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RESEARCH ARTICLE

Flavonoid Profiling, Molecular Docking, and Modulatory Effects of *Artemisia herba- alba* Leaf Extract on ACE2 and TMPRSS2 Gene Expression

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ABSTRACT

Several studies have reported the potential antiviral activity of Artemisia species, which is related mainly to their flavonoid constituents. Transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) are critical SARS-CoV-2 entry factors. In this study, the phytochemical composition and modulatory effects of *Artemisia herba-alba* leaf extract on the gene expression of ACE2 and TMPRSS2 were investigated. To identify the flavonoid profile, HPLC was used. Cytotoxicity was estimated in A549 carcinoma and HDFn fibroblasts using an MTT assay ($IC_{50} = 114.8$ $\mu g/mL$). The real-time PCR results revealed significant upregulation of TMPRSS2 gene expression (2.4-fold, $p \leq 0.01$; p value = 0.0011), whereas ACE2 expression remained unchanged. Furthermore, a molecular docking study suggested the potential binding affinity of hesperidin and rutin for TMPRSS2 and ACE2. Therefore, both in vitro and in silico results indicated that *A. herba-alba* extract may interact with the viral entry pathway.

Keywords: ACE2, Artemisia herba-alba, COVID-19, Natural antiviral activity, TMPRSS2

Introduction

In 2019, the world faced a major health challenge caused by SARS-CoV-2, later known as coronavirus disease 2019.[1] Many studies have reported the effects of medicinal plants and their active constituents as important therapies against COVID-19.[2] TMPRSS2 was shown to be an important target for preventing and reducing the severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] Additionally, angiotensin-converting enzyme 2 (ACE2) is a zinc- and chloride-dependent dipeptidyl carboxypeptidase I.[4] ACE2 is involved in heart function regulation and functions as a functional receptor on the cell membrane for coronavirus, which is related to SARS-CoV-2.[5] Both the ACE2 protein and the TMPRSS2 protein facilitate the attachment of the viral spike glycoprotein, thus allowing the virus to enter host cells.[6,7] ACE2 and TMPRSS2 genes are co-expressed on secretory cells in the nasal mucosa and absorptive enterocytes in the small intestine, as determined by single-stranded RNA sequencing analysis of goblet cells and lung type 2 pneumocytes.[8] The first contact point for the virus is the olfactory epithelium and respiratory tract in the nasal mucosa, where SARS-CoV-2 susceptibility and transmissibility are thought to be related to the expression of these genes.[9] The efficacy of many natural compounds against COVID-19 has been investigated. Most studies have used computational molecular docking techniques only.[10]

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