

Área: ORG

Toxicokinetic-Toxicodynamic Modeling of the Optimized Hydroalcoholic Extract of *Luehea divaricata* (Malvaceae) in *Drosophila melanogaster*

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Keywords: Natural Products, Brazilian Folk Medicine, Açoita-cavalo, Response Surface Methodology, Antioxidants, GUTS.

Highlights

- The hydroalcoholic extraction of phenolic, flavonoid, and triterpene content from *L. divaricata* leaves were optimized using Response Surface Methodology (RSM-CCD).
- The extracts exhibit high *in vitro* antioxidant capacity and strong correlation with the phenolic content.
- GUTS Modeling reveal a non-monotonic hazard dynamics (IT) and slow depuration-repair kinetics, suggesting complex mechanism but overall low toxicological risk, with a stable $LC_{50} = 33.35$ mg/mL, and low chronic effects.

Abstract

Luehea divaricata (Malvaceae), commonly known in Brazil as “Açoita-Cavalo”, is widely used in folk medicine, believed to possess diverse therapeutic properties. Despite its traditional use, little is actually known about its phytotherapeutic potential in the scientific literature. In this study, the extraction of phenolic (TPC), flavonoid (TFC), and triterpene (TTC) content from leaves of *L. divaricata* was optimized via RSM-CCD design, with ethanol proportion and sonication time as variables. Antioxidant activity was assessed via DPPH, FRAP, and CUPRAC assays, while the toxicological profile of the optimized extract was evaluated in *Drosophila melanogaster* under constant exposure (10–50 mg/mL) for seven days. Survival data were modeled using the GUTS-RED framework in both Stochastic Death (SD) and Individual Tolerance (IT) models. The optimal extraction condition was achieved at 77.6% ethanol and 95.2 minutes of sonication, yielding expected values of 59.7 mgGAE/g for TPC, 13.6 mgQE/g for TFC, and 0.26 mgCE/g for TTC ($D = 0.97$). TPC showed a strong Spearman correlation with antioxidant capacity ($r > 0.92$), whereas TFC and TTC displayed weak or no correlation ($r < 0.2$). In the toxicological assessment under constant exposure, the IT model provided the best fit (AIC = 787.27; NRMSE = 8.07%; NSE = 0.94), indicating an average threshold $m_w = 33.53$ mg/mL with a narrow tolerance distribution ($F_5 = 4.20$; $\beta = 2.55$). The modeled hazard function displayed a non-monotonic pattern with an early risk-band between 1-4 days following a drop over time. Absorption/depuration kinetics were relatively slow ($k_d = 0.4576$ d⁻¹; $DRT_{95} = 6.55$ days), suggesting persistence but low cumulative toxicity, likely influenced by the presence of lipophilic compounds such as triterpenes. As consequence, $LC_{50}(t)$ stabilized after approximately 6 days, converging toward m_w , consistent with low chronic toxicity. However, under pulsed exposure, the SD model outperformed IT (NSE = 0.812 vs. 0.731; NRMSE = 5.03% vs. 6.34%), indicating a primarily acute mode of action in dynamic conditions. Overall, the extract exhibited a complex toxicological mechanism that cannot be classified solely as acute or chronic/cumulative, yet remained of relatively low toxicity across both exposure scenarios. These findings support the safe use of *L. divaricata* as a potential phytotherapeutic agent while emphasizing the relevance context exposure dependence in accurately characterizing the complex natural product toxicodynamics.

Acknowledgments

