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Identification of Natural Liver X Receptor Agonists as the Treatments or Supplements for the Management of Alzheimer and Metabolic Diseases

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Abstract : Cholesterol plays an essential role in the regulation of the progression of numerous important diseases including atherosclerosis and Alzheimer disease so the generation of suitable cholesterol-lowering reagents is urgent to develop. Liver X receptor (LXR) is a ligand-activated transcription factor whose natural ligands are cholesterols, oxysterols and glucose. Once being activated, LXR can transactivate the transcription action of various genes including CYP7A1, ABCA1, and SREBP1c, involved in the lipid metabolism, glucose metabolism and inflammatory pathway. Essentially, the upregulation of ABCA1 facilitates cholesterol efflux from the cells and attenuates the production of beta-amyloid (ABeta) 42 in brain so LXR is a promising target to develop the cholesterol-lowering reagents and preventative treatment of Alzheimer disease. Engelhardia roxburghiana is a deciduous tree growing in India, China, and Taiwan. However, its chemical composition is only reported to exhibit antitubercular and anti-inflammatory effects. In this study, four compounds, engelheptanoxides A, C, engelhardiol A, and B isolated from the root of Engelhardia roxburghiana were evaluated for their agonistic activity against LXR by the transient transfection reporter assays in the HepG2 cells. Furthermore, their interactive modes with LXR ligand binding pocket were generated by molecular modeling programs. By using the cell-based biological assays, engelheptanoxides A, C, engelhardiol A, and B showing no cytotoxic effect against the proliferation of HepG2 cells, exerted obvious LXR agonistic effects with similar activity as T0901317, a novel synthetic LXR agonist. Further modeling studies including docking and SAR (structure-activity relationship) showed that these compounds can locate in LXR ligand binding pocket in the similar manner as T0901317. Thus, LXR is one of nuclear receptors targeted by pharmaceutical industry for developing treatments of Alzheimer and atherosclerosis diseases. Importantly, the cell-based assays, together with molecular modeling studies suggesting a plausible binding mode, demonstrate that engelheptanoxides A, C, engelhardiol A, and B function as LXR agonists. This is the first report to demonstrate that the extract of Engelhardia roxburghiana contains LXR agonists. As such, these active components of Engelhardia roxburghiana or subsequent analogs may show important therapeutic effects through selective modulation of the LXR pathway.

Keywords : Liver X receptor (LXR), Engelhardia roxburghiana, CYP7A1, ABCA1, SREBP1c, HepG2 cells
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