

药用植物资源在水产动物疾病控制中的研究进展*

胡洋^{1,2} 张旭^{1,2,3} 王欢^{1,2} 单立鹏^{1,2} 刘镭^{1,2} 陈炯^{1,2**}

(1 宁波大学 农产品质量安全危害因子与风险防控国家重点实验室 宁波 315211)

(2 宁波大学海洋学院 宁波 315832 3 无锡天香菊生物科技研究院有限公司 无锡 214200)

摘要 随着生活水平的不断提高,人们对水产品的需求量日益增加,水产养殖业得到飞速发展。然而,各种寄生虫、细菌和病毒诱发的疾病给水产养殖业造成了巨大的经济损失,严重制约了水产养殖业的快速稳定发展。作为传统的防治手段,抗生素等化学合成药物常用于水产养殖过程。大量化学合成药物的滥用诱发了药物残留、耐药菌等环境污染问题,危害人类健康。因此,具有多种有效活性成分的中草药因其天然、安全、副作用小等原因,成为探索新型防控水产病害暴发手段的研究对象。当前,中草药常被用于调节水产动物的免疫力、生长速度和预防疾病暴发等。同时,中草药还可用于改善养殖环境,降低环境因子对水产动物的胁迫。然而,目前的研究主要集中在从中草药中获取防控疾病暴发的复合有效成分,存在药效不稳定、活性成分不明确等问题,无法满足生产高效、廉价、稳定防治剂的需求。论述了当前中草药在防控水产动物疾病暴发中的应用及其作用机制,揭示了对中草药活性分子作用机制研究的不足,强调了中草药作为一种更环保、更有效的水产养殖疾病防控手段进行应用的潜力,对其抗病机制的深入研究尤为重要。

关键词 中草药 活性成分 抗生素 免疫增强剂 水产病害

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中草药是一种药用植物及其提取物的统称,常被用于改善人体健康并预防、治疗多种疾病,多年来其应用范围已逐渐扩大到提高养殖动物健康水平和抗病能力上^[1]。中草药在水产养殖中的应用由来已久,由于其易制备、成本低廉、副作用小、天然安全等优点常被用于水产动物的治疗剂和饲料添加剂,以促进养殖对象的生长发育,提高免疫和抗病能力^[2-6]。近年来,随着水产养殖规模的不断扩大和养殖环境恶化,由病毒、细菌和寄生虫等诱发的各种疾病给水产养殖业造成了巨大的经济损失,同时各种化学合成药物如抗生素的使用日益受到世界范围内多个国家的限制,导致天然、安全、高效防治剂的研发迫在眉睫。自1990年以来,中草药作为水产动物的饲料添加剂在预防和治疗多种疾病等方面的作用引起了研究人员的广泛关注,尤其是近年来已成为水产动物药物研发的热点^[7]。Tadese

等^[8]列举了中草药对水产动物的多种有益功效,包括促进生长、抗应激、增强食欲、提高免疫力、抗菌、抗虫和抗病毒等,而上述种种积极作用归因于中草药中含有的酚类、生物碱、醌类、萜类、内酰胺和肽化合物等有效成分。

中草药是合成理想防治剂的重要来源,从中草药中筛选活性物质是开发新型无公害防治剂的一条重要捷径。本文通过对现有中草药在水产养殖中的应用案例进行分类和总结,展示了中草药在水产养殖中应用的动态变化,以期促进中草药在水产养殖过程中的推广使用。同时本文还对中草药活性物质在防治水产病害中作用的研究进行概述,分析了当前研究中的不足并阐明了未来研究的重点。

1 中草药抗寄生虫活性

水产动物感染寄生虫后会出现大量死亡,造成严重的经济损失,常见杀虫剂,如吡喃唑酮和阿维菌素等

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**通讯作者,电子信箱:jchen1975@163.com

化学药物的滥用易造成药物残留和耐药寄生虫的产生。中草药天然、安全、副作用小,使用中草药来治疗水产动物的寄生虫病不仅能取得理想的治疗效果,而且还可以有效降低消费者对食品安全的恐慌。虽然已有一些关于中草药抗寄生虫的报道,如松属植物的松脂类化合物,虎爪豆(*Mucuna pruriens*)、绿茶和番木瓜(*Carica papaya*)的粗提取物等均可以有效杀灭水产动物体内的寄生虫,但当前的研究依旧无法满足消费者日益增长的食品安全需求(表1)^[9-11]。同时,受寄生虫生活习性和不同发育阶段的影响,导致中草药在抗寄生虫病中应用的研究更加具有挑战性。

