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基于网络药理学探讨乳香的抗炎作用机制

王璐琼*，辛　敏，徐瑶瑶，王　革，高银鹤，赵　烽#

烟台大学药学院分子药理学与药物评价教育部重点实验室，山东省高校新型药物传递系统与生物技术药物协同创新中心，山东 烟台

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摘　要

目的：乳香是橄榄科乳香属植物乳香树树皮渗出的树脂。现代临床研究表明，乳香的主要药理有抗炎活性、抗肿瘤活性、神经保护活性及抗病毒、抗菌活性，但其抗炎活性的机制尚不明确。方法：本研究通过TCMSP、Swiss、Venny2.1、Gene Cards等数据库进行检索，对乳香的有效活性成分，有效活性成分对应的靶点基因及相关的抗炎信号通路进行了研究。构建了“成分－靶点”网络，进行了靶点蛋白的相互作用分析、GO生物功能和KEGG通路富集分析。结果：从乳香中分析筛选出12个活性成分，包括乳香脂酸、因香酚、甘遂醇等；52个靶点基因，包括PRKCH、PRKCG、NOS2、PTPN2、PRKCE等；8条炎症相关的信号通路，如NF-κB信号通路，TRP信号通路等。讨论：乳香可以通过PRKCH、PRKCG等靶点基因，以及NF-κB，TRP等信号通路发挥抗炎作用，乳香“多成分－多靶点－多通路”的作用特点，为乳香及其成分的临床应用提供了研究方向和科学依据。

关键词

乳香，炎症，网络药理学，基因靶点，炎症通路

Studies on the Anti-Inflammatory Mechanism of Frankincense Based on Network Pharmacology

Luqiong Wang*, Min Xin, Yaoyao Xu, Ge Wang, Yinhe Gao, Feng Zhao#

Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Key Laboratory of Molecular Pharmacology and Drug Evaluation, Ministry of Education, School of Pharmacy, Yantai University, Yantai Shandong

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*第一作者。
#通讯作者。

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Abstract

Objective: Frankincense is a resin exudated from the bark of frankincense trees in the genus Frankincense of olive family. Modern clinical studies show that the main pharmacological activities of Frankincense include anti-inflammatory, anti-tumor, neuroprotective, antiviral and antibacterial activities, but the mechanism of its anti-inflammatory activity remains unclear. Methods: In this study, the active ingredients of frankincense, corresponding target genes of active ingredients and related anti-inflammatory signaling pathways were studied by searching TCMSP, Swiss, Venny2.1, Gene Cards and other databases. The "component-target" network was constructed to analyze the interaction of target proteins, GO biological function and KEGG pathway enrichment. Results: According to the research results, 12 active components were screened out from frankincense, including frankincense lipoic acid, fenol, glycerol, etc. 52 target genes, including PRKCH, PRKCG, NOS2, PTPN2, PRKCE, etc. 8 inflammatory related signaling pathways, such as NF-κB signaling pathway, TRP signaling pathway, etc. Discussion: Frankincense can exert anti-inflammatory effects through target genes such as PRKCH and PRKCG, as well as NF-κB and TRP signaling pathways. The "multi-component-multi-target-multi-pathway" action characteristics of frankincense provide research direction and scientific basis for clinical application of frankincense and its components.

Keywords

Frankincense, Inflammation, Network Pharmacology, Gene Target, Inflammatory Pathways

1. 引言

炎症是机体为了确保在感染和组织损伤期间的正常运转，由免疫系统提供的一种基本反应，炎症反应是维持正常组织稳态所必需的[1] [2]。炎症的分子机制是一个非常复杂的过程，它是通过识别与感染或组织损伤相关的特定分子模式而启动的，整个过程由参与促炎分子选择性表达的几个关键调控因子介导，长期的慢性炎症对机体损伤极大[3] [4] [5]。

