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Review

Biopharmaceutical characters and bioavailability improving strategies of ginsenosides

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ABSTRACT

Deglycosylation is the most important gastrointestinal metabolism in which ginsenosides are split off from glycosyl moieties by the enzymes secreted from intestinal microflora, and two possible metabolic pathways of protopanaxdiol-type ginsenosides (PPD-type ginsenosides) and protopanaxtriol-type ginsenosides (PPT-type ginsenosides) have been concluded. The former is deglycosylated at C-3 and/or C-20, and transformed to protopanaxdiol (PPD). By comparison, the latter is deglycosylated at C-6 and/or C-20, and eventually transformed to protopanaxtriol (PPT) instead. The pharmacokinetic behavior of PPD-type ginsenosides and PPT-type ginsenosides is different, mainly in a faster absorption and elimination rate of PPT-type ginsenosides, but almost all of ginsenosides have a low oral bioavailability, which is relevant to the properties, the stability in the gastrointestinal tract, membrane permeability and the intestinal and hepatic first-pass effect of ginsenosides. Fortunately, its bioavailability can be improved by means of pharmaceutical strategies, including nanoparticles, liposomes, emulsions, micelles, *etc.* These drug delivery systems can significantly increase the bioavailability of ginsenosides, as well as controlling or targeting drug release. Ginsenosides are widely used in the treatment of various diseases, the most famous one is the Shen Yi capsule, which is the world's first clinical application of tumor neovascularization inhibitors. Hence, this article aims to draw people's attention on ocotillol-type ginsenosides, which have prominent anti-Alzheimer's disease activity, but have been overlooked previously, such as its representative compound-Pseudoginsenoside F_{11}(PF_{11}), and then provide a reference for the druggability and further developments of ocotillol-type ginsenosides by utilizing the homogeneous structure between dammarane-type ginsenosides and ocotillol-type ginsenosides.

1. Introduction

Ginsenosides are the main effective constituents of Araliaceae *panax* genus plants, such as *P. Ginseng*, *P. notoginseng* and *P. quinquefolius*. Based on their mother nucleus structures, ginsenosides are divided into four types: dammarane-type ginsenosides, ocotillol-type ginsenosides, oleanane-type ginsenosides and others. Dammarane-type ginsenosides further contain two groups: PPD-type ginsenosides and PPT-type ginsenosides [1], which have been found to have a range of pharmacological activities, including immunomodulatory, anticancer, antifatigue, anti-aging [2], antidiabetic [3], antidepressant-like[4]and neuroprotective effect [5], and they act on many signaling pathways such as hippocampal BDNF [4], JNK/P38 MAK, CDK5 [5], p62–Keap1–Nrf2 [6], ERK/P38 MARK, JNK and P13K/AKt-eNOS signaling pathways [7]. The representative compounds of dammarane-type ginsenosides are ginsenoside-Rb_1, Rb_2, Rd., Re, Rg_1, Rg_2, 20(*S*)-PPD, 20(*S*)-PPT and other components. Ocotillol-type ginsenosides, tetracyclic triterpene saponins with a side chain containing furan ring, are a kind of unique components of American ginseng [8], and research on these compounds has grown in recent years. PF_{11} is the representative compound of ocotillol-type ginsenosides, and it has been found that it can improve learning and memory ability [9], antagonize the neuroprotective effect of morphine addiction [10] and reduce the neurotoxicity of methamphetamine [11], improve ethanol induced injury to the nervous system [12] and other pharmacological effects. Its efficacies are based on a variety of mechanisms such as inhibition of free radical formation, stimulation of endogenous antioxidant release [13], blocking multiple signaling pathways such as TLR4/MyD88, TAK1/IKK/NF-kB, Akt and MAPKs [14], and therefore PF_{11} shows good neuroprotective effect and may serve as a potential therapeutic agent for the treatment of

