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Liquiritin: A natural flavonoid with potential cardiovascular protection

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REVIEW ARTICLE

Abstract

Liquiritin is a flavonoid glycoside extracted from traditional Chinese medicine, *Radix et Rhizoma Glycyrrhizae*. The provided evidence has demonstrated that liquiritin is found beneficial in treating cardiovascular diseases. Inflammation and oxidation play key roles in cardiovascular diseases. In this review, the natural sources, biosynthesis, pharmacology and molecular docking of liquiritin were reviewed for the first time. Additionally, we have highlighted the target prediction of liquiritin. Docking results displayed that the three targets with the largest difference in VINA scores were toll-like receptor 4 (TLR4), Kelch-like ECH-associated protein 1 (Keap-1), and adenosine monophosphate-activated protein kinase (AMPK), which suggested that liquiritin was likely to act on TLR4, Keap-1, and AMPK. The present study provides theoretical basis for future development and research of liquiriritin in treating cardiovascular diseases.

Keywords: biosynthesis; cardiovascular diseases; liquiritin; molecular docking; pharmacology

Introduction

Numerous studies have reported that oxidative stress and inflammation strongly predict ischemic heart disease (atherosclerosis, thrombosis, acute myocardial infarction, and ischemia-reperfusion injury), cardiac remodeling (hypertension, cardiac hypertrophy, cardiac fibrosis, cardiac apoptosis, and heart failure), ventricular arrhythmias and atrial fibrillation, and other adverse cardiac events. The inflammatory cascade response is recognized as a causative factor in the growth of cardiovascular diseases (Amin *et al.*, 2020; García *et al.*, 2017; Zhang and Dhalla, 2024). Improving coronary microvascular remodeling and increasing myocardial perfusion could be the promising strategies for the treatment of cardiovascular diseases (Yang *et al.*, 2023). Conventional drugs have adverse effects, and as alternatives, medicinal plants have become more acceptable by the public and medical professionals. Therefore, antioxidant and anti-inflammatory medicinal plants have potential role in the treatment of cardiovascular disease by protecting vascular endothelium, prevent lipid oxidation, and augment endogenous antioxidant system (Adegbola *et al.*, 2017).

Liquiritin is a flavonoid derived from *Radix et Rhizoma Glycyrrhizae*, which is a widely used traditional Chinese medicine with antioxidative stress, anti-inflammatory, and antiapoptosis effects (Qin *et al.*, 2022). Liquiritin has cardiovascular protective (Mou *et al.*, 2021), neuroprotective (Nakatani *et al.*, 2017), antidiabetic vascular (Zhang *et al.*, 2013), antidepressant (Liu *et al.*, 2022), skin protective (Li *et al.*, 2021), antitumor (He *et al.*, 2017),

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hypolipidemic (Weng *et al.*, 2021), anti-rheumatoid arthritis (Zhai *et al.*, 2019), pulmonary protective (Liu *et al.*, 2020), hepatoprotective (Chen *et al.*, 2019), and anti-COVID-19 effects (Zhang *et al.*, 2021). At present, studies on the pharmacological effects of liquiritin have been reported (Guo *et al.*, 2024; Qin *et al.*, 2022; Qiu *et al.*, 2024). Here, we mainly focused on the biosynthesis, cardiovascular protection, and prediction of cardiovascular disease-related targets of liquiriritin to provide theoretical basis for future development and research of liquiriritin in treating cardiovascular diseases.

Biosynthesis of Liquiritin

In the biosynthesis of liquiritin, the genes of the *G. uralensis* flavonoid pathway with known function (*GuPAL1*, *GuC4H1*, *Gu4CL1*, *GuCHS1*, *GuCHR1*, *GuCHI1*, and *GuUGT1*) are involved (Yin *et al.*, 2020). The substrate phenylalanine was incubated with GuPAL1 to produce cinnamic acid. Similarly, recombinant yeast containing GuC4H1 catalyzes the production of coumaric acid from cinnamic acid. In the presence of Gu4CL1, coumaric acid reacts with coenzyme A (CoA) to obtain coumaroyl–CoA. When the same amount of recombinant GuCHS1 and GuCHR1 as well as malonyl-CoA was added, isoliquiritigenin was obtained. GuCHI1 was able to isomerize isoliquiritigenin into liquiritigenin. Thus, GuPAL1, GUUC4H1, Gu4CL1, GuCHS1, GuCHR1, and GuCHI1 form a complete liquiritigenin biosynthesis pathway with phenylalanine as the precursor. In the last step, liquiritin was synthesized under the catalysis of GuUGT1 and the action of uracil-diphosphate glucose (UDP-glucose) as a sugar donor (Figure 1).

