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Triterpenoid and Saponin Enriched Extract from *Ananas comosus* (L.) Merr. Residue Attenuates Oxidative Stress in *Caenorhabditis elegans* by Targeting SRC/ESR1/PTPN11 and Modulating Alanine, Aspartate, and Glutamate Metabolism

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ABSTRACT: To realize the value-added utilization of pineapple (*Ananas comosus* (L.) Merr., AC) residue, this study isolated and purified an extract rich in triterpenoids and saponins (ACRP). Its main components are eclalbasaponin I, ginsenoside Rh4, and trifoside C. At a concentration of 1 mg/mL, ACRP reduced the malondialdehyde (MDA) level in *Caenorhabditis elegans* (*C. elegans*) by 80.15%. Meanwhile, it increased the activities of total superoxide dismutase (T-SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) by 136.34%, 39.62%, and 150.44%, respectively. Network pharmacology and molecular docking results suggested that the core components of ACRP may target oxidative stress-related proteins, including SRC, ESR1, and PTPN11. Metabolomic analysis further indicated that the antioxidant effects of ACRP might involve the regulation of alanine, aspartate, and glutamate metabolism. This study clarifies the putative molecular antioxidant mechanism of ACRP and provides a preliminary theoretical basis for the high-value utilization of pineapple processing by-products.

Keywords: *Ananas comosus* (L.) Merr. residue; Triterpenes and saponins; Component analysis; Molecular docking; Antioxidant activity; Untargeted metabolomics

1. Introduction

Pineapple (*Ananas comosus* (L.) Merr., AC) is an economically important fruit with a global market value of approximately \$9 billion. It contains abundant bioactive components with anti-inflammatory, antioxidant, and immunoregulatory activities (Hikal et al., 2021; Mohd Ali et al., 2020). Accumulating evidence indicates that these active components exert beneficial biological effects via multiple molecular targets and signaling pathways (Chong et al., 2024; Tallei et al., 2024). Therefore, in-depth studies on the

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bioactive mechanisms of pineapple-derived components are crucial to clarify their health benefits and support the high-value development of the pineapple industry chain.

With the continuous increase in both the cultivation area and yield of AC, its processing by-products (including peel, core, pomace, leaves, etc., accounting for 60–80% of the fresh fruit mass (Tran et al., 2023)) have become a prominent issue in terms of resource waste and environmental pollution (Sarangi et al., 2022). Therefore, the resource utilization of AC residue (AR) represents a critical breakthrough for alleviating environmental pressure and enhancing the economic sustainability of the industry. Existing studies have validated the high-value potential of AR. Fermented AR has been used in livestock breeding to improve product quality and antioxidant activity (Lu et al., 2024), while AR has also been applied in fruit wine brewing (Sabino et al., 2023) and as a renewable adsorbent for eco-friendly materials (Tran et al., 2023). Despite these promising applications, AR obtained by conventional pressing still contains abundant functional components such as water-insoluble polyphenols, triterpenoids, and saponins that remain underutilized. Therefore, the efficient extraction and bioactivity development of these functional constituents, particularly water-insoluble triterpenoids and saponins from AR, will not only improve resource utilization efficiency but also offer technical support for the development of functional foods and other high-value-added AR products.

Triterpenoids and saponins in fruits are natural active components composed of triterpenoid glycosides linked to sugar chains via glycosidic bonds. They exhibit surface activity and diverse physiological functions, including anti-inflammatory, antioxidant and metabolic regulatory effects (Baky et al., 2022). For example, citrus triterpenoids could stimulate Caco-2 cells to secrete glucagon-like peptide-1, showing potential hypoglycemic activity (Lv et al., 2025). Triterpenes from *Rosa roxburghii* displayed significant anti-inflammatory and α -glucosidase inhibitory activities (S. Zhang et al., 2024), while ginseng fruit saponins exerted anti-photoaging and antioxidant effects by alleviating UV-induced damage (T. Li et al., 2024). However, most of these studies remain at the level of crude extracts, lacking precise separation and structural identification of monomeric compounds, as well as systematic establishment of structure-activity relationships. Although AR is also rich in triterpenoids and saponins, related research is nearly absent, and the composition, structural characteristics, and mechanisms of action of its bioactive constituents remain unclear. Current bioactivity evaluations are mostly limited to simple *in vitro* indicators, lacking in-depth validation using *in vivo* models and molecular targets, which makes it difficult to establish a comprehensive link between components and bioactivities. Therefore, systematic exploration of the triterpenoids and saponins in AR and their underlying bioactive mechanisms is crucial for achieving its full utilization and high-value application.

Based on the aforementioned research gaps, this study aims to move beyond the crude extract level and systematically elucidate the antioxidant mechanisms of AR. We first investigated the *in vitro* antioxidant activity of the AR crude extract (ACR) and its effect on the antioxidant capacity of *Caenorhabditis elegans* (*C. elegans*). Subsequently, the crude extract (ACR) was separated and purified to obtain its purified fraction (ACRP), and the major constituents of ACRP were accurately identified. Network pharmacology and molecular docking were employed to analyze the molecular targets of key compounds (triterpenoids and

saponins) in ACRP within the protein network associated with oxidative stress. Furthermore, we validated the *in vitro* and *in vivo* antioxidant activities of ACRP and utilized non-targeted metabolomics to explore relevant metabolic pathways, thereby revealing the underlying mechanisms by which ACRP enhances the antioxidant capacity of *C. elegans*. These findings provide a preliminary scientific basis for the potential development of ACRP in functional foods and health products, while also offering insights into mitigating the environmental impact and low-value waste associated with the increasing annual production of pineapple (AC) and its processing by-products.

2. Materials and methods

2.1 Preparation of ACR and ACRP

AC was purchased from the local market (Yangjiang, China), peeled, and AR was obtained by pressing the flesh to collect the residue. AR was further mixed with water (1:1 g/mL) and crushed using a wall-breaking machine. Anhydrous ethanol was added to the crushed mixture until the final concentration reached 60%, and the mixture was extracted for 30 min under ultrasonic power of 600 W, followed by centrifugation, rotary evaporation, and freeze-drying to obtain ACR. ACR was mixed with water at a ratio of 1:10 (g/mL). Based on our previous study, LX-8 macroporous resin exhibited the highest adsorption capacity (2675.10 µg/g) and desorption rate ($55.55 \pm 1.34\%$) for polar compounds among five types of macroporous resins under optimized conditions (Lee et al., 2025). Therefore, LX-8 macroporous resin, a polar resin with a particle size of 0.315–1.00 mm and a surface area of 300–400 m²/g, was selected for subsequent experiments. The resin was activated according to the manufacturer's instructions and added to the mixed solution at a ratio of 0.1:10 (resin:solution, g/mL). The mixture was then subjected to adsorption for 12 h on a constant-temperature shaker at 25 °C and 180 rpm. The resin containing ACRP was washed three times with water until no impurities remained, then transferred to an 80% ethanol solution for desorption at 25 °C and 180 rpm for 12 h (Zong et al., 2025). Finally, ACRP was obtained via rotary evaporation and freeze-drying.

2.2 *In vitro* antioxidant activity of ACR and ACRP

The *in vitro* antioxidant activities of ACR and ACRP were evaluated at various concentrations (0.0625, 0.125, 0.25, 0.5, 1, 2 and 4 mg/mL), with ascorbic acid as the positive control (Zhou et al., 2025). Briefly, DPPH radical scavenging activity was measured by mixing 100 µL of sample with 100 µL of 80 µmol/L methanolic DPPH solution. The mixture was incubated at 25 °C for 30 min, and the absorbance was recorded at 517 nm. For ABTS radical scavenging activity, 40 µL of sample was mixed with 160 µL of ABTS working solution, followed by incubation at 25 °C for 8 min, and the absorbance was measured at 734 nm. Hydroxyl radical scavenging activity was determined by mixing the sample with FeSO₄, salicylic acid-ethanol solution, and H₂O₂. The reaction system was incubated at 37 °C for 30 min, and the absorbance was detected at 510 nm.

