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Systems pharmacology dissection of the mechanisms and therapeutic potential of Cassiae semen for hepatoprotection and brightening eyes

Systems pharmacology dissection of the mechanisms and therapeutic potential of *Cassiae* semen for hepatoprotection and brightening eyes

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Abstract

***Cassiae* semen has been shown to play significant roles in reversing "liver fire" to improve vision. The systems mechanism of *Cassiae* semen for hepatoprotection and brightening eyes has not been fully explored. The systems pharmacology approach is proposed to dissect the potential pharmacological mechanism of *Cassiae* semen for hepatoprotection and brightening eyes. The results showed that 26 active components of *Cassiae* semen that connected with 230 targets were obtained. Gene ontology enrichment, network and pathway analysis explored that *Cassiae* semen is responsible for hepatoprotection and brightening eyes. The current study will contribute to the research and development of functional foods.**

Keywords: Brightening eyes, *Cassiae* semen, Functional food, Hepatoprotection, Systems pharmacology

1. Introduction

As a well-known functional food, *Cassiae* semen has been shown to be responsible for keeping a healthy lifestyle and preventing various diseases. Modern pharmacological studies revealed that crude extracts and pure components of *Cassiae* semen played an important role in clearing heat in the liver and sharpen vision [1].

Although *Cassiae* semen has been proven to be the effective agents for hepatoprotection and brightening eyes, the relationship between the active compounds, the related potential targets, the relevant pathways and the pharmacological effect of *Cassiae* semen at the system level has not been fully elucidated and warranted further exploration. A systematic approach to decipher the potential therapeutic mechanism of *Cassiae* semen on hepatoprotection and brightening eyes is urgently needed.

Alternatively, the emergence of systems pharmacology method provides an opportunity to contribute to uncovering the complex mechanisms of functional agents for the treatment of various diseases. Growing evidence reveals that systems pharmacology approach exerts a significant role in deciphering the bioactive components, the potential targets, related pathways, and the underlying therapeutic mechanisms of functional foods and medicinal herbs against various diseases [2–4]. With this understanding, the application of systems pharmacology method is potential for interpreting the pharmacological mechanisms of functional foods for the treatment of various diseases from a systematic view.

Therefore, in the current study, an integrated framework that combined pharmacokinetic screening, potential targets prediction, gene ontology enrichment analysis, network construction, as well as pathway analysis was developed to

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explore the pharmacological effect of *Cassiae semen* for hepatoprotection and brightening eyes based on the systems pharmacology strategy.

2. Materials and method

2.1. Compound database of Cassiae semen

Chemical ingredients of *Cassiae* semen were collected from two phytochemical databases: ETCM (the Encyclopedia of Traditional Chinese Medicine) [5], and TCMSP (Traditional Chinese Medicine Database and Analysis Platform) [6], and then manually supplemented from massive references [7–10]. Glycoside compounds in functional foods are usually hydrolyzed to corresponding aglycones by colonic bacteria, speeding up the absorption [11]. Therefore, these aglycone chemicals were manually added into the database of *Cassiae* semen [3,8,12–14].

2.2. Active compounds screening

Oral bioavailability evaluation

To eliminate the compounds with poor OB values, we employed a robust model OBioavail 1.1 to calculate the OB values of ingredients of *Cassiae* semen [15,16]. The compounds with suitable OB values (OB $\geq$ 40%) were selected as candidate bioactive ingredients for subsequent research.

Drug-likeness calculation

A robust *in silico* model [17] was employed to filter the ingredients with favorable DL indexes from molecule database of *Cassiae* semen [18]. The DL value of each ingredient was calculated based on Tanimoto coefficient (as displayed in Eq. (1)).

$$\mathrm{T(A,\ B)} = \frac{A \cdot B}{|A|^2 + |B|^2 - A \cdot B} \tag{1}$$

where A displays the molecular descriptors of compounds in *Cassiae* semen, and B is the average molecular descriptor of drugs and drug-like molecules in DrugBank database (http://www.drugbank.ca). The average DL value of all molecules in DrugBank is 0.18 which is set as the threshold of DL index [19].

2.3. Identifying therapeutic targets of Cassiae semen

First of all, we obtained the potential targets of active ingredients of *Cassiae* semen from TCMSP [6] and SEA (Similarity Ensemble Approach) [20] databases. Secondly, the molecular information of these bioactive ingredients was sent to the databases of DrugBank [21] and TTD [22] for mining their corresponding targets supported by the publications. Thirdly, a robust wide-scale text mining of PubMed was implemented to obtain the compound-target interactions using the molecular information as search terms.

