Effective Components-Targets-Mechanism-Chinese Prescription Strategy (ETMC), A New Strategy for Chinese Prescription Development: A Case Study in Danlou Tablet

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Research

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Effective Components-Targets-Mechanism-Chinese Prescription Strategy (ETMC), A New Strategy for Chinese Prescription Development: A Case Study in Danlou Tablet

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Abstract

Background: Chinese prescription is a combination medicine used by Chinese medical workers to treat various diseases and has saved countless human lives. By studying the effective substances, therapeutic targets, and mechanism of Chinese prescription, Western researchers can better understand the great value of Chinese prescription.

Methods: In this study, a new strategy was proposed for the development of Chinese prescription: the effective components (E)-targets (T)-mechanism (M)-Chinese prescription (C) strategy, namely the ETMC strategy.

Results: The proposed strategy used the chemical compositions of the Chinese prescription as the source of ligands to predict the corresponding targets for discovering the mechanism of Chinese prescription, which was helpful to further screen out effective substances from the chemical compositions of Chinese prescription. Here an example on development of Danlou tablet was performed to introduce the application of ETMC.

Conlusions: A novel strategy for Chinese prescription development, ETMC, along with its application was provided in the current study, which contributed to the further development, wider application and internationalization of Chinese prescription.

Background

Chinese prescription (CP), also known as Chinese formula (CF), is a special kind of medicine that has been clinically used in China for thousands of years, contributed to the prosperity and civilization of the China and the surrounding countries (Luan et al., 2020). Its advantages of definite curative effects and acceptable adverse effects have gradually attracted the attention of Western medical workers on CP (Xiong et al., 2017). But the concern of Western medical workers on CP has not yet

turned into full recognition, due to the lack of clear effective components, specific targets and exact therapeutic mechanism for CP and even Chinese medicine (Chan et al., 2010; Hao et al., 2017). With the rise of network pharmacology, this disadvantaged situation of CP has been partially improved (Luo et al., 2020; Tao et al., 2013). However, the range of effective components, targets, and mechanisms of the CP predicted by the classic network pharmacology strategy is too large to be further narrowed, which makes it difficult to choose a suitable research direction from it, which hinders the basic research and modernization of CP. However, the effective ingredients, targets, and mechanisms determined by this strategy of studying the effective ingredients and mechanisms of traditional Chinese medicine compound prescriptions through network pharmacology is too large to be further narrowed, which makes it difficult for medical workers to choose a suitable research direction from them, thereby Inhibit basic research and modernization of CP. Therefore, it is imperative to propose a new CP development strategy that can help focus research directions.

Here, we propose the effective components (E)-targets (T)-mechanism (M)-Chinese prescription (C) strategy, abbreviated as ETMC. ETMC refers to a novel CP development strategy and its brief steps are as follows: Firstly, the chemical compositions of the CP are used as the source of ligands (also the candidate effective components) to reversely fish the corresponding targets. Targets obtained in the preceding step are further analyzed by bioinformatics technology to determine a number of physiological and pathological functions-related signal pathways. Then molecular docking is performed between all chemical compositions of CP and targets on different signal pathways. According to the molecular docking results, a few chemical compositions that are superior to the original ligand of the target are screened out from all chemical component of CP, which considered as effective components of CP. Similarly, corresponding targets of these effective components are also screened out from all the targets, which considered as specific targets of CP. Besides, an example on development of Danlou tablet (DLT), one of the commercial CP against cardiovascular diseases was performed to better demonstrate the application of ETMC strategy.

Methods

Collection of Chemical Compositions of DLT

The collection of chemical compositions of DLT was based on the previous research (Dong et al., 2013). Then compositions mentioned above were further classified according to their herbal source which determined via Chinese medicine and chemical composition database from Shanghai Institute of organic chemistry of CAS [http://www.organchem.csdb.cn.].

Target Prediction and Selection

Target prediction of chemical compositions of DLT was performed via SwissTargetPrediction webtool [http://www.swisstargetprediction.ch] (Daina et al., 2019). The most probable macromolecular targets of chemical compositions of DLT were estimated which founded on a combination of 2D and 3D similarity with a library of 370'000 known actives on more than 3000 proteins from three different species. Then intersection analysis was performed on targets predicted by different chemical compositions of DLT, and those targets that had at least five intersections were selected for subsequent research.

Bioinformatics Analysis

Protein-protein interaction (PPI) information of selected targets mentioned above was evaluated by the online tool STRING (Search Tool for the Retrieval of Interacting Genes) (Szklarczyk et al., 2015). Gene ontology analysis (GO) was performed via STRING and verified by an online bioinformatic tool DAVID [https://david.ncifcrf.gov/home.jsp] (Huang et al., 2009).

Molecular Docking

The three-dimensional geometric coordinates of the X-ray crystal structures of selected targets, ACHE (PDB ID: 4ey7), ADORA1 (5n2s), AKR1B1 (1ah3), AKR1B10 (1zua), ALOX15 (1lox), CBR1 (1wma), CYP19A1 (3s7s), EGFR (3lzb), ESR1 (1qku), FYN (2dq7), HSD17B1 (6mnc), MET (3cth), PTGS1 (2oye), SQLE (6c6p), TTR (6e6z) were obtained from the Protein Data Bank (PDB). Molecular docking was performed by Accelrys Discovery Studio (version 3.0; Accelrys, San Diego, CA, USA). Chemical compositions of DLT were energy minimized with the CHARMm force field and the CDOCKER protocol was performed for semiflexible molecular docking. Based on the docking results, chemical compositions whose –CDOCKER Interaction Energy scores were greater than the targets' original ligands score were screened out as effective components of DLT.

