



在线全文

枸杞多糖改善高原低氧环境雌性大鼠生殖损伤的机制研究*

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【摘要】目的 探讨枸杞多糖(*Lycium barbarum polysaccharide*, LBP)对高原低氧环境所致的雌性大鼠生殖系统损伤的改善作用及其机制。**方法** 将生理同步化后的30只雌性Wistar大鼠随机分为平原对照(C)组、高原低氧(H)组和高原低氧+枸杞多糖(H-LBP)组,每组10只。C组置于海拔1500 m地区(氧气体积分数18.55%),H组和H-LBP组置于海拔4010 m地区(氧气体积分数12.70%)。然后H-LBP组大鼠灌胃75mg/kg枸杞多糖,C组和H组均灌胃生理盐水,每天1次,连续14 d。实验过程中记录大鼠发情周期变化,实验结束后检测大鼠血清中生殖激素水平、卵巢组织和子宫组织氧化应激水平的变化,HE染色观察卵巢组织和子宫组织形态学的变化。利用网络药理学方法构建“成分-靶点-通路”网络图,展开核心靶点和作用通路分析。**结果** 与C组相比,H组大鼠的发情周期紊乱,血清生殖激素水平降低(均 $P<0.05$),同时卵巢和子宫组织中氧化应激损伤增加且发生病理性损伤。而与H组相比,当给予枸杞多糖后,H-LBP组大鼠发情周期趋于正常,且H-LBP组大鼠血清中雌激素(estradiol, E2)、孕酮(progesterone, P)、促黄体生成素(luteinizing hormone, LH)和抗缪勒管激素(anti-müllerian hormone, AMH)水平升高(均 $P<0.05$);卵巢组织中丙二醛(malondialdehyde, MDA)含量降低,超氧化物歧化酶(superoxide dismutase, SOD)活力、还原型谷胱甘肽(glutathione, GSH)含量升高;同时子宫组织中MDA含量降低,SOD活力增加(均 $P<0.05$),且枸杞多糖明显改善了高原低氧环境所致的雌性大鼠生殖器官病理损伤。通过网络药理学分析共得到枸杞多糖对高原低氧生殖损伤有改善作用的潜在靶点76个,靶点主要涉及钙通道、PI3K-Akt、MAPK和HIF-1等信号通路。**结论** 枸杞多糖可改善雌性大鼠由于高原低氧所致的生殖损伤,其作用机制可能与调控PI3K-Akt、MAPK和HIF-1等通路等有关。

【关键词】 高原低氧 枸杞多糖 生殖损伤 氧化应激 网络药理学

***Lycium barbarum* Polysaccharide Improves Reproductive Injury in Female Rats Exposed to High-Altitude Hypoxic Environment: Investigation of the Mechanisms Involved** ZHANG Xiaojing¹, ZHONG Yan^{1,2}, MU Hongfang¹, LIU Feifei^{1,2}, CHANG Xiwen¹, WANG Rong^{1,2△}. 1. Department of Pharmacy, The 940th Hospital of Joint Logistics Support Force of Chinese People's Liberation Army, Lanzhou 730050, China; 2. College of Pharmacy, Gansu University of Chinese Medicine, Lanzhou 730000, China

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【Abstract】 Objective To investigate the protective effect of *Lycium barbarum polysaccharide* (LBP) on reproductive system damage induced by exposure to high-altitude hypoxic environment in female rats, and to explore the mechanisms involved. **Methods** After undergoing physiological synchronization, 30 female Wistar rats were randomly and evenly assigned to 3 groups, including a plain control (C) group, a high-altitude hypoxia (H) group, and a high-altitude hypoxia + LBP (H-LBP) group. The C group was placed in a region at an altitude of 1500 m above sea level (with an oxygen volume fraction of 18.55%), while the H group and the H-LBP group were placed in a region at an altitude of 4010 m above sea level (with an oxygen volume fraction of 12.70%). Rats in the H-LBP group were fed with LBP at 75 mg/kg via gastric gavage, while the C and H groups received normal saline once a day for 14 days in a row. Changes in estrous cycles were documented throughout the experiment. At the end of the experiment, the serum levels of reproductive hormones and the levels of oxidative stress in the ovarian and uterine tissues were measured. Morphological changes in the ovarian and uterine tissues were assessed using hematoxylin-eosin (HE) staining. A component-target-pathway network diagram was constructed using network pharmacology methods to analyze the key targets and pathways. **Results** Compared with the C group, rats in the H group had disrupted estrous cycles and significantly lower serum levels of reproductive hormones (all $P<0.05$). In addition, rats in the H group had increased oxidative stress damage and experienced pathological damage in the ovarian and uterine tissues. However, compared with those of the H group, the estrous cycle in the H-LBP group became normalized after the administration of LBP and the serum levels of estradiol (E2), progesterone (P), luteinizing hormone (LH), and anti-Müllerian hormone (AMH) were significantly increased in H-LBP group (all $P<0.05$). In the ovarian tissue, the malondialdehyde (MDA) content was significantly reduced, superoxide dismutase

