A Preliminary Study on the Antioxidant Activity of *Lycium ruthenicum* Polysaccharides *in vitro/in vivo* and its Protective Mechanism on Oxidized Damaged Cells

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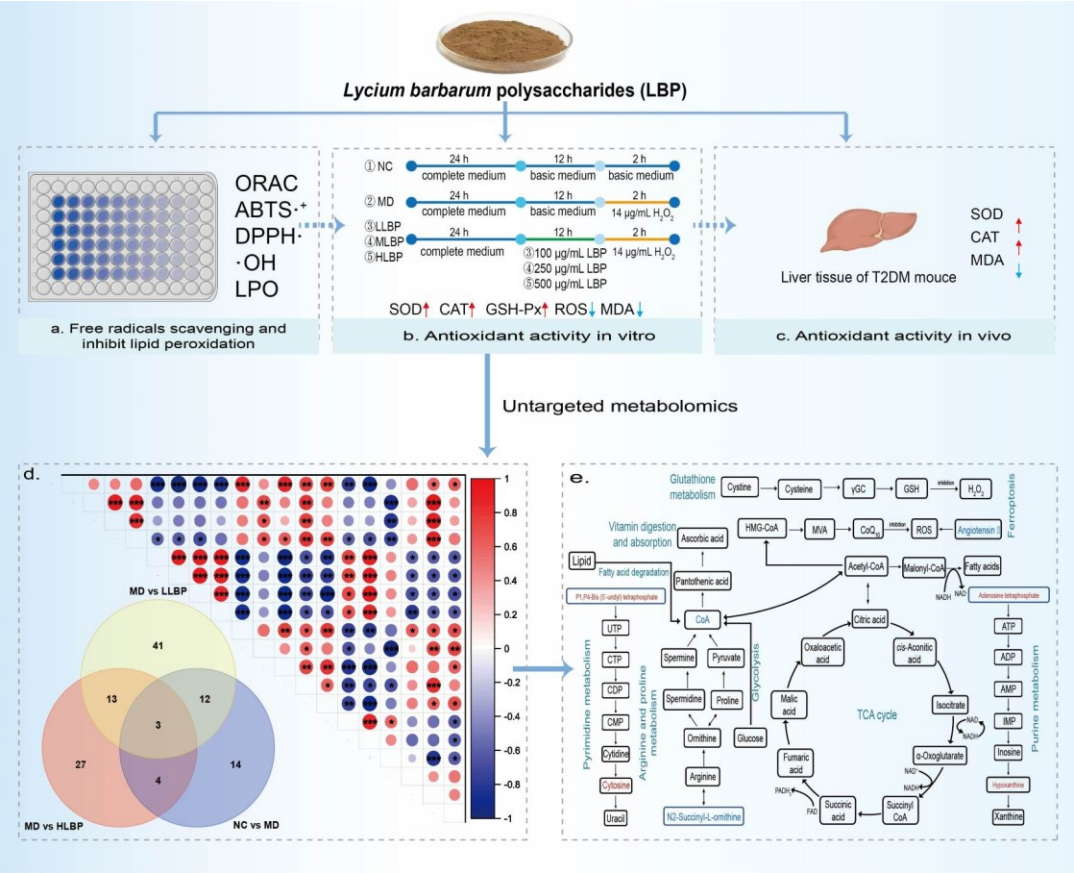
GRAPHICAL ABSTRACT



A Preliminary Study on the Antioxidant Activity of *Lycium ruthenicum* Polysaccharides *in vitro/vivo* and its Protective Mechanism on Oxidized Damaged Cells

