龙眼肉化学成分库构建及其治疗贫血机制的网络药理学研究

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摘要：目的 构建龙眼肉化学成分库，联合网络药理学初步探讨龙眼肉治疗贫血的作用机制。**方法** 归纳整理近年来关于龙眼肉药效化学成分的文献并构建成分库，通过 SwissTargetPrediction 预测龙眼肉中活性成分，利用 OMIM、DrugBank、GeneCards 等数据库收集贫血病症的靶点基因，筛选成分与疾病之间的交集靶点，进行蛋白互作，建立“龙眼肉-活性成分-靶点-疾病”网络，GO 富集以及 KEGG 分析。**结果** 共收集化合物 256 种，包括 12 种糖类、27 种多酚类、147 种挥发性成分、2 种甾醇类、12 种有机酸、13 种脂类、11 种核苷类、29 种氨基酸类、3 种其他类有机成分以及多种微量元素。筛选后获得活性成分 32 个；交集靶点 24 个，TOP1、TERT、MPO、PARP1 等可能为关键靶点；生物功能 87 个，涉及细胞因子介导的信号通路、基因表达的正向调控、细胞因子活性等；通路 15 个，癌症通路、丝裂原活化蛋白激酶信号通路、碱基切除修复系统等可能为关键通路。**结论** 本研究建立了龙眼肉化学成分库，基于网络药理学初步探讨龙眼肉治疗贫血的潜在活性成分、靶点信息和作用机制，为龙眼肉的药理药效研究与资源开发提供有价值的参考。

关键词：龙眼肉；药效化学成分；贫血；网络药理学

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Construction of Chemical Constituents Database of Longan Arillus and Study on Network Pharmacology of Its Mechanism of Treating Anemia

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ABSTRACT: OBJECTIVE To establish the chemical component database of Longan Arillus, and preliminarily explore the mechanism of Longan Arillus in the treatment of anemia combined with network pharmacology. **METHODS** Summarized and established a database of pharmacodynamic chemical components of Longan Arillus by literature research method. Predicted the active components in Longan Arillus through Swiss TargetPrediction, collected the target genes related to anemia using OMIM, DrugBank, GeneCards, screened the intersection targets between components and diseases, conducted protein interaction, established the “Longan Arillus-active components-target-diseases” network, GO enrichment and KEGG analysis. **RESULTS** The chemical composition database of Longan Arillus was established and 256 compounds were collected, including 12 saccharides, 27 polyphenols, 147 volatile components, 2 sterols, 12 organic acids, 13 lipids, 11 nucleosides, 29 amino acids, 3 other organic components and various trace elements. The 32 active ingredients were obtained after screening. There were 24 intersection targets, and TOP1, TERT, MPO, PARP1, etc. could be key targets. There were 87 biological functions, involving cytokine mediated signal pathways, positive regulation of gene expression, cytokine activity, etc. There were 15 pathways, including cancer pathway, mitogen activated protein kinase signaling pathway, base excision repair system and so on. **CONCLUSION** The component library of Longan Arillus has been established. Potential active ingredients, target information and action mechanism of Longan Arillus in the treatment of anemia has been preliminarily discussed. This study can provide a valuable reference for pharmacological and pharmacodynamic research and resource development of Longan Arillus.

KEYWORDS: Longan Arillus; pharmacochemical composition; anemia; network pharmacology

龙眼肉(Longan Arillus)为无患子科植物龙眼(*Dimocarpus longan* Lour.)的假种皮，具有补益心脾、养血安神之效，是药食两用药材。关于龙眼肉物种起源[1-2]、活性成分[3-6]、物质提取方法[7-8]和药理作用[9-10]等方面均有详细综述。龙眼核、果皮、假种皮、叶、花等部位的化学成分和药理作用已有报道[11-13]。但是，缺乏对龙眼肉化学成分进行系统整理归纳，未建立起化学成分库，阻碍了

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成分与药理药效的关联性研究，基于网络药理学研究龙眼肉治疗贫血的研究亦未见报道。

贫血是单位容积血液内红细胞数和血红蛋白含量低于正常，造成贫血的原因有多种，如缺铁、出血、溶血、造血功能障碍等[14]。中医认为贫血归于血虚，治疗血虚常通过益气生血相互调节来治疗[15-16]。龙眼肉被视为补气益血的中药，《折肱漫录》记载：“功与人参并”，《理虚元鉴》亦说：“功并人参”[17]。已有研究报道基于网络药理学探讨龙眼叶治疗 2 型糖尿病[18]，但目前龙眼肉治疗贫血或血虚的作用机制尚未阐明。本研究旨在通过整理归纳龙眼肉化学成分(不涉及龙眼肉再加工后所含成分)，构建成分数据库，探索建立成分与药理药效的关联性，联合网络药理学将贫血与血虚相联系，探究龙眼肉治疗贫血的关键靶点和通路信息，为研究龙眼肉成分与药理药效关联性及其药用资源开发提供依据。

1　化学成分与方法

1.1　龙眼肉化学成分

已报道的龙眼肉含化学成分共有 256 种，包括 12 种糖类(S1~S12)、27 种多酚类(P1~P27)、147 种挥发性成分(V1~V147)、2 种甾醇类(ST1~ST2)、12 种有机酸(O1~O12)、13 种脂类(L1~L13)、11 种核苷类(N1~N11)、29 种氨基酸类(A1~A29)、3 种其他类(OT1~OT3)以及多种微量元素。

1.1.1　糖类　龙眼肉中糖类物质可呈游离状态，或与蛋白质、脂肪结合成复杂多糖，见图 1。龙眼肉中含有果糖、葡萄糖、蔗糖[19-22]，不同产地和品种含量存在差异[23]。多糖成分分为酸性杂多糖[24-27]、中性多糖[26]、多糖-蛋白质复合物[26-27]和 α、β 2 种半缩醛羟基构型并存的吡喃环多糖[28]。酸性杂多糖由甘露糖、鼠李糖、半乳糖醛酸、葡萄糖、半乳糖、木糖、阿拉伯糖等 7 种单糖组成，不同品种间含量存在差异。

1.1.2　多酚类　龙眼肉中多酚类化合物见图 2，主要为黄酮类[22,29-34]、黄烷醇类[35]、酚酸类[22,31-33,35-36]、复合多酚[36]和其他多酚[27,31,33]，不同部位和品种之间成分、含量亦有差异[37]，该类成分与抗氧化作用密切相关。

1.1.3　挥发性成分　龙眼肉中挥发性成分见图 3，可分为酯类(V1~V41)、醇类(V42~V70)、醛类(V71~V84)、萜类(V85~V105)、烷烃类(V106~V119)、烯烃类(V120~V125)、芳香族(V126~V144)和含氮杂环(V145~V147)。Wong 等[38]用 GC-MS 在龙眼果实中鉴别出 61 个挥发性成分，其中酯类占 68.4%，萜类占 27.1%。杨晓红等[39]利用 GC-MS 技术，报道鲜龙眼肉中分离出 35 个挥发性组分，并最终鉴定出苯并噻唑、苯并异噻唑、新戊酸 6-苧烯酯等 27 种挥发性物质。Zhang 等[40]通过 GC-MS 检测发现新鲜龙眼与变质龙眼成分种类和含量均存在差别，分析得到挥发性成分分别为 28 种和 22 种，主要含烯烃和酯类。Zhang 等[41]采用 HS-SPME-GC-MS 检测方法从 4 种龙眼果肉中鉴定出 62 种挥发性成分，其中包括醇类、酯类、酮

