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**File: ■ Licorice (*Glycyrrhiza glabra*, Fabaceae)
■ Blood Pressure
■ Systematic Review/Meta-analysis**

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RE: Constituents of Licorice Root Reveal Different Effects on Blood Pressure

Wu T, Yang J, Xia J, Sun G. Effects of licorice functional components intakes on blood pressure: A systematic review with meta-analysis and NETWORK toxicology. *Nutrients*. November 2, 2024;16(21):3768. doi:10.3390/nu16213768.

Licorice (*Glycyrrhiza glabra*, Fabaceae) root is consumed as food and medicine throughout the world. Often used to prevent or treat gastrointestinal, respiratory, and liver diseases, licorice consumption is not without potential adverse effects (AEs) that include hypokalemia, hypertension (HT), and metabolic alkalosis. Glycyrrhizic acid (GA) and licorice flavonoids (LF) are suspected to be responsible for these AEs which are dose-dependent and can be influenced by individual genes. These authors conducted a systematic review and meta-analysis on the impact of GA and LF-based interventions on systolic blood pressure (SBP) and diastolic blood pressure (DBP) by using network toxicology, transcriptomic databases, and multiple online databases to explore the etiology of licorice-induced blood pressure fluctuations.

PubMed, Cochrane Library, Medline, Embase, EBSCO, ScienceDirect, and Web of Science databases were searched from inception to August 31, 2024. Eligible studies were randomized, population-controlled trials that used licorice or licorice components orally. Excluded studies lacked baseline or post-intervention data, full texts, or conventional control groups, or were observational studies, case reports, reviews, abstracts, or animal studies. Cochrane Risk of Bias Tool was utilized for assessment.

The Pro Tox-3.0 database was used to find organ-specific toxicity and toxicological endpoints of GA; GeneCards, Online Mendelian Inheritance in Man (OMIM), and Therapeutic Target Database (TTD) were used to find HT-related genes; and the gene expression omnibus (GEO) database was used to retrieve the GSE71994 dataset. The top 50 genes were identified using the STRING database, and these biomarkers were narrowed down using support vector machine-recursive feature elimination algorithm (SVM-Rep), Lasso Regression, and Random Forests algorithms. The interaction between GA and these HT biomarkers was then analyzed and divided into high and low groups to determine possible mechanisms of action.

Of the 490 original articles analyzed, eight articles were selected for quantitative analysis. One article was categorized into three studies according to dose; another, into

five studies. A third article was categorized into two studies according to population. A total of 14 studies were included for analysis.

Five studies analyzed the efficacy of GA on SBP and DBP. Supplementation with GA increased SBP ($P < 0.001$) and DBP ($P < 0.001$) significantly compared to control. Low heterogeneity was found. Nine studies analyzed the efficacy of LF on SBP and DBP. No significant between-group differences were seen. There was significant heterogeneity among studies.

Subgroup analysis revealed a correlation between GA intake, intervention duration, and abnormal elevations in SBP. A correlation between GA intake and abnormal elevations in DBP was also observed; however, it was not associated with duration. LF could not be analyzed due to high heterogeneity. There was low risk of bias for random sequence generation ($n = 2$), allocation concealment ($n = 2$), blinding of participants and personnel ($n = 7$), blinding of outcome assessment ($n = 6$), incomplete outcome data ($n = 8$), selective reporting ($n = 6$), and other bias ($n = 7$). There was high risk of bias for random sequence generation ($n = 1$), allocation concealment ($n = 2$), blinding of participants and personnel ($n = 1$), blinding of outcome assessment ($n = 1$), and other bias ($n = 1$). There was unclear risk of bias for random sequence generation ($n = 5$), allocation concealment ($n = 4$), blinding of outcome assessment ($n = 1$), and selective reporting ($n = 2$).

The researchers determined that GA had potential toxicity and met level 4 oral toxicity classification; however, GA had poor bioavailability which may decrease its metabolism in vitro. Probable toxicological effects included nephrotoxicity, respiratory toxicity, cardiotoxicity, immunotoxicity, nutritional toxicity, acetylcholinesterase inhibition, pregnane X receptor modulation, and NADH-quinone oxidoreductase inhibition.

A total of 197 genes within the GSE71994 dataset were selected using the MEpink module for further analysis. One hundred twenty-two genes were found to be associated with HT from the GeneCards, OMIM, and TTD databases, and the top 50 were selected for subsequent analysis. After using the SVM-Rep, there were five genes that could be utilized as biomarkers for HT (i.e., calmodulin 3 [CALM3], cluster of differentiation 9 [CD9], growth factor independent 1B transcriptional repressor [GFI1B], myosin light chain kinase [MYLK], and Ras Suppressor Protein 1 [RSU1]).

GFI1B, MYLK, and RSU1 were significantly upregulated in patients who were hypertensive and had predictively high accuracy; however, CALM3 and CD9 demonstrated no significant differences and had lower predictive accuracy. Molecular docking between the key biomarkers and GA observed that GA can bind via hydrogen bonding, van der Waals forces, hydrophobic interactions, and electrostatic interactions to GFI1B, MYLK, and RSU1 protein receptors. Similar findings were seen with glycyrrhetic acid and GFI1B, MYLK, and RSU1. Gene set enrichment analysis revealed that GA may influence the nitrogen metabolism pathway, further contributing to abnormal fluctuations in blood pressure.

The authors conclude that GA has a negative effect on blood pressure; however, LF has no effect. They recommend that hypertensive individuals use caution with GA-containing foods. The authors declare no conflicts of interest.

—*Dani Hoots*

Referenced article can be accessed at <https://www.mdpi.com/2072-6643/16/21/3768>.