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## 槟榔多酚的抗缺氧药理作用

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**[摘要]** 槟榔药材及制剂广泛应用于临床, 槟榔多酚为其主要化学成分之一, 具有抗氧化、抗炎、抗菌等作用。随着高原活动的不断增加, 高原低氧引起的组织氧化损伤严重影响了高原作业能力, 因此, 抗缺氧药物的研究尤为重要。最新研究表明槟榔多酚通过改善缺氧机体血气指标, 提高组织超氧化物歧化酶、谷胱甘肽过氧化氢酶活性, 清除机体过多的自由基, 对缺氧引起的氧化应激损伤具有保护作用。槟榔多酚的抗缺氧及保护组织氧化损伤的作用提示其可作为潜在的抗缺氧药物, 具有一定的开发前景。

**[关键词]** 槟榔多酚; 抗氧化; 抗缺氧; 化学成分

## Anti-hypoxic pharmacological effects of betelnut polyphenols

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### ABSTRACT

*Areca catechu* L. medicinal materials and their preparations are widely used in clinical practice. Betelnut polyphenol is one of the main chemical components with antioxidant, anti-inflammatory, and antibacterial effects. With continuous increase of high altitude activities, tissue oxidative damage caused by high altitude hypoxia seriously affects the ability to work, and the studies on anti-hypoxia drugs are particularly important. Recent studies have shown that betelnut polyphenols have protective effects on oxidative stress injury caused by hypoxia via improving blood gas index of hypoxic organism, increasing

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superoxide dismutase glutathione catalase activity, and scavenging excessive free radicals. The effects of betelnut polyphenols against hypoxia and oxidative damage protection suggest that betelnut polyphenols can be used as potential anti-hypoxia drugs and possess clinical prospects.

**KEY WORDS** betelnut polyphenols; antioxidant; anti-hypoxia; chemical composition

槟榔(*Areca catechu* L.)为多年生棕榈科植物槟榔树的种子, 又名仁频、白槟榔、橄榄子、洗瘴丹、青仔、大腹子、榔玉、槟榔子、洗瘴脑、仙瘴丹、螺果、宾门及宾门药钱等<sup>[1]</sup>, 居我国著名的“四大南药”(槟榔、益智仁、砂仁、巴戟天)之首, 其果皮、花、种子均可入药。槟榔作为一种传统的本草中药, 临床应用广泛, 文献记载最早可追溯至汉代, 在中国引种已有2 100余年, 药用历史已有1 800多年, 入药最早记录在《李当之药录》中<sup>[2]</sup>。槟榔有抗寄生虫、抗菌、调节血脂及血糖等作用。目前, 国内外研究多集中在槟榔生物碱的药理活性和安全性等方面, 对槟榔多酚和其他化合物的研究多为成分分析, 药理作用研究较少。最新研究<sup>[3-6]</sup>表明槟榔多酚具有良好的抗高原缺氧作用。槟榔多酚的抗氧化和抗缺氧作用有望为预防和治疗高原病的药物研究提供新思路。

### 1 槟榔多酚的主要成分

槟榔含有多种化学成分, 从槟榔中已分离得到60多种化合物, 包括多酚类(31.1%)、多糖类(18.7%), 脂肪酸类(14.0%), 鞣质类、氨基酸、三萜类、矿物质、槟榔红色素及维生素等其他类(12.0%), 粗纤维类(10.8%), 水分类(9.9%), 灰分类(3.0%)及生物碱类(0.5%)等多种物质<sup>[7-11]</sup>。按照多酚的化学结构

可将其分为类黄酮和非类黄酮2大类<sup>[12-13]</sup>。其中类黄酮主要化学成分为儿茶素、表儿茶素、没食子儿茶素没食子酸酯、异鼠李素及木犀草素等; 非类黄酮主要化学成分为香草酸、阿魏酸等。王明月等<sup>[14]</sup>研究表明: 槟榔成熟果中所含的多酚种类和数量比槟榔幼果多, 且槟榔多酚中含量最多的是儿茶素(高达0.161%), 其次是单宁(0.0622%)、表没食子儿茶素(0.0241%)、表儿茶素(0.0164%)、表没食子儿茶素没食子酸酯(0.0077%)及没食子酸(0.00136%)。张春梅等<sup>[15]</sup>采用反相高效液相色谱-二极管阵列检测法(reversed phase high performance liquid chromatography-diode array detection, RP-HPLC-DAD)检测, 发现槟榔花提取物中含有没食子酸、表儿茶素、阿魏酸、香豆酸、芦丁和柚皮素6种多酚类物质。祁静<sup>[16]</sup>采用毛细管电泳法确定槟榔多酚提取物中含有表儿茶素、儿茶素、阿魏酸、绿原酸、柚皮素及山奈素。Yuan等<sup>[17]</sup>从槟榔果仁中发现了2种新的黄酮类化合物, 即calquiquelignan M和calquiquelignan N, 该2种化合物对HepG2细胞有中等细胞毒活性, IC<sub>50</sub>值分别为49.8和53.6 μmol/L。槟榔多酚类化学成分见表1。槟榔多酚在槟榔中占比较高, 其中儿茶素及表儿茶素在槟榔果实及种子中含量较高<sup>[10]</sup>, 在抗氧化及抗缺氧方面具有进一步研究的价值。