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(SOD) activity was increased, and the content of reduced glutathione (GSH) was increased. In addition, in the uterine tissue, the MDA content was reduced and SOD activity was increased (all $P < 0.05$), with LBP significantly improving the pathological damage to the reproductive organs of female rats caused by high-altitude hypoxic environment. Through network pharmacology analysis, we identified 76 potential targets for the protective effect of LBP against high-altitude hypoxia-induced reproductive injury, and the targets were mainly involved in the signaling pathways such as calcium channels, PI3K-Akt, MAPK, and HIF-1. **Conclusion** LBP can ameliorate high-altitude hypoxia-induced reproductive damage in female rats. The mechanisms involved may be associated with the regulation of PI3K-Akt, MAPK, and HIF-1 pathways.

【Key words】 High-altitude hypoxia *Lycium barbarum* polysaccharide Reproductive injury
Oxidative stress Network pharmacology

全球有超过1.4亿人口居住在高海拔地区^[1]。高原环境主要有低压、低氧、寒冷、强辐射等特征,其中低氧是影响机体正常生命活动的主要因素^[2]。当大鼠暴露于高海拔缺氧后,精子发生、精子数量和活力受到影响^[3]。LIU等^[4]发现缺氧条件会导致大鼠孕酮(progesterone, P)和促黄体生成素(luteinizing hormone, LH)减少,且发生了激素表达的改变。课题组前期实验结果表明高原低氧暴露14 d会造成雌性大鼠生殖系统损伤^[5],而长期处于低氧环境所致生殖系统损伤可能是造成高原地区人群生育率低的主要原因之一^[6]。如何缓解高原环境对机体生殖系统的损伤进而提高高原常驻人群的生育率成为亟待解决的问题。

枸杞多糖(*Lycium barbarum* polysaccharide, LBP)是从传统中药枸杞子中提取的一种水溶性多糖,具有生殖系统保护、抗氧化及抗衰老、免疫调节、抗肿瘤、抗辐射、神经保护、抗癌等作用^[7]。枸杞多糖能改善雷公藤多苷引起的卵巢颗粒细胞的增殖受限,细胞凋亡增多,减轻雷公藤多苷对卵巢颗粒细胞的损伤程度^[8];可使糖尿病大鼠睾丸、附睾的质量明显增加,精子计数显著增多,精子活率明显提高,睾丸组织病理损伤明显改善,对糖尿病引起的生殖损伤有明显保护作用^[9];还能改善全氟辛酸^[10]、己烯雌酚^[11]和辐射^[12]等引起的生殖损伤。然而,枸杞多糖是否对高原低氧环境暴露导致的机体生殖损伤具有改善作用尚未见报道。因此,本研究主要探究枸杞多糖对高原低氧环境所导致的雌性大鼠生殖系统损伤的保护作用,为改善高原低氧生殖损伤提供具有疗效的药物。

1 材料与方法

1.1 实验试剂与仪器

枸杞多糖(含量>60%)为昊轩生物公司产品;左炔诺孕酮炔雌醚片(国药准字H11021378,生产批号:43210703)为华润紫竹药业有限公司产品;多聚甲醛固定液为武汉赛维尔生物科技有限公司产品(货号:G1101-3ML);大鼠雌激素(estradiol, E2) ELISA试剂盒(货号:MB-

2116A)、大鼠P ELISA试剂盒(货号:MB-6832A)、大鼠促卵泡生成素(follicular-stimulating hormone, FSH) ELISA试剂盒(货号:MB-2107A)、大鼠LH ELISA试剂盒(货号:MB-6623A)和大鼠抗缪勒管激素(anti-mullerian hormone, AMH) ELISA试剂盒(货号:MB-6799A)均为江苏酶标生物科技有限公司产品;BCA蛋白浓度测定试剂盒(货号:PC0020)为北京索莱宝科技有限公司产品;超氧化物歧化酶(superoxide dismutase, SOD)试剂盒(货号:A001-3)、还原型谷胱甘肽(glutathione, GSH)试剂盒(货号:A006-2-1)和丙二醛(malondialdehyde, MDA)试剂盒(货号:A003-1-2)均为南京建成生物工程研究所产品。

Spectra Max i3型全自动荧光酶标仪为美国Molecular公司产品;Mettler AE 240电子天平为上海梅特勒-托利多仪器有限公司产品;CKX53倒置显微镜为日本Olympus公司产品;MDF-U2086S超低温冰箱为日本三洋公司产品;3K15型高速台式冷冻离心机为德国Sigma公司产品等。

