

## ABSTRACT

Inhibiting phosphodiesterase (PDE) is nowadays one of the more promising mechanisms for cognitive enhancers to improve memory function in diseases associated with cognitive dysfunction (CD). The available treatment agents for treating the condition of CD are currently limited. Consequently, it is imperative to investigate herbal therapy as a potential substitute for the management and prevention of CD targeting phosphodiesterase-4B (PDE4B) is one of the possible therapeutic targets for CD. The objectives of this study were to use TLC-densitometry analysis to identify and quantify quercetin, sinigrin, and chlorogenic acid in coffee, white cabbage, and red onion extracts, respectively, to predict molecular interaction between test compounds and PDE4B by *in silico* studies, to determine PDE4B inhibitory activity *in vitro* as a preliminary study for further investigations, and to evaluate the memory-improving properties of combination extract (coffee, red onion, and white cabbage) in mice with CD induced by scopolamine, however the current research has gaps in these experiments.

The ethanol extracts from white cabbage and red onion were made by maceration separately, while the infusion method was used to create an aqueous extract of coffee. TLC-densitometry was performed to quantitatively analyze quercetin, sinigrin, and chlorogenic acid in the extracts of coffee, red onion, and white cabbage, respectively. The Morris Water Maze (MWM) test was used to assess spatial memory following the administration of combination extract (coffee 160 mg/kg, red onion 30 mg/kg, and white cabbage 330 mg/kg). Further investigation was conducted using Western blot and ELISA to measure the activities of cAMP, PKA, CREB, and BDNF in the mouse hippocampal tissues.

The amounts of quercetin ( $420.57 \pm 45.63$  mg/g), sinigrin ( $117.18 \pm 7.22$  mg/g), and chlorogenic acid ( $23.65 \pm 4.66$  mg/g) in the extracts of red onion, white cabbage, and coffee were measured using TLC-densitometry, respectively. *In silico* studies showed the moderate scoring for chlorogenic acid ( $\Delta G_{\text{bind}} = -21.501$  kcal/mol) and quercetin ( $\Delta G_{\text{bind}} = -17.252$  kcal/mol) against PDE4B. *In vitro* assay for PDE4B inhibition displayed that combination extract had better  $IC_{50}$  ( $0.109 \pm 0.002$   $\mu\text{M}$ ) than combination standard  $IC_{50}$  ( $0.117 \pm 0.001$   $\mu\text{M}$ ) and rolipram as reference drug  $IC_{50}$  ( $0.113 \pm 0.001$   $\mu\text{M}$ ). Under behavioral tests, animals with scopolamine-induced CD showed improved memory after taking the combination extract by raising the cAMP, PKA, CREB, and BDNF levels as well as by improving escape latency time. To conclude, the extracts from coffee, red onion, and white cabbage are good sources of chlorogenic acid, quercetin, and sinigrin, respectively. The combination extract increased memory performance by modifying the cAMP/PKA/CREB/BDNF pathway in mice with scopolamine-induced CD.

**Keywords:** White cabbage, Coffee, Red onion, PDE4B, Scopolamine, Cognitive enhancer