INTISARI

Pentagamavunon-0 (PGV-0) adalah inhibitor kuat enzim histon deasetilase-2 (hda-2) yang selanjutnya berpotensi merangsang neurogenesis dan meningkatkan fungsi kognitif pada pasien Alzheimer's. Namun, bioavailabilitasnya yang rendah menjadi kendala utama. Oleh karena itu, pengembangan PGV-0 dalam bentuk *self-nano emulsifying drug delivery system* (SNEDDS) bertujuan meningkatkan bioavailabilitas PGV-0 dan diharapkan mampu meningkatkan distribusi PGV-0 ke otak untuk menghambat aktivitas enzim hda-2. Penelitian ini bertujuan untuk mengoptimalkan sintesis PGV-0, mengembangkan formula SNEDDS PGV-0 yang stabil, serta mengevaluasi bioavailabilitas oral dalam serum dan distribusinya ke jaringan otak, efek anti-Alzheimer's, dan penelusuran mekanisme neurogenesis-gliogenesis SNEDDS PGV-0 dalam otak mencit Alzheimer's yang diinduksi monosodium glutamat (MSG). Sintesis PGV-0 dimodifikasi dengan mempersingkat durasi reaksi menjadi 2 jam dan menggunakan etanol dan akuades untuk pencucian dan rekristalisasi. Optimasi formula SNEDDS PGV-0 dilakukan melalui skrining eksipien, analisis diagram *pseudo-ternary*, karakterisasi nanoemulsi dan uji stabilitas. Validasi metode KCKT dilakukan sebelum penetapan kadar PGV-0 dalam serum dan homogenat otak mencit. Efek anti-Alzheimer's SNEDDS PGV-0 dievaluasi secara *in vivo* menggunakan tiga uji perilaku, yaitu *open-field test*, *novel object recognition task* dan *8-radial arm maze*. Analisis ekspresi gen neurogenesis dan gliogenesis dilakukan dengan q-PCR pada sampel otak. Hasil penelitian menunjukkan bahwa modifikasi sintesis PGV-0 menghasilkan senyawa dengan kemurnian 99,28±0,057% dengan total rendemen mencapai 14,28%. Susunan eksipien formula optimal SNEDDS PGV-0 terdiri dari miglyol (15% v/v), Tween 80 (75% v/v), dan PEG 400 (10% v/v) yang telah terbukti stabil selama penyimpanan. Penggunaan formula optimal tersebut meningkatkan bioavailabilitas oral PGV-0 dalam serum dan distribusi PGV-0 ke dalam otak mencit serta memperbaiki fungsi kognitif, kemampuan *learning*, dan memori pada mencit Alzheimer's yang diinduksi MSG. Selain itu, Formula optimal SNEDDS PGV-0 juga meningkatkan neurogenesis melalui peningkatan ekspresi doublecortin (*dcx*) dan penurunan ekspresi *Hairy and enhancer of split 5* (*Hes5*) serta gliogenesis (peningkatan ekspresi *Nuclear factor IA* (*NFIA*)) pada mencit Alzheimer's yang diinduksi MSG. Hasil penelitian ini dapat dijadikan dasar ilmiah untuk pengembangan sediaan SNEDDS PGV-0 sebagai kandidat anti-Alzheimer’s baru.

Kata Kunci: Pentagamavunon-0, neurogenesis, bioavailabilitas, Alzheimer’s, histon deasetilase-2

ABSTRACT

Pentagamavunon-0 (PGV-0) is a potent inhibitor of HDAC-2, which has the potential to promote neurogenesis and improve cognitive function in Alzheimer's patients. However, its low bioavailability has been a significant limitation. Therefore, developing PGV-0 as SNEDDS was a promising strategy to facilitate its delivery into the brain and effectively inhibit HDAC-2 activity. This study aims to optimize the synthesis of PGV-0, develop a stable PGV-0 SNEDDS formula, and evaluate the oral bioavailability in serum and its distribution in brain tissue, anti-Alzheimer's effects, and the impact of SNEDDS PGV-0 on neurogenesis gene expression in the brains of MSG-induced Alzheimer's mice. PGV-0 synthesis was adjusted by shortening the reaction duration to 2 hours and using different solvents for rinsing and recrystallization. Excipient screening, pseudo-ternary diagram analysis, nanoemulsion characterization and stability studies were used to optimize the SNEDDS PGV-0 formula. Before analyzing PGV-0 levels in mouse serum and brain homogenates, the HPLC method was validated. The anti-Alzheimer's effect of SNEDDS PGV-0 was evaluated in vivo using three behavioral tests: open-field-test, novel object recognition task and 8-radial arm maze. Gene expression analysis of neurogenesis and gliogenesis was investigated on brain samples using q-PCR. Modifications of PGV-0 synthesis resulted in compounds with a purity of 99.28 ± 0.057% and a total yield of 14.28%. Studies have demonstrated that the optimal excipient composition of SNEDDS PGV-0 includes miglyol (15% v/v), Tween 80 (75% v/v), and PEG 400 (10% v/v), and it maintains stability during storage. The optimal formula increased the oral bioavailability of PGV-0 in serum and the distribution of PGV-0 in the brain of mice and improved cognitive function, learning ability, and memory in MSG-induced Alzheimer's mice. In addition, SNEDDS PGV-0 optimal formula also improved neurogenesis through increased expression of doublecortin (dcx) and decreased expression of Hairy and enhancer of split 5 (Hes5) and gliogenesis (increased expression of Nuclear Factor IA (NFIA)) on MSG-induced Alzheimer's mice. These findings provide a scientific foundation for SNEDDS PGV-0 advancement as a novel candidate for Alzheimer's therapy.

Keywords: Pentagamavunon-0, neurogenesis, bioavailability, Alzheimer’s, histone deacetylase-2