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A novel approach to antibiotics and antifungals: Testing the effectiveness of *Azadirachta indica* extracts

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Azadirachta indica (neem) extracts have proven themselves to be a promising tool because they are natural and don't cause the harmful side effects of most artificial substances. Preliminary research has shown that certain natural substances can be used without the fear of a new resistant strain developing. Current treatments are plagued by artificial substances that can have harmful side effects to the body and may not be effective for multiple uses. Thus, this project aims to determine the effectiveness of natural substances as antibacterial and antifungal. Early research suggested that the neem oil would be the most effective extract because it would envelop the bacteria and fungi. Cultures of bacteria, specifically *Staphylococcus epidermidis* and *Serratia marcescens*, and cultures of fungi, specifically *Aspergillus niger* and *Saccharomyces cerevisiae,* were cultured and placed in separate plates. Zones of inhibitions were created using neem leaf extract, neem soap, neem oil, a water control and antibacterial soap control disks. The diameters of the zones where growth has stopped were compared using statistical significance tests to see if any of the natural extracts were more effective than the controls. The zones that were significantly different from the controls' zones were compared amongst each other to see if one extract was more effective than the other. This analysis has shown that the natural substances are extremely effective and significantly stronger than antibiotic and antifungal substances and the artificial substances in the soap. The remainder of the plate was then considered to be the pool of potential resistant strands. Thus repetitions were completed with each of the treatments. Since the growth was still inhibited without resistance, it became apparent that the neem extracts could have many practical purposes in treatments of infections. Given that only a few trials were completed, the experiment would have to be completed with more trials to prove the consistent effectiveness.

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A novel small-molecule compound disrupts influenza A virus PB2 cap-binding and inhibits viral replication

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Objectives: The conserved residues 318-483 in the PB2 subunit of influenza A polymerase is an independently folded cap-binding domain (PB2cap) that exhibits a distinct binding mode from other host cap-binding proteins, which suggests that PB2cap might be an ideal drug target. This study aimed to identify a new class of anti-influenza inhibitors that specifically disrupts the interaction between PB2cap and host cap structures.

Methods: An innovative fluorescence polarization assay was established for primary screening, followed by cap-binding inhibitory activity, antiviral efficacy and cytotoxicity evaluations of the selected compounds. The best compound was characterized by multi-cycle virus growth assay, cross-protection test, synergism evaluation, mini-replicon assay, binding affinity analysis, docking simulation and mouse study.

Results: Several PB2 cap-binding inhibitors were discovered. The compound 7-(4-hydroxy-2-oxo-2H-chromen-3-yl)-6H,7H,8H-chromeno[3',4':5,6]pyrano[3,2-c]chromene-6,8-dione, designated PB2-39, was identified as a potent inhibitor of replication of multiple subtypes of influenza A virus, including H1N1, H3N2, H5N1, H7N7, H7N9 and H9N2 *in vitro* and H1N1, H5N1 and H7N9 in vivo. Combinational treatment with the influenza virus release inhibitor zanamivir and PB2-39 exerted a synergistic anti-influenza effect. Mechanistic experiments supported that PB2-39 suppressed viral polymerase activity. Docking and binding affinity analyses demonstrated that PB2-39 interacted with the PB2 cap-binding pocket, suggesting its role as a cap-binding competitor.

Conclusions: Our study provides new insights for the strategic development of novel cap-binding inhibitors of influenza A viruses.

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