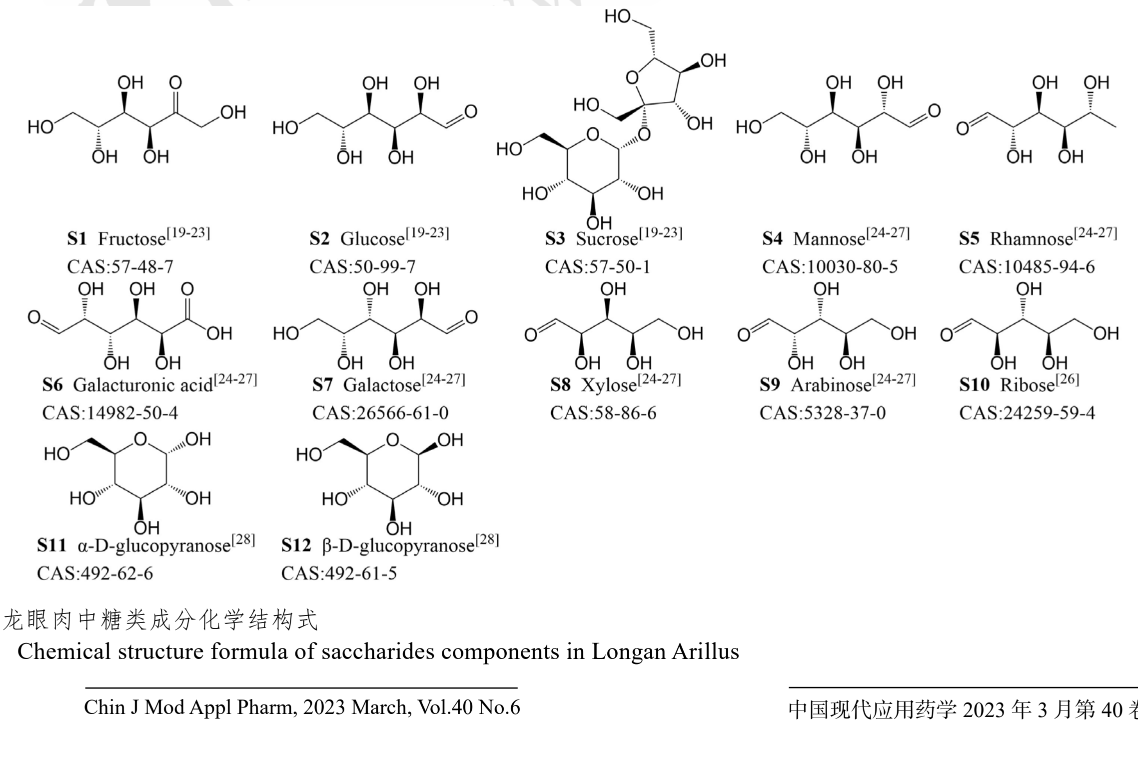


图 1　龙眼肉中糖类成分化学结构式

Fig. 1　Chemical structure formula of saccharides components in Longan Arillus

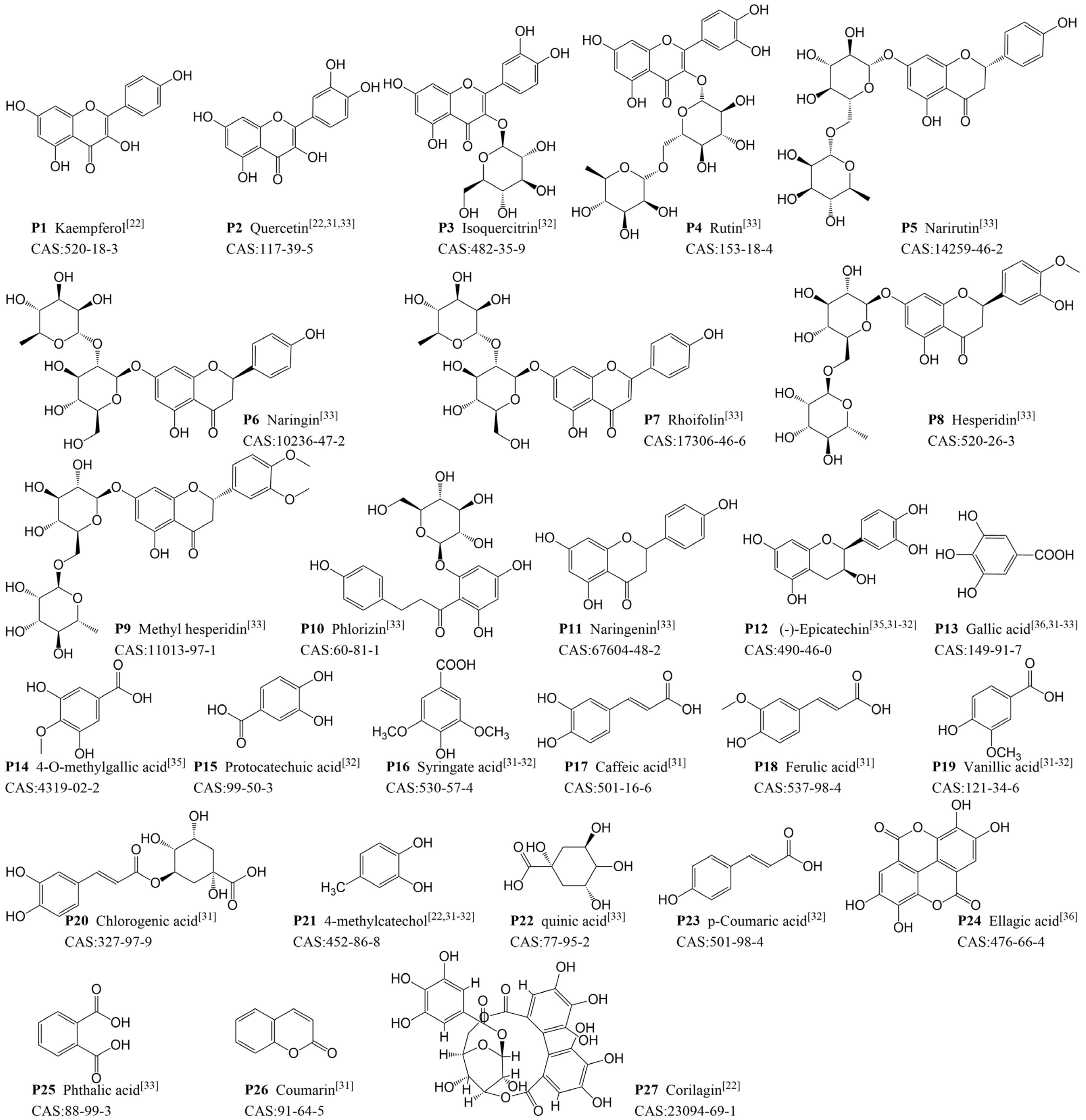


图 2 龙眼肉中多酚类成分化学结构式

Fig. 2 Chemical structure of polyphenols in Longan Arillus

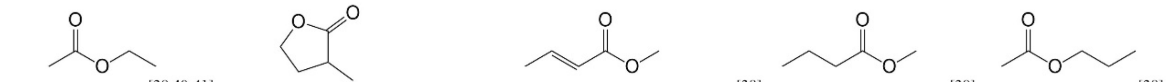
类等。Chen 等[42]采用 GC-MS、SPME 分析龙眼果肉含有 29 个挥发性组分。各色谱峰对应的质谱图经联用仪的计算机谱库检索并与标准谱图对照进行定性[38-42]。

1.1.4　皂苷类　郑玲[43]将龙眼肉提取液同人参皂苷-1 标准品进行薄层、紫外以及液相分析发现龙眼肉中含有相同的皂苷成分。但肖维强[44]将龙眼肉提取液与人参皂苷 Rg_1、Rb_1 对照品进行对照分析，证明龙眼肉中不存在人参皂苷 Rg_1、Rb_1 成分。

1.1.5　甾醇类　龙眼肉中含甾醇类化合物(图 4)包括 β-谷甾醇、β-胡萝卜苷[22,45]。

1.1.6　有机酸类　龙眼肉中有机酸成分含丁二酸、苹果酸、柠檬酸、葡萄糖酸、阿拉伯糖酸、4-*O*-甲基葡萄糖酸、奎宁酸、月桂酸、草酸、乳酸、乙酸[22,26]、二十四碳酸[45]，见图 5。

1.1.7　脂类　龙眼肉中含有少量脂类物质，见图 6。Ryu 等[46]从龙眼肉中分离出 6 个脑苷脂成分，分别为大豆脑苷脂 I、II，龙眼脑苷脂 I、II，苦瓜脑苷脂 I 以及商陆脑苷脂(L1~L6)，它们均具有 2-羟基脂肪酸的鞘氨醇型或植物鞘氨醇型的葡糖脑苷脂



