

Introduction : Gotu kola leaf extract (*C. asiatica* L. Urban) and turmeric rhizome (*C. Longa* L.) can improve cognitive function. Research The development of these candidate phytopharmaceutical preparations has not been widely carried out so that it becomes the basis for research on these preparations to improve cognitive function.

Objectives: preclinical and clinical trials of candidate phytopharmaceutical preparations of the extract combination, assessing pharmacodynamic activity, acute toxicity, subchronic toxicity, tolerability, and safety in healthy volunteers as well as effectiveness and safety to improve cognitive function in MCI patients.

Methods: An exploratory study was carried out in making capsules of a combination of extracts with CPOTB, testing the pharmacodynamic activity of these phytopharmaceutical candidate preparations in a rat model of stroke. Acute and subchronic toxicity tests were conducted using a quasi pre and post-test-only controlled group design, and phase 1 and 2 clinical trials using a randomized controlled trial method.

The results: 27 stroke model animals were tested using Y-Maze and the results showed that normal rats had higher spontaneous alternation behavior (80%) than stroke model rats (58.34%). In the pharmacodynamic activity test, the mixed-dose extract was not inferior to donepezil ($p > 0.05$) and significantly different from the placebo. Acute toxicity test, obtained LD50 value greater than 2,000 mg/kg does not cause toxic effects on important organs. In the subchronic toxicity test, there was an increase in SGOT, SGPT, and creatinine but the histology of the liver and kidneys did not differ from the control group. In phase 1 clinical trials, there was no effect of increasing the dose of the combination of *C. asiatica* L. Urban extract. and *C. longa* L. on liver and kidney function. The average increase in MoCA-Ina in MCI subjects was highest in the medium-dose group (combination of Gotu kola leaf extract at a dose of 562.5 mg/day and turmeric rhizome 300 mg/day) and was significant at $p < 0.001$, followed by a high dose group with a combination of Gotu kola leaf extract at a dose of 750 mg/day. and turmeric rhizome 400 mg/day and $p < 0.001$, then the small dose group combined with Gotu kola leaf extract at a dose of 375 mg/day and turmeric rhizome 200 mg/day and $p = 0.035$.

Conclusion: The development of candidate phytopharmaceuticals for the combination of Gotu kola leaf extract (*C. asiatica* L. Urban) and turmeric rhizome (*C. Longa* L.) according to CPOTB has been successful. Acute toxicity test with LD50 value greater than 2,000 mg/kg and subchronic showed that administration of the preparation did not cause toxic effects in stroke model rats. The increase in cognitive function was obtained by the addition of a combination of Gotu kola leaf extract and turmeric rhizome extract which was highest at high and medium doses.

Keywords: Clinical trial, *centella asiatica*, *curcuma longa*, cognitive impairment, MoCA-Ina

INTISARI

Pendahuluan : ekstrak daun pegagan (*C. asiatica* L. Urban) dan rimpang kunyit (*C. Longa* L.) dapat memperbaiki fungsi kognitif. Riset Pengembangan sediaan kandidat fitofarmaka tersebut belum banyak dilakukan sehingga menjadi dasar penelitian sediaan tersebut untuk memperbaiki fungsi kognitif.

Tujuan : uji praklinik dan klinik sediaan kandidat fitofarmaka kombinasi ekstrak tersebut, mengkaji aktivitas farmakodinamik, toksisitas akut, toksisitas subkronik, tolerabilitas dan keamanan pada relawan sehat serta efektivitas dan keamanan untuk meningkatkan fungsi kognitif pada pasien MCI.

Metode : dilakukan penelitian eksploratif dalam membuat sediaan kapsul kombinasi ekstrak dengan CPOTB, uji aktivitas farmakodinamik sediaan kandidat fitofarmaka tersebut pada model tikus stroke. Uji toksisitas akut dan subkronis dengan eksperimen quasi *pre and post test-only controlled group design*, serta uji klinik fase 1 dan 2 dengan metode *randomized controlled trial*.

Hasil penelitian : 27 hewan uji model stroke dilakukan tes menggunakan Y-Maze dan didapatkan hasil bahwa tikus normal memiliki perilaku alternasi spontan lebih tinggi (80%) dibandingkan tikus model stroke (58,34%). Pada uji aktivitas farmakodinamik, ekstrak kombinasi berbagai dosis tidak lebih inferior dibanding dengan pemberian donepezil ($p > 0.05$) dan berbeda bermakna dengan plasebo. Uji toksisitas akut, didapatkan nilai LD₅₀ lebih besar dari 2.000 mg/kg tidak menyebabkan efek toksik pada organ-organ penting. Pada uji toksisitas subkronik, terdapat peningkatan SGOT, SGPT dan kreatinin namun gambaran histologi hepar dan ginjal tidak ada perbedaan dengan kelompok kontrol. Pada uji klinis fase 1, tidak ada pengaruh kenaikan dosis pemberian sediaan kombinasi ekstrak *C.asiatica* L.Urban. dan *C.longa* L. terhadap fungsi hepar dan ginjal. Rerata peningkatan MoCA-Ina pada subjek MCI tertinggi pada kelompok dosis sedang (kombinasi ekstrak daun pegagan dosis 562,5mg/hari dan rimpang kunyit 300mg/hari) dan bermakna $p < 0,001$, diikuti kelompok dosis tinggi kombinasi ekstrak daun pegagan dosis 750 mg/hari dan rimpang kunyit 400mg/hari dan bermakna $p < 0,001$, kemudian kelompok dosis kecil kombinasi ekstrak daun pegagan dosis 375 mg/hari dan rimpang kunyit 200mg/hari dan bermakna $p = 0,035$).

Kesimpulan : Telah berhasil dilakukan pengembangan kandidat fitofarmaka sediaan kombinasi Ekstrak daun pegagan (*C. asiatica* L. Urban) dan rimpang kunyit (*C. Longa* L.) sesuai CPOTB. Uji toksisitas akut dengan nilai LD₅₀ lebih besar dari 2.000 mg/kg dan subkronis menunjukkan pemberian sediaan tidak menimbulkan efek toksik pada tikus model stroke. Peningkatan fungsi kognitif didapatkan dengan penambahan sediaan kombinasi ekstrak daun pegagan dan rimpang kunyit yang tertinggi pada dosis tinggi dan dosis sedang.

Kata kunci: uji klinik, *Centella Asiatica*, curcumin, cognitive impairment, MoCA-Ina