1.1 抗指环虫

作为单殖吸虫类的一种,指环虫(*Dactylogyrus* spp.)能够寄生于绝大多数经济鱼类和观赏鱼中,由其诱发的鱼类疾病是最为常见的寄生虫病害之一,对水产养殖业造成了巨大的经济损失。前人先后对川楝、沙地柏、黄花烟草、槟榔、青蒿、苦参、七叶树外种皮、鸦胆子、独活、鸡血藤、牵牛子等中草药的粗提物及其活性成分进行杀指环虫活性研究,结果发现20.0 mg/L剂量的川楝素在48 h时可以杀灭100%的指环虫,但因用量大、价格高在渔业生产中无法推广应用^[12]。对多种中草药进行筛选发现,蛇床子(*Fructus cnidii*)^[12]、鸡血藤(*Caulis spatholobi*)^[13]、鸦胆子(*Fructus bruceae*)^[13]、七叶树种子(seeds of *Aesculus chinensis*)^[13]、银杏外种皮(exopleura of *Ginkgo biloba*)^[14]、羊金花(*Dature sramoniun*)^[15]、博落回(*Macleaye cordata*)^[15-16]、小果博落回(*M. icrocarpa*)^[15-16]、盾叶薯蓣(*Dioscorea zingiberensis*)^[17]、牛蒡子(*Arctium lappa*)^[18]、重楼(*Rhizorma paridis*)^[19]等具有较好的杀虫活性并值得进一步研究。

深层次研究发现,中草药中的一些活性成分展现了良好的抗虫潜力,如从蛇床子中分离获得的蛇床子素($C_{15}H_{16}O_3$)在48 h时的百分百杀指环虫浓度为1.6 mg/L,金鱼急性攻毒发现其半数致死浓度(lethal concentration 50%, LC_{50})为6.749 mg/L,较甲苯咪唑更安全^[20]。从银杏外种皮获得2种活性化合物——银杏酸 $C_{13:0}$ 和 $C_{15:1}$,在48 h时对欧洲鳗鲡中拟指环虫的百分百杀灭浓度分别为2.5 mg/L和6.0 mg/L^[21]。牛蒡子提取物牛蒡子苷元和牛蒡子苷展现了既安全又高效的抗虫活性,其在48 h时对中型指环虫的半数有效浓度(concentration for 50% of maximal effect, EC_{50})分别为

0.62 mg/L和3.55 mg/L,其 LC_{50} 分别为8.47 mg/L和14.14 mg/L^[22]。更有趣的是,将蛇床子素的母体结构7-羟基香豆素进行修饰改造得到的化合物的抗虫活性要远远高于其先导化合物^[23]。对香豆素类化合物的杀虫活性和急性毒性分析发现,取代基团和取代位点的差异对香豆素类化合物的杀虫活性或急性毒性都会产生不同程度的影响。在此基础上,开展了香豆素类化合物杀虫构效关系的研究,结果发现香豆素母环上的7、8位取代位点是活性关键位点,其中7位取代位点被杂环化合物取代时能显著提高化合物的杀虫活性。此外,对牛蒡子苷元改造后的衍生物进行抗虫活性评价,结果发现咪唑类牛蒡子苷元衍生物能够在抗虫的同时降低对金鱼的毒性,可以被进一步开发^[24]。

1.2 抗三代虫

单殖吸虫纲中的三代虫(*Gyrodactylus* spp.)有寄生虫界的“果蝇”之称,能够寄生于绝大多数养殖和观赏鱼类,给水产养殖业造成了极大危害。早些时候研究发现,檀香(*Santalum album*)的氯仿提取物能完全杀灭寄生在金鱼中的三代虫^[25]。此外,Fridman等^[26]使用大蒜提取物来治疗孔雀鱼中的三代虫病,结果发现7.5 ml/L剂量的大蒜水提取物能够显著减少鱼体上三代虫的数量。类似的研究发现,生姜的乙醇提取物也可以显著降低寄生在孔雀鱼上的三代虫数量^[27]。另有研究表明,博落回乙酸乙酯(80 mg/L)和石油醚(100 mg/L)提取物在48 h时均可以杀灭金鱼体内100%的三代虫^[28]。深入研究发现,倍半萜烯类化合物莜术二酮可以通过破坏三代虫表皮,导致其ATP供应不足来发挥其杀虫活性^[29]。相同的结果在对牛蒡子苷元衍生物的研究中也被发现^[30]。

