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Protective Mechanism of Aqueous Extract From *Ixeris sonchifolia* in Myocardial Ischemia–Reperfusion Injury: Insights From Network Pharmacology and Experimental Validation

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ABSTRACT

Ixeris sonchifolia (Bge.) Hance, commonly known as *kudiezi* (KDZ), has a bitter taste, acrid nature, and is cold in property. It is used for treating pain, heat, and detoxification, and additionally serves as both food and fodder. Previous pharmacological studies indicate cardiovascular protective effects of KDZ. However, its efficacy against myocardial ischemia–reperfusion injury (MI/RI) remains insufficiently studied. Mice were pretreated with KDZ aqueous extract via oral gavage for three consecutive days. On the fourth day, a myocardial ischemia/reperfusion (40 min/60 min) model was surgically induced. Echocardiography data showed significant improvements in left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) in the KDZ-treated group. TTC staining showed that KDZ treatment significantly reduced the infarct size compared with the model group. These findings confirmed that KDZ aqueous extract mitigated injury and preserved cardiac function. Ultra high performance liquid chromatography–mass spectrometry (UHPLC–MS) analysis identified 86 chemical components. Network revealed ten hub targets—including AKR1B1, CA2, XDH, ADORA1, ACHE, EGFR, TNF, IL-2, RPS6KA3, NOX4—that are critically involved in oxidative stress and inflammatory pathways. Based on KEGG enrichment analysis, the screened genes showed significant enrichment in the AGE-RAGE signaling pathway. Experimental results confirmed that the KDZ aqueous extract reduced serum AGEs levels and inhibited the expression of the oxidative regulatory proteins gp91-phox and p47-phox, as well as that of RAGE. This study demonstrated the KDZ aqueous extract attenuated MI/RI by targeting the AGE-RAGE-NOX axis.

1 | Introduction

Coronary heart disease (CHD), one of the most prevalent cardiovascular diseases (CVDs), shows rising global prevalence and significant mortality. Clinically, thrombolytic therapy or

primary percutaneous coronary intervention (PPCI) restores myocardial perfusion. However, reperfusion itself can cause severe irreversible damage—including myocardial infarction expansion and life-threatening arrhythmias—collectively termed myocardial ischemia/reperfusion injury (MI/

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RI) (Heusch 2024; Heusch and Gersh 2016). Currently, few clinically effective agents are available for MI/RI prevention (Bellis et al. 2020), highlighting an urgent unmet therapeutic need.

Kudiezi (KDZ) is the dried whole plant of *Ixeris sonchifolia* (Bge.) Hance (Asteraceae). Traditionally used for pain relief, heat clearance, and detoxification, it also serves as food and fodder. Clinical studies show adjunctive KDZ therapy with conventional treatments (e.g., aspirin, isosorbide nitrate, rosuvastatin) significantly improves angina management in coronary heart disease (CHD) patients, enhancing therapeutic outcomes and modifying electrocardiographic parameters without severe adverse events (Yu et al. 2018). Preclinical studies demonstrate that KDZ alleviates myocardial injury secondary to cerebral ischemia in rats by modulating oxidative stress and enhancing antioxidant defenses (Liu, Cai, et al. 2017). These findings support KDZ's potential for ameliorating MI/RI and warrant further investigation.

Network pharmacology integrates systems biology, bioinformatics, and pharmacology to study complex interactions among bioactive compounds, therapeutic targets, and disease pathways. This approach differs from conventional ones by offering a comprehensive view of drug effects, achieved through mapping interactions across multiple components, targets, and pathways (Deng et al. 2025; Zhao et al. 2023). This study evaluated KDZ aqueous extract efficacy against MI/RI in vivo. UHPLC-MS characterized the extract's chemical composition. Using literature evidence, we prioritized active components among these compounds for network analysis. Based on this analysis, we predicted key therapeutic targets and mechanisms, which we subsequently validated through experiments.

2 | Materials and Methods

2.1 | Chemicals and Reagents

Thiobarbituric acid (TBA) assay kits (Jiancheng Bioengineering, Nanjing), mouse advanced glycation end products (AGEs) ELISA Kits (CSB-E09414m) (Cusabio, Wuhan, China), and primary antibodies against gp91-phox (sc-130543), p47-phox (sc-17845), RAGE (sc-365154), and GAPDH (sc-166545) (Santa Cruz, CA, USA) were commercially sourced.

2.2 | Preparation of Aqueous Extracts of KDZ

KDZ herb (harvested April 2023, Shanxi Province) was authenticated as dried *Ixeris sonchifolia* (Bge.) Hance (Asteraceae). The aqueous extract was prepared following a published methodology (Liu et al. 2020): Briefly, dry KDZ powder was mixed with water at a ratio of 1:10 (w/v) and subjected to two rounds of reflux extraction (1 h followed by 0.5 h). The solution was filtered, and the filtrates were combined and concentrated. Hydrochloric acid was added to adjust pH to 2, followed by the addition of four volumes of 95% ethanol to precipitate impurities. After centrifugation at 1050 g for 5 min, the supernatant was concentrated

under reduced pressure until ethanol-free. The final aqueous solution was adjusted with distilled water to a concentration of 0.5 g crude drug per mL.

2.3 | Animal Experiment

2.3.1 | Experimental Animals

All animal procedures, including randomization, blinding, humane endpoints, and post-operative analgesia, were conducted in strict compliance with the ethical guidelines and received approval from the Animal Experimentation Ethics Committee of Changzhi Medical College (Approval No. DW2021098). Male C57BL/6 mice (8-week-old, 22–27 g) were purchased from SPF Biotechnology Co. Ltd. (Beijing, China) [License No. SCXK (Jing) 2019-0010]. All mice were acclimated for 7 days under standard conditions (12-h light/dark cycle) with free access to food and water before the start of experiments.

2.3.2 | Myocardial Ischemia/Reperfusion Injury Model and Treatment

Mice were anesthetized by intraperitoneal (i.p.) injection of 1.25% tribromoethanol (0.2 mL per 10 g body weight). After orotracheal intubation and mechanical ventilation establishment (tidal volume: 275 μ L; rate: 135 strokes/min), a left thoracotomy was performed to expose the heart. The left anterior descending (LAD) artery was occluded for 40 min. This was achieved by placing an 8–0 suture approximately 1 mm below the left atrium and then tying it over PE-50 tubing. Successful occlusion was indicated by immediate epicardial pallor, ST-segment elevation, and QRS complex widening on the ECG. After 40 min of ischemia, the suture was released to initiate 60 min of reperfusion, as confirmed by epicardial hyperemia and ST-segment normalization (Figure 1a,b). Sham-operated mice underwent identical procedures without LAD occlusion. Animals were excluded from analysis if LAD occlusion was unsuccessful (e.g., lack of ST elevation) or if major surgical complications (e.g., pneumothorax) occurred.

