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Research paper

Deciphering the multi-scale mechanisms of *Tephrosia purpurea* against polycystic ovarian syndrome (PCOS) and its major psychiatric comorbidities: Studies from network pharmacological perspective

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ABSTRACT

Tephrosia purpurea (T. purpurea), a plant belonging to Fabaceae (pea) family, is a well-known Ayurvedic herb and commonly known as Sarapunkha in traditional Indian medicinal system. Described as "*Sarwa wranvishapaka*", *i.e.* having a capability to heal all types of wounds, it is particularly recognized for its usage in splenomegaly. Towards exploring the comprehensive effects of *T. purpurea* against polycystic ovarian syndrome (PCOS) and three comorbid neuropsychiatric diseases (anxiety, depression, and bipolar disorder), its constituent phytochemicals (PCs) were extensively reviewed and their network pharmacology evaluation was carried out in this study. The complex regulatory potential of its 76 PCs against PCOS is enquired by developing and analyzing high confidence tripartite networks of protein targets of each phytochemical at both pathway and disease association scales. We also developed a high-confidence human Protein-Protein Interaction (PPI) sub-network specific to PCOS, explored its modular architecture, and probed 30 drug-like phytochemicals (DPCs) having multi-module regulatory potential. The phytochemicals showing good binding affinity towards their protein targets were also evaluated for similarity against currently available approved drugs present in DrugBank. Multi-targeting and synergistic capacities of 12 DPCs against 10 protein targets were identified and evaluated using molecular docking and interaction analyses. Eight DPCs as a potential source of PCOS and its comorbidity regulators are reported in *T. purpurea.* The results of network-pharmacology study highlight the therapeutic relevance of *T. purpurea* as PCOS-regulator and demonstrate the effectiveness of the approach in revealing action-mechanism of Ayurvedic herbs from holistic perspective.

1. Introduction

Polycystic ovarian syndrome (PCOS), a genetic condition of ovarian dysfunction is the most common form of endocrinopathy with a global prevalence of 6–10% amongst women of reproductive age (Goodarzi et al., 2011). The complex and heterogeneous nature of PCOS is associated with both non-reproductive and reproductive morbidity. Apart from anovulation, amenorrhea, hirsutism (hyperandrogenism), and infertility observed in women with PCOS, risen BMI is prevalent in 30–70% of cases (Vrbikova and Hainer, 2009). Long-term morbidity factors associated with PCOS include sub-fertility, obstetrical complications, diabetes mellitus, cardiovascular disease, malignancy, and psychiatry in some cases.

Stein and Leventhal, in 1935, were the first to describe PCOS as a combination of signs and symptoms related to androgen excess and dysfunction of ovaries, hence called as Stein- Leventhal syndrome

Abbreviations: ADMET, (Absorption Distribution Metabolism Excretion, and Toxicity); BPs, Biochemical-pathways; CADD, Computer-aided drug-design; DPCs, Drug-like phytochemicals; GDA, Gene-disease association; GO, Gene Ontology; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IMPPAT, (Indian medicinal plants, and therapeutics); KDD, Knowledge-based data discovery; MODE, Molecular complex detection algorithm; NIH, National Institutes of Health; OIA, Ovulation-inducing agent; PCIDB, Phytochemical interaction database; PCOS, Polycystic ovarian syndrome; PPI, Protein-protein interaction; PCOS-PIN, PCOS specific PPI network; PCs, Phytochemicals; PP-DA, PCOS-protein—Disease-association; T_c, Tanimoto coefficient; TCMSP, Traditional Chinese Medicine Systems Pharmacology; *T.purpurea*, *Tephrosia purpurea*.

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