1.3 抗小瓜虫

小瓜虫病是水产养殖过程中危害最大的鱼类病原虫之一,它由多子小瓜虫寄生于鱼体表和鳃上引起的,严重时全身皮肤和鳍条布满白色的包囊,俗称“白点病”。小瓜虫具有分布广、无宿主专一性等特点,不仅能够给几乎所有养殖鱼类造成巨大的经济损失,而且也能给观赏渔业造成相当程度的危害^[31]。自特效药物孔雀石绿和汞盐禁止使用以来,国内外相继开展了小瓜虫病的防治研究。近年来,国内外很多学者运用活性跟踪法从天然产物中发现了一些抗小瓜虫活性分子(图1),如奎宁^[32]、血根碱^[33]、二氢血根碱^[34]、二氢白屈菜红碱^[34]、五没食子酰葡萄糖^[35]、白

薇苷^[36]、白屈菜红碱^[37]、制霉菌素^[38]、盾叶薯蓣皂苷^[39]、补骨脂定^[40]及桑皮酮^[41]等。此外,深入研究还发现从中药厚朴中提取的厚朴酚结构简单、抗虫活性高,是通过取代基修饰和结构改造开发药物的理想对象^[42]。研究显示,0.6 mg/L 剂量的厚朴酚能够完全杀灭小瓜虫掠食体,浓度为 0.8 mg/L 的厚朴酚可作用于小瓜虫包囊前体,除直接破坏其表膜外还能抑制其二分裂繁殖,厚朴酚剂量为 1.0 mg/L 时能完全阻止小瓜虫包囊的孵化。同时,将 1.5 mg/L 剂量的厚朴酚用于在体小瓜虫可影响其繁殖力,降低掠食体的产生数量^[42]。

1.4 抗其他寄生虫

车轮虫 (*Trichodina* spp.) 常诱发鱼苗和鱼种大规模死亡,前人的研究表明苦参提取物及印楝素等均可以有效杀灭斑马鱼和鳊体内的车轮虫^[43-44]。以大黄鱼体表和鳃组织脱落的刺激隐核虫 (*Cryptocaryon irritans*) 包囊孵育的幼虫为试验对象,使用 40 mg/L 剂量的贯众处理 2 h 后发现隐核虫的死亡率达 100%,同时使用浓度为 200 mg/L 的苦皮藤素处理隐核虫幼虫 4 h 后其死亡率达 100%。令人惊喜的是,双氢青蒿素也展现了较好的抗虫活性,当其浓度为 200 mg/L 时,隐核虫在 3 h 的死亡率大于 50%,然而提高双氢青蒿素的浓度和延长处理时间并不能使隐核虫全部死亡^[45-46]。

表 1 中草药的抗虫活性

Table 1 The anti-parasitic activity of Chinese herbal medicine

名称	有效剂量	物种	杀灭寄生虫种类	参考文献
蛇床子	70 mg/L	金鱼	指环虫	[12]
鸡血藤	64.92 mg/L	金鱼	指环虫	[13]
鸦胆子	49.96 mg/L	金鱼	指环虫	[13]
七叶树种子	7.33 mg/L	金鱼	指环虫	[13]
银杏酚酸	1.70 mg/L	金鱼	指环虫	[14]
小果博落回	16 mg/L	金鱼	指环虫	[16]
盾叶薯蓣	17.0 mg/L	金鱼	指环虫	[17]
大蒜	12.5 mL/L	孔雀鱼	三代虫	[26]
生姜	200 ppt	孔雀鱼	三代虫	[27]
博落回	80 mg/L	金鱼	三代虫	[28]
奎宁	60 mg/kg	虹鳟	小瓜虫	[32]
白薇苷	2 mg/L	草鱼	隐核虫	[36]
白屈菜红碱	8 mg/L	金鱼	小瓜虫	[37]
补骨脂定	0.8 mg/L	金鱼	小瓜虫	[40]
厚朴酚	0.6 mg/L	金鱼	小瓜虫	[42]
印楝素	0.8 mg/L	斑马鱼	车轮虫	[43]
贯众	40 mg/L	大黄鱼	隐核虫	[45]
苦皮藤	200 mg/L	大黄鱼	隐核虫	[46]

