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Original Article

Uncovering potential pharmacological actions of puerarin against cystitis glandularis via bioinformatics assay

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Abstract: Objectives: Puerarin, rich in Pueraria radix, is a functional isoflavone compound that exerts the antioxidant and anti-inflammatory effects for potential application. Cystitis glandularis (CG), a cell proliferative disorder, refers to the pathological changes from mucosa and submucosa of bladder epithelium. Current available chemo-treatment is few in clinical prescription. Methods: This report aimed to evaluate that puerarin exhibits anti-CG benefit based on its promising pharmacological activity. Methodologically, network pharmacology analysis of puerarin against CG was determined, and molecular docking approach was used to reveal and characterize potential anti-CG targets of puerarin. Results: Bioinformatics analysis data indicated that 332 puerarin's and 852 CG's genes were screened entirely, and 83 overlapped genes between puerarin and CG were identified. Additionally, the core targets of puerarin against CG were identified, and an interrelationship network of puerarin acting on CG was characterized. Biological function enrichment data indicated that puerarin mediated transcription factor binding effect, functional enzyme activity, and regulation of key gene expression for exerting anti-inflammatory, anti-oxidative stress actions. Enrichment pathway data disclosed that puerarin-mediated anti-CG activity might be mainly involved in direct regulation of inflammation- and oxidative stress-related molecular pathways. In molecular docking analysis, puerarin directly bound to protein kinase B (AKT1), estrogen receptor 1 (ESR1), epidermal growth factor receptor (EGFR) target proteins. Conclusions: Overall, those in-silico data imply that puerarin is a naturally-derived compound that may be used for adjuvant therapy with CG.

Keywords: Puerarin, cystitis glandularis, bioinformatics analysis, potential target, mechanism

Introduction

Cystitis glandularis (CG) is a pathological lesion induced by reactive metaplasia of bladder's urothelium from chronic and recurrent irritation, accompanied with hematuria sometime [1]. The epidemiological data show that morbidity of CG among bladder disorders accounts for about 2%. And increased diagnostic rate for CG is marked as medical endoscopy is applied widely [2]. However, existent controversy is still in CG. It is believed that CG may be a precancerous lesion that should be managed promptly [3]. It is reported suggest that specific cyclooxygenase-2 inhibitor agent can be prescribed for preventing the recurrence of CG after postoperation [4]. In clinical practice, the effectiveness of pharmacotherapy on CG is uncertain and the risk of side effect is found [5]. Thus, it is currently still insufficient drug therapy for CG applied clinically. To address this challenge, potential anti-CG candidate ingredients, especially from natural products, is targeted for exploring timely. It is evidenced that immunopotentiation and anti-inflammatory actions of traditional Chinese medicine (TCM) are demonstrated based on basic and clinical findings [6]. Mounting studies have indicated that TCM may suppress the inflammatory stress against inflammatory diseases via mediating metabolic reprogramming and macrophage polarization [7]. *Radix Puerariae*, an ancient Chinese herb,

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has been traditionally applied for the preventing and treating of various diseases in China [8]. Puerarin, a promising flavonoid isolated from *Radix Puerariae*, exhibits a wide spectrum of biological activities, including anti-oxidant, anti-inflammatory properties [9]. Experimental data report that puerarin may exert potential anti-inflammatory effects *in vitro* and *in vivo* through regulating molecular pathways [10, 11]. Taken together, we speculate that puerarin may be possibly applied for CG management on the basis of its promising pharmacological properties. Thus, to begin with, pharmacological target and underlying mechanism of puerarin against CG should be studied preclinically. Along with development of computer and medicine science, network pharmacology can function as a bioinformatic platform to underline the anti-disease target, action mechanism of natural extract or compound [12]. Molecular docking is an *in silico* structure-based technique aiming to assist in drug discovery, characterized with ligand-target interaction, structure-activity relationship [13]. Therefore, in this research, network pharmacology analysis was firstly applied to investigate the interrelated and core genes of puerarin on CG and to enrich the functions and pathways of puerarin against CG, and then to unmask the main anti-CG targets of puerarin by using molecular docking assay, finally providing theoretical basis for the preclinical investigation of puerarin potential use against CG.