1.1.1 实验动物与分组

SPF级健康雌性Wistar大鼠来源于济南朋悦实验动物繁育有限公司,动物许可证号为SCXK(鲁)2022 0006。灌胃给予左炔诺孕酮炔雌醚片调整雌性大鼠生理周期至同步化后将生理周期已同步化的大鼠随机分成3组,即平原对照(C)组、高原低氧(H)组和高原低氧+枸杞多糖(H-LBP)组,每组10只。C组置于兰州(海拔1 500 m,氧气体积分数18.55%),H组和H-LBP组快速运输至青海玉树巴塘(海拔4 010 m,氧气体积分数12.70%)24 h后开始实验,运输途中果冻补充水分。H-LBP组大鼠给予75 mg/kg枸杞多糖灌胃,C组和H组均给予生理盐水灌胃,每天1次、连续14 d,实验过程中各组大鼠自由获取饮水。

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1.1.2 生理周期的观察和取材

每天上午7:00—7:30、下午17:00—17:30进行阴道脱落细胞涂片检查,根据大鼠阴道脱落细胞的形态学变化

确定其发情状态,每一次涂片所观察到的发情周期状态计为0.5 d,根据连续14 d的涂片结果进行发情周期中各个阶段的持续时间统计。具体操作如下:固定大鼠以暴露其阴道后将提前润湿的消毒棉签旋转插入大鼠阴道内,在阴道内轻轻转动后取出并均匀地涂抹在载玻片上。自然风干、无水乙醇固定、晾干、结晶紫染色、冲洗、镜检。在实验的第15天,每实验组大鼠眼眶静脉丛采血检测生殖激素后,处死大鼠,随机选取3只进行氧化应激水平的测定,从每实验组剩余的7只中随机选取3只大鼠进行HE染色以观察卵巢和子宫组织的病理学损伤。

1.1.3 氧化应激水平的测定

取3组大鼠卵巢和子宫组织($n=3$)。称量大鼠卵巢和子宫组织,加入相应体积的氯化钠溶液制备质量分数10%组织匀浆液。严格按照试剂盒相关要求检测大鼠卵巢和子宫组织中SOD活力、GSH含量和MDA含量。

1.1.4 生殖激素水平的测定

3组大鼠眼眶静脉丛采血($n=10$),室温静置2 h后,3 000 r/min离心20 min,取上清液即血清保存备用。ELISA试剂盒测定血清中E2、P、FSH、LH和AMH水平。

1.1.5 HE染色观察卵巢和子宫组织病理学改变

取3组大鼠卵巢和子宫组织($n=3$),并用多聚甲醛固定液固定。石蜡包埋、切片、脱蜡、染色、脱水、封片。镜下观察卵巢和子宫组织结构。

1.2 网络药理学

1.2.1 枸杞多糖相关靶点的筛选

枸杞多糖的化学成分主要包含木糖、甘露糖、阿拉伯糖、鼠李糖、半乳糖、葡萄糖、蔗糖、赤藓糖和岩藻糖等组成^[13]。基于PubChem(<https://pubchem.ncbi.nlm.nih.gov/>)数据库,确认枸杞多糖活性成分的化学结构。在SwissTarget(<http://swisstargetprediction.ch/>)数据库中上传其2D结构,由此则可得潜在靶点。以“high altitude hypoxic reproductive injury”和“hypoxic reproductive injury”为关键词在GeneCards(<https://www.genecards.org/>)数据库检索,重获取高原低氧生殖损伤相关靶点。将枸杞多糖活性成分的靶点和高原低氧生殖损伤的靶点上传至 Venny平台(<https://bioinfo.cnbc.csic.es/tools/venny/>)制作韦恩图,得到交集靶点,即为枸杞多糖对高原低氧生殖损伤保护作用的潜在靶点。

1.2.2 蛋白相互作用网络图(PPI)和富集分析

将枸杞多糖对高原低氧生殖损伤保护作用的潜在靶点上传至 STRING数据库(<https://cn.string-db.org/>),下载PPI的TSV格式信息,并导入Cytoscape3.7.1软件进行拓扑分析,筛选枸杞多糖对高原低氧生殖损伤保护作用的关

键靶点。

将枸杞多糖、高原低氧生殖损伤的交集靶点上传至 DAVID数据库(<https://david.ncifcrf.gov/>),进行GO分析和KEGG通路富集分析,并利用微生信平台(<https://www.bioinformatics.com.cn/>)制作气泡图。

1.2.3 “成分-靶点-途径”的网络构建

根据筛选得到交集靶点、富集通路,利用Cytoscape3.7.1软件进行枸杞成分-靶点-途径的网络图构建,表达网络图中的相互作用关系。

1.3 统计学方法

实验数据采用GraphPad Prism统计软件进行统计学分析。数据用 $\bar{x} \pm s$ 表示。组间数据用two-way ANOVA进行对比分析(用Sidak multiple comparisons test进行P值校正), $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 动物实验