Liquiritin in the Prevention and Treatment of Cardiovascular Diseases

Septic cardiomyopathy

Septic cardiomyopathy (SCM) is a heart dysfunction caused by severe sepsis and septic shock that can increase the risk of heart failure with high mortality and morbidity. The pathogenesis of SCM is related to inflammatory response, apoptosis, energy metabolism disorder, and oxidative stress (Gong *et al.*, 2022). Liquiritin has good therapeutic effect on SCM. Liquiritin could attenuate lipopolysaccharide (LPS)-induced mouse cardiac dysfunction and reduce mortality based upon the restoration of *ejection fraction* (EF), fractional shortening (FS), left ventricular end-diastolic diameter (LVEDs), heart rate, maximal rate of pressure development (dp/dtmax; mmHg/s) and maximal rate of pressure decay (dp/dtmin; mmHg/s). Liquiritin also could enhance the phosphorylation of AMP-activated protein kinase α2 (AMPKα2) and decrease the phosphorylation of mammalian target of rapamycin complex 1 (mTORC1), inhibitor of nuclear factor kappa B (IκBα), and nuclear factor-kappa-B p65 (NF-κB/p65), which suggested that liquiritin reduced inflammation, oxidative stress, and apoptosis, and improved metabolism by regulating AMPKα2-dependent signaling pathway (Mou *et al.*, 2021).

Coronary heart disease

Coronary heart disease (CHD) is characterized by chronic immunoinflammatory, fibroproliferative disease fueled by lipids, which can be prevented and treated by

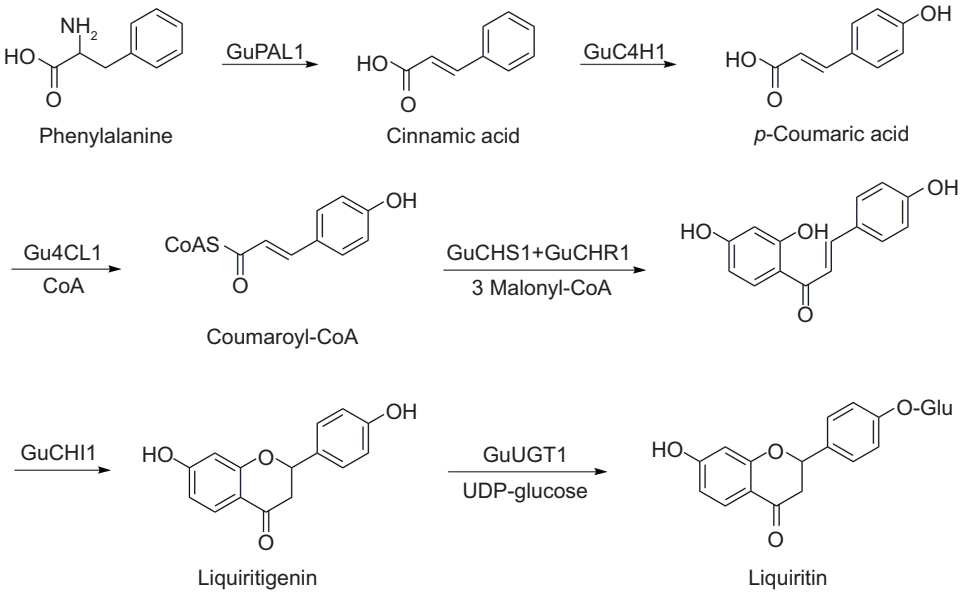

Figure 1. Biosynthetic pathway of liquiritin.

reducing the risk of lipoprotein-mediated disease (Shaya *et al.*, 2022). Flavonoids are dietary polyphenolic compounds with a variety of proposed beneficial cardiovascular effects (Goetz *et al.*, 2016). Liquiritin significantly inhibited cell proliferation and migration in oxidized low-density lipoprotein (ox-LDL)-induced human vascular smooth muscle cells (hVSMCs), remarkably decreased B-cell lymphoma 2 (Bcl-2) and sirtuin 1 (SIRT1) protein expression and the Bcl-2– Bcl-2-associated X-protein (BAX) ratio, and increased BAX protein expression. Liquiritin has obvious prevention and treatment effect on CHD by regulating the proliferation and migration of hVSMCs via increasing SIRT1 expression, which could provide new ideas for CHD treatment (Yuan *et al.*, 2022).

