Network pharmacology combined with metabolomics and lipidomics to reveal the hypolipidemic mechanism of *Alismatis Rhizoma* in hyperlipidemic mice

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Fig. S1. The overlaid total ion chromatogram of QC in the metabolomics analysis. (A) Positive ion mode, (B) Negative ion mode.
Fig. S2. The overlaid total ion chromatogram of QC in the lipidomics analysis. (A) Positive ion mode, (B) Negative ion mode.
**Fig. S3.** PCA score plots of QC samples in the (A) metabolomics and the (B) lipidomics analyses.
Fig. S4. The correlation of QC samples in the (A) metabolomics and the (B) lipidomics analyses.
Fig. S5. Pathway analysis of differential metabolites (lipids) from the (A) metabolomics and the (B) lipidomics analyses.
Fig. S6. The TIC of AR extracts in positive mode detected by UHPLC-Q-TOF/MS.
Fig. S7. The XIC of prototypes and metabolites detected in plasma after oral administration of AR.
Fig. S8. Gene-Metabolite Interaction Network. The circles represent the genes and the rectangles represent the metabolites and lipids.
**Fig. S9.** Sankey diagram between the active compounds and correlated key targets. The thickness of the ribbon is negatively correlated with the docking score.
Fig. S10. Docking mode between the alisol A 23-acetate and IL1B (A); Docking mode between the 12,22-dihydroxy-alisol G and MMP9 (B).
Table S1. The nutritional composition of AR powder used in this study.

<table>
<thead>
<tr>
<th>Composition</th>
<th>Content (per 100 g)</th>
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<td>Water</td>
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<tr>
<td>Ashes</td>
<td>2.6 g</td>
</tr>
<tr>
<td>Fats</td>
<td>3.8 g</td>
</tr>
<tr>
<td>Proteins</td>
<td>22.8 g</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>60.7 g</td>
</tr>
<tr>
<td>Na</td>
<td>16.9 mg</td>
</tr>
<tr>
<td>K</td>
<td>788 mg</td>
</tr>
<tr>
<td>Mg</td>
<td>942 mg</td>
</tr>
<tr>
<td>Energy</td>
<td>1560 kJ</td>
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Table S2. The primer sequences for qPCR.

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<th>Gene</th>
<th>Forward</th>
<th>Reverse</th>
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<td>TACTGCCGTTTTCACAAAGTGC</td>
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<tr>
<td>PPARG</td>
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<tr>
<td>ALB</td>
<td>CAGCGGAGCAACTGAAGACT</td>
<td>AAGGTTCAGACCCTCAGTCG</td>
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<tr>
<td>MMP9</td>
<td>CTCTCCTGGCTTTCGCTG</td>
<td>TAGCGGTACAAGTGTCGGCTC</td>
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<td>TNF</td>
<td>CCCTCACACTCAAAACCAC</td>
<td>ACAAGGTACAACCCTCAGG</td>
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<td>IL1B</td>
<td>GCAGTGGTTCAGGCTTAAT</td>
<td>GCTGCTTCAGACACTTCGCA</td>
</tr>
<tr>
<td>β-actin</td>
<td>CACTGTGAGTCGCGTCC</td>
<td>TCATCCATGGCGAAGTGTTG</td>
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Table S3. Food intake of mice fed with AR and simvastatin for 4 weeks.

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<tr>
<th>Week</th>
<th>HFD (g/mouse*day) n=8</th>
<th>SIM (g/mouse*day) n=8</th>
<th>AR (g/mouse*day) n=8</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>6.42 ± 0.89</td>
<td>6.95 ± 1.63</td>
<td>6.75 ± 1.44</td>
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<tr>
<td>2</td>
<td>6.11 ± 0.67</td>
<td>6.81 ± 0.92</td>
<td>6.39 ± 0.95</td>
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<tr>
<td>3</td>
<td>5.53 ± 0.46</td>
<td>5.71 ± 0.76</td>
<td>5.97 ± 0.79</td>
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<tr>
<td>4</td>
<td>5.71 ± 0.93</td>
<td>5.92 ± 0.65</td>
<td>5.66 ± 0.81</td>
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Table S4. Metabolic pathways of AR against hyperlipidemia in metabolomics analysis.

