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抗抑郁药用植物研究进展 *

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摘要：近年来，虽然药用植物被用于临床治疗精神紊乱和行为异常等相关性疾病，如：抑郁、焦虑、癫痫、记忆力衰退、失眠、老年痴呆和药物中毒等，但是，有关药用植物抗抑郁作用的研究性报道较少，且不够系统。本综述主要归纳和总结了具有抗抑郁作用的药用植物及其活性提取物，包括药用植物粗提物和单体活性成分等天然产物，为充分开发利用我国药用植物资源以及民间传统用药提供科学依据，促进高效安全抑郁症治疗方法的研究。

关键词：药用植物；抑郁；强迫游泳实验；槟榔；贯叶连翘

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Research Progresses on Antidepressant Activity of Medicinal Plants*

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ABSTRACT: In recent years, medicinal plants have been used in clinical treatment of such psychotropic and behavioural disorders as depression, anxiety, seizures, hypomnesis, insomnia, dementia and drug intoxication. There have been limited reports on Chinese medicinal plants having antidepressant activity. This article summarized medicinal plants against depression and their active extracts, including crude extracts and monomer compositions. The present study could provide scientific credence to the traditional medicines and full development and utilization of medicinal plant resources in China. Furthermore, the study could promote the development of more effective and safe remedies against depression.

Key words: Medicinal plants; Depression; Forced swimming test; Areca catechu L.; Hypericum perforatum L.

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前言

据世界卫生组织报告，全世界约 4.5 亿人患有心理疾病或存在行为异常，这占据了全球疾病负担的 12.3%，预计到 2020 年将达到 15%[1]。抑郁症是最常见的心理疾病，也是严重影响情绪、身体健康和行为表现的精神类疾病，患者症状反映了脑部单胺神经递质(去甲肾上腺素[Norepinephrine]，5- 羟色胺[5-hydroxytryptamine]和多巴胺[Dopamine])的变化[2]，常伴有自杀倾向，每年大约发生 1000~2000 万例患者自杀事件[3]。当前治疗抑郁症的药物主要以化学合成药物为主，但存在副作用大、复发率高等缺点，临床应用具有局限性，因此开发可长期服用、疗效好且毒性小的药物成为该领域的研究重点，目前，抗抑郁药用植物的开发备受研究者关注。研究证明，我国多种药用植物提取物具有抗抑郁活性，但是有关药用植物抗抑郁作用的系统性报道仍较少。本文对具有抗抑郁作用的药用植物进行归纳和总结，为充分研究开发利用我国药用植物资源奠定基础。

1 抑郁症及其发病机制

抑郁症是由个体行为、心理和生理异常的共同作用所致，患者某些情绪及行为表现和焦虑症是相似的，例如重度恐惧，广泛性焦虑障碍，创伤后应激障碍，自我强迫[4]。心境恶劣障碍(Dysthymic Disorder)[5]，精神障碍(Psychotic Depression)[6]，产后抑郁(Postpartum Depression)[7]，季节性情感障碍(Seasonal Affective Disorder)[8]也是抑郁症的几种类型。目前对于抑郁症的病因及病理机制尚不清楚，研究发现有几种类型的抑郁症往往发生在一个家族内，推测可能与遗传相关，然而抑郁症也常发生在没有家族史的人群身上[9]。抑郁症发生机制存在几种假说，包括单胺假说和皮质激素受体假说等。单胺假说推测抑郁症可能是由大脑中枢神经系统内单胺类神经递质(去甲肾上腺素[NE]/5- 羟色胺[5-HT])传输功能缺失引发，此假说发展于抗

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抑郁药的作用机制，例如三环类抗抑郁药（TCA）或单胺氧化酶抑制剂（MAOI）可以促进单胺类神经递质的传输[10]。皮质激素受体假说则通过细化分析下丘脑 - 垂体 - 肾上腺（HPA）轴系统功能的变化，认为皮质激素受体信号（CRS）受损是导致抑郁症发病的重要机制[11]。最新研究表明，抑郁症还可能与神经退行性疾病以及海马区域的神经发育减少相关[12]。尽管用单胺假说来解释抑郁症发生是不充分的，但是单胺类神经递质传输的控制仍然是有效的治疗方法。