2.1.1 各组大鼠发情周期变化的比较

大鼠的发情周期主要分为发情前期、发情期、发情后期和发情间期。发情前期涂片可见大量大而圆的有核上皮细胞、少量角化上皮细胞;发情期可见角质化无核上皮细胞、少量有核上皮细胞;发情后期可见有核上皮细胞、角化上皮细胞及白细胞;发情间期可见大量白细胞和少量黏液。通过对各组大鼠阴道脱落细胞形态学观察,发现与C组大鼠相比,H组大鼠发情周期紊乱,其发情后期延长,发情间期缩短(均 $P < 0.05$);而枸杞多糖能改善高原低氧引起的大鼠发情周期的紊乱,使H-LBP组发情周期恢复到C组水平。见图1。

2.1.2 各组卵巢组织和子宫组织氧化应激指标检测结果比较

结果如图2A所示:与C组比较,H组卵巢组织和子宫组织中GSH含量减少和SOD活力降低,同时脂质过氧化物MDA含量增加(均 $P < 0.05$);与H组相比,H-LBP组卵巢组织和子宫组织中GSH含量增加和SOD活力升高,MDA含量减少(均 $P < 0.05$)。

2.1.3 各组生殖激素水平的比较

如图2B所示。与C组相比,H组大鼠血清中E2、P、LH和FSH水平下降($P < 0.05$);与H组相比,H-LBP组提高大鼠血清中E2、P、LH和FSH水平($P < 0.05$)。该结果表明枸杞多糖可显著改善高原低氧导致的机体生殖激素分泌紊乱。此外,卵巢储备标志物AMH含量在高原低氧暴露后显著减少,而枸杞多糖能明显升高AMH水平,提高卵巢储备。

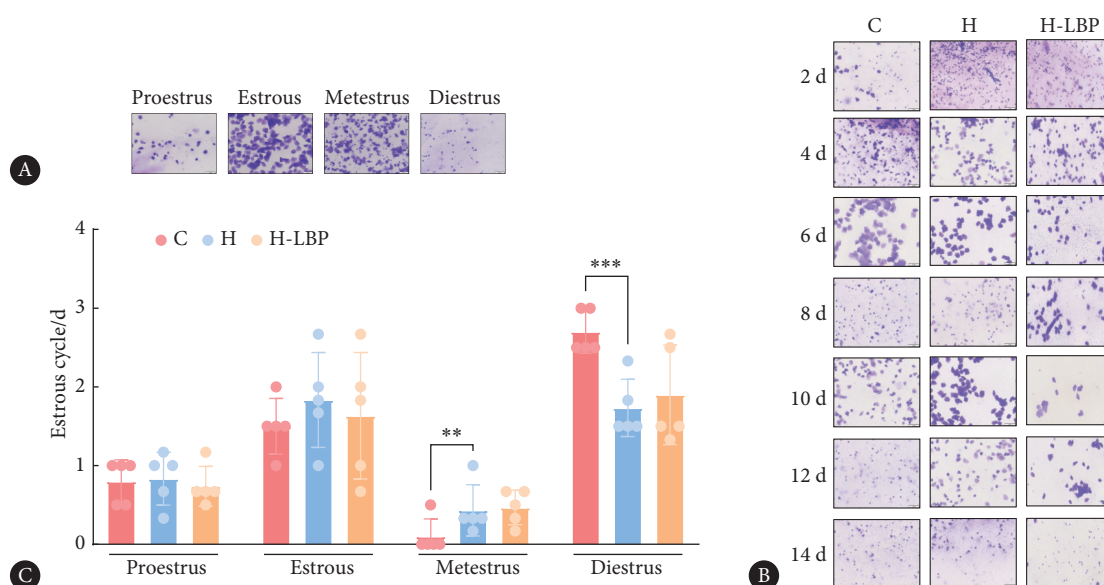
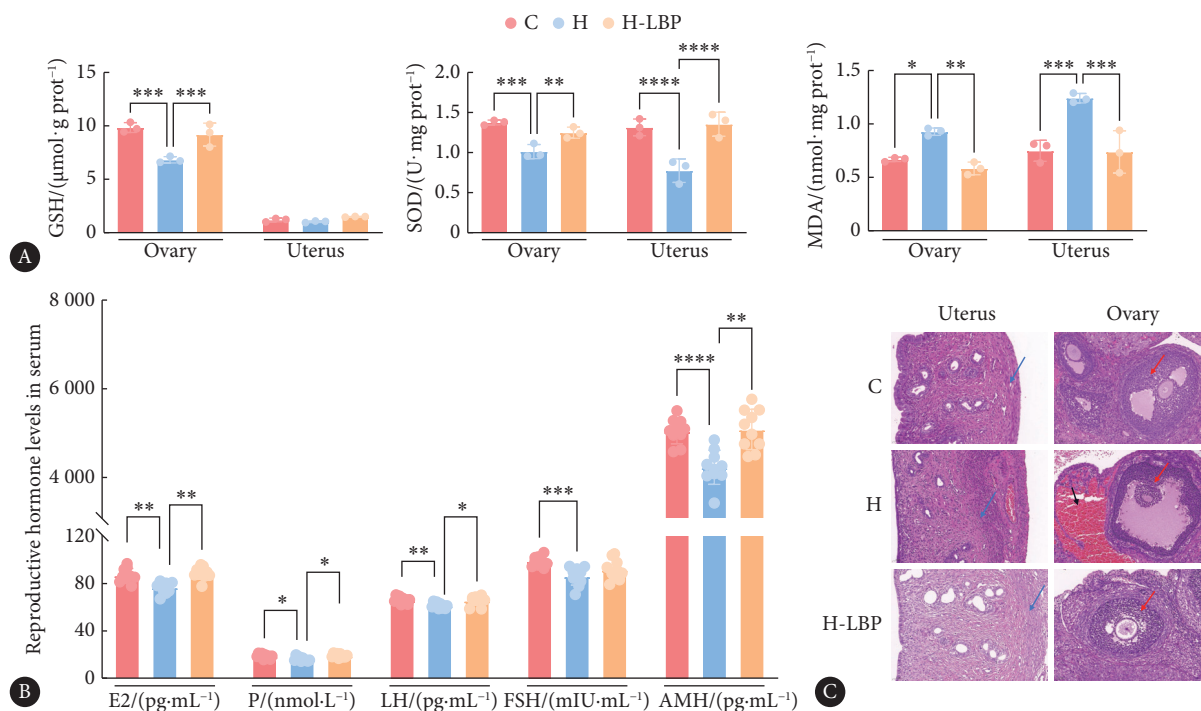


