·基础研究·

基于“成分-靶点-通路”的鹿茸网络药理学研究△

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［摘要］　**目的：**基于网络药理学研究鹿茸活性成分-靶点-通路及其药理机制。**方法：**利用网络药理学分析平台(BATMAN-TCM)获取鹿茸活性成分及其对应靶点；利用 STRING 平台构建蛋白互作网络(PPI)，依据度值和介数筛选关键靶蛋白；利用 ClueGO 插件对关键靶基因进行基因本体(GO)生物过程富集；利用 Metascape 数据库分析靶点的(KEGG)信号通路。**结果：**获得 17-β-雌二醇、α-雌二醇、视黄醇、雌酮等 14 个成分及 306 个靶点，发现了 MED1、ADCY1、RXRA、CXCR4、ESR1、DRD2 等 26 个关键靶点。ClueGO 分析 57 个 GO 生物过程得到 G 蛋白耦合受体蛋白信号通路的负调节、一氧化氮生物合成、前列腺发育等 7 个子簇。KEGG 信号通路富集主要涉及癌症、内分泌系统、癌症特定类型、抗肿瘤耐药性、免疫系统、物质依赖、信号转导等 7 大类 68 条信号通路。**结论：**鹿茸是通过多成分、多靶点、多信号通路协调发挥治疗疾病作用，其中在治疗骨质疏松症和抗肿瘤方面具有潜在的优势。

［关键词］　中药化学；鹿茸；网络药理学；靶点；通路
［中图分类号］　R282.74；R285.5　　［文献标识码］　A　　［文章编号］　1673-4890(2019)09-1236-10
doi：10.13313/j.issn.1673-4890.20190213008

Study on Pilose Antler Network Pharmacology Based on “Ingredients-Targets-Pathways”

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［**Abstract**］　**Objective**：To study the active component-target-pathway and its pharmacological mechanism of velvet antler based on network pharmacology. **Methods**：The antler active components and their corresponding targets were obtained by using the network pharmacology analysis platform(BATMAN-TCM). The protein interaction network(PPI) was constructed by STRING platform，and the key target proteins were screened according to the degree and the median value. The ClueGO plug-in was used. Key target genes are enriched in gene ontology(GO) biological processes；the target(KEGG) signaling pathway is analyzed using the Metascape database. **Results**：14 major active components such as 17-β-estradiol，artemisia，alpha-estradiol，retinol and estrogen ketone and 306 targets were obtained. OPRM1，ADCY1，TNF，SCN1B and DRD2 were found. 26 key targets such as GRB2. ClueGO analysis of 57 GO biological processes resulted in negative regulation of G protein-coupled receptor protein signaling pathway，nitric oxide biosynthesis，and prostate development. The KEGG signaling pathway is mainly involved in seven major types of 75 signaling pathways including cancer，endocrine system，specific types of cancer，anti-tumor resistance，immune system，substance dependence，and signal transduction. **Conclusion**：The study revealed the main active components of antler and related multidimensional action pharmacology mechanism by pharmacology network，providing the scientific basis for the development and application of antler.

［**Keywords**］　traditional Chinese medicine chemistry；antler；network pharmacology；target；pathway

△［基金项目］　国家自然科学基金项目(81373936)；吉林省科技发展计划重点项目(20160209006YY)
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鹿茸 *Cervi Cornu* Pantotrichum 为鹿科动物梅花鹿 *Cervus nippon* Temminck 或马鹿 *Cervus elaphus* Linnaeus 的雄鹿未骨化密生茸毛的幼角[1]。其性温，味甘、咸，归肝、肾经，首载于《神农本草经》，列为中品[2]，具有壮肾阳、益精血、强筋骨、调冲任、托疮毒[1]的功能。鹿茸是目前发现的唯一能够完全再生的哺乳动物器官[3]，研究发现，鹿茸中含有蛋白质、氨基酸、多糖、多肽、脂类、矿物质、激素、多胺、生长因子等成分[4-5]，是古今中外通用的名贵中药材。现代药理学研究表明，鹿茸具有壮肾阳、促智并改善记忆障碍、抗抑郁、抗衰老、抗疲劳、抗肝损伤、保护心肌、调节血糖、提高免疫功能、抗肿瘤及性激素样作用等多种药理活性[6]。

虽然有关鹿茸化学成分、药理机制及临床应用的研究不断涌现[7-9]，但均未系统、整体地分析鹿茸中成分、靶点、通路和疾病的相互关系。网络药理学、整合药理学等概念的相继提出，以及分子生物学、生物信息学、计算机技术的不断发展，为阐明中医药科学内涵提供了新的思路与方法，其整合生物信息学、分子生物学及各大数据库信息，系统地研究“成分-靶点-通路-疾病”之间相互作用，探究中医药“多组分、多靶点、多通路”的药理机制，与中医药整体观、辨证论治、组方配伍、协同增效等原则不谋而合[10]。本研究利用网络药理学的技术方法，探索鹿茸主要物质基础、关键靶点、疾病之间的相互作用关系，为进一步阐明鹿茸药理机制提供新的方法与思路。

1　材料与方法

1.1 鹿茸成分与靶点挖掘

利用中药分子机制生物信息学分析平台 BATMAN-TCM（http：//bionet. ncpsb. org/batman-tcm/index. php/Home/Index/index）挖掘鹿茸的化学成分，并利用该服务器的“成分-靶点相似性”原理，设置阀值“Score cutoff = 30”，计算化学成分对应的潜在靶点，最后利用 Cytoscape 网络图形处理软件构建“化学成分-潜在靶点”网络。BATMAN-TCM 收录了包括 TCMID 数据库中的 46 914 个方剂、8159 种中药及 25 210 个中药化合物，该平台的靶点预测功能是基于 Perlman 等[11]的 SITAR 理念（Similarity-based Inference of drug-TARgets），利用药物靶点相似性原理来预测已知中药化合物的潜在靶点，具有速度快、准确度较高的特点。