<table>
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<th>Match Status</th>
<th>P-value</th>
<th>Impact</th>
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<td>0.056953</td>
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<tr>
<td>2</td>
<td>Linoleic acid metabolism</td>
<td>1/5</td>
<td>0.089683</td>
<td>0</td>
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<tr>
<td>3</td>
<td>Cysteine and methionine metabolism</td>
<td>2/33</td>
<td>0.12363</td>
<td>0.1263</td>
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<tr>
<td>4</td>
<td>Glycine, serine and threonine metabolism</td>
<td>2/34</td>
<td>0.1299</td>
<td>0.08668</td>
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<tr>
<td>5</td>
<td>Valine, leucine and isoleucine biosynthesis</td>
<td>1/8</td>
<td>0.13972</td>
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<tr>
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<td>Taurine and hypotaurine metabolism</td>
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<td>0.28571</td>
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<tr>
<td>7</td>
<td>Biosynthesis of unsaturated fatty acids</td>
<td>2/36</td>
<td>0.14265</td>
<td>0</td>
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<tr>
<td>8</td>
<td>Glycerophospholipid metabolism</td>
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<td>9</td>
<td>Arachidonic acid metabolism</td>
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<td>0.33292</td>
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<tr>
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<td>alpha-Linolenic acid metabolism</td>
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<tr>
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<td>Arginine biosynthesis</td>
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<td>Histidine metabolism</td>
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<tr>
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<td>18</td>
<td>Pentose phosphate pathway</td>
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<tr>
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Table S5. Metabolic pathways of AR against hyperlipidemia in lipidomics analysis.

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<th>Impact</th>
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<td>4</td>
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<td>0.19615</td>
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<td>Steroid biosynthesis</td>
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<td>0.22528</td>
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## Table S6. Characterization of prototype compounds of AR extracts based on UHPLC-QTOF-MS/MS.

<table>
<thead>
<tr>
<th>No.</th>
<th>t&lt;sub&gt;R&lt;/sub&gt; (min)</th>
<th>Formula</th>
<th>Experimental (m/z)</th>
<th>Calculated (m/z)</th>
<th>Error (ppm)</th>
<th>Characteristics ions</th>
<th>Identification</th>
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<td>529.3489*</td>
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<td>16-oxo-Alisol A 23-acetate</td>
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<td>11.19</td>
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<td>487.3418</td>
<td>0.4</td>
<td>353.2482</td>
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<td>487.3412</td>
<td>487.3418</td>
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<td>11-anhydro-16-oxo-Alisol A</td>
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<td>489.3575</td>
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<td>355.2635</td>
<td>11-deoxy-16-oxo-Alisol A</td>
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<td>547.3629</td>
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<td>471.3469</td>
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<td>381.2787, 339.2684</td>
<td>Alisol F 24-acetate</td>
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<td>15.98</td>
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<td>Alisol K 23-acetate</td>
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<tr>
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<td>Characteristics ions</td>
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<tr>
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*: dehydrated form of compound was detected as the major peak in MS because dehydration in-source occurs easily, and the peak of undehydrated compound was too weak to get enough MS/MS fragments, therefore identification was based on MS/MS fragments of dehydrated form.
Table S7. Characterization of prototypes and metabolites of AR triterpenes in plasma based on UHPLC-QTOF-MS/MS.

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<th>No.</th>
<th>Name</th>
<th>RT (min)</th>
<th>Experimental m/z</th>
<th>Calculated m/z</th>
<th>Error (ppm)</th>
<th>Characteristic ions</th>
<th>Formula</th>
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<td>355.2636</td>
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<td>515.3725</td>
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<td>C_{32}H_{50}O_{5}</td>
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*: dehydrated form of compound was detected as the major peak in MS because dehydration in-source occurs easily, and the peak of undehydrated compound was too weak to get enough MS/MS fragments, therefore identification was based on MS/MS fragments of dehydrated form; P: prototypes; M: metabolites; #: confirmed with reference standards.
Table S8. The hub genes filtrated from PPI by CytoHubba.

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<th>Degree</th>
<th>EPC</th>
<th>BottleNeck</th>
<th>EcCentricity</th>
<th>Closeness</th>
<th>Radiality</th>
<th>Betweenness</th>
<th>Stress</th>
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Table S9. KEGG enrichment analysis of 83 genes.

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Table S10. The docking scores between 6 key targets and the corresponding components.

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Table S10 (continued)

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