乳香作为传统中药，功效为活血定痛，消肿生肌[6]。现有研究表明乳香具有抗炎的药理活性[7] [8] [9] [10]，但其抗炎活性的机制尚不明确。网络药理学是研究植物中各个成分和靶点的药理相关作用机制的一门学科[11] [12] [13]，本文通过构建乳香、炎症、靶点三者之间的相互作用关系，对乳香的主要抗炎成分及发挥抗炎机制的主要通路进行了研究，以期为乳香及其成分的临床应用提供科学依据。

2. 方法

2.1. 数据库与软件

TCMSP 分析平台(http://tcmspw.com/tcmsp.php)；GeneCards 数据库(http://www.swisstargetprediction.ch/)；Swiss 分析平台(https://www.genecards.org/)；生物信息在线工具 Venny2.1 (https://bioinfogp.cnb.csic.es/tools/venny/)；蛋白质相互作用数据库 String (https://string-db.org/)；Cytoscape3.8.0 软件。

2.2. 乳香活性成分的筛选

通过中药系统药理学数据库与分析平台(TCMSP)，以口服生物利用度(oral bioavilability, OB) ≥ 30%、类药性(druglikeness, DL) ≥ 0.18 为筛选原则[14]，检索出乳香中主要活性成分，将活性成分输入 swiss 网站，得到其对应的靶点蛋白及相应的基因名。

2.3. 炎症相关靶点筛选

以“inflammation”为关键词，在 GeneCards 数据库中检索炎症相关基因并去重[15]。

2.4. 获得乳香治疗炎症的靶基因

将乳香活性成分基因与炎症基因导入 Venny2.1 中，得到交集靶基因，即为乳香潜在的抗炎靶点基因。

2.5. 构建蛋白质相互作用(PPI)网络分析

将 2.3 项下获取的共同靶基因所对应的靶蛋白上通过 String 平台进行蛋白质－蛋白质相互作用(protein-proteininteraction, PPI)网络分析[16] [17] [18]。将乳香潜在的抗炎靶点基因导入，并将其 TSV 格式的结果导入 Cytoscape3.8.0 软件中[19]，构建 PPI 网络图，并构建“关键活性成分－核心靶点“网络图。

2.6. GO 分析和 KEGG 通路富集分析

通过微生信网站在线工具对乳香抗炎相对应的抗炎靶点基因集进行分析，并绘制 GO 气泡图和 KEGG 条形图[20]。

3. 结果

3.1. 乳香中含有的活性成分

在乳香的 127 个化学成分中，根据筛选条件获得 12 个活性成分，具体信息见表 1。12 个活性成分对应的靶基因去除重复项共 60 个。

Table 1. Active pharmaceutical ingredients in olibanum
表 1. 乳香中含有的活性成分

活性成分编码	活性成分名称	OB(%)	DL
MOL001215	tirucallol	42.12	0.75
MOL001229	cis-resveratrol	41.13	0.18
MOL001234	thunbergol	33.12	0.19
MOL001235	9-C-Retinal	35.05	0.19
MOL001243	3alpha-Hydroxy-olean-12-en-24-oic-acid	39.32	0.75
MOL001255	Boswellic acid	39.55	0.75
MOL001259	(3R, 4R, 4aR, 6aR, 6bS, 8aR, 11R, 12S, 12aR, 14aR, 14bS)-3-hydroxy-4, 6a, 6b, 8a, 11, 12, 14b-heptamethyl-14-oxo-1, 2, 3, 4a, 5, 6, 7, 8, 9, 10, 11, 12, 12a, 14a-tetradecahydropicene-4-carboxylic acid	39.82	0.74
MOL001272	incensole	45.59	0.22
MOL001281	L-alpha-Palmitin	36.66	0.22

Continued

MOL000208	Aromadendrene	55.74	0.19
MOL000474	(−)-Epoxycaryophyllene	35.94	0.19
MOL000858	Glycerol palmitate	36.66	0.22