Cardiac hypoxia/reoxygenation injury

Myocardial hypoxia/reoxygenation (H/R) injury is caused by an initial reduction in blood flow to the heart, preventing it from receiving adequate oxygen, and subsequent recovery of blood through an occlusive coronary artery opening with adverse effects (Deng *et al.*, 2021). Flavonoids are dietary polyphenols and have a good effect on preventing H/R injury (Jiang *et al.*, 2018). Liquiritin could significantly prevent myocardial H/R injury. Liquiritin remarkably reduced the rate of H/R damage via increasing H9c2 cell (cell model used as an alternative for cardiomyocytes) viability level and preserving mitochondria after H/R. Liquiritin preserved mitochondrial mass, prevented the collapse of mitochondrial membrane potential ($\Delta\Psi m$), decreased the elevation of reactive oxygen species (ROS), and attenuated the overload of mitochondrial Ca^{2+} (Thu *et al.*, 2021).

Cardiac hypertrophy

Cardiac hypertrophy is usually characterized by myocardial cell enlargement and thickening of the ventricular wall, and its pathogenesis is closely related to autophagy, oxidative stress, and inflammation (Tham *et al.*, 2015). Flavonoids could obviously relieve cardiac hypertrophy (Fu *et al.*, 2022). Liquiritin markedly improved hypertrophy-related cardiac dysfunction, decreased LVESd and LVEDd, and restored LVEF and LVFS. Liquiritin could also decrease heart size, cardiac cross-sectional area (CSA), and heart weight/body weight (HW/BW), and inhibited the *messenger RNA* (mRNA) expression of A type natriuretic peptide (ANP), B type natriuretic peptide (BNP), and β-myosin heavy chain (β-MHC). *In vitro*, liquiritin inhibited Ang II-induced hypertrophy in neonatal rat cardiomyocytes (NRCMs) via activating cyclic adenosine monophosphate-activated protein/protein kinase/liver kinase B1/AMPKα2 (cAMP/PKA/LKB1/AMPKα2) signaling (Aiyasiding *et al.*, 2022). Liquiritin could decrease the ATE1 protein levels and TAK1 and JNK1/2 phosphorylation induced by angiotensin II (Ang II), which attenuated Ang II-induced cardiomyocyte hypertrophy by regulating the ATE1/TAK1-JNK1/2 pathway (Mo *et al.*, 2022).

Diabetic cardiomyopathy

Diabetic cardiomyopathy (DCM) is characterized by diastolic abnormalities in the early stages as well as clinical heart failure with hypertension and coronary artery disease in the later stages (Jia *et al.*, 2018). The role of flavonoids in protecting the heart from diabetes-induced cardiomyopathy has been studied extensively, and its alleviating DCM is mainly related to the hypoglycemic, antioxidant, anti-inflammatory, and antiapoptotic effects (Jubaidi *et al.*, 2021). Liquiritin effectively down-regulated left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic diameter (LVDd), and left ventricular end-systolic diameter (LVDs) accompanied with up-regulation of left ventricular ejection fraction (LVEF), reduced size of the heart, and myocardial fibrosis with lower expressions of Collagen type I and Collagen type II, inhibited the inflammatory cytokine release, NF-κB phosphorylation, and mitogen-activated protein kinases (MAPKs), which indicated that liquiritin has a protective effect against high fructose-induced myocardial fibrosis via suppression of NF-κB and MAPKs signaling pathways (Zhang *et al.*, 2016).

Aconitine-induced cardiotoxicity

Aconitine is an active compound derived from Aconitum species, highly toxic to the heart. Therefore, early intervention and treatment must be carried out for the cardiotoxicity caused by aconitine (Wei *et al.*, 2021). Liquiritin could reduce the release of LDH, inhibit the mRNA expression of *Cavl.2* and *Kv4.3* in rat cardiomyocytes induced by aconitine, and reduce the toxic effects of aconitine (Dong *et al.*, 2009). Liquiritin also reduced the mRNA overexpression of *SCN5A* and *Cavl.2* genes, increased the mRNA under-expression of *Kv4.3* gene induced by aconitine, and effectively improved the abnormal expression of potassium, sodium, and calcium ion channels in cardiomyocytes (Liu *et al.*, 2008).

Acute myocardial infarction

Acute myocardial infarction (AMI) is the main cause of death because of CHD, and its pathogenesis is closely related to free radicals, ROS, calcium overload, mitochondrial dysfunction, inflammation, and neutrophil-mediated vascular injury (Jung *et al.*, 2022). Flavonoids have a good effect on the prevention of AMI (Hua *et al.*, 2022).

Liquiritin improved left ventricular systolic pressure (LVSP), +dp/dtmax, -dp/dtmax, and left ventricular end-diastolic pressure (LVEDP) levels, alleviated pathological changes and cardiac fibrosis, and decreased the overexpression of toll-like receptor 4 (*TLR4*), *MyD88*, and *NF-κB*, which demonstrated liquiritin as a potential compound that could alleviate AMI via inhibiting the TLR4/MyD88/NF-κB signal pathway (Zhou *et al.*, 2022).

