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Network pharmacology and molecular docking verification to verify the potential mechanism of EGCG in the treatment of essential hypertension

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Abstract: *Epigallocatechin-3-gallate (EGCG) has beneficial effect on treat hypertention. The related mechanism of EGCG against hypertention has yet to be revealed. The purpose of this article is to predict the mechanism of action of EGCG in treatmenting of hypertension. The chief active components, relevant targets, and the target genes of EGCG were retrieved by the databases TCMSP, Swiss Target Prediction and Pharm Mapper database, and the related target of "essential hypertension" was collected in GeneCards, OMIM and TTD database. The common target of EGCG-essential hypertension was obtained through Venny 2.2.0 online website, and the protein-protein interaction network of common target was constructed and visualized using String database to screen out the core target of EGCG in the treatment of essential hypertension. Functional enrichment (GO) analysis was performed by gene ontology and Kyoto Encyclopedia of Genes and Genomes to construct the network map of "EGCG-core target-major pathway-essential hypertension". Finally, the core target was tested for molecular docking with EGCG by Sybyl software. A total of 140 common targets of "EGCG-essential hypertension" were selected, and there were 23 core targets. The pathways involved cancer pathway, MAPK signaling pathway, PI3K-Akt signaling pathway, etc. Molecular docking score indicated that EGCG was well bound to the core target protein. This research clarified the mechanism of EGCG in the treatment of hypertension systematically, providing new potential ideas and a theoretical foundation for further experimental and clinical research.*

Keywords: *Epigallocatechin gallate (EGCG); essential hypertension; network pharmacology; protein-protein interaction network*

1. Introduction

Essential Hypertension(EH) is a clinical syndrome in which blood pressure in the blood vessels continuously rises. According to the World Health Organization, one in every three adults worldwide has EH, which accounts for approximately half of all deaths from cardiac disease and stroke[1], also considered the silent killer[2].EH is expected to be 60% more prevalent worldwide by 2025, affecting 1.56 billion people,according to the world health organization [3]. It remains one of the most important modifiable contributing factors to the burden of coronary artery disease, stroke, and chronic kidney disease[4-6]. EH can be easily diagnosed, and a wide variety of inexpensive therapies are available to effectively control it[7,8]. Now, common antihypertensive drugs include five classes: calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), diuretics, and beta blockers.Although a number of signaling pathways involved in the development of EH have been reported over the past few decades, and various treatments targeting antihypertensive mechanisms have emerged, the blood pressure of half of hypertensive patients is currently not well controlled.

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The compound epigallocatechin-3-gallate (EGCG), the major polyphenolic compound present in green tea, EGCG has been reported to protect renal function in several renal disease models[9],such as acute kidney injury[10], cisplatin-induced nephrotoxicity[11], and obstructive nephropathy[12]. and has also shown numerous Cardiovascular health promoting activity[13]. EGCG has beneficial effects on a broad spectrum of hypertension disorders, including renovascular hypertension[14] and spontaneous hypertension[15].However, the effects of EGCG on hypertension remain unclear.

Recently, network pharmacology has been used to explore the therapeutic effects and therapeutic targets of Chinese medicinal herbs and bioactive compounds. Up to now, the research on TCM for a target gene, and has lacked a whole view and syndrome has been limited to explaining its mechanisms and pathways differentiation view of TCM[16].The “network target, multi- components” concept of network pharmacology is the most suitable tool to explore the therapeutic effects of herbal medicine at the molecular level[17].In this study, we observed that EGCG treatment could decrease SBP in paharmacological mechanism and molecular docking verification based on network pharmacology,and attempts to enhance our understanding about its therapeutic potential in treating hypertention.