2.4. Potential targets of hepatoprotection and brightening eyes

To decipher the underlying mechanism of action of *Cassiae* semen in hepatoprotection and brightening eyes, massive literature and databases of GeneCards [23], TTD [22] and DrugBank [21] were used to acquire the therapeutic targets of hepatoprotection and brightening eyes. Finally, the targets of hepatoprotection were obtained by searching the keywords including hepatitis, liver injury, liver fibrosis, inflammation, liver cancer, oxidative damage, and fatty liver disease. The potential targets for brightening eyes were acquired by related keywords, containing dry eye syndrome, conjunctivitis, and cataract.

2.5. Gene ontology and pathway enrichment analysis

To explore the underlying mechanism through biological process and signaling pathways, the Metascape database [24] was employed to implement gene ontology and pathway analysis based on the hepatoprotection-related genes and brightening eyes-related genes. In the present work, we extracted the representative enriched GO annotations of the top 20 clusters and enriched biological pathways of the top 15 clusters.

2.6. Network construction and analysis

To interpret the intricate relationships among active ingredients, biological targets, diseases, and pathways, we built compound-target-disease (C-T-D) networks and target-pathway (T-P) network. T-P network was built based on target proteins and corresponding enriched pathways. All networks were constructed by means of Cytoscape 2.8.1, which is a popular visualization interface for probing the complicated biological interactions [24].

3. Results and discussion

3.1. Active components filtration from Cassiae semen

A total of 137 molecules of *Cassiae* semen are extracted from TCMSP and ETCM databases, as well as plentiful literatures, including 124 constituents and 13 aglycones (13 hydrolysis products of 53 glucoside-type constituents) as displayed in Table S1 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal). Finally, 22 molecules pass through these ADME filtering criteria, and most of them display various pharmacological activities, such as aloe emodin (M072), stigmasterol (M071), and galangin (M067). For example, aloe emodin with satisfactory ADME parameters (OB = 83.38%, DL = 0.24) exhibited hepatoprotective activity through reducing hepatocyte death induced by CCl_4 in *vivo* model [25].

Additionally, we manually added the literature-based active compounds which had high contents in *Cassiae* semen but low OB values such as chrysophanic acid (M002, OB = 18.64%), aurantio-obtusin (M114, OB = 31.55%) and emodin (OB = 24.40%). For example, chrysophanic acid, one marker for quality control of *Cassiae* semen in Chinese Pharmacopoeia 2020 edition, has a poor OB value, but the content of this anthraquinone compound is extremely high (53.8–1661.1 μg/g) in *Cassiae* semen [26], which relatively increases the absolute OB index. 26 compounds were finally selected as the potential active compounds of *Cassiae* semen, and the structures and ADME parameters were exhibited in Table 1.

3.2. Target identification of Cassiae semen

The results of target exportation displayed that 26 active compounds were found interacting with 375 target proteins (as displayed in Table S2 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)). In order to focus on the therapeutic effect on hepatoprotection and brightening eyes, the potential targets related to these two pharmacological mechanisms were explored, which resulted in 1105 hepatoprotection-related targets and 499 brightening eyes-related targets (Table S3 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)). Finally, 26 active ingredients of *Cassiae* semen were confirmed to have connections with 149 hepatoprotection-related targets (Table S4 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)) and 81 brightening eyes-related targets (Table S5 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)).

Among these 149 hepatoprotection-related targets, a few of them (like TNF, IL6, ABCB11, HMOX1 and CYP1A1) have been documented to be implicated in several hepato-related pathological mechanisms, including hepatitis, liver injury, liver fibrosis, inflammation, liver cancer, oxidative damage, and fatty liver disease. For example, TNF (tumor necrosis factor) plays a vital role in the progression of nonalcoholic fatty liver disease (NAFLD) via up-regulating several key enzymes linked with inflammation, lipid metabolism and fibrosis in the liver [27].

