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Research article

Network pharmacology study to identify molecular pathways involved in the anti-diabetic activity of *Syzygium cumini* seed constituents

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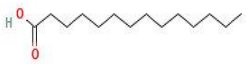
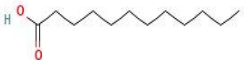
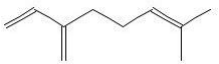
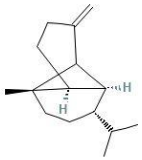
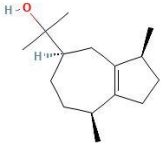
Abstract: Diabetes is characterized by hyperglycemia and insulin resistance, which significantly increase the risk of morbidity and mortality. *Syzygium cumini* seeds have been used traditionally in the management of diabetes, though the precise molecular mechanisms underlying their effects are not yet fully understood. The present study aimed to elucidate the molecular mechanisms through which *S. cumini* seed extract exerts its beneficial effects in diabetes, employing a network pharmacology approach. The constituents of *S. cumini* seeds were identified from online databases. Eligible constituents were then used to identify target genes through four databases. Genes associated with diabetes were retrieved from two databases. The overlapping genes were selected as the target genes for further analysis. A protein–protein interaction network was constructed using Cytoscape and the STRING database, which helped identify hub genes. This network was then used to perform gene ontology and pathway enrichment analyses. Among the 66 identified constituents, 29 were eligible for inclusion in the analysis. Database screening revealed 986 genes targeted by the selected active constituents, with 392 genes associated with diabetes. Of these, 112 genes overlapped. Following network development, the top 10 hub genes with the highest degree scores were selected for pathway enrichment analysis. The pathway enrichment analysis indicated that *S. cumini* may exert beneficial effects in diabetes by modulating several pathways related to RNA-mediated miRNA transcription, AGE-RAGE signaling, and HIF-1 signaling through multiple genes. The underlying mechanisms may involve enhanced cellular responses to oxidative stress, improved oxidative stress metabolism, and an elevated anti-inflammatory response. The current study provides promising evidence of the beneficial effects of *S. cumini* seed therapy in the management of diabetes. The findings of this study offer a potential direction for future molecular research to confirm the efficacy of *S. cumini* seeds in diabetic

conditions through the pathways described.

Keywords: *Syzygium cumini*; network pharmacology; gene ontology; KEGG; hub genes; diabetes; advanced glycation end products; miRNA

Appendix

Table S1. Details of *Syzygium cumini* seed constituents included in the study analysis.

PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
11005	Myristic acid	$C_{14}H_{28}O_2$	228.37	CCCCCCCCCCCCCC(=O)O	
11467	gamma-Terpineol	$C_{10}H_{18}O$	154.25	CC(=C1CCC(CC1)(C)O)C	
3893	Lauric acid	$C_{12}H_{24}O_2$	200.32	CCCCCCCCCCCC(=O)O	
31253	Myrcene	$C_{10}H_{16}$	136.23	CC(=CCCC(=C)C=C)C	
57339298	beta-Copaene	$C_{15}H_{24}$	204.35	CC(C)[C@@H]1CC[C@]2([C@@H]3[C@H]1C2C(=C)CC3)C	
227829	Guaiol	$C_{15}H_{26}O$	222.37	C[C@H]1CC[C@H](CC2=C1CC[C@@H]2C)C(C)(C)O	

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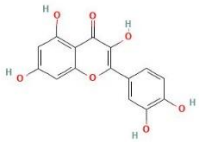
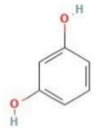
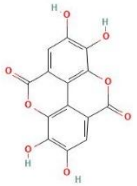
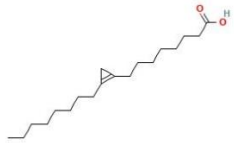
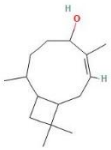
PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
5280343	Quercetin	$C_{15}H_{10}O_7$	302.23	C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O	
5054	Resorcinol	$C_6H_6O_2$	110.11	C1=CC(=CC(=C1)O)O	
5281855	Ellagic acid	$C_{14}H_6O_8$	302.19	C1=C2C3=C(C(=C1O)O)OC(=O)C4=CC(=C(C(=C43)OC2=O)O)O	
7463	p-Cymene	$C_{10}H_{14}$	134.22	CC1=CC=C(C=C1)C(C)C	
12921	Sterculic acid	$C_{19}H_{34}O_2$	294.5	CCCCCCCCC1=C(C1)CCCCCCCC(=O)O	
91704770	Caryophyllenyl alcohol	$C_{15}H_{26}O$	222.37	CC1CCC(/C(=C\CC2C1CC2(C)C)/C)O	