表1 槟榔各部位多酚类化学成分

Table 1 Chemical composition of polyphenols in different parts of *Areca catechu* L.

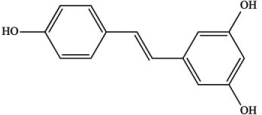
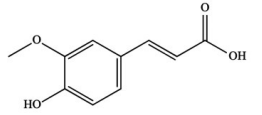
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|----|--------|---|--------|------|------|
| 1  | 反式白藜芦醇 |  | 成熟种子   | 乙醇提取 | [18] |
| 2  | 阿魏酸    |  | 成熟种子   | 乙醇提取 | [18] |

表 1(续)

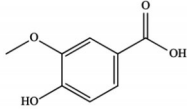
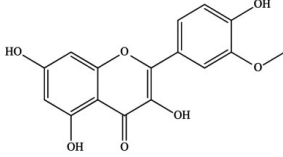
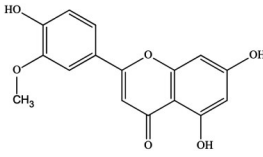
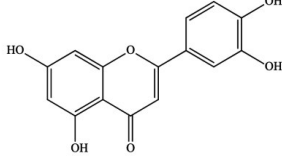
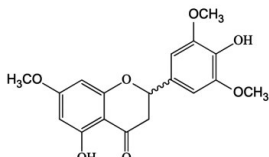
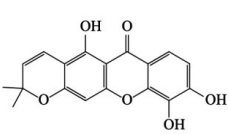
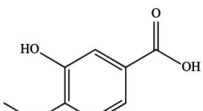
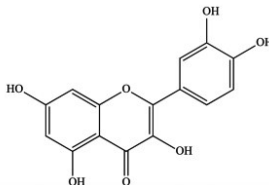
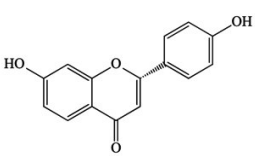
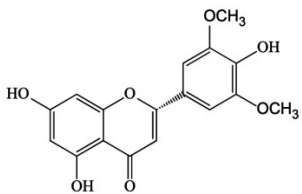
| 编号 | 化合物名称                     | 分子结构式   | 槟榔提取部位 | 提取溶剂 | 参考文献 |
|----|---------------------------|---|--------|------|------|
| 3  | 香草酸                       |    | 成熟种子   | 乙醇   | [18] |
| 4  | 异鼠李素                      |    | 新鲜果实   | 乙醇   | [19] |
| 5  | 金圣草黄素                     |    | 新鲜果实   | 乙醇   | [19] |
| 6  | 木犀草素                      |    | 新鲜果实   | 乙醇   | [19] |
| 7  | 4',5-二羟基-3',5',7-三甲氧基黄烷酮  |   | 新鲜果实   | 乙醇   | [19] |
| 8  | 巴西红厚壳素                    |  | 新鲜果实   | 乙醇   | [19] |
| 9  | 3-羟基-4-甲氧基苯甲酸             |  | 新鲜果实   | 乙醇   | [19] |
| 10 | 槲皮素                       |  | 成熟种子   | 乙醇   | [20] |
| 11 | 甘草素                       |  | 成熟种子   | 乙醇   | [20] |
| 12 | 5,7,4'-三羟基-3',5'-二甲氧基二氢黄酮 |  | 成熟种子   | 乙醇   | [20] |

表 1(续)