2.3 *In vivo* antioxidant activity of ACR and ACRP

The *in vivo* antioxidant capacity of ACR and ACRP was determined by exploring its impact on the antioxidant capacity of *C. elegans* (Lee et al., 2023). After synchronization, *C. elegans* were randomly divided

into 7 groups (100 μ L each): NFD (control, NGM + OP50 without extracts), ACR-L (0.1 mg/mL), ACR-M (0.5 mg/mL), ACR-H (1 mg/mL), ACRP-L (0.1 mg/mL), ACRP-M (0.5 mg/mL), ACRP-H (1 mg/mL). After 3-day intervention, worms were collected, cleaned, homogenized and centrifuged for supernatant. Subsequently, the antioxidant related biochemical indicators such as malondialdehyde (MDA), total superoxide dismutase (T-SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) levels were measured according to the requirements of the test kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) (Lee et al., 2024).

2.4 Component analysis based on HPLC-MS/MS

The Acquity UPLC H-Class ultra-high performance liquid chromatograph was equipped with a photodiode matrix (PDA) detector system and a mass spectrometry system (Xevo G2-XS QToF, Waters, Milford, USA) coupled. DAD was used to monitor signals in the 190-600 nm wavelength range with a resolution of 2 nm. ACRP was dissolved in 80% methanol solution, filtered through a microporous membrane (0.22 μ m), and the sample (20 μ L) was injected into an ACQUITY UPLC BEH C18 (1.7 μ m 2.1*50 mm, Waters, Milford, USA) high-performance liquid chromatography column at 40 °C. A two-stage MS/MS spectrum was obtained in the positive and negative ion modes of electric spray ionization (ESI), and the compound names of ACRP triterpenes and saponins compounds were matched in Waters Traditional Medicine Library 2.0 (Y. Zhang et al., 2023).

2.5 Network pharmacology analysis

Based on HPLC-MS/MS analysis, key active components in ACRP were identified and screened. Fifteen characteristic small molecules with high response values and classified as triterpenoids and saponins were initially selected. Potential protein targets for each compound were predicted using the SwissTargetPrediction (<http://swisstargetprediction.ch/>) database, and target nomenclature was standardized against the Uniprot (<https://www.uniprot.org/>) database. According to the target prediction output, 11 core components with comprehensive and reliable target information were further chosen for subsequent network pharmacology analysis (C. Wang et al., 2023).

Oxidative stress was used as a keyword and inputted into GeneCards (<https://www.genecards.org/>) database to screen key disease protein targets, and the data was exported to select protein targets with the score > 1 for subsequent network pharmacology analysis and molecular docking studies. ACRP regulated disease-related protein targets was analyzed by jvenn (<https://jvenn.toulouse.inra.fr/app/example.html>) platform, and the results were visualized and analyzed using Cytoscape 3.8.0 software.

The Go ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment pathway of ACRP intervention in oxidative stress was analyzed by David (<https://david.ncifcrf.gov/tools.jsp>) database, with a screening criterion of $P < 0.05$, and ranking Gene ratio in the top 10 from high to low. GO pathway enrichment analysis included biological process (BP), molecular function (MF), and cellular composition (CC) analysis.

The data of ACRP regulating oxidative stress-related protein targets was imported into STRING (<https://string-db.org/>) database to assess protein-protein interaction (PPI) network, and the results were imported into Cytoscape 3.8.0 software for visual analysis. The betweenness, closeness and degree values were obtained through the cytoNCA program, and the key protein targets were screened for subsequent molecular docking studies based on the median of these results.

2.6 Molecular docking study

The 3D structure of key proteins obtained from PPI analysis were downloaded through searching PDB (<https://www.rcsb.org/>) database, and these structures were imported into AutoDock Tools 1.5.7 software to finish dehydration and hydrogen bonding treatment as protein receptors. The 2D structure of the active substances in ACRP were obtained by searching PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) database, and these structures were imported into Chem 3D 23.1.1 software to minimize energy, served as a small molecule ligand through achieving hydrogenation treatment in AutoDock Tools 1.5.7 software. It was studied about the binding ability of small molecule ligands to protein receptors through molecular docking in AutoDock Tools 1.5.7 software and visualization analysis in Pymol 2.3 software (Vidal-Limon et al., 2022).

2.7 Non-targeted metabolomics analysis

Following 3 days of ACRP intervention (0 and 1 mg/mL), *C. elegans* was collected, and sample pretreatment and liquid chromatography–mass spectrometry (LC-MS) analysis were carried out according to the previously described method (Lee et al., 2024). Three independent biological replicates were performed per group. The results were imported into Progenesis QI software (Waters Corporation, Milford, USA) for standardization and then matched against the HMDB (<http://www.hmdb.ca/>) and Metlin (<https://metlin.scripps.edu/>) databases to obtain detailed metabolite information. Metabolite annotation confidence levels were assigned according to the Metabolomics Standards Initiative (MSI), with all reported metabolites classified as Level 2 (putatively annotated compounds) or higher based on accurate mass matching and MS/MS fragmentation patterns. Furthermore, characteristic metabolites were screened by calculating variable importance for the projection (VIP) and p value for different groups of samples, with screening conditions of $VIP > 1$ and $P < 0.05$. The obtained characteristic metabolites were matched with the KEGG (<https://www.kegg.jp/kegg/pathway.html>) database to obtain potential key metabolic pathway information (Chang et al., 2023).

2.8 Statistical analysis

Data analysis and drawing were conducted through IBM SPSS Statistics 26 software and Origin 2019b 32Bit software, respectively. All experimental results were repeated at least three times and expressed as mean $\pm$ SD. Statistical differences were calculated using one-way analysis of variance. Duncan's test was used to compare the mean values, and $P < 0.05$ was considered significant. The correlation between the antioxidant capacity and specific metabolites of ACRP-treated *C. elegans* was determined by Spearman's correlation analysis.

3. Results

3.1 The antioxidant activity of ACR in vitro and in vivo

The *in vitro* and *in vivo* antioxidant activity of ACR was preliminarily investigated in this study, and ACR was found to have a strong ability to scavenge DPPH radicals, ABTS radicals and hydroxyl radicals in vitro, with the strongest ability to scavenge ABTS radicals, followed by hydroxyl radicals (Fig. 1A-C). In the study of the *in vivo* antioxidant activity of ACR, ACR could significantly reduce the MDA level in *C. elegans* and significantly increase the secretion levels of antioxidant enzymes (T-SOD, GSH-Px and CAT) (Fig. 1D-G). Compared with the NFD group, the MDA level in *C. elegans* of the ACR-H group significantly reduced by 82.95%, and the levels of T-SOD, GSH-Px and CAT significantly increased by 92.76%, 36.60% and 119.28%, respectively. (Fig. 1D-G, $P < 0.05$). These results demonstrated the potential *in vitro* and *in vivo* antioxidant activity of ACR, providing a reference for further research on the composition and antioxidant activity mechanism of ACRP.