2 药用植物抗抑郁作用研究现状

当前大多数研究集中于疗效更好的新型药物开发，其中选择性 5-HT 再摄取抑制剂（SSRIs），5-HT、NE 再摄取抑制剂（SNRIs）以及 NE 能和特异性 5-HT 能抗抑郁药已逐渐替代了单胺氧化酶抑制剂（MAOI），三环类抗抑郁药（TCA）和四环类抗抑郁药（Ttracyclica）等抗抑郁药，临床主要应用 SSRIs 类药物，如氟西汀（Fluoxetine），帕罗西汀（Paroxetine），舍曲林（Setraline），氟伏沙明（Fluvoxoxamine），西酞普兰（Citalopram），但是药物临床评估证实它们的毒副作用大，复发率较高以及药物的相互作用较大，与这些化学合成药物相比，药用植物的价格低廉，毒副作用较小，可以长期服用，这些优势极大的推动了抗抑郁活性天然产物的开发，其中药用植物对中枢神经系统相关性疾病的治疗功效备受关注，尤其是抑郁症。下表归纳总结了已被报道具有抗抑郁作用的药用植物及其相关药用部位和有效提取物（表 1）。

表 1 我国抗抑郁药用植物种类 *

Table 1 A brief description of Chinese medicinal plants having antidepressant property

Number	Latin Name	Family	Medicinal Part	Extract used
1	Acanthopanax senticosus (Rupr. et Maxim.) Harms.[13]	Araliaceae	Stem bark	Aqueous
2	Acorus calamus L.[14]	Araceae	Rhizome	Methanolic
3	Akebia quinata (Houtt.) Decne.[15]	Lardizabalaceae	Fruit	Ethanolic
4	Albizia julibrissin Durazz.[16]	Fabaceae	Bark	Ethanolic
5	Anemarrhena asphodeloides Bge[17]	Liliaceae	Rhizome	Sarsasapogenin
6	Apocynum venetum L.[18]	Apocynaceae	Leaves	Ethanolic-aqueous
7	Areca catechu L.[19,20]	Arecaceae	Areca nut	Dichloromethane
8	Astragalus membranaceus (Fisch.) Bunge.[21]	Fabaceae	Root	Aqueous
9	Bacopa monnieri (L.) Wettst.[22]	Scrophulariaceae	Aerial parts	Methanolic
10	Bupleurum chinense DC.[23,24]	Apiaceae	Root	Aqueous
11	Centella asiatica (L.) Urb.[25]	Apiaceae	Leaves	Isopropyl alcohol- aqueous
12	Cimicifuga foetida L.[26]	Ranunculaceae	Root	Ethanolic
13	Citrus medica L. var. sarcodactylis Swingle[27]	Rutaceae	Fruit	Ethanolic- butyl alcohol
14	Crocus sativus L.[28]	Iridaceae	Flower	Aqueous and ethanolic
15	Curcuma longa L.[29]	Zingiberaceae	Rhizome	Aqueous
16	Curcuma petiolata Salisb.[30]	Zingiberaceae	Root	Aqueous
17	Cyperus rotundus L.[31]	Cyperaceae	Rhizome	Ethanolic
18	Descurainia sophia (L.)Webb ex Prant[32]	Brassicaceae	Seed	Ethanolic
19	Epimedium brevicornum Maxim.[33]	Berberidaceae	Aerial parts	Aqueous
20	Eucommia ulmoides Oliver[34]	Eucommiaceae	Bark	Ethyl acetate
21	Gastrodia elata Bl.[35]	Orchidaceae	Rhizome	Aqueous-ethanolic
22	Ginkgo biloba L.[36]	Ginkgoaceae	Leaves	Aqueous, Ethanolic
23	Glycyrrhiza uralensis Fisch. ex DC.[37]	Fabaceae	Root	Liquiritin and isoliquiritin
24	Gossypium spp.[38]	Malvaceae	Seed	Flavonoids
25	Gynostemma pentaphyllum (Thunb.) Makino[39]	Cucurbitaceae	Rhizome	Ethanolic
26	Hypericum perforatum Linn. Sp. Pl.[40,41]	Hypericaceae	Aerial parts	Hyperoside, isoquercitrin and miquelianin
27	Hypericum sampsonii Hance[42]	Clusiaceae	Root, Stem, Leaves	Ethanolic
28	Lilium brownii F. E. Br. ex Spae var. viridulum Baker[43]	Liliaceae	Stem	Saponins
29	Magnolia officinalis Rehd. et E. H. Wils.[44]	Magnoliaceae	Bark	Magnolol
30	Millettia pulchra (Dunn) Kurz var.laxior (Dunn) Z.Wei[45]	Fabaceae	Root	Polysaccharides
31	Momordica charantia L.[46]	Cucurbitaceae	Leaves	Methanolic
32	Morinda officinalis F.C How[47,48]	Rubiaceae	Root	Ethanolic

