

# A Network Pharmacology Based Analysis of The Potential Mechanisms of Compound Danshen Dripping Pill for Treatment of Diabetic Retinopathy

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## Research

**Keywords:** Danshen, diabetic retinopathy, traditional Chinese medicine, network pharmacology

**Posted Date:** June 30th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-37961/v1>

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# Abstract

**Background:** Diabetic retinopathy (DR) has become a worldwide concern in recent years because of the high prevalence and vision-threat. The limited therapies have been in stark contrast to its high prevalence. On top of that, almost all the treatments, like laser, are applied only at the end stage of this disease. However, with the development of network pharmacology, a traditional Chinese medicine (TCM), Compound Danshen Dripping Pill (CDDP), may bring some new insights into the early intervention of DR.

**Methods:** The active compounds and potential targets of CDDP and DR-related targets were collected from the TCMSP, UniProt, GeneCards and OMIM databases. And protein-protein interactions (PPI) information was achieved from the STRING database. The gene enrichment analysis of GO and KEGG was carried out by “clusterProfiler” in R software. The collected data was then used to form network maps of compound-target and PPI, or visualized by the software of Cytoscape.

**Results:** 54 compounds and 50 targets were identified for CDDP against DR. Among the predicted effective compounds, 29 tanshinones from Radix Salviae (Danshen) were identified. And the core targets might be estrogen receptor (ESR1), androgen receptor (AR), caspase-3 (CASP3), Interleukin-6 (IL6) and vascular endothelial growth factor A (VEGFA) in 50 targets. There were 266 significantly correlated biological processes such as steroid hormone response, oxidative stress and apoptosis enriched out. Besides, The 50 targets significantly participate in 97 pathways and mainly enriched in advanced glycation end products (AGE)-receptor for advanced glycation end products (RAGE), fluid shear stress and atherosclerosis, apoptosis and VEGF signal pathway et al.

**Conclusions:** The mechanisms of CDDP for treating DR may involve multi-compound, multi-target and multi-pathway synergistic effects. It may participate in the regulation of steroid hormone response, oxidative stress, apoptosis and hemodynamics in diabetic retina. Tanshinones and luteolin from Radix Salviae were probably responsible for the effectiveness of CDDP on DR.

## 1. Introduction

Diabetic retinopathy (DR) is common and serious ocular complication of diabetes, with a high blindness rate. The estimated prevalence of DR in China is 34.5% in people with diabetes mellitus (DM), with 0.99% for vision-threatening DR.<sup>1</sup> The rate in rural China is higher than that in urban areas, which is about 43% in DM including 6.3% for vision-threatening DR.<sup>2</sup> At present, the treatments of DR, such as laser, intraocular administration of anti-vascular endothelial growth factor (VEGF) agents and surgical intervention, all aim at reserving impaired vision but not ameliorating. All of these treatments are invasive and carried on the end stage of this disease because of the significant sight-threatening side effects.<sup>3</sup> Therapies for early retinopathy, except for managing systemic risk factors such as hyperglycemia, hypertension and dyslipidemia et al, is also significant. Modern medical therapies are based on the understanding of pathophysiological mechanisms underlying the development of DR which still need

plenty of critical efforts. In the meantime, traditional Chinese medicine (TCM), as a different medical system, may provide some clues for preventing or treating DR from the early stage.

The application of TCM in diabetic retinopathy has a long history in China, and some effective TCM treatments for DR have been found in clinical practice.<sup>4</sup> TCM characterized by multi-compounds might synergistically regulate multi-targets of complex diseases like DR. The developing network biology indicates that complex diseases may involve a cascade of changes that are interactive and should be viewed as a whole.<sup>5,6</sup> This concept is similar to the organic conception of the human body in TCM. Based on the holism, regulating multiple core targets simultaneously could be more effective for complex diseases than single ones. From this point of view, TCM therapies of interest may have some information about the optimum combination of core targets of diseases. However, also limited by the multi-compounds and multi-targets of TCM, the researches about the effective compounds or targets of TCM for diseases are relatively difficult and slow. Network pharmacology may provide some insights into the network of biological effects of TCM, and helps to identify core targets of complex diseases.

To understand the mechanism of TCM on DR, we investigated a therapeutic pure TCM drop, Compound Danshen Dripping Pill (CDDP). The effectiveness and safety of CDDP treating or delaying DR have been studied in clinical trials.<sup>7,8</sup> And it has been recommended for DR treatment.<sup>9</sup> But the mechanisms underlying the anti-DR effects of CDDP are poorly understood. In this study, with the help of network pharmacology, we analyzed the compounds and targets of CDDP and DR-related targets to explore the potential molecular targets and mechanisms of CDDP for the treatment of DR.

## 2. Materials And Methods

### 2.1. Screening active compounds of CDDP

The recipe composition of CDDP includes the root and rhizome of Radix Salviae (RS, danshen), the root and rhizome of Panax notoginseng (Burk.) F. H. Chen (PN, sanqi) and Borneolum Syntheticum (BS, bingpian). We identified the chemical compounds of each herb of CDDP from Traditional Chinese Medicine Systems Pharmacology Database (TCMSP),<sup>10</sup> and selected candidate compounds which have oral bioavailability (OB)  $\geq 30\%$  and drug-likeness (DL)  $\geq 0.18$ .<sup>11</sup> Additionally, in combination with relevant literature,<sup>12,13</sup> the compounds whose biological activity and pharmacological action were reported were also included in the candidate active compounds. Salvianolic acid B and tanshinone I from RS, and L-borneol, D-borneol, isoborneol from BS were included in the follow-up study, although the OB or DL values of the above components are lower than 30% or 0.18. Eventually, a main active compounds data set of CDDP was established. The structure, biological activity and other details of the compounds were achieved by the Pubchem database.<sup>14</sup>

### 2.2. Identification of potential targets of CDDP

The primary targets of CDDP was excavated from the TCMSP database.<sup>10</sup> The target protein name of CDDP was converted into a gene name though the UniProt database.<sup>15</sup> By inputting the target protein name and defining the species as "Homo sapiens", the non-human targets were eliminated.