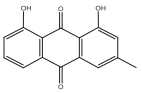
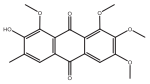
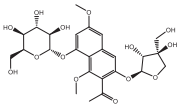
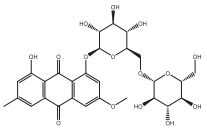
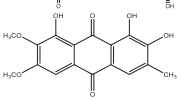
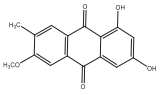
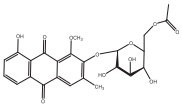
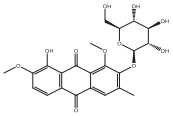
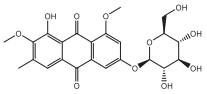
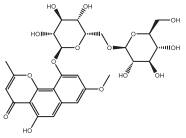
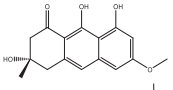
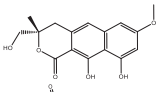
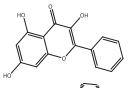
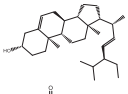
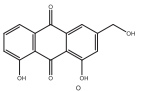
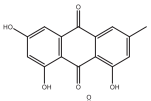
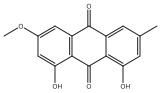
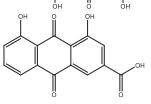
3.3. Gene ontology enrichment analysis

As displayed in Fig. 1, the biological processes for hepatoprotection were dominated by response to lipopolysaccharide, regulation of defense response, response to drug, response to wounding, and apoptotic signaling pathway. These biological processes have direct links with the pathological process of hepatoprotection-related diseases, such as liver injury, inflammation, oxidative damage, liver cancer et al. For example, lipopolysaccharides (LPS) have been identified as the major cofactors in the pathogenesis of liver injury [28].

In terms of brightening eyes, the enriched GO ontologies were mainly enriched in response to drug, steroid metabolic process, response to lipopolysaccharide, and circulatory system process, etc. These biological processes are linked with the pathogenesis of dry eye syndrome, conjunctivitis, and cataract. For example, the improper use of medicines leads to eye disease, such as conjunctivitis, and dry eye diseases. Improper or over-used medicines, like benzalkonium chloride, induce the abnormal gene expression of inflammatory markers on the ocular surface [29].

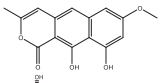
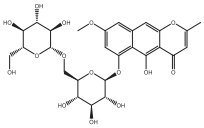
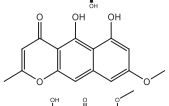
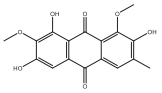
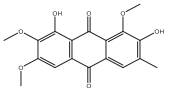
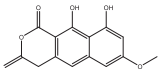
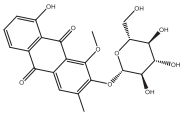
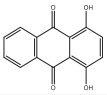
As mentioned in Fig. 1, several major GO annotations were significantly enriched in biological processes for both hepatoprotection and brightening eyes, such as response to lipopolysaccharide, response to drug, apoptotic signaling pathway, steroid metabolic process, and positive regulation of smooth muscle cell proliferation. These findings echoed the direct connection of hepatoprotection and brightening eyes as we mentioned above. For example, biological process of response to lipopolysaccharide was not only implicated in the pathological process of hepatoprotection-related diseases as we mentioned above, but also involved in pathogenesis of ocular diseases [30,31].

Table 1. The structures and ADME profiles of potential active compounds.

Mol ID	Molecular name	CAS	OB (%)	DL	Structure
M002	Chrysophanic acid	481-74-3	18.64	0.21	
M004	Chrysoobtusin	70588-06-6	72.84	0.44	
M027	Cassitoroside	170384-73-3	45.33	0.83	
M028	Physcion 8-gentiobioside	84268-38-2	41.65	0.63	
M032	1-Desmethylobtusin	90985-57-2	83.10	0.37	
M036	1,3-Dihydroxy-6-methoxy-7-methyl anthraquinone	—	69.14	0.27	
M043	Obtusifolin-2-O-β-D-(6'-O-acetyl) glucopyranoside	—	40.37	0.87	
M048	1,7-Dimethoxyl-2,8-dihydroxyl-3-methylanthraquinone -2-O-β-D-glucopyranoside	—	53.03	0.86	
M051	2,8-Dimethoxyl-l,6-dihydroxy-3-methylanthraquinone -6-O-β-D-glucopyranoside	—	43.52	0.87	
M057	Isorubrofusarin 10-gentiobioside	200127-93-1	40.12	0.67	
M060	Torosachrysone	93798-36-8	65.56	0.27	
M061	Cassialactone	80489-64-1	75.42	0.30	
M067	Galangin	548-83-4	45.49	0.21	
M071	Stigmasterol	83-48-7	43.83	0.76	
M072	Aloe emodin	481-72-1	83.38	0.24	
M073	Emodin	518-82-1	24.40	0.24	
M074	Physcion	521-61-9	22.29	0.27	
M085	Rhein	478-43-3	47.07	0.28	