Material and methods

Screening of puerarin-linked targets

The 2D chemical structure of puerarin was retrieved from the PubChem (https://pubchem.ncbi.nlm.nih.gov) database. The structure was subsequently imported into the SwissTargetPrediction (https://www.swisstargetprediction.ch), SuperPred (https://prediction.charite.de), and PharmMapper (https://www.lilab-ecust.cn/pharmmapper) databases to predict puerarin-linked potential therapeutic targets. Target identifiers were standardized and corrected using the UniProt (http://sparql.uniprot.org) database via the ID mapping tool.

Screening of CG-linked targets

Potential targets associated with cystitis glandularis were retrieved from the GeneCards (http://www.genecards.org), DisGeNET (http://www.disgenet.org), TTD (https://idrblab.org/ttd), and MalaCards (https://www.malacards.org) databases. Finally, the predicted targets of puerarin and the disease-related targets were mapped using the Venn diagram tool on the Bioinformatics platform (https://www.bioinformatics.com.cn) to identify the intersecting targets for subsequent analysis.

Identification of core targets and PPI network construction

The intersecting targets were imported into the STRING database (version 11.5) to construct a protein-protein interaction (PPI) network. The species was restricted to *Homo sapiens*, the minimum required interaction confidence score was set to 0.7, and isolated nodes were hidden while other parameters were kept as default. The resulting *TSV* data file was exported. The PPI network was then visualized using Cytoscape (version 3.8.0). The CytoHubba plugin was employed to perform topological analysis on the network nodes. Core targets were identified based on the Maximum Clique Centrality (MCC) algorithm, and the core network was visualized.

Analysis of GO and KEGG annotation and enrichment in core targets

The core target genes were uploaded to the DAVID (Database for Annotation, Visualization, and Integrated Discovery, https://david.ncifcrf.gov) database for functional enrichment analysis, including Gene Ontology (GO) analysis covering biological process (BP), cellular component (CC), and molecular function (MF), as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Enrichment results were filtered based on the false discovery rate (FDR, adjusted *P*-value) < 0.05 for multiple-comparison correction. Bubble charts for GO terms and KEGG pathways were generated based on FDR values by using the Bioinformatics online plotting tool.

Molecular docking procedure

Based on the topological ranking of the PPI network, relevance to cystitis glandularis, and key pathways identified in KEGG enrichment, three core targets - AKT1, EGFR, and ESR1 - were selected for molecular docking validation.