图 1 各组大鼠发情周期的变化

Fig 1 Changes in the estrous cycle of rats in each group

A, Morphology of vaginal exfoliative cells during the estrous cycle (crystal violet staining, original magnification $\times 200$); B, changes in the morphology of vaginal exfoliative cells during the estrous cycle per day in each group (crystal violet staining, original magnification $\times 200$); C, changes in the estrous cycle in each group. ** $P < 0.01$, *** $P < 0.001$. $n = 5$.

图 2 大鼠卵巢和子宫组织中氧化应激水平 (A)、血清中生殖激素水平 (B) 及卵巢和子宫组织的病理变化 (C, HE 染色 $\times 200$)Fig 2 Oxidative stress levels in the ovarian and uterine tissues (A), serum levels of reproductive hormones (B), and pathological changes in the ovary and uterus of rats (C, HE staining $\times 200$)

GSH: glutathione; SOD: superoxide dismutase; MDA: malondialdehyde; E2: estradiol; P: progesterone; LH: luteinising hormone; FSH: follicular-stimulating hormone; AMH: anti-mullerian hormone. Blue arrows indicate endometrium, the black arrow indicates ovarian congestion, and red arrows indicate ovarian granulosa cells in fig C. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. $n = 3$ in each group for fig A, and $n = 10$ in each group for fig B.

2.1.4 各组卵巢和子宫组织病理学变化比较

卵巢组织和子宫组织HE染色结果如图2C所示。

子宫组织: C组子宫内膜上皮细胞排列紧密、胞核大

小均一, 固有层腺体丰富、间质细胞密度中等; 而H组子宫内膜上皮细胞明显固缩变薄; H-LBP组子宫内膜上皮细胞紧密排列, 核染色减弱。

卵巢组织: C组卵巢组织结构完整, 可见多个不同发育的卵泡细胞, 细胞大而圆、胞浆丰富, 颗粒细胞呈多层、形态完整; 而H组闭锁卵泡增多, 颗粒细胞层减少, 排列松散, 卵巢中的静脉充血和扩张; H-LBP组闭锁卵泡减少, 颗粒细胞增多。

2.2 网络药理学

2.2.1 枸杞多糖和高原低氧生殖损伤交集靶点PPI网络构建

SwissTarget数据库筛选枸杞多糖得出潜在靶点166个。GeneCards数据库检索高原低氧生殖损伤的靶点2867个, 利用VENNY在线平台, 选枸杞多糖的靶点和高原低氧生殖损伤的靶点取交集, 得到枸杞多糖对高原低

氧生殖损伤保护作用的靶点76个(图3A)。在STRING数据库导入交集靶点分析, Cytoscape 3.7.1进行PPI互作图(图3B)。76个节点相互作用产生了279个蛋白互作边, 平均度值为7.44, 在PPI网络图中节点越大、颜色越深, 对应的度值越大; 连线越粗、颜色越深, 两者之间联系越紧密。