(*continued on next page*)

Table 1. (continued)

Mol ID	Molecular name	CAS	OB (%)	DL	Structure
M086	Toralactone	41743-74-2	46.46	0.24	
M108	Rubrofusarin gentiobioside	24577-90-0	40.12	0.67	
M109	Rubrofusarin	3567-00-8	45.55	0.24	
M114	Aurantio-obtusin	67979-25-3	31.55	0.37	
M117	Obtusin	70588-05-5	81.43	0.40	
M123	Isotoralactone	80503-54-4	63.25	0.24	
M126	Obtusifolin 2-glucoside	120163-18-0	42.41	0.81	
M129	Quinizarin	81-64-1	47.34	0.19	

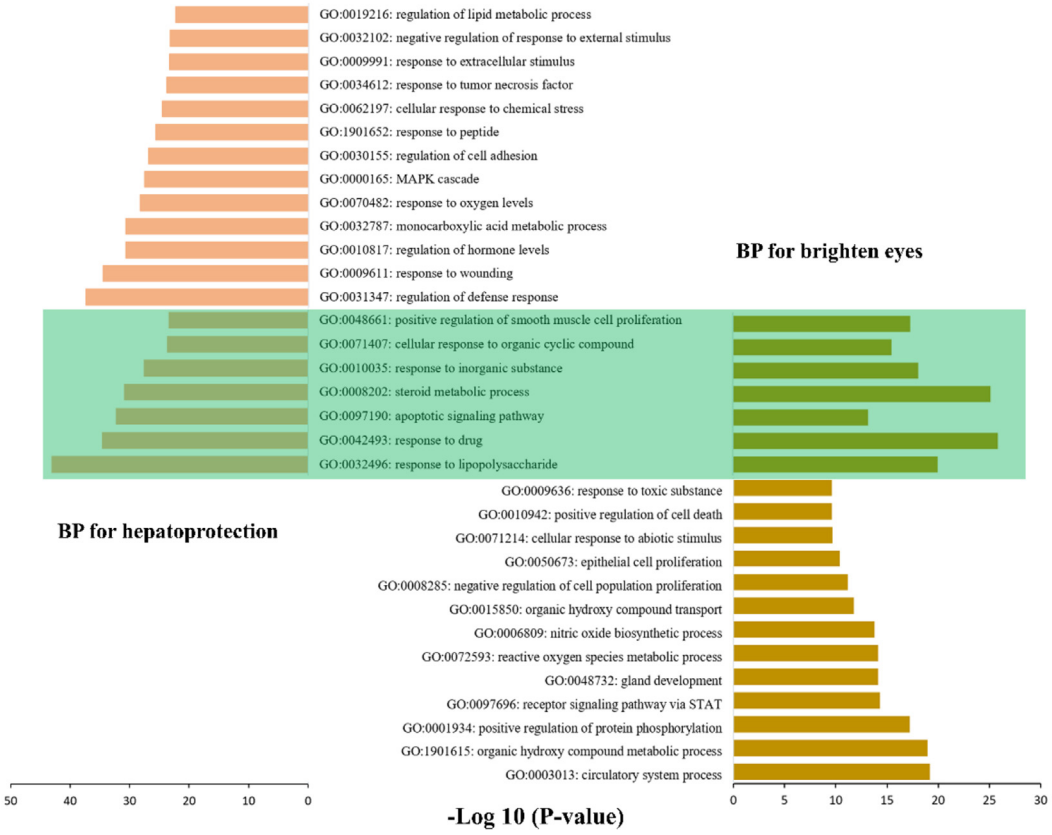


Fig. 1. GO enrichment analysis showing the targets of Cassiae semen for hepatoprotection and brightening eyes. The green part displays the shared GO terms for hepatoprotection and brightening eyes.

3.4. Pharmacologic analysis of Cassiae semen

3.4.1. C-T-D network of hepatoprotection

As recorded in the Compendium of Materia Medica, a classic and comprehensive Chinese medicine book, *Cassiae* semen showed the beneficial effects in nourishing the liver. The active ingredients, related targets, and corresponding diseases were employed to construct the C-T-D network of *Cassiae* semen for hepatoprotection, as displayed in Fig. 2.