The animals were randomly assigned to the following groups: (1) Sham: Underwent the surgical procedure except for LAD occlusion and received saline gavage. (2) MI/R: Underwent 40 min of LAD occlusion followed by 60 min of reperfusion and received saline gavage. (3) KDZ + MI/R: Pretreated with KDZ by daily intragastric gavage at doses of 17.75, 35.5, or 70.95 mg/kg (corresponding to 0.5 $\times$, 1 $\times$, and 2 $\times$ of the human clinically equivalent dose, respectively) for 3 consecutive days before surgery. The doses and pretreatment schedule were determined based on a comprehensive review of the literature (Liu, Tao, et al. 2017; Zhai et al. 2010) and our preliminary experiments.

2.3.3 | Transthoracic Echocardiography

Mice were positioned and secured on the operating table, and their chest hair was removed. After applying coupling gel, parasternal short-axis B-mode images of the left ventricle (LV) were obtained using a VINNO G65 ultrasound system

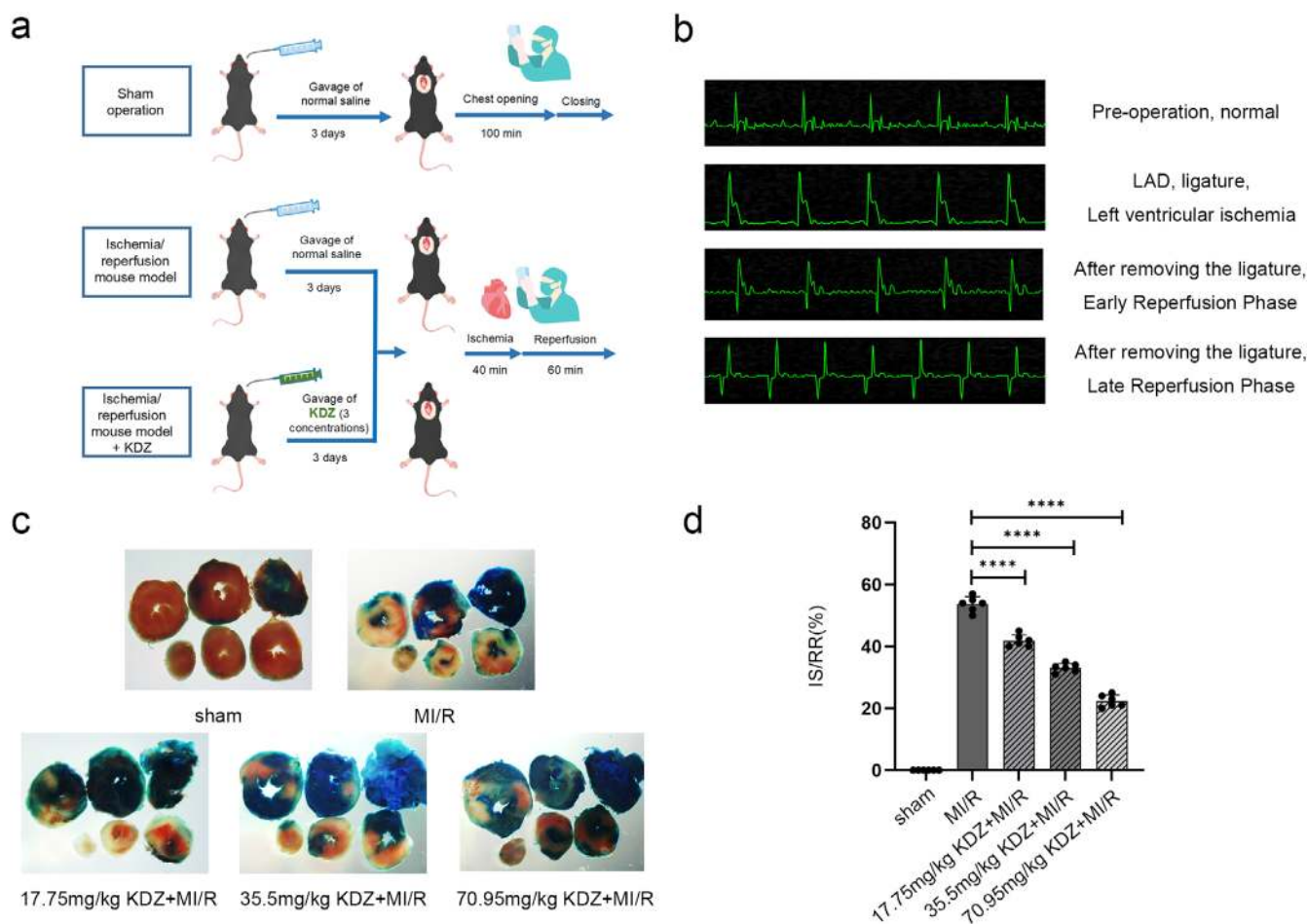


FIGURE 1 | KDZ reduces myocardial infarct size in mice with ischemia/reperfusion injury. (a) Experimental timeline. (b) Representative ECG tracings at baseline, 40min post-ligation, early reperfusion phase, and late reperfusion phase. (c) Cross-sections of Evans blue/TTC-stained ventricles: Non-ischemic zone (blue), ischemic risk region (RR, red), and infarct size (IS, white). (d) Infarct size as a percentage of the risk region. Data = mean $\pm$ SD ($n = 6$); **** $p < 0.0001$ versus I/R group; one-way ANOVA with Tukey's post hoc test.

equipped with an X10-23 L probe (23 MHz). M-mode tracings were acquired at the maximum diameter of the left ventricle. Cardiac function indices (Liang et al. 2022)—including the left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left ventricular internal dimension at end-diastole (LVIDd), left ventricular internal dimension at end-systole (LVIDs), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) — were calculated using the cardiac function analysis software package of the system.

2.3.4 | 2,3,5-Triphenyltetrazolium Chloride (TTC) Staining

Mouse hearts were isolated and cannulated via the ascending aorta. After 60 min reperfusion, sequential perfusion with 2 mL warm 1% TTC solution was performed. The LAD was re-occluded by retying the encircling suture, followed by perfusion with 200 μ L 70% methylene blue to define the non-ischemic region. After freezing and trimming, the right ventricle and atria were removed. The left ventricle was sectioned transversely into six slices and fixed in 10% formalin (Lai et al. 2021; Tian et al. 2016). The myocardium unstained by

methylene blue was considered the risk region (RR), while the region unstained by TTC was identified as the infarct size (IS). To account for variations in the area at risk, infarct size was normalized and is presented as a percentage of the risk region (IS/RR%). Each stained section was digitally photographed and analyzed with ImageJ (NIH) to calculate their respective percentages.