2. Materials and methods

2.1. Software and database

This study uses Cytoscape 3.9.0 software, Sybyl-X 2.1.1 software (Tripos Corporation), and Discovery Studio 4.5 software. Database including TCMSP database(https://old.tcmsp-e.com/ tcmsp.php), PubChem database

(https://pubchem.ncbi.nlm.nih.gov/),SwissTargetPrediction(http://www.swisstargetprediction.ch/), PharmMapper (http://www.lilab-ecust.cn/pharmmapper/), GeneCards database (HTTPS: / / www.genecards.org/), OMIM database (https://omim.org/) and providing database (https://db.idrblab.net/ttd/), UniProt database (http://www.uniprot.org/) , Venny 2.2.0 (https://bioinfogp.cnb.csic.es/tools/venny/), the STRING database (https://cn.string-db.org/), DAVID database (https://david.ncifcrf.go V/home. JSP), PDB database (https://www.rcsb.org/), micro letter online website (http://www.bioinformatics.com.cn/login/). The soft operating environment is Windows 10x64.

2.2. Selecting active components and targets of EGCG

All of effective chemical components containing in EGCG were obtained from Traditional Chinese Medicine Systems Pharmacology(TCMSP[18]), for the previous research, the selected candidate ingredients must meet the requirements of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18.Chemical components of the 2 d structure were obtained from PubChem database,then uploaded to the Swiss Target Prediction and PharmMapper database, the research species was defined as “Homo sapiens”, take the Target with probability>0 and PharmMapper score ≥4.0 in Swiss Target Prediction. All the targets were de-duplicated and verified by UniProt database as potential active targets for EGCG, that is, human species, and take the Target with probability>0 and PharmMapper score ≥4.0 in Swiss Target Prediction. All the targets were de-duplicated and verified by UniProt database as potential active targets for EGCG.

2.3. Selecting targets of hypertention

Targets for essential hypertension were collected from GeneCards database, OMIM database and providing database using the key words "Essential hypertension". The target of essential hypertension can be obtained after weight removal. On the Venny2.2.0 online software mapping, we inputted the targets of chemical components and hypertention, respectively. A Venny diagram was subsequently drawn to obtain the common targets of components and hypertention.

2.4. Protein-protein interaction (PPI) network

In order to visually describe the interactions among different target proteins, we obtained the common targets of EGCG and essential hypertensionused through STRING database, and the species restriction was set to "Homo Sapines", and the confidence score was set as high confidence "0.9" . Besides, Cytocsape 3.9.0 Software was exploited to screen central proteins and rand them according to

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the degree of association between proteins (Degree >2 median, Betweenness Centrality and Closeness Centrality > mean).

2.5. Medicine-compound- target-disease

According to the compounds and targets screened, we then constructed the "medicine-compound-target-disease" network using Cytoscape 3.9.0 software. Nodes represented the core target, major pathway of EGCG, and disease, while edges represented the relationships among them.

2.6. Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

DAVID database was used to conduct Gene Ontology (GO) functions and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses for the porential therapeutic targets of EGCG against Hypertention[15], genomes (GO) functions and genomes (Kegg) genomes Biological process (BP), Molecular function (MF), Cellular component (CC) and KEGG pathway were ranked according to P<0.05 and FDR<0.05. Finally, by microscopic letter online website, draw a bar chart and the bubble chart, to visualize the results.

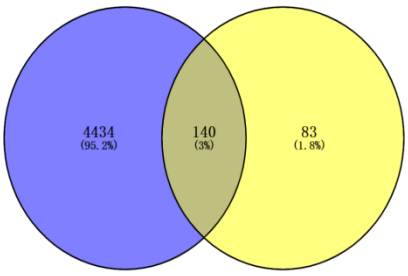
2.7. Molecular docking

The 2D molecular structure of EGCG was extracted from PubChem database, and the protein molecular structure of the top 3 core targets ranked by degree value was extracted from PDB database. Sybyl-X 2.1.1 was used for molecular interconnection, and the interconnection score was used as the index to evaluate the ability of intermolecular binding. Discovery Studio 4.5 software was used to visualize the combined patterns.