1.2 蛋白互作网络构建与关键靶点筛选

为了明确鹿茸靶点群中的“关键靶点”，利用 STRING 平台（https：//string-db. org/）构建靶点群蛋白互作网络（protein protein interaction network，PPI network），设置物种为“Homo sapiens”（智人）进行操作，最低相互作用阀值设为中等“medium confidence = 0.4”，并用 Cytoscape 软件的“Network Analyzer”功能对 PPI 网络进行拓扑属性分析，计算网络整体的“节点度值分布（Node Degree Distribution）、介数中心性（Betweenness Centrality）”2 个重要拓扑参数，以 Degree 和 Betweenness 的均数为“卡值”，选取 Degree 和 Betweenness 同时在卡值之上的靶点为“关键靶点”，研究关键靶点可能的药理作用。Degree 反映了网络节点与其他节点的连接数目，Betweenness 是网络中所有最短路径中经过该节点的路径数目与最短路径总数之比，Degree 与 Betweenness 是衡量一个节点在网络中重要性的两个主要拓扑参数，也是判断一个靶蛋白是否为“关键靶点”的重要依据[12]。

1.3 GO 生物过程富集

关键靶点的 GO 生物过程注释利用 Cytoscape 软件中的“ClueGO”插件对鹿茸的关键靶点进行 GO（gene ontology）生物过程富集，建立 GO 生物过程层级关系图，分析关键靶点在体内可能的生物过程。

1.4 KEGG 信号通路分析

信号通路分析利用 Metascape 数据库（http：//metascape. org/gp/index. html#/main/step1）将鹿茸关键靶点进行 KEGG（Kyoto Encyclopedia of Genesand Genomes）信号通路富集，物种与背景设置均为“Homo sapiens”（智人）进行操作，研究关键靶点投射的 KEGG 信号通路与疾病之间的相互关系，明确鹿茸可能的药理机制。

1.5 网络图构建和分析

Cytoscape 3.6.1 构建鹿茸“成分-关键靶点-通路”网络图，利用 Network Analyzer 插件计算 Degree 值，网络拓扑学分析成分、关键靶点及信号通路相互之间的关系，研究鹿茸可能针对潜在靶点和信号通路的治疗作用及其发挥药效的主要机制。

2　结果

2.1 鹿茸成分与潜在靶点

在 BATMAN-TCM 服务器共挖掘到鹿茸成分 14 个(见表 1)，对应的潜在靶点 306 个。如图 1 所示，14 个正方形节点为鹿茸中的成分，306 个六边形节点代表鹿茸的潜在靶点，363 条边代表靶点和化学成分之间的相互作用，充分体现了鹿茸多成分、多靶点的特点。

2.2 蛋白互作与关键靶点分析

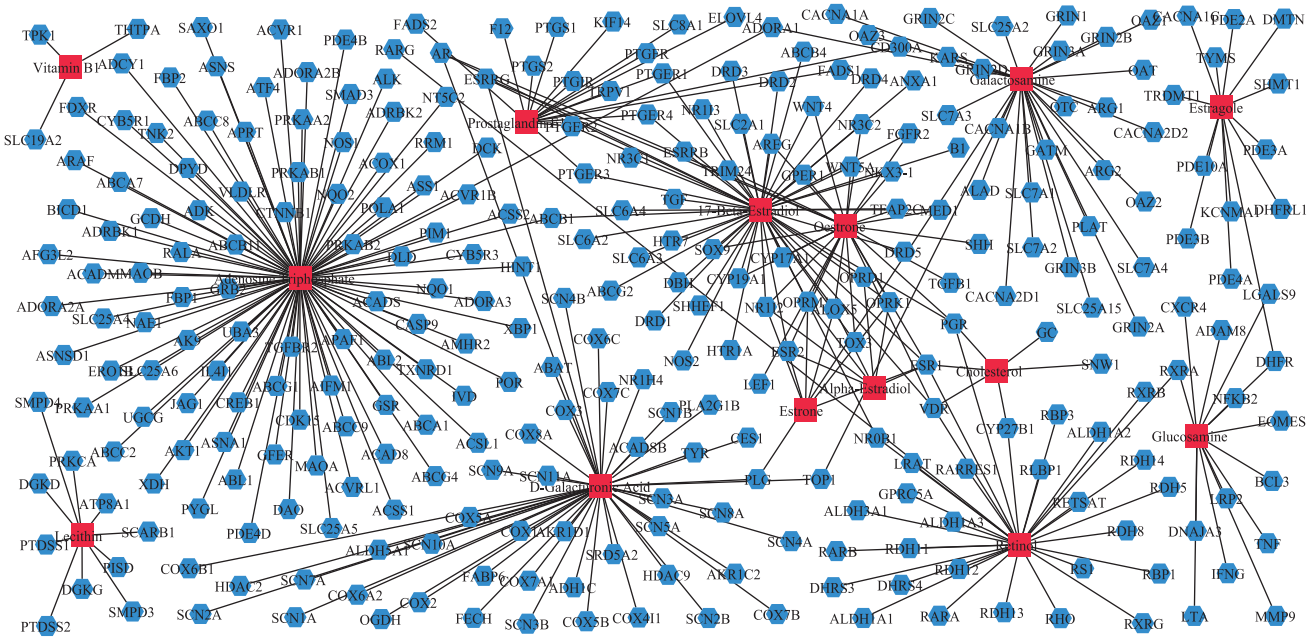
为研究各潜在靶点在体内的相互作用关系，寻找关键靶点，将潜在靶点蛋白群进行 PPI 网络分析(见图 2)，结果共发现 212 个靶蛋白可以发生相互作用，产生 488 条代表蛋白之间相互作用的边，其中度值、介数越大颜色越深，说明蛋白相互作用越强。PPI 网络平均度值为 4.60，平均介数为 3.56×10^{-2}，度值、介数超过平均值的靶蛋白共有 26 个(见表 2)，说明这 26 个靶点在 PPI 网络中处于关键位置，可能是鹿茸实现药理效应的关键靶点。