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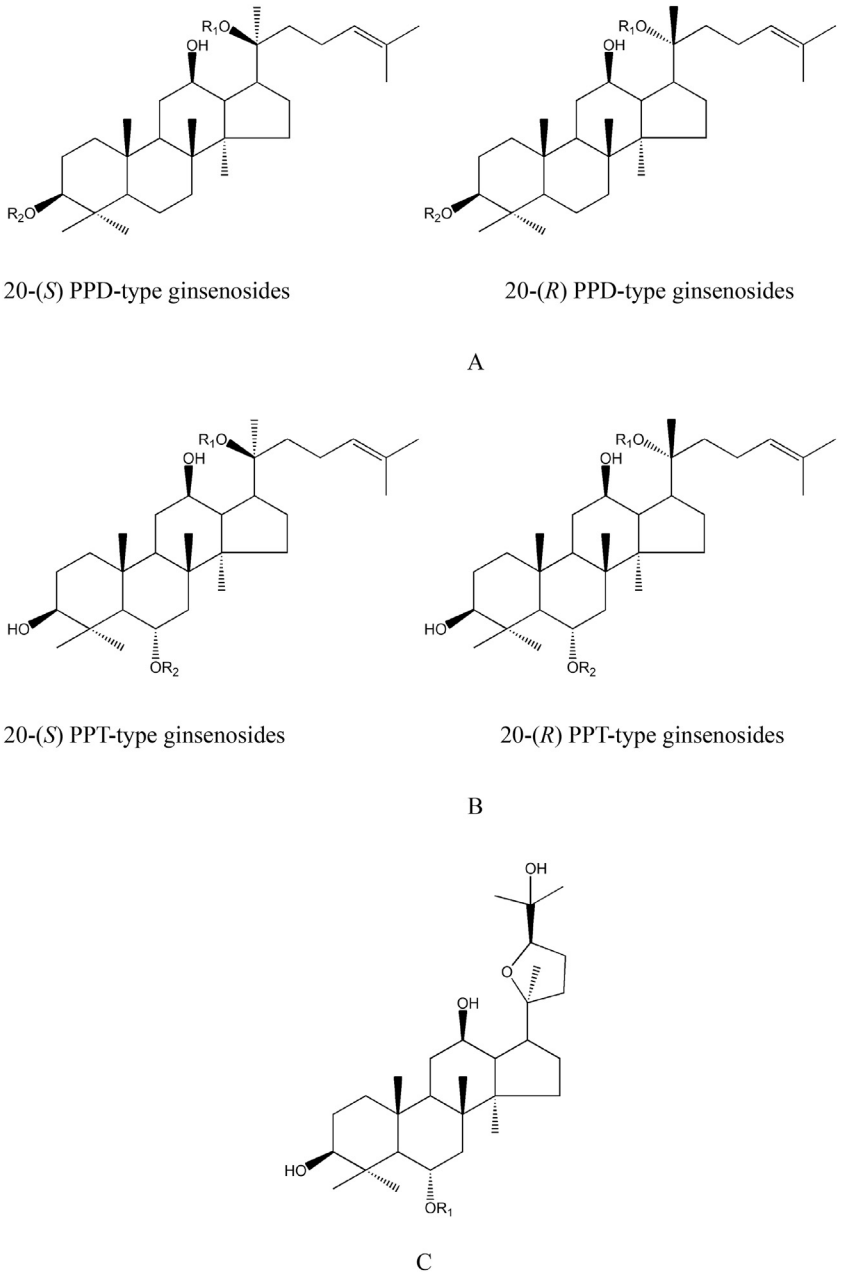

Fig. 1. The structures of PPD-type ginsenosides core(A),PPT-type ginsenosides core(B) and Ocotillol-type ginsenosides core(C).

Alzheimer's disease (AD). However, the low oral bioavailability of ginsenosides is well known, like PF_{11}, and the whole class of ocotillol-type ginsenosides may face the same problem. Therefore, in this report, an inductive and comparative analysis between dammarane-type ginsenosides and ocotillol-type ginsenosides is conducted in gastrointestinal metabolism and oral availability two aspects by utilizing the similarity of chemical structures of ginsenosides. The biopharmaceutical and pharmacokinetic properties of dammarane-type ginsenosides and ocotillol-type ginsenosides are finally summarized to provide a scientific basis for the further development of highly efficient preparations with high bioavailability.

2. Chemical structure

PPD-type ginsenosides and PPT-type ginsenosides have the same mother nucleus and side chain, the difference is whether there is a hydroxyl in position C-6 [15]. Ocotillol-type ginsenosides are similar to dammarane ginsenosides in parent structure, and are the side chain double bond oxidative cyclization product of PPT-type ginsenosides [16]. The chemical structures of the three sapogenins are shown in Fig. 1. The structures of ginsenosides differ in the pattern structure of their substituents, and the various R group substituents are shown in Table 1. Early studies showed that [17]many ginsenosides were defined as soluble, and their solubility didn't vary dramatically as pH changed, but decreased significantly if the number of sugar moieties reduced. In addition, when examined the pH stability of ginsenosides [18], PPD was found to be relatively stable in pH 1.2, 6.8 and 7.4 buffer solutions, but PPT was prone to degrade in pH 1.2 buffer solutions. Above all, the differences of these properties may be closely related to the structure.

3. Gastrointestinal metabolism

Traditional Chinese medicine is usually taken by oral administration with the form of simple recipe or compound prescription, and the sites