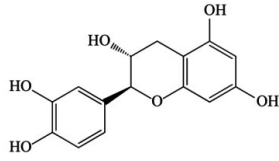
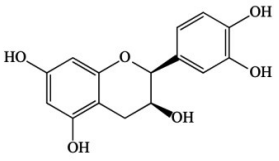
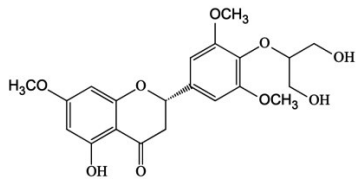
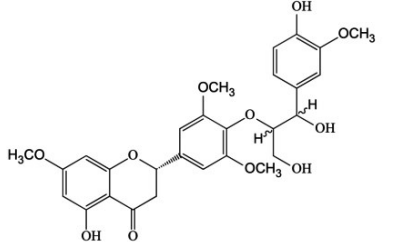
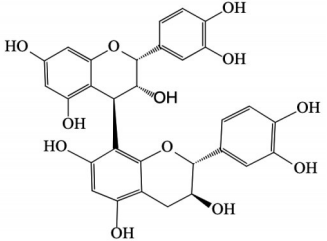
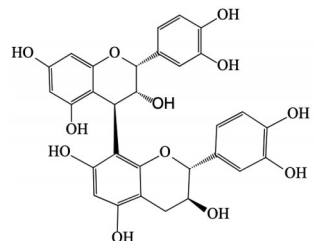
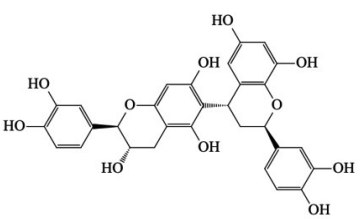
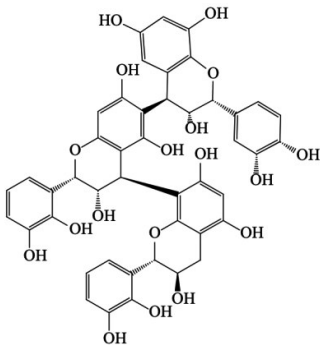
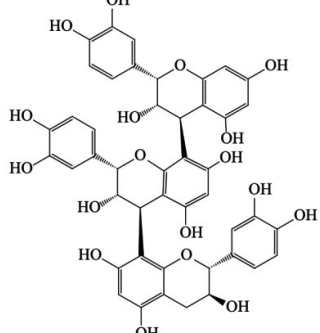
| 编号 | 化合物名称             | 分子结构式   | 槟榔提取部位 | 提取溶剂                    | 参考文献 |
|----|-------------------|---|--------|-------------------------|------|
| 13 | 儿茶素               |    | 成熟种子   | 乙醇                      | [20] |
| 14 | 表儿茶素              |    | 成熟种子   | 乙醇                      | [20] |
| 15 | Calquiquelignan M |    | 槟榔     | 乙醇(提取)、<br>三氯甲烷<br>(萃取) | [17] |
| 16 | Calquiquelignan N |   | 槟榔     | 乙醇(提取)、<br>三氯甲烷<br>(萃取) | [17] |
| 17 | 原花青素 B1           |  | 成熟种子   | 乙醇                      | [21] |
| 18 | 原花青素 B2           |  | 成熟种子   | 乙醇                      | [21] |
| 19 | 原花青素 B7           |  | 成熟种子   | 乙醇                      | [21] |

表 1(续)

| 编号 | 化合物名称                       | 分子结构式  | 槟榔提取部位 | 提取溶剂 | 参考文献 |
|----|-----------------------------|--|--------|------|------|
| 20 | 表儿茶素-(4→8)-表儿茶素-(4β→8)-儿茶素. |   | 成熟种子   | 乙醇   | [21] |
| 21 | 表儿茶素-(4β→6)-表儿茶素-(4β→8)-儿茶素 |  | 成熟种子   | 乙醇   | [21] |