3. Results

3.1. Screening results of EGCG compounds and Essential hypertension targets

The targets of EGCG were 136 (TCMSP), 51 (PharmMapper) and 44 (Swiss Target Prediction) by compound target prediction database. After correction and screening by UniProt database. A total of 223 candidate targets for EGCG were obtained. There were 4566 targets related to essential hypertension (GeneCards), 31 targets (OMIM), 13 targets (TTD) collected in the disease target database, and 4574 targets related to essential hypertension were obtainedl. A Venn diagram was drawn by inputting223 drug targets and 4574 EGCG targets into the online software Venny2.1. 140 common potential targets were obtained to the ingredients and EGCG.(Figure1).



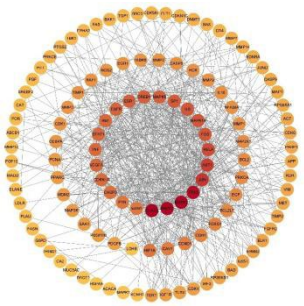


Figure 1: Venn diagram of 140 latent common targets for "EGCG-Essential Hypertension". The blue areas represent the potential targets for EH, the yellow areas represent the potential targets.
Figure 2: PPI network of 140 overlapping genes. Nodesrepresent the protein targets. The darker the color, more the numbers of edges, stronger the interaction between nodes, and greater the significance in the PPI network.

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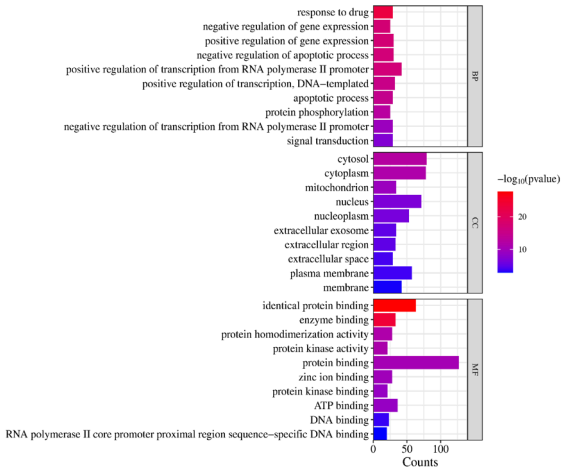
3.2. PPI network and core target screening results

To elucidate the mechanism accounting for the interation of these overlaping genes, the 140 common targets were analyzed in the STRING database, and then a As PPI network was constructed with 140 nodes, 646 edges and an average node degree of 9.23(Figure2). Each edges represent interactions between targets, nodes represent targets. The degree value is positively correlated with the color of targets. The redder the node color, the more closely the node plays a role in the network. Among PPI common targets of "EGCG-essential hypertension", 23 core targets with close relationship were screened out through analysis, namely the core targets of EGCG in treating essential hypertension (Table1),these genes were STAT3, MAPK1,MAPK3, TP53,JUN,AKT1,RELA, MAPK14, FOS,IL6,SP1,MAPK8,CREB1,ESR1,EGFR,RB1,STAT1,TNF,VEGFA,CDKN1A,CASP3,EDN1 and FYN.

3.3. GO and KEGG enrichment analysis of common targets of "EGCG-Essential hypertension"

In ordor to clarify the effect and underlying mechanism of these EGCG active components on hypertention, we selected three parts of biological process(BP,383),cellular composition(CC,48),and molecular function(MF,73) from 140 common targete in GO functional enrichment analysis (P<0.05 and FDR<0.05). The top 10 GO terms were comfirmed and visualized respectively: biological processes including positive transcription regulation of RNA polymerase II promoter, transcriptional regulation, positive regulation of gene expression, and negative regulation of apoptosis process (Figure3). The molecular processes including protein binding, enzyme binding, ATP binding, protein homodimer activation (Figure3). In addition,the cell components mainly involve nucleus, nuclear plasma, plasma membrane, cytoplasm and cellular fluid(Figure3).To further illustrate how EGCG affects hypertention by these latent targets,a total of 150 pathways were enriched by KEGG pathway enrichment analysis,in which the top 20 pathways(P<0.05 and FDR<0.05) mainly including cancer pathway, viral infection, MAPK signaling pathway, PI3K-Akt signaling pathway, lipid and atherosclerosis, Ras signaling pathway and other biological signaling pathways(Figure4). The above signaling pathways may be closely related to the effect of EGCG in treating essential hypertension.analysis of top 10 closely related biological functions.Bubble chart of the pathway fron GO-BP,GO-CC, GO-MF enrich