2.3.5 | Hematoxylin and Eosin (H&E) Staining

After fixation in 10% neutral buffered formalin, left ventricular tissues were processed through graded ethanol and xylene, paraffin-embedded, and sectioned at 4 μ m thickness. Dewaxed sections were stained with H&E for histological evaluation using light microscopy.

2.3.6 | Determination of Oxidative Stress

Serum was collected from the abdominal aorta and separated by centrifugation (1500 $\times$ g, 4°C, 10 min). The levels of malondialdehyde (MDA) and the activity of total superoxide dismutase (T-SOD) in the serum were determined using commercial

thiobarbituric acid (TBA) assay kits, following the manufacturer's protocols.

2.4 | Network Pharmacology

2.4.1 | UHPLC–MS Analysis of Aqueous Extracts of KDZ

KDZ aqueous extracts were chemically profiled using UHPLC–MS (Thermo Vanquish/Agilent 6230) with electrospray ionization (ESI). Chromatographic separation employed a Zorbax Eclipse XDB-C18 column (2.1 × 100 mm, 1.7 μm) with 0.3 mL/min flow rate, using mobile phases: (A) 0.1% formic acid (aq.) and (B) acetonitrile. The gradient program was: 0–1 min, 2% B, 1–5 min to 4.3% B, 5–14 min to 12% B, 14–16 min to 14% B, 16–18 min to 16% B, 18–22 min to 21% B, 22–24 min to 50% B, 24–26 min to 90% B, 26–28 min, 90% B, 28–30 min to 2% B, followed by equilibration at 2% B from 30 to 33 min. Chromatographic conditions: 2 μL injection volume, 35°C column temperature. MS parameters: Ion source temperature 350°C, Voltages: Positive mode (capillary +35 V, tube lens +110 V, source +4.0 kV), Negative mode (capillary –35 V, tube lens –110 V, source –3.0 kV), Collision energy 6–10 V.

2.4.2 | Screening of KDZ Active Compounds and Collection of Targets

Bioactive compounds were identified by cross-referencing the chemical profile obtained from UHPLC–MS analysis with existing *Kudiezi*-related literature, and prioritized based on phytochemical relevance, ADME parameters (e.g., oral bioavailability and drug-likeness), and preliminary antioxidant activity validation (Table S3). The search terms “*Ixeris sonchifolia*”, “*kudiezi*” and “composition” were used to query the PubMed and CNKI databases. The structures of these candidate compounds were then submitted to SwissTargetPrediction (<http://www.swisstargetprediction.ch>; accessed May 2025) to predict their potential protein targets (Daina et al. 2019). Targets of all active compounds were obtained and imported into the Universal Protein database (UniProt; <https://www.uniprot.org/>; version 2025_01, accessed May 2025) for name standardization. Subsequently, focusing on *Homo sapiens*, we selected for further analysis those potential targets with a prediction probability of ≥ 0.7 .

2.4.3 | Identification of the MI/RI Target Genes

Potential therapeutic targets of KDZ against MI/RI were identified through a network pharmacology approach. First, MI/RI-associated genes were retrieved from the following databases (all accessed in May 2025) using the search term “myocardial ischemia/reperfusion injury”. OMIM (all curated entries) (Amberger et al. 2015), CTD (inference score > 20) (Davis et al. 2023), GeneCards (version 5.24; relevance score > 1.0) (Stelzer et al. 2016), and DisGeNET (version 25.1; score > 0.1) (Pinero et al. 2015). Second, the compound–target and disease–target interaction networks were constructed and visualized using Venny 2.1.0 (<https://bioinfoq.cnb.csic.es/tools/venny/>).

Finally, the intersection of these networks was analyzed to identify overlapping targets, which were considered potential key therapeutic targets for KDZ in MI/RI.

2.4.4 | Protein–Protein Interaction (PPI) Network Analysis

Experimentally validated targets were analyzed in the STRING database (<https://cn.string-db.org>; version 12.0; accessed May 2025) (Szklarczyk et al. 2019) for the species *Homo sapiens*, with a minimum required interaction confidence score of > 0.7 . The resulting protein–protein interaction network was then imported into Cytoscape (<https://cytoscape.org>; version 3.10.1; accessed June 2025) (Demchak et al. 2018) for topological analysis. Hub targets were identified based on multiple centrality parameters (degree, betweenness, and closeness). Nodes exceeding the 85th percentile in all three measures were defined as hubs.

2.4.5 | Pathway and Functional Enrichment Analysis

Functional enrichment analysis of the overlapping targets was performed using the DAVID bioinformatics database (Davis et al. 2023). This analysis included Gene Ontology (GO) annotation across biological processes, cellular components, and molecular functions (BP/CC/MF), as well as KEGG pathway analysis, with a significance threshold of $p < 0.01$. The enriched GO terms and KEGG pathways were visualized as a heatmap and a bubble chart, respectively. Additionally, integrated compound–target–pathway (C–T–P) networks were constructed and visualized using Cytoscape (version 3.10.1).

2.5 | Verification of Molecular Mechanisms

2.5.1 | Enzyme-Linked Immunosorbent Assay

The levels of serum AGEs were measured by using ELISA kits following the manufacturer's instructions.

2.5.2 | Western Blot Analysis

Approximately 75 mg of ischemic left ventricular tissue was homogenized in lysis buffer. Equal amounts of protein (20 μg) were separated by 10% SDS-PAGE and transferred to PVDF membranes. After blocking, membranes were incubated overnight at 4°C with primary antibodies: anti-gp91-phox (1:500), anti-p47-phox (1:500), anti-RAGE (1:500), and anti-GAPDH (1:1000). Following incubation with a horseradish peroxidase (HRP)-conjugated secondary antibody (1:1000, 90 min, RT), bands were quantified using ImageJ with GAPDH as loading control.

2.6 | Statistical Analysis

Data were analyzed using GraphPad Prism 10.0 with results expressed as mean $\pm$ standard deviation (SD). One-way ANOVA followed by Tukey's post hoc test was used for multiple

comparisons, while Student's *t*-test was used for comparisons between two groups. A $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | KDZ Significantly Attenuated MI/RI in Mice

Compared with the MI/R controls, KDZ treatment significantly and dose-dependently reduced the infarct size (IS; expressed as % of RR) ($p < 0.0001$; Figure 1d). Histological examination showed that myocardial tissue from the sham group maintained normal morphology, with orderly cell arrangement, clear cell boundaries, and tightly connected fibers without infarction. In contrast, the MI/R group exhibited disorganized, variably sized cardiomyocytes; loosely arranged fibers with widened intercellular spaces; fiber degeneration/swelling; interstitial edema; and neutrophil infiltration. KDZ treatment induced dose-dependent improvements: the 17.75 mg/kg group demonstrated structural recovery with residual inflammation, the 35.5 mg/kg group showed partial protection despite persistent vacuolar degeneration, and the 70.95 mg/kg group achieved near-normal histology featuring orderly cells, uniform staining, clear boundaries, and absent edema/infiltration (Figure 2h). Furthermore, KDZ administration significantly improved left ventricular function compared with the MI/R group, as evidenced by increased LVEF and LVFS (Figure 2d,e) and decreased LVIDs and LVESV (Figure 2f,g). No significant differences were observed in LVIDd and LVEDV among all groups ($p > 0.05$).

