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Mechanistic insights into the inhibition of nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome by 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one to attenuate atherosclerosis: A multi-computational study

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ABSTRACT Background: Atherosclerosis (AS) is a chronic inflammatory disease driven by endothelial dysfunction and excessive activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome. 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one, a flavonoid abundant in medicinal plants, has been reported to exhibit anti-inflammatory and cardioprotective properties. However, its molecular mechanism in modulating NLRP3 remains unclear. **Methods:** To elucidate the molecular basis of 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one-mediated NLRP3 inhibition, a multi-computational strategy was employed, integrating density functional theory (DFT), molecular docking, molecular dynamic (MD) simulation, and molecular mechanics/generalized born surface area free energy decomposition. DFT calculations were used to characterize the molecular stability and electronic distribution of 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromen-4-one. Molecular docking predicted potential binding residues within the NLRP3 active site. Subsequently, 200 ns MD simulations and free energy landscape (FEL) analyses were performed to assess the stability and dynamic behavior of the complex. **Results:** DFT analysis revealed a stable frontier orbital distribution conducive to hydrogen-bond formation. Docking and MD results demonstrated that 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one binds tightly within the NLRP3 pocket through hydrogen bonding and hydrophobic interactions, particularly involving Glu135, Leu242, and Trp245. The root mean square deviation and root mean square fluctuation profiles indicated high conformational stability, while the FEL map showed a single deep energy basin, confirming thermodynamic robustness. Free energy decomposition analysis revealed that van der Waals and electrostatic interactions were the primary driving forces for complex stabilization. **Conclusion:** This study provides comprehensive molecular evidence that 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one inhibits NLRP3 inflammasome activation through stable binding and favorable energetic contributions, potentially mitigating inflammation-associated vascular injury. These findings offer a theoretical basis for developing 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl) chromen-4-one-derived inhibitors as promising therapeutic candidates for the prevention and treatment of AS.

KEYWORDS Nucleotide-binding oligomerization domain-like receptor protein 3, 3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one, Molecular docking, Molecular dynamics simulation, Free energy calculation.

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