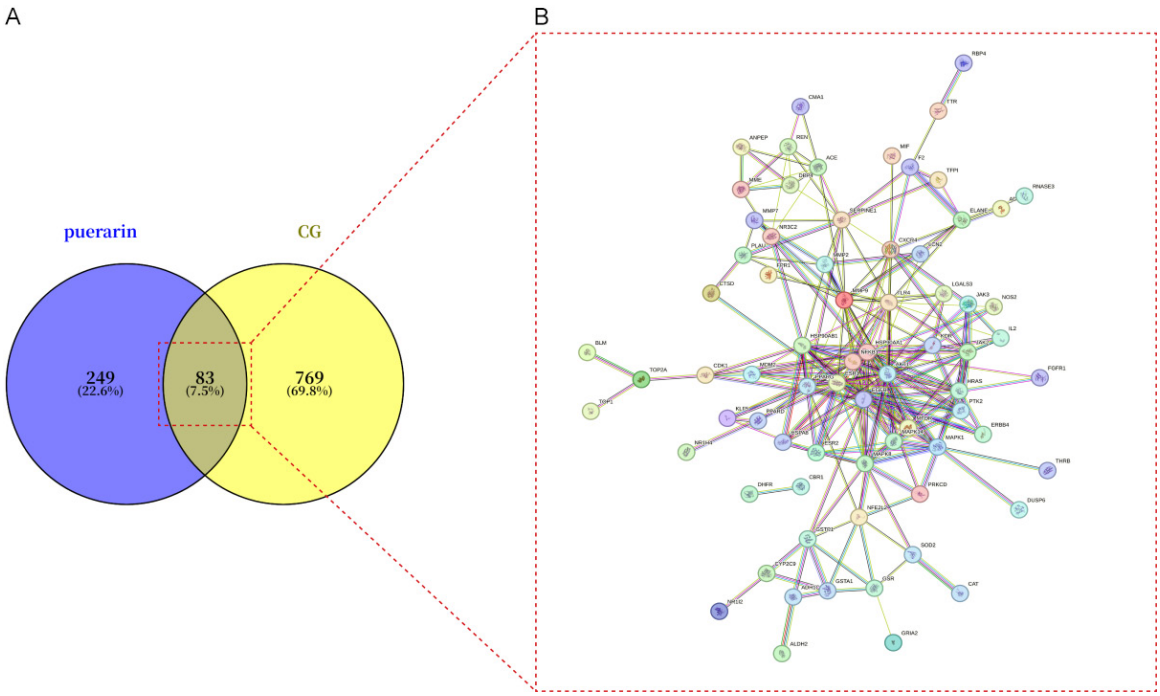

Figure 1. After network pharmacology analysis, Venn diagram exhibited all puerarin genes and cystitis glandularis (CG)-related genes (A) before further being screened out all overlapped target genes between puerarin and CG (B).

The 3D structure of puerarin was obtained from PubChem, and the crystal structures of the corresponding proteins were retrieved from the RCSB PDB (https://www.rcsb.org) database. To ensure docking accuracy, AutoDock Vina (version 1.2.0) and its auxiliary tool AutoDock Tools were utilized. Protein and ligand preparation included hydrogen addition, Gasteiger charge calculation, and merging of nonpolar hydrogens. The proteins were defined as receptors and puerarin as the ligand; all files were converted to the PDBQT format compatible with AutoDock. The rationality of the docking parameters was evaluated by calculating the Root Mean Square Deviation (RMSD) between the docked conformation and the original co-crystallized ligand. An RMSD value ≤ 4.0 Å was considered indicative of high conformational consistency.

Results

Correlative targets of puerarin and CG

Potential targets of puerarin were collected from databases, and a total of 332 drug-related targets were identified. Concurrently, 852 disease-related targets were collected from disease databases. A Venn diagram was generated by using the Bioinformatics platform (**Figure 1A**), revealing 83 intersecting targets shared between puerarin and cystitis glandularis. Subsequently, the STRING database was used to retrieve PPI data for these 83 targets, and the resulting PPI network of therapeutic targets and functionally related proteins was constructed (**Figure 1B**).

Topological analysis of the PPI network and screening of core targets

The intersecting protein targets were imported into Cytoscape 3.8.0. The CytoHubba plugin was utilized to calculate the topological parameters of the PPI network nodes. Based on the MCC algorithm scores, the top 10 nodes were extracted according to the ranking. These core targets were identified as: AKT1, ESR1, EGFR, Nuclear Factor Kappa B Subunit 1 (NFKB1), Heat Shock Protein 90 Alpha Family Class B Member (HSP90AB1), Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1), Mitogen-activated Protein Kinase 8 (MAPK8), Peroxisome Proliferator-Activated Receptor Gamma (PPARG), Mechanistic Target Of Rapamycin (MTOR), and Mitogen-activated Protein Kinase 1 (MAPK1). The visualization of the core target network is presented in **Figure 2**.

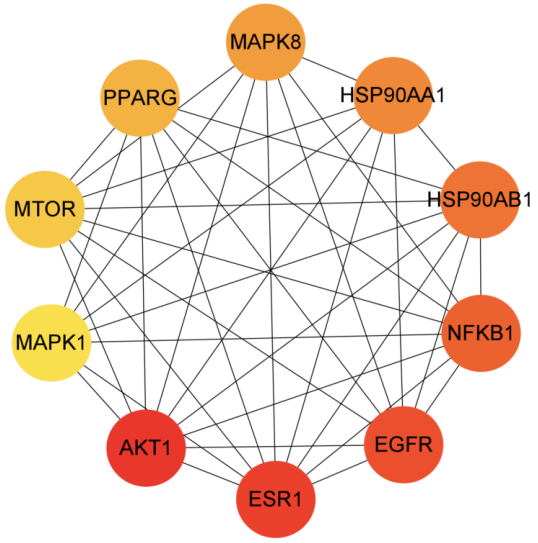

Figure 2. After being identified these core targets in puerarin against CG, a protein-protein interaction (PPI) network was created for association analysis.