3.2 | KDZ Active Compounds and Target Screening

UHPLC–MS analysis identified 86 constituents in KDZ aqueous extract, classified into six categories: nucleosides, flavonoids, organic acids, amino acids, phenylpropanoids, and triterpenes. Chromatographic profiles and compound identities are detailed in Figure 3 and Supplementary Table S1. Thirty-one candidate bioactive compounds were selected based on literature evidence (Table 1), including 16 flavonoids (e.g., apigenin, luteolin) and 15 organic acids (e.g., gallic acid, caffeic acid).

Following deduplication, intersection analysis of 178 compound-related targets and 986 MI/RI-associated genes identified 108 shared potential targets (Figure 4a; Table S2). These overlapping targets were used to construct a compound-target-disease network (Figure 4d). Network topology analysis revealed that flavonoid constituents (apigenin, luteolin, quercetin) exhibited significantly higher node degrees than non-flavonoids (median degree: 15 vs. 6; Mann–Whitney *U* test, $p < 0.01$). Ten hub targets—AKR1B1, CA2, XDH, ADORA1, ACHE, EGFR, TNF, IL-2, RPS6KA3, and NOX4—were identified based on a degree centrality cutoff of > 11 , underscoring their potential key functional roles within the network.

3.3 | PPI Network Analysis

Analysis of the 108 shared targets generated a PPI network containing 104 nodes and 470 edges (Figure 4c). Sixteen network hub

targets (degree ≥ 10) were identified via cytoNCA in Cytoscape 3.10.1. The top five targets by degree centrality were STAT3 (degree = 35), EGFR (33), AKT1 (32), IL6 (32), and TNF (31).

3.4 | Enrichment Analysis of MI/RI Ameliorated by KDZ

Among 108 potential therapeutic targets, GO enrichment analysis ($p < 0.05$) identified 596 significant terms, encompassing 414 biological processes (BP), 61 cellular components (CC), and 121 molecular functions (MF). KEGG pathway analysis revealed significant enrichment in the top 20 pathways (Figure 5b), most notably AGE-RAGE signaling (KEGG: hsa04933; $p = 1.2 \times 10^{-16}$) and HIF-1 signaling (KEGG: hsa04066; $p = 1.15 \times 10^{-14}$). Cancer-related terms were excluded during curation to focus on MI/RI pathophysiology.

To delineate KDZ's cardioprotective mechanism, we constructed a compound-target-pathway (C-T-P) network integrating the 20 most enriched pathways with corresponding compounds and targets (Figure 5c). Integrating target prediction, pathway enrichment, and network topology analyses, we identified a set of key targets—including AKR1B1, MAPK1, MAPK3, EGFR, CA2, AKT1, PIK3R1, TNF, PRKCA, PRKCB, ADORA1, and XDH. These targets are centrally involved in oxidative stress and inflammatory cascades, highlighting them as critical mediators of KDZ's therapeutic effects against MI/RI.

3.5 | KDZ Administration Attenuated MI/RI-Induced Oxidative Stress

The model group had significantly increased serum MDA and decreased T-SOD activity compared to the sham group ($p < 0.05$). In contrast, the administration of KDZ led to a substantial decrease in serum MDA content ($p < 0.05$) and an increase in T-SOD activity ($p < 0.05$) (Figure 2b,c).

3.6 | KDZ Inhibited Serum AGEs and Myocardial Expression of RAGE, NOX2, and p47-Phox

To validate network pharmacology predictions, we examined serum levels of AGEs and the expression of key proteins in the AGE-RAGE pathway (RAGE) and NADPH oxidase subunits (gp91-phox/NOX2, p47-phox). Compared with the MI/R group, pretreatment with KDZ (17.75, 35.5, or 70.95 mg/kg) for 3 days significantly and dose-dependently reduced serum AGEs levels and inhibited the expression of RAGE, NOX2, and p47-phox. ELISA results showed that serum AGEs levels were significantly decreased in the medium- and high-dose KDZ groups ($p < 0.05$ and $p < 0.0001$, respectively) (Figure 6e). Quantitative analysis further revealed dose-dependent reductions in protein expression (Figure 6b,d). Specifically, the expression levels of RAGE were reduced by approximately 43%, 55%, and 72% in the low-, medium-, and high-dose groups, respectively. Corresponding reductions for gp91-phox were 25%, 42%, and 64%, and for p47-phox were 40%, 52%, and 60%. The high-dose KDZ group exhibited the most pronounced inhibitory effects, effectively attenuating MI/RI.