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Lycium ruthenicum polysaccharides (LRP) are known to possess antioxidant effects. However, a systematic evaluation across chemical, cellular, and *in vivo* models have been lacking. The underlying metabolomic mechanisms also remain unexplored. This study systematically evaluated the antioxidant effects of LRP through *in vitro* assays, H_2O_2-induced AML12 hepatocytes, and liver tissue from mice, supplemented by untargeted metabolomic analysis of cell extracts to explore LRP's antioxidant mechanisms. Results showed that LRP possessed significant oxygen radical absorbance capacity and potent scavenging activity against ABTS•$^+$, DPPH•, and •OH radicals *in vitro*. In AML12 cells, LRP increased activities of antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), and glutathione reductase (GSH-Px), while effectively reducing intracellular reactive oxygen species (ROS) and malondialdehyde (MDA) levels (P<0.05). In mouse liver tissues, LRP may have slightly improved SOD and CAT levels while decreasing MDA levels (P>0.05). Furthermore, untargeted metabolomics revealed that LRP attenuated oxidative damage by modulating metabolic pathways, particularly glutathione metabolism, the tricarboxylic acid (TCA) cycle, and amino acid metabolism. These findings confirm the significant antioxidant potential of LRP, supporting its promise as a functional food ingredient.

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Keywords: Lycium ruthenicum Murray; Metabolomics; Bioactive compounds; Phytochemicals

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INTRODUCTION

Phytochemicals such as polysaccharides, polyphenols, and flavonoids have received extensive attention because of their beneficial biological effects, including antioxidant, hypoglycemic, anti-tumor, and other activities (Öz *et al.* 2023; Gogoi *et al.* 2025). Among these bioactive constituents, plant polysaccharides, which are macromolecules composed of numerous monosaccharides linked by glycosidic bonds (Huang *et al*. 2025). Moreover, polysaccharides have high thermal stability, excellent biocompatibility, and low toxicity, making them effective functional food ingredients for combating oxidative stress (Xue *et al.* 2024). Such compounds can exert exceptional antioxidative effects through three complementary mechanisms: (1) direct scavenging of reactive oxygen species (ROS) (Tang *et al*. 2025), (2) activation of the enzymatic

antioxidant system (Song *et al*. 2025), (3) regulation of signaling pathways (Yang *et al.* 2025).

Lycium ruthenicum Murray, a medicinal and edible plant, is rich in anthocyanins, polyphenols, and essential amino acids (Dong *et al.* 2025). With expanding cultivation and growing research interest, this species has attracted increasing attention in recent studies. To date, most studies have focused on its salt stress tolerance and anthocyanin composition (Liu *et al.* 2025). Nevertheless, emerging evidence has begun to highlight the bioactive potential of *L. ruthenicum* polysaccharides (LRP) (Liu *et al.* 2024; Lu *et al.* 2025; Zhao *et al.* 2026). Despite these promising findings, two fundamental knowledge gaps persist: (1) lack of comprehensive antioxidant evaluation of LRP spanning chemical scavenging, cellular protection, and *in vivo* models; and (2) lack of exploration of LRP's antioxidant mechanisms. These limit the development of LRP as a functional food ingredient for oxidative stress mitigation.

This study assessed the antioxidant capacity of LRP *in vitro* and *in vivo*, and elucidated the potential regulatory mechanisms of LRP in AML12 cells by non-targeted metabolomics. By integrating chemical, cellular, and *in vivo* models with metabolomic profiling, this work can provide evidence supporting the potential of LRP as a functional food against oxidative stress-related diseases.

EXPERIMENTAL

Materials

Lycium ruthenicum Murray was obtained from Beijing Tongrentang Health Pharmaceutical (Qinghai) Co., Ltd. (Bar Code: 6971315920533). Ascorbic acid and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Aladdin Reagent (Shanghai) Co., Ltd. 2,2'-Azobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was from Shanghai Yuanye Bio-Technology Co., Ltd. The assay kits for catalase (CAT), glutathione reductase (GSH-Px), malonaldehyde (MDA), reactive oxygen species (ROS), and superoxide dismutase (SOD) were obtained from Nanjing Jiancheng Bioengineering Institute. The C57BL/6 mice were purchased from the Laboratory Animal Center of Zhengzhou University (SCXK (Yu) 2017-0001). The AML12 cells were from Procell Life Science & Technology Co., Ltd.