GO and KEGG enrichment analysis findings

GO and KEGG enrichment analyses were performed using the Bioinformatics platform. The resulting bubble charts illustrated the distribution of GO terms (**Figure 3A-C**) and KEGG pathways (**Figure 3D**).

The GO analysis revealed that the core targets were primarily involved in the following BPs: *positive regulation of nitric oxide biosynthetic process, negative regulation of apoptotic process, MAPK cascade, response to heat, protein phosphorylation, signal transduction, response to estrogen, cellular response to amino acid starvation, negative regulation of gene expression, and negative regulation of autophagy*.

Regarding CCs, the targets were mainly enriched in the *cytosol, nucleoplasm, nucleus, cytoplasm, protein-containing complex, mitochondrion, secretory granule lumen, ficolin-1-rich granule lumen, perinuclear region of cytoplasm, and dendritic growth cone*. Notably, several cellular component terms had FDR > 0.05 without statistically significant enrichment, which only provided suggestive information for the subcellular distribution of core targets.

For MFs, enrichment was observed in *nitric-oxide synthase regulator activity, identical protein binding, protein phosphatase binding, ATP binding, enzyme binding, protein kinase activity, kinase activity, transcription coactivator binding, protein serine kinase activity, and protein serine/threonine kinase activity*.

KEGG pathway analysis indicated that the core targets were significantly enriched in 105 signaling pathways (*FDR < 0.05*). The predominant pathways included *Pathways in cancer, Chemical carcinogenesis - receptor activation, Prostate cancer, Pancreatic cancer, Lipid and atherosclerosis, Endocrine resistance, Th17 cell differentiation, Estrogen signaling pathway, PI3K-Akt signaling pathway, and Prolactin signaling pathway*.

Molecular docking results

Based on the topological centrality in the PPI network, clinical relevance to cystitis glandularis, and KEGG enrichment results, molecular docking analysis was performed for three core targets: AKT1, EGFR, and ESR1. Crystal structures of these proteins were retrieved from the PDB database. Structures with intact coordinates and co-crystallized ligands were selected. A grid box measuring 40 × 40 × 40 Å was established centered on the coordinates of the original ligand. The optimal docking conformations were visualized using PyMOL (version 2.5).

AKT1: Docking was performed by using the crystal structure 3096 (ligand: IQ0). The grid box center was set at (x: 9.643, y: -7.835, z: 10.604). The original ligand IQ0 formed a hydrogen bond with residue SER-205 of the 3096 protein, with a binding energy of -14.43 kcal/mol. Puerarin formed a hydrogen bond with the residue of SER-205, exhibiting a binding energy of -9.238 kcal/mol (**Figure 4A**).

EGFR: Docking was performed by using the crystal structure 1M17 (ligand: AQ4). The grid box center was set at (x: 21.697, y: -0.022, z: 52.186). The original ligand AQ4 formed a hydrogen bond with residue ASP-831 of the 1M17 protein, with a binding energy of -7.427 kcal/mol. Puerarin formed hydrogen bonds with residues of ASP-831, THR-830, THR-766, and LYS-721, exhibiting a binding energy of -8.466 kcal/mol (**Figure 4B**).

ESR1: Docking was performed by using the crystal structure 3ERT (ligand: OHT). The grid