33	Nelumbo nucifera Gaertn.[49]	Nymphaeaceae	Fruit, seed	Ethanolic
34	Paeonia lactiflora Pall.[50,51]	Ranunculaceae	Root	Ethanolic
35	Panax ginseng C. A. Mey.[52]	Araliaceae	Root	Saponins
36	Panax notoginseng (Burk.) F. H. Chen ex C. Y. Wu et K.m. Feng[53]	Araliaceae	Stem, Leaves	Saponins
37	Perilla frutescens (L.) Britt.[54]	Lamiaceae	Leaves	Apigenin
38	Piper laetispicum C.DC.[55]	Piperaceae	Stem	Laetispicine
39	Polygala tenuifolia Willd.[56]	Polygalaceae	Root	Ethanolic
40	Polygonum multiflorum Thunb.[57]	Polygonaceae	Root	Aqueous
41	Psychotria rubra (Lour.) Poir.[58]	Rubiaceae	Root	Ethanolic
42	Pueraria lobata (Willd.) Ohwi[59]	Fabaceae	Root	Aqueous-ethanolic
43	Schisandra chinensis (Turcz) Baill.[60]	Magnoliaceae	Fruit	Aqueous, ethanolic
44	Scutellaria baicalensis Georgi[61]	Lamiaceae	Root	Baicalin
45	Trichilia connaroides (Wightet Arn.) Bentv[62]	Meliaceae	Root	Ethanolic
46	Valeriana officinalis L.[63]	Caprifoliaceae	Root, Stem	Ethanolic
47	Zanthoxylum bungeanum Maxim.[64]	Rutaceae	Fruit	Polyphenols
48	Ziziphus jujuba Mill. var. spinosa (Bunge) Huex H. F. Chow[65]	Rhamnaceae	Seed	Alkaloids and saponins

* The data is obtained from Google Scholar.

3 抗抑郁药用植物疗效筛选

迄今为止，药用植物抗抑郁作用研究主要停留在动物实验观察上，所采用的动物模型有强迫游泳实验（FST）[66]，悬尾实验（TST）[67]，5- 羟色胺酸诱导甩头行为模型[68]，嗅球切除模型（OBX）[25]，利血平诱导眼睑下垂[69]，育亨宾增强模型[70]等，其中强迫游泳实验和悬尾实验是两个经典的抗抑郁药筛选方法。抗抑郁药用植物活性物质的研究主要集中在粗提物和大类或单体成分两个方面，粗提物主要是醇提物，水提物和有机溶剂萃取物，大类或单体活性成分研究相对深入，包括皂苷（Saponins），黄酮（Flavonoids），多酚（Polyphenols）及生物碱类物质（Alkaloids）。根据文献报道，因实验所采用的动物对象和药物作用方式的不同，无法精确评估 48 种药用植物抗抑郁作用的强弱，故排除药用植物对大小鼠抑郁模型及作用方式导致的些许差异，分析药用植物粗提物和大类或单体活性成分在有效的作用时间内对强迫游泳动物的抗抑郁作用（图 1 和图 2），筛选作用较强的药用植物，为从事抗抑郁天然产物开发的研究者提供信息帮助，同时也为服用中草药的抑郁症患者提供治疗选择。