The LRP was extracted in the laboratory. *Lycium ruthenicum* Murray was dried, pulverized, and sieved. The powder was sequentially defatted, dealcoholized, and extracted with hot water. The extract was concentrated, deproteinized, and precipitated. The crude polysaccharide pellet was washed and lyophilized to obtain LRP, giving a yield of 1.921% ± 0.074%. The procedure and structural features refer to elsewhere (Li *et al.* 2025).

Free Radical Scavenging and Lipid Peroxidation Inhibition

The ORAC was measured in the same way with some modifications (Yuri *et al.* 2022). Briefly, LRP was mixed with 150 μL of 8.16×10^{-2} μmol/L fluorescein sodium and incubated at 37 °C for 10 min. After adding 25 μL of 153 mmol/L 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) solution, the area under the curve (AUC) of fluorescence intensity was recorded to establish a calibration curve, and Trolox solution was used as the control. The ORAC values were obtained as follows,

$$AUC = f_0\times0.5+(f_0+f_1+\ldots+f_{n-1}+f_n)+f_n\times0.5 \quad (1)$$

where f_0, f_{n-1}, f_n is the relative fluorescence intensities of the *0, n-1*, and *n* measuring points, respectively.

The corresponding radical scavenging activities were determined using ABTS, DPPH, and the Fenton reaction system. They were determined using modified methods (Alodaini *et al.* 2025). Scavenging activity (%) was calculated as follows,

$$Scavenging\ activity(\%) = \frac{(A_0 - A_{00}) - (A_S - A_{S0})}{A_0 - A_{00}} \times 100\% \quad (2)$$

where A_S is the absorbance of sample group, A_{S0} is the absorbance of sample control group, A_0 is the absorbance of blank control group, and A_{00} is the absorbance of blank group.

Lipid peroxidation inhibitory ability was evaluated using egg yolk homogenate and the thiobarbituric acid method (Deng *et al*. 2024). The lipid peroxidation inhibition rate (IR) was calculated as follows.

$$IR(\%) = \frac{A_0 - (A_S - A_{S0})}{A_0} \times 100\% \quad (3)$$

where A_S is the absorbance of sample group, A_{S0} is the absorbance of sample control group, and A_0 is the absorbance of black control group.

Assay of Antioxidant Activity *In Vitro*

The general steps of the cell experiment were shown in Graphical Abstract (b). The levels of SOD, CAT, GSH-Px, MDA, and ROS were analyzed using commercial kits.

Assay of Antioxidant Activity *In Vivo*

The steps of the animal experiment were shown in Graphical Abstract (c). After intervention, mice were fasted and anesthetized, and liver tissue was obtained. The levels of SOD, CAT, and MDA in mouse liver tissue were measured using commercial kits.

Untargeted Metabolomic Analysis of Cell Extracts

The steps of the experiment were shown in Graphical Abstract (d). Metabolites in cells from the MLRP and HLRP groups were measured by Beijing Biomarker Technologies Co., Ltd, with some modifications of the method from the previous study (Wang *et al.* 2016).

Statistical Analysis

Statistical analyses were performed using SPSS 25.0. The data that fitted a normal distribution were expressed as means ± SD. The Spearman correlation coefficient was used to judge the correlation between different metabolites and antioxidant indices. $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Free Radical Scavenging and Lipid Peroxidation Inhibition

As shown in Figs. 1A and B, fluorescence decay rates decreased dose-dependently with increasing concentrations of both Trolox and LRP. The ORAC of LRP was 435.5 μmol TE/100 g DW. In radical scavenging assays (Fig. 1C to E), LRP demonstrated potent activity with 50% inhibition concentrations (IC_{50}) of 0.080 mg/mL for $ABTS^{\bullet+}$, 0.084 mg/mL for DPPH•, and 0.343 mg/mL for •OH. Notably, LRP significantly inhibited lipid

peroxidation with IC_{50} of 0.88 mg/mL (Fig. 1F).