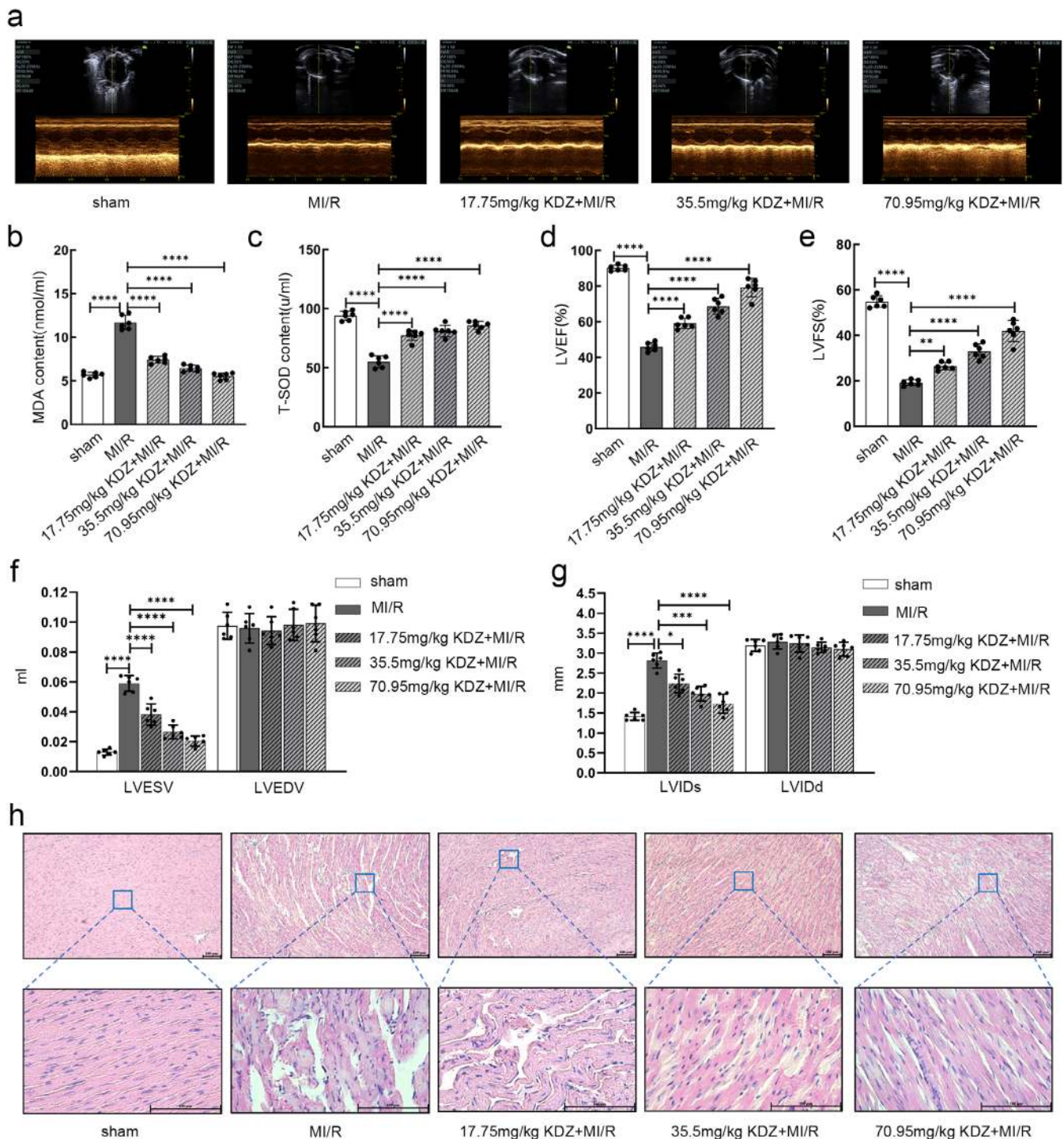


FIGURE 2 | KDZ attenuates myocardial ischemia/reperfusion injury (MI/RI) in mice. (a) Representative transthoracic echocardiograms. (b, c) Oxidative stress markers: (b) Malondialdehyde (MDA) and (c) Total superoxide dismutase (T-SOD). (d–g) Quantification of cardiac function parameters: (d) Left ventricular ejection fraction (LVEF); (e) Fractional shortening (LVFS), (f) Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV); (g) Left ventricular internal dimension at end-systole (LVIDs) and left ventricular internal dimension at end-diastole (LVIDd); (h) Typical images of the left ventricle stained with H&E (scale bar, 100 μ m). Data = mean $\pm$ SD ($n = 6$); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ versus MI/R group; one-way ANOVA with Tukey's post hoc test.

4 | Discussion

Myocardial ischemia/reperfusion injury (MI/RI) poses a significant clinical challenge in coronary heart disease treatment. Although timely revascularization is essential, it unintentionally aggravates tissue damage through oxidative burst, calcium

overload, and sterile inflammation (Bellis et al. 2020; Heusch 2024; Heusch and Gersh 2016). Despite advances in thrombolytic therapy and primary percutaneous coronary intervention (PPCI), no clinically effective drugs specifically target reperfusion injury. Here, our findings demonstrate that KDZ aqueous extract—an herbal medicine clinically used for angina (Yu et al. 2018)—protects

