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Research Article

An *in-silico* assessment suggests the potential effects of goji (fruit of *Lycium barbarum* L.) against aging-related diseases

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Abstract: Consuming herbal products as food and medicine have been accepted by people of different cultural backgrounds for sustaining healthy aging. The mechanism of anti-aging is mystery since the complex chemical composition of herbals as well as the systems reactions in organisms. Here, the anti-aging ingredients of goji are studied using a network pharmacology methodology. Metabolites of goji were collected based on the open databases, resulting in a database of potential targets. The aging-related targets were identified, which were further applied for Gene Ontology (GO) enrichment analysis. Afterwards, network analyses were performed to reveal the linkages between the aging-related genes and the related ingredients. The results show that 58 ingredients of goji are linked to 90 aging-related genes, and the genes and ingredients of greater importance are revealed by networks. This study provides a preliminary overview on the anti-aging ingredients of goji, which hints the potential effects of goji against aging-related diseases.

Keywords: goji; network pharmacology; aging; food-medicinal use

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1 Introduction

The globally aging population results in challenges to public health. Aging results in a wide variety of chronic diseases, such as hearing loss, chronic obstructive pulmonary disease, diabetes, depression and dementia and the overarching need for geriatric care[1,2]. These syndromes cannot be cured using specific drugs, instead, food-medicinal plants and their derived products are often consumed for nursing and sustaining the elderly's health in different cultural backgrounds[1,3].

Goji (fruit of *Lycium barbarum* L., known as gǒu qǐ in Chinese) has been used as food and medicine since millennia, and is well-known for its nourishing functions especially for anti-aging[4,5]. In recent years, advertised as "super food", goji is among the most popular anti-aging botanicals in the global market, also based on a sound body of phytochemical and pharmacological studies[4]. The complex metabolite profile of (medicinal) plants results challenges to pharmacological studies, not to mention formulas derived from such primary extracts. The application of network analysis has provided a tool for a systematic preliminary assessment[6-8]. *In-silico* assessment provides important clues for drug discovery studies. Recently, the potential functions of goji in the management of diabetes, retinitis pigmentosa, some cancers, hypertension and Alzheimer's disease (AD) were postulated *in-silico*[9-12]; in the meanwhile, some of the bioactivities/functions have been proved by *in vivo* studies and clinic trials[13,14]. Therefore, a comprehensive understanding on the potential effects of goji on aging-related diseases as well as the corresponding ingredients are of great importance for its further development.

Using the methodology of network pharmacology, this study aims to sort out the ingredient-target-disease linkages for goji's potential effects on aging-related diseases, thus, to provide clues for elucidating the anti-aging functions of goji, as well as to inspire the anti-aging targeted products development.

2 Methods

2.1 Database of chemical ingredients

To construct a database of chemical ingredients of goji, "*Lycium*" was used as the keyword to search in databases including Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)[15], Integrative Pharmacology-based Research Platform of Traditional Chinese Medicine (TCMIP, http://www.tcmip.cn/TCMIP/), Traditional Chinese Medicine on Immuno-Oncology (TCMIO)[16] and HIT 2.0[17]. The cross-database results were then checked manually as follows: ingredients sourced from *Lycium chinense* Mill. were removed firstly to generate ingredient lists, which were then linked using the function "VLOOKUP" in Microsoft Excel 2019; after that, a union list was generated by removing the repeated ingredients. The canonical SMILES (Simplified molecular-input line-entry system) codes of the ingredients were then obtained from the database TCMIO[16]. Supplementary searches were performed in

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PubChem (https://pubchem.ncbi.nlm.nih.gov/) if the SMILES code was not available in TCMIO. Thus, the database of chemical ingredients was constructed (Supplementary material).

2.2 ADME assessment and target prediction of ingredients

To evaluate the properties of pharmacokinetics and pharmacology of the ingredients, ADME (absorption, distribution, metabolism and excretion) assessment was performed using SwissADME[18]. The canonical SMILES codes of the ingredients were pasted to the webserver, and the parameters of "Pharmacokinetics" and "Druglikeness" were recorded manually. Those ingredients with "high" gastrointestinal (GI) absorption was accepted. Regarding to the druglikeness analysis, those ingredients with at two "Yes" for the five indices (namely Lipinski, Ghose, Veber, Egan and Muegge) were accepted. Ingredients fulfilled both two conditions were accepted for further analysis.

SwissTargetPredication[19] was employed to perform target prediction of the above accepted ingredients. Canonical SMILES codes of the ingredients were pasted to the webserver, selecting the species "*Homo sapiens*", and the targets were then computed. The results were exported and integrated into one table for further analysis.

