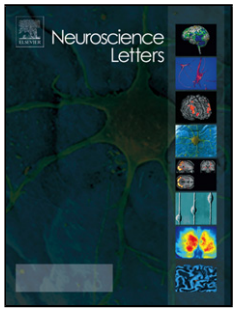

Title: Borneol enhances the antidepressant effects of asiaticoside by promoting its distribution into the brain

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Borneol enhances the antidepressant effects of asiaticoside by promoting its distribution into the brain

HIGHLIGHTS

- Borneol in the asiaticoside-borneol formula promotes asiaticoside distribution into the rat brain.
- The combination of borneol and asiaticoside significantly reduces the immobility time of rats in FST, while asiaticoside or borneol shows no significant effects.
- The combination of borneol and asiaticoside significantly increases the ratio of time in center to that in periphery in the OFT, while asiaticoside or borneol shows no significant effects.

ABSTRACT

Asiaticoside (AS) has antidepressant effects, with poor druggability characterized with inaccessibility into the brain. Here, we assessed AS distribution in the asiaticoside-borneol formula (FAB), with AS administrated orally. High performance liquid chromatography (HPLC) was applied for AS detection. The antidepressant effects of both FAB and AS were evaluated. Rats were subjected to behavioral despair paradigms and chronic unpredictable stress model (CUS) after acute and chronic drug administration, respectively. Hippocampal 5-HT, NE, BDNF, and TNF-α levels were detected, and pathological changes were observed by H&E staining. AS was detected in rat brain tissues after FAB administration, while AS was not detected when administered alone, indicating that borneol (BOR) promoted its distribution into the rat brain. Interestingly, FAB significantly reduced the immobility time in modified forced swimming test (FST) unlike AS used as a single therapy, also reversing sucrose intake more significantly compared with AS. Furthermore, FAB upregulated BDNF and 5-HT more significantly compared with AS, which revealed a possible multi-mechanism of action.

Keywords:
Asiaticoside-borneol formula
Asiaticoside
Borneol
CUS
Depression

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1. Introduction

WHO predicted that depression will become the leading cause of disease burden globally by 2030[1]. It is therefore urgent to design adequate and effective treatments for depression. Several therapeutic regimens are currently known, including tricyclic drugs, monoamine oxidase inhibitors, serotonin–norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs); however, they are responsible for a wide range of side effects such as cardiac toxicity, hyperpiesia, sexual dysfunction, and sleep disorders, with low success rates[2]. These shortcomings prompt the search for alternative treatments. Traditional Chinese medicines (TCMs) with therapeutic potential for depression, such as Chinese St. John's Wort and other TCM complex prescriptions, have attracted much attention[3-4].

AS was reported to show neurological activities[5], but poor distribution into the brain hinders its use as an anti-depressive drug. Based on the TCM theories, BOR is considered an upper guiding drug in traditional Chinese formulations to significantly increase drug concentration in the brain. Indeed, BOR was shown to enhance drug accumulation in brain tissues and bioavailability, e.g. in the case of geniposide[6].

In this study, we assessed whether BOR enhances the anti-depressant effects of AS by promoting its distribution into the brain, in a rat model of chronic unpredictable stress.

2. Materials and methods

2.1. Materials

AS was isolated from the total saponin fraction of *Centella asiatica* by silica gel column chromatography, eluted with dichloromethane/methanol/water (16/6/1 in volume); 3g total saponin *was loaded into the column, which contained 800mL* 200-mesh silica gel in 4x60 cm column). Fluoxetine (FLU) and jujuboside A were purchased from Aladdin Industrial Corporation, Ltd. (Shanghai, China). BOR was obtained from Shanghai Leiyunshang Pharmaceutical co., Ltd. (Shanghai, China). 5-HT, NE, BDNF and TNF-α ELISA kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu). Acetonitrile of HPLC grade was acquired from Merck (Darmstadt, Germany). Pure water was prepared using a Milli-Q purification system (Millipore, Milford, MA, USA). Tween-80, polyethylene glycol (400) and propanediol were of AR grade.

2.2. FAB preparation and drug administration

BOR (1 g) was dissolved in propanediol; then, polyethylene glycol-400 and tween-80 were added with stirring to obtain the BOR solution. AS (300 mg) was added into the BOR solution to yield FAB, which was diluted with saline to 100 mL. The AS solution was prepared the same way without BOR. The animals were treated orally with FAB, AS, and BOR solutions, respectively, at 1 mL/100g BW. Acute administration included 2 oral doses, 23h and 1h, respectively, before the behavioral test. Chronic administration was performed orally at 1h before stress