3.2. 筛选炎症相关靶点

经 GeneCards 数据库检索并去除重复靶点基因，共得到 43491 个炎症相关靶点基因，以 Score ≥ 3 筛选，获得 2773 个相关基因；将乳香的 60 个活性成分靶点基因与筛选出的 2773 个炎症靶点基因通过 Venny2.1 取交集，得到 52 个共同靶点基因即潜在的抗炎靶点，如图 1。

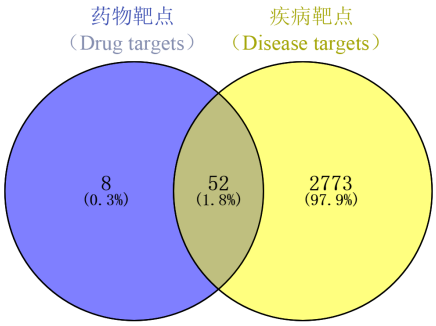

Figure 1. Venn plot of compositional targets and inflammation-related targets in olibanum
图 1. 乳香的成分靶点与炎症相关靶点的韦恩图

3.3. 构建蛋白质相互作用(PPI)网络

构建 52 个乳香潜在抗炎靶点的 PPI 网络图可以预测各靶点蛋白的相互作用关系[21] [22]。如图 2 所示，该网络图包含节点 52 个，边 147 条，其中 ESR1、PTGS2、CYP3A4、PRKCD 等靶点在该 PPI 网络中位于核心位置，提示在抗炎作用中起关键调控作用。

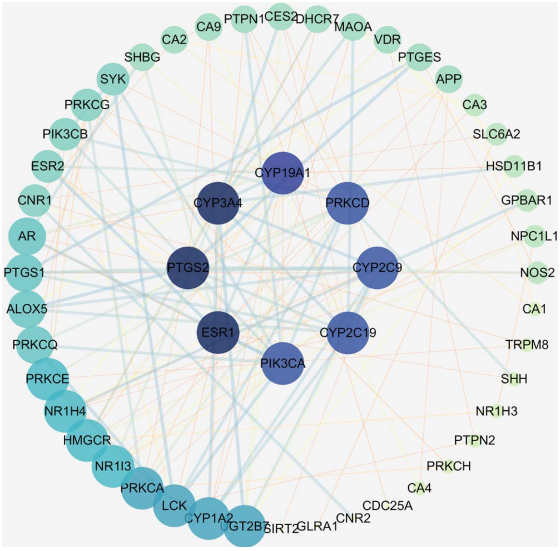

Figure 2. The protein interaction network of olibanum
图 2. 乳香靶点蛋白相互作用网络

3.4. 构建“活性成分－核心靶点”网络

对乳香的 12 个活性成分所对应的 52 个核心靶点构建“活性成分－核心靶点”网络图，见图 3。该网络共有节点 64 个，边 226 条，图中黄色代表活性成分(序列号)，红色代表靶点，化合物和靶点的关联由各条边来表示。活性成分对应核心靶点的度值如表 2 所示，RX4 和 RX10 都作用于 32 个核心靶点，提示这两个成分是乳香发挥抗炎作用的主要活性成分。

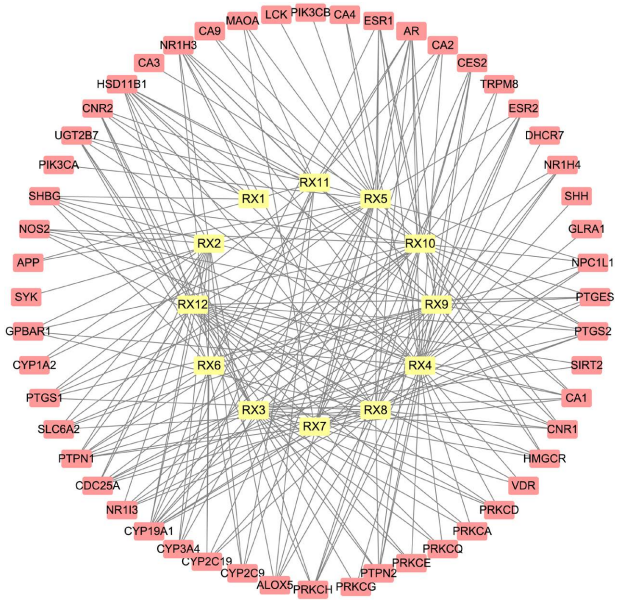

Figure 3. The network diagram of active components and targets
图 3. 活性成分和靶点的网络作用图