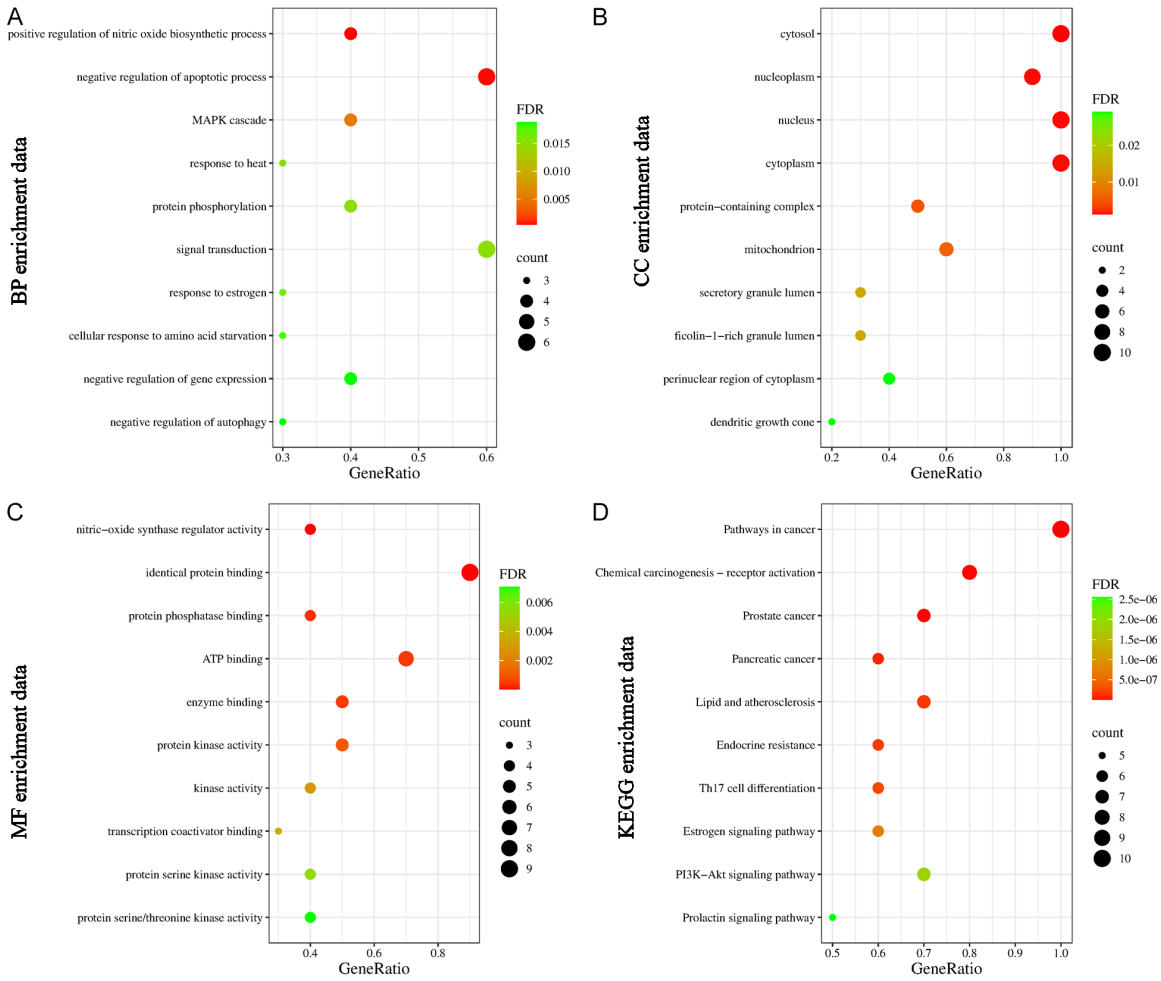

Figure 3. GO annotation analysis results from core targets highlighted top biological functions in visualization details, including BP enrichment data (A), CC enrichment data (B), MF enrichment data (C). KEGG enrichment analysis of core targets aimed to disclose the signaling pathways in puerarin against CG (D).

box center was set at (x: 30.01, y: -1.913, z: 24.206). The original ligand OHT formed a hydrogen bond with residue ARG-394 of the 3ERT protein, with a binding energy of -9.935 kcal/mol. Puerarin formed a hydrogen bond with residue of THR-347, exhibiting a binding energy of -6.949 kcal/mol (**Figure 4C**).