### ***2.3. collection of DR-related Targets***

The differential expressed genes of DR were obtained from the GeneCards database<sup>16</sup> and the OMIM database<sup>17</sup> with the keyword of "Diabetic Retinopathy." Genes with a P-value < 0.05 were considered to be of significant differential expression in DR.

### ***2.4. Network Construction and Merge***

Venn analysis was carried out to achieve the common target gene set of CDDP and DR through the online platform of Bioinformatics and Evolutionary Genomics.<sup>18</sup> The network of "CDDP-compound-target-DR " was constructed and visualized with Cytoscape 3.7.1 software and analyzed with Network Analyzer.

PPI data was achieved from the STRING database. Data that the minimum required interaction score > 0.4 was chosen. The network of protein-protein interaction visualized with Cytoscape software and core targets were selected according to the degree value of the nodes.

### ***2.5. Bioinformatic analysis***

Bioconductor package "org.Hs.eg.db" was used to convert the target into entrezID in R software. According to the transformed entrezID, "clusterProfiler" was used to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analysis of the target genes with significant changes of  $P < 0.05$  and  $Q < 0.05$ . The top 20 significant categories of GO and KEGG analysis were carried out in the form of a bar chart.

## **3. Results**

### **3.1. Compound-target analysis of CDDP**

The network of compound-target was carried out as **Figure 1**. Eighty-one compounds of CDDP were identified as the candidate compounds from the TCMSP database. The total 81 compounds were input into the UniProt database to identify the corresponding targets. Seventeen compounds were deleted because no relevant targets have been recorded yet in the database. After deduplication, a total of 64 potential active ingredients were finally obtained (**Figure 1, the outer circle**). RS, PN, and BS had 55 (**Figure 1, red dot**), 7 (**Figure 1, green dot**), 2 (**Figure 1, yellow dot**) active compounds, respectively. These compounds had a median degree value (edges) of 9.22, indicating a multi-targeting effect of CDDP, among which quercetin, luteolin and tanshinone IIA had the highest degree value of 78, 29 and 22. Sixty-four compounds were related to 109 targets (**Figure 1, the inner grid**). The total targets of CDDP in our study were shown highly related to nuclear hormone receptor superfamily such as nuclear receptor

coactivator (NCOA), prostaglandin G/H synthase 1 (PTGS1), alpha-1A adrenergic receptor (ADRA1A), estrogen receptor 1 (ESR1), androgen receptor (AR) and cholinergic signal regulators including muscarinic acetylcholine receptor M1-5 (CHRM1-5) and acetylcholinesterase (ACHE), according to the degree value of nodes.

### 3.2. The candidate targets of CDDP against DR

The 109 CDDP targets were merged with 2702 DR-related target genes. After the intersection of the two, 50 candidate targets of CDDP against DR were identified (**Figure 2a**), with 27 targets of RS (**Figure 2a**), 43 targets of PN (**Figure 2a**), and 1 target of BS (**Figure 2a**). The 50 targets were related to 54 active compounds of CDDP (**Table 1**). Quercetin and luteolin, had the highest degree value of 39 and 17. And 29 tanshinones (**Table 1**<sup>superscript</sup>) were identified. These compounds may be the representative compounds of CDDP against DR. Eventually, the interaction of 54 potential effective compounds and 50 candidate targets was formed the network of CDDP-compound-target-DR (**Figure 2b**). ACHE, ESR1 and AR were maximally targeted with 26, 20 and 20 edges, respectively.

### 3.3. PPI networks analysis

In order to reveal the mechanisms of action underlying CDDP's effects on DR, the PPI network analysis was applied to show the protein interaction network of the candidate targets of CDDP against DR (**Figure 3**). Interleukin-6 (IL6), epidermal growth factor receptor (EGFR), CASP3 and VEGFA with the degree of 38, 37, 37 and 36, respectively, might be the core targets in the network (**Figure 3a**). To better understand the role of CDDP in the PPI network, we merged the PPI network and the CDDP-compound-target-DR network (**Figure 2b**) as **Figure 3b**. After the intersection, new order of the nodes was formed based on degree value. The top 5 targets were ESR1, AR, CASP3, IL6 and VEGFA with 50, 46, 42, 40 and 39 edges, respectively.

### 3.4. GO and KEGG enrichment analysis

To analysis what biological processes CDDP might involve in when applied to DR, GO analysis was carried out. 266 GO terms were significantly enriched ( $P\text{-adjust} < 0.05$ ) based on the biological process (**Supplementary Table 1**). The top 20 terms were shown in **Figure 4**. The highly enriched GO terms included steroid hormone response, oxidative stress, apoptosis et al.

The pathways that were significantly influenced by CDDP for the treatment of DR were identified by KEGG pathway analysis. 97 significantly enriched pathways were identified (**Supplementary Table 2**), and the top 20 pathways were shown in **Figure 5**. The results showed that the common targets were mainly concentrated in the advanced glycation end-products and receptor for advanced glycation end-products (AGE-RAGE) signaling pathway, fluid shear stress and atherosclerosis, apoptosis, tumor necrosis factor (TNF), hypoxia-inducible factor-1 (HIF-1), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and

VEGF signaling pathway, which regulate many biological processes like oxidative stress, blood pressure, hemodynamic change, apoptosis, inflammation, retinal ischemia, proliferation and differentiation.<sup>19-26</sup>