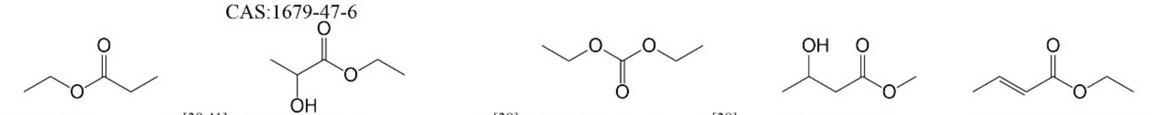
V1 Ethyl acetate[38,40-41]
CAS:141-78-6

V2 Dihydro-3-methyl-2(3H)-furanone[38]
CAS:1679-47-6

V3 Methyl (E)-but-2-enoate[38]
CAS:623-43-8

V4 Methyl butanoate[38]
CAS:623-42-7

V5 Propyl acetate[38]
CAS:109-60-4



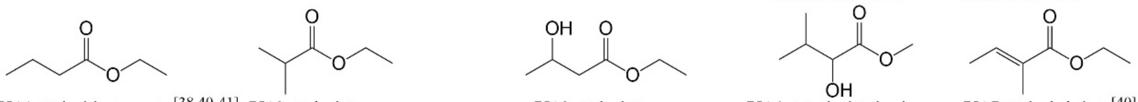
V6 Ethyl propanoate[38,41]
CAS:105-37-3

V7 Ethyl 2-hydroxypropanoate[38]
CAS:97-64-3

V8 Diethyl carbonate[38]
CAS:105-58-8

V9 Methyl 3-hydroxybutanoate[38]
CAS:1487-49-6

V10 Ethyl (E)-but-2-enoate[38,40-41]
CAS:623-70-1



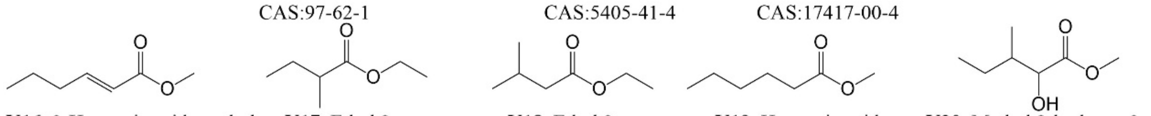
V11 Ethyl butanoate[38,40-41]
CAS:105-54-4

V12 Ethyl 2-methylpropanoate[38]
CAS:97-62-1

V13 Ethyl 3-hydroxybutanoate[38]
CAS:5405-41-4

V14 Methyl 2-hydroxy-3-methylbutanoate[38]
CAS:17417-00-4

V15 Ethyl tiglate[40]
CAS:5837-78-5



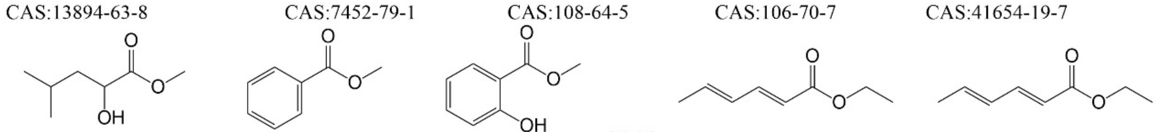
V16 2-Hexenoic acid, methyl ester, (E)-[41]
CAS:13894-63-8

V17 Ethyl 2-methylbutanoate[38,41]
CAS:7452-79-1

V18 Ethyl 3-methylbutanoate[38]
CAS:108-64-5

V19 Hexanoic acid methyl ester[41]
CAS:106-70-7

V20 Methyl 2-hydroxy-3-methylpentanoate[38]
CAS:41654-19-7



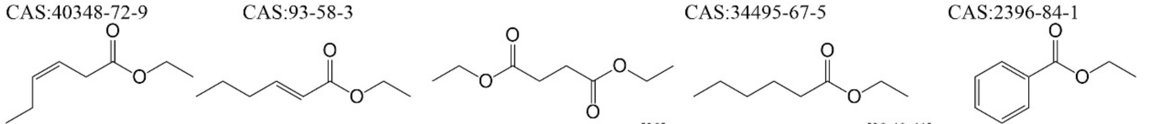
V21 Methyl 2-hydroxy-4-methylpentanoate[38]
CAS:40348-72-9

V22 Benzoic acid methyl ester[40]
CAS:93-58-3

V23 Methyl salicylate[40-41]
CAS:119-36-8

V24 Ethyl (E,Z)-hexa-2,4-dienoate[38,41]
CAS:34495-67-5

V25 Ethyl (E,E,)-hexa-2,4-dienoate[38,41]
CAS:2396-84-1



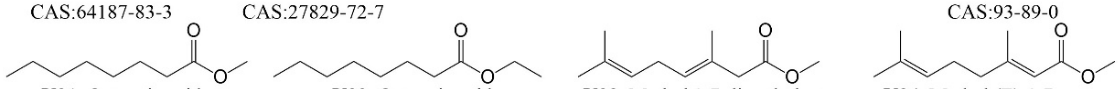
V26 Ethyl (Z)-hex-3-enoate[38]
CAS:64187-83-3

V27 Ethyl (E)-hex-2-enoate[38]
CAS:27829-72-7

V28 Diethyl butanedioate[38]
CAS:123-25-1

V29 Ethyl hexanoate[38,40-41]
CAS:123-66-0

V30 Benzoic acid ethyl ester[38,40-41]
CAS:93-89-0



V31 Octanoic acid methyl ester[41]
CAS:111-11-5

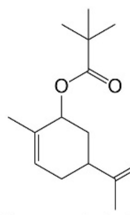
V32 Octanoic acid ethyl ester[38,40-41]
CAS:106-32-1

V33 Methyl 3,7-dimethylocta-3,6-dienoate[38]
CAS:104178-46-3

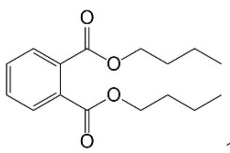
V34 Methyl (E)-3,7-dimethylocta-2,6-dienoate[38,41]
CAS:1189-09-9

V35 Ethyl decanoate[38,40-41]
CAS:110-38-3

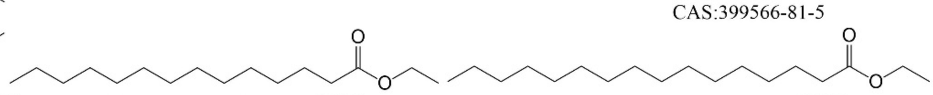
V36 Ethyl dodecanoate[38,41]
CAS:106-33-2



