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厦门大学

硕 士 学 位 论 文

几种中成药中砷的含量和形态分析及其体外生物利用度研究

Study on Content and Speciation of Arsenic in Some Chinese Traditional Medicine and in Vitro Bioaccessibility

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摘　要

中药是一个复杂的体系，按来源可分为动物药、植物药、矿物药，按处方可分为单味药、复方药，此外还有原药材、中成药，煎煮、炮制、水飞，片剂、饮液、颗粒、药丸等形式的细分，这成为中药中砷含量和形态分析的瓶颈。通过调研，发现中药中的砷主要有两种来源：一种是在种植、加工、制造过程中被污染而引入可溶性砷盐；另一种以雄黄等矿物类药材及其制剂入药而引入不溶性砷盐。由此，本论文选取六种有代表性的中药：天王补心丹、参茸补肾片、黄芩等三种不含矿物类药材的中药和六神丸、牛黄解毒片、雄黄等三种含矿物类药材的中药来进行相关的探索。

本论文由四个部分组成：1.文献综述；2.中药中砷的含量检测；3.中药中砷的形态分析；4.中药中砷的体外生物有效性研究。

第一章文献综述，主要介绍了砷的性质、运用和毒害，总结了砷含量检测和形态分离的方法，综述了体外生物有效性的研究现状，并在此基础上提出了本论文的研究设想。

第二章主要是对中药中砷盐检测方法进行改进：采用微波消解处理样品，电感耦合等离子质谱法检测中药中的总砷含量，期间对湿法消解、干法灰化、微波消解三种前处理方法进行比较，结果发现：采用微波消解法、以浓硝酸-高氯酸（4:1）为消解液、分两档消解 10 分钟，可以比较准确地反映药丸中砷的水平；建立在线化学蒸气发生，电感耦合等离子体质谱法检测六神丸等含矿物类药材的中药中可溶性砷的含量，该方法较以往的二乙基二硫代氨基甲酸银法简单，方法检出限为 0.36μg/L、回收率在 87.4%~97.75%之间、RSD（n=10）在 3%以内。

在第三章中首先建立高效液相色谱-电感耦合等离子体质谱联用装置，对交换柱类型、流动相的组成、洗脱方式等色谱条件和等离子体气流量、干扰扣除等质谱条件进行优化，结果发现：采用 Hamilton PRP X-100（250*4.1mm，10mm id）阴离子交换柱、以 15mM 磷酸氢二氨(pH=6)为流动相、采用等度洗脱，15min 内六种形态得以分离，线性范围不小于两个数量级，检出限分别为 0.986μg/L(AsC)、

0.756μg/L(AsB)、0.568μg/L(AsⅢ)、0.893μg/L(DMA)、0.941μg/L(MMA)、0.742μg/L(AsⅤ)，RSD（n=10）均小于 10%。然后将所建立的联用装置运用于海产品、生物样品、化妆品等实际样品，与同类文献具有可比性，所建立的装置符合研制方法的预期目标，同时还发现：海产品总砷含量较高，但超过 99％的砷是有机砷；生物样品由污染源而定；化妆品中主要是无机砷。最后将所建立的联用装置运用于中药实际样品，期间对石油醚快速溶剂萃取、甲醇/水（1:1）超声溶剂提取、盐酸回流三种不同的前处理方法进行比较，结果发现：在天王补心丹等不含矿物类药材的中药中，除含 As（III）、As（V）外还存在低浓度的 DMA 和微量的 AsC，采用甲醇/水（1:1）超声提取较合理；而在六神丸等含矿物类药材的中药中，主要是无机砷，DMA 、AsC 等基本可以忽略，采用盐酸回流较合理。

第四章建立中药体外生物有效性的研究方法，采用电感耦合等离子体质谱对中药在胃肠道溶解部分进行了总砷测定，研究中药的生物利用度；采用高效液相色谱-电感耦合等离子体质谱对中药在胃肠道溶解部分进行砷的形态分析，观察消化前后各形态的变化情况，结果发现：中药中的砷在人体胃肠道环境下不能完全溶解，其总砷的生物利用度在 80%以下；主要在胃过程中溶出；在天王补心丹等不含矿物类药材的中药中部分有机砷可能转化成无机砷；在六神丸等含矿物类药材的中药中部分不溶态的二硫化二砷可能被溶解。

本文的创新点在于：

（1）对二乙基二硫代氨基甲酸银法进行改进，将在线化学蒸气发生-电感耦合等离子体质谱法运用于中药中可溶性砷的检测，操作简单，灵敏度高；

（2）对几种中药的体外生物有效性进行探索，进一步加强各种形态在人体内代谢的研究，为砷的安全性评价提供一定的参考价值。

关键词：中药；砷；电感耦合等离子体质谱；高效液相色谱；

Abstract

In the field of arsenic speciation analysis, experts and scholars from home and abroad have done much reseach, however, few of which covered Chinese traditional medicine.