Antioxidant Activity *In Vitro*

As shown in Fig. 2A, cell viability exhibited clear improvement with increasing concentrations of LRP, reaching maximum recovery at the highest tested concentration (500 µg/mL). Although the LLRP group showed no statistically significant difference compared to the MD group ($P>0.05$), both MLRP and HLRP treatments significantly enhanced viability ($P<0.01$). In Fig. 2B to D, compared to the MD group, MLRP and HLRP treatments significantly increased the activities of key antioxidant enzymes. SOD activity rose 2.0-fold, CAT activity increased 5.7-fold, and GSH-Px activity was elevated by 1.9-fold ($P<0.01$). Simultaneously, these treatments markedly decreased oxidative damage biomarkers ($P<0.01$). MDA level decreased by 68% (Fig. 2E), and intracellular ROS production was reduced by 49% relative to the MD group (Fig. 2F). Overall, these results demonstrate that LRP protects against H_2O_2-induced damage by synergistically enhancing endogenous antioxidant defenses and mitigating oxidative damage.

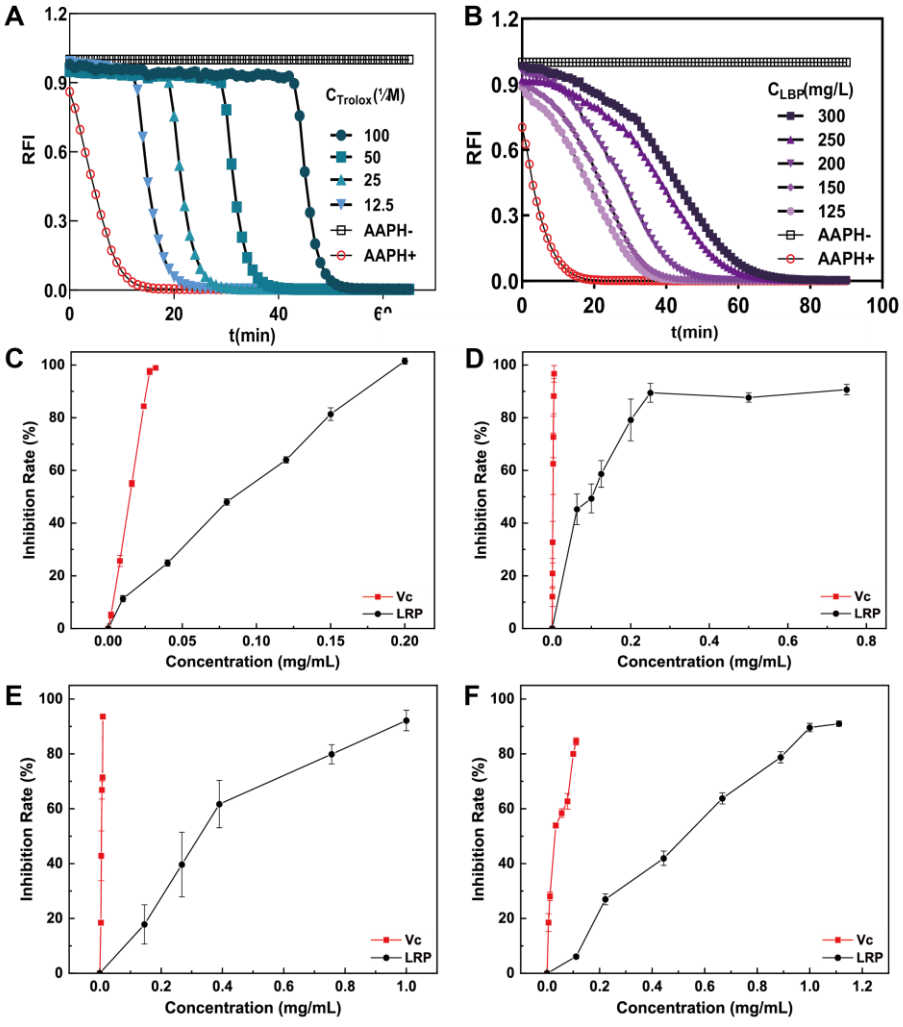

Fig. 1. Free radical scavenging and lipid peroxidation inhibition capacity of Vc and LRP. A-B: The result of ORAC. C-E: ABTS•$^+$, DPPH•, •OH scavenging ability of LRP; F: Effect of LRP on inhibition activity of lipid peroxidation.

Antioxidant Activity *In Vivo*

In T2DM mouse livers, LRP treatment showed modest effects on hepatic antioxidant markers. SOD and CAT activities showed non-significant increases, while MDA content decreased marginally compared with the MD group (P>0.05, Fig. 3).

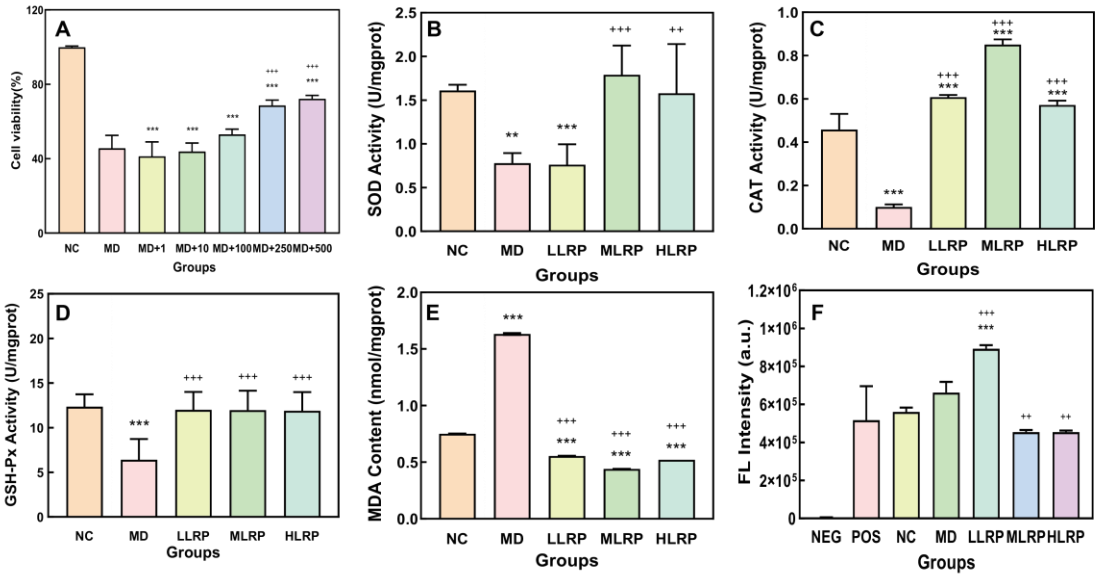

Fig. 2. Antioxidant activity of LRP *in vitro*. A: The effect of LRP intervention dose (μg/mL) on the viability of H_2O_2-induced AML12 cells; B-D: Cellular SOD, CAT, and GSH-Px viability; E: Cellular MDA level. F: Fluorescence intensity of ROS in various cellular test solutions. NEG: AML12 cells + PBS. POS: AML12 cells + probe + ROS. The rest: different treatment groups + probe. Compared with NC group, * P<0.05, ** P<0.01, *** P<0.001. Compared with MD group, + P<0.05, ++ P<0.01, +++ P<0.001.