## 4. Discussion

In TCM theory, RS is supposed to be the most responsible herb for CDDP's effects. According to our putative active compounds of CDDP for DR, RS has 48 among a total of 54 active compounds with 27 targets. 45 of 48 active compounds are specific in the herb, indicating that RS may play a vital role in the formula consistent with TCM theory. RS have shown some anti-diabetic properties by regulating multiple pathways and biological processes related to the development of diabetes.<sup>27</sup> Thus anti-diabetic compounds are expected to be identified from it. In our study, Tanshinones were identified as the major effective compounds of RS demonstrating multiple bioactivities. It is suggested that tanshinones could be therapeutic agents for diabetes as insulin sensitizer and AMPK pathway activators.<sup>28-30</sup> Early application of tanshinones may prevent the progress of DR. Besides, many tanshinones have shown anti-inflammatory effect,<sup>31</sup> and total tanshinones exhibit a stronger effect than a single one.<sup>32</sup> Since inflammation is supposed to play a vital role in DR, the application of tanshinones could also be beneficial for DR in this respect. Among the tanshinones, tanshinone IIA stood out with the highest node degree. It has been suggested exerting anti-angiogenesis, anti-oxidative stress, anti-inflammatory effects in the retina through suppressing VEGF, AGE, NF- $\kappa$ B pathway.<sup>33-35</sup> There were still some non-specific compounds of CDDP at the top of the list (Table 1), which could not be ignored. Polyphenols like quercetin and luteolin have been suggested to be therapeutic for DR.<sup>36</sup> Luteolin from RS is believed to have effects on activating anti-inflammatory, antioxidant responses, neuroprotective effects and regulating relaxation, lipid profile via acting on multiple signaling pathways.<sup>37-42</sup> Taken together, tanshinones and luteolin may be responsible for the effectiveness of CDDP against DR.

For PN, although 5 compounds have 43 targets, most of them like quercetin could be found in plenty of Chinese herbs, and PN is less dosage in the formula, the compounds identified were not suggested as the representative compounds for CDDP. The situation of BS is almost the same as PN. But their compatibility with RS is necessary according to TCM theory. Pharmacokinetics showed that the bioavailability of PN extract significantly increased when co-administered with BS through oral administration in rats.<sup>43</sup> It suggests that BS might work as a potential absorption enhancer, and an upper ushering to brain drug.<sup>44</sup> Although there is no significant difference in pharmacokinetic parameters between single RS or PN extract and combination treatment through oral administration,<sup>43</sup> the combination treatment enhanced RS compounds in the brain and cerebrospinal fluid while decreasing the distribution of PN compounds via inner ear administration in guinea pigs.<sup>45</sup> These researches indicate that herb-herb interactions may improve pharmacokinetic behaviors of CDDP's active compounds.

Our results indicated that the predominant targets of CDDP against DR were ESR1, AR, CASP3, IL6 and VEGFA. ESR and AR are steroid hormone receptor. ESR signaling has shown its importance in ischemia-induced angiogenesis<sup>46,47</sup> and neural injury gradually<sup>48-50</sup>. But the effects of sex hormones in DR are not

fully understood and quite controversial at present.<sup>51</sup> Estrogen could be neuroprotective<sup>52,53</sup> or useless<sup>54</sup> or harmful<sup>55</sup>. Its neuroprotective effect may be related to anti-apoptosis and anti-autophagy effects, while androgen is more pro-apoptotic<sup>56</sup>. From our results, CDDP could have a potential influence on both ESR and AR signaling. Furthermore, CDDP showed a potential influence on CASP-3, a downstream executioner of apoptosis in DR,<sup>57-60</sup> in our study and its inhibitory effect on CASP-3 expression has been reported.<sup>61</sup> Combining with the GO enrichment analysis, CDDP was strongly indicated involved in the regulation of steroid hormone response and apoptosis in DR.

Chronic inflammation has been suggested by growing evidence playing a prominent role in the pathogenesis of DR.<sup>62-64</sup> IL-6, one of the inflammatory mediators, is found elevated in diabetic retinopathy.<sup>65-67</sup> IL-6 is a pleiotropic cytokine, and its effects could be quite different through activating different pathways. Binding to membrane-bound IL-6 receptor and gp130, IL-6 activates classical IL-6 signaling pathway, which is supposed to be regenerative and protective; while binding to the soluble IL-6 receptor, IL-6 activates IL-6 trans-signaling pathway which is chronic pro-inflammatory and resulting in endothelial cell dysfunction and vascular leakage.<sup>68-70</sup> both pathways could be activated in the retina under high glucose.<sup>71,72</sup> Meanwhile, IL-6 is highly correlated with the aqueous level of VEGF in DR.<sup>73</sup> The correlation between VEGF and the pathogenesis of DR is uncontroversial, especially for proliferative DR.<sup>21,74,75</sup> Downstream events of VEGF include survival, proliferation, and permeability.<sup>76</sup> It is supposed to improve the survival of retinal cells in the first place. But over time, it disrupts the outer blood-retinal barriers (BRB) and acts as a pathologic angiogenic stimulus.<sup>77,78</sup> These studies indicate the feasibility of CDDP against DR by targeting these predicted targets and their biological processes. Our results showed that CDDP might regulate multiple targets of DR, including inflammatory cytokines and growth factors et al.