Molecular Docking

We searched the targets related to the cardiovascular diseases and discovered their protein data bank (PDB) structures. Major targets closely associated with cardiovascular diseases are TLR4 (Zhang *et al.*, 2022), Kelch-like ECH-associated protein 1 (Keap-1) (Han *et al.*, 2022), AMPK (Wu and Zou, 2020), phosphoinositide 3-kinase (PI3K; Qin *et al.*, 2021), Janus kinase 1 (JAK-1; Shen *et al.*, 2019), *NLRP3* (Wang *et al.*, 2020), glycogen synthase kinase-3 beta (GSK3β; Zeng *et al.*, 2019), p38 mitogen-activated protein kinase (p38 MAPK; Tang *et al.*, 2022), extracellular signal-regulated kinase (ERK; Gallo *et al.*, 2019), and transient receptor potential vanilloid 1 (TRPV1; Castrejón-Téllez *et al.*, 2022). Therefore, these targets were selected for docking with liquiritin so as to find its main target. PDB formats of TLR4 (PDB code: 3VQ2) (Ohto *et al.*, 2012), Keap-1 (PDB code: 4L7B) (Jnoff *et al.*, 2014), AMPK (PDB code: 4ZHX) (Langendorf *et al.*, 2016), PI3K (PDB code: 1E7V) (Walker *et al.*, 2000), JAK-1 (PDB code: 6RSH) (Itteboina *et al.*, 2016), NLRP3 (PDB code: 6NPY) (Sharif *et al.*, 2019), GSK3β (PDB code: 6Y9R) (Buonfiglio *et al.*, 2020), p38 MAPK (PDB code: 3GCP) (Simard *et al.*, 2009), ERK (PDB code: 7AUV) (Munck *et al.*, 2021), and TRPV1 (PDB code: 7LQZ) (Nadezhdin *et al.*, 2021) were downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The structure of liquiritin was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/). CB-DOCK was used for molecular docking and virtual screening of its possible targets (Liu *et al.*, 2020). The greater the VINA score differences between liquiritin and ligand, the more likely liquiritin was to act on the target. Docking results showed that the three targets with the largest difference in VINA scores were TLR4, Keap-1, and AMPK, which suggested that liquiritin was likely to act on TLR4, Keap-1, and AMPK (Table 1 and Figure 2).

Conclusion

Liquiritin has cardioprotective effects, which demonstrated that liquiritin could act on anti-inflammatory

Table 1. Docking results of liquiritin with different targets.

Targets	Chemicals	Vina score	Cavity score	Center (x, y, z)	Size (x, y, z)
TLR4	Liquiritin	–8.1	3602	–27, –16, 28	33, 25, 25
	TAK-242	–7.1	3602	–27, –16, 28	33, 21, 21
Keap-1	Liquiritin	–10.6	8498	1, –4, –26	35, 35, 35
	ML334	–10.3	8498	1, –4, –26	35, 35, 35
AMPK	Liquiritin	–8.8	12237	81, 9, 34	35, 35, 33
	A769662	–8.7	12237	81, 9, 34	35, 35, 33
PI3K	Liquiritin	–9.7	21290	34, 42, 33	35, 34, 35
	LY294002	–9.8	21290	34, 42, 33	35, 34, 35
JAK-1	Liquiritin	–8.7	2107	33, 12, 228	25, 25, 25
	KHE	–9.1	2107	33, 12, 228	27, 27, 27
NLRP3	Liquiritin	–8.6	12731	89, 94, 81	35, 34, 35
	MCC950	–10.3	12731	89, 94, 81	35, 34, 35
GSK3β	Liquiritin	–7.1	725	–8, –10, 24	25, 25, 25
	LY2090314	–8.8	725	–8, –10, 24	24, 24, 24
p38 MAPK	Liquiritin	–9.3	1674	18, –3, 18	25, 25, 25
	SB203580	–11.1	1674	18, –3, 18	23, 23, 23
ERK	Liquiritin	–7.3	1484	–13, –6, 31	25, 25, 25
	SCH772984	–9.2	1484	–13, –6, 31	33, 33, 33
TRPV1	Liquiritin	–8.5	3899	149, 112, 134	31, 25, 25
	Resiniferatoxin	–10.5	3899	149, 112, 134	31, 24, 24