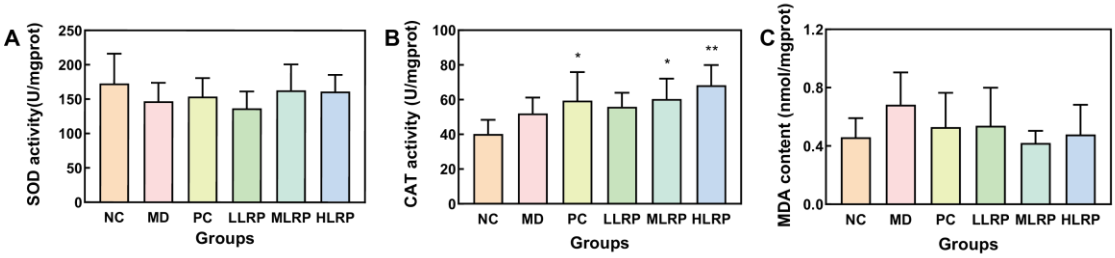

Fig. 3. Antioxidant activity of LRP *in vivo*. A-C: SOD, CAT, and MDA viability. Compared with the NC group, * P<0.05, ** P<0.01

Untargeted Metabolomic Analysis of Cell Extracts

Differential metabolites were defined based on thresholds of |fold change (FC)| > 1.0, P<0.05, and variable importance in projection (VIP) score>1.0. Detailed counts are provided in Fig. 1d. Pathway enrichment analysis revealed that the MLRP group exhibited significant enrichment in the purine metabolism pathway and the ABC transporters pathway compared to the MD group (Fig. 4A). Similarly, the HLRP group showed enrichment in the purine metabolism and the porphyrin metabolism pathways (Fig. 4B).

Figure 5 shows the correlation analysis between cellular oxidative stress-related indexes and DAMs. Based on FC magnitude and P-value, eight signature metabolites with notable correlations were identified. These included cytosine, P1, P4-Bis (5'-uridyl)

tetraphosphate, adenosine tetraphosphate, hypoxanthine, coenzyme A (CoA), N2-succinyl-L-ornithine, angiotensin II, and CDP-4-dehydro-6-deoxy-D-glucose (Table 1). Figure 1e indicated that these metabolites are involved in key metabolic pathways such as arginine and proline metabolism, purine and pyrimidine metabolism, TCA cycle, glutathione metabolism, and cofactor/vitamin metabolism.

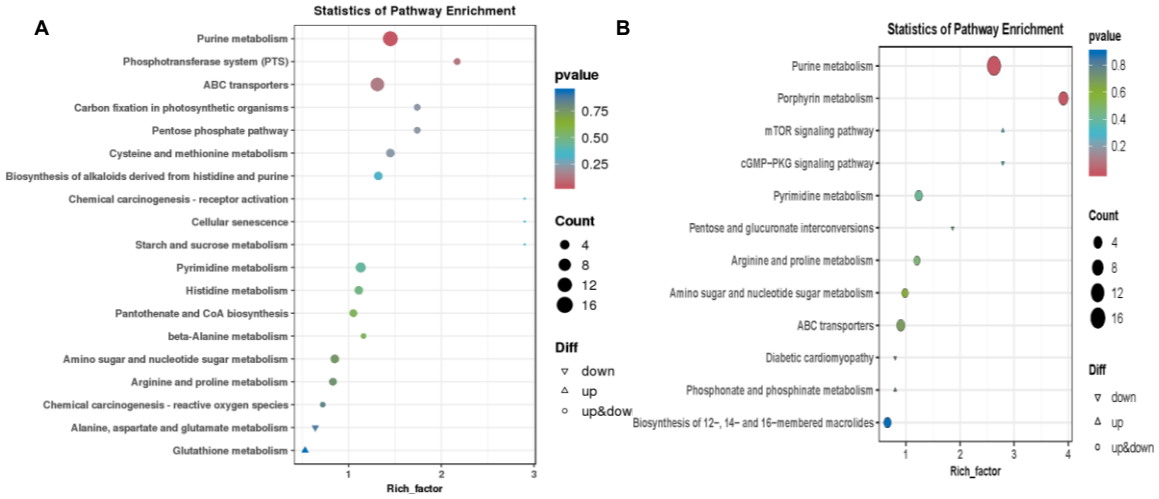

Fig. 4. Analyses of metabolic pathways. A-B: Volcano plot and KEGG pathway enrichment dotplot for MLRP vs MD; C-D: Volcano plot and KEGG pathway enrichment dotplot for HLRP vs MD. A high-resolution version is available upon request.