At present, several biological processes and pathways have been proposed to participate in the development of DR including oxidative stress, AGE, protein kinase C (PKC) activation, inflammation, VEGF, sorbitol, erythropoietin, the renin-angiotensin system (RAS), peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ ).<sup>79,80</sup> These processes or pathways could be the potential therapeutic targets for DR. As our results indicated, the mechanisms underlying the effect of CDDP for DR might involve in multiple pathways. A total of 97 KEGG pathways were enriched out including the AGE-RAGE and VEGF pathway, fluid shear stress and atherosclerosis, apoptosis et al. AGE-RAGE and VEGF pathways play critical roles in DR and has been discussed a lot.<sup>19-21, 81-87</sup> Except for the biochemical changes, physiological changes also play a role in the process of DR. Hemodynamic dysfunction has been found in DR and may precede clinical DR.<sup>88-92</sup> Hemodynamic parameters, wall shear rate and wall shear stress are suggested reduced in the early stage of DR, as well as retinal blood velocity and flow, which could be markers of microvasculopathy.<sup>88,93,94</sup> Atherosclerosis has also been considered associated with the severity of DR, manifesting increased macrovascular artery intima-media wall thickness and accompanied by wider retinal vessel diameter in DR.<sup>95-97</sup> These studies emphasize the vital role of hemodynamic changes in the early stage of DR. CDDP in TCM theory is characterized by improving blood circulation

(Pharmacopoeia of the People's Republic of China). The early application of CDDP in NPDR patients can significantly shorten the retinal circulation time and reduce capillary hemangioma, hard exudates, retinal hemorrhaging.<sup>8</sup> And CDDP may also have an anti-atherosclerosis property.<sup>98</sup> The potential regulation on hemodynamics through fluid shear stress and atherosclerosis pathway may make CDDP a suitable medicine for an early intervention of DR. Besides, fluid shear stress is related to the release of vasodilatory factors nitric oxide (NO).<sup>99-101</sup> As we all know, blood pressure has been suggested as one of the risk factors of DR.<sup>102</sup> The regulation of fluid shear stress and atherosclerosis pathway by CDDP may affect blood pressure control. And anti-hypertension of RS has been reported by some researches.<sup>103-105</sup> In summary, CDDP may be beneficial in the early stage of DR by acting on AGE-RAGE, VEGF, fluid shear stress and atherosclerosis, and apoptosis pathway.

Except for vascular dysfunction, retinal neurodegeneration has been recognized in DR with growing evidence. New insights suggest that vascular dysfunction and neural degeneration may be parallel in this disease. Thus physiological changes of DR should be viewed as changes of retinal neurovascular unit.<sup>79,106</sup> The unit includes the interaction of vascular cells, retinal glial cells and neural cells. Because of the interaction, elevated pro-inflammatory or pro-angiogenesis cytokines in DR may contribute to both the blood-retina barrier (BRB) disruption and synaptic or neuronal degeneration.<sup>79</sup> Cholinergic signaling may be blunted in diabetic retina, which may associate with synaptic degeneration, resulting in endothelium-dependent vasodilatation dysfunction and ischemia.<sup>107,108</sup> And CHRM has been suggested to play an important role in retinal neuron survival<sup>109,110</sup> and insulin release stimulation.<sup>111-113</sup> It is rational to hypothesize that active cholinergic signaling could be protective in DR. In the compound-target network of CDDP, it showed that CDDP might have a potential regulation on cholinergic signaling through CHRM1-5 and ACHE (Fig. 1). Although it is not clear what exact role of cholinergic signaling plays in DR, therapies targeting cholinergic signaling could be worth trying considering the neuroprotective effects of its agonists towards other neural degenerative diseases like Alzheimer's and Parkinson's diseases.<sup>114</sup>

## 5. Conclusions

The relatively scarce data of CDDP in the public TCM database and the incomplete interaction of protein interactome may constrain our results. Nevertheless, we identified some very likely candidates to explain the mechanisms behind the effect of CDDP against DR. ESR1, AR, CASP3, IL6 and VEGFA may be the center targets in the action network of CDDP against DR involved in steroid hormone response, oxidative stress and apoptosis processes. Regulation of steroid hormone response may be the primary mechanism of CDDP for DR. But the exact role of steroid hormone in DR needs more investigations. Except for the well-known DR-related AGE-RAGE, apoptosis and VEGF pathway, CDDP has been indicated to participate in the regulation of fluid shear stress and atherosclerosis pathway. It seems that CDDP could have a potential effect on hemodynamics consistent with TCM theory. These results indicated that the early application of CDDP in DR might be beneficial from hemodynamics, oxidative stress and apoptosis improvement. And the therapeutic compounds may be tanshinones and luteolin, since the regulation of most of the targets. In summary, this study showed that the underlying mechanism of CDDP treating DR

might involve multi-compound, multi-target and multi-pathway synergistic effects. Those data may bring new insights for further investigations and new strategies for the prevention or treatment of DR from an early stage.

## **Abbreviations**

DR	Diabetic retinopathy
CDDP	Compound Danshen Dripping Pill
TCM	Traditional Chinese medicine
DM	Diabetes mellitus
VEGF	Vascular endothelial growth factor
RS	Radix salviae
PN	Panax notoginseng
BS	Borneolum syntheticum
TCMSP	Traditional Chinese Medicine Systems Pharmacology
NCOA	Nuclear receptor coactivator
PTGS	Prostaglandin G/H synthase
ADRA1A	Alpha-1A adrenergic receptor
ESR	Estrogen receptor
AR	Androgen receptor
CHRM	Muscarinic acetylcholine receptor M
ACHE	Acetylcholinesterase
PPI	Protein-protein interactions
IL6	Interleukin-6
EGFR	Epidermal growth factor receptor
CASP3	Caspase-3
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
AGE	Advanced glycation end-products
RAGE	Receptor for advanced glycation end-products
TNF	Tumor Necrosis Factor
HIF	Hypoxia-inducible factor
BRB	Blood-retina barrier
PKC	Protein kinase C
RAS	renin-angiotensin system
PPAR- $\alpha$	Peroxisome proliferator-activated receptor $\alpha$

AMPK	Adenosine 5`-monophosphate (AMP)-activated protein kinase
NF-κB	Nuclear factor kappa-B

## Declarations

**Author Contributions:** X.Z. and L.W. contributed to this article equally. Conceptualization, X.Z. and L.W.; methodology, X.Z. and L.W.; writing-original draft preparation, X.Z. and L.W.; writing-review and editing, X.H.; supervision, Y.Z. All authors have read and agreed to the published version of the manuscript.

**Data Availability Statement:** The datasets used during the current study are available from the corresponding author on reasonable request.