2.3 GO 生物过程富集

按照 P 值(校正)<0.01 的标准，利用 ClueGO 插件对 26 个关键靶点进行 GO 生物过程富集研究。结果 26 个关键靶点可以参与体内 57 个 GO 生物过程(见图 3)，包括 G 蛋白耦合受体蛋白信号通路的负调节、一氧化氮生物合成、前列腺发育、钠离子输送的调节等方面调控。

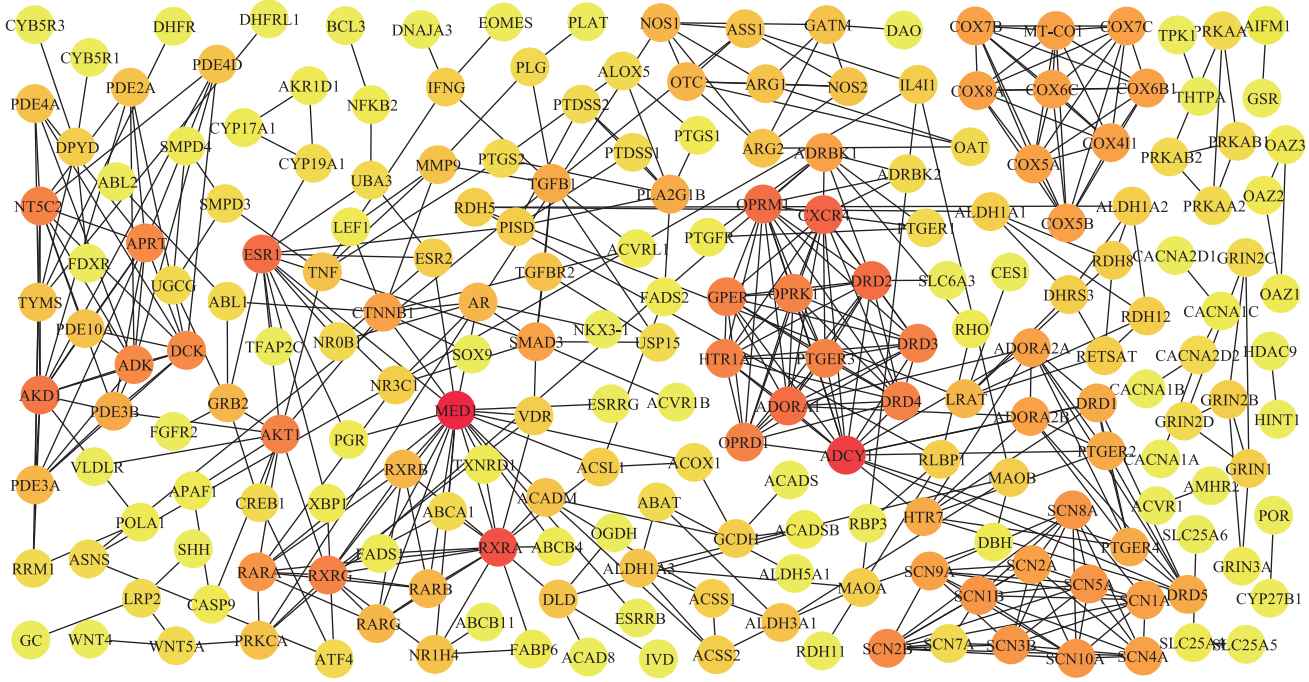
表 1　鹿茸筛选后得到的 14 个成分

序号	化学成分	中文名称	PubChem CID
1	17-Beta-Estradiol	17-β-雌二醇	66795326
2	Glucosamine	氨基葡萄糖	439213
3	Adenosine Triphosphate	三磷酸腺苷	5957
4	Estragole	对烯丙基茴香醚	8815
5	Alpha-Estradiol	α-雌二醇	68570
6	Retinol	视黄醇	445354
7	Lecithin	卵磷脂	161844
8	Galactosamine	半乳糖	24154
9	Cholesterol	胆固醇	5997
10	Estrone	雌激素酮	5870
11	*D*-Galacturonic Acid	*D*-半乳糖醛酸	439215
12	Prostaglandin E1	前列腺素 E_1	5280723
13	Vitamin B1	维生素 B_1	6042
14	Oestrone	雌酮	5870