Results

Collection of Chemical Compositions of DLT

Dan-Lou Tablet (DLT), a commercial CP developed from *Gualou Xiebai Baijiu Tang* has been clinically used for the treatment of cardiovascular diseases such as Coronary disease, myocardial infarction and so on (Mao et al., 2016). DLT is composed of ten herbs: *Trichosanthes kirilowii* Maxim. (Gualoupi), *Allium macrostemon* Bge. (Xiebai), *Pueraria lobata* (Willd.) Ohwi (Gegen), *Salvia miltiorrhiza* Bge. (Danshen), *Astragalus membranaceus* (Fish.) Bge. var. mongholicus (Bge.) Hsiao (Huangqi), *Alisma orientalis* (Sam.) Juzep. (Zexie), *Drynaria fortune* (Kunze) J. Sm. (Gusuibu), *Ligusticum chuanxiong* Hort. (Chuanxiong), *Paeonia lactiflora* Pall. (Chishao) and *Curcuma longa* L. (Yujin) (Li et al., 2019b). According to the previous report, the chemical compositions of DLT were classified according to their herbal source **(Figure 1 and Supplementary Figure 1)**. The classification results showed that the chemical compositions in DLT were mainly derived from the Minister drugs Gegen and Danshen, and few chemical compositions from the Monarch drug Gualoupi and Minister drug Yujin were detected in DLT.

Prediction and Selection of Targets Corresponding to Chemical Compositions of DTL

Next, target fishing was performed to predict corresponding targets of all chemical compositions of DLT. The results showed that a total of 529 targets were predicted, including the same target predicted by different chemical components. Chinese medicine has the advantage of “multiple targets effect”. And the “multiple targets effect” here not only refers to multiple targets corresponding to multiple chemical components, but also refers to a single target corresponding to multiple chemical components. According to the "single-target superposition" theory of Chinese medicine, different chemical compositions of traditional Chinese medicine can be combined with a single target one after another in superposition effects of concentration and time differences, which is one of the key reasons why traditional Chinese medicine can play a highly effective and long-lasting therapeutic effect (Cai et al., 2015). Therefore, intersection analysis was performed on targets predicted by different chemical compositions of DLT, and those targets that had at least five intersections were selected as key targets for subsequent research (Figure 2).

Protein–protein Interaction Network (PPI) and Gene Ontology (GO) Analysis

In order to clarify the connection between key targets selected above and biological functions, PPI network complex was constructed with selected key targets and their corresponding chemical compositions of DLT (Figure 3). Gene ontology analysis (GO) is a commonly used for defining genes or protein product to identify unique biological properties of high-throughput transcriptome or genome data (Ashburner et al., 2000). Therefore, GO analysis was performed after construction of PPI network. Results showed that about half of all key targets were particularly enriched in regulation of lipid metabolic process and the oxidation-reduction process, which were the two main biological processes that DLT could potentially regulate (Figure 3).

Effective Components Screening from Chemical Compositions of DLT

Furthermore, effective components of DLT were screened out from chemical compositions of DLT via molecular docking. Results showed that certain targets were regulated by corresponding chemical components of DLT, whose regulatory effects were better than the original ligands of the targets (Figure 4 and Supplementary Table 1). So far, the number of potential targets of DLT has been significantly limited, and effective components of certain targets were determined among several chemical compositions of DLT.

The Relationship between Key Targets and Effective Components of DLT against Cardiovascular Diseases

Multiple targets were reported to be associated with cardiovascular diseases (CD), including potential targets of DLT, ALOX15 (myocardial infarction), ACHE (coronary diseases), ESR1 (coronary diseases), ADORA1 (myocardial ischaemia), AKR1B1 (myocardial ischaemia) and AKR1B10 (myocardial ischaemia) (Halade et al., 2017; Işık et al., 2019; Li et al., 2019a; Louttit et al., 1999; Ananthakrishnan et al., 2009). Here, by ETMC strategy, it was demonstrated that the anti-cardiovascular effects of Chinese prescription DLT were due to its regulation on CD-related targets by eight effective components of DLT (Figure 5).

Discussion

Chinese medicine has gradually attracted widespread attention from Chinese and Western medical researchers due to its excellent efficacy and minimal side effects. Revealing the effective components of Chinese medicine not only helps the further development of Chinese medicine, but also facilitates the modernization and internationalization of Chinese medicine. In this study, a new strategy for Chinese prescription development, ETMC, was proposed to screen out the effective components with potential therapeutic effects from the complex chemical compositions of traditional Chinese medicine, which contributed to clear directions for Chinese medicine researches.

CP is a special administration mode of Chinese medicine based on the theory of traditional Chinese medicine, which is a combination of different Chinese medicines to exert better, longer-lasting and safer effects than using a single Chinese medicine alone. However, the unclear pharmacodynamic mechanism and targets of CP limits the expansion of its indications, and this obstacle can be eliminated through the proposed ETMC strategy, a combined application of computer simulation technology, network pharmacology and bioinformatics. ETMC strategy is beneficial for

determination of the pharmacodynamic targets corresponding to effective components in CP. And biological processes that involve these targets are useful to determine the mechanism CP.

Multiple studies reported that the association of chemical compositions of CP with potential targets can be predicted through classic network pharmacology research process. However, it is difficult to determine fewer but more valuable effective components and key targets from a large number of chemical components and potential targets in the prediction results of network pharmacology. In the example of applying the ETMC strategy in this study, a few effective components of DLT and their targets closely related to cardiovascular diseases were identified. Most of effective components of DLT are able to regulate multiple targets, which was consistent with "single-target superposition" theory of Chinese medicine. And targets corresponding to effective components of DLT have also been reported to be closely related to cardiovascular disease, the indication for DLT. Therefore, the ETMC strategy, as a simple and important new CP development strategy, needs to be promoted.

Conslusions

A novel strategy for CP development, ETMC, along with its application was provided in the current study, which contributed to the further development, wider application and internationalization of CP.

Abbreviations

CP, Chinese prescription; CF, Chinese formalua; ETMC, effective components-targets-mechanism-Chinese prescription strategy; DLT, Danlou tablet; PPI, protein-protein interaction; STRING, search tool for retrieval of interacting genes; GO, gene ontology.

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Author’s contributions

YG conceived the concept of this article. YG performed all the experiments and wrote the manuscript. YJ designed and made all figures. YG gave comprehensive advice and critically revised the manuscript. All authors approved the final version of this manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declared no competing financial or commercial conflict of interest.