2.3 Intersection of predicted targets and aging-related genes

The aging-related human genes were retrieved from the database GenAge[20]. After that, the predicted targets and aging-related genes were linked using the function "VLOOKUP" in Microsoft Excel 2019 based on the key field "Common name" in SwissTargetPredication and "HGNC (Human Genome Organization Gene Nomenclature Committee) Symbol" in GenAge. The intersection of genes from the two lists was compiled for further analysis.

2.4 Gene Ontology (GO) enrichment

The genes obtained above were then uploaded to Metascape[21] and STRING[22] (search tool for the retrieval of interacting genes/proteins) for GO enrichment analysis. Four enrichments, including GO molecular functions, GO biological processes, GO cellular components and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway, were analyzed and visualized separately in Metascape. Meanwhile, the disease enrichment of the intersection genes was performed in STRING and was then visualized with TBtools[23].

2.5 Network analysis

Networks were constructed to present the linkages between ingredients and target genes, as well as the protein-protein interaction (PPI) among targets. The ingredient-target network was constructed using Cytoscape[24] with the data generated in section 2.2 and 2.3. The PPI analysis was performed in STRING[22] and the network was visualized using Cytoscape[24]. The importance of the ingredients and the target genes was evaluated by their degrees in the networks.

3 Results

3.1 Ingredients of goji linking to aging-related human genes

Following the flow chart Fig. 1, 58 ingredients of goji were found to link with aging-related human genes. The cross-database retrieval shows that there are 270 ingredients of goji indexed in the databases. The follow-up ADME assessment indicates that 84 of these are active in pharmacokinetics and druglikeness, while 102 of these are with low GI absorption but active in druglikeness. The follow-up target predication shows that these 84 active ingredients link to 836 human genes. These 836 genes are then compared with the 307 aging-related human genes extracted from GenAge, and their intersection includes 90 genes. The 90 genes relate to 58 ingredients of goji. The ingredients and the number of their linked aging genes are shown in Supplementary material.

3.2 GO enrichment of the aging-related genes linking to ingredients of goji

The results of the four enrichment analyses, namely GO molecular functions, GO biological processes, GO cellular components and KEGG pathway, are obtained from Metascape. The following parameters are applied: min overlap is three, *P* value cutoff is 0.01 and minimum enrichment is 1.5. There are 115 GO terms of molecular functions identified under these conditions. As is shown in Fig. 2A, the related genes play important in kinase binding, among others. For example, the top two best *P*-value terms, GO:0004712 and GO:0004672, which stand for "protein serine/threonine/tyrosine kinase activity" and "protein kinase activity" separately, include 31 and 30 of the 90 aging-related human genes. With regards to the enrichment on GO biological processes, the top three best *P*-value terms are GO:0009725, GO:1901699 and GO:0071417 (Fig. 2B), indicating the importance of these genes on cell response to hormone,

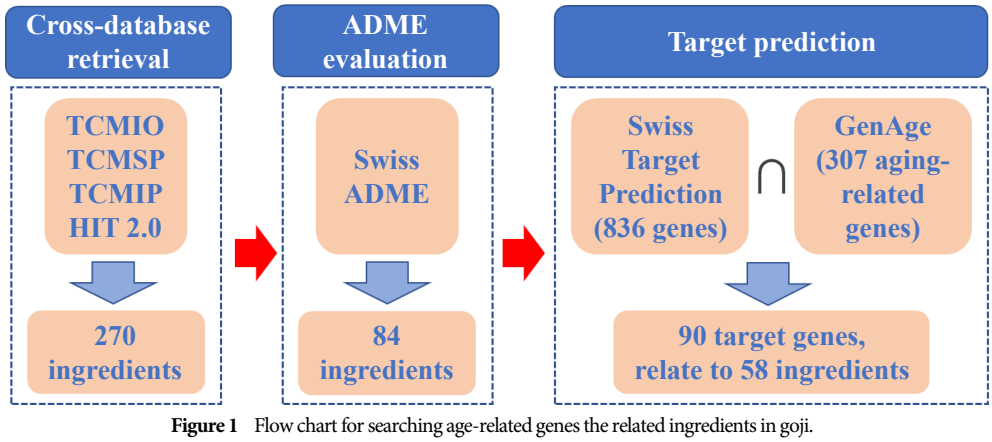

Figure 1 Flow chart for searching age-related genes the related ingredients in goji.