V37 Limonen-6-ol,pivalate[39]
CAS:399566-81-5

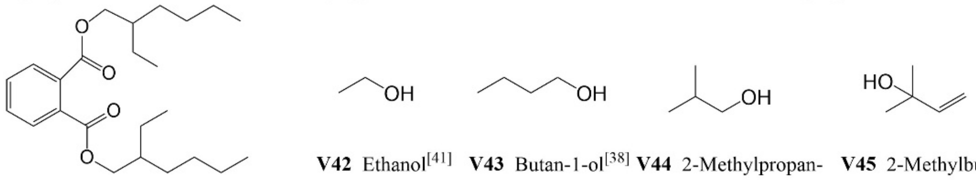


V38 Dibutyl phthalate[39]
CAS:84-74-2



V39 Ethyl tetradecanoate[38,41]
CAS:124-06-1

V40 Ethyl hexadecanoate[38,41]
CAS:628-97-7



V41 Bis(2 - ethylhexyl)phthalate[39]
CAS:117-81-7

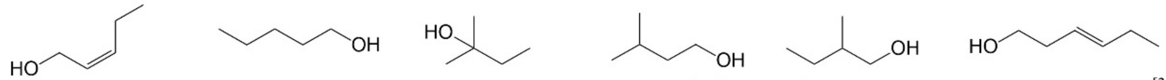
V42 Ethanol[41]
CAS:64-17-5

V43 Butan-1-ol[38]
CAS:71-36-3

V44 2-Methylpropan-1-ol[38]
CAS:78-83-1

V45 2-Methylbut-3-en-2-ol[38]
CAS:115-18-4

V46 Pent-1-en-3-ol[38]
CAS:616-251



V47 (Z)-Pent-2-en-1-ol[38,41] CAS:1576-95-0

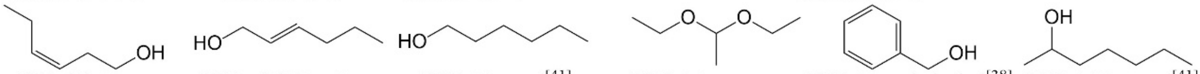
V48 Pentan-1-ol[38,41] CAS:71-41-0

V49 2-Methylbutan-2-ol[38] CAS:75-85-4

V50 3-Methylbutan-1-ol[38,40] CAS:123-51-3

V51 2-Methyl-1-Butanol[41] CAS:137-32-6

V52 (E)-Hex-3-en-1-ol[38,41] CAS:928-97-2



V53 (Z)-Hex-3-en-1-ol[38,41] CAS:928-96-1

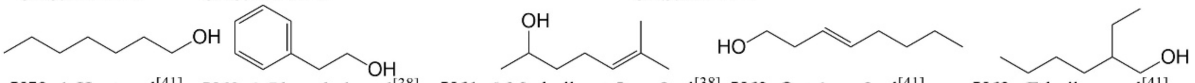
V54 (E)-Hex-2-en-1-ol[38] CAS:928-95-0

V55 Hexanol[41] CAS:111-27-3

V56 1,1-Diethoxyethane[38] CAS:105-57-7

V57 Benzyl alcohol[38] CAS:100-51-6

V58 2-Heptanol[41] CAS:543-49-7



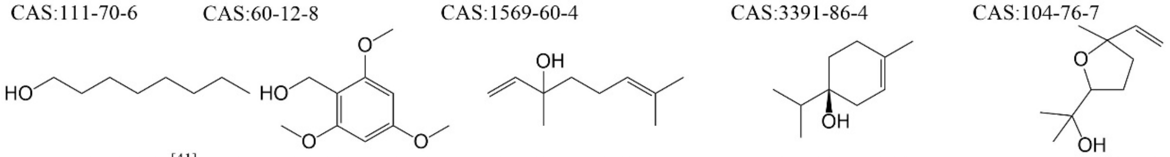
V59 1-Heptanol[41] CAS:111-70-6

V60 2-Phenylethanol[38] CAS:60-12-8

V61 6-Methylhept-5-en-2-ol[38] CAS:1569-60-4

V62 Oct-1-en-3-ol[41] CAS:3391-86-4

V63 Ethylhexanol[41] CAS:104-76-7



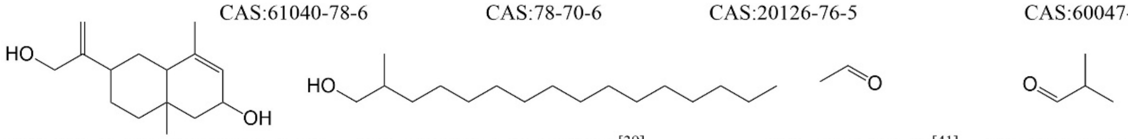
V64 Octanol[41] CAS:111-87-5

V65 2,4,6-Trimethoxybenzyl alcohol[39] CAS:61040-78-6

V66 3,7-Dimethyl-1,6-octadien-3-ol[38,40-41] CAS:78-70-6

V67 (R)-4-Methyl-1-(1-methylethyl)-3-cyclohexen-1-ol[40] CAS:20126-76-5

V68 cis-Linalol oxide (furanoid)[38] CAS:60047-17-8

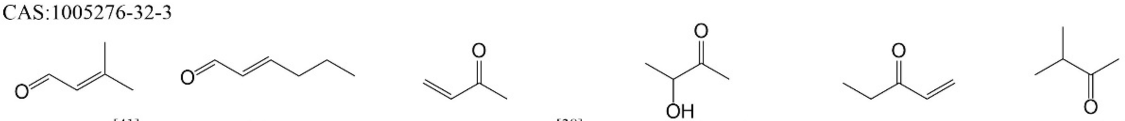


V69 Bicyclo[4.4.0]dec-2-ene-4-ol,2-methyl-9-(prop-1-en-3-ol-2-yl)-[42] CAS:1005276-32-3

V70 2-Methyl-1-hexadecanol[39] CAS:2490-48-4

V71 Acetaldehyde[41] CAS:75-07-0

V72 Methylpropanal[38] CAS:78-84-2



V73 Prenal[41] CAS:107-86-8

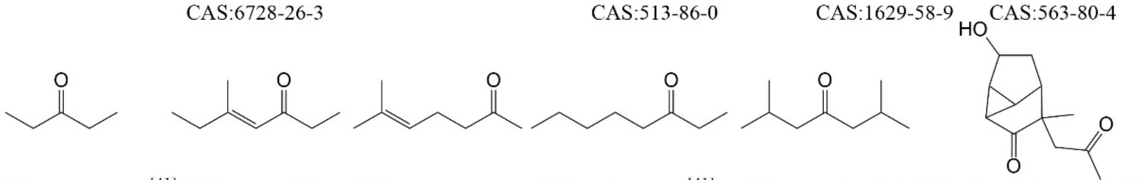
V74 (E)-Hex-2-enal[38,40] CAS:6728-26-3

V75 But-3-en-2-one[38] CAS:78-94-4

V76 3-Hydroxybutan-2-one[38] CAS:513-86-0

V77 Pent-1-en-3-one[38] CAS:1629-58-9

V78 3-Methylbutan-2-one[38] CAS:563-80-4



V79 3-Pentanone[41] CAS:96-22-0

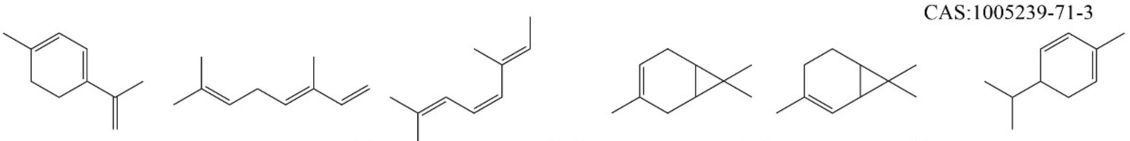
V80 5-Methyl-4-hepten-3-one[40] CAS:1447-26-3

V81 5-Hepten-2-one,6-methyl-[41] CAS:110-93-0

V82 3-Octanone[41] CAS:106-68-3

V83 2,6-Dimethyl-4-heptanone[41] CAS:108-83-8

V84 Cicyclo[3.3.0.0(2,8)]octan-3-one,7-hydroxy-4-methyl-4-(propan-2-on-1-yl)-[42] CAS:1005239-71-3



