Antimicrobial Action of Essential Oils and CuO Nanoparticles Against Pathogenic Proteins: Elucidation of the Inhibitory Mechanism through Molecular Dynamics and Free Energy Calculations

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Abstract

In this study, we present our efforts to computationally design self-disinfecting bio-nano coatings based on optimal combinations of specific structures possessing antimicrobial properties. These structures incorporate copper-based nanoparticles (NPs) and bioactive compounds, such as essential oils (EOs) coming from non-edible plants. EOs are natural, safe, easily biodegradable, and particularly effective substances against bacteria, fungi and viruses. Due to the multi-component nature of EOs, their antimicrobial action is not attributable to a specific mechanism, but it is rather a synergistic effect on multiple targets in the cells. For this reason, EOs may prevent antimicrobial (AMR) resistance and therefore fight multi-drug resistant bacteria and viruses.

This work elucidates the binding mechanism of selected EOs and Cu-based NPs against protein targets that directly relate to pathogenic actions, in order to further identify optimal structural and energetic patterns that result in enhanced bioactivity. In particular, a combination of advanced biomolecular modeling approaches was applied to study the binding modes and interactions at the molecular level between a large set of EOs/CuO NPs and selected pathogens, namely, *Staphylococcus aureus*, *SARS-CoV-2*, and *Escherichia coli*. The selection of the aforementioned pathogens was based on their current clinical significance. Molecular docking, extensive all-atom molecular dynamics (MD) simulations, and energetic analyses based on the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) methodology identified the primary structural and thermodynamic parameters that drive binding, along with the individual energy contributions, which favor complex formation, i.e., van der Waals, hydrophobic,

electrostatic, and entropy effects between proteins of the microorganisms and essential oils/Cu NPs.

Based on the above scheme, a rational selection of promising EOs and CuO NPs from a comprehensive set of candidates was obtained to provide insight into the nature of host-guest interactions. This information may be particularly helpful to design new formulations with enhanced antimicrobial activity, and to establish a correlation between favorable interactions and physiological responses to the pathogens, for further exploitation. Moreover, the elucidation of the interactions between CuO NPs and the virus proteins facilitates the discovery of NP-containing structures to be used as promising antimicrobial agents.