The C-T-D network (Fig. 2) showed the 149 targets and 26 active ingredients related to hepatoprotection. As displayed in Fig. 2 and Table S4 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal), Emodin (M073), rhein, galangin, aloe emodin (M072), chrysophanic acid (M002), physcion (M074), and stigmasterol, hit by 52, 38, 38, 36, 35, 33, and 32 targets, respectively, were the main ingredients of *Cassiae* semen for the treatment of hepato-related diseases because of the dominant positions in network. For example, one of the major anthraquinones in *Cassiae* semen, emodin protected against acute liver injury through down-regulating the target TLR4 and its downstream molecules in the animal model [32].

Besides, Fig. 2 suggested eight hub therapeutic targets of *Cassiae* semen as the hub targets for the treatment of hepato-related diseases, including IL6, SLC37A4, ACHE, IL2, PTGS2, PTPN1, and NOS2, linked with 16, 13, 12, 12, 12, 12, and 10 active compounds (Table S4 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)). Interestingly, nearly half of the compounds (7 of 16 active ingredients) were experimentally confirmed to possess hepatoprotective effects via regulating IL6 expression, including chrysophanic acid [33], galangin [34], emodin [32], rhein [35], aurantio-obtusin [36], aloe emodin [37], and physcion [38]. All these findings indicated that *Cassiae* semen has the hepatoprotective activities through regulating multiple therapeutic targets.

3.4.2. C-T-D network of brightening eyes

The C-T-D network (Fig. 3) displayed 26 compounds and 81 targets implicated in eye diseases. Among them, emodin (M073), stigmasterol (M071), galangin, rhein, aloe emodin (M072), chrysophanic acid (M002) and physcion (M074), connected with 32, 32, 26, 22, 20, 18, and 18 target proteins (as shown in Table S5 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)), respectively, were the hub ingredients of *Cassiae* semen for the treatment of ocular disorders, due to their topological properties in the C-T-D network and high contents in herb medicine. In fact, 4 of 7 compounds were experimentally validated to have therapeutic effects on ocular diseases, such as emodin [39], galangin [40], aloe emodin [41], and chrysophanic acid [42]. For

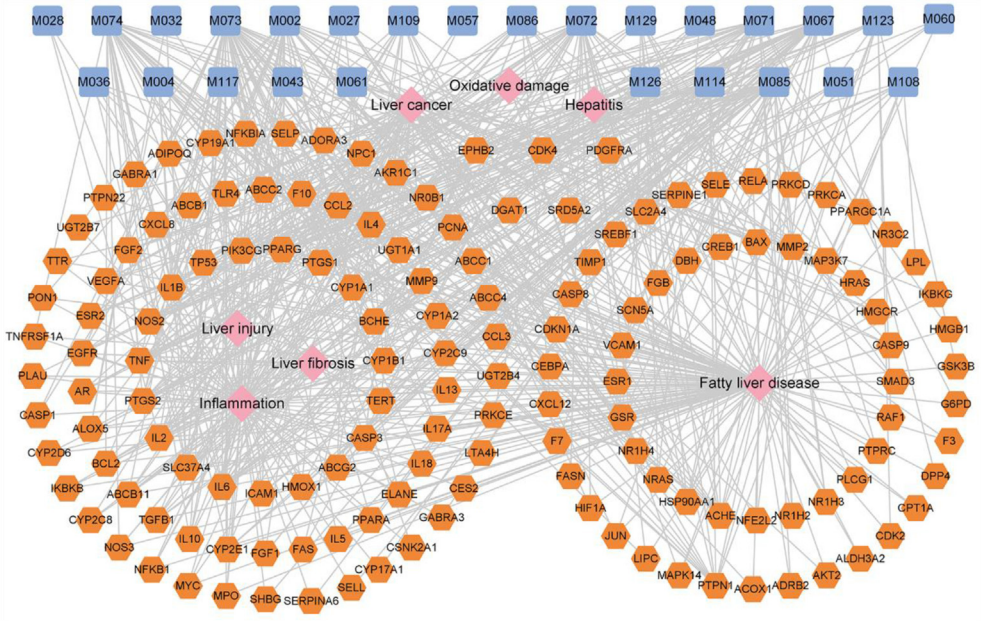


Fig. 2. The C-T-D network of Cassiae semen for hepatoprotection. The light blue nodes are the bioactive compounds of Cassiae semen, the orange nodes represent the target proteins, and the pink nodes indicate the liver-related diseases.

