JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Research Paper

Development of glutathione-conjugated asiatic acid-loaded bovine serum albumin nanoparticles for brain-targeted drug delivery

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Keywords
asiatic acid; blood–brain barrier; bovine serum albumin; brain-targeted drug delivery; glutathione

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Received February 4, 2015
Accepted June 21, 2015

doi: 10.1111/jphp.12460

Abstract

Objective Asiatic acid, a well-known plant-based neuroprotective pentacyclic triterpenoid, has major limitation for its bioavailability in the brain. The objective of this study is to develop novel bovine serum albumin (BSA) nanoparticles coupled with glutathione (natural tripeptide) to enhance drug delivery to brain.

Methods Asiatic acid-loaded BSA nanoparticles were prepared by using modified desolvation technique. Conjugation of glutathione with asiatic acid-loaded BSA nanoparticle was done by carbodiimide reaction using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC). In-vivo biodistribution study of asiatic acid solution, and conjugated and unconjugated asiatic acid-loaded BSA nanoparticles, at the dose equivalent to 75 mg/kg was evaluated, through intravenous administration to Wistar rats. Asiatic acid has very weak chromophore so high-pressure liquid chromatography-based novel pre-derivatization method was developed using p-toluidine as a coupling agent to improve sensitivity.

Key findings The results showed 10-fold more bioavailability of asiatic acid in the brain after 5 h with glutathione-conjugated asiatic acid-loaded BSA nanoparticles as compared with asiatic acid solution with 627.21% drug targeting efficiency to the brain.

Conclusion The present investigation demonstrated enhanced delivery of asiatic acid using glutathione and hence served as a potential ligand to improve brain targeting efficiency.

Introduction

Asiatic acid is a pentacyclic triterpene isolated from various plants like *Centella asiatica* and *Shorea robusta*, which are well known as traditional herbs in Indian and Chinese medicinal system. Asiatic acid is reported as one of the major active constituents of above-mentioned herbs, responsible for their various pharmacological activity.[1] Neuroprotection is one of the major pharmacological activity reported for asiatic acid in both in-vitro and in-vivo models.[2,3] However, previous studies have shown that the penetrability of asiatic acid inside the brain is limited due to the presence of defensive mechanism of brain. Brain is tightly dissevered from the circulating blood by a unique barrier like the blood–brain barrier (BBB), blood cerebrospinal fluid barrier, blood tumour barrier, various efflux transporter proteins like P-glycoprotein (P-gp), multidrug resistant protein, breast cancer resistant protein, etc. Free diffusion transposition through the interstitium of the brain is restricted by complex anatomy of BBB.[4–7] Therefore, therapeutic efficacy of asiatic acid is restricted due to its low penetrability into the brain as well as the P-gp efflux of drug which restricts its longer stay in the brain.

Various strategies like lipid-mediated drug delivery, specific endogenous transporter, disruption of BBB, intracerebroventricular, intranasal, molecular Trojan horses (antibodies) have been explored to facilitate the penetration of neurotherapeutics inside the brain. All these strategies failed to serve the complete benefits of brain-targeted drug delivery system because only few of them are safe and efficient for drug delivery application.[6,7] Out of all, receptor-mediated drug delivery has been found to be a quite