Table 2. Active pharmaceutical ingredients and degree in olibanum
表 2. 乳香中活性成分的度值信息

序列号	活性成分编码	活性成分名称	度值
RX1	MOL000208	Aromadendrene	5
RX2	MOL000474	(-)-Epoxycaryophyllene	14
RX3	MOL000858	Glycerol palmitate	20
RX4	MOL001215	tirucallol	32
RX5	MOL001229	cis-resveratrol	23
RX6	MOL001234	thunbergol	15
RX7	MOL001235	9-C-Retinal	9
RX8	MOL001243	3alpha-Hydroxy-olean-12-en-24-oic-acid	25
RX9	MOL001255	Boswellic acid	24
RX10	MOL001259	(3R, 4R, 4aR, 6aR, 6bS, 8aR, 11R, 12S, 12aR, 14aR, 14bS)-3-hydroxy-4, 6a, 6b, 8a, 11, 12, 14b-heptamethyl-14-oxo-1, 2, 3, 4a, 5, 6, 7, 8, 9, 10, 11, 12, 12a, 14a-tetradecahydropicene-4-carboxylic acid	32

Continued

RX11	MOL001272	incensole	17
RX12	MOL001281	L-alpha-Palmitin	20

3.5. GO 富集分析

对乳香抗炎靶点进行 GO 功能富集，获得功能注释[23]。乳香抗炎靶点被功能注释到的前 8 个生物过程 GO-BP (Biological Process)，分子功能 GO-MF (Molecular Function)和细胞组成 GO-CC (Cellular Component)如图 4 所示。

