

Title: Unlocking the Immunomodulatory Potential of Rosmarinic Acid Isolated from *Punica granatum* L. using Bioactivity-Guided Approach: *In Silico*, *In Vitro*, and *In Vivo* Approaches

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Abstract: Background: *Punica granatum* L. is well-known for its multifaceted therapeutic potential, including anti-inflammatory and immunomodulatory activities.

Aim: This study aimed to characterize an immunomodulatory compound isolated from *Punica granatum* L. using a bioactivity-guided approach.

Methods: Chromatographic techniques were adopted for isolation and purification of secondary metabolites. *In silico*, *in vitro*, and *in vivo* methods were performed to characterize the therapeutic potential of the isolated compound.

Results: Using preparative thin-layer chromatography, rosmarinic acid was isolated from F4 (column chromatography product obtained from a butanolic fraction of the extract). The impact of rosmarinic acid was assessed in rats using the neutrophil adhesion test, DTH response, and phagocytic index. In immunized rats, rosmarinic acid demonstrated significant immunomodulatory potential. Computational experiments, like molecular docking and molecular dynamics, were also conducted against two targeted receptors, Cereblon (PDB ID: 8AOQ) and human CD22 (PDB ID: 5VKM). Computational studies suggested that an increase in phagocytic index by rosmarinic acid could be attributed to inhibiting Cereblon and CD22. Pharmacokinetics and toxicity prediction also suggested the drug-likeness of rosmarinic acid.

Conclusion: Rosmarinic acid is a potential candidate, but extensive research needs to be done to translate this molecule from bench to bedside.

Keywords: *Punica granatum* L., rosmarinic acid, immunomodulatory activity, Cereblon, CD22, immune response

<https://eurekaselect.com/article/138960>

DOI: [10.2174/0109298673291064240227094654](https://doi.org/10.2174/0109298673291064240227094654)