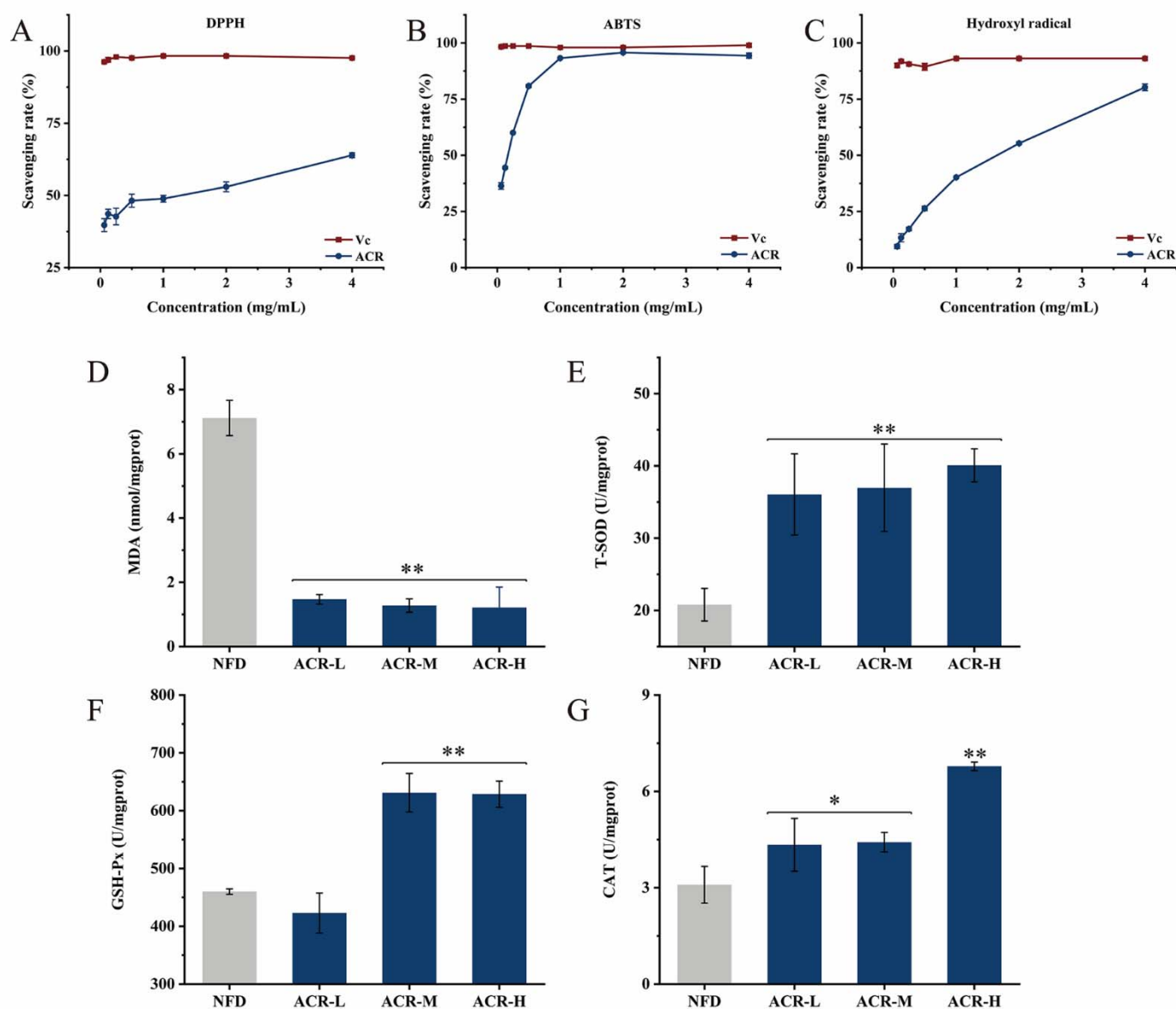


Fig. 1 The antioxidant activity *in vitro* and *in vivo* of ACR. The activity of ACR in clearing DPPH radicals (A), ABTS radicals (B), and hydroxyl radicals (C). The effect of ACR on the activities of MDA (D), T-SOD (E), GSH-Px (F) and CAT (G) in *C. elegans*.

3.2 Component analysis of ACRP

HPLC-MS/MS was employed to characterize the chemical composition of ACRP. A total of 15 triterpenoids and saponins with the highest response values were identified, namely chenodeoxycholic acid, doustere-4-ene-3,6-dione, eclalbasaponin I, ginsenoside Rg2, notoginsenoside R2, trifoside C, daturametelin C, musk ketone, ganoderic acid S, betulonic acid, ginsenoside Rh4, cimisine B, bullatantriol, soyasaponin III, methylgibberellic acid Q (Table S1). These results define the major triterpenoid and saponin components of ACRP, providing a solid basis for exploring its antioxidant mechanisms and offering preliminary support for its potential application in the food industry.

3.3 Network pharmacology analysis of ACRP intervention in oxidative stress

To clarify the material basis and potential molecular mechanisms underlying the antioxidant effects of ACRP, 11 core components with complete target protein information and abundant of predicted targets in the databases were further selected for subsequent network pharmacology analysis (Fig. 2). Based on these components, network pharmacology analysis was performed to investigate the relationships between the 11 key components and oxidative stress. A total of 263 targets were predicted for these compounds, and 8424 oxidative stress-related targets were retrieved from public databases. Comparative analysis revealed 242 overlapping targets between the two datasets (Fig. 3A). Using these overlapping targets, we then constructed a component-target network, which contained 253 nodes (11 active components and 242 overlapping targets) and 431 edges (Fig. 3B). The node names of active substances were listed in Table S2. These results suggest that ACRP may exert its antioxidant effects by regulating multiple targets associated with oxidative stress.

To further elucidate the biological functions of these 242 potential targets, we performed GO and KEGG pathway enrichment analyses. In the KEGG enrichment pathway, pathways in cancer, neuroactive ligand-receptor interaction and chemical carcinogenesis-receptor activation were considered the main pathways through which ACRP intervened in oxidative stress (Fig. 3C). Regarding GO enrichment, positive regulation of transcription by RNA polymerase II, signal transduction and negative regulation of transcription by RNA polymerase II mainly participated in BP, plasma membrane, cytosol and cytoplasm mainly participated in CC, and protein binding, identical protein binding and ATP binding mainly participated in MF (Fig. 3D).

To identify the core protein targets among these 242 candidates, the overlapping targets were imported into the STRING platform for protein-protein interaction (PPI) network analysis (Fig. S1). After removing targets without interactions, a PPI network consisting of 182 nodes and 430 edges was constructed. Subsequently, a three-step topological screening was performed to identify key protein targets, including SRC, ESR1, MAPK1, JUN, MAPK3, and PTPN11. Detailed information on these hub targets is provided in Table S3.