## 2 槟榔多酚的抗氧化作用

### 2.1 体外抗氧化作用

槟榔多酚类化合物能够清除 49.78% 的羟自由基, 且抗氧化能力随多酚含量的增加而增强<sup>[22]</sup>。Lin 等<sup>[23]</sup>发现槟榔花的水提取物抗氧化活性能力强于 50% 的甲醇提取物; 铁离子还原/抗氧化能力法 (ferric ion reducing antioxidant power, FRAP) 和超氧阴离子自由基清除实验表明: 槟榔花提取物的抗氧化活性与总酚含量呈正相关。Sari 等<sup>[24]</sup>研究发现: 槟榔树的果、叶、花序及壳中多酚的含量及其抗氧化活性差异较大, 且抗氧化活性与多酚含量有关, 槟榔多酚的含量从高到低依次为果、叶、花序、壳; 槟榔的抗氧化活性强度从大到小依次为果、叶、花序、壳。蒋晨凤<sup>[25]</sup>发现烟熏槟榔壳中的多酚成分为绿原酸、香草酸、原儿茶酸、对羟基苯甲酸和槲皮素; 体外抗氧化活性研究表明该 5 种酚类化合物中原儿茶酸的抗氧化活性最强。Dsouza 等<sup>[26]</sup>研究表明槟榔叶的三氯甲烷和甲醇提取物有显著的抗氧化活性。此外, Chavan 等<sup>[27]</sup>使用 80% 的丙酮可得到多酚的最大提取量和槟榔碱的最小提取量, 提取物中总酚的含量为 407.47 mg/g、槟榔碱为 1.73 mg/g, 且自由基清除法和 FRAP 清除实验表明槟榔提取物的抗氧化作用与多

酚含量有关, 并通过高效液相色谱法 (high performance liquid chromatography, HPLC) 和液质联用 (liquid chromatography-mass spectrometry, LC-MS) 色谱图确认了槟榔提取物中有儿茶素和表儿茶素。

### 2.2 体内抗氧化作用

Lee 等<sup>[28]</sup>的研究结果表明: 槟榔多酚提取物对  $H_2O_2$  诱导的中国仓鼠肺成纤维细胞 V79-4 氧化应激损伤有保护作用, 其保护作用与消除自由基, 增强过氧化氢酶 (catalase, CAT)、超氧化物歧化酶 (superoxide dismutase, SOD) 和谷胱甘肽过氧化氢酶 (glutathione peroxidase, GPX) 等抗氧化酶的活性有关。袁列江等<sup>[29]</sup>研究发现槟榔粗提取物、水溶出物和乙酸乙酯萃取物均能显著提高小鼠血清中的 SOD 水平。同时, 3 种提取物能降低小鼠血清中丙二醛 (malondialdehyde, MDA) 的浓度, 证明槟榔提取物在体内有很好的抗氧化作用。宋菲等<sup>[30]</sup>的实验发现  $H_2O_2$  可导致人正常成人纤维细胞 (human skin fibroblast, HSF) 线粒体膜肿胀, 使线粒体功能受损; 而表儿茶素和没食子酸均能降低  $H_2O_2$  引起的这种损伤, 其对 HSF 的保护作用可能是通过清除活性氧 (reactive oxygen species, ROS), 抑制线粒体膜损伤而实现的。

### 3 槟榔多酚的抗缺氧作用

研究<sup>[6,31]</sup>发现: 槟榔多酚粗提取物能显著增强H9C2细胞的耐缺氧能力, 其作用机制与提高细胞内抗氧化酶的活性和下调缺氧细胞中*Nrf2* mRNA表达有关。进一步通过大孔吸附树脂纯化槟榔多酚粗提取物, 并进行高原实地缺氧实验, 结果表明槟榔多酚能够显著改善缺氧大鼠的血气指标, 与缺氧模型组相比, 当多酚剂量为800 mg/kg时, 大鼠的pH、标准碳酸氢盐(standard bicarbonate, SBC)、动脉血氧饱和度(oxygen saturaton, SatO<sub>2</sub>)分别增加了0.82%、7.70%、4.51%, 动脉血二氧化碳分压(partial pressure of pcarbon dioxide, PaCO<sub>2</sub>)降低了11.01%; 当多酚剂量为1 600 mg/kg时, 大鼠的pH、SBC、SatO<sub>2</sub>分别增加了0.96%、7.95%、5.69%, PaCO<sub>2</sub>降低了12.39%; 同时能提高肝、肺、心组织中GSH和SOD的酶活性, 降低肝、肺、心组织中MDA的含量<sup>[3-4]</sup>。由此可知, 槟榔多酚的抗缺氧作用与其改善大鼠的低氧血症、增强组织的抗氧化酶活性、减轻脂质过氧化和氧化应激损伤的作用有关。