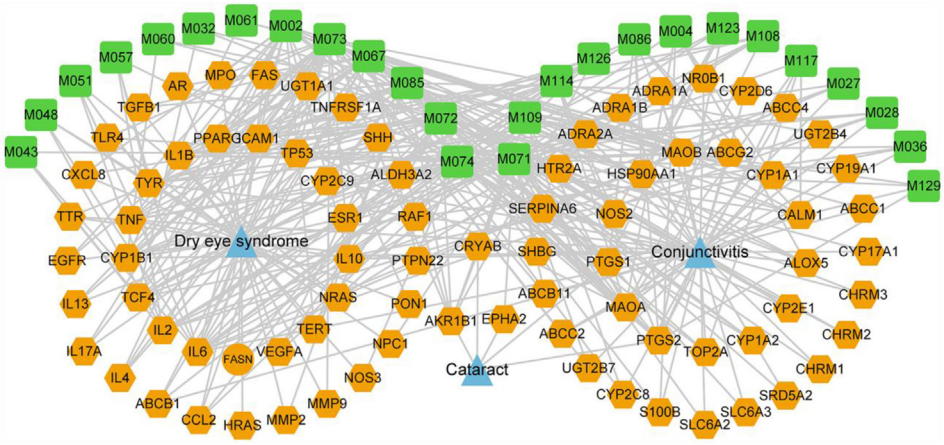


Fig. 3. The C-T-D network of Cassiae semen for brightening eyes. The green, orange, and blue nodes represent bioactive compounds, target proteins, and related ophthalmic diseases, respectively.

example, emodin, which targeted 32 eye diseases-related genes, has been showed to ameliorate conjunctivitis and cataract in rat models as mentioned above [43].

Besides, the C-T-D network also showed seven hub therapeutic targets of *Cassiae* semen for the treatment of ocular disorders including IL6, PTGS2, IL2, MAOA, NOS2, TCF4, and PTGS1, targeted by 16, 12, 12, 12, 10, 10, and 9 compounds (Table S5 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)), respectively. Among them, several inflammatory cytokines (IL6 and IL2) and enzymes (PTGS2, PTGS1 and NOS2) have been proved to be implicated in the pathology of ocular diseases. For example, some new medications (like se-lactoferrin, topical 0.05% cyclosporine A) suppressed the secretion of several inflammatory genes (like IL6 and PTGS2), and then beneficial effects on the treatment of dry eye disease [40,44].

3.5. Target-pathway network analysis

To shed light on the underlying mechanism of action of *Cassiae* semen, KEGG pathway enrichment analysis was carried out by Metascape toll, and the typical pathways of the top 15 clusters (one pathway per cluster) were displayed in Fig. 4 (Table S6 (https://www.jfda-online.com/cgi/editor.cgi?article=3417&window=additional_files&context=journal)). Several representative pathways were intensively connected with targets of hepatoprotection and/or brightening eyes. For the targets of hepatoprotection, AGE-RAGE signaling pathway in diabetic complications exhibited the lowest -log10 adjusted P value ($-\log_{10}(P) = 44.46$), as followed by pathways in cancer ($-\log_{10}(P) = 43.52$), chagas disease ($-\log_{10}(P) = 33.76$), and non-alcoholic fatty liver disease ($-\log_{10}(P) = 28.40$), which may be the interaction pathways to display the synergistic therapeutic effects of hepatoprotection. For example, AGE-RAGE signaling pathway in diabetic complications has been documented to play a pathological role in numerous types of hepatic diseases, like non-alcoholic fatty liver, hepatic steatosis, and hepatic fibrosis, through improved production of oxidative stress and inflammatory reactions [45,46].

In terms of brightening eyes, the enriched KEGG pathways were dominated by pathways in cancer ($-\log_{10}(P) = 16.21$), AGE-RAGE signaling pathway in diabetic complications ($-\log_{10}(P) = 15.98$), drug metabolism ($-\log_{10}(P) = 15.08$), and serotonergic synapse ($-\log_{10}(P) = 14.99$). Several cross-road signaling pathways in cancer (like Jak-STAT, PI3K-Akt, and MAPK signaling pathways) were involved in the pathological mechanism of dry eye syndrome, conjunctivitis, and cataract [47–49]. For example, MAPKs can induce the production of inflammatory cytokines (like IL1B, and TNF) and MMPs (such as MMP9), which play an important role in the pathogenesis of dry eye diseases [47].

