



TITLE: Beyond Desensitisation: The Impact of *Erythroxylum cuneatum* on Morphine-Impaired Signaling

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ABSTRACT (upto 300 words)

Chronic morphine use triggers desensitisation of its receptor, inhibiting essential internalisation processes and contributing to addiction, marked by increased withdrawal, tolerance, and dependence. Conventionally, methadone has been employed as a positive control to reverse these effects by promoting receptor resensitisation and internalisation. However, seeking alternative treatments with potentially lesser side effects or improved efficacy is crucial. In this study, we explore the efficacy of *Erythroxylum cuneatum*, a promising candidate against morphine addiction. We employed the human neuroblastoma cell line, SK-N-SH, in an experimental setup involving pre-treatment with morphine to assess the roles of *E. cuneatum* and methadone in mitigating withdrawal symptoms. The cytosolic fraction of these cells was isolated for protein analysis focusing on the expression levels of G protein-coupled receptor kinase 2 (GRK 2), β -arrestin 1/2, and clathrin heavy chain, which are pivotal in receptor internalisation dynamics. Our findings indicate a significant decrease in the expressions of GRK 2, β -arrestin 1/2, and clathrin heavy

chain following prolonged morphine exposure, suggesting receptor desensitisation. Remarkably, treatment with *E. cuneatum* demonstrated effects comparable to those of methadone, notably enhancing receptor internalisation. In conclusion, *E. cuneatum* extract shows potential as an anti-addiction agent, stimulating the internalisation and resensitisation of morphine-desensitised receptors. These findings propose *E. cuneatum* as a viable alternative to methadone in treating morphine addiction, paving the way for further pharmacological investigations.

BIOGRAPHY (upto 200 words)

Noor Azuin Binti Suliman has completed her PHD at the age of 30 years from Universiti Putra Malaysia, Malaysia. He is a lecturer in Physiology Unit, Faculty of Medicine, Universiti Sultan Zainal Abidin, Malaysia. He has over 10 publications that have been cited over 200 times, and his publication h-index is 4.

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Mode of Presentation: Oral, online.

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