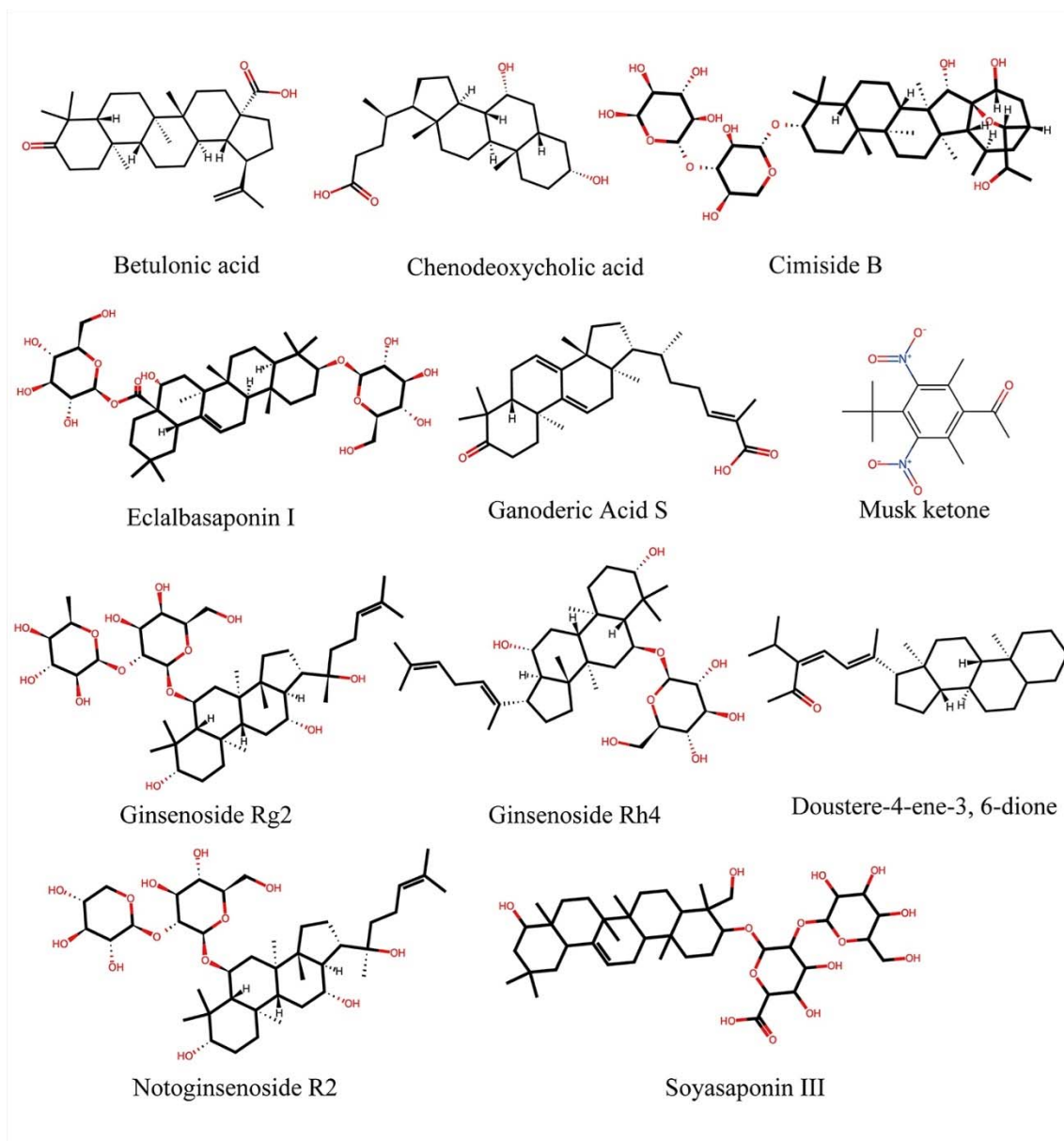


Fig. 2 The structure of ACRP major triterpenoids and saponins.

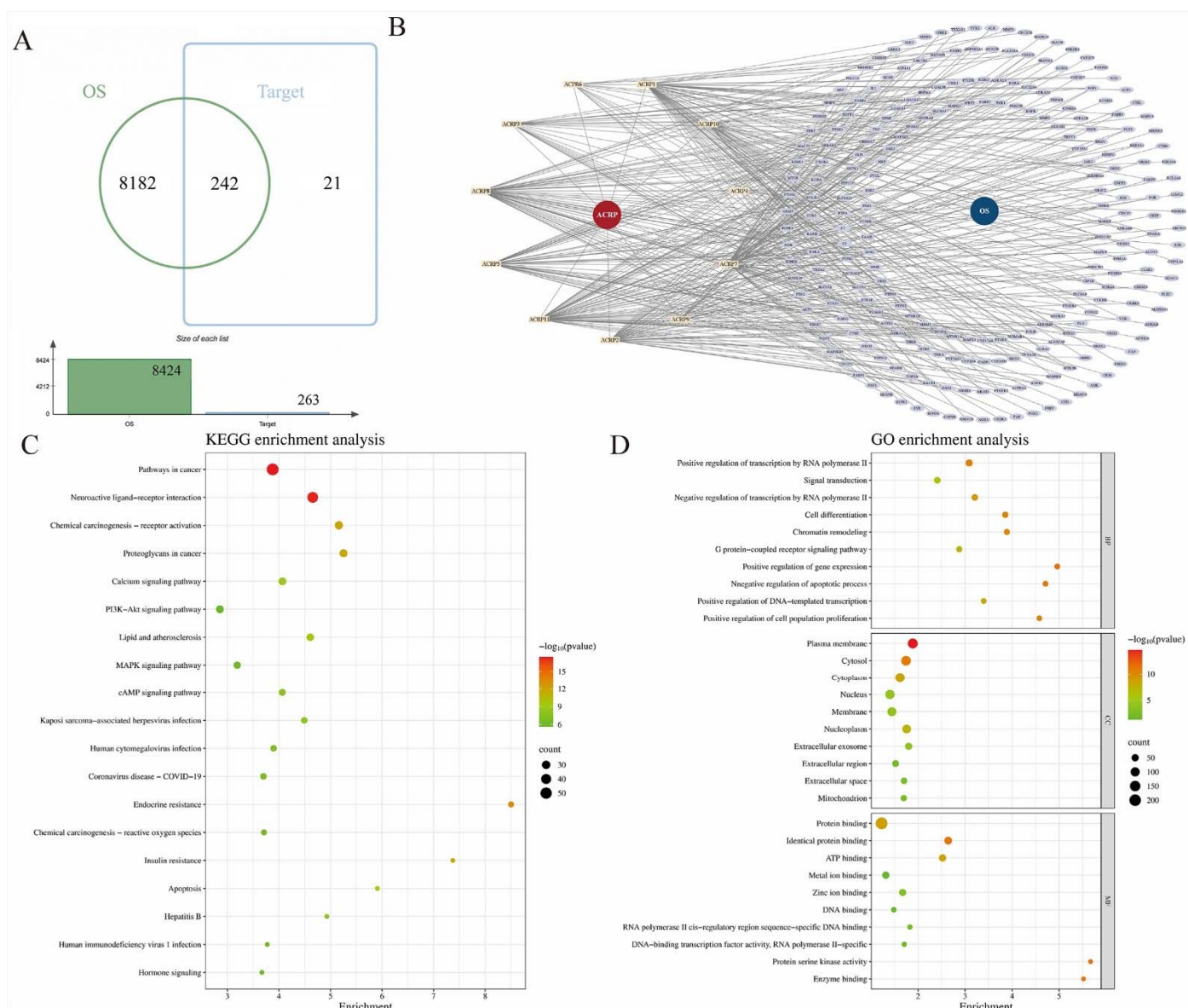


Fig. 3 Network pharmacology analysis of key small molecules in ACRP and oxidative stress diseases. A: Venn diagram. B: Network Diagram of ACRP-Regulated Oxidative Stress-Related Proteins. C: KEGG enrichment analysis. D: GO enrichment analysis. E-H: Protein-protein interaction (PPI) network analysis and screening of core protein targets.

3.4 Molecular docking

The binding energies and docking sites between key triterpenoids and saponins in ACRP and core target proteins were analyzed using molecular docking techniques (Fig. 4, Table 1). Molecular binding energies below -4.5 kcal/mol indicated strong autonomous molecular docking ability between protein receptors and small molecule ligands, suggesting that key small molecules in ACRP could autonomously dock with oxidative stress-related core protein targets (Fig. 4, Table 1). The minimum binding energy between ganoderic acid S and PTPN11 was -7.38 kcal/mol, and the binding energy between doustere-4-ene-3, 6-dione and ESR1 was -6.93 kcal/mol (Fig. 4, Table 1). Notably, this value is comparable to the binding affinities of known estrogen receptor ligands reported in recent studies, including 17β -estradiol, bisphenol A, and diethylstilbestrol, for which binding energies for ESR1 range from -8.29 to -9.94 kcal/mol (N. Li et al., 2025). The similarity in binding affinity suggests a high probability of specific interaction between

doustere-4-ene-3,6-dione and ESR1. In addition, small molecule ligands could bind to large molecule protein receptors through hydrogen bonding forces. Among them, the binding site between ganoderic acid S and PTPN11 was LYS-378, with a hydrogen bond length of 2.0. The binding site between doustere-4-ene-3, 6-dione and ESR1 was LYS-520, with a hydrogen bond length of 2.4 (Fig. 4, Table 1). These results indicated that ACRP key small molecules could autonomously bind to oxidative stress related core protein targets through hydrogen bonding, thereby exerting potential health improvement effects.