Subject paper focuses on analysis of arsenic in some Chinese traditional medicine.Total four chapters:1. Literature review; 2. Determination of arsenic in Chinese traditional medicine; 3. Analysis of arsenic speciation in Chinese traditional medicine; 4.Study on in vitro bioavailability of arsenic in Chinese traditional medicine.

Chapter I was an overview of the research background,the property，application and toxicity of arsenic,the content and speciation detection methods,and the study of in vitro bioavailability were introduced in this chapter.

Chapter II comprises of two parts:1).Total arsenic of Chinese traditional medicine were treated with microwaving digestion method and determined by inductively coupled plasma mass spectrometry. Comparison of there treat methods were conducted to find the best one.The results showed microwaving digestions more convenient, quick and finally selected in this study as the treat method. 2).Soluble arsenic of Chinese traditional medicine was treat with hydrochloric acid and determined by online chemical vapor generation - inductively coupled plasma mass spectrometry.Compared to Ag-DDC,this method is more simple,the detection limit reachs 0.36μg/L,the recovery obtaines 87.4%,and RSD（n=10）is within 3%.

In the third chapter, the association device of high performance liquid chromatography-inductively coupled plasma mass spectrometry were set up for the analyse of arsenic speciation, conditions were optimized, and the result showed: using Hamilton PRP X-100 (250*4.1mm, 10mm id) anion exchange column, with 15mM $(NH_4)_2HPO_4$(PH=6) as the mobile phase, can analyse six arsenic speciation within 15 min,and the linear range is not less than two orders of magnitude, the detection limit is 0.986μg/L(AsC), 0.756μg/L (AsB),0.568μg/L (AsⅢ),0.893μg/L(DMA),0.941μg/L (MMA),0.742μg/L(AsⅤ),RSD（n=10）is within10%.Then the association device of high performance liquid chromatography -

inductively coupled plasma mass spectrometry was applied to analyse arsenic s peciation in aquatic products,biological samples and cosmetics.The results sh-ow ed that:more than 99% of the arsenic in seafood is organic,such as AsB and A sC, minimal toxicity; biological samples decided by sources; cosmetics only co-ntain inorganic arsenic.Finally the association device was applied to Chinese tra ditional medicine.Compare of the there treat methods,ASE,SON,HCL,were cond ucted to find the best one. The results showed that the main forms of ars-enic in HuangQin are As (III) and As (V), as well as low concentrations of AsC and DMA,can use SON;but in XiongHong they are As (III) and As (V),DMA and AsC can be ignored,so using HCL is more appropriate.

In Chapter IV, the method of in vitro bioaccessibility was established to determined the capability of solution of Chinese traditional medicine in gastroi-ntestinal track.After Chinese traditional medicine were digested in gastrointestin-al track, the content and speciation of arsenic in the digestion fluid were anal-yzed.Arsenic in gastrointestinal fluid is not completely dissolvable. Bioaccessibi-lity of total arsenic was below 80%. Inorganic arsenic increased after gastroint-estinal digestion. It is possible that some organic arsenic transferred into inorg-anic arsenic.

The main innovation of this thesis is:(1) Developed online chemical vapor generation - inductively coupled plasma mass spectrometry technique to deter-minate soluble arsenic in Chinese traditional medicine.Compared to Ag-DDC, t-his method is more simple,convenient and quick. (2) The soluteion and transfer of arsenic in Chinese traditional medicine by method of in vitro bioaccessibil-ity have a great signification to farther study how arsenic in high arsenic food can change and release from matrix and whether it will transfer from one sp-eciation to another in human gastrointestinal track.

Keyword: Chinese traditional medicine,Arsenic,Inductively coupled plasma mass spectrometry, High performance liquid chromatography.

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