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FIGURE LEGENDS & TABLES

Figure legends

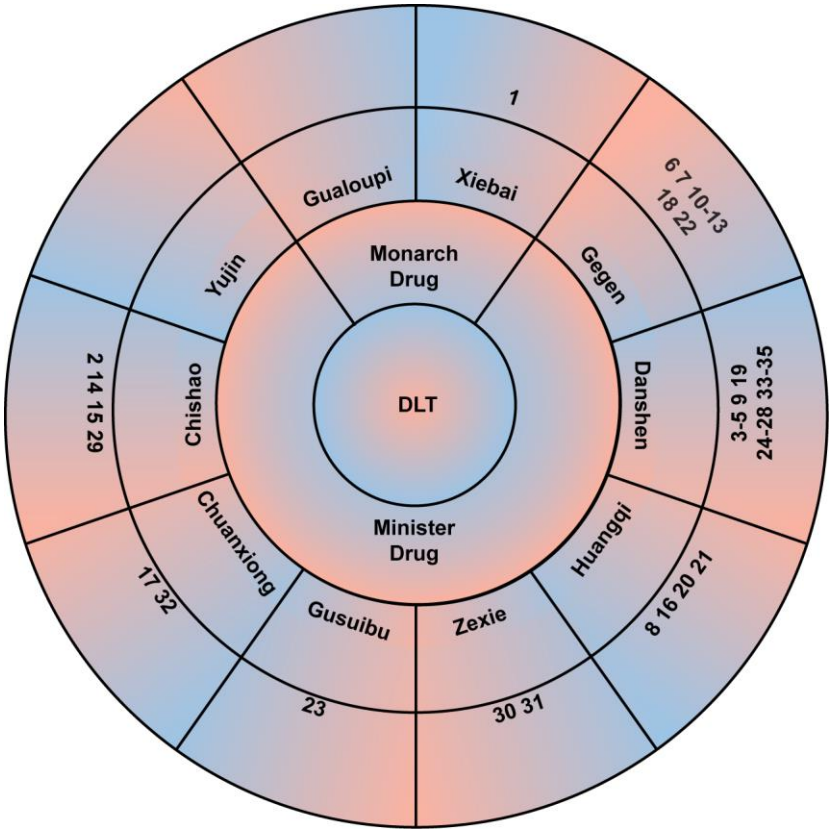
Figure 1 Collection and classification of chemical compositions of DLT according to their herbal source. 1, adenosine; **2**, gallic acid; **3**, danshensu; **4**, 5-HMF; **5**, protocatechuic acid; **6**, daidzein; **7**, 3′-hydroxyl puerarin; **8**, chlorogenic acid; **9**, protocatechuic aldehyde; **10**, puerarin; **11**, mirificin; **12**, 3′-methoxy puerarin; **13**, genistein; **14**, paeoniflorin; **15**, ethyl gallate; **16**, calycosin; **17**, ferulic acid; **18**, genistin; **19**, salvianolic acid; **20**, formononetin; **21**, 1,3-dicaffeoylquinic acid; **22**, 4′-methoxy puerarin; **23**, naringin; **24**, salvianolic acid E; **25**, rosmarinic acid; **26**, tanshindiol C; **27**, salvianolic acid B; **28**, salvianolic acid C; **29**, benzoyl paeoniflorin; **30**, 11-anhydro-alisol F; **31**, alisol C; **32**, senkyunolide A; **33**, dihydrotanshinone I; **34**, tanshinone I; **35**, cryptotanshinone

Figure 2 The compounds-targets network of chemical compositions of DLT and their key targets. The yellow circles represented chemical compositions of DLT. The pink rectangles represented the protein targets. Every chemical composition of DLT and its predicted targets were connected by grey straight lines.

Figure 3 PPI network constructed with key targets of DLT and GO analysis. Red cycles represented genes involved in lipid metabolic process (GO-term, GO: 0006629; count in gene set, 20 of 1192; false discovery rate, 9.01E-08), blue cycles represented genes involved in oxidation-reduction process (GO-term, GO: 0055114; count in gene set, 16 of 923; false discovery rate, 1.67E-06).

Figure 4 Modulatory effects of effective components of DLT on key targets involved in biological processes regulated by DLT. All the key targets of DLT were divided into two parts based on the biological processes they were involved in. The pink rectangles represented the key targets of DLT. The yellow rectangles below each pink rectangle represented effective components of DLT that could regulate the key target.

Figure 5 ETMC network diagram of DLT against cardiovascular diseases. The relationship between herbal source, effective components, potential targets and indications of DLT were shown in this diagram. Green lines linked effective components of DLT (yellow rectangles) to their herbal source (brown rectangles). Red lines linked effective components of DLT (yellow rectangles) to their targets (pink rectangles). All the targets were classified according to their related diseases.