To understand how LRP influences cellular metabolism to exert antioxidant effects, differentially abundant metabolites (DAMs) in the treatment groups were examined. The analysis identified 47 DAMs in the MLRP group and 69 in the HLRP group, with 16 metabolites overlapping between the two groups (Graphical Abstract).

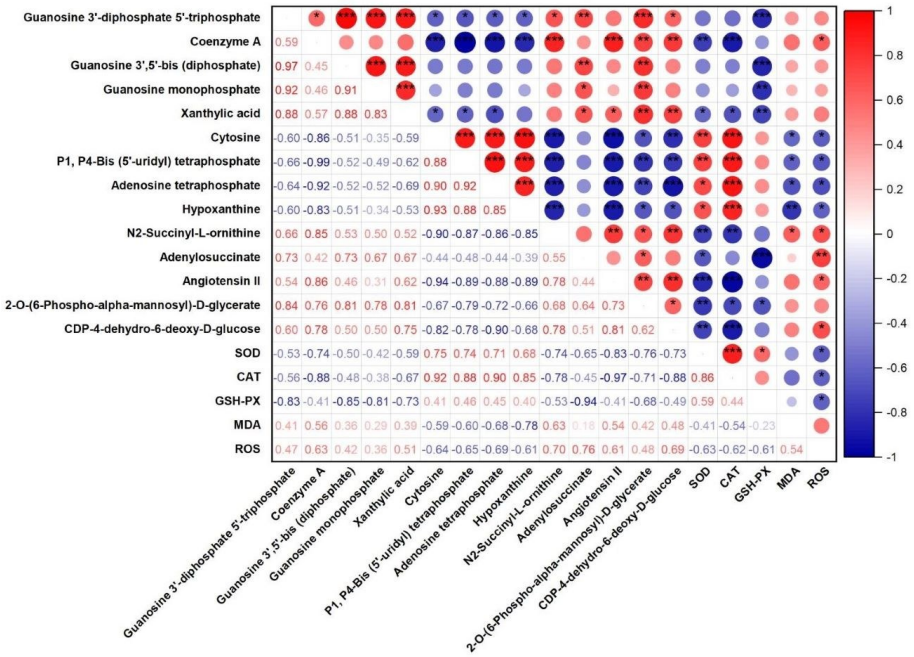

Fig. 5. Correlation analysis between cellular oxidative stress-related indexes and differentially abundant metabolites. * P<0.05, ** P<0.01, *** P<0.001.

Among these, 14 metabolites with consistent alterations were selected for correlation analysis with key oxidative stress markers (SOD, CAT, GSH-Px, MDA, and ROS).

Table 1. Consistently Altered Metabolites and Their Classification

Categorization	Metabolite	FC		Change
		MLRP	HLRP	
Nucleotides and derivatives	Guanosine 3'-diphosphate 5'-triphosphate	0.176	0.219	↓
	Guanosine 3',5'-bis (diphosphate)	0.624	0.574	↓
	Guanosine monophosphate	0.625	0.540	↓
	Xanthylic acid	0.698	0.695	↓
	Cytosine *	1.327	1.083	↑
	P1,P4-Bis (5'-uridyl) tetraphosphate *	1.473	1.170	↑
	Adenosine tetraphosphate *	4.001	1.823	↑
	Hypoxanthine *	1.313	1.040	↑
	Adenylosuccinate	0.001	0.001	↓
Coenzymes and cofactors	Coenzyme A *	0.344	0.609	↓
Amino acids and derivatives	N2-Succinyl-L-ornithine *	0.649	0.746	↓
Hormones	Angiotensin II *	0.493	0.839	↓
Sugars and derivatives	2-O-(6-Phospho-alpha-mannosyl)-D-glycerate	0.368	0.464	↓
	CDP-4-dehydro-6-deoxy-D-glucose *	0.746	0.882	↓
* Eight metabolites were selected based on correlation analysis and significant differences.				