2.2.2 GO功能和KEGG通路富集分析

利用DAVID数据库对枸杞多糖发挥高原低氧生殖损伤保护作用的76个靶点进行GO富集分析($P < 0.05$), 获得生物过程(biological process, BP)、细胞组分(cellular component, CC)、分子功能(molecular function, MF)分别为297、49、62条, 利用微生信工具作图。由图3C可

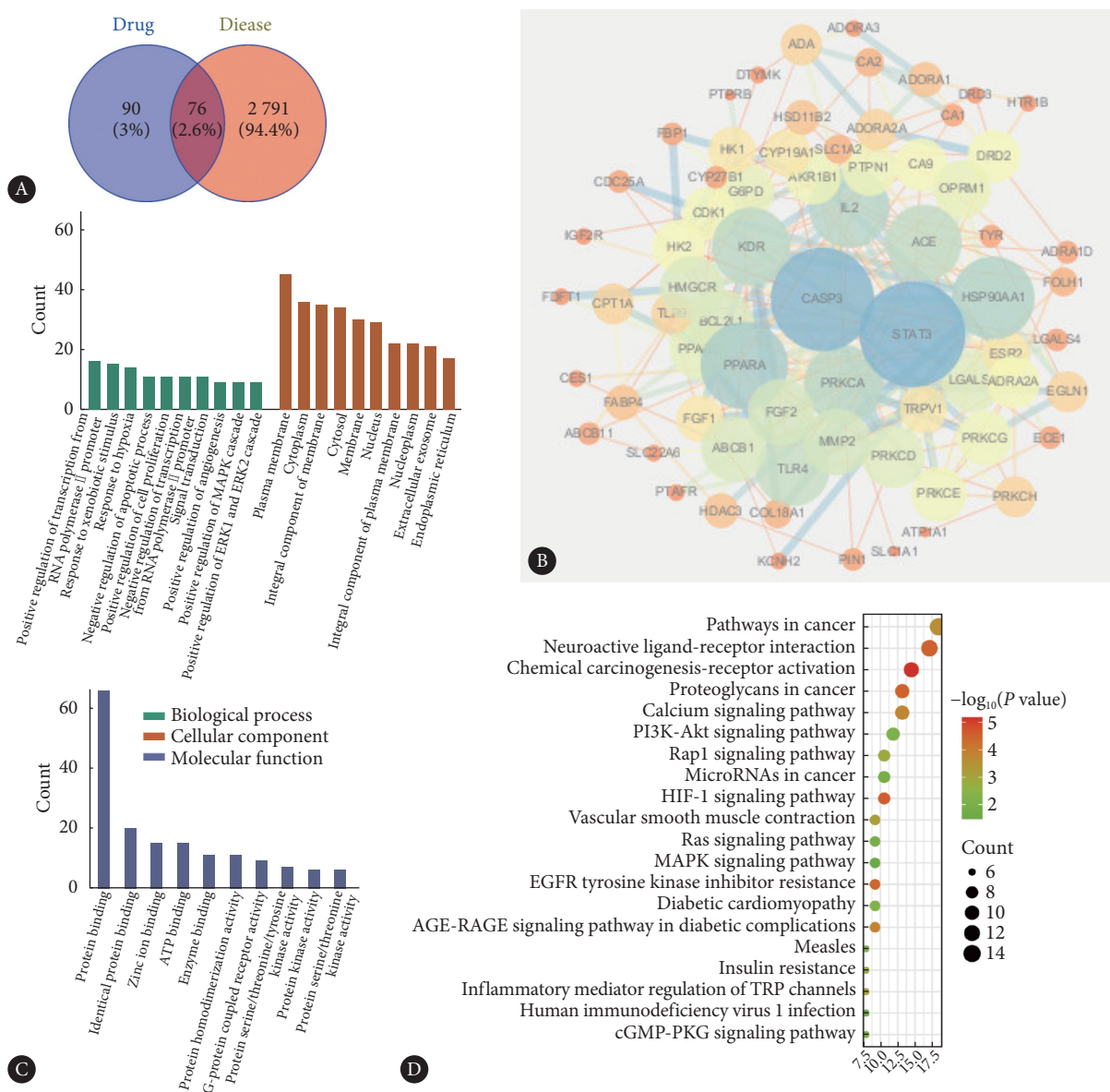


图3 枸杞多糖和高原低氧生殖损伤交集靶点PPI网络及富集分析图

Fig 3 PPI network of intersecting targets of LBP and high-altitude hypoxic reproductive injury and enrichment analysis diagram

A, Wayne diagram of common targets of LBP and high-altitude hypoxic reproductive injury; B, protein-protein interaction relationship diagram; C, GO enrichment histogram; D, KEGG signaling pathway enrichment bubble plot.