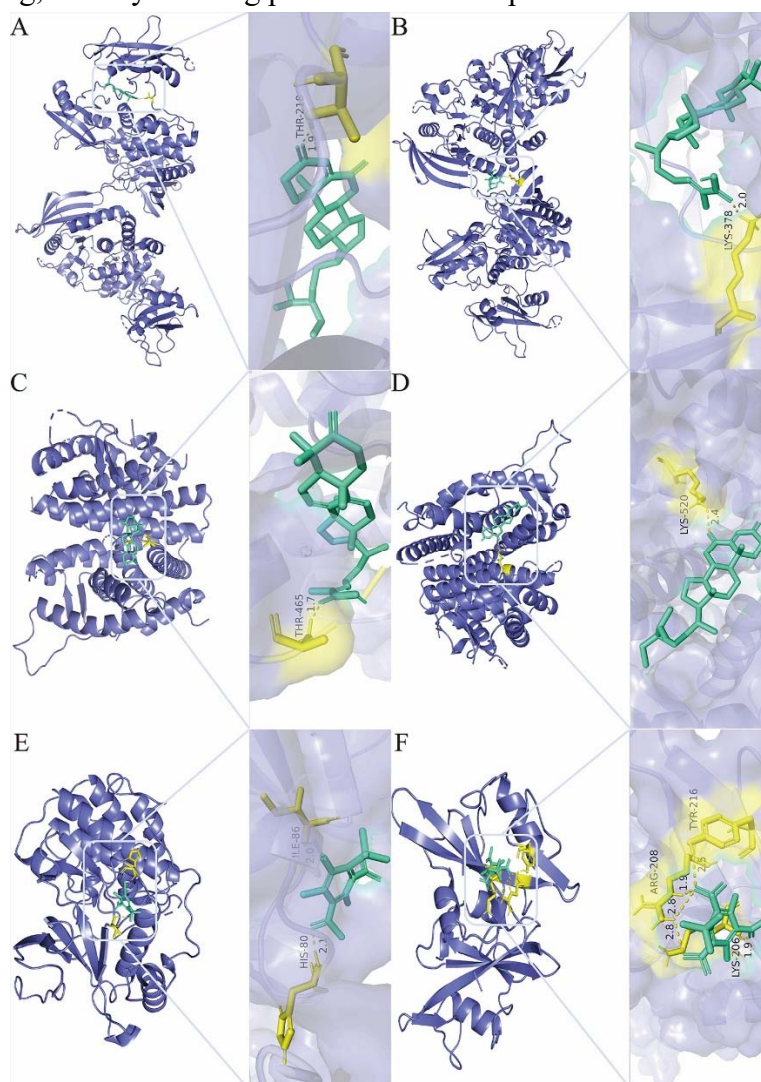


Fig. 4 The result diagram of molecular docking.

Table 1 Docking information between ACRP key small molecule ligands and core protein target molecules.

Number	Ligand name	Protein name	Binding energy (kcal/mol)	Combining sites	Hydrogen bond length
A	Doustere-4-ene-3, 6-dione	PTPN11	-5.45	THR-218	1.9
B	Musk ketone	SRC	-5.57	ARG-208	2.8, 2.8, 1.9
C	Musk ketone	MAPK1	-6.07	TYR-216	2.5
D	Ganoderic Acid S	ESR1	-6.7	LYS-206	1.9
E	Doustere-4-ene-3, 6-dione	ESR1	-6.93	HIS-80	2.1
F	Ganoderic Acid S	PTPN11	-7.38	ILE-86	2.0
				THR-465	1.7
				LYS-520	2.4
				LYS-378	2.0

3.5 The antioxidant activity of ACRP *in vitro* and *in vivo*

The *in vitro* and *in vivo* antioxidant activity of ACRP was investigated to validate the nutritional activity of ACRP (Fig. 5). The ability of ACRP to scavenge DPPH radicals, ABTS radicals and hydroxyl radicals increased with increasing concentration, and its ability to scavenge ABTS radicals was stronger than its ability to scavenge other radicals, which was consistent with the *in vitro* antioxidant activity evaluation of ACR (Fig. 5A-C). Moreover, the *in vitro* free radical scavenging activity of ACRP was superior to ACR at the same concentration, indicating that the antioxidant activity of ACR was closely related to its rich triterpenoid and saponin active substances (Fig. 5A-C). Furthermore, it was found that ACRP could significantly enhance the antioxidant capacity of *C. elegans* by reducing MDA levels and increasing the secretion of antioxidant enzymes (Fig. 5D-G). Compared with the NFD group, the level of MDA in the ACRP-H group was significantly reduced by 80.15%, while the levels of T-SOD, GSH-Px and CAT were significantly increased by 136.34%, 39.62% and 150.44%, respectively (Fig. 5D-G, $P < 0.05$). These results further validated the functional activity of ACRP and confirmed that triterpenoids and saponins are the core active components responsible for the antioxidant activity of pineapple residue extract.

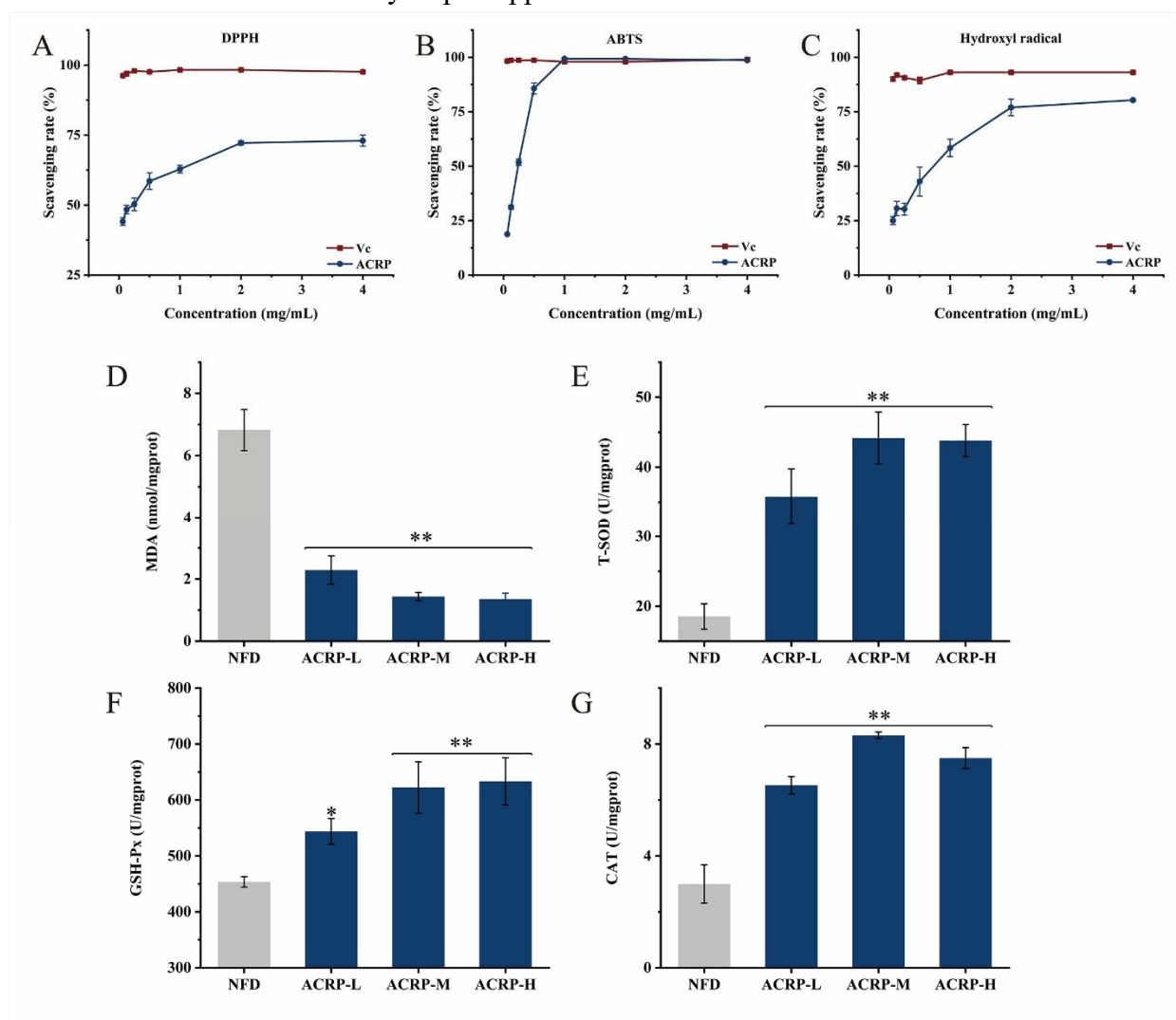


Fig. 5 The antioxidant activity *in vitro* and *in vivo* of ACRP. The activity of ACRP in clearing DPPH radicals (A), ABTS radicals (B) and hydroxyl radicals (C). The effect of ACRP on the activities of MDA (D), T-SOD (E), GSH-Px (F) and CAT (G) in *C. elegans*.