根据文献报道，排除抗抑郁作用明显弱于其它的刺五加，合欢，黄芪，佛手等 10 几种药用植物。分析结果发现，药用植物粗提物中槟榔二氯甲烷萃取物的抗抑郁作用较强，槟榔二氯甲烷萃取物（4 mg·kg^{-1}）能够显著降低强迫游泳小鼠的不动时间，木桶乙醇提物，假马齿苋甲醇提取物和升麻乙醇提取物也具有良好的抗抑郁作用，最小作用剂量达到 20 mg·kg^{-1}。药用植物大类或单体活性成分的抗抑郁作用要明显强于粗提物，其中贯叶连翘金丝桃苷（Hyperoside），异槲皮素（Isoquercitrin）和槲皮素 -3-O- 葡萄糖醛酸苷（Miquelianin）的抗抑郁作用最强，最小作用剂量均达到了 0.6 mg·kg^{-1}，大叶茹大叶素（5 mg·kg^{-1}）在 FST 中也显示出良好的抗抑郁作用。本研究简要描述在强迫游泳动物实验中显示出较强抗抑郁作用的两种药用植物 - 槟榔（Areca catechu L）和贯叶连翘（Hypericum perforatum Linn. Sp. Pl）。

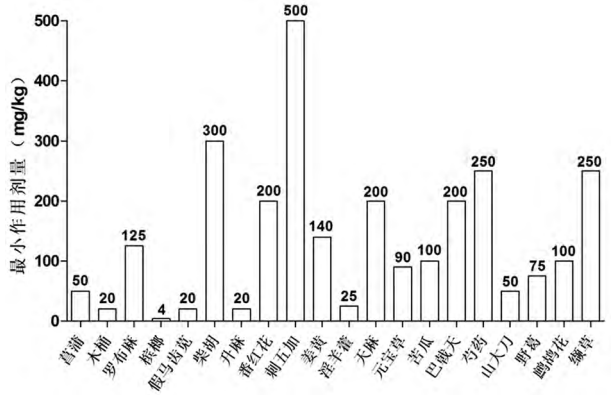

图 1 药用植物粗提物在动物模型强迫游泳实验中的抗抑郁作用 *

Fig. 1 Antidepressant effects of the crude extract from medicinal plants in forced swimming test

* The data is obtained from Google Scholar.

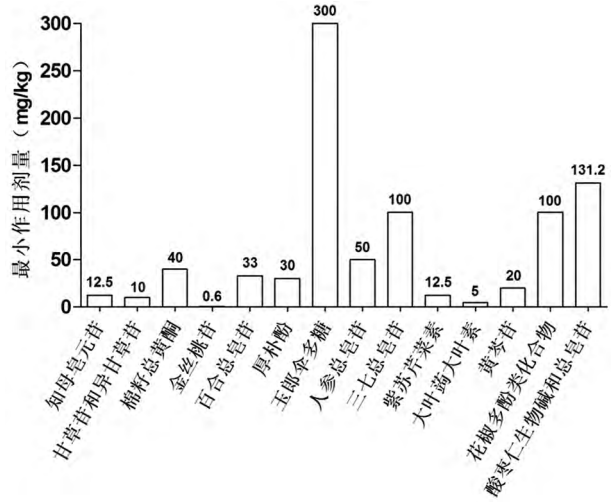

图 2 药用植物大类或单体活性成分在动物模型强迫游泳实验中的抗抑郁作用 *

Fig. 2 Antidepressant effects of active constituents from medicinal plants in forced swimming test

* The data is obtained from Google Scholar.

3.1 槟榔(Areca catechu L)

槟榔为棕榈科植物(Palmae),属常绿乔木,茎直立,高10 m~30 m,主要分布于我国广西,福建,台湾,广东和海南等,是我国"四大南药"(槟榔,益智,砂仁,巴戟)之首,槟榔已被列入《中国药典》,作为民间传统用药,主治疟疾,痢疾,蛔虫,绦虫以及姜片虫引起的肠道疾病[71]。

槟榔抗抑郁作用的研究报道不多,药效物质研究并不深入,其作用机制可能与单胺假说相应。Dar A 等[19]采用 FST,TST,育亨宾宁碱试验以及运动试验来研究槟榔的抗抑郁作用,实验结果证明 4 mg·kg^{-1}~80 mg·kg^{-1} 的槟榔乙醇提取物显著缩短强迫游泳和悬尾动物的不动时间,进一步研究发现槟榔二氯甲烷萃取物可以抑制大鼠脑部单胺氧化酶 A 型(MAO-A),半数抑制浓度为(IC50)为(665± 65.1) μg·mL^{-1},而其生物碱成分,如槟榔碱和槟榔啶则没有展现出抑制 MAO 的作用[20]。李亚军等[72]通过小鼠悬尾实验证明槟榔果的蒂、种子、壳部分的乙醇提取物中,其氯仿萃取相与氟西汀一样能够缩短小鼠游泳的不动时间,表现出较强的抗抑郁活性,同时进一步鉴定出 10 个化合物单体,其中 6 个酚类化合物单体 - 异鼠李素(Isorhamnetin)、金圣草黄素(Chrysoerio)、木犀草素(Luteolin)、4',5- 二羟基 -3',5',7- 三甲氧基二氢黄酮(4',5-Dihydroxy-3',5',7-trinrthoxyflavonone)、大黄素甲醚(Physcion)和大黄酚(Chrysophanol)与单胺氧化酶 A 型(MAO-A)结合度较好,结果推测槟榔中酚类成分可能是槟榔抗抑郁的有效组分。

