

Article

Chitosan-Modified Nanobilosomal Gel for the Transdermal Delivery of Thymol and Silibinin for Rheumatoid Arthritis Management: Synergistic Effect and Improved In Vivo Articular Restoration

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Abstract

Rheumatoid arthritis (RA) management via conventional monotherapy is often limited by poor transdermal flux and suboptimal articular accumulation. This study seeks to bridge a critical gap in monotherapy by engineering chitosan-coated nanobilosomal gel co-encapsulated with thymol and silibinin (CH-TH+SB-BG) in a 3:1 stoichiometric ratio. Compared with monotherapeutics, the CH-TH+SB-BG showed the highest drug content and a sustained drug release profile, accompanied by higher skin permeation and deposition, indicating the fluidizing effect of thymol and the dermal reservoir of silibinin. Interestingly, CH-TH+SB-BG was cytocompatible, owing to its higher IC₅₀ than that of the pure drugs. A marked reduction in the paw volume and arthritic score and significant normalization of hematological, biochemical, and inflammatory biomarkers, compared with the monotherapeutics, indicate the synergistic anti-inflammatory potential of the developed gel. Furthermore, the dual loading effectively reduced oxidative stress, confirmed by a significant decrease in malondialdehyde level along with the restoration of glutathione and superoxide dismutase levels. The Bliss independence model mathematically validated pharmacological synergy. Radiographic and histopathological analysis confirmed the near-complete articular restoration and marked reduction in pannus formation. In conclusion, the developed transdermal gel can be a more effective and safer alternative to long-term oral administration, opening the way for novel topical management of RA.

Keywords: chitosan; transdermal drug delivery; nanobilosomal gel; thymol; silibinin; rheumatoid arthritis; synergism



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1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune and inflammatory disease with a global prevalence of 0.5–1%, especially in Western countries. It is characterized by pain, joint swelling, and bone or cartilage destruction, which significantly affect patients' mobility and quality of life. Beyond the complex pathogenesis, it is believed that RA involves undesirable immune responses (such as protein modifications, gene expression,