Discussion

Urinary bladder refers to a functional organ that stores urine, and the bladder triangle is a site that is susceptible to induction of tumor and inflammation [14]. Cystitis is a common urinary tract disorder, accounting for more than 60% of urinary tract infections, and it can be divided into acute simple cystitis and recurrent cystitis [15]. CG, one of the forms of cystitis, is controversial as the clinical manifestation of CG ranges from benign state to malignancy [16]. It is reported that chronic inflammation and abnormal immuneregulation is directly involved in pathogenetic development of CG [17]. Mounting data manifest that immunomodulatory or anti-inflammatory medication can help relieve the clinical symptoms of patient with CG. And it is interestingly found that parts of natural bioactive ingredients may be a candidate option for the management of CG [18]. Puerarin is reported with promising pharmacological activities, including anti-inflammatory, anti-oxidative, and immunomodulation, and those benefits can contribute to effectively manage inflammatory diseases such as endocrine dysfunctions by causing the release of cytokines and activating inflammatory pathway [19]. However, the potential action of puerarin on CG is still untouched, in which expedites the

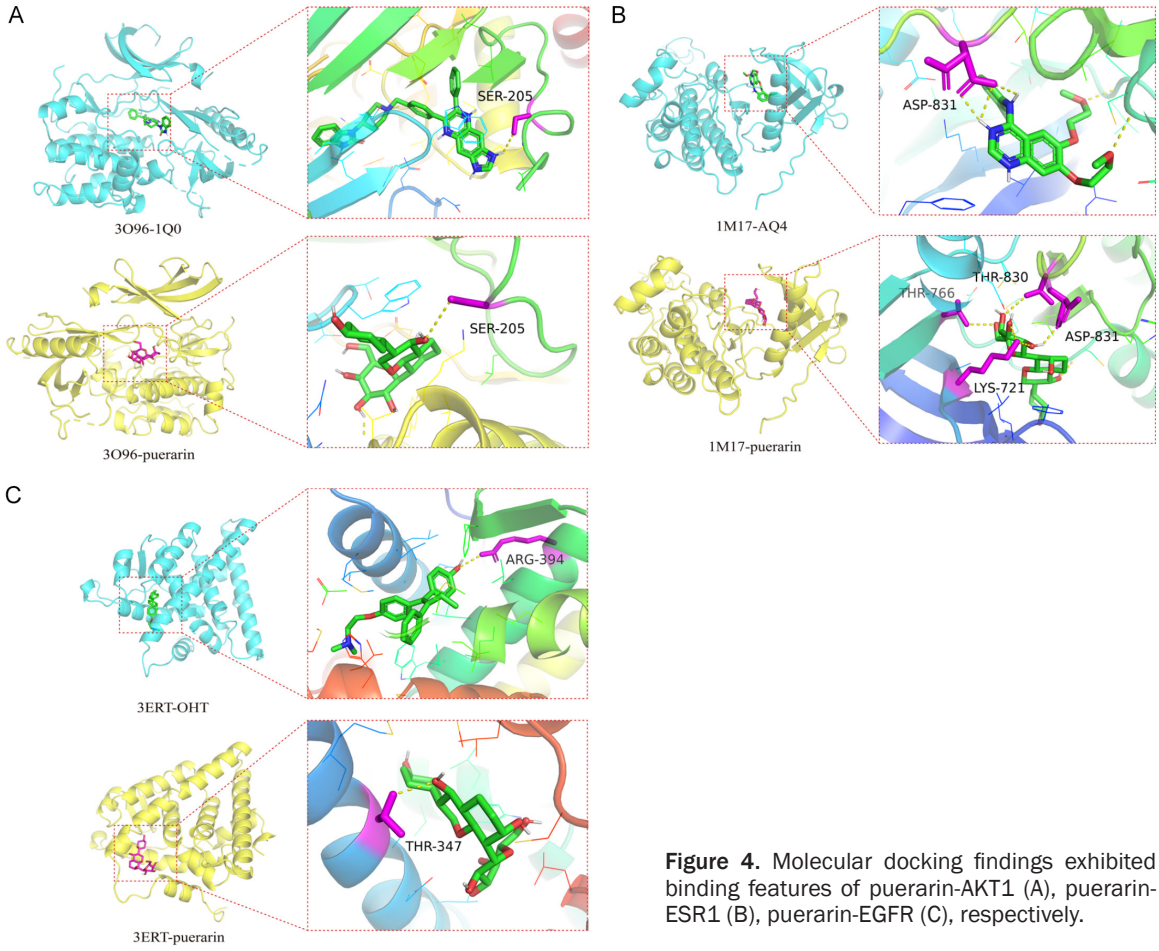

Figure 4. Molecular docking findings exhibited binding features of puerarin-AKT1 (A), puerarin-ESR1 (B), puerarin-EGFR (C), respectively.