V85 1,3,8-p-Menthatriene[40-41] CAS:18368-95-1

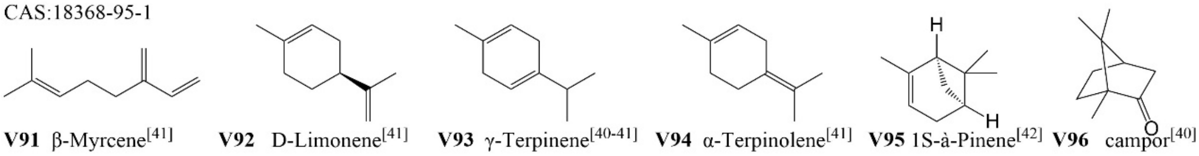
V86 (E)-β-Ocimene[38] CAS:3779-61-1

V87 allo Ocimene[39-40] CAS:673-84-7

V88 3-Carene[40] CAS:13466-78-9

V89 2-Carene[40] CAS:554-61-0

V90 α-Phellandrene[40] CAS:99-83-2



V91 β-Myrcene[41] CAS:123-35-3

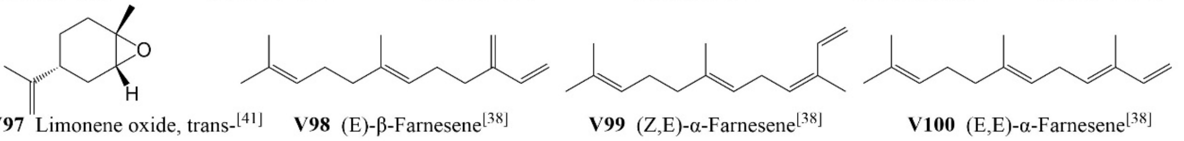
V92 D-Limonene[41] CAS:5989-27-5

V93 γ-Terpinene[40-41] CAS:99-85-4

V94 α-Terpinolene[41] CAS:586-62-9

V95 1S-à-Pinene[42] CAS:7785-26-4

V96 campor[40] CAS:464-49-3



V97 Limonene oxide, trans-[41] CAS:42477-94-1

V98 (E)-β-Farnesene[38] CAS:18794-84-8

V99 (Z,E)-α-Farnesene[38] CAS:26560-14-5

V100 (E,E)-α-Farnesene[38] CAS:502-61-4

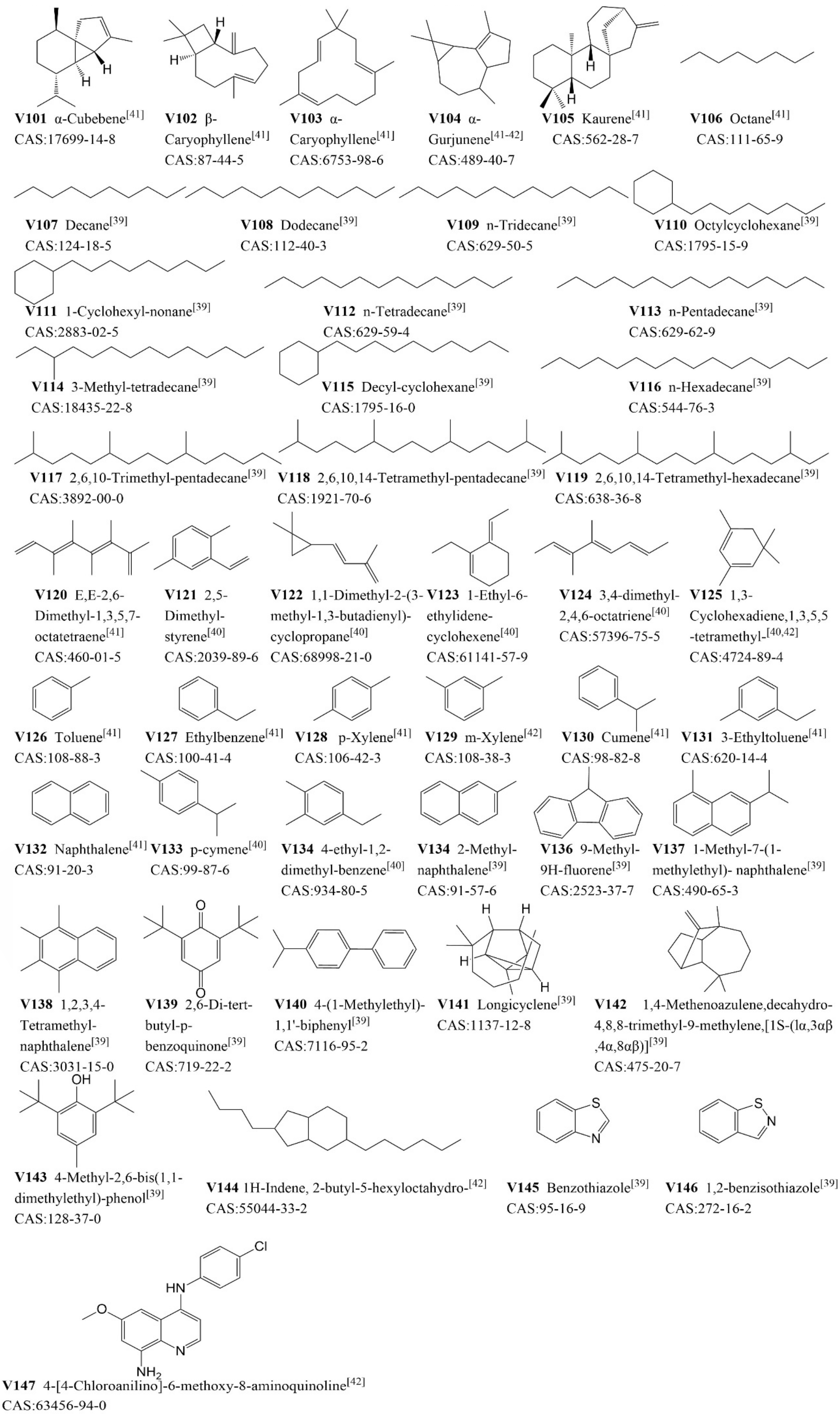
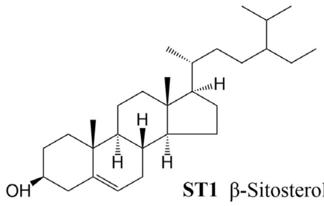
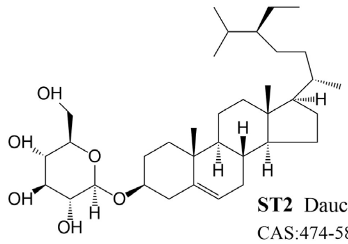


图 3 龙眼肉中挥发性成分化学结构式

Fig. 3 Chemical structural of volatile components in Longan Arillus

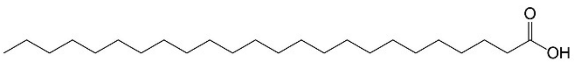


ST1 β-Sitosterol[22,45]
CAS:83-46-5

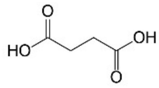


ST2 Daucosterol[45]
CAS:474-58-8

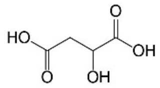
图 4 龙眼肉中甾醇类成分化学结构式
Fig. 4 Chemical structural formula of sterols in Longan Arillus



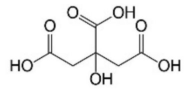
O1 Tetracosanoic acid[45]
CAS:557-59-5



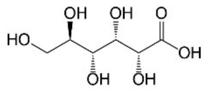
O2 Succinic Acid[22,26]
CAS:110-15-6



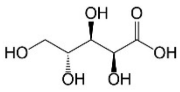
O3 Malic acid[22,26]
CAS:6915-15-7



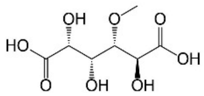
O4 Citric acid[22,26]
CAS:77-92-9



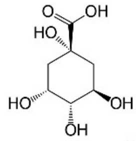
O5 Gluconic acid[22]
CAS:526-95-4



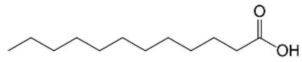
O6 Arabinonic acid[22]
CAS:488-30-2



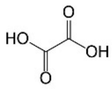
O7 4-O-methyl-glucaric acid[22]
CAS:4120-73-4



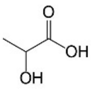
O8 Quinic acid[22]
CAS:77-95-2



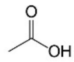
O9 Lauric acid[22]
CAS:143-07-7



O10 Oxalic acid[26]
CAS:144-62-7



O11 Lactic acid[26]
CAS:50-21-5



O12 Acetic acid[26]
CAS:64-19-7

图 5 龙眼肉中有机酸类成分化学结构式
Fig. 5 Chemical structure formula of organic acids in Longan Arillus

的几何异构体，其中龙眼脑苷脂 I、II 是从龙眼果肉中分离出来的特有成分。李立等[47]用氯仿-甲醇(2∶1)溶液萃取研究发现龙眼肉中分别含有溶血磷脂酰胆碱、磷脂酰胆碱、磷脂酰肌醇、磷脂酰丝氨酸、磷脂酰乙醇胺、磷脂酸和磷脂酰甘油等 7 种磷脂类成分。文献未报道此 7 种成分的明确结构。本研究参考文献中的中文名称，列出此 7 种成分的结构式(L7~L13，见图 6)。

1.1.8 核苷类　龙眼肉中核苷类化合物主要为核苷[22,45,48-49]、脱氧核苷[50]、核苷衍生物[48]，见图 7。

1.1.9 氨基酸类　龙眼肉中氨基酸成分共 29 种，见图 8，其中除色氨酸(酸解时被破坏)外常见氨基酸均含(A1~A19)，且干制品中含量明显下降[22,25,51-52]，不同品种龙眼肉中含量存在显著差异[53]。龙眼肉果浆中还含有苯丝氨酸、半胱氨酸、α-氨基丁酸等 10 种氨基酸衍生物(A20~A29)[32]。

1.1.10 微量元素　通过原子吸收光谱法测定得到龙眼肉中含有铜、锰、锌、铁、钙、钾、镁、钠、磷、硒共 10 种微量元素[54-55]，不同品种含量略有不同[25]。

1.1.11 其他类　本研究首次从龙眼肉中分离得到 7,8-二甲基咯嗪、(2*S*,3*S*,4*R*,10*E*)-2-[(2’*R*)-2’-羟基二十四碳酰胺]-l0-十八碳烯-1,3,4-三醇和甘露醇共 3 种物质[45]，见图 9。

1.2 龙眼肉活性成分靶点筛选

通过数据库来筛选靶点，各数据库标准不同，产生的结果也就不同。为保证靶点信息准确统一，活性成分靶点筛选均采用 SwissTargetPrediction 数据库(http://www.swisstargetprediction.ch/)。将“1.1”项下整理的龙眼肉成分在 PubChem 数据库(https://pubchem.ncbi.nlm.nih.gov)和化源网(https://www.chemsrc.com)进行结构确认，并利用 ChemBiodraw 将其化学结构一一画出。最后将各成分的 SMILES 格式依次导入 SwissADME 并提交，以满足 GI absorption 为 High，Druglikeness 中 Lipinski、Ghose、Veber、Egan、Muegge 5 个方面有≥2 为 yes 的条件筛选龙眼肉活性成分。通过采集所得靶点较多，为提高结果可信度，选取 Probability 值≥0.2 的靶点信息。在 SwissTargetPrediction 数据库检索成分及其靶点的过程中存在一定局限性，有成分与靶点不完整的