3.2 贯叶连翘(Hypericum perforatum Linn. Sp. Pl)

贯叶连翘为金丝桃科(Hypericaceae)多年生草本植物,又被称为"贯叶金丝桃"、"圣约翰草",高 20cm~60 cm,在河北,山西,陕西,山东,江苏及河南等地均有分布,是我国传统的中药材之一,其药用历史悠久,最早被《本草纲目拾遗》收载,其性味辛、涩苦、平,具有清热解毒,收敛止血,利湿等功效。

贯叶连翘提取物因抗抑郁疗效及副作用小成为抗抑郁的首选药用植物,目前已被《美国药典》[USP/NF]收录[73]。贯叶连翘抗抑郁作用备受研究者关注,其抗抑郁活性成分和作用机制研究较为深入,研究发现贯叶连翘化学成分主要是挥发油(0.05%~0.3%,包括 α- 松萜和桉叶素),蒽酮类化合物,类胡萝卜素,香豆素,黄酮类化合物(0.5%~1%,包括金丝桃苷,槲皮素和芦丁),萘并二蒽酮类(0.1%~0.3%,其中 80%~90%是金丝桃苷和假金丝桃素),酚酸,氧杂蒽酮和原花青素[74],这些化学成分中金丝桃素[75],氧杂蒽酮[76]已被证明具有抗抑郁作用。Butterweck V 等[77]研究证明贯叶连翘黄酮类物质抗抑郁作用显著,进一步采用多层螺旋逆流(MLCCC)色谱和高效液相色谱(HPLC)分离得到三个具有抗抑郁作用的单体成分槲皮素 -3-O- 葡萄糖醛酸苷(Miquelianin),金丝桃苷(Hyperoside)和异槲皮素(Isoquercitrin),且剂量为 0.6 mg·kg^{-1} 能显著降低强迫游泳大鼠的不动时间。另外,贯叶连翘药效物质的抗抑郁作用机制研究亦有报道,Bladt S 等[78]研究发现贯叶连翘提取物通过抑制单胺氧化酶(MAO)实现抗抑郁作用,Chatterjee S S 等[79]则研究发现贯叶连翘提取物中抗抑郁作用的主要活性成分是贯叶金丝桃素(HYP),它通过抑制 5-HT,DA,NE 等单胺类神经递质及 C- 氨基丁酸、L- 谷氨酸等氨基酸类神经递质的重吸收起抗抑郁作用。

4 结论

本文简述抑郁症及其发病机制,同时对药用植物抗抑郁作用研究现状进行分析,归纳总结了能够治疗和缓解抑郁症的 48 种药用植物,筛选出抗抑郁作用较强的药用植物 - 槟榔(Areca catechu L)和贯叶连翘(Hypericum perforatum Linn. Sp. Pl),有效提取物分别为槟榔二氯甲烷萃取物和贯叶连翘金丝桃苷(Hyperoside)、异槲皮素(Isoquercitrin)及槲皮素 -3-O- 葡萄糖醛酸苷(Miquelianin)。本文主要对单种药用植物的抗抑郁作用作了归纳总结,在治疗选择上,方药的抗抑郁疗效也较为显著,如柴胡、当归、白芍、茯苓、白术、甘草组成的逍遥散,半夏、厚朴、茯苓、生姜和苏叶等组成的半夏厚朴汤等。当前抗抑郁作用药用植物的研究性报道较少,且大多停留在对其粗提取物的动物实验观察上,其抗抑郁活性成分的研究有待于深入考察,药效物质的抗抑郁作用机理更需要全面深入的探究,相信随着技术发展和深入的学术研究,抑郁症治疗将会有巨大突破。

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