**Funding:** This research received no external fund.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest.

**Consent for publication:** Written informed consent for publication was obtained from all participants.

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## Table

Table 1  
The potential effective ingredients of CDDP

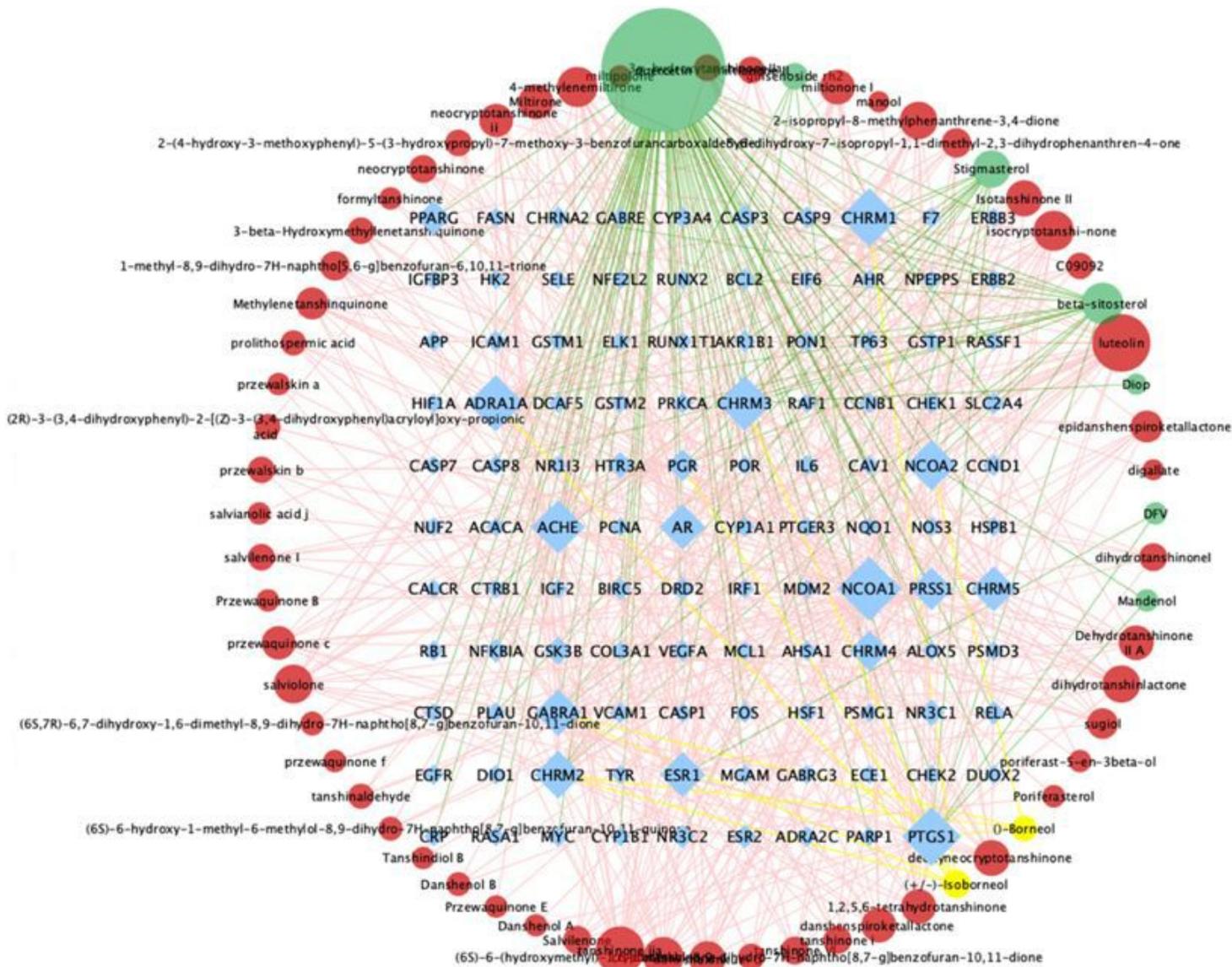
Compounds	Degree	Source
Quercetin	40	Panax notoginseng
Luteolin	17	Radix Salviae
Tanshinone iia <sup>a</sup>	6	Radix Salviae
Beta-sitosterol	6	Panax notoginseng
Cryptotanshinone <sup>a</sup>	5	Radix Salviae
Dehydrotanshinone II A <sup>a</sup>	4	Radix Salviae
Dan-shexinkum d <sup>a</sup>	4	Radix Salviae
Dihydrotanshinlactone	4	Radix Salviae
Tanshinone i <sup>a</sup>	4	Radix Salviae
Stigmasterol	4	Panax notoginseng
2-isopropyl-8-methylphenanthrene-3,4-dione <sup>a</sup>	3	Radix Salviae
4-methylenemiltirone <sup>a</sup>	3	Radix Salviae
2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-3-benzofurancarboxaldehyde	3	Radix Salviae
Przewalskin b	3	Radix Salviae
Isocryptotanshi-none <sup>a</sup>	3	Radix Salviae
Isotanshinone II <sup>a</sup>	3	Radix Salviae
Miltionone I <sup>a</sup>	3	Radix Salviae
Miltionone II <sup>a</sup>	3	Radix Salviae
(2R)-3-(3,4-dihydroxyphenyl)-2-[(Z)-3-(3,4-dihydroxyphenyl)acryloyl]oxy-propionic acid	3	Radix Salviae
Salvilenone I	3	Radix Salviae
Tanshinone VI <sup>a</sup>	3	Radix Salviae
Poriferasterol	2	Radix Salviae
Przewalskin a	2	Radix Salviae