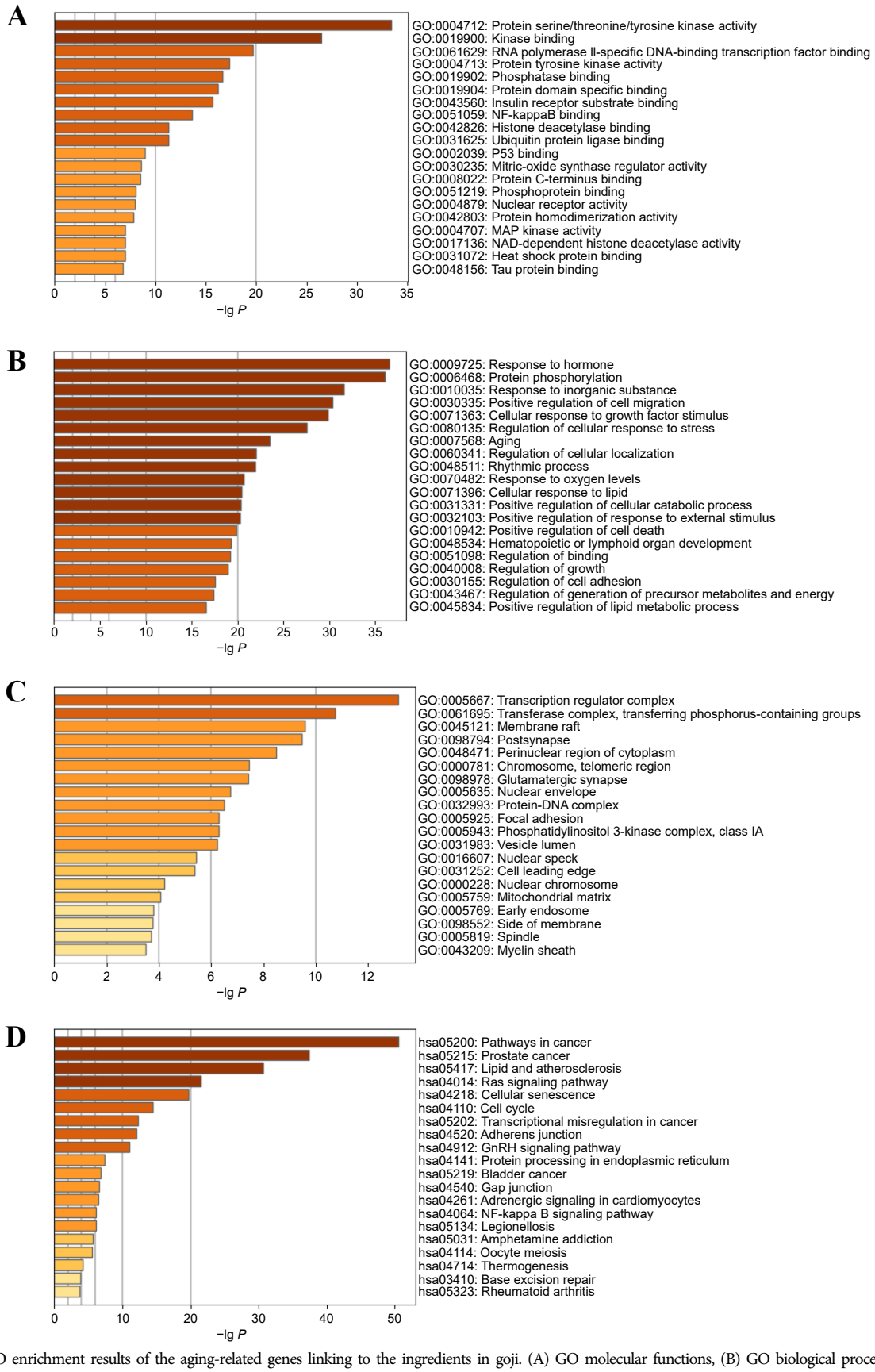

Figure 2 GO enrichment results of the aging-related genes linking to the ingredients in goji. (A) GO molecular functions, (B) GO biological processes, (C) GO cellular components, (D) KEGG pathway.

nitrogen compound and organonitrogen compound. Compared to molecular functions and biological processes, the related genes play a less important role in cellular components. As is shown in Fig. 2C, the top related term GO:0005667, of which the biological

meaning is "transcription regulator complex", has a *P*-value of ca. 13, which is much lower that of the former categories. The enrichment of KEGG pathway (Fig. 2D) shows that the related genes are important in cancer, as is indicated by the high *P*-values of the terms hsa05200 (pathways in cancer), hsa05215 (prostate cancer), hsa05205 (proteoglycans in cancer) and hsa05206 (microRNAs in cancer).