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297 **Figure 1**

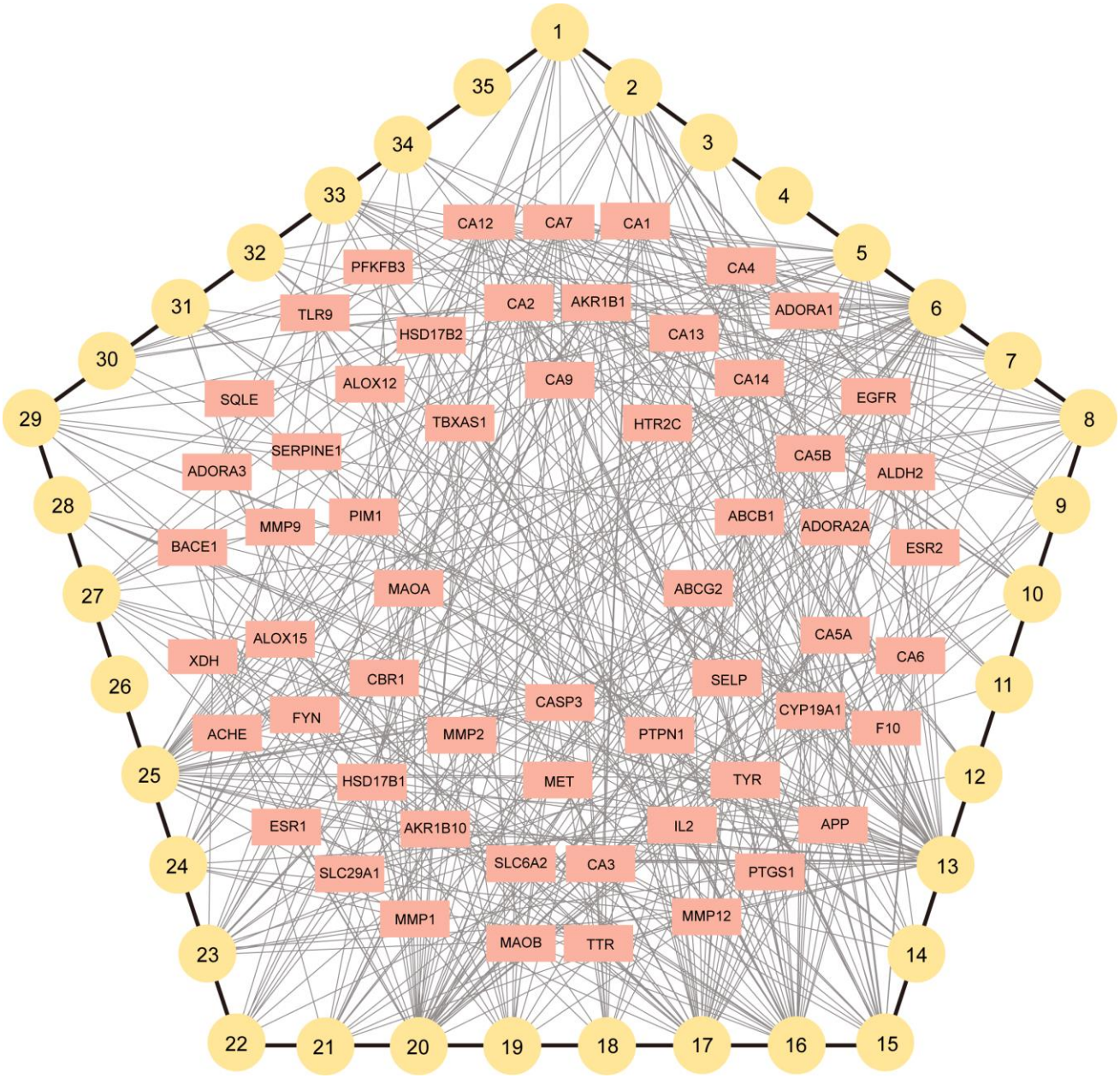
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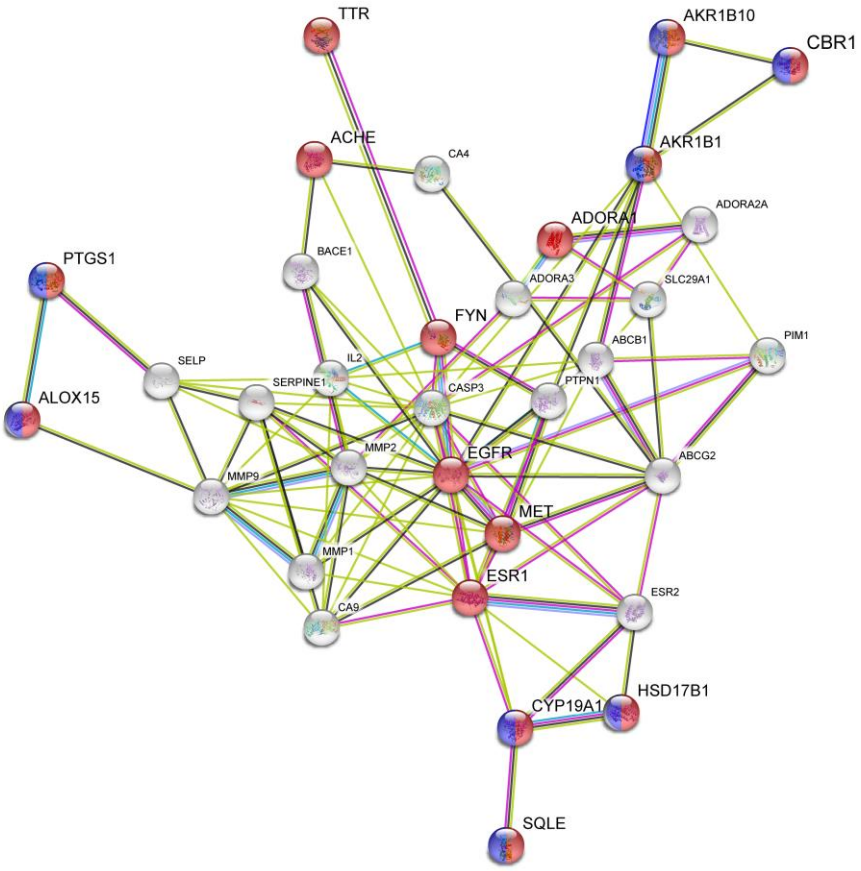
Figure 2



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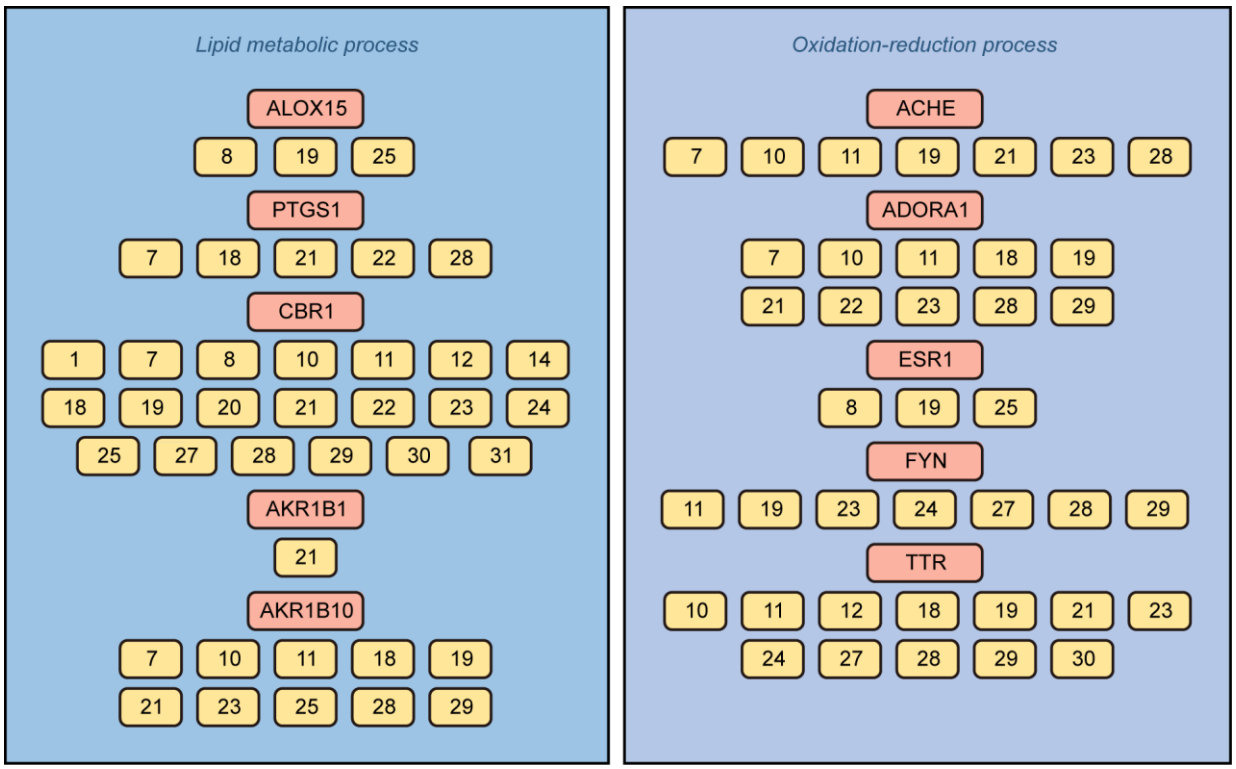