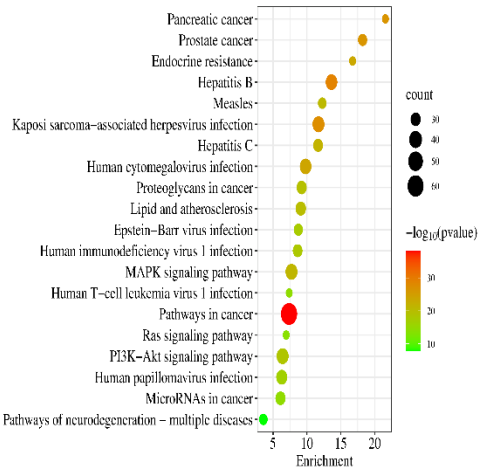


Figure 3: Gene Ontology enrichment analysis of top 10 closely related biological functions.Bubble chart of the pathway fron GO-BP, GO-CC, GO-MF enrichment analysis. (left)

Figure 4: The top 20 signaling pathways from KEGG.(right)

3.4. "EGCG- Core target-Main pathway-Essential Hypertension" network

The visual network diagram of "EGCG- Core Target - Major Pathway - Essential Hypertension" using Cytoscape3.9.0 software (Figure 5), it shows 23 core targets (orange circle) and three major pathways of action (yellow inverted triangle) associated with EGCG (blue hexagon) and essential hypertension (green triangle). The results fully demonstrated that EGCG played a role in the treatment of essential hypertension by acting on multiple targets and then cross-acting on multiple pathways.

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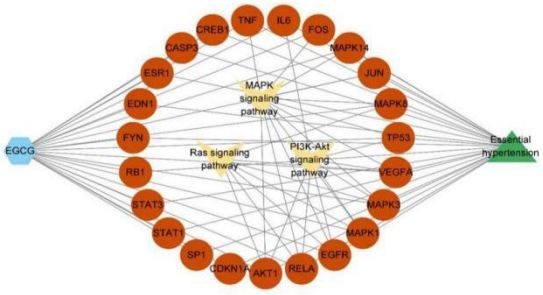

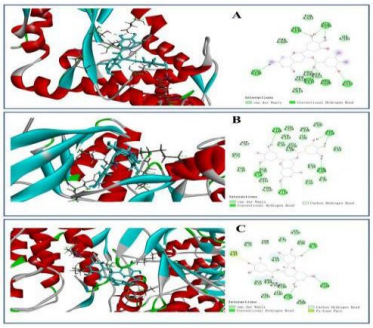

Figure 5: "EGCG-core target-major pathway-essential hypertension" network. (left)

Figure 6: The docking results of core target molecules (A.EGCG-STAT3, B.EGCG-MAPK1, C.EGCG-MAPK3)(right)

3.5. Verification results of molecular dockig

Subsequently, we selected the first three targets (STAT3,MAPK1,and MAPK3) with high scoress from 140 latent targets for molecular docking(Table2 and Figure 6, the score is all greater than 4.5), among these, MAPK3 is the best, suggesting that EGCG has a good binding ability with the core target, and the combination with MAPK3 is the strongest. The molecular docking pattern of EGCG and the core target protein (Figure6). The docking scores of EGCG with MAPK3 was 5.25 (Figure 6(A)). Meanwhile, MAPK1 and STAT3 were also interacted with EGCG were 4.99 and 6.27,respectively (Figure 6(B–C)).The small molecule ligand (EGCG) is shown with the blue Stick, and the ligand's connection mode to the amino acid in the target protein is marked with the green dashed line. The results showed that the binding bonds between EGCG and target proteins were mainly conventional hydrogen bonds, C-H bonds and van der Waals forces.

