**Discovery of Corneal-Protective Phenolics from *Dialium cochinchinense* leaves for Dry Eye Disease: Mechanistic Insights and Molecular Validations**

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**Background and aims:** Dry eye disease (DED) requires innovative therapeutic strategies targeting both inflammation and oxidative stress. *Dialium cochinchinense*, a medicinal plant native to Vietnam, has been traditionally used to treat microbial infections, malaria, and inflammatory conditions, though scientific evidence supporting these uses is limited. This study aimed to evaluate the potential of *D. cochinchinense* leaf extracts for DED treatment and to identify their bioactive compounds and underlying molecular mechanisms using *in silico* models.

**Methods.** Anti-inflammatory activity was assessed using ELISA assay and immunoblotting in LPS-stimulated macrophages. Antioxidant and corneal-cytoprotective effects were examined in bovine corneal epithelial cells subjected to benzalkonium chloride-induced ROS elevation and cell death. An advanced bioactive molecular networking strategy was then employed to prioritize and isolate key phytochemicals from *D. cochinchinense* leaves. Network pharmacology was used to explore the underlying molecular mechanisms, while molecular docking and dynamics simulations were performed to validate key compound-target interactions.

**Results.** This study is the first to show that *D. cochinchinense* leaf extracts inhibit NF-κB signaling in macrophages and exert antioxidant and cytoprotective effects against oxidative damage in corneal epithelial cells. Bioactive molecular networking led to the discovery of one new compound, 6*S*,9*R*-2′-*O*-sinapoyl-roseoside, along with 11 known phenolic derivatives. Of these, 10 exhibited strong corneal-protective activity *in vitro*. Network pharmacology analysis identified 65 overlapping targets between these compounds and DED, primarily enriched in the PI3K/AKT and MAPK signaling pathways. Molecular docking and dynamics simulations confirmed stable, high-affinity binding of the lead compounds to key protein targets: AKT1, PIK3CA, IGFR1, and EGFR (1).

**Conclusion/Discussion.** These findings demonstrate for the first time that *D. cochinchinense* leaves and their bioactive constituents are promising natural candidates for DED treatment.

**Reference:**

(1) Nguyen, Thi Tuyet Nhung, et al. "Application of bioactive molecular networking to identify corneal-cytoprotective compounds from *Dialium cochinchinense* Pierre. leaves." Current Plant Biology (2025): 100489.