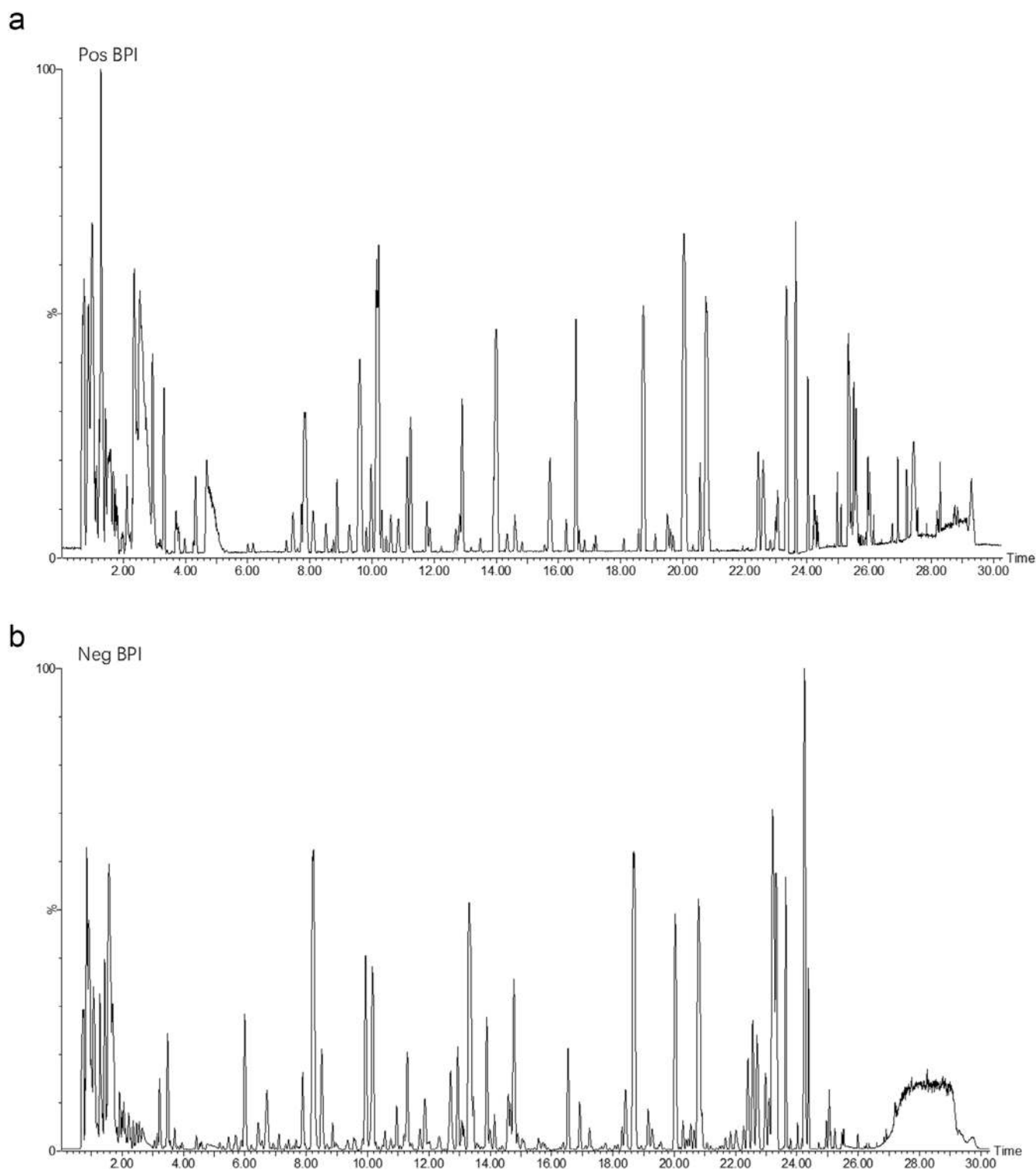


FIGURE 3 | Base peak ion (BPI) chromatograms of KDZ aqueous extract acquired by UHPLC–MS: (a) Positive ion mode and (b) negative ion mode.

against MI/RI. Treatment dose-dependently reduced infarct size (maximal effect at 70.95 mg/kg), preserved myocardial ultrastructure, and improved cardiac function (enhanced LVEF and LVFS; reduced LVIDs and LVESV). These results supported KDZ's traditional application in *huoxue huayu* (blood-activating and stasis-resolving) and revealed its repurposing potential for cardioprotection.

Chinese herbal medicine is widely recognized for its complex composition and multi-target effects. Network pharmacology systematically predicts drug efficacy and mechanisms by mapping interactions among drugs, targets, and pathways (Deng et al. 2025; Li et al. 2023; Zhang, Zhu, et al. 2019; Zhao et al. 2023). Our integrated strategy—combining UHPLC–MS phytochemical profiling, target prediction, and experimental

TABLE 1 | Flavonoids and organic acids of chemical active ingredients in KDZ.

ID	Chemical name	Molecular formula
KDZ1	5, 7-dihydroxy-4'-methoxy-flavone-7-rutinoside	C ₂₈ H ₃₂ O ₁₄
KDZ2	Luteolin-7-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside	C ₂₁ H ₂₀ O ₁₁
KDZ3	Quercetin	C ₁₅ H ₁₀ O ₇
KDZ4	Quercetin-3-O-glucuronide	C ₂₁ H ₁₈ O ₁₃
KDZ5	Rutin	C ₂₇ H ₃₀ O ₁₆
KDZ6	Luteolin	C ₁₅ H ₁₀ O ₆
KDZ7	Luteolin-7-O-β-D-glucoside	C ₂₁ H ₂₀ O ₁₁
KDZ8	Luteolin-7-O-β-D-glucuronic acid methyl ester	C ₂₂ H ₂₀ O ₁₂
KDZ9	Luteolin-7-O-β-D-glucuronate ethyl ester	C ₂₃ H ₂₂ O ₁₂
KDZ10	Luteolin-7-O-glucuronide	C ₂₁ H ₁₈ O ₁₂
KDZ11	Luteolin-7-O-β-gentiobioside	C ₂₇ H ₃₀ O ₁₆
KDZ12	Apigenin-7-O-β-D-glucuronide	C ₂₁ H ₁₈ O ₁₁
KDZ13	Apigenin-7-o-β-D-glucuronic acid methyl ester	C ₂₂ H ₂₀ O ₁₁
KDZ14	Apigenin-7-O-β-glucoside	C ₂₁ H ₂₀ O ₁₀
KDZ15	Apigenin	C ₁₅ H ₁₀ O ₅
KDZ16	Isorhamnein-3-O-glucopyranoside	C ₂₂ H ₂₂ O ₁₂
KDZ17	3, 4-dihydroxycafeoyl tartaric acid	C ₁₃ H ₁₂ O ₉
KDZ18	3, 5-dicafeoyl quinic acid	C ₂₅ H ₂₃ O ₁₂
KDZ19	Ferulic acid	C ₁₀ H ₁₀ O ₄
KDZ20	P-hydroxybenzoic acid	C ₇ H ₆ O ₃
KDZ21	Succinic acid	C ₄ H ₆ O ₄
KDZ22	Chicoric acid	C ₂₂ H ₁₈ O ₁₂
KDZ23	Caffeic acid	C ₉ H ₈ O ₄
KDZ24	Caffeic acid ethyl ester	C ₁₁ H ₁₂ O ₄
KDZ25	Quinic acid	C ₇ H ₁₂ O ₆
KDZ26	Chlorogenic acid	C ₁₆ H ₁₈ O ₉
KDZ27	Taraxacin B	C ₁₁ H ₁₀ O ₇
KDZ28	Vanillic acid	C ₈ H ₈ O ₄
KDZ29	Linoleic acid	C ₁₈ H ₃₂ O ₂
KDZ30	Protocatechuic acid	C ₇ H ₆ O ₄
KDZ31	Palmitic acid	C ₁₆ H ₃₂ O ₂

validation—revealed that KDZ's efficacy stemmed from synergy among 31 bioactive components, primarily flavonoids like apigenin, luteolin, and quercetin. These compounds jointly regulate 108 therapeutic targets, with flavonoids showing higher network connectivity, aligning with their established roles in reducing oxidative stress and inflammation (Lv et al. 2017). Pathway analysis identified the AGE-RAGE pathway as the core mechanism, highlighting its pathophysiological significance.

The receptor for advanced glycation end products (RAGE) is expressed in endothelial cells, cardiomyocytes, and immune cells. Its activation by non-enzymatically generated AGEs induces inflammatory and oxidative responses, playing a key role in diabetes and related complications (Park et al. 2015). The pathogenic effects of the AGE-RAGE axis on cardiovascular disorders—such as myocardial infarction (Ku et al. 2015), myocardial fibrosis (Liang et al. 2022), hypertension (Selejan et al. 2018), myocarditis (Bangert et al. 2015), atherosclerosis (Yamagishi and Matsui 2018), and related conditions—are increasingly recognized. Crucially, evidence suggests these effects are not solely dependent on underlying diabetes (Kosmopoulos et al. 2019). Upon ligand binding, RAGE activates a series of intracellular signal transduction cascades, such as the JAK/STAT pathway, NADPH oxidase system, and MAPK pathway (Awan et al. 2024; Zhou et al. 2024). These RAGE-mediated signaling pathways ultimately converge to activate nuclear factor κB (NF-κB), thereby triggering critical downstream effects including elevated pro-inflammatory mediator production, sustained inflammatory amplification, and autoregulatory RAGE upregulation (Khalid et al. 2022; Tanase et al. 2022). Conversely, inhibiting AGE production, disrupting RAGE-ligand binding, or silencing RAGE expression can effectively impair the AGE-RAGE axis function, thereby delaying or ameliorating these diseases. This RAGE-driven feed-forward cycle thereby sustains cellular damage from initial inflammatory triggers, progressively aggravating tissue injury. Blockade of AGE/RAGE signaling therefore offers significant translational potential for cardiovascular therapeutics (Lee et al. 2019; Vianello et al. 2025; Wang et al. 2024).