Compounds	Degree	Source
Danshenol B <sup>a</sup>	2	Radix Salviae
Salvilenone	2	Radix Salviae
Danshenspiroketallactone	2	Radix Salviae
Deoxyneocryptotanshinone <sup>a</sup>	2	Radix Salviae
Miltipolone	2	Radix Salviae
Miltirone <sup>a</sup>	2	Radix Salviae
Neocryptotanshinone ii <sup>a</sup>	2	Radix Salviae
Prolithospermic acid	2	Radix Salviae
Ginsenoside rh2	2	Panax notoginseng
(+/-)-Isoborneol	1	Borneolum Syntheticum
Poriferast-5-en-3beta-ol	1	Radix Salviae
Sugiol	1	Radix Salviae
Digallate	1	Radix Salviae
5,6-dihydroxy-7-isopropyl-1,1-dimethyl-2,3-dihydrophenanthren-4-one	1	Radix Salviae
3 $\alpha$ -hydroxytanshinone II a <sup>a</sup>	1	Radix Salviae
Formyltanshinone <sup>1</sup>	1	Radix Salviae
3-beta-Hydroxymethylenetanshiquinone <sup>a</sup>	1	Radix Salviae
Methylenetanshinquinone <sup>a</sup>	1	Radix Salviae
Przewaquinone c <sup>a</sup>	1	Radix Salviae
(6S,7R)-6,7-dihydroxy-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione <sup>a</sup>	1	Radix Salviae
Tanshinaldehyde <sup>a</sup>	1	Radix Salviae
Epidanshenspiroketallactone	1	Radix Salviae
C09092	1	Radix Salviae
Neocryptotanshinone <sup>a</sup>	1	Radix Salviae

Compounds	Degree	Source
1-methyl-8,9-dihydro-7H-naphtho[5,6-g]benzofuran-6,10,11-trione <sup>a</sup>	1	Radix Salviae
Salviolone	1	Radix Salviae
(6S)-6-hydroxy-1-methyl-6-methylol-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-quinone <sup>a</sup>	1	Radix Salviae
Tanshindiol B <sup>a</sup>	1	Radix Salviae
Przewaquinone E <sup>a</sup>	1	Radix Salviae
(6S)-6-(hydroxymethyl)-1,6-dimethyl-8,9-dihydro-7H-naphtho[8,7-g]benzofuran-10,11-dione <sup>a</sup>	1	Radix Salviae
DFV	1	Panax notoginseng

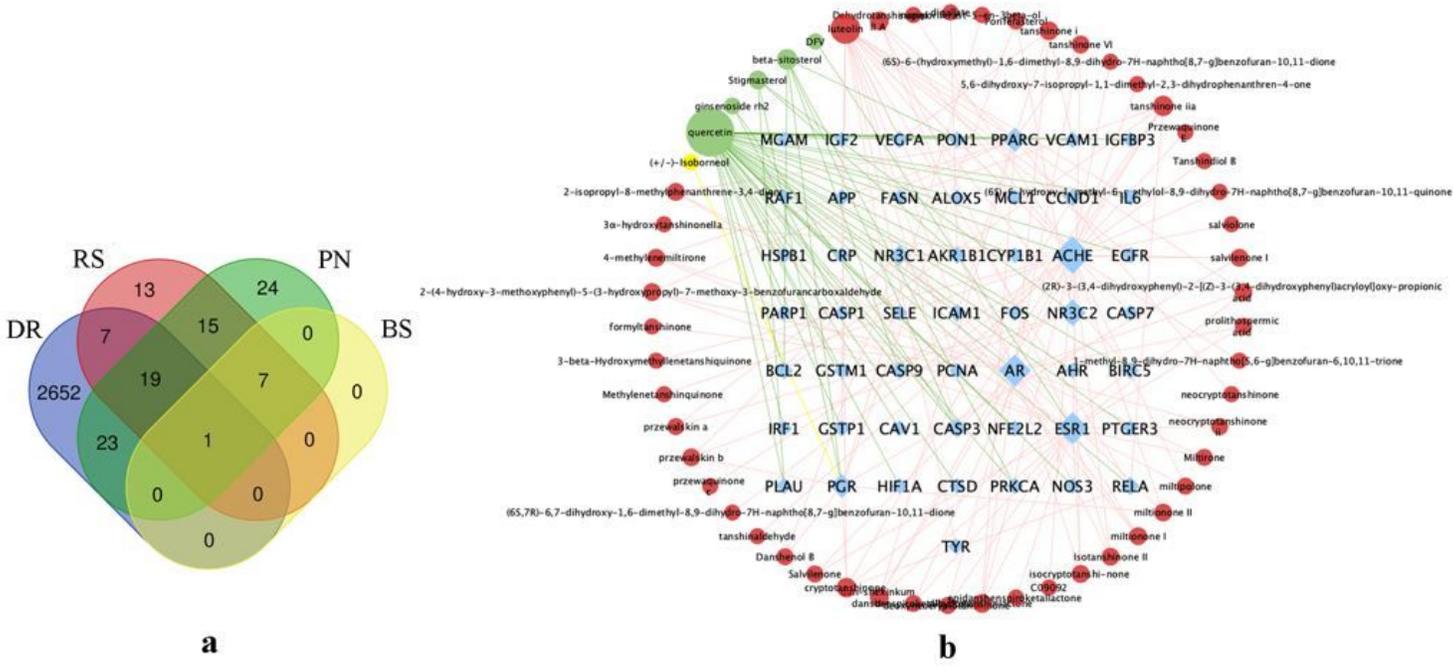
<sup>a</sup> Identified tanshinones.