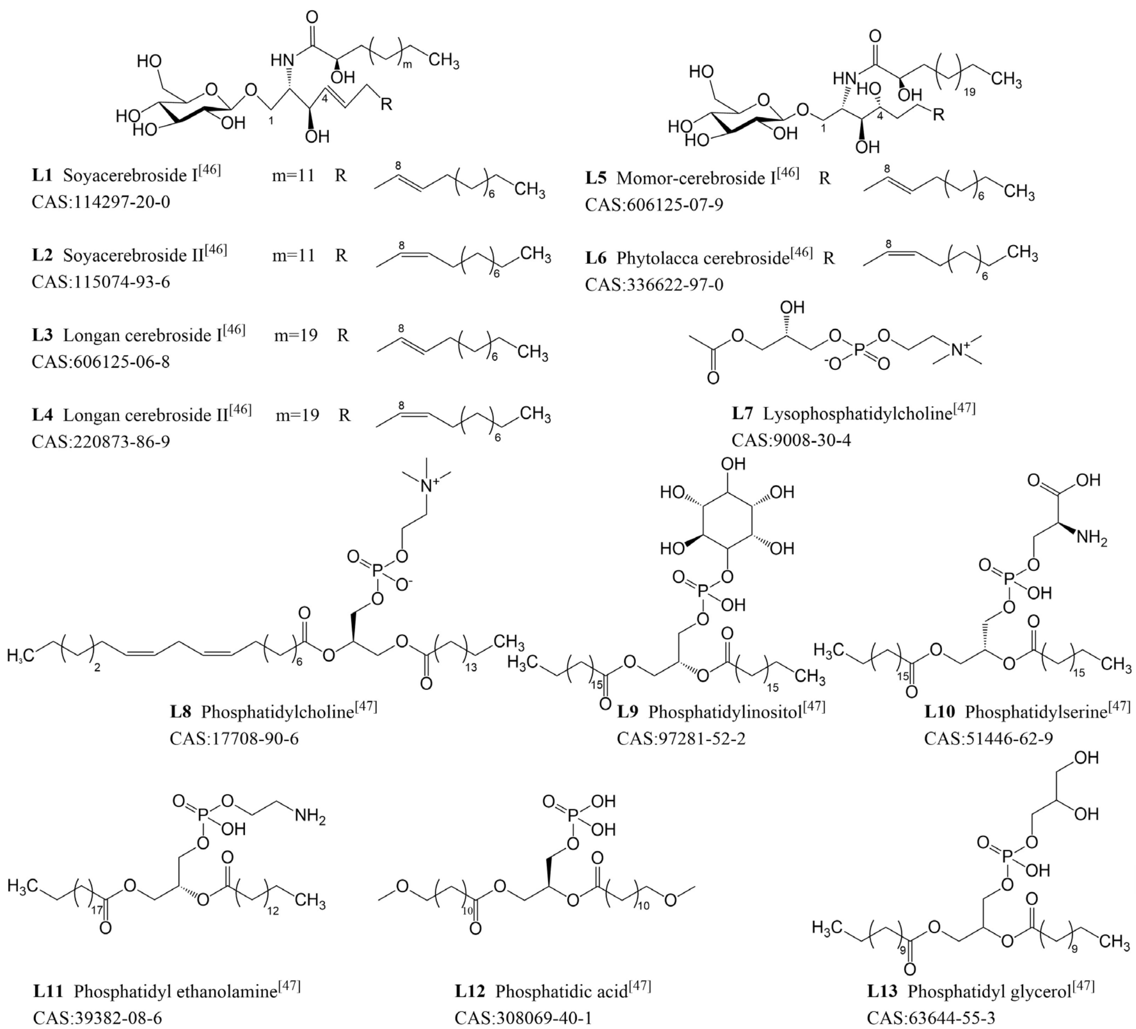


图 6 龙眼肉中脂类成分化学结构式

Fig. 6 Chemical structural formula of lipid components in Longan Arillus

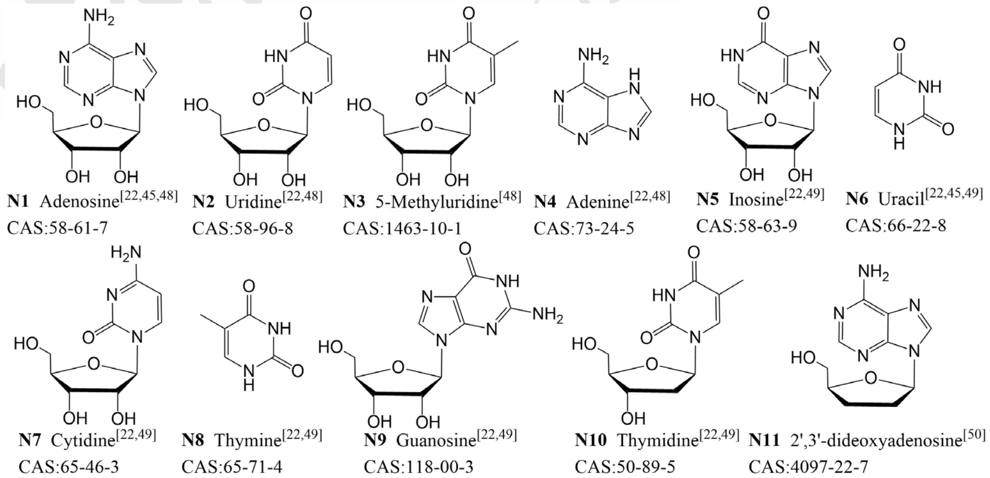


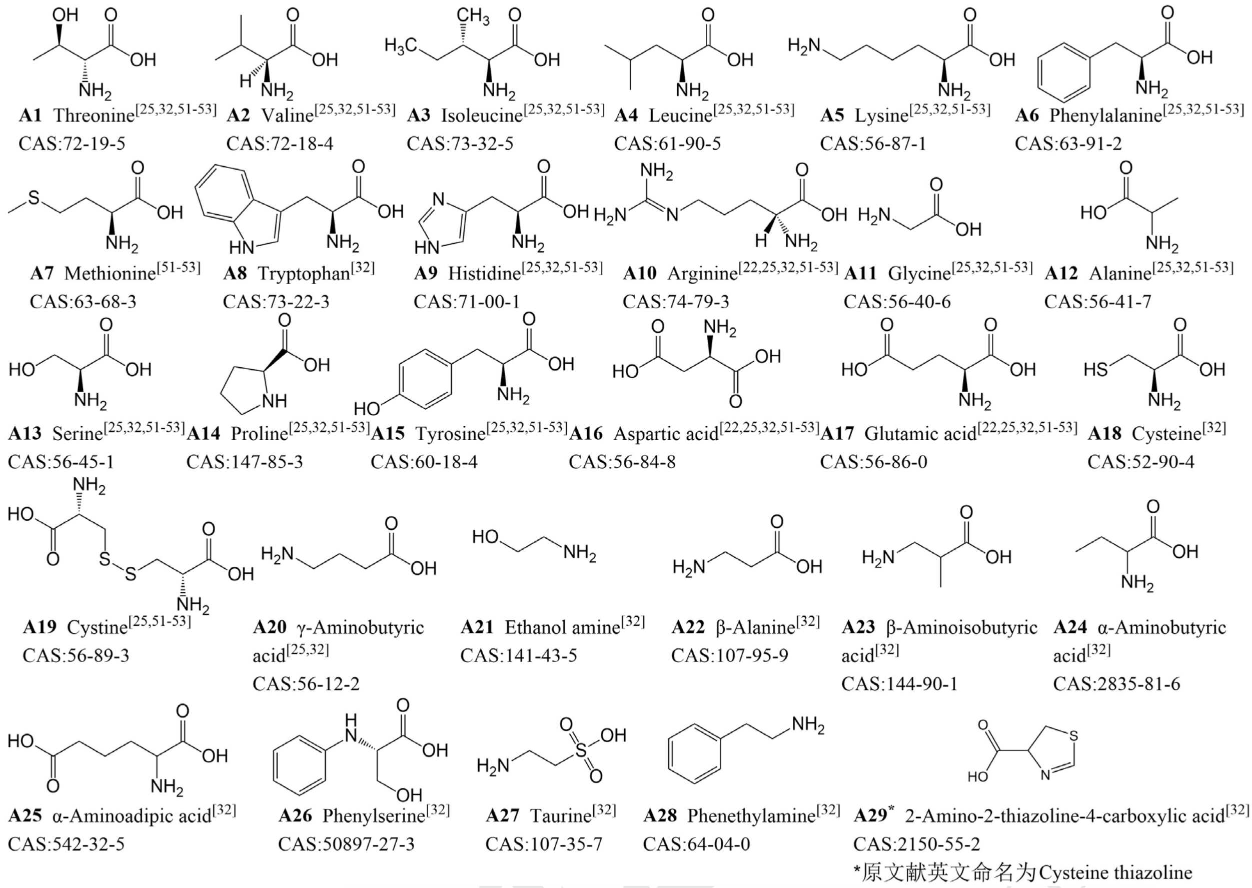
图 7 龙眼肉中核苷类成分化学结构式

Fig. 7 Chemical structure of nucleosides in Longan Arillus

情况，但整体准确性和完整性较高，符合相关要求。

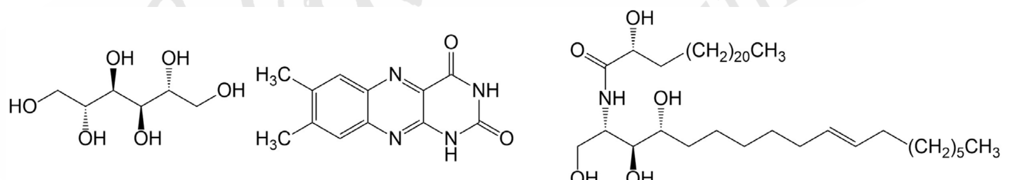
1.3 贫血疾病靶点筛选

通过 OMIM(https://www.omim.org/)、DrugBank (https://go.drugbank.com/)、GeneCards(https://www.genecards.org/)数据库，以“anemia”“aplasticanemia”为关键词，搜索疾病靶点。选取 3 个数据库共同收录的靶点作为贫血疾病靶点，采用 UniProt 数据库 (https://www.uniprot.org/)对蛋白靶点名称转为基



A1 Threonine[25,32,51-53] CAS:72-19-5
A2 Valine[25,32,51-53] CAS:72-18-4
A3 Isoleucine[25,32,51-53] CAS:73-32-5
A4 Leucine[25,32,51-53] CAS:61-90-5
A5 Lysine[25,32,51-53] CAS:56-87-1
A6 Phenylalanine[25,32,51-53] CAS:63-91-2
A7 Methionine[51-53] CAS:63-68-3
A8 Tryptophan[32] CAS:73-22-3
A9 Histidine[25,32,51-53] CAS:71-00-1
A10 Arginine[22,25,32,51-53] CAS:74-79-3
A11 Glycine[25,32,51-53] CAS:56-40-6
A12 Alanine[25,32,51-53] CAS:56-41-7
A13 Serine[25,32,51-53] CAS:56-45-1
A14 Proline[25,32,51-53] CAS:147-85-3
A15 Tyrosine[25,32,51-53] CAS:60-18-4
A16 Aspartic acid[22,25,32,51-53] CAS:56-84-8
A17 Glutamic acid[22,25,32,51-53] CAS:56-86-0
A18 Cysteine[32] CAS:52-90-4
A19 Cystine[25,51-53] CAS:56-89-3
A20 γ-Aminobutyric acid[25,32] CAS:56-12-2
A21 Ethanol amine[32] CAS:141-43-5
A22 β-Alanine[32] CAS:107-95-9
A23 β-Aminoisobutyric acid[32] CAS:144-90-1
A24 α-Aminobutyric acid[32] CAS:2835-81-6
A25 α-Aminoadipic acid[32] CAS:542-32-5
A26 Phenylserine[32] CAS:50897-27-3
A27 Taurine[32] CAS:107-35-7
A28 Phenethylamine[32] CAS:64-04-0