注：■ 表示鹿茸成分；⬢ 表示潜在靶点。

图 1　鹿茸 14 个活性成分-306 个靶蛋白网络图



注：颜色由浅到深代表度值、介数从小到大。

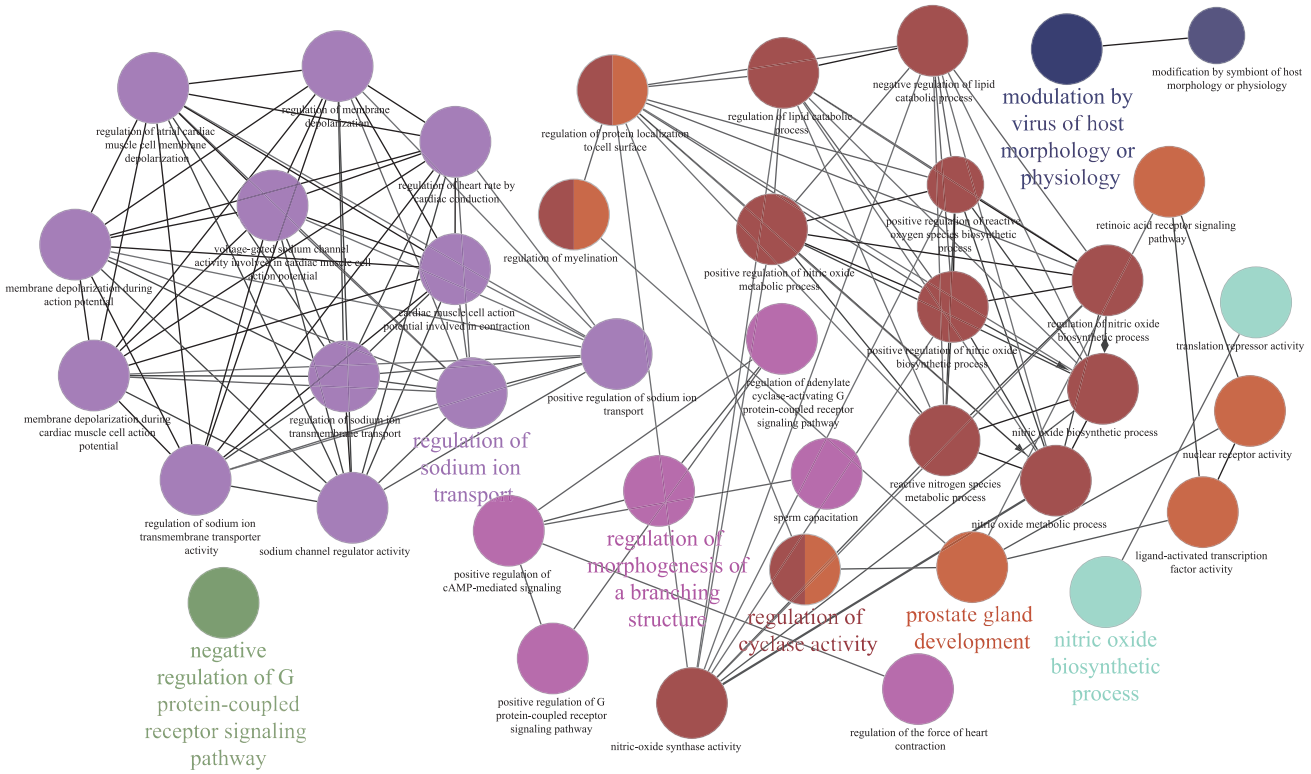
图 2　鹿茸靶蛋白 PPI 网络图

表 2　鹿茸 26 个关键靶点的拓扑参数

序号	靶点	中文名称	靶基因	Uniprot ID	Degree	Betweenness
1	Thyroid receptor-interacting protein 2	甲状腺受体相互作用蛋白 2	MED1	Q15648	22	0. 230 2
2	Adenylate cyclase type 1	腺苷酸环化酶 1 型	ADCY1	Q08828	18	0. 071 4
3	Retinoic acid receptor RXR-alpha	视黄醇受体 RXR-α	RXRA	P19793	16	0. 111 8
4	C-X-C chemokine receptor type 4	CXC 趋化因子受体 4 型	CXCR4	P61073	14	0. 060 2
5	Estrogen receptor	雌激素受体	ESR1	P03372	13	0. 174 5
6	D(2)dopamine receptor	D(2)多巴胺受体	DRD2	P14416	13	0. 070 3
7	Mu-type opioid receptor	Mu 型阿片受体	OPRM1	P35372	13	0. 058 5
8	RAC-alpha serine/threonine-protein kinase	RAC-α 丝氨酸/苏氨酸蛋白激酶	AKT1	P31749	11	0. 376 4
9	Retinoic acid receptor RXR-gamma	视黄醇受体 RXR-γ	RXRG	P48443	11	0. 238 5
10	Cytosolic purine 5′-nucleotidase	细胞溶质嘌呤 5′-核苷酸酶	NT5C2	P49902	11	0. 091 4
11	Sodium channel subunit beta-2	钠通道亚基 β-2	SCN2B	O60939	10	0. 059 9
12	Sodium channel subunit beta-1	钠通道亚基 β-1	SCN1B	Q07699	9	0. 057 4
13	Sodium channel subunit beta-3	钠通道亚基 β-3	SCN3B	Q9NY72	9	0. 057 4
14	Retinoic acid receptor alpha	维甲酸受体 α	RARA	P10276	9	0. 228 1
15	Catenin beta-1	连环蛋白 β-1	CTNNB1	P35222	8	0. 088 3
16	Mothers against decapentaplegic homolog 3	母亲反对 decapentaplegic 同系物 3	SMAD3	P84022	8	0. 049 0
17	Beta-adrenergic receptor kinase 1	β-肾上腺素能受体激酶 1	ADRBK1	P25098	8	0. 374 1
18	cGMP-inhibited 3′, 5′-cyclic phosphodiesterase B	cGMP 抑制 3′, 5′-环磷酸二酯酶 B	PDE3B	Q13370	7	0. 209 5
19	Growth factor receptor-bound protein 2	生长因子受体结合蛋白 2	GRB2	P62993	6	0. 041 7
20	Lecithin retinol acyltransferase	卵磷脂视黄醇酰基转移酶	LRAT	O95237	6	0. 036 4