4. Discussion

Hypertension is one of the leading causes of mortality and morbidity worldwide, affected by environmental and genetic factors. Approximately 15% of the world population has hypertension, and most of these patients either do not receive any treatment or do not achieve BP target even if they are receiving treatment [19]. Although a number of signaling pathways involved in the development of hypertension have been reported over the past few decades, and various treatments targeting antihypertensive mechanisms have emerged, the blood pressure of half of hypertensive patients is currently not well controlled. Human research on the molecular mechanism of hypertension is still continuing and has been developed to the level of epigenomics. In recent years, increasing evidence has shown that DNA methylation plays an important role in gene regulation, is one of the causes of hypertension in epigenetic disorders[20] .

Green tea is a widely consumed beverage worldwide. Polyphenols, also known as catechins, are the major compounds found in green tea; of these polyphenols, epigallocatechin-3-O-gallate (EGCG) is the most abundant accounting for 50%–80% of total phenols found on green tea ([21], [22]). EGCG has been a research focus in recent years due to its high antioxidant activity and anti-inflammatory properties ([23],[24], [25]). Studies have shown that EGCG was effective in protecting cultured retinal ganglion cells (RGC) against H2O2-induced oxidative-stress injury by attenuating intracellular ROS generation ([26]). In addition, EGCG has been shown to have some protective properties in the cardiovascular system ([27], [28]). However, the effects of EGCG on delaying the progression of hypertension have not yet been elucidated.Considering the potential genetic interactions, we aimed to investigate the anti-hypertention effects of EGCG through network pharmacological analyses.In this study, there were 223 targets of EGCG screened by TCMSP,PharmMapper and swiss Target Prediction. Additionally, we screened 4574 potential targets of Essention hypertention by GeneCards,OMIM and TTD. Following the intersection of these targets, 140 latent targets were discovered to be associated with both active ingredients of EGCG and Hypertention. Then, we established a D-C-D-T network and PPI network. Among them, 23 targets, such as STAT3, MAPK1, MAPK3, etc, had higher degree values and were identified as potential core targets for EGCG in the treatment of Hypertention. Based on the enrichment analysis, we found that EGCG could play a potential role in the treatment of Hypertention by intervening multiple signaling pathways.

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The pathophysiology of EH is a highly complex mechanism. Some scholars reported that multiple signaling-associated pathways, including the JAK2/STAT3 pathway, play a significant function in the pathophysiology of EH [29,30]. Bioavailability of quercetin has been found to be involved in anti-hypertension, specially EH. Moreover, The stimulation of JAK2/STAT3 pathway via Ang II has been shown in experimental studies, both in vitro and in vivo, and therefore play a vital role in the development of Ang II-dependent hypertension[31] .

5. Conclusions

The innovation of this paper is our first discovery of active compounds, latent targets, and molecular mechanisms of EGCG in EH, which provides us with a better understanding on the therapeutic role of EGCG on EH. In conclusion, the chemical components in EGCG, the core targets including STAT3, MAPK1, and MAPK3, as well as the signaling pathways such asJAK2/STAT3 pathway, etc, are the potential mechanisms accounting for the effects of EGCG in the treatment of EH. Despite these considerable findings, there are still some limitations in this study that should be addressed. Firstly, we may ignore the roles of some compounds and target genes in hypertention due to the continuous updates of the public databases. Secondly, additional animal experiments and clinical experiments are required to further support and verify the specific mechanism of EGCG in the treatment of EH.

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