As mentioned in Fig. 4, 54 targets and four signaling pathways in green area were implicated in both brightening eyes and hepatoprotection, which corresponds well with the direct connection between hepatic and ocular diseases. Among them, pathways in cancer, and AGE-RAGE signaling pathway in diabetic complications were considered as the major pathways in both hepatic and ocular diseases, due to their own characters and their related cross-road pathways.

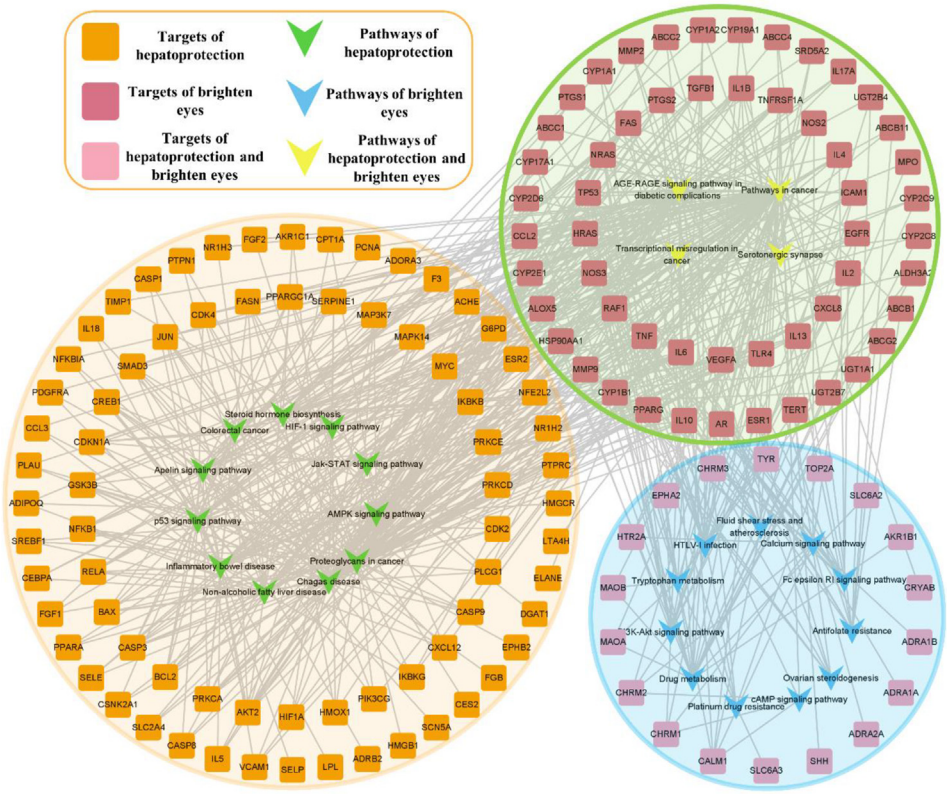


Fig. 4. Target-pathway network of Cassiae semen.

4. Conclusions

The major findings were summarized as follows. (1) 26 active components (like emodin, rhein, galangin, aloe emodin, chrysophanic acid, and physcion) of *Cassiae* semen with satisfactory pharmacokinetic properties were obtained. (2) 230 relevant protein targets were identified to have interactions with the screened compounds, which included 149 hepatoprotection (like IL6, SLC37A4, ACHE, IL2, PTGS2, PTPN1, and NOS2) and 81 brightening eyes relevant targets (such as IL6, PTGS2, IL2, MAOA, NOS2, TCF4, and PTGS1). (3) The GO enrichment analysis was performed for biological process to obtain the biological functional annotation involved in hepatoprotection and brightening eyes. (4) The C-T-D network of hepatoprotection and brightening eyes were built to clarify the therapeutic mechanisms of *Cassiae* semen from a holistic perspective. (5) The pathway analysis was developed to disclose the representative hepatoprotection and brightening eyes-related pathways perturbed by multiple targets at the pathway level. The current study has provided a promising method to holistic and systematic interpret the complex pharmacological mechanisms of *Cassiae* semen for hepatoprotection and brightening eyes, which will have a profound effect on future research and development of functional foods.

Conflict of interest

The authors declared no conflict of interest.

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