续表 2

序号	靶点	中文名称	靶基因	Uniprot ID	Degree	Betweenness
21	Nitric oxide synthase	一氧化氮合酶	NOS1	P29475	6	0. 105 4
22	Thymidylate synthase	胸苷酸合成酶	TYMS	P04818	5	0. 072 9
23	Dihydrolipoyl dehydrogenase	二氢硫辛酰脱氢酶	DLD	P09622	5	0. 046 2
24	Tumor necrosis factor	肿瘤坏死因子	TNF	P01375	5	0. 076 4
25	Protein kinase C alpha type	蛋白激酶 Cα 型	PRKCA	P17252	5	0. 466 3
26	Medium-chain specific acyl-CoA dehydrogenase	中链特异性酰基辅酶 A 脱氢酶	ACADM	P11310	5	0. 090 9



注：● 表示病毒对宿主形态或生理的调节；● 表示 G 蛋白偶联受体蛋白信号通路负调节；● 表示一氧化氮生物合成过程；● 表示前列腺发育；● 表示环化酶活性的调节；● 表示分支结构形态发生的调节；● 表示钠离子转运的调节。

图 3　鹿茸 57 个 GO 生物过程

2. 4 KEGG 信号通路分析

将 26 个关键靶点进行 KEGG 信号通路富集研究，结果按照 lg*P* 值共筛选出 7 大类 68 条信号通路，如图 4、表 3 所示，包括雌激素信号通路、乳腺癌、子宫内膜癌等特定类型癌症通路，缝隙连接、Rap1 信号等免疫系统通路，趋化因子等信号转导通路，白细胞跨内皮迁移、Wnt 信号等抗肿瘤通路以及物质依赖性、内分泌系统等通路。

2. 5 生物通路分析

通过 Cytoscape 3. 6. 1 构建“成分-关键靶点-通路”网络图(见图 5)，包含 108 个节点(14 个成分、26 个关键靶点和 68 条生物信号通路)和 285 条边，其四边形代表鹿茸成分，圆形代表关键靶点，三角形代表信号通路，线代表成分、关键靶点和信号通路之间的关系。其度值较大的成分有三磷酸腺苷、视黄醇、17-*β*-雌二醇，度值分别为 10、6、3，其分别与 10 个、6 个、3 个关键靶点相关。其度值较大的靶点有 AKT1、GRB2、PRKCA，度值分别为 51、34、33，其分别与 51 条、34 条、33 条信号通路相关。其度值较大的信号通路有癌症信号通路、甲状腺激素信号通路、癌蛋白多糖信号通路，度值分别为 10、7、6，其分别与 10 个、7 个、6 个关键靶点相关。

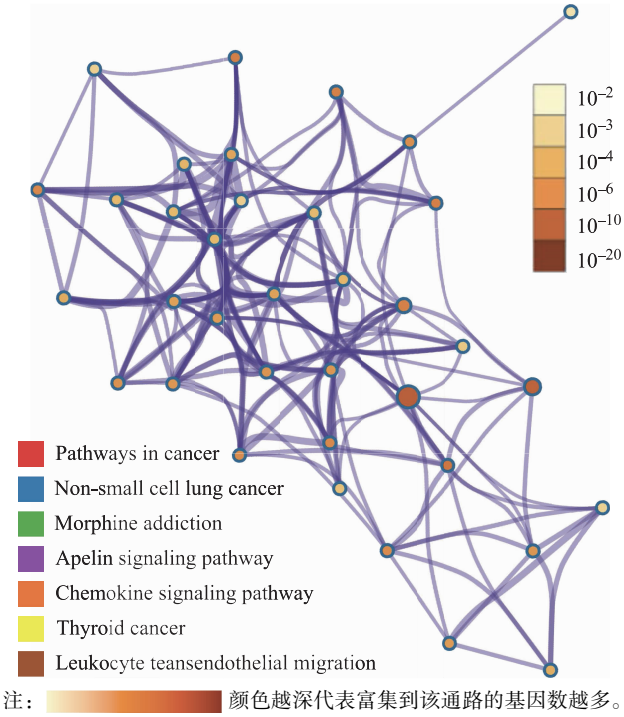


图 4　鹿茸 7 条主要 KEGG 信号通路富集图

3　讨论

通过对鹿茸“成分-关键靶点-通路”网络进行分析，发现鹿茸 14 个成分分别调控 26 个关键靶点，Clue GO 分析得到 7 个子簇 57 个 GO 生物过程及 7 大类 68 条 KEGG 信号通路，呈现出鹿茸多成分、多靶点、多通路整合调节作用的网络特点。其中，鹿茸成分三磷酸腺苷、视黄醇和氨基葡萄糖分别通过 ADCY1、AKT1、CTNNB1、GRB2、SMAD3、PRKCA、RARA、RXRA、RXRG、CXCR4 10 个关键靶点直接作用于癌症信号通路(表 3，1)。将网络分析结果与文献报道进行相互印证可见，三磷酸腺苷具有较强的抗人食管癌细胞增殖作用[13]，视黄醇代谢相关基因 LRAT 和 RDH12 对宫颈鳞癌细胞具有抑制效果[14]，氨基葡萄糖具有抗肿瘤和免疫增强作用[15]。PI3K/Akt 信号通路(表 3，37)是癌症信号通路(表 3，1)中重要途径，是调控肿瘤发生的重要通路之一[16]。

