Liposomal Delivery of *Marrubium vulgare* Polyphenols: Nanotechnology Approach to Enhance Anti-Inflammatory and Analgesic Activity

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The aerial parts of horehound (*Marrubium vulgare* L.), a medicinal species widely distributed within Mediterranean biodiversity, constitute a valuable natural source of polyphenolic compounds with recognized health-promoting properties. However, their therapeutic application is limited by poor chemical stability and low bioavailability, which restrict their effective use in biomedical and nutraceutical contexts. In this study, a liposomal formulation of *M. vulgare* polyphenolic extract (MV-Lipos) was developed using the thin-film hydration method, in line with biodiversity valorisation strategies aimed at enhancing the functional potential of native plant resources. The extract was first characterized by LC-MS analysis prior to encapsulation. The resulting nanoliposomes were evaluated for their physicochemical properties, including particle size, polydispersity index (PDI), zeta potential, encapsulation efficiency (%EE), stability in simulated gastrointestinal fluids, and in vitro release profile. Biological performance was assessed through cytotoxicity, antioxidant, and anti-inflammatory assays in LPS-stimulated macrophages. The formulation showed nanosized vesicles ranging from 115 to 149 nm with an encapsulation efficiency of 82%, good colloidal stability (zeta potential between –36.3 and –52.6 mV), and a relatively uniform dispersion (PDI = 0.66). In vivo studies demonstrated that MV-Lipos significantly enhanced analgesic and anti-inflammatory effects in mice, reducing writhing responses by up to 75.9% and paw edema by 72% at 100 mg/kg, with efficacy comparable to ibuprofen. A 28-day subacute toxicity assessment confirmed the safety of the formulation, with no adverse effects observed. Additionally, in silico docking studies supported the experimental outcomes, suggesting plausible molecular interactions responsible for the observed bioactivities.