great effort to investigate the pharmacological activity of puerarin against CG. Network pharmacology analysis showed that the bioactive component of puerarin with 332 target genes were selected, in which 852 target genes of CG were screened. Further biological prediction assay suggested that those overlapped targets between puerarin and CG were functionally linked to inflammatory response, oxidative stress, and molecular metabolism. All core targets of puerarin against CG were discriminated to be AKT1, ESR1, EGFR, NFKB1, HSP90AB1, HSP90AA1, MAPK8, PPARG, MTOR, and MAPK1 through further bioinformatics calculation. Noticeably, those core targets were found with participation in BPs including inflammation, oxidative stress, and cell necrosis, and then prohibition of current biological functions might help reduce inflammatory stress and tissue impairment on CG. It is reported that puerarin exhibits notable protective actions against metabolic dysfunction via regulating inflammatory/oxidative stress-, autophagy-related molecular mechanisms [20]. Puerarin suppresses the cell proliferation and progression of bladder cancer through multi-targets and multi-pathways [21, 22]. However, there is less research regarding puerarin acting on CG until now. Molecular docking analysis data showed that AKT1, ESR1, EGFR target proteins resulted in the forceful affinities and binding energy with puerarin. It is presumed that AKT1, ESR1, EGFR may be anti-CG pharmacological targets of puerarin based on present bioinformatics assessment. Protein kinase B (AKT1), a serine/threonine kinase, acts as a central transducer for regulating cellular survival pathway [23]. AKT1 may be a potential anti-cystitis target for naturally-isolating compound based on preclinical investigation [24]. Puerarin targets AKT1 activity for regulating cell death-dependent ferroptosis to inhibit oxidative stress-related damage *in vitro* [25]. It is reported that AKT1 can link with apoptosis/oxidative stress-related PI3K/Akt signaling pathway to manage cerebral ischemia/reperfusion [26]. And current

KEGG enrichment finding revealed PI3K-Akt molecular pathway involved in puerarin against CG. ESR1, a cellular receptor, is associated with immune cell infiltration and immunosuppressive action [27]. EGFR, a transmembrane tyrosine kinase receptor, modulates the crucial cell processes including cellular proliferation, differentiation and survival. It may be a context-dependent modulator for endothelial inflammation [28]. It is interestingly surmised that ESR1 and EGFR may be potential pharmacological targets for mediating inflammation, oxidative stress and apoptosis. And current KEGG enrichment finding revealed estrogen signaling pathway involved in puerarin against CG. Overall, these KEGG pathways might be associated with the pathological mechanisms of CG, such as chronic inflammation, epithelial hyperplasia, and potential precancerous changes.

However, these limitations in current research were that brief discussion of puerarin exerting the potential actions against CG via regulating multi-target, and multi-pathway manners. Due to the relatively limited number of core target genes identified in this study, the constructed "puerarin-core target-CG" interaction network might not have fully captured the complex overall picture of biological regulation. Thus, the prediction conclusions derived from the limited gene set were only of an assumed nature. These findings would be rigorously verified through *in vitro* cell experiments or *in vivo* animal models to confirm the true response of the core targets and the dose-effect relationship, thereby compensating for the quantitative evaluation shortcomings of the dry-method predictions. In other words, substantial experimental validation on current bioinformatics analysis results needed to be implemented. All findings were based on *in silico* predictions and required functional validation via subsequent *in vitro* cell experiments (such as using CG cell models or bladder epithelial cell inflammation models) and *in vivo* animal experiments (such as CG animal models).

Conclusion

In this research, a network pharmacology approach is employed to exhibit puerarin acting on CG through regulation of inflammation-, oxidative stress- and apoptosis-related mechanisms, including PI3K-Akt, estrogen signaling pathways. Molecular docking analysis initially uncovers that AKT1, ESR1, EGFR may be potential pharmacological targets of puerarin against CG. Interestingly, puerarin may be a promising candidate compound for the treatment with CG. And more researches are needed to be further explored before its future available application.

Disclosure of conflict of interest

None.

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