The enrichment of related genes on diseases was also analyzed. As is shown in Fig. 3, there are 22 disease terms with enrichment of no less than 10 of the related genes, which implies the potential functions in diverse diseases of goji and its ingredients.

3.3 Network analysis

The application of networks allows for the analysis of relationship between ingredients and target genes, in the meanwhile, the PPI provide a solution to find the important proteins. Figure 4 shows the PPI network of the 90 aging-related genes. The importance of the proteins can be evaluated by their degree values in the network. Accordingly, 14 genes are found to be with degrees of over 100, including *AKT1*, *HSP90AA1*, *JUN*, *EGFR*, *ESR1*, *MAPK3*, *STAT3*, *VEGFA*, *IL6*, *HIF1A*, *MTOR*, *MDM2*, *EP300* and *ERBB2*, and the higher degrees suggest their more important roles in the interactions among them. Using the

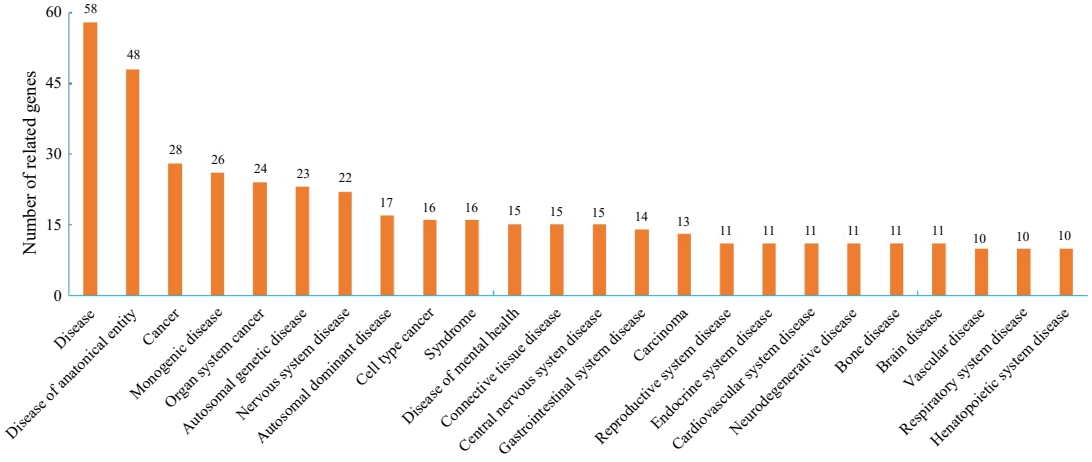

Figure 3 Enrichment on disease terms of the aging-related genes linking to the ingredients in goji.