### 4 槟榔多酚预防高原肺水肿的作用

高原肺水肿(high altitude pulmonary edema, HAPE)是一种可危及生命的非心源性肺水肿<sup>[32]</sup>, 若不

及时预防与治疗, 将严重影响高原作业人群的健康。预防及治疗HAPE的药物主要有碳酸酐酶抑制剂乙酰唑胺、糖皮质激素类地塞米松、β受体激动剂沙美特罗<sup>[33]</sup>、支气管扩张剂氨茶碱<sup>[34]</sup>等, 但这些药物均有一定程度的不良反应, 因此, 有必要寻找安全有效的治疗HAPE的药物。有学者<sup>[5,35]</sup>在前期槟榔多酚抗缺氧研究的基础上, 更深入地研究槟榔多酚对急性高原病是否有预防保护作用, 他们通过在海拔4 010 m的高原实地实验室进行辅助跑台力竭运动, 建立大鼠HAPE模型, 研究槟榔多酚的强抗氧化能力对于HAPE的预防保护作用。实验结果表明: 与对照组相比, 给予槟榔多酚低、中、高剂量后大鼠的血氧饱和度分别升高1.79%、6.10%和4.63%(均P<0.01); 大鼠肺含水量分别降至(79.07±0.26)%、(78.49±0.30)%和(78.10±0.38)%; 同时肺泡灌洗液蛋白质含量相比于模型组显著减低, 基本降低至正常水平。病理组织观察发现: 与模型组相比, 预防性给予槟榔多酚后, 大鼠的肺泡结构趋于完整, 肺泡壁变薄, 腔内渗出减少, 炎症细胞减少。由此可知, 槟榔多酚预防HAPE的发生与减轻肺水肿、维持肺泡毛细血管通透性、改善氧化应激损伤有关。综上所述, 槟榔多酚对高原低氧引起的氧化应激损伤有一定的保护作用, 同时对HAPE有预防作用。

槟榔多酚抗氧化、抗缺氧及其他药理作用见表2。

表2 槟榔多酚的作用及其活性成分

Table 2 Roles and active components of betelnut polyphenols

| 药理作用    | 活性物质                         | 作用机制                                      | 参考文献         |
|---------|------------------------------|---|--------------|
| 抗氧化     | 酚酸、花青素和黄酮类                   | 清除自由基, 增强CAT、SOD和GPX等抗氧化酶的活性              | [3, 27]      |
| 抗缺氧     | 多酚类                          | 提高细胞内抗氧化酶的活性, 下调缺氧细胞中 <i>Nrf2</i> 的mRNA表达 | [6, 31]      |
| 预防高原肺水肿 | 多酚类                          | 减轻肺水肿, 维持肺泡毛细血管通透性, 改善氧化应激损伤及病理损伤         | [5, 35]      |
| 消炎、镇痛   | 黄酮类、花青素类                     | 抑制NO、TNF-α、IL-6、IL-1β、PGE2和ROS的形成         | [36-40]      |
| 抗菌      | 巴西红厚壳素、儿茶素、表儿茶素和表没食子儿茶素没食子酸酯 | 抑制MRSA、结核分枝杆菌H37Rv等                       | [19, 41, 42] |
| 改善骨质疏松  | 多酚类                          | 与调节肠道微生物、减轻炎症有关                           | [43]         |

CAT: 过氧化氢酶; SOD: 超氧化物歧化酶; GPX: 谷胱甘肽过氧化氢酶; *Nrf2*: 核因子相关因子2; NO: 一氧化氮; TNF-α: 肿瘤坏死因子-α; IL-6: 白细胞介素-6; IL-1β: 白细胞介素-1β; PGE2: 前列腺素E2; ROS: 活性氧; MRSA: 耐甲氧西林金黄色葡萄球菌。

## 5 结 语

槟榔多酚具有抗氧化和抗缺氧作用。目前对于槟榔多酚的抗氧化作用以体外研究为主,而槟榔多酚在体内的抗氧化、抗缺氧作用及其机制和有效成分的研究鲜有报道。槟榔多酚的主要成分为儿茶素和表儿茶素<sup>[14, 16, 20]</sup>,其在抗缺氧方面的作用仍有进一步研究的价值。同时,在槟榔多酚的提取工艺优化、质量标准建立、抗缺氧的有效组分和安全性评价等方面仍需进行深入研究。研究<sup>[3, 35]</sup>表明槟榔多酚抗缺氧效果优于红景天胶囊。此外,红景天胶囊的原料药为中药红景天,红景天属于高海拔植物,生长环境特殊,不易获取,且种植不易,过度开采也不利于高原生态环境;而槟榔资源丰富,原料药易得。因此,槟榔多酚在抗缺氧和保护组织氧化损伤方面可作为潜在药物,具有一定的开发应用前景。

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