NADPH oxidase (NOX) serves as a key source of reactive oxygen species (ROS) in cardiomyocytes. Crosstalk between oxidase systems sustains oxidative stress, which drives cardiovascular pathogenesis (Zhang, Murugesan, et al. 2019). Notably, physiological levels of ROS derived from specific isoforms (e.g., NOX2) regulate essential cellular functions including proliferation, migration, and differentiation (Yan et al. 2024). However, excessive ROS production from activated NOXs contributes to cardiovascular pathogenesis. Genetic ablation of NOX2 attenuates NADPH oxidase activity, conferring cardioprotective effects after myocardial infarction: diminished cardiomyocyte apoptosis, preserved ventricular function, and increased survival rates (Looi et al. 2008; Qin et al. 2007). Each NOX isoform exhibits specific cellular expression patterns and subcellular localization. Cardiomyocytes express NOX1 (Matsuno et al. 2012), NOX2 (Krijnen et al. 2003), NOX4 (Ago et al. 2010), and NOX5 (Hahn et al. 2012). Among these isoforms, NOX1, NOX2, and NOX5 primarily generate superoxide anion (O₂⁻), whereas NOX4 directly produces hydrogen peroxide (H₂O₂). Critically, AGE-RAGE axis activation further amplifies NOX-mediated ROS production,

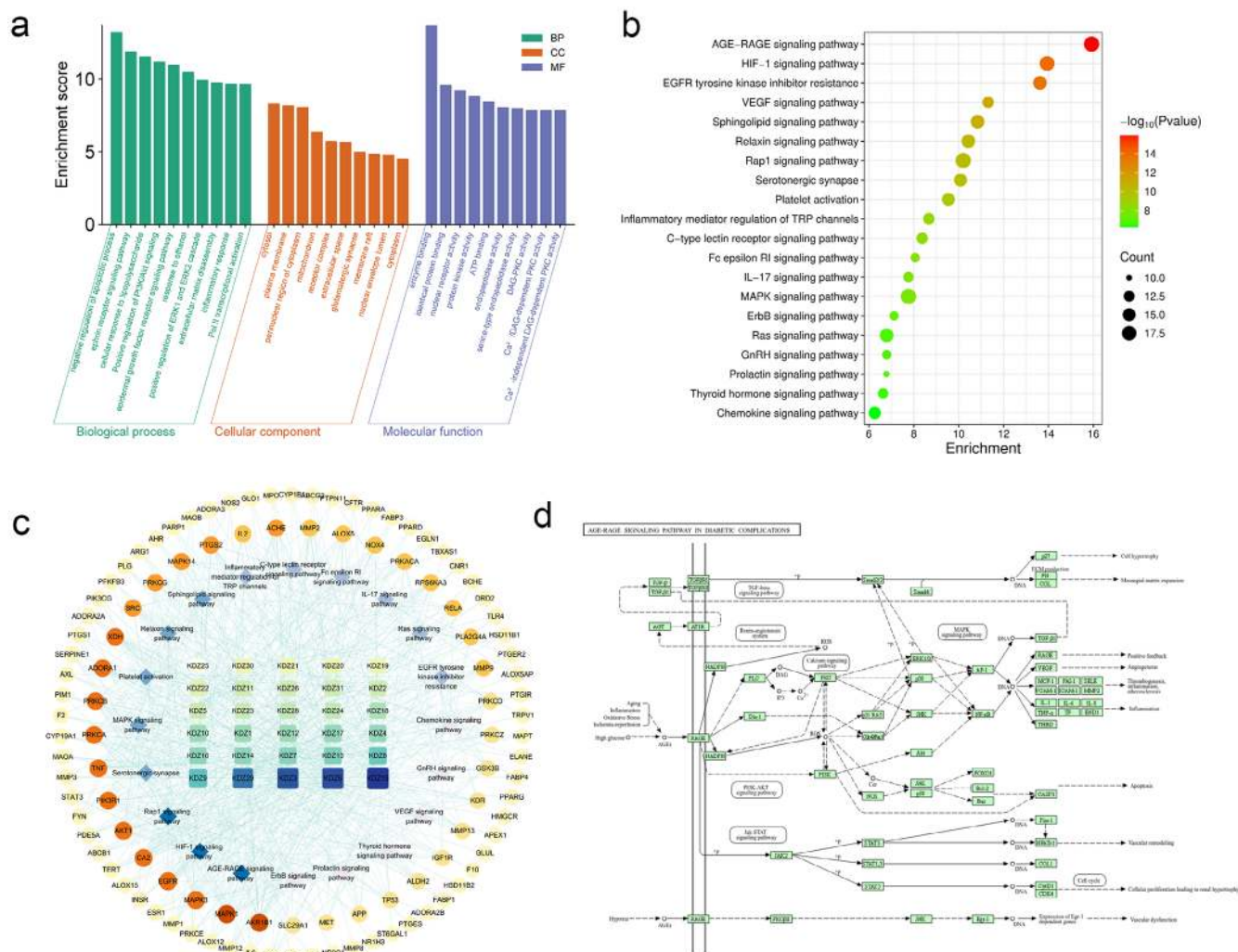


FIGURE 5 | Enrichment analysis of potential targets in the treatment of MI/RI with KDZ. (a) Gene ontology (GO) enrichment of KDZ-MI/RI shared targets: Top 10 terms for biological processes (BP, green), cellular components (CC, red), and molecular functions (MF, blue). (b) Bubble diagram KEGG pathway enrichment analysis of the top-20 major enriched pathways of KDZ against MI/RI. Count represents the number of genes (values are proportional to bubble size). (c) Compound-target-pathway (C-T-P) network for KDZ's anti-MI/RI effects. (d) AGE/RAGE signaling pathway subnetwork.

metabolic reprogramming, and mitochondrial protection (Tekin et al. 2010; Loor and Schumacker 2008). Although not experimentally validated, the significant enrichment of HIF-1-related targets suggests that KDZ may also exert cardioprotective effects by modulating oxygen adaptation. Given that KDZ components (e.g., luteolin, apigenin) modulate HIF-1 α activity under oxidative stress (Monti et al. 2020; Ding et al. 2023) and that HIF-1 can regulate RAGE expression in hypoxia (Puddighinu et al. 2017), it is plausible that KDZ confers cardioprotection through a dual mechanism: inhibiting the AGE-RAGE inflammatory cascade while simultaneously activating HIF-1-mediated protective pathways. The precise mechanisms by which KDZ orchestrates these protective pathways to mitigate MI/RI warrant further investigation.