A29* 2-Amino-2-thiazoline-4-carboxylic acid[32] CAS:2150-55-2
*原文献英文命名为Cysteine thiazoline

图 8 龙眼肉中氨基酸类成分化学结构式
Fig. 8 Chemical structural formula of amino acids in Longan Arillus



OT1 Mannitol[45] CAS:69-65-8
OT2 7,8-Dimethylalloxazine[45] CAS:1086-80-2
OT3 ((2S,3S,4R,10E)-2-[(2'R)-2'-hydroxylignoceroylamino]-10-octadec-ene-1,3,4-triol[45] CAS:923582-43-8

图 9 龙眼肉中其他类成分化学结构式
Fig. 9 Chemical structural of other components in Longan Arillus

因名称。

1.4 蛋白互作网络(protein-protein interaction，PPI)的构建

运用 VENNY 2.1.0(https://bioinfogp.cnb.csic.es/tools/venny/)得到疾病与龙眼肉活性成分交集靶点信息，将交集靶点上传至 STRING 数据库(https://cn.string-db.org/)，选择 Homo sapiens，置信度蛋白质参数评分值>0.40，隐藏不互动的单一蛋白，获取蛋白相互作用信息，绘制 PPI，并将数据导入 Cytoscape 3.9.1 软件作进一步分析。

1.5 “龙眼肉-活性成分-靶点-疾病”网络的构建

根据上述步骤得到的“龙眼肉-活性成分-靶点”“疾病-靶点”以及交集靶点相关信息，在 Cytoscape 3.9.1 软件中构建出“龙眼肉-活性成分-靶点-疾病”网络模型。

1.6 GO 富集功能分析和 KEGG 通路富集分析

将交集靶点输入 DAVID 6.8 数据库(https://david.ncifcrf.gov/tools.jsp)，选择 Homo sapiens，进行 GO 功能富集和 KEGG 通路富集分析(按 Count 值排序)。

2 结果

2.1 龙眼肉活性成分筛选

龙眼肉成分库共有 256 种成分，以上成分经过 SwissTargetPrediction 最终获得 186 个靶点信息，32 种活性成分，其中多酚类成分 13 种(山柰酚、槲皮素、丁香酸、对香豆酸、鞣花酸、没食子酸、阿魏酸、原儿茶酸、柚皮素、香豆素、咖啡酸、柯里拉京、香草酸)，挥发性成分 9 种{2-甲基-9-(丙-1-烯-3-醇-2-基)-二环[4.4.0]葵-2-烯-4-醇、己酸甲酯、2-庚醇、3-辛酮、辛酸甲酯、α-甲基-γ-丁内酯、1-庚醇、己酸乙酯、4-甲基-2,6 二叔丁基苯酚}，氨基酸类成分 7 种(苯丙氨酸、γ-氨基丁酸、苯乙胺、谷氨酸、蛋氨酸、酪氨酸、α-氨基己二酸)，有机酸成分 3 种(丁二酸、二十四碳酸、月桂酸)。

2.2 贫血疾病靶点筛选

经 OMIM、DrugBank、GeneCards 数据库搜索贫血人类靶点，去重后共得到 1 013 个疾病靶点。

2.3 PPI 的构建

将龙眼肉活性成分靶点与疾病靶点进行交集共获得 24 个交集靶点，通过构建韦恩图进行可视化处理，见图 10。交集靶点在 STRING 数据库获取蛋白互作信息，将其导入 Cytoscape 3.9.1 软件绘制 PPI，见图 11。网络共有 22 个靶点基因相互作用，33 条边，平均节点度为 2.64，通过颜色反映靶点的 Degree 值大小。其中拓扑异构酶 1(TOP1)、端粒酶逆转录酶(TERT)、髓过氧化物酶(MPO)、多聚 ADP 核糖转移酶(PARP1)等基因为龙眼肉中活性成分与贫血疾病相关的核心基因。