3.6 The effect of ACRP on metabolites in *C. elegans*

To further clarify the potential metabolic mechanism underlying the antioxidant activity of ACRP, we investigated its effect on metabolites in *C. elegans* (Fig. 6). Principal Component Analysis (PCA) and Partial Least Squares-Discriminant Analysis (PLS-DA) showed significant differences in metabolite profiles between *C. elegans* treated with high-concentration ACRP and untreated controls. Permutation tests confirmed that the model was not overfitted, ensuring the reliability of the results (Fig. 6A-C). Compared with the NFD group, the ACRP-H group exhibited significant changes in 344 metabolites. Among these, 250 were significantly upregulated and 94 were significantly downregulated (Fig. 6D, F). Variable Importance in Projection (VIP) score analysis identified key differential metabolites, with significantly upregulated metabolites primarily including dimethylphysostigmine and 6-(7-Hydroxy-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-7-yl)-N-methyl-2-naphthamide, and downregulated metabolites mainly consisting of 1-O-Cinnamoylglucose, 1-Nitro-5-hydroxy-6-glutathionyl-5,6-dihydronaphthalene, 4-Hydroxypropranolol glucuronide, 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone and posatirolin (Fig. 6E).

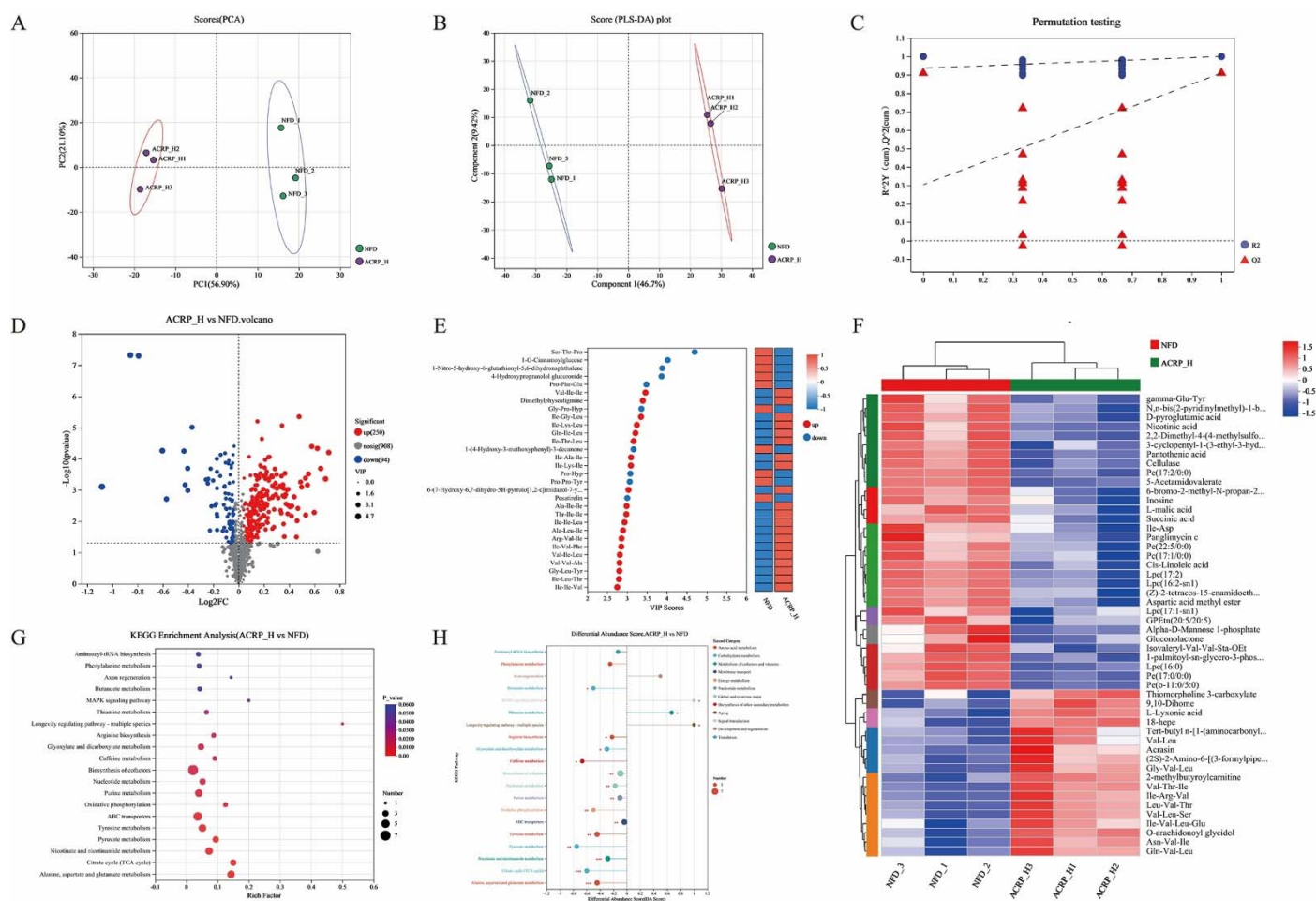


Fig. 6 The effect of ACRP on metabolites in *C. elegans*. A: PCA analysis. B: PLS-DA analysis. C: Permutation testing. D: Volcanic chart. E: VIP score chart. F: Heatmap. G and H: KEGG enrichment analysis.

KEGG enrichment analysis was performed to identify potential metabolic pathways through which ACRP regulates characteristic metabolites in *C. elegans* (Fig. 6G, H). Three screening criteria were used to

prioritize pathways: (1) based on the number of characteristic metabolites, the top five pathways were biosynthesis of cofactors, ABC transporters, alanine, aspartate and glutamate metabolism, nicotinate and nicotinamide metabolism, and tyrosine metabolism; (2) based on the rich factor, the top five were longevity regulating pathway-multiple species, MAPK signaling pathway, citrate cycle (TCA cycle), axon regeneration, and alanine, aspartate and glutamate metabolism; (3) based on statistical significance, the top five were alanine, aspartate and glutamate metabolism, TCA cycle, nicotinate and nicotinamide metabolism, pyruvate metabolism, and tyrosine metabolism. Notably, alanine, aspartate and glutamate metabolism was the only pathway consistently identified by all three screening methods, suggesting it may be a core metabolic pathway mediating the antioxidant effect of ACRP. These results indicate that ACRP alters the metabolite levels of *C. elegans*, linking ACRP intervention to metabolic regulation.

3.7 Metabolic mechanism and correlation analysis

To decipher the metabolic pathway mechanism underlying the antioxidant capacity of ACRP in *C. elegans*, the association between ACRP-regulated metabolites and antioxidant-related metabolic pathways was analyzed. ACRP was found to modulate multiple metabolic pathways centered on the TCA cycle, including tyrosine metabolism, pyruvate metabolism, alanine, aspartate and glutamate metabolism, and nicotinate and nicotinamide metabolism (Fig. 7A). Specifically, ACRP mediates the interconversion of key TCA cycle intermediates (*e.g.*, (S)-Malate, fumarate, succinate) through metabolites such as tyramine, 6-hydroxynicotinate, and L-asparagine (Fig. 7A). These metabolites further extend to downstream pathways, including isoquinoline alkaloids biosynthesis, glyoxylate metabolism and oxidative phosphorylation, indicating that ACRP improves intracellular substance metabolism through a complex interconnected network centered on the TCA cycle and involving multiple amino acid and energy metabolic pathways (Fig. 7A).

To further substantiate the link between ACRP, metabolites, and antioxidant activity, we analyzed the correlation between antioxidant-related biochemical indicators and key metabolites in *C. elegans*. MDA levels were significantly positively correlated with 1-O-Cinnamoylglucose, 4-hydroxypropranolol glucuronide, 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone, 1-Nitro-5-hydroxy-6-glutathionyl-5,6-dihydronaphthalene, and posatiirelin (Fig. 7B, C). Additionally, 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone was significantly negatively correlated with SOD activity, and posatiirelin was significantly negatively correlated with CAT levels. These correlations directly link ACRP-induced metabolic changes to antioxidant biochemical responses, providing critical insights into how ACRP enhances antioxidant capacity through metabolite modulation and metabolic pathway regulation.

