

Supporting Information for

Curcumin diethyl γ -aminobutyrate, a prodrug of curcumin, for enhanced

treatment of inflammatory pain

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S1. Computational modelling of potential toxicity of CUR-2GE.

The computational modelling of potential toxicity of CUR-2GE was performed using ProTox-II ¹. As shown in Table S1, the toxicity level of CUR-2GE, curcumin, and GABA ethyl ester ranked at class 4, 4, and 5, respectively, which are considered safe.

Table S1. Computational modelling of potential toxicity of CUR-2GE.

No	Variables	Compound		
		CUR-2GE	Curcumin	GABA ethyl ester
1	Toxicity class (1-5)	Class 4 (Harmful if swallowed)	Class 4 (Harmful if swallowed)	Class 5 (May be harmful if swallowed)
2	Predicted LD ₅₀ (mg/kg)	1300 mg/kg	2000 mg/kg	5000 mg/kg
3	Hepatotoxicity	Inactive	Inactive	Inactive
4	<i>Toxicity endpoints</i>			
	A. Carcinogenicity	Inactive	Inactive	Active
	B. Immunotoxicity	Active	Active	Inactive
	C. Mutagenicity	Inactive	Inactive	Inactive
	D. Cytotoxicity	Inactive	Inactive	Inactive
5	<i>Nuclear receptor signaling pathways</i>			
	A. Aryl hydrocarbon Receptor (AhR)	Inactive	Inactive	Inactive
	B. Androgen Receptor (AR)	Inactive	Inactive	Inactive
	C. Androgen Receptor Ligand Binding Domain (AR-LBD)	Inactive	Inactive	Inactive
	D. Aromatase	Inactive	Inactive	Inactive
	E. Estrogen Receptor Alpha (ER)	Inactive	Inactive	Inactive
	F. Estrogen Receptor Ligand Binding Domain (ER-LBD)	Inactive	Inactive	Inactive
	G. Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma)	Inactive	Active	Inactive
6	<i>Stress response pathways</i>			
	A. Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	Inactive	Active	Inactive
	B. Heat shock factor response element (HSE)	Inactive	Active	Inactive
	C. Mitochondrial Membrane Potential (MMP)	Inactive	Active	Inactive
	D. Phosphoprotein (Tumor Suppressor) p53	Inactive	Active	Inactive
	E. ATPase family AAA domain-containing protein 5 (ATAD5)	Inactive	Inactive	Inactive

References

- (1) Banerjee, P.; Eckert, A. O.; Schrey, A. K.; Preissner, R. ProTox-II: A Webserver for the Prediction of Toxicity of Chemicals. *Nucleic Acids Res.* **2018**, *46* (W1), W257–W263. <https://doi.org/10.1093/nar/gky318>.