INTISARI

Adult neurogenesis merupakan serangkaian proses dari *neural stem cells* (NSCs) yang berproliferasi dan berdiferensiasi (*neural lineage differentiation*) menjadi sel neuron baru. Proses ini diyakini dapat memperbaiki kerusakan otak akibat *brain disorders* yang disebabkan salah satunya oleh terganggunya keseimbangan asetilasi-deasetilasi histon oleh adanya overekspresi HDA2 dalam mekanisme epigenetik. Senyawa kurkumin yang diformulasikan dalam *self-nanoemulsifying drug delivery system* (SNEDDS) telah menunjukkan potensinya sebagai HDA2 *inhibitor* baik secara *in silico* dan *in vitro*. Secara *in vivo* SNEDDS kurkumin memberikan perbaikan aktivitas neurobiologis dan modulasi *TrkB,* reseptor *brain-derived neurotrophic factor* (*Bdnf*) yang terlibat dalam modulasi neurogenesis, sehingga berpotensi untuk dikembangkan sebagai *brain disorder treatment agent*. Penelitian ini bertujuan untuk mengetahui mekanisme aksi formulasi SNEDDS kurkumin dengan melihat pengaruhnya terhadap level ekspresi gen *Hda2*, *Bdnf,* gen-gen neurogenik (*NeuN*, *Map2*, *Tuj1*), dan gliogenik (*Gfap, S100β, Olig2*) pada model *brain disorders*, serta mengetahui karakteristik ukuran globul sediaan SNEDDS kurkumin.

Proses karakterisasi ukuran globul SNEDDS kurkumin yang terdiri dari campuran miglyol:smix (Tween 20 dan Tween 80):PEG 400 (1:8:1) menggunakan *Zetasizer Nano.* Subjek penelitian menggunakan mencit jantan galur Balb/c yang diinduksi *brain disorders* dengan menggunakan etanol 10% v/v p.o. selama 21 hari (kronis, *withdrawal*) dan dipejani SNEDDS kurkumin dosis 20 atau 40 mg/kgBB p.o. selama 21 hari. *Brain dissection* dilakukan 24 jam setelah pemejanan terakhir. SNEDDS kurkumin memiliki karakteristik yang baik dengan ukuran globul <50 nm dan variasi distribusi ukuran yang kecil (PdI<0,2). Pengamatan ekspresi gen pada otak menggunakan *two-step* semi kuantitatif *reverse transcriptase – polymerase chain reaction* (RT-PCR) dan *real-time* qPCR. SNEDDS kurkumin tidak mempengaruhi ekspresi *Hda2*, namun ada pengaruh signifikan *Bdnf* pada dosis 40 mg/kgBB, menandakan kemungkinan teraktivasinya Bdnf/TrkB oleh kurkumin pada model mencit *brain disorder*. Tidak ada stimulasi neurogenesis teramati pada SNEDDS, namun suspensi kurkumin 40 mg/kgBB meningkatkan *mature* neuron (*NeuN*). Dalam proses gliogenesis, SNEDDS kurkumin meningkatkan *mature* astrosit (*S100β*), menurunkan astrosit reaktif (*Gfap*), dan tidak mempengaruhi oligodendrosit (*Olig2*) pada mencit model *brain disorder* yang diinduksi etanol.

Kata kunci : kurkumin, *self-nanoemulsifying drug delivery system*, HDA2, neurogenesis, BDNF

ABSTRACT

Adult neurogenesis consists of a sequential process initiated by proliferating and differentiating neural stem cells (NSCs) following neural lineage differentiation to generate new neuron cells. This mechanism is believed as an emerging way to repair brain damage in brain disorders. In term of the epigenetic system, some believed that brain disorders resulted due to the HDAC2 overexpression caused by histone acetylation-deacetylation imbalance.

The curcumin formulated in self-nanoemulsifying drug delivery system (SNEDDS) has shown its potential to downregulate HDAC2 in silico and in vitro. Moreover, an in vivo study also revealed the improvement of neurobehavior activities, and neurogenesis-related TrkB modulation, a receptor of brain-derived neurotrophic factor (Bdnf), by SNEDDS curcumin. Thus, this evidence suggests SNEDDS curcumin to be developed as a brain disorders treatment agent. This research aims to determine the mechanism of action of SNEDDS curcumin by observing its effects on Hdac2, Bdnf, neurogenic genes (NeuN, Map2, Tuj1), and gliogenic genes (Gfap, S100β, Olig2) in animal model of brain disorders, along with the nano emulsion globule characterization of the formulated SNEDDS curcumin.

The globule size characterization of SNEDDS curcumin consisting miglyol:smix(Tween 20 and Tween 80):PEG 400 (1:8:1) was determined by Zetasizer Nano. The Balb/c mice orally given ethanol 10% v/v for 21 days is used as the brain disorders model (chronic, withdrawal). The next day, SNEDDS curcumin 20 or 40 mg/kg body weight was administrated via oral gavage for 21 days. The brain dissection is done 24 hours after the last gavage. Gene expression was measured using two-step semi-quantitative reverse transcriptase – polymerase chain reaction (RT-PCR) and real-time quantitative PCR. The nano emulsion characterization showed an evenly distributed <50 nm globule size of curcumin nano emulsion (PdI<0,2). SNEDDS curcumin did not alter Hdac2 expression, but SNEDDS curcumin 40 mg/kg body weight upregulated Bdnf. This hallmarks the activation of Bdnf/TrkB signaling by SNEDDS curcumin in brain disorder model. Neurogenesis upregulation was shown by the increasing mature neuron (NeuN) by curcumin suspension 40 mg/kgBB, but not SNEDDS curcumin. In gliogenesis, SNEDDS curcumin upregulated astrocyte mature (S100β), downregulated reactive astrocyte (Gfap), and no significant change was observed in oligodendrocyte (Olig2) in ethanol induced mice model of brain disorder.

Keywords : curcumin, self-nanoemulsifying drug delivery system, HDAC2, neurogenesis, BDNF