## Figures



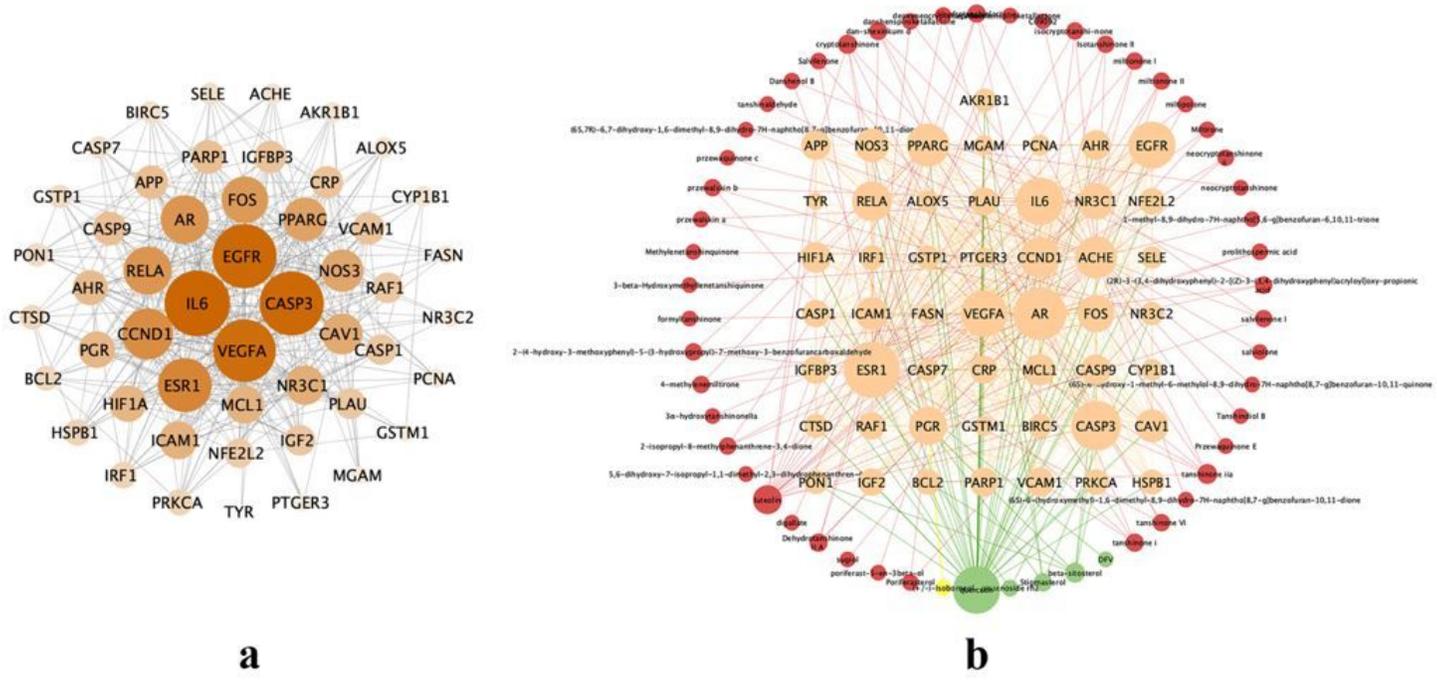
**Figure 1**

Compound-target network of CDDP: 64 compounds (the outer circle) and 109 targets (blue diamond) were identified. Fifty-five compounds were identified from RS (red dot), seven from PN (green dot), and two from BS (yellow dot). The size was based on the degree value.