表 3　鹿茸 7 大类 68 条 KEGG 信号通路及相关靶基因

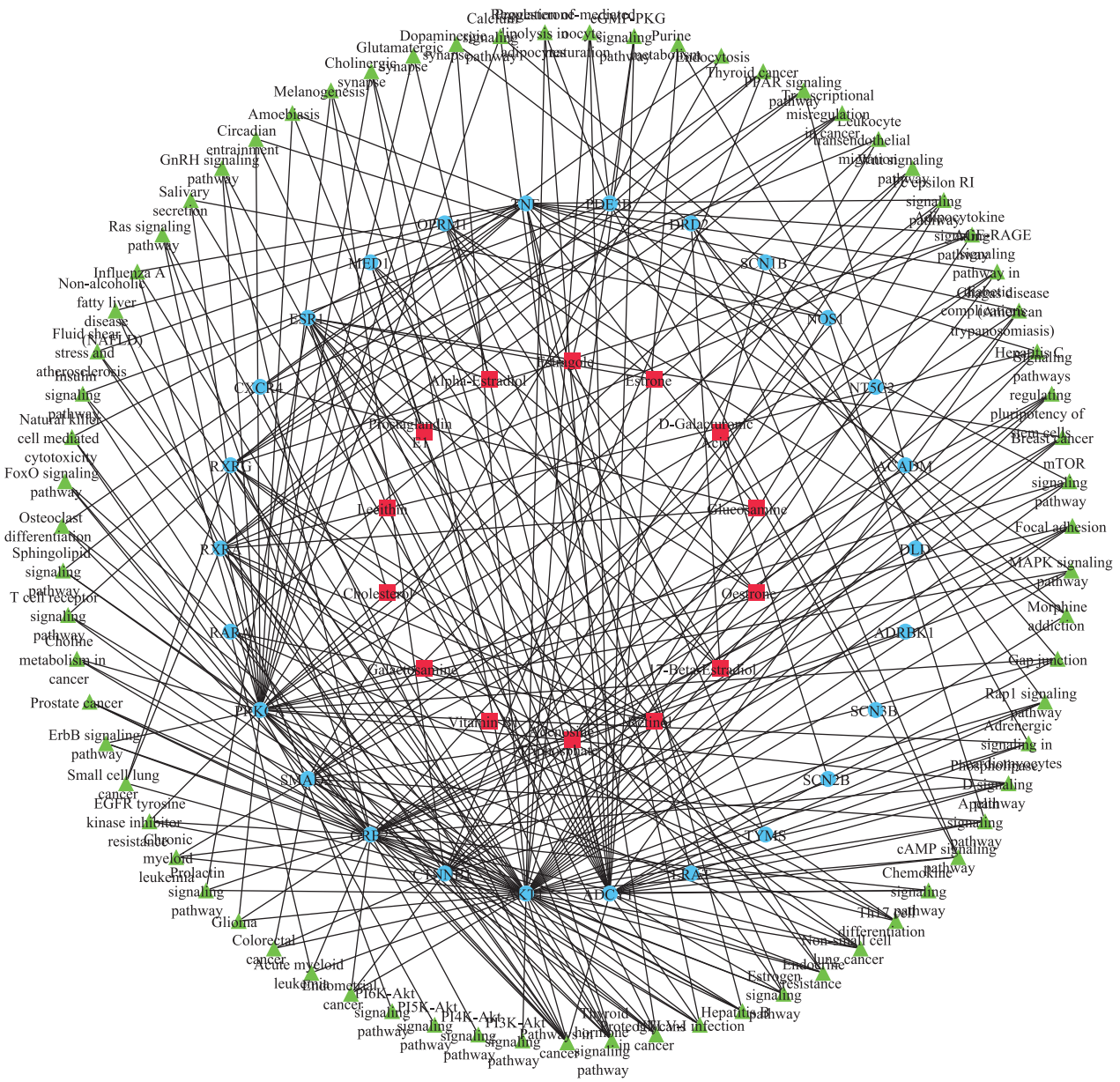
分类	序号	KEGG 信号通路	靶基因	lg*P*
癌症：概述	1	Pathways in cancer	ADCY1，AKT1，CTNNB1，GRB2，SMAD3，PRKCA，RARA，RXRA，RXRG，CXCR4	−11.127 4
	2	Thyroid hormone signaling pathway	AKT1，CTNNB1，ESR1，MED1，PRKCA，RXRA，RXRG	−10.409 3
癌症：特定类型	3	Non-small cell lung cancer	AKT1，GRB2，PRKCA，RXRA，RXRG	−8.290 9
	4	Endocrine resistance	ADCY1，AKT1，ESR1，GRB2，MED1	−7.178 2
	5	Estrogen signaling pathway	ADCY1，AKT1，ESR1，GRB2，OPRM1	−7.133 2
	6	Proteoglycans in cancer	AKT1，CTNNB1，ESR1，GRB2，PRKCA，TNF	−7.086 8
	7	Hepatitis B	AKT1，GRB2，SMAD3，PRKCA，TNF	−6.298 0
	8	Fc epsilon RI signaling pathway	AKT1，GRB2，PRKCA，TNF	−6.021 0
	9	Adipocytokine signaling pathway	AKT1，RXRA，RXRG，TNF	−5.995 3
	10	AGE-RAGE signaling pathway in diabetic complications	AKT1，SMAD3，PRKCA，TNF	−5.366 3
	11	Chagas disease(American trypanosomiasis)	ADCY1，AKT1，SMAD3，TNF	−5.314 6
	12	HTLV-I infection	ADCY1，AKT1，CTNNB1，SMAD3，TNF	−5.072 0
	13	Hepatitis C	AKT1，GRB2，RXRA，TNF	−4.883 7
	14	Signaling pathways regulating pluripotency of stem cells	AKT1，CTNNB1，GRB2，SMAD3	−4.782 2
	15	Breast cancer	AKT1，CTNNB1，ESR1，GRB2	−4.721 8
	16	mTOR signaling pathway	AKT1，GRB2，PRKCA，TNF	−4.640 8
	17	Endometrial cancer	AKT1，CTNNB1，GRB2	−4.629 0
	18	Acute myeloid leukemia	AKT1，GRB2，RARA	−4.504 0