It is worth noting that the reperfusion period used in this study (60 min) was chosen based on our previously validated model, which reliably captures early reperfusion events such as oxidative burst and inflammatory cytokine release (Tian et al. 2016; Lai et al. 2021). While this timeframe is sufficient for assessing

the acute molecular mechanisms underlying KDZ-mediated cardioprotection, it does not permit evaluation of long-term structural changes or chronic functional recovery. Future studies employing extended reperfusion intervals (e.g., 24 h to several weeks) will be necessary to determine whether the observed early benefits translate into sustained improvement in myocardial remodeling and function.

5 | Conclusions

Taken together, UHPLC-MS analysis identified 86 chemical components in KDZ aqueous extract, falling into six categories: nucleosides, flavonoids, organic acids, amino acids, phenylpropanoids, and triterpenes. Network pharmacology predicted KDZ's mechanisms against MI/RI. This integrated approach demonstrates that KDZ aqueous extract mitigates MI/RI by inhibiting the AGE-RAGE-NOX-ROS signaling cascade. Its antioxidative activity arises from interrupting this pathological pathway, accounting for the cardioprotective effects. Our findings establish a

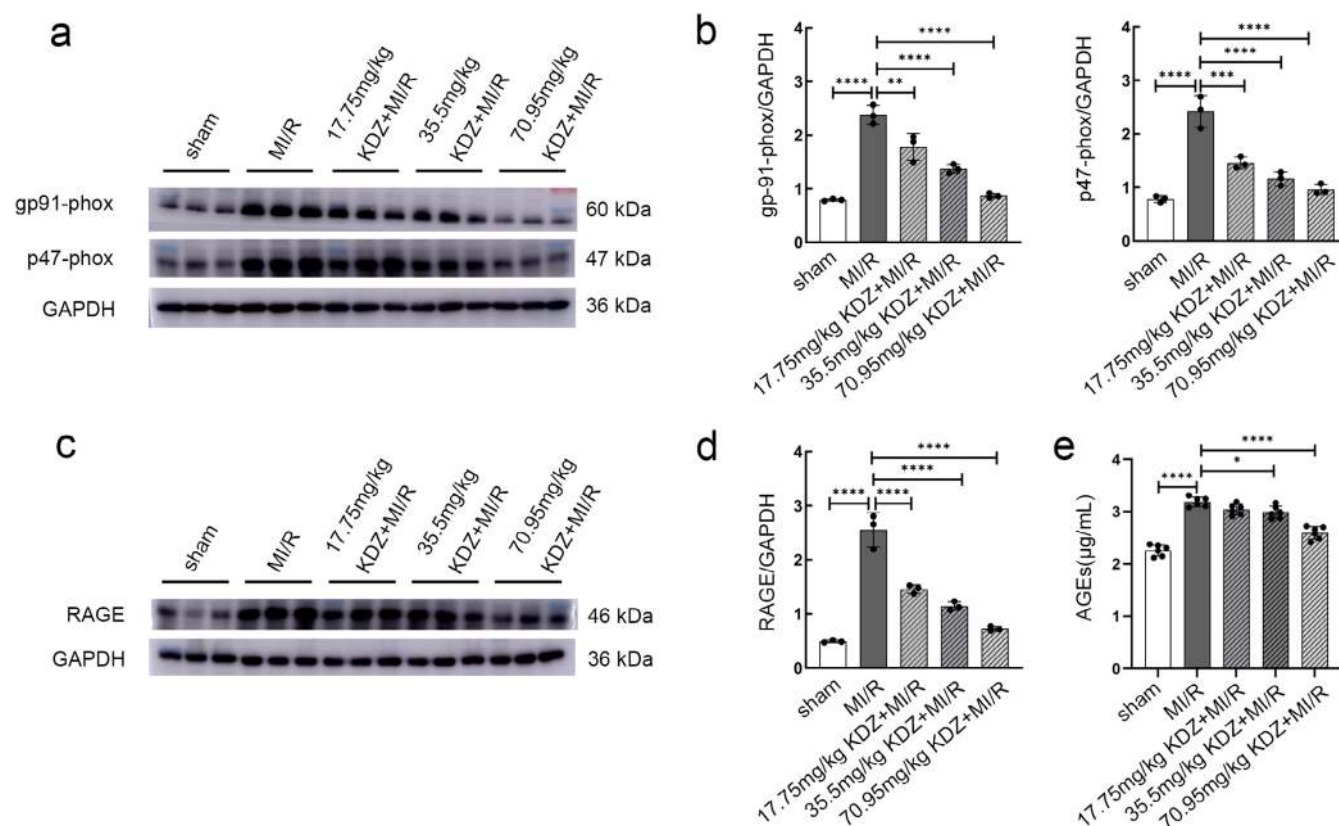


FIGURE 6 | KDZ suppresses serum AGEs and the expression of RAGE, NOX2, and p47-phox in myocardial tissue. (a) Representative western blots of gp91-phox and p47 in left ventricular tissues. (b) Quantification of gp91-phox and p47-phox protein levels ($n=3$). (c) RAGE expression detected by western blot ($n=3$). (d) RAGE quantification. (e) The levels of serum AGEs ($n=6$). Data are presented as mean $\pm$ SD. Percentage reductions for the low-, medium-, and high-dose groups compared to the MI/R group are reported in the results section; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ versus MI/R group; one-way ANOVA with Tukey's post hoc test.

pharmacological basis for KDZ's efficacy against MI/RI and inform therapeutic development of natural anti-MI/RI agents.

Author Contributions

Xiaoxia Tian: data curation, writing – original draft. **Longtai Chen:** methodology, validation. **Jiazhaohu Chu:** validation. **Fang Liu:** resources. **Kuan Liu:** validation. **Baoyi Chen:** software, visualization. **Sijing Feng:** validation. **Lina Lai:** funding acquisition, project administration, writing – review and editing.

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Ethics Statement

This research adhered to the Declaration of Helsinki guidelines and received ethical approval from the Animal Experimentation Ethics Committee of Changzhi Medical College.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data supporting the findings of this study are available in the article and its Tables S1 and S2. For additional information, inquiries can be addressed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Results of UHPLC–MS analysis of Aqueous Extracts of KDZ. **Table S2:** Intersection analysis of compound targets and myocardial ischemia–reperfusion injury (MI/RI)-associated genes. **Table S3:** Bioactive compounds in aqueous extracts of KDZ: identification, ADME parameters, and screening results.