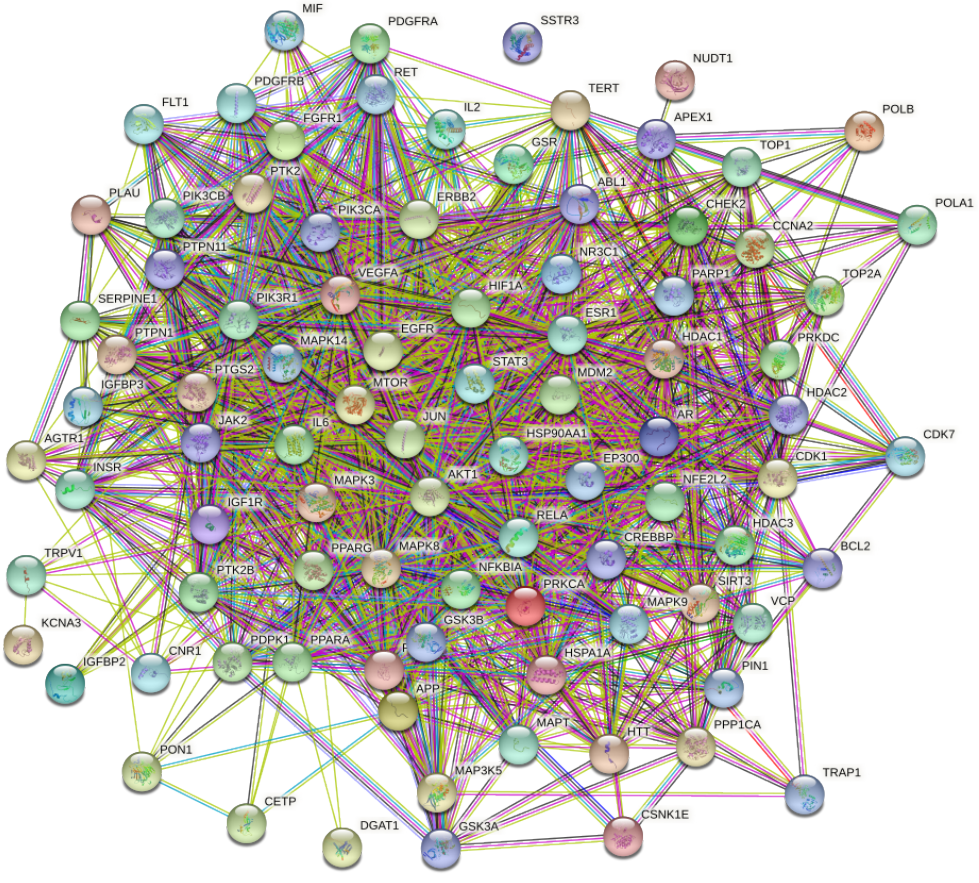

Figure 4 PPI network of aging-related genes linking to the ingredients in goji.

same methodology, the network of ingredients and genes was calculated. Amongst the ingredients, withanolide A ranks the first with a degree values of 21, meaning it relates to 21 genes. Twenty-two of the 58 ingredients have degree values of no less than 10. Moreover, the number of related ingredients of each gene was also calculated. The result shows that linkage between 14 genes link to over 10 ingredients.

4 Discussion

The composition and biological process in organisms are complex, therefore, the event of one chemical ingredient affects in one organism will practically lead to reactions of systems. Herbal medicines have even more intricate situation since their compositions often comprise of hundreds of chemical ingredients. Biomolecular network-based analysis may provide a holistic methodology for pharmacological studies on herbal medicines especially for those aiming at drug discovery[6,7].

Goji is a traditional food and medicine in Eastern Asia especially in China, and is also an emerging healthy food in the worldwide due to its evidence-based bioactivities which may link to its traditional functions[4,5]. The cross-database retrieval and the target prediction shows that 58 out of the 270 ingredients of goji link with 90 aging-related human genes. The follow-up network analysis reveals the interactions among the "nodes", by which the hot nodes can be found. The PPI network and the ingredient–gene network provide useful clues for finding out those genes and ingredients of greater importance, which is helpful for further discoveries.

However, the current network pharmacology has its limitations. Firstly, the database does not keep up with the most recent research frontier. For example, researchers have isolated dozens of new ingredients belonging to the spermidines from goji, and their bioactivities against AD have also been proved in 2016[14], but these compounds have not been inventoried in any of the databases. Secondly, polymers (mainly polysaccharides) are not available to be analyzed. For example, polysaccharides are thought to be the active compounds with a variety of benefits especially for immunoregulation[25], but such macromolecules are not included. Thirdly, some active compounds are omitted during the ADME assessment. For example, zeaxanthin in goji has been demonstrated to benefit eyesight and is among the most useful ingredients in goji[13,26], but its GI absorption is low, which is a key factor of pharmacokinetics. According to our analysis, there are 102 ingredients with good druglikeness properties but perform poorly in pharmacokinetics. Fourthly, the results of network pharmacology can only hint the potential activities which requiring as a next step a targeted pharmacological assessment (e.g. *in vitro*) or clinical assessment. Therefore, the current network pharmacology can provide useful clues for drug discovery, but supplementary measures should be arranged.

5 Conclusion

Using the methodology of network pharmacology, this study has found that 58 out of the 270 ingredients of goji are linked with 90 aging-related human genes, indicating the material fundamentals of goji's functions in anti-aging. The network analysis helps find out the ingredients and genes of greater importance. As a result, this study provides a preliminary overview on the anti-aging ingredients of goji, which provides clues for further research. Considering the limitations of the methodology, such as the outdated ingredient databases and the ignorance of active ingredients by poor pharmacokinetics, we suggest referring to the new literature for collecting ingredients, and to accept ingredients of poor pharmacokinetics but with good druglikeness properties. Nevertheless, many herbal medicines are consumed for long-term as food, so that the benefit functions can be accumulated even with poor pharmacokinetics. Food-medicinal plant resources and their related traditional knowledge consist of a treasure house for healthcare, the application of multi-disciplinary methodology allows to demystify the traditional wisdom and make such knowledge benefits human health widely.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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Electronic Supplementary Material (ESM)

The online version contains supplementary material available at https://www.researchgate.net/publication/358635639_Supplementary-data_for_GOJI-network_pharmacology

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