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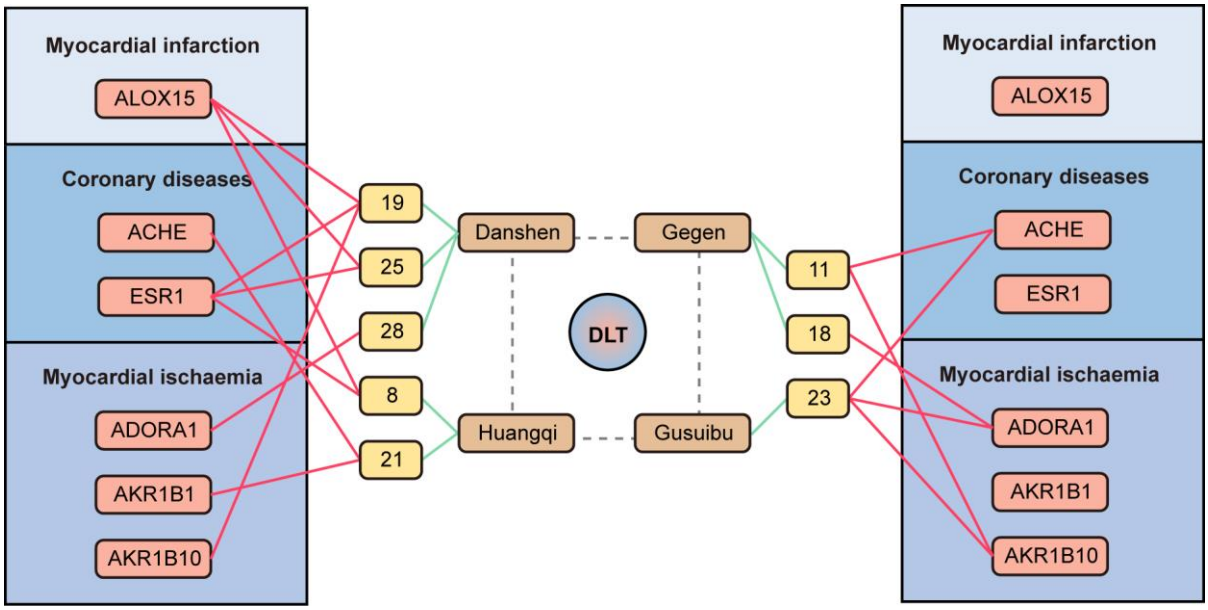