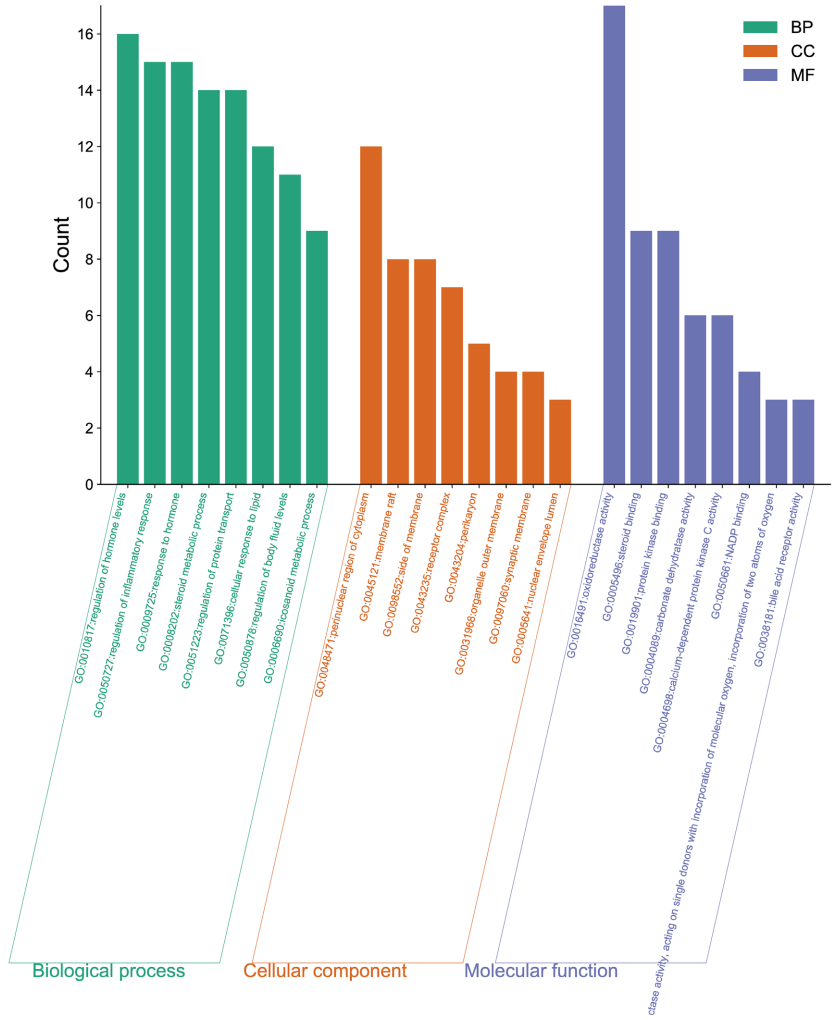

Figure 4. The biological process, cell composition, molecular function of GO analysis
图 4. GO 分析的生物过程，细胞成分，分子功能

3.6. KEGG 通路富集分析

对乳香的 52 个抗炎靶点基因进行 KEGG 通路富集分析，选取 KEGG 富集显著性统计前 8 条通路($P < 0.05$，FDR < 0.05)绘制气泡图[24]。如图 5 所示，乳香抗炎靶点涉及的 NF-κB 信号通路，TRP 信号通路等多条信号通路与炎症密切相关，故推测乳香主要通过这些途径起到抗炎作用。

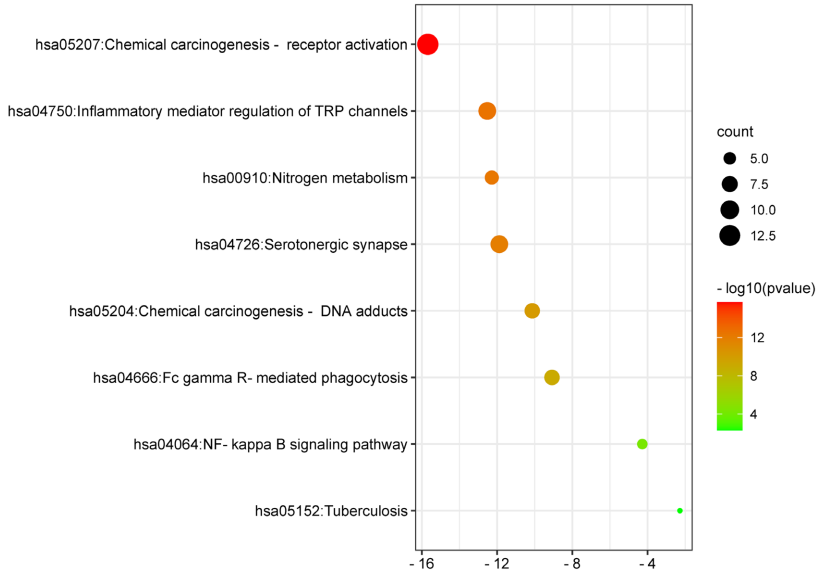

Figure 5. KEGG pathway analysis
图 5. KEGG 通路分析

4. 结论

乳香作为传统天然药物，具有多成分、多靶点和多通路的作用特点。本文通过网络药理学方法，对乳香活性成分及其对应抗炎靶点进行筛选和分析，构建了抗炎的“成分－靶点－通路”作用机制。结果表明，乳香主要是以乳香脂酸、因香酚、甘遂醇等 12 种活性成分为物质基础，以 PRKCH、PRKCG、NOS2、PTPN2、PRKCE 等 52 个蛋白作为主要作用靶点，经由 NF-κB 信号通路，TRP 信号通路等抗炎相关通路起到抗炎作用。本文对乳香抗炎机制的分析研究，可为进一步深入开展乳香的抗炎作用机制研究提供新的思路和方向。

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