得, BP主要富集在RNA聚合酶 II 启动子的转录正调控、对外来刺激的反应、对缺氧的反应、凋亡过程负调控、细胞增殖的正调控等; CC主要富集在等离子体膜、细胞质、胞质; MF主要富集在蛋白质结合、酶结合、锌离子结合、ATP结合、丝氨酸/苏氨酸激酶活性等。利用DAVID数据库对交集靶点进行KEGG富集分析($P < 0.05$), 得到57条信号通路, 利用微生信工具对Count值前20位进行作图(图3D), 可知主要钙信号通路、PI3K-Akt信号通路、

MAPK信号通路、HIF-1信号通路、Rap1信号通路等。

2.2.3 活性成分-靶点-通路网络

将枸杞多糖活性成分, 枸杞多糖与高原低氧生殖损伤的交集靶点和KEGG富集的通路构建活性成分-靶点-通路网络(图4)。对关键靶点通过富集分析发现, 枸杞多糖可能通过作用于CASP3、STAT3、KDR等不同靶点从而调控钙通道、PI3K-Akt、MAPK、HIF-1等信号通路, 进而影响细胞增殖与凋亡、MAPK级联反应、炎症反应等。

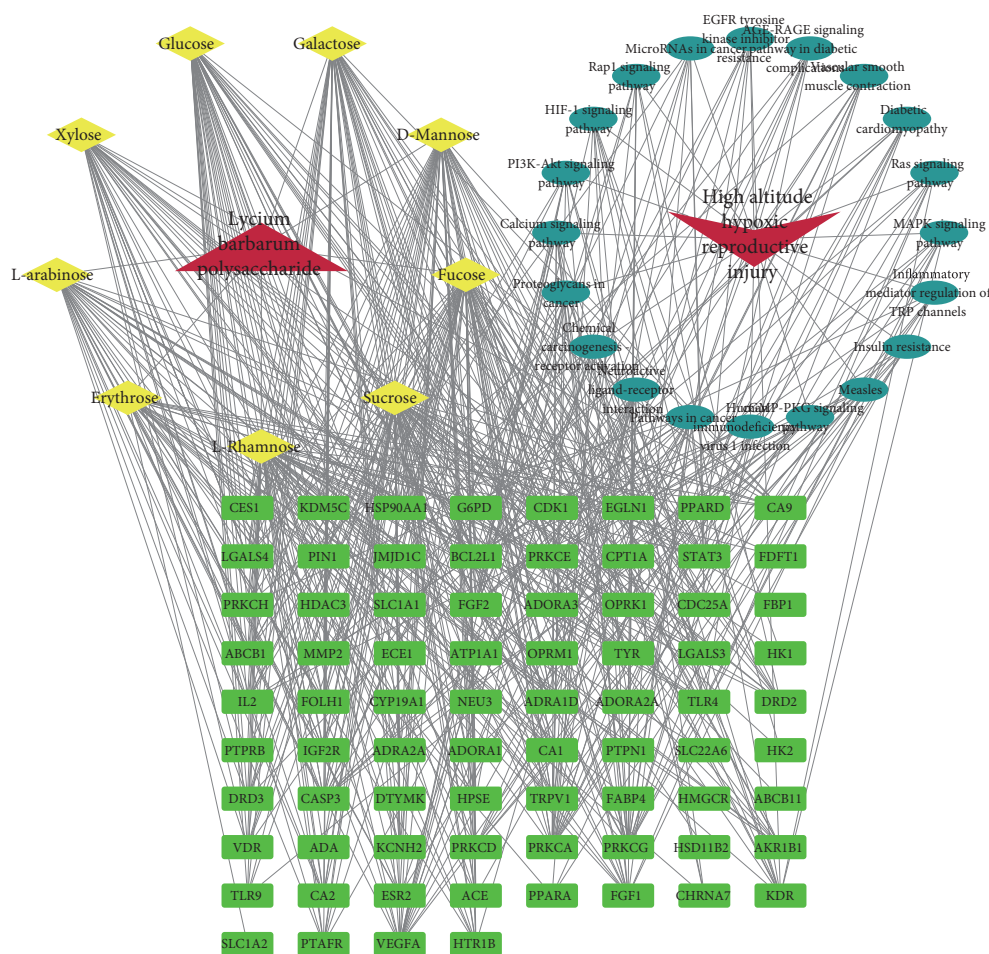


图4 活性成分-靶点-通路网络

Fig 4 Active ingredient-target-pathway network

Red upward arrows indicate LBP; red downward arrows indicate high altitude hypoxic reproductive injury; yellow diamonds indicate the main active components of LBP; green rectangles indicate intersecting targets; blue circles indicate enrichment pathways.