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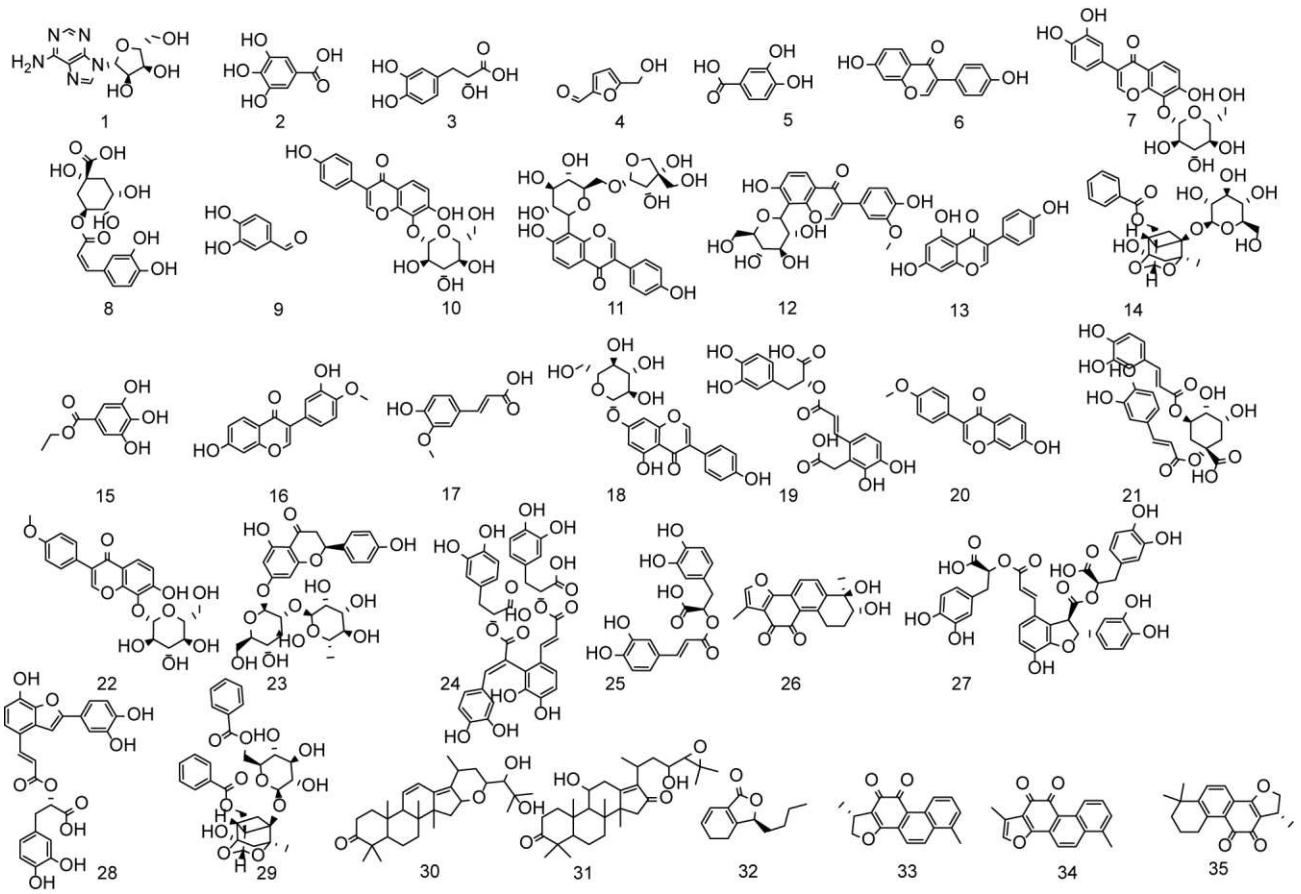
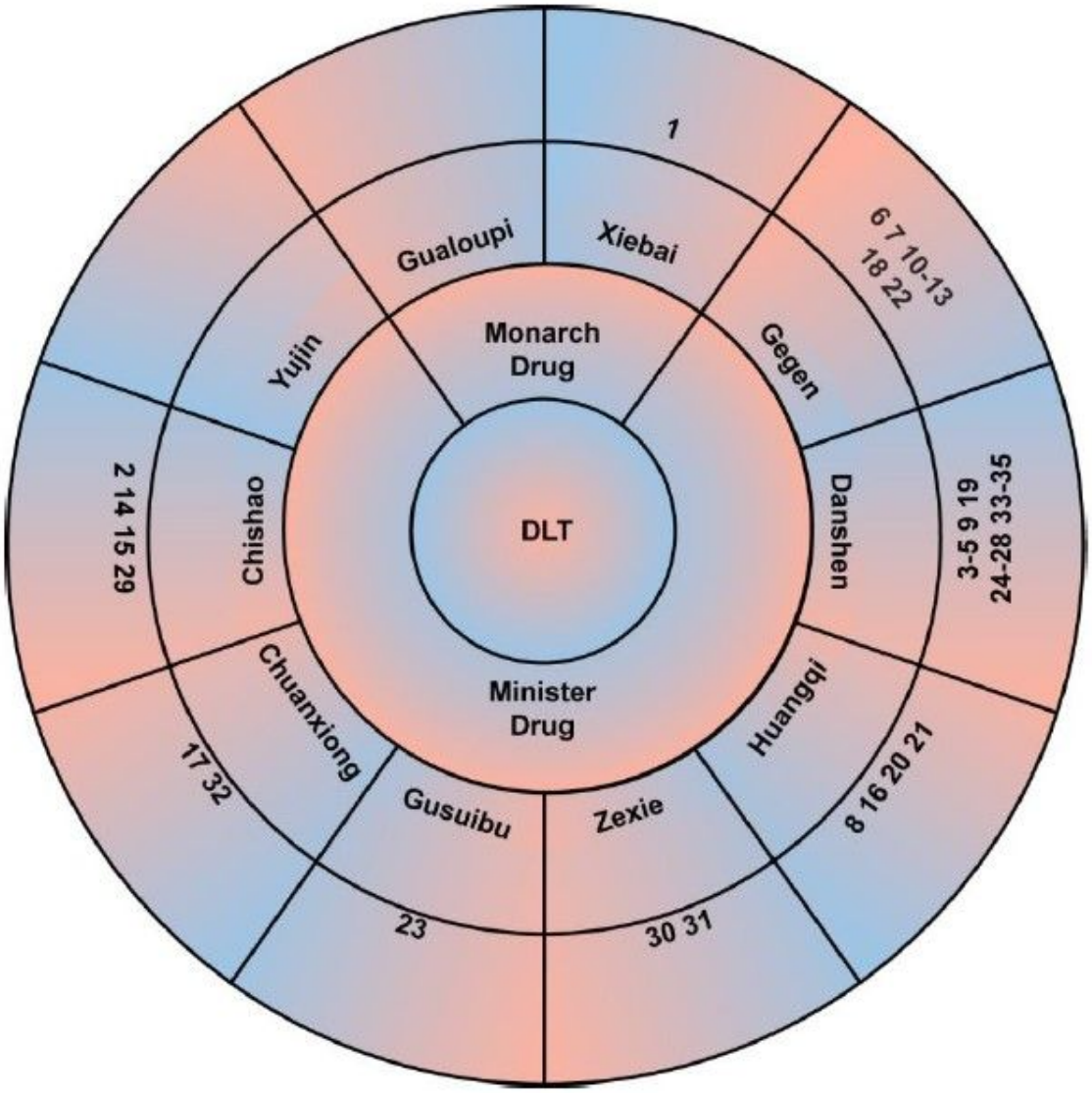