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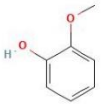
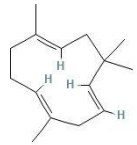
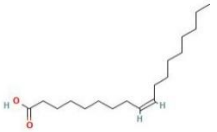
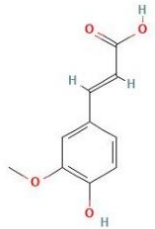
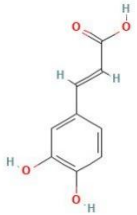
PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
460	Guaiacol	$C_7H_8O_2$	124.14	COC1=CC=CC=C1O	
5281520	Humulene	$C_{15}H_{24}$	204.35	C/C/1=C\CC(/C=C/C/C(=C/CC1)/C)(C)C	
445639	Oleic acid	$C_{18}H_{34}O_2$	282.5	CCCCCCCC/C=C\CCCCCCCC(=O)O	
445858	Ferulic acid	$C_{10}H_{10}O_4$	194.18	COC1=C(C=CC(=C1)/C=C/C(=O)O)O	
689043	Caffeic acid	$C_9H_8O_4$	180.16	C1=CC(=C(C=C1/C=C/C(=O)O)O)O	

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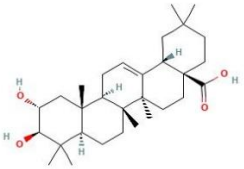
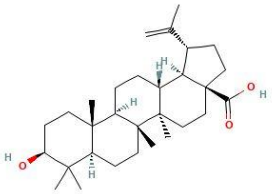
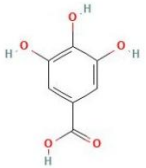
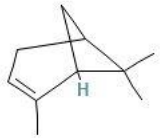
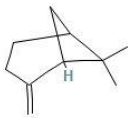
PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
73659	Maslinic acid	$C_{30}H_{48}O_4$	472.7	C[C@@]12CC[C@@H]3[C@@]([C@H]1CC=C4[C@]2(CC[C@@]5([C@H]4CC(CC5)(C)C)C(=O)O)C)(C[C@H]([C@@H](C3(C)C)O)O)C	
64971	Betulinic acid	$C_{30}H_{48}O_3$	456.7	CC(=C)[C@@H]1CC[C@]2([C@H]1[C@H]3CC[C@@H]4[C@]5(CC[C@@H](C([C@@H]5CC[C@]4([C@@]3(CC2)C)C)(C)C)O)C)C(=O)O	
370	Gallic acid	$C_7H_6O_5$	170.12	C1=C(C=C(C(=C1O)O)O)C(=O)O	
6654	alpha-Pinene	$C_{10}H_{16}$	136.23	CC1=CCC2CC1C2(C)C	
14896	beta-Pinene	$C_{10}H_{16}$	136.23	CC1(C2CCC(=C)C1C2)C	

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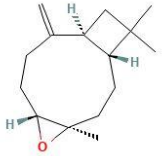
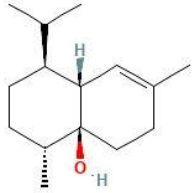
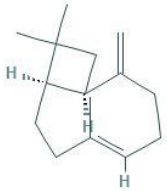
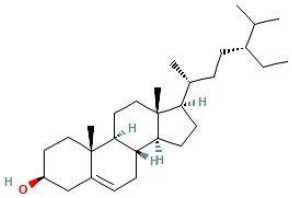
PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
1742210	Caryophyllene oxide	$C_{15}H_{24}O$	220.35	C[C@@]12CC[C@@H]3[C@H](CC3(C)C)C(=C)CC[C@H]1O2	
12046149	Epicubenol	$C_{15}H_{26}O$	222.37	C[C@@H]1CC[C@H]([C@H]2[C@@]1(CCC(=C2)C)O)C(C)C	
6429274	(E)-2-epi-beta-caryophyllene	$C_{15}H_{24}$	204.35	C/C/1=C\CCC(=C)[C@@H]2CC([C@@H]2CC1)(C)C	
222284	beta-Sitosterol	$C_{29}H_{50}O$	414.7	CC[C@H](CC[C@@H](C)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C)C(C)C	

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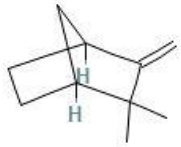
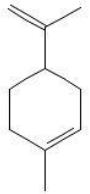
PubChem CID	Name	Molecular formula	Molecular weight (g/mol)	SMILES	Molecular structure
6616	Camphene	$C_{10}H_{16}$	136.23	CC1(C2CCC(C2)C1=C)C	
22311	Limonene	$C_{10}H_{16}$	136.23	CC1=CCC(CC1)C(=C)C	
5280450	Linoleic acid	$C_{18}H_{32}O_2$	280.4	CCCCC/C=C\C/C=C\CCCCCCCC(=O)O