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Systematic Analysis of the Molecular Mechanisms Mediated by Coffee in Parkinson's disease Based on Network Pharmacology Approach

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Abstract

Many epidemiological studies have associated coffee consumption with a reduced Parkinson's disease (PD) risk, but the molecular mechanisms remain unclear. In this study, systematic pharmacological and bioinformatics approaches were employed to explore the bioactive components and potential mechanisms mediated by coffee in PD. We identified 12 active compounds in coffee associated with 47 PD-related targets, which might exert synergism because some targets were enriched in multiple signaling pathways and biological processes. The compound–target network and protein–protein interaction network exemplified the multi-component and multi-target effect mediated by coffee in PD. Furthermore, a molecular docking assessment verified the great activity between active compounds identified in coffee and PD-related targets. These results showed that the bioactive components of coffee exerted synergistic effects against PD-associated targets through numerous pathways and provided a new perspective for scientific research exploring the multi-component and multi-target mechanisms mediated by coffee in PD.

Keywords: Network pharmacology; Coffee; Parkinson's disease; Molecular docking; Multi-target

Introduction

Parkinson's disease (PD) is recognized as the second-most common neurodegenerative disease of aging after Alzheimer's disease. PD is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain. The resulting lack of dopamine in motor control areas of the brain leads to the characteristic manifestations of tremor, rigidity, bradykinesia, and postural instability. PD can also present with non-motor symptoms, such as dementia, sleep disturbance, anosmia, autonomic dysfunction, and depression. To date, the primary therapy for PD targets the dopaminergic pathway to ameliorate PD symptoms, but the long-term use of these drugs may lead to undesirable side effects, including the commonly reported levodopa-induced involuntary movements [1]. No current intervention can slow or halt the progressive disease course. Therefore, avoiding risk factors and reducing disease risk represent potentially useful strategies for preventing the occurrence and development of PD [2].

Coffee is one of the most commonly consumed beverages worldwide and its consumption has been negatively correlated with the risks of several chronic diseases, such as diabetes, cardiovascular disease, neurodegenerative disorders, and cancer. Coffee consumption has also consistently been associated with a reduced risk of PD. Several important early studies demonstrated that increased coffee consumption significantly decreased PD risk in a dose-dependent manner [3]. Caffeine represents the most commonly investigated component among coffee's constituents and has been associated with neuro protective effects, mediated by the inhibition of lipid peroxidation and the reduction of reactive oxygen species production. Our previous study found that lower absolute levels of caffeine and caffeine metabolite profiles served as promising diagnostic biomarkers for early PD, which was consistent with the neuro protective effects of caffeine that were previously reported by epidemiologic and experimental studies[4].

Materials and Methods

Screening active compounds and pharmacokinetic predictions

The primarily chemical compounds in coffee were mined by searching literature indexed by PubMed and the Web of Science. The compound structures were identified in Pub Chem. Information regarding the absorption, distribution, metabolism, and excretion (ADME) properties of each compound identified with potential biological activity were acquired from SWISSADME and we applied the gastrointestinal (GI) absorption and bioavailability scores as screening parameters to reflect the absorption and similarity with existing drugs [5].

Network construction

A compound–target (C–T) network was constructed for the compounds identified in coffee, which was able to systematically describe multiple interactions between the compounds in coffee and their related targets. Protein–protein interaction (PPI) data were obtained from the STRING database. We selected a confidence score of > 0.4, with the species restricted to "Homo sapiens," to construct the PPI network. All visualized network models were generated using Cytoscape an open software package project for visualizing, integrating, modeling, and analyzing interaction networks. The topological feature of each node in the network was assessed by calculating three parameters

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with Centiscape2.2 in Cytoscape software, including "degree centrality (DC)," "betweeness centrality (BC)," and "closeness centrality (CC)". DC reflects the relative importance of a node in a network, while BC represents the probability that a signal passes through the nodes; higher DC and BC values indicate more important nodes [6]. CC reflects the network tightness; a tighter network has higher efficiency. Clustering sub networks were produced using the Molecular Complex Detection (MCODE) algorithm (Bader & Hogue, 2003) in Cytoscape software, with K-core = 2, to identify the most significant modules in the PPI networks. Hub genes were screened by CytoHubba in Cytoscape software, using the maximal clique centrality (MCC) method. MCC represents a topological analysis method in CytoHubba for identifying featured nodes and hub genes in PPI networks [7].

Molecular docking

We performed molecular docking via AutoDock Vina to explain the mechanism and binding activity between active components and target proteins. The structures of compounds were downloaded in SDF format from the Pub Chem database, and the SDF format was transformed into a mol2 format file using Chem 3D software. Receptor structures were downloaded from the RCSB Web site in PDB format. Py Mol software was used to remove solvent molecules and ligands, and Auto Dock Tools was used to add hydrogen atoms and charges, with default settings selected for all other parameters, and the results were saved in pdbqt format. Finally, Auto Dock Vine was used to perform molecular docking analysis [8]. The theoretical binding affinities were predicted based on the docking scores. The protein–ligand interactions were identified using Discovery Studio Visualizer 2020. We also performed molecular docking between positive drugs (selegiline and rasagiline) and the target protein monoamine oxidase B (MAOB) to demonstrate the rationality of the molecular docking model [9].

Discussion

In this study, in view of the complexity of the active ingredients found in coffee and the diversity of potential regulatory targets identified in humans, for the first time, we employed NP approaches, which integrated chemical, pharmacokinetic, and pharmacological data mined from several databases, to explore the bioactive components and mechanisms underlying the effects of coffee on PD. We identified 12 active compounds in coffee that potentially act on 47 PD-related targets to exert synergism and performed enrichment analysis to identify multiple signaling pathways and biological processes [10]. The C–T network and the PPI network exemplified the characteristics of the multi-component and multi-targeted effects of coffee on PD. These results are consistent with the reported complexity of PD pathogenesis, and allow for a better understanding of the interactions that occur among the target genes [11].

Conclusion

On the basis of the principles of NP, this study systematically explored the synergistic effects and molecular mechanism exerted by coffee against PD. We found that coffee may play a beneficial role against PD through antioxidant, neuro protective and anti-inflammatory activity, mitochondrial protection, apoptosis inhibition, the regulation of multiple neurotransmitters, and the maintenance of BBB integrity [12]. These results are consistent with the reported complexity of PD pathogenesis and involve many biological processes, providing a new perspective for scientific research on the multi-component and multi-target mechanisms through which coffee acts against PD, and providing new clues for experimental researchers to design new experiments and optimize resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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