续表 3

分类	序号	KEGG 信号通路	靶基因	lg*P*
	19	Colorectal cancer	AKT1，CTNNB1，SMAD3	-4.390 2
	20	Glioma	AKT1，GRB2，PRKCA	-4.306 0
	21	Prolactin signaling pathway	AKT1，ESR1，GRB2	-4.189 4
	22	Focal adhesion	AKT1，CTNNB1，GRB2，PRKCA	-4.172 9
	23	Chronic myeloid leukemia	AKT1，GRB2，SMAD3	-4.170 9
	24	EGFR tyrosine kinase inhibitor resistance	AKT1，GRB2，PRKCA	-4.032 5
	25	Small cell lung cancer	AKT1，RXRA，RXRG	-3.953 2
	26	ErbB signaling pathway	AKT1，GRB2，PRKCA	-3.922 8
	27	Prostate cancer	AKT1，CTNNB1，GRB2	-3.907 9
	28	MAPK signaling pathway	AKT1，GRB2，PRKCA，TNF	-3.757 6
	29	Choline metabolism in cancer	AKT1，GRB2，PRKCA	-3.741 5
	30	T cell receptor signaling pathway	AKT1，GRB2，TNF	-3.690 7
	31	Sphingolipid signaling pathway	AKT1，PRKCA，TNF	-3.516 8
	32	Osteoclast differentiation	AKT1，GRB2，TNF	-3.393 4
	33	FoxO signaling pathway	AKT1，GRB2，SMAD3	-3.374 0
	34	Natural killer cell mediated cytotoxicity	GRB2，PRKCA，TNF	-3.364 4
	35	Insulin signaling pathway	AKT1，GRB2，PDE3B	-3.317 6
	36	Fluid shear stress and atherosclerosis	AKT1，CTNNB1，TNF	-3.281 4
	37	PI3K-Akt signaling pathway	AKT1，GRB2，PRKCA，RXRA	-3.273 7
	38	Non-alcoholic fatty liver disease(NAFLD)	AKT1，RXRA，TNF	-3.220 5
	39	Influenza A	AKT1，PRKCA，TNF	-3.032 4
	40	Ras signaling pathway	AKT1，GRB2，PRKCA	-2.694 0
免疫系统	41	Morphine addiction	ADCY1，GRK2，OPRM1，PDE3B，PRKCA	-7.295 3
	42	Gap junction	ADCY1，DRD2，GRB2，PRKCA	-5.570 7
	43	Rap1 signaling pathway	ADCY1，AKT1，CTNNB1，DRD2，PRKCA	-5.490 7
	44	Adrenergic signaling in cardiomyocytes	ADCY1，AKT1，PRKCA，SCN1B	-4.721 8
	45	Phospholipase D signalingpathway	ADCY1，AKT1，GRB2，PRKCA	-4.698 2
	46	Salivary secretion	ADCY1，NOS1，PRKCA	-3.864 2
	47	GnRH signaling pathway	ADCY1，GRB2，PRKCA	-3.835 8
	48	Circadian entrainment	ADCY1，NOS1，PRKCA	-3.781 1
	49	Amoebiasis	ADCY1，PRKCA，TNF	-3.781 1
	50	Melanogenesis	ADCY1，CTNNB1，PRKCA	-3.715 9
	51	Cholinergic synapse	ADCY1，AKT1，PRKCA	-3.583 4
	52	Glutamatergic synapse	ADCY1，GRK2，PRKCA	-3.560 8
	53	Dopaminergic synapse	AKT1，DRD2，PRKCA	-3.393 4
	54	Calcium signaling pathway	ADCY1，NOS1，PRKCA	-2.968 8
物质依赖性	55	Apelin signaling pathway	ADCY1，AKT1，SMAD3，NOS1，PDE3B	-6.389 8
	56	Regulation of lipolysis in adipocytes	ADCY1，AKT1，PDE3B	-4.528 0
	57	cAMP signaling pathway	ADCY1，AKT1，DRD2，PDE3B	-4.181 4
	58	Progesterone-mediated oocyte maturation	ADCY1，AKT1，PDE3B	-3.781 1
	59	cGMP-PKG signaling pathway	ADCY1，AKT1，PDE3B	-3.107 2
	60	Purine metabolism	ADCY1，PDE3B，NT5C2	-3.018 0

续表 3

分类	序号	KEGG 信号通路	靶基因	lg*P*
信号转导	61	Chemokine signaling pathway	ADCY1，GRK2，AKT1，GRB2，CXCR4	-5.795 5
	62	Endocytosis	GRK2，SMAD3，CXCR4	-2.527 0
内分泌系统	63	Thyroid cancer	CTNNB1，RXRA，RXRG	-5.351 7
	64	Th17 cell differentiation	SMAD3，RARA，RXRA，RXRG	-5.231 9
	65	PPAR signaling pathway	ACADM，RXRA，RXRG	-4.152 8
	66	Transcriptional misregulation in cancer	RARA，RXRA，RXRG	-2.982 7
耐药性：抗肿瘤	67	Leukocyte transendothelial migration	CTNNB1，PRKCA，CXCR4	-3.560 8
	68	Wnt signaling pathway	CTNNB1，SMAD3，PRKCA	-3.272 5