Supplementary Figure 1

Figures



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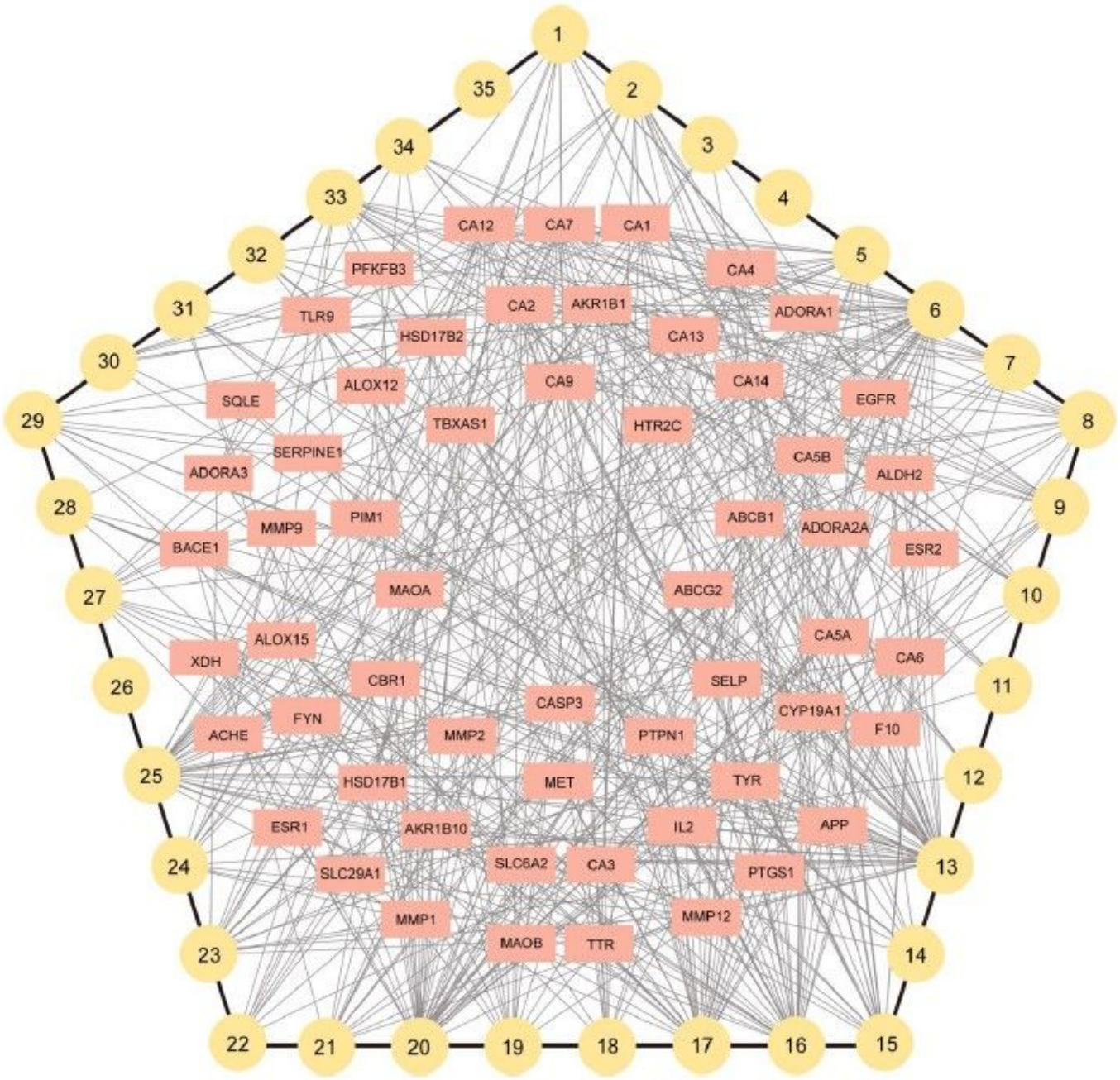

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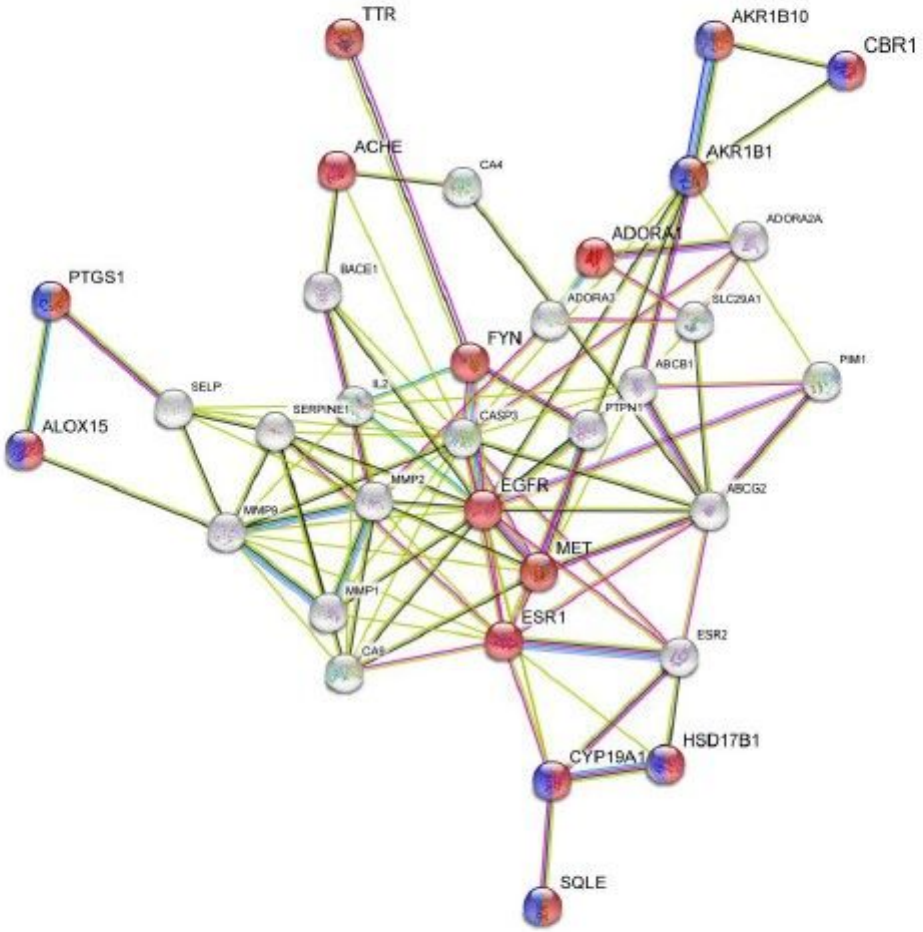

