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Identification of Effective Plant Metabolites in Inhibition of HTLV-1 Virus Protease Using Network Analysis Approach

Zahra Khosravi-Amin[1], Eisa Kohan-Baghkheirati*[1,2], Mitra Kheirabadi[1,2]

[1]Department of Biology, Faculty of Science, Hakim Sabzevari University, Iran

[2]Research Core of Systems Phytopharmacology, Hakim Sabzevari University University, Iran

***Corresponding author: e.kohan@hsu.ac.ir**

Introduction

Retroviruses are RNA viruses that contain two copies of the genome. They were named in 1970 with the discovery of reverse transcriptase (RNA-dependent DNA polymerase). This group of viruses infects a wide range of vertebrates and causes various types of diseases, including cancer, AIDS, autoimmune diseases, diseases of the nervous system, bones, and joints (Weiss, 1996). The most powerful cancer-causing oncovirus belonging to the *Deltaretrovirus* genus and the *Orthoretrovirinae* subfamily is the Human T-lymphotropic virus type 1 (HTLV-1) (Hoshino, 2012; Taabi et al., 2008). HTLV-1 infects patients through transmission with contaminated blood products, sexual transmission, and transmission from mother to child through breastfeeding for more than 6 months (Hino, 2011; Roucoux et al., 2005). This virus causes adult T-cell leukemia (ATL), HTLV-related myelopathy/tropical spastic paraposis, and uveitis (Lairmore et al., 2011). The success of HIV protease inhibition in treating patients infected with this virus has led to the consideration of HTLV-1 virus protease inhibition as an important target for treatment (Soltani et al., 2019). Unfortunately, there is currently no definitive treatment or vaccine available for HTLV-1 infection (Martin et al., 2016). Plants have been used for more than 5000 years in the synthesis of a wide range of secondary metabolites, such as alkaloids, polyphenols, terpenoids, etc., which serve as raw materials for treating various human diseases. In this research, key metabolites involved in the inhibition of HTLV-1 protease have been identified and introduced by network analysis approach.

Material and Methods

Literature review was done to list effective plants in inhibiting HTLV-1 and HIV protease by Google Scholar and PubMed databases. The keywords used for the search were "Plant secondary metabolites", "plant extract", "HTLV-1 protease", and "HIV protease". To establish the relationship between the plants and their metabolites, the KNApSAcK Family database (http://www.knapsackfamily.com) was utilized. This database provided information on the name of the metabolites associated with each plant, their chemical formula, chemical structure, and spatial shape. If the scientific name of the plant was not available in the database, synonyms were searched from the plant list (www.theplantlist.org) database. To identify key metabolites in inhibition of htlv1 protease, data was further analyzed as a bipartite network by Cytoscape v.3.9.1 and the Cytohubba plugin. The nodes in the network were ranked based on eight parameters defined in the plugin and top 100 nodes in each parameter were listed. Metabolites that appeared in more than five repetitions across these eight parameters were selected as the top metabolites. The high ranked metabolites are subject to further studies.

Result and Discussion

The results obtained from the PubMed and Google Scholar databases revealed a total of 1,211 medicinal plants for the treatment of HTLV-1 virus. Among these, 990 plant species were found to possess medicinal metabolites suitable for treatment. The metabolites of these 990 plant species were extracted from the KNApSAcK_Family database, resulting in the identification of 20,046 metabolites. Out of these, 11,763 metabolites were found in only one plant species, while 8,282 metabolites were present in multiple plant species. Based on the findings, the *Leguminosa* family emerged as the most promising family with 38 percentage, whereas the *Myrtaceae* and *Zingibraceae* families exhibited the least impact with only 2 percentage in the conducted HTLV-1 and HIV studies. Classification based on plant types indicated that both trees and grass plants had an equal share of research. Furthermore, the analysis revealed that leaves were the most extensively studied plant part, accounting for 31 % of the research focus, followed by roots with 16 %. A plant-metabolite bipartite network was constructed using Cytoscape 3.7.1 software which consisted of 12,386 nodes and 19061 edges. To identify the top metabolites within the network, all nodes were evaluated by 8 Cytohubba parameters and the top 100 nodes for each parameter were listed. Subsequently, nodes were classified based on their presence in the eight parameters. The nodes with a rank of 5 or more (i.e. presence in the top 100 list of $\geq$5 parameters), were chosen and resulted in the selection of 77 metabolites with potential anti-HTLV-1 and anti-HIV properties. Among these, Syringic acid and Luteolin raised out respectively with eight and seven repetitions, indicating their potential as a target for the design of antiviral drugs for HTLV-1.

Conclusions

The results of the present study indicate that plant secondary metabolites can be important and valuable compounds for the treatment of viral diseases, including HTLV-1 and HIV viruses. Based on network analysis parameters, 77 metabolites in plant species may have potential effects on HTLV-1 and HIV protease as the top metabolites with more than 5 repetitions. The largest number of metabolites belong to flavonoids that suggest them as suitable candidates for future drug design studies and experimental investigation on inhibition of viral protease, especially HTLV-1 and HIV proteases.

Keywords: HTLV-1 protease, Medicinal plant, Drug design, Bipartite network.

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Declaration of conflict of interest

No potential conflict of interest was reported by the authors.

Statement on ethics

We confirm that this work is original and all experiments have been conducted at Hakim Sabzevari University in Iran. No part of the data has been published before nor is being considered for publication elsewhere.