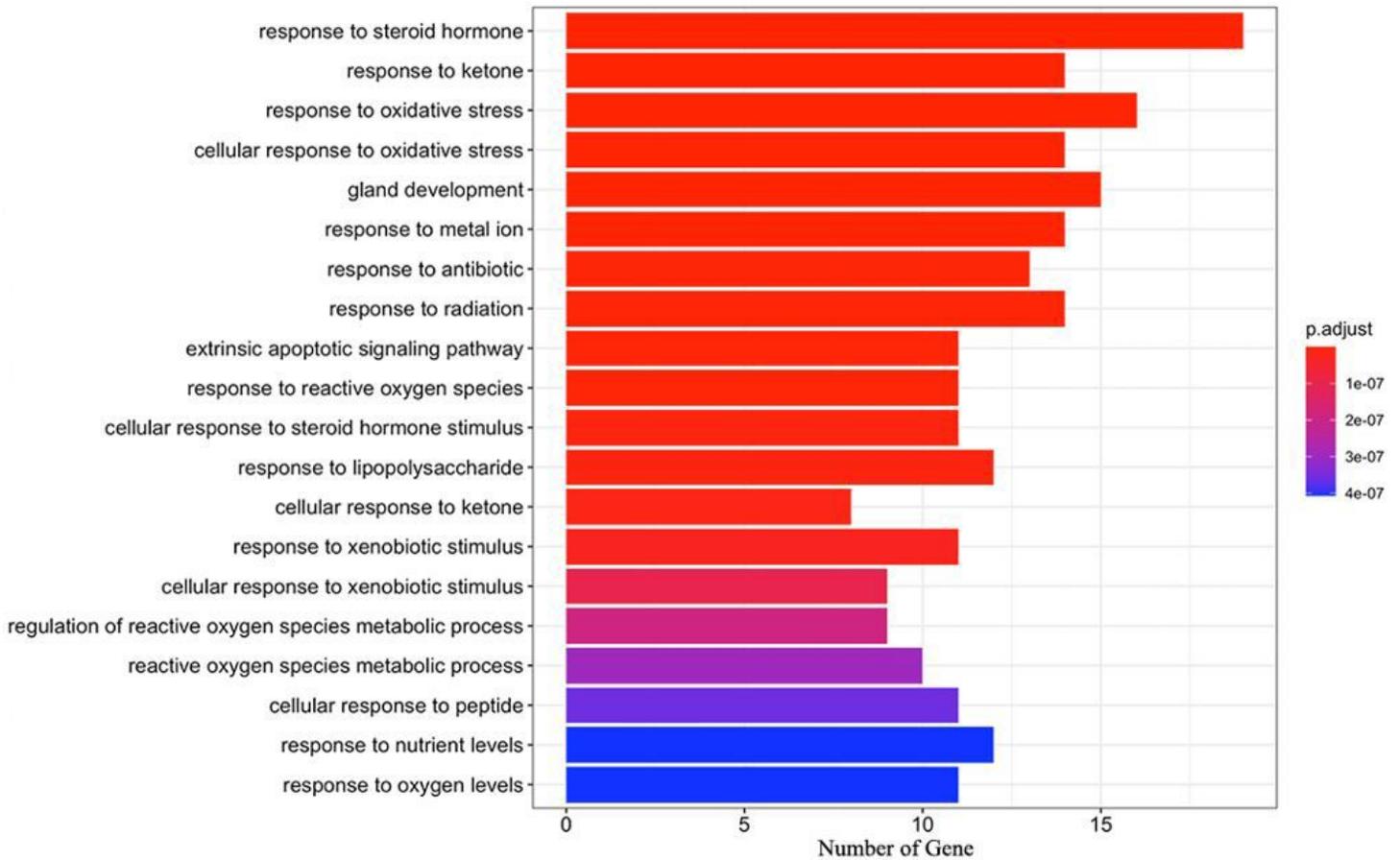
**Figure 2**

CDDP-DR common targets: (a) Venn map of CDDP-DR common targets; (b) Network of CDDP-compound-target-DR: Fifty common targets (blue diamond) were identified after merging the targets of CDDP and DR. Forty-eight compounds were identified from RS (red dot), five from PN (green dot) and one from BS (yellow dot). The size is based on the degree value.



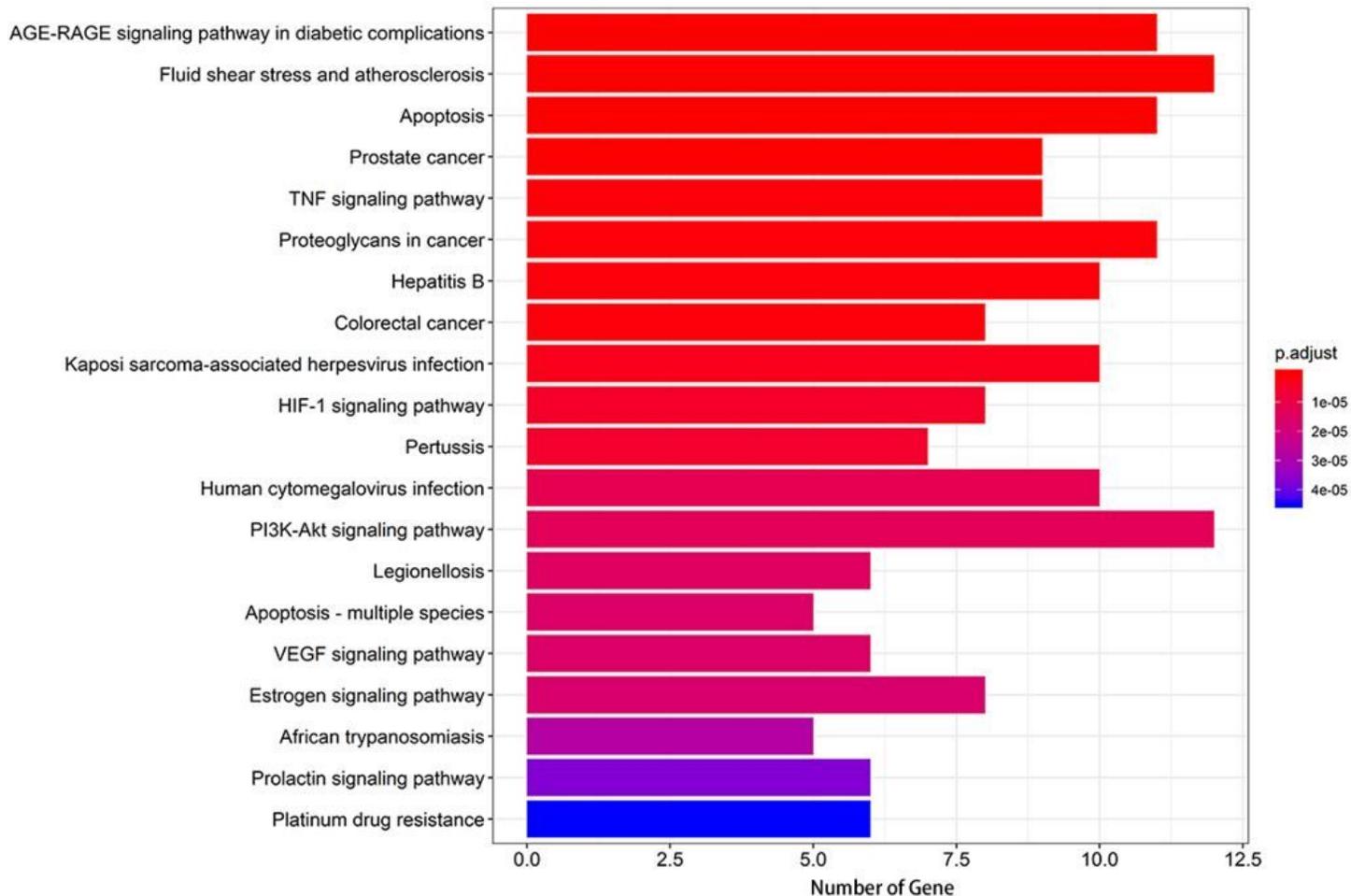
**Figure 3**

PPI network of CDDP against DR: (a) PPI network of the 50 candidates. The bigger and darker nodes represent higher degree value; (b) PPI merge network of CDDP against DR. PPI network was merged with the CDDP-compound-target-DR network (Figure 2b). The size is based on the degree value.



**Figure 4**

The biological process of candidate targets of CDDP against DR. The top 20 GO functional categories with P-adjust < 0.05 were selected.



**Figure 5**

KEGG pathway enrichment of candidate targets of CDDP against DR. The top 20 pathways with P-adjust < 0.05 were selected.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.pdf](#)