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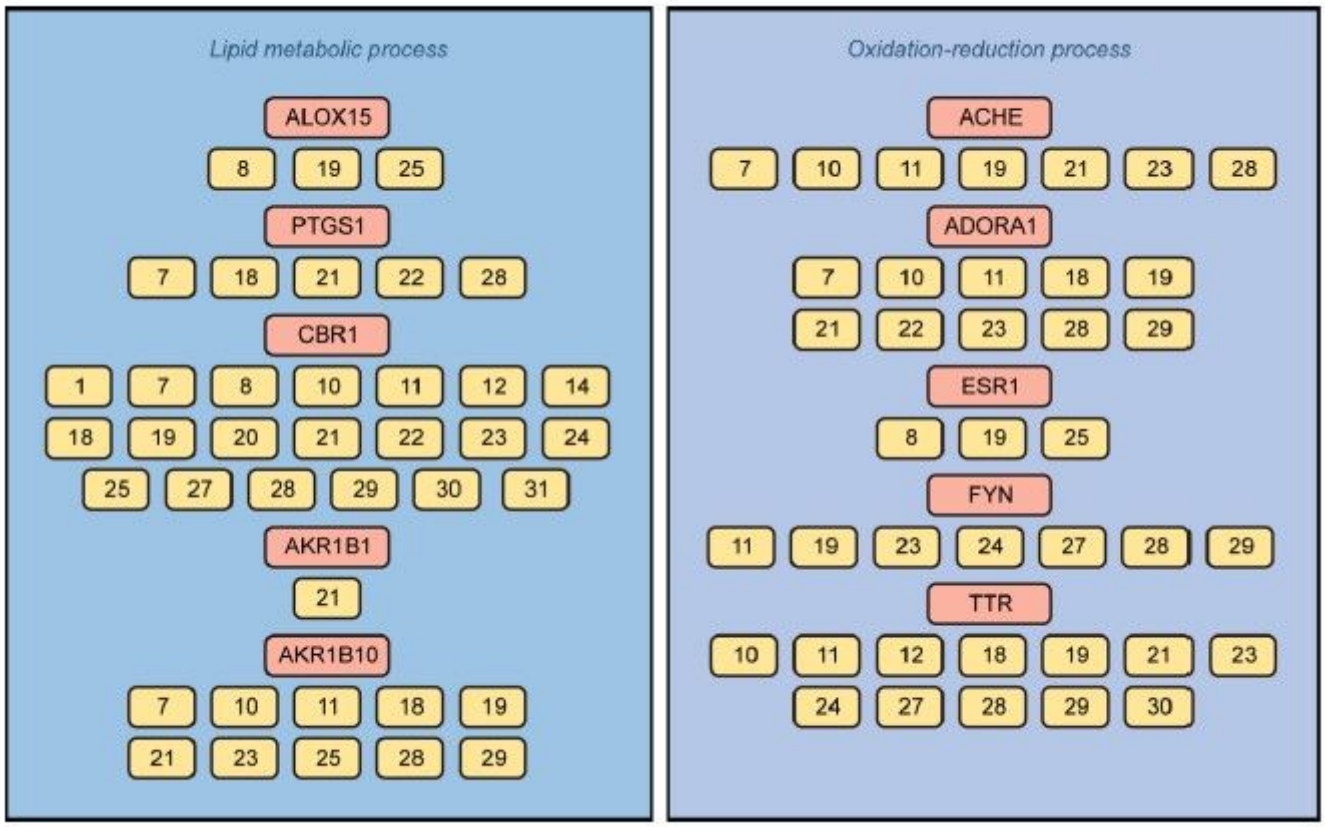

Figure 4

Modulatory effects of effective components of DLT on key targets involved in biological processes regulated by DLT. All the key targets of DLT were divided into two parts based on the biological processes they were involved in. The pink rectangles represented the key targets of DLT. The yellow rectangles below each pink rectangle represented effective components of DLT that could regulate the key target.

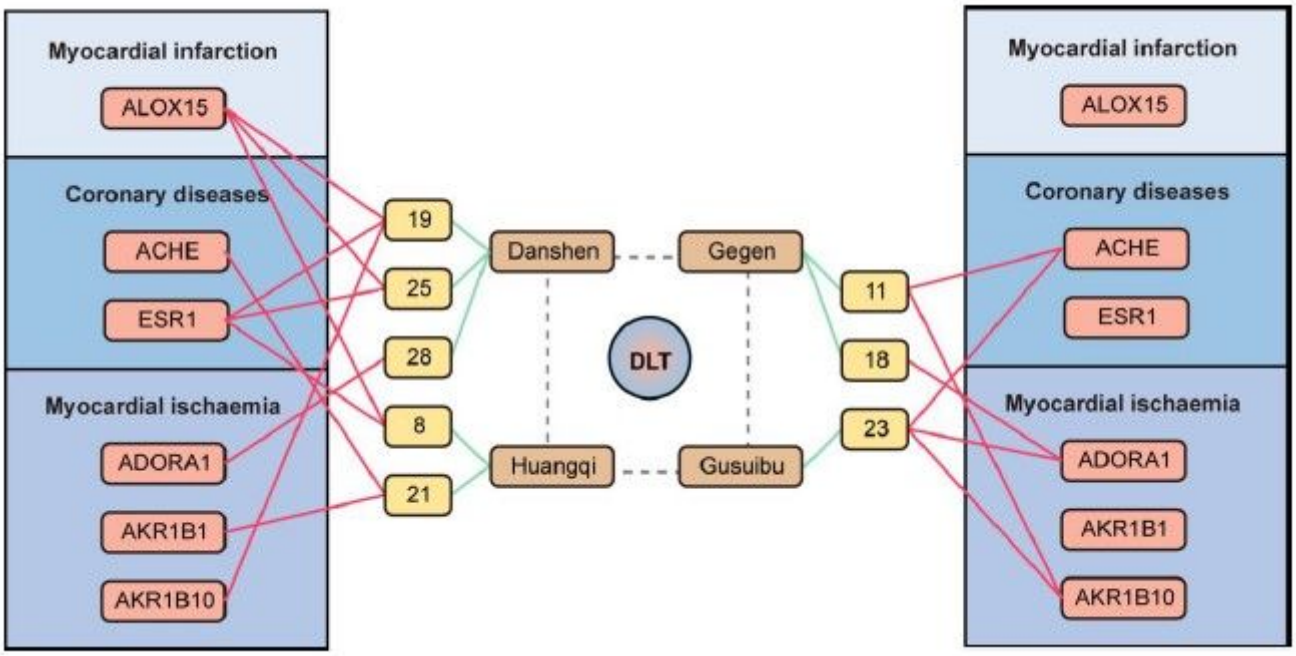

Figure 5

ETMC network diagram of DLT against cardiovascular diseases. The relationship between herbal source, effective components, potential targets and indications of DLT were shown in this diagram. Green lines linked effective components of DLT (yellow rectangles) to their herbal source (brown rectangles). Red lines linked effective components of DLT (yellow rectangles) to their targets (pink rectangles). All the targets were classified according to their related diseases.