3 讨论

氧是机体生理代谢的基本元素, 当低海拔人群移居至高海拔后, 机体会通过代偿反应来适应高原环境, 而一部分不适应高原环境的人群则会出现各组织器官的低氧损伤^[14]。由于学习和工作的需要, 人们会长期处于高原低氧环境中。有研究表明长期暴露于高原低氧环境会对机体的生殖机能产生不可忽视的影响^[4]。枸杞多糖为我

国传统中药材枸杞子的主要活性成分, 具有多种生物活性, 尤其在生殖保护方面具有重要作用^[15]。有研究表明枸杞多糖可以提升生殖细胞抗氧化能力^[16]。因此, 本研究主要通过将雌性Wistar大鼠急进高原实地环境后给予枸杞多糖, 检查其各项生殖相关指标, 探讨枸杞多糖对高原低氧环境所导致雌性大鼠生殖系统损伤的保护作用。

高原低氧会导致组织氧气供应失衡从而产生氧化应激。MDA作为脂质氧化的终产物, 反映机体过氧化损伤

情况, SOD、GSH是衡量机体抗氧化能力大小的重要标志^[17]。而氧化应激会影响女性生育机能, 主要包括女性月经周期紊乱、卵巢和子宫结构损伤^[14]等。大多产生生殖损伤的因素都与氧化应激息息相关。糖尿病^[18]、辐射^[19]等均能引起雌性大鼠机体GSH含量和SOD活力的降低, MDA含量升高, 升高氧化应激水平。当给予枸杞多糖后, 枸杞多糖能显著改善高原低氧环境暴露导致的卵巢和子宫组织中MDA含量升高、GSH含量和SOD活力的降低, 缓解氧化应激。

雌性激素是一类主要的女性荷尔蒙, 它能促进女性性器官成熟并维持正常生殖功能, 且在控制生殖行为和调节神经内分泌系统方面起着核心作用^[20]。FSH和LH由垂体的促性腺激素细胞分泌, 其中FSH不仅能够诱导卵泡生长和发育, 也是有腔卵泡的主要生存因子^[21]。E2和P是女性胚胎着床和怀孕所必需的关键内源性激素^[22]。为避免发情周期对实验结果的影响, 本研究首先对大鼠提前使用左炔诺孕酮炔雌醚片以进行生理同步化^[23]。本研究结果表明, 高原低氧暴露会导致雌性大鼠生殖激素紊乱, 而枸杞多糖可使生殖激素恢复正常水平。卵巢和子宫内环境对哺乳动物卵细胞产生和胚胎植入很重要^[24]。研究表明, 高原低氧暴露会导致卵巢和子宫发生明显的病理变化, 给予枸杞多糖后子宫内膜上皮细胞紧密排列, 卵巢闭锁卵泡减少。

从网络药理学角度, 枸杞多糖对大鼠高原低氧生殖损伤的保护机制是通过多靶点多通路发挥疗效。枸杞多糖可能通过调控钙通道、PI3K-Akt、MAPK、HIF-1、Rap1等信号通路发挥高原低氧生殖损伤保护作用。PI3K-Akt信号通路是目前公认的与生殖内分泌相关通路, 其中PI3K是细胞中重要的信号转导分子, 可激活下游分子Akt1。Akt协同其他激酶共同调节卵泡及卵母细胞的发育, 并在卵泡形成过程中调控颗粒细胞的凋亡^[25]。MAPK在整个妊娠过程和分娩过程中, 它在女性生殖器官中的作用相当复杂, 在滋养层分化和侵袭、分娩期间子宫肌层静止或激活以及胎盘生长中发挥重要作用^[26]。HIF-1能在健康的卵泡中被激活, 对卵泡的发育至关重要^[27]。因此PI3K-Akt、MAPK、HIF-1等信号通路可能是枸杞多糖保护高原低氧所致雌性大鼠生殖损伤的关键通路。

综上所述, 枸杞多糖能改善高原低氧暴露导致的机体氧化应激反应, 从而使生殖激素分泌趋于正常, 减轻机体卵巢和子宫的病理损伤, 为枸杞多糖开发为高原低氧生殖损伤的保护产品提供理论参考依据。同时应用网络药理学的方法对其机制进行了初步探究, 但由于其存在一些局限性, 有待后续对网络药理学推测的机制进一步验证。

* * *

作者贡献声明 张晓静负责论文构思、经费获取、研究方法和审读与编辑写作, 钟艳负责正式分析、调查研究、研究方法和初稿写作, 牟宏芳负责调查研究和初稿写作, 刘菲菲和常熙雯负责正式分析和调查研究, 王荣负责研究项目管理、提供资源和监督指导。所有作者已经同意将文章提交给本刊, 且对将要发表版本进行最终定稿, 并同意对工作的所有方面负责。

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利益冲突 所有作者均声明不存在利益冲突

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