



MODULATORY ACTIVITY OF TERPINOLENE ON POTASSIUM CHANNELS IN HUMAN UMBILICAL ARTERIES AND *IN SILICO*

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ABSTRACT

Introduction: Given the global rates of maternal-fetal morbidity and mortality caused by hypertensive syndromes during pregnancy, various research groups have initiated investigations using ex vivo models of human umbilical vessels, aiming to understand their function under pathophysiological conditions, due to the relevance of these vessels for fetal survival. In this context, this study explores a less-studied perspective: the action of natural products on human umbilical vasculature, such as terpinolene, a monoterpene synthesized by Asian plants like black currant (*Ribes rubrum*) and turmeric (*Curcuma longa*). Literature records cite terpinolene as a bioactive compound with relevant pharmacological properties, including antifungal, antibacterial, anti-inflammatory, antinociceptive, and antioxidant effects. However, its vascular potential in animal or human vessels has yet to be described.

Objective: To evaluate the modulatory activity of terpinolene on potassium channels in human umbilical arteries, characterizing the interaction between terpinolene and potassium (K⁺) ion channels in silico through molecular docking. **Materials and Methods:** After approval from the Ethics Committee of the Regional University of Cariri (No. 3,832,881), fragments of human umbilical cords were donated by parturients through informed consent. The tests were conducted on rings (3-5 mm) cut from human umbilical arteries (HUA) that were previously dissected to remove Wharton's jelly, which were subjected to isometric tension recording in an organ bath. The experiments evaluated the involvement of a variety of K⁺ channels. Terpinolene (1 – 3,000 µM) was added to the arterial preparations during contractions evoked by serotonin (10 µM), pre-incubated with K⁺ channel blockers: BaCl₂ (500 µM) as a selective blocker for inward rectifier potassium channels (KIR), 4-Aminopyridine (1 mM) as a selective blocker for voltage-dependent potassium channels (K_v), Tetraethylammonium (1 mM) as a selective blocker for large-conductance calcium-sensitive potassium channels (BKCa), or glibenclamide (10 mM). To investigate the mechanism of action of terpinolene, the structures of terpinolene and potassium channels were obtained from the Protein Data Bank repository. **Results:** All K⁺ channel blockers used affected the potency and efficacy of the relaxing response of terpinolene. Molecular docking studies indicated terpinolene's affinity for KATP, BKCa, and KIR channels, with more significant binding energy values for the KIR channel, suggesting that the vasorelaxant mechanism promoted by terpinolene involves the activation of potassium channels (BKCa, K_v, KATP, and KIR) in this effect. **Conclusions:** It is suggested that terpinolene may be a vasoactive regulator of umbilical vasculature, representing a potential candidate for a vasodilator drug with clinical utility during pregnancy.