In the case of LRP (Li *et al.* 2025), SEM showed a relatively smooth surface, indicating a uniform molecular arrangement that may help interact with oxidative species. The monosaccharide composition of LRP is characterized by high levels of galacturonic acid, arabinose, galactose, and rhamnose, all of which have been linked to antioxidant activity (Chen *et al*. 2025). Notably, galacturonic acid could contribute carboxyl groups that work together with hydroxyl groups, enhancing electron-donating ability. Besides monosaccharide composition, the pattern of glycosidic linkages also impacts antioxidant activity, with β-type links often associated with stronger effects (Ao *et al.* 2025). Additionally, polysaccharides with lower molecular weights generally exhibit higher antioxidant potential because of easier access to reductive hydroxyl groups (Chen *et al*. 2024). Collectively, the reducing properties of LRP can be attributed to its smooth surface, specific monosaccharide composition rich in acidic sugars and distinctive molecular structure.

LRP protects against H_2O_2-induced oxidative damage by modulating multiple metabolic pathways (Fig. 1e), which is consistent with previous reports (Karagiannis *et al.* 2024). Specifically, LRP influences amino acid metabolism—where arginine serves as a precursor for nitric oxide and modulates SIRT1-related pathways to reduce apoptosis, while proline helps maintain mitochondrial redox balance (Zhao *et al.* 2021; Feng *et al.* 2023). It also regulates nucleotide metabolism; uridine alleviates oxidative stress, whereas imbalances in purine and pyrimidine metabolism exacerbate it (Wu *et al.* 2025). Furthermore, LRP affects cofactor and vitamin metabolism, including pantothenic acid and CoA biosynthesis—pathways known to influence mitochondrial function and antioxidant capacity (Lee *et al.* 2023). Glutathione metabolism further underscores mitochondrial reliance on the ascorbate-glutathione cycle to neutralize ROS (Decros *et al.* 2023).

However, as these findings are based on untargeted metabolomics, further validation of the identified differential metabolites and their specific roles is warranted.

CONCLUSIONS

1. This study systematically demonstrated the antioxidant activity of *Lycium ruthenicum* polysaccharides (LRP) *in vitro* and *in vivo*. The key insight is that LRP was found to exert potent antioxidant effects through a dual mechanism: direct radical scavenging (ORAC: 435.5 μmol TE/100 g DW; IC_{50}: 0.080 mg/mL for $ABTS^{\bullet+}$, 0.084 mg/mL for DPPH•, 0.343 mg/mL for •OH) and enhancement of endogenous antioxidant defenses (SOD: 2.0-fold, CAT: 5.7-fold, GSH-Px: 1.9-fold), while reducing oxidative damage markers in H_2O_2-induced AML12 cells.
2. Untargeted metabolomics revealed that LRP attenuated oxidative damage by modulating key metabolic pathways including glutathione metabolism, TCA cycle, and amino acid metabolism. This provides the metabolomic-level insight into how LRP combats oxidative stress by regulating cellular metabolism.
3. These findings establish that the polysaccharides from *Lycium ruthenicum* are potent natural antioxidants. The present work advances the field by providing a comprehensive evaluation spanning chemical, cellular, and *in vivo*, and by elucidating the metabolomic mechanisms underlying LRP's protective effects. This positions LRP as a promising functional food ingredient for oxidative stress-related diseases, with a clearer mechanistic understanding than previously available.

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