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Decoding Atorvastatin Induced Arthritis: A Systems Pharmacology Approach Integrating Pharmacovigilance, Bioinformatics, and Pathway Enrichment

Dr. E Maheswari, Bindu MA and Brunda MA.

Faculty of Pharmacy, Department of Pharmacy Practice, M.S. Ramaiah University of Applied Sciences, Bangalore, Karnataka.

INTRODUCTION

Atorvastatin is administered for the treatment of hyperlipidaemia and cardiovascular complications. Hyperlipidaemia is a common metabolic condition characterized by higher levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C).

OBJECTIVE

This study aimed to investigate the novel signals of atorvastatin employing integrative strategies that combines network pharmacology and molecular docking. The predicted drug-target interactions were then verified in silico using molecular docking, which evaluated the binding affinity and interaction patterns of atorvastatin at potential target locations.

METHOD

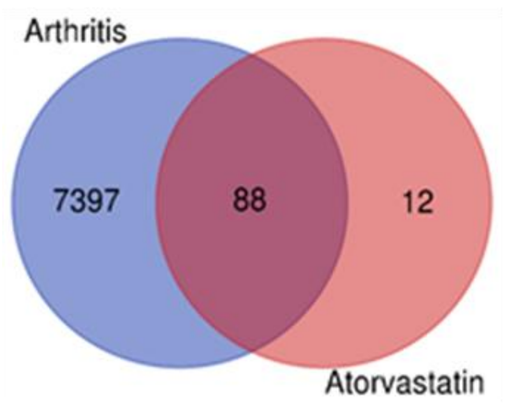
A case and non-case disproportionality analysis on atorvastatin was executed using a real-world data from the FAERS database. The signal was considered as positive if number of events (n)>2, Proportional Reporting Ratio (PRR)>2 and Chi square >4. Hub genes identified through Gene Ontology (GO) was refined using string followed by cytohubba.

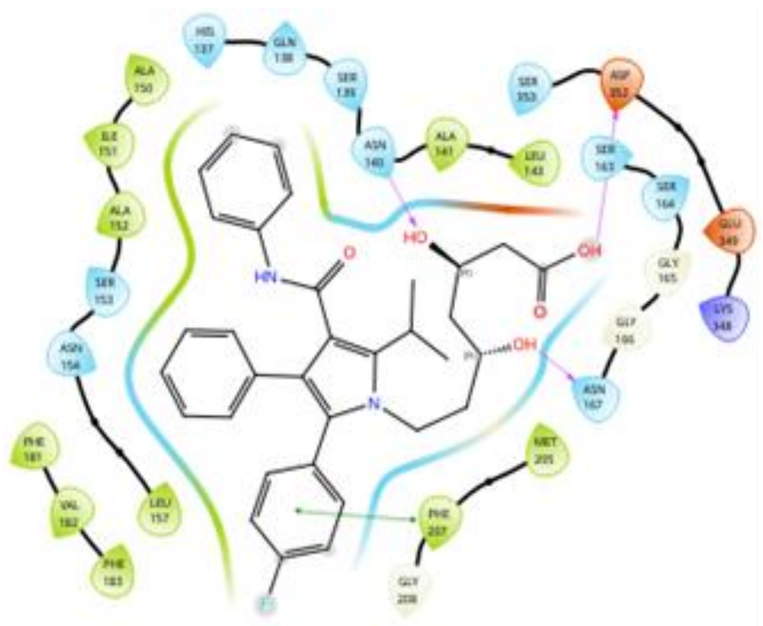
Protein-Protein Interaction (PPI) networks of atorvastatin induced signal was constructed by STRING. Binding affinity of atorvastatin with the identified targets was assessed using molecular docking simulations.

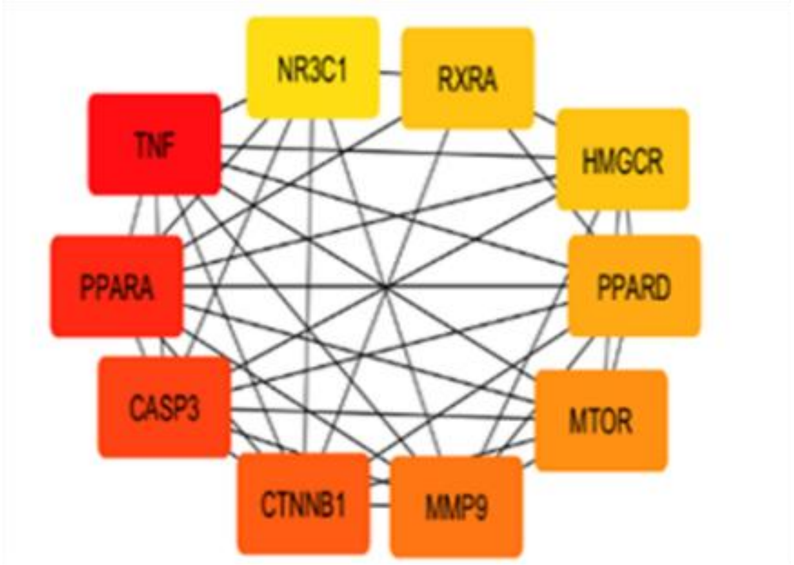
RESULTS

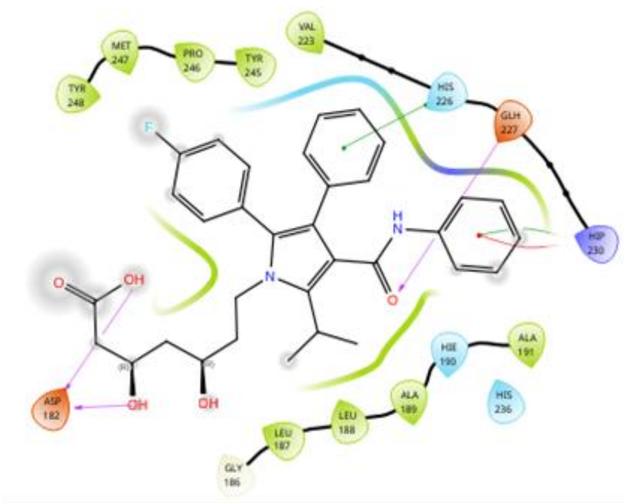
Molecular docking

Analysis of the literature revealed that atorvastatin's binding to MMP9 and CASP3 is linked to the activation of inflammatory processes, which may aid in the development of arthritis. Molecular docking studies were conducted utilizing CASP3 (PDB ID: 7XN4) and MMP9 (PDB ID: 4XCT) to examine the interactions between atorvastatin and arthritis-related proteins to understand the underlying mechanism. It was discovered that atorvastatin has binding affinities of -6.84 kcal/mol for CASP3 and -7.688 kcal/mol for MMP9.









CONCLUSIONS

The bioinformatics and molecular docking studies revealed strong binding affinities indicating a strong correlation between atorvastatin and arthritis. Evidence suggests that atorvastatin increases LPS-induced MMP-9 production through ERK and CREB phosphorylation is hypothesised to upsurge the release of inflammatory cytokines through CASP3 activation. The authors suggest to conduct further experimental validation, pharmacogenetic and pharmacoepidemiological research and greater clinical awareness among health care practitioners to improve patient safety, especially among patients prone to inflammatory diseases like arthritis.

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CONTACT INFORMATION

maheswarieswar@gmail.com

+91 9620451165