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Integrating Network Pharmacology and *In Silico* Molecular Docking Approaches to Establish Mechanism of Bioactive Compounds of *Carthamus tinctorius* L in the Treatment of Arteriovenous Fistula Stenosis

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SUMMARY. In recent years, the study of traditional Chinese medicine (TCM) on arteriovenous fistula stenosis (AFS) has gradually deepend, and more and more TCM drugs are being used in the treatment of the disease. The current research aims to explore the lead candidates of *Carthamus tinctorius* L (CT) to develop their probable mechanisms of CT involved in the treatment of AFS relied on integrating network pharmacology and in silico molecular docking analysis. The bioactive active chemical ingredients and potential protein targets of CT were obtained by using Traditional Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP). Therapeutic targets concerned to AFS were procured from DisGeNet and OMIM databases to develop protein-protein interaction (PPI) and drug-ingredient-target-disease networks by Cytoscape 3.8.2. The KEGG platform which stands for Kyoto Encyclopedia of Genes and Genomes was used for analysis of Gene Ontology (GO) and identifying common targets of CT-AFS to bio-enrichment analysis through metascape platform. Finally, the shortlisted macromolecular targets and their corresponding active ingredients were analyzed by molecular docking analysis. A total of 643 target genes related to AFS were obtained from DisGeNet and OMIM. The top 10 targets out of common 58 targets related to CT-AFS were obtained by intersecting therapeutic targets based upon the highest degree within the PPI network were TNF, IL6, JUN, AKT1, TP53, IL1B, CASP3, EGFR, MMP9 and CCL2. Furthermore, the molecular docking analysis has revealed that beta-sitosterol and stigmasterol were found to be potential leads in the CT with high values of binding energy with akt-1 target protein indicating its potential as a promising lead. It has been concluded that based upon the integration of network pharmacology with molecular docking, it has been revealed the beta-sitosterol as well as stigmasterol of CT were responsible for the therapeutic potential for the treatment of AFS via interacting with the multiple targets.

RESUMEN. En los últimos años, el estudio de la medicina tradicional china (MTC) sobre la estenosis de la fístula arteriovenosa (SAF) se ha profundizado gradualmente y cada vez se utilizan más fármacos de la MTC en el tratamiento de la enfermedad. La investigación actual tiene como objetivo explorar los principales candidatos de Carthamus tinctorius L (CT) para desarrollar sus probables mecanismos de CT implicados en el tratamiento de AFS basándose en la integración de la farmacología de red y el análisis de acoplamiento molecular in silico. Los ingredientes químicos activos bioactivos y los posibles objetivos proteicos de la CT se obtuvieron utilizando la pla-

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taforma de análisis y base de datos farmacológicos del sistema de medicina tradicional china (TCMSP). Cytoscape 3.8.2 adquirió objetivos terapéuticos relacionados con AFS de las bases de datos DisGeNet y OMIM para desarrollar interacciones proteína-proteína (PPI) y redes fármaco-ingrediente-objetivo-enfermedad. La plataforma KEGG, que significa Enciclopedia de genes y genomas de Kyoto, se utilizó para el análisis de la ontología genética (GO) y para identificar objetivos comunes de CT-AFS para el análisis de bioenriquecimiento a través de la plataforma Metascape. Finalmente, las dianas macromoleculares preseleccionadas y sus correspondientes ingredientes activos se analizaron mediante análisis de acoplamiento molecular. Se obtuvo un total de 643 genes diana relacionados con AFS de DisGeNet y OMIM. Los 10 objetivos principales de los 58 objetivos comunes relacionados con CT-AFS se obtuvieron mediante la intersección de objetivos terapéuticos basados en el grado más alto dentro de la red PPI: TNF, IL6, JUN, AKT1, TP53, IL1B, CASP3, EGFR, MMP9 y CCL2. Además, el análisis de acoplamiento molecular ha revelado que se descubrió que el beta-sitosterol y el estigmasterol eran pistas potenciales en la TC con valores elevados de energía de unión con la proteína diana akt-1, lo que indica su potencial como pista prometedora. Se ha llegado a la conclusión de que, basándose en la integración de la farmacología en red con el acoplamiento molecular, se ha revelado que el beta-sitosterol y el estigmasterol de la CT eran responsables del potencial terapéutico para el tratamiento del SFA mediante la interacción con múltiples objetivos.