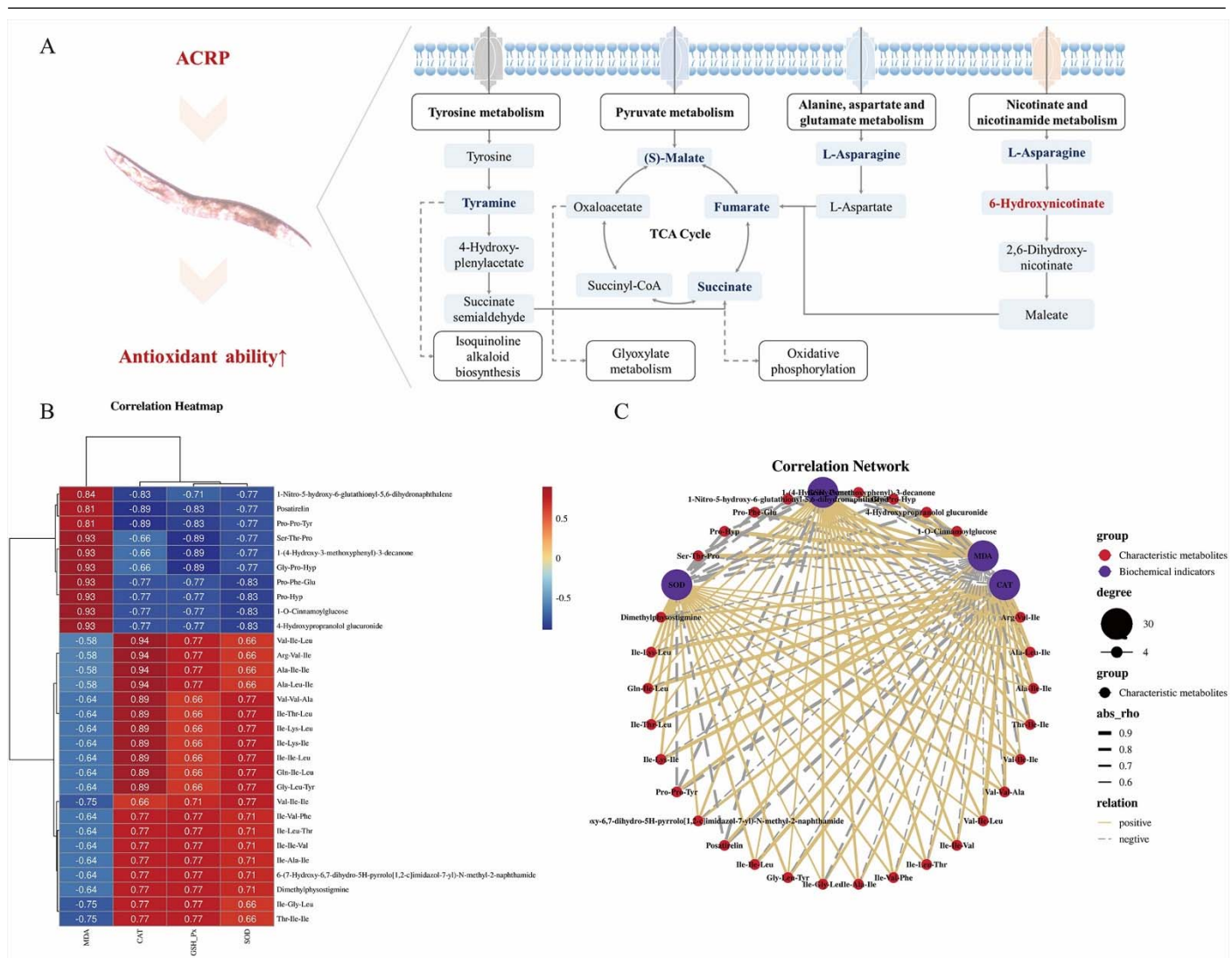


Fig. 7 Mechanism and correlation analysis of ACRP improving the antioxidant capacity of *C. elegans*. A: Mechanism analysis. B and C: Correlation analysis between antioxidant biochemical indicators and characteristic metabolites in *C. elegans* treated with ACRP.

4. Discussion

This study confirmed that ACR exhibits excellent in vitro antioxidant activity and enhances the antioxidant capacity of *C. elegans*, with small molecule active substances playing an important role. Consistent with previous findings, the ethanol extract of dried ginger showed better in vitro antioxidant activity and higher polyphenol recovery than the water extract, indicating a strong correlation between small molecule active substances such as polyphenols and flavonoids and antioxidant activity (Mustafa & Chin, 2023). In addition, the enhancement of antioxidant activity has been supported to be significantly associated with anti-aging, immune enhancement, anti-inflammatory and regulation of gut microbiota (Naliyadhara et al., 2023), indicating that ACR may offer multi-nutritional benefits and could serve as a potential candidate for further evaluation in functional food development. ACRP, a purified fraction of ACR obtained via macroporous resin, was identified to be rich in triterpenoids and saponins, with betulonic acid, chenodeoxycholic acid, eclalbasaponin I, ganoderic acid S, ginsenoside Rg2, ginsenoside Rh4, musk ketone, notoginsenoside R2, soyasaponin III, and trifoside C as the main components. The rationale for purifying ACR to obtain ACRP is to enrich the core antioxidant active components (triterpenoids and saponins) while

reducing interference from inactive substances, thereby facilitating the exploration of the specific antioxidant mechanism of ACR's active ingredients. Each of these core components has been previously reported to possess biological activities associated with antioxidant defense.

Betulonic acid, as a typical triterpenoid compound, has been proven to have diverse biological properties including antibacterial, anti-inflammatory and lipid metabolism regulation effects (Lou et al., 2025). Chenodeoxycholic acid could regulate the metabolism of bile acids in mice by promoting the growth of *A. muciniphila* in gut microbiota, which inhibited the IL-17 and TNF signaling pathways (L. Zhang et al., 2024), thus slowing down chronic liver injury caused by CCl₄. Eclalbasaponin I from *Aralia elata* (Miq.) has been found to alleviate hydrogen peroxide-induced cell damage by inhibiting apoptosis levels and reactive oxygen species content, and the alleviation effect was closely related to autophagy (W. Wang et al., 2018). Meanwhile, it has been confirmed that the effect of ginsenoside Rg₂ had the effect in regulating neurological disorders (S. Liu et al., 2023), ginsenoside Rh₄ was benefited to inhibit lung cancer cell metastasis, and musk ketone had neuroprotective effects on neural stem cells, further affecting their response to oxidative stress and inflammation (Molloy & Barry, 2024; Y. Zhang et al., 2022). Notoginsenoside R₂ could improve the proteinuria, renal function and renal pathology of diabetes nephropathy mice, reduce lipid accumulation and oxidative stress by inhibiting JNK/STAT1 phosphorylation and CD36 overexpression (Guo et al., 2025). Collectively, these studies support ACRP's core components as key mediators of its antioxidant activity, providing a theoretical basis for its application in functional food development.

In the analysis of the key triterpenoid and saponin small molecule targets of ACRP and oxidative stress-related protein targets, it was indicated that SRC, ESR1, MAPK1, JUN, MAPK3 and PTPN11 were key protein targets. These core targets are closely associated with oxidative stress regulation and related physiological processes. SRC protein is a non-receptor tyrosine kinase that promotes tumor cell proliferation and metastasis by activating the MAPK/ERK signaling pathway (Kim et al., 2017). ESR1, a member of the nuclear receptor superfamily, plays a crucial role in physiological and pathological processes including the reproductive, skeletal, cardiovascular, and nervous systems (Hevener et al., 2021). Both SRC and ESR1 have been reported to be involved in oxidative stress responses (Tallei et al., 2025), which further supports their role as key targets mediating ACRP's antioxidant activity. The ability of ACRP to regulate these key targets highlights its potential as a functional food ingredient, as it can target multiple pathways associated with oxidative stress and disease. Although experimental validation of these predicted targets, such as Western blotting or qRT-PCR for MAPK pathway proteins, was not performed, the convergence of network pharmacology, molecular docking, and metabolomics evidence supports a putative link between ACRP's components, their targets, and antioxidant activity. Molecular docking confirmed direct interactions between ACRP's core triterpenoid and saponin components and oxidative stress-related targets, while metabolomic analysis connected ACRP-induced metabolic changes to these pathways. Together, these findings offer a mechanistic hypothesis to guide future experimental validation.