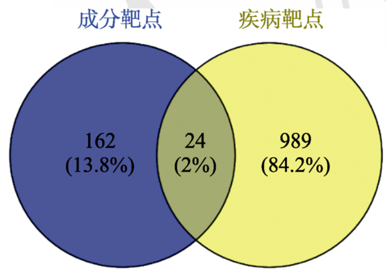


图 10 药物与疾病靶点韦恩图

Fig. 10 Venny diagram of drug and disease targets

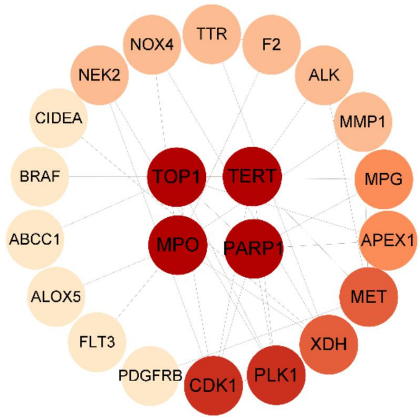


图 11 龙眼肉治疗贫血的 PPI 网络

Fig. 11 PPI network of Longan Arillus in the treatment of anemia

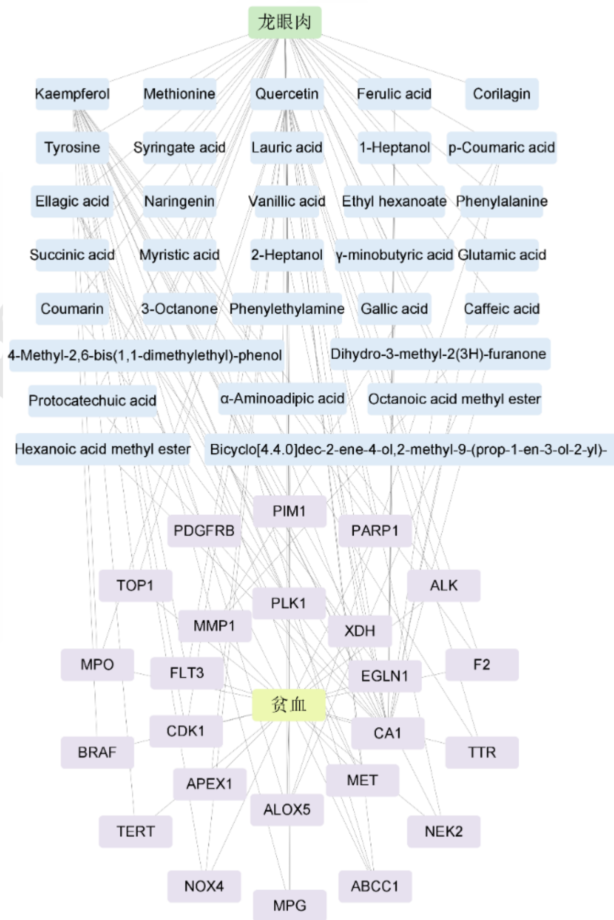


图 12 “龙眼肉-活性成分-靶点-疾病”网络图

Fig. 12 Network diagram of “Longan Arillus-active ingredients- target-disease”

2.4 “龙眼肉-活性成分-靶点-疾病”网络

使用 Cytoscape 3.9.1 软件进行网络构建，结果见图 12，图中紫色为交集靶点，蓝色为龙眼肉的活性成分，龙眼肉中槲皮素(Quercetin)成分对应的靶点数最多。

2.5 GO 富集功能分析和 KEGG 通路富集分析

通过 DAVID 6.8 数据库对交集靶点进行 GO 富集分析，共获得 87 个 GO 条目，涉及的生物过程(biological process，BP)条目有 50 个，包括细胞因子介导的信号通路(cytokine-mediated signaling pathway)、药物反应(response to drug)、基因表达的正向调控(positive regulation of gene expression)、缺氧反应(response to hypoxia)以及脂多糖细胞反应(cellular response to lipopolysaccharide)；细胞组成(cellular component，CC)条目有 21 个，包括细胞外间隙(extra cellular space)、胞外区(extra cellular region)、血小板 α 颗粒腔(platelet alpha granule lumen)、质膜外侧(external side of plasma membrane)和细胞表面(cell surface)；分子功能(molecular function，MF)条目有 16 个，包括细胞因子活性(cytokine activity)、酶结合(enzyme binding)、蛋白酶结合(protease binding)、整合素结合(integrin binding)和生长因子活性(growth factor activity)等。BP、CC、MF 条目按 Count 值排序选前 5 条绘图，做 GO 富集分析，见图 13。通过 DAVID 6.8 数据库对龙眼肉活性成分与贫血疾病的交集靶点基因进行 KEGG 通路富集分析，获得 15 条通路，包括癌症通路(Pathways in cancer)、急性髓系白血病(Acute myeloid leukemia)、丝裂原活化蛋白激酶信号通路(MAPK signaling pathway)、癌症中 miRNA(MicroRNAs in cancer)、碱基切除修复系统(base excision repair)等。按 Count 值排序将前 10 条绘图表示，见图 14。

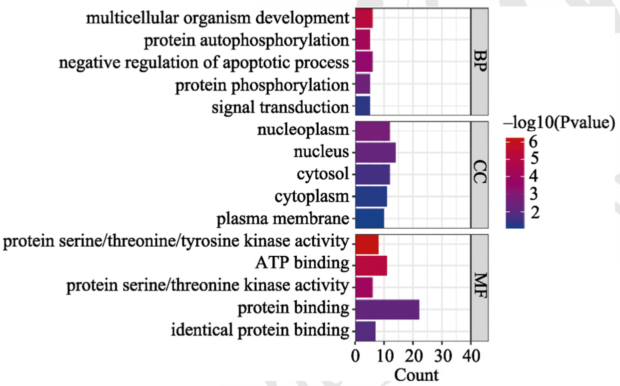


图 13 龙眼肉治疗贫血的 GO 富集分析

Fig. 13 GO enrichment analysis of Longan Arillus in the treatment of anemia

3 讨论与展望

龙眼肉作为广西传统地道药材，是“桂十味”中药食两用的代表性品种。龙眼肉具有广泛药理作用，如抗焦虑[56-58]、抗氧化[59-63]、抗衰老[64-65]、免疫调节[66-67]等。但研究过程中仍有诸多问题需要解决，成分对其药理作用的机制尚未明确。

本研究通过文献整理建立较为完整的龙眼肉化学成分数据库，利用所建立的成分库，联合网络药理学探讨龙眼肉治疗贫血的可能作用机制。

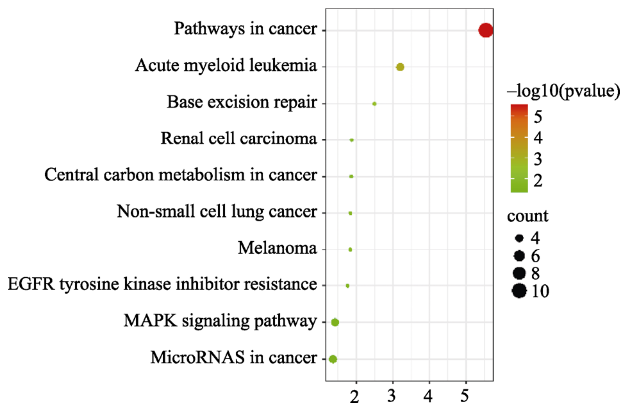


图 14 龙眼肉治疗贫血的 KEGG 富集分析

Fig. 14 KEGG enrichment analysis of Longan Arillus in the treatment of anemia

结合“龙眼肉-活性成分-靶点-疾病”网络与研究表明，多酚类中槲皮素对实验性慢性肾衰大鼠肾性贫血具有显著防治作用[68]。氨基酸与铁形成螯合物，增加身体对铁的吸收，可用于治疗缺铁性贫血[69]。在甘氨酸螯合铁中添加 γ-氨基丁酸可能会提高其治疗缺铁性贫血的有效性[70]。由此认为龙眼肉中多酚类和氨基酸类成分可能是改善贫血的活性成分。靶点研究中 TOP1 是龙眼肉的核心靶点之一，与核蛋白基因 NUP98 融合形成的 NUP98-TOP1 可用于轻度贫血[71]，获得性再生障碍性贫血患者外周血单个核细胞中的 TERT 与红细胞和血红蛋白水平有相关性[72]。MPO 与血清铁蛋白显著相关，其指数用于早期缺铁性贫血的诊断[73]。PARP1 参与调节骨髓或血液系统的细胞分化，而再生障碍性贫血又是一种骨髓造血功能衰竭综合征，故 PARP1 对再生障碍性贫血有影响[74-75]。由此认为龙眼肉可通过改变 DNA 的拓扑状态，改善红细胞、血红蛋白和血清铁蛋白水平等方式治疗贫血。根据 KEGG 富集分析显示龙眼肉治疗贫血主要通过癌症通路、急性髓系白血病、MAPK 信号通路等来改善贫血。研究表明 40%~64%的恶性肿瘤患者患有贫血[76]，可见通过调节癌症通路可以改善贫血。急性髓系白血病是再生障碍性贫血患者免疫抑制治疗后最严重的继发性事件[77-78]，与贫血的发生关系密切。MAPK 信号通路参与介导细胞生长、发育、分裂和分化等多种生理及病理过程，研究显示该通路对于再生性障碍贫血的治疗有积极意义[79-80]。MiRNA- 200C 可能在范可尼贫血途径下游中起调控作用[81]，从而改善贫血。

综上所述，网络药理学初步探索研究建立了

龙眼肉成分-药理的关联性。龙眼肉治疗贫血具有多成分、多靶点、多途径的特点，网络药理学预测结果与现有文献研究成果一致，可对龙眼肉药效成分研究与治疗贫血机制提供依据和参考。期望本研究可以为后期科研工作者基于网络药理学及分子对接研究龙眼肉治疗其他病症提供有价值的参考，龙眼肉成分库也将依据研究进展不断更新。

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