Endocytosis
Thyroid cancer
PPAR signaling pathway
Transcriptional misregulation in cancer
Leukocyte transendothelial migration
Melanogenesis
Amoebiasis
Circadian entrainment
GnRH signaling pathway
Salivary secretion
Ras signaling pathway
Influenza A
Non-alcoholic fatty liver disease (NAFLD)
Fluid shear stress and atherosclerosis
Insulin signaling pathway
Natural killer cell mediated cytotoxicity
FoxO signaling pathway
Osteoclast differentiation
Sphingolipid signaling pathway
T cell receptor signaling pathway
Choline metabolism in cancer
Prostate cancer
ErbB signaling pathway
Small cell lung cancer
EGFR tyrosine kinase inhibitor resistance
Chronic myeloid leukemia
Prolactin signaling pathway
Glioma
Colorectal cancer
Acute myeloid leukemia
Endometrial cancer
PI3K-Akt signaling pathway
Estrogen signaling pathway
Hepatitis B
Toxoplasmosis
Human cytomegalovirus infection
Thyroid hormone signaling pathway
Pathways in cancer
Hepatitis C
Pathways regulating pluripotency of stem cells
Breast cancer
mTOR signaling pathway
Focal adhesion
MAPK signaling pathway
Morphine addiction
Gap junction
Rap1 signaling pathway
Adrenergic signaling in cardiomyocytes
Dopaminergic synapse
Glutamatergic synapse
Cholinergic synapse
Purine metabolism
Epsilon RI signaling pathway
Toll-like receptor signaling pathway
RAGE signaling pathway
Chagas disease (American trypanosomiasis)
Alpha-Estradiol
Estrone
Progesterone
D-Galactosamine
Glucosamine
Cholesterol
Oestrone
Galactosamine
17-Beta-Estradiol
Vitamin D3
Caffeine
Theophylline
Cortisone
Cortisol
Prednisolone
Dexamethasone
Testosterone
Estradiol
Estriol
Estradiol benzoate
Estradiol 17-beta-dehydrogenase
Estrogen receptor
Progesterone receptor
Androgen receptor
Glucocorticoid receptor
Mineralocorticoid receptor
Thyroid hormone receptor
Vitamin D receptor
Retinoic acid receptor
Peroxisome proliferator-activated receptor
Liver X receptor
Farnesoid X receptor
Pregnane X receptor
Constitutive androstane receptor
Vitamin A
Retinol
Retinoic acid
Cholecalciferol
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徐婷婷[17]报道特异性诱导视黄醇 X 受体 RXRA 形成 RXRA-LBD 四聚体可阻止 PI3K/AKT 信号通路激活从而抑制癌细胞增殖。网络分析结果显示视黄醇可直接作用于视黄醇 X 受体 RXRA，推测鹿茸可能通过作用于此靶点从而影响癌症信号通路发挥药效。从图 5 分析推测三磷酸腺苷、视黄醇和氨基葡萄糖是鹿茸潜在的抗肿瘤成分，并通过癌症通路、PI3K/AKT 等信号通路发挥抗肿瘤作用。此外，邹三鹏等[18]研究发现 17-β-雌二醇能够有效抑制 MHCC97H 肝癌细胞的侵袭；曹容华等[19]研究表明接种肿瘤后同时注射前列腺素 E1 7 d 对肿瘤有抑制作用。网络分析结果显示鹿茸中 17-β-雌二醇、前列腺素 E1 能够作用到 ESR1、Med1、PRKCA 关键靶点，推测鹿茸可能通过作用于这些靶点从而影响癌蛋白多糖等信号通路发挥药效。结合文献报道以及网络分析结果，表明鹿茸在治疗肿瘤疾病方面具有潜在的优势。

卢贺等[20]发现鹿茸调节 cAMP/cGMP 信号通路（表 3，59）归经于肾脏、肝脏发挥治疗骨关节炎的作用，并可以激活 Smad3 蛋白（表 2，16），调控软骨细胞增殖和分化促进关节软骨的修复，从而对骨关节炎大鼠起到治疗作用[21]。石晓征等[22]发现梅花鹿茸 Ⅰ 型胶原可激活 Wnt 信号通路（表 3，68），显著提高骨质疏松大鼠的骨密度。李文凯等[23]研究表明三磷酸腺苷可通过促进骨髓间充质干细胞成骨转化治疗骨质疏松。网络分析结果显示三磷酸腺苷可通过 AKT1 蛋白直接作用于骨细胞分化信号通路（表 3，32）；同时，17-β-雌二醇也能够通过 AKT1 靶点直接作用于骨细胞分化信号通路，表明鹿茸可能通过作用于此靶点影响骨细胞分化信号通路发挥药效，推测鹿茸在抗骨关节炎、治疗骨质疏松症方面具有潜在的优势。

网络药理学挖掘鹿茸中含有 17-β-雌二醇、雌酮等雌激素，长期服用外源性雌激素是乳腺癌发生的高危因素之一[24]。有研究证实短期（小于 5 年）、单纯雌激素制剂的药物应用不增加乳腺癌的风险，而长期（超过 10 年）、雌孕激素联合用药等情况将增加乳腺癌的风险[25-27]，由此可见乳腺癌危险的增加取决于雌激素的剂量和治疗时间。鹿茸中雌激素主要包括雌二醇、雌酮，其中梅花鹿茸中雌二醇、雌酮质量分数分别为 0.103、0.289 $\mu g \cdot g^{-1}$，马鹿茸中雌二醇、雌酮质量分数分别为 0.090、0.434 $\mu g \cdot g^{-1}$[28]，其雌激素含量较低，且鹿茸作为中药长期服用的情况也很少见。但值得注意的是，对于有乳腺癌病史的患者，还应充分评估患者风险，准确掌握鹿茸用药指征。

本文从网络药理学角度探讨并揭示了鹿茸的主要成分、作用靶点、相关生物信号通路。网络分析推测鹿茸除了在抗骨关节炎、治疗骨质疏松症的作用之外，在抗肿瘤方面具有潜在的优势。本文为进一步研究鹿茸的作用机制提供理论参考，为鹿茸的进一步开发应用提供科学依据。

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(收稿日期：2019-02-13　　编辑：王丽英)