. The MS was operated in the positive electrospray ionization (ESI) mode with multiple reaction monitoring (MRM). The LC system was equipped with a Phenomenex Gemini column (2.0 × 50 mm i.d., 5 μm, Phenomenex Company, CA, USA). The mobile phase consisted of a mixture of 0.1% formic acid in water and 0.1% formic acid in methanol. The flow rate was set at 0.4 mL/min, and column temperature and injection volume are 25°C and 10 μL, respectively. The limit of detection (LOD) and the limit of quantification (LOQ) are 0.6 ng/mL and 2.0 ng/mL, respectively. The pharmacokinetic parameters of atractylenolide I after oral administration of ethanolic (95%) atractylodis extract are presented in Table 3. The pharmacokinetic data indicate that atractylenolide I was absorbed very quickly in the body.

When simultaneous determination for atractylenolide I, II, and III was performed in blank rat plasma, atractylenolide II was found in real samples, atractylenolide III was found in plasma at different time points, and the pharmacokinetic curve of atractylenolide III showed an irregular pattern.[9]

Table 2
Pharmacokinetic parameter of 3-*n*-butylphthalide after intravenous administration dose 5 mg/kg.

Parameter	Values
$AUC_{0\text{-}6h}$ (ng·h/mL)	1140.16
Apparent volume of distribution (V_c) (L/kg)	1.22
Half-life ($t_{1/2}$) (distribution) (h)	0.098
$t_{1/2}$ (elimination) (h)	2.62
Clearance (Cl) (L/h kg)	3.67

AUC = area under the concentration-time curve.