Metabolomic analysis identified dimethylphysostigmine, 1-O-Cinnamoylglucose, 1-Nitro-5-hydroxy-6-glutathionyl-5,6-dihydronaphthalene, 4-Hydroxypropranolol glucuronide, 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone and posatiorelin as key metabolites regulated by ACRP. These metabolites are closely linked to ACRP's antioxidant activity. Evidence suggests that 1-O-Cinnamoylglucose improves brain tissue morphology and reduces inflammation by regulating gut microbiota structure and tight junction protein expression (ZO-1, Occludin, Claudin 1) in mice (Mao et al., 2024). Spearman's correlation analysis further revealed a significant positive correlation between 1-O-Cinnamoylglucose and MDA levels ($r = 0.93$, Fig. 7B, C). Given that this metabolite was downregulated by ACRP and positively correlated with MDA (a marker of lipid peroxidation, Fig. 6E), its downregulation may contribute to alleviating lipid peroxidation and oxidative damage. Additionally, 1-Nitro-5-hydroxy-6-glutathionyl-5,6-dihydronaphthalene is associated with lipid accumulation (Zheng et al., 2022). 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone was identified as a key metabolite in gut microbiota-mediated constipation improvement. Although this metabolite was downregulated by ACRP, it showed a strong negative correlation with SOD activity ($r = -0.77$, Fig. 7B, C). As SOD is a major antioxidant enzyme responsible for scavenging reactive oxygen species, the downregulation of this metabolite may contribute to increased SOD activity and enhanced free radical scavenging capacity. Posatiorelin, a non-peptide TRH agonist, increases seizure thresholds and reduces mortality in mice (Zhao et al., 2024). Notably, posatiorelin acts as a downstream effector of the core oxidative stress-related target ESR1, and our data confirmed a significant negative correlation between posatiorelin and CAT activity ($r = -0.89$, Fig. 7B, C), suggesting that ACRP-mediated downregulation of posatiorelin contributes to elevated CAT activity and strengthened antioxidant defense.

The consistent identification of alanine, aspartate, and glutamate metabolism across multiple screening criteria highlights its central role in mediating the antioxidant effects of ACRP. This is consistent with previous findings that betulinic acid, one of the core triterpenoid components of ACRP, improves gut microbiota structure and generates short-chain fatty acids by regulating PPAR activity, thereby playing an active role in regulating blood glucose and lipid levels in diabetic mice; notably, alanine, aspartate and glutamate metabolism is recognized as the key signaling pathway for lipid metabolism regulation (Lin et al., 2025). Meanwhile, alanine, aspartate and glutamate metabolism plays important roles in improving colitis and alleviating associated tissue injury (C. Liu et al., 2023; Yang et al., 2025). These findings suggest the physiological regulatory effects of ACRP mediated by metabolites, such as maintaining gut health, balancing lipid metabolism, and exerting neuroprotection, which further point to potential metabolic mechanisms underlying the antioxidant efficacy of ACRP. At the same time, the exploration of these metabolic pathways provides a preliminary theoretical basis at the target and pathway levels for the comprehensive effects of ACRP in antioxidant defense, metabolic balance maintenance, and inflammation relief, as well as for its potential application in the development of functional foods (such as intestinal health products and metabolic regulation foods).

Integrating the above metabolic pathway insights with our earlier component analysis and target prediction results, we can preliminarily outline a potential antioxidant mechanism of ACRP. Specifically, we have identified the core triterpenoid and saponin components of ACRP and suggest a correlation between these small-molecule active substances and the herb's antioxidant activity, which points to its potential multifunctionality. Meanwhile, potential key targets of oxidative stress (SRC, ESR1, MAPK) associated with ACRP have been predicted through network pharmacology analysis and molecular docking techniques, combined with *in vitro* antioxidant and *C. elegans* models, as well as metabolomic analyses of characteristic metabolites and pathways. These findings offer a preliminary framework for understanding the antioxidant activity of ACRP from the perspective of "active ingredient-target-metabolic pathway", providing new directions for its potential application as a functional food or nutritional enhancer in the fields of gut health, metabolic regulation, and the industrialization of natural active substances.

However, several limitations should be acknowledged. First, there is a cross-species discrepancy between the *in vivo* validation in *C. elegans* and the human-centered databases used for target prediction, which weakens the direct link between the observed phenotype and the proposed molecular targets. Nonetheless, the key pathways involved are evolutionarily conserved between *C. elegans* and humans, with high sequence homology and established roles in oxidative stress responses. In addition, although the main small-molecule components of ACRP have been identified, the individual antioxidant mechanisms of these components remain unclear. Furthermore, the current conclusions regarding the targeting of SRC, ESR1, and PTPN11, as well as the regulation of alanine, aspartate, and glutamate metabolism, are primarily based on *in silico* and metabolomic analyses without direct experimental validation (*e.g.*, Western blotting, qRT-PCR, and targeted metabolomics). Therefore, these mechanisms should be regarded as putative rather than confirmed. Future research will be essential to clarify the content of each component in ACRP and verify their individual antioxidant activities. Further investigations into the intervention effects of ACRP on metabolic syndrome, gut inflammation, and other related diseases, as well as its dose-response relationship, regulatory mechanisms on gut microbiota, and potential value in neuroprotection and liver injury repair, will help expand the scope of functional food development centered on ACRP. More comprehensive detection indicators will also be adopted in subsequent studies to fully and systematically elucidate the integrated antioxidant mechanism of the extract.

5. Conclusion

This study systematically investigated the antioxidant activity and underlying mechanism of ACR (crude extract from *Ananas comosus* (L.) Merr. residue) and its purified fraction ACRP, which was enriched in triterpenoids and saponins through macroporous resin purification. The results showed that ACRP exhibited significant *in vitro* free radical scavenging activity against DPPH, ABTS, and hydroxyl radicals. Experiments in *C. elegans* demonstrated that ACRP enhanced antioxidant capacity *in vivo* by increasing the activities of T-SOD, GSH-Px, and CAT, while reducing MDA levels. Through network pharmacology and molecular docking analysis, the core triterpenoid and saponin components of ACRP were identified. These included

eclalbasaponin I, ganoderic acid S, ginsenoside Rg2, ginsenoside Rh4, and trifoside C. These compounds were found to interact with oxidative stress related core targets, including SRC, ESR1, MAPK1, JUN, MAPK3, and PTPN11, indicating a putative interaction. Metabolomic analysis further revealed key metabolites that may be involved in ACRP's antioxidant effect, namely dimethylphysostigmine, 1-O-Cinnamoylglucose, 1-Nitro-5-hydroxy-6-glutathionyl-5,6-dihydronaphthalene, 4-Hydroxypropranolol glucuronide, 1-(4-Hydroxy-3-methoxyphenyl)-3-decanone, and posatirelin. Among the metabolic pathways, alanine, aspartate and glutamate metabolism emerged as a potential core pathway. Correlation analysis confirmed direct links between these metabolic changes and antioxidant biochemical indicators.

In summary, these findings suggest a putative regulatory network involving components, targets, and metabolic pathways that may underlie the antioxidant activity of ACRP. This work provides insights into the material basis and potential molecular mechanisms of its effects. While further experimental validation of the predicted targets is needed, this study provides preliminary scientific evidence for the industrialization of ACRP as a natural antioxidant and for the development of related functional products. In addition, it contributes to the high-value utilization of pineapple processing by-products and offers new insights into the antioxidant mechanisms of extracts derived from pineapple residue.

Supporting Information Description

Supporting information for the top 15 triterpenes and saponins in ACRP were identified by HPLC-MS/MS technology.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

This study does not involve any human or animal testing.

Clinical trial number

Not applicable.

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