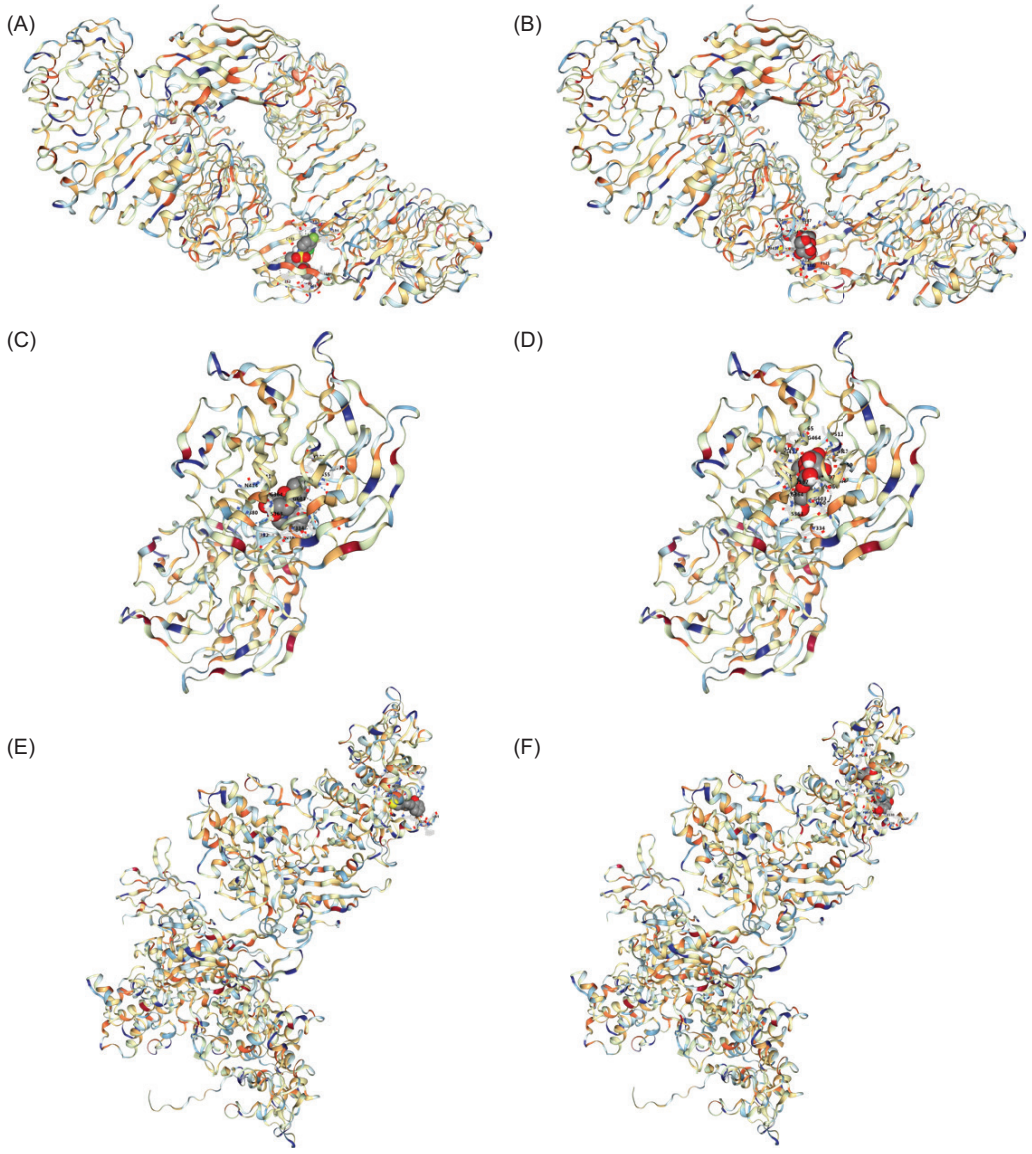

Figure 2. Binding of liquiritin with TLR4, Keap-1, and AMPK. (A) TAK-242–TLR4 complex, (B) Liquiritin–TLR4 complex, (C) ML334–Keap-1 complex, (D) Liquiritin–Keap-1 complex, (E) A769662–AMPK complex, and (F) liquiritin–AMPK complex.

and antioxidant targets, such as TLR4, Keap-1, AMPK, PI3K, JAK-1, NLRP3, GSK3β, p38 MAPK, ERK, and TRPV1. Comparison of docking results displayed that the three targets with the highest VINA scores were TLR4, Keap-1, and AMPK, which suggested that liquiritin was likely to act on TLR4, Keap-1, and AMPK. This could provide theoretical basis for future development and research of liquiriritin in treating cardiovascular diseases.

Conflict of Interest

The authors declared no conflict of interest.

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