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Immunosuppressive Effect of Caffeine and Metformin in The *Drosophila* Model of Autoinflammatory Disease

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ABSTRACT

In the quest to find new indications for existing drugs, drug repurposing has emerged as a promising strategy. However, a significant obstacle has been the lack of a robust, high-throughput, in vivo preclinical system suitable for screening and investigating these new uses. This study addresses this challenge by introducing Drosophila larvae as a potential in vivo platform for evaluating drugs with immunomodulatory properties. To determine the suitability of Drosophila larvae for assessing the immunomodulatory effect of drug candidates, we performed phenotypical and molecular assays using two well-known immunomodulatory compounds, caffeine and metformin, that have been previously investigated using mammalian models. Our preliminary results demonstrated that caffeine and metformin were relatively harmless for Drosophila larvae and could improve their lifespan. Further molecular analysis suggested that both caffeine and metformin influenced gene expression in Drosophila larvae, particularly in the NF-κB and JAK-STAT pathways, which are analogous to immune-related pathways in mammals. Both caffeine and metformin showed promising results in the autoinflammatory Drosophila model, indicating a potent immunosuppressive activity. Additional analysis revealed that these compounds did not exhibit antibacterial or immunostimulant properties in the *Staphylococcus aureus*-infected wildtype and immunodeficient Drosophila. In conclusion, our study suggests that the observed immunosuppressive effects of caffeine and metformin in Drosophila larvae align with those seen in the mammalian models. This study highlights the suitability of Drosophila larvae as a model organism for drug repurposing, especially in the screening of newly discovered chemicals for their immunomodulatory properties before proceeding to mammalian animal models.

Keywords: Vinegar fly, larvae, drug repositioning, autoinflammatory, immunosuppressive agents