2 中草药抗菌活性

由各种致病菌诱发的细菌病在水产养殖过程中频发,其发病率和死亡率极高,给水产养殖业造成了巨大的经济损失,其中以弧菌、嗜水气单胞菌和链球菌等最为严重。众所周知,抗生素等化学合成药物的使用虽然可以在短时间内有效阻断由细菌诱发的多种疾病暴发,但是化学合成药物的滥用容易产生耐药菌和环境污染^[7]。由于上述原因,一些天然、安全、副作用小的中草药及其活性分子的抗菌活性被逐渐研究和报道(表

2),如黄芪多糖 (*Astragalus polysaccharides*)^[47]、丝兰 (*Yucca smalliana* Fern.)^[48]、猪鬃草 (*Adiantum capillus veneris*)^[49]、薄荷 (*Mentha longifolia*)^[50] 和小檗碱^[51] 等。

2.1 抗嗜水气单胞菌

嗜水气单胞菌 (*Aeromonas hydrophila*) 是一种水生条件性致病菌,可诱发皮肤溃疡和出血性败血症等多种水产动物主要疾病。研究者分别在饲料中添加杜仲 (*Eucommia ulmoides* Oliv.)、葡萄籽 (*Vitis vinifera* L.)、银杏 (*Ginkgo biloba* L.) 和马郁兰 (*Origanum majorana* L.) 粗提物,可以有效提高鲤 (*Cyprinus carpio*) 的抗氧

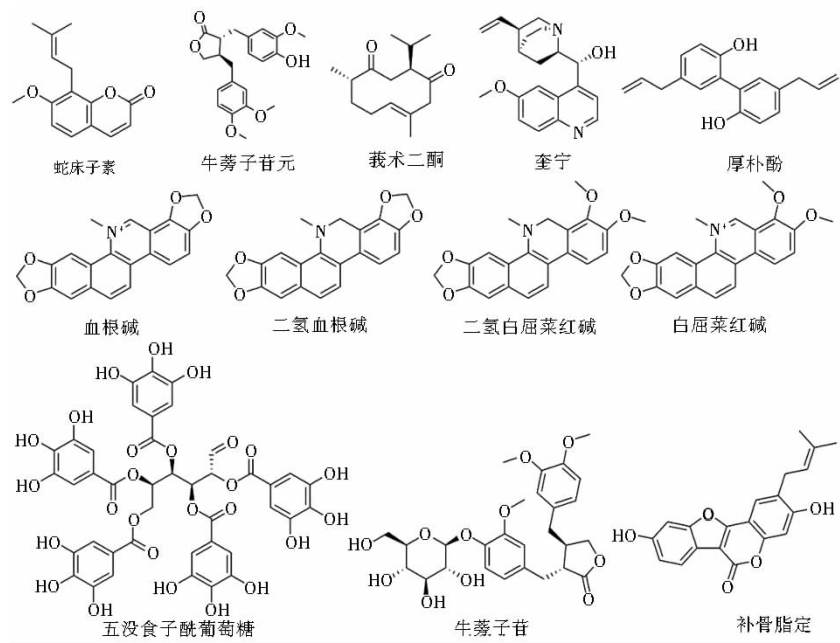


图1 抗虫活性单体化学结构式
Fig. 1 The chemical structure of anti-parasites compounds

表2 中草药的抗菌活性
Table 2 The anti-bacterial activity of Chinese herbal medicine

名称	有效剂量	物种	功能	参考文献
黄芪多糖	100 mg/kg	鲫	提高抗病能力	[47]
丝兰	0.1%	尼罗罗非鱼	提高抗病水平	[48]
猪鬃草	2%	鲤	增强对不同致病菌的杀菌活性	[49]
薄荷	0.2%	虹鳟	提高对细菌性疾病的抵抗力	[50]
小檗碱	1 g/kg	尼罗罗非鱼	增强抗病能力	[51]
京尼平苷	100 mg/kg	鲫	提高对嗜水气单胞菌的抗性	[52]
迷迭香	10 g/kg	尼罗罗非鱼	增强抗病能力	[53]
葡萄籽	30 g/kg	鲤	提高对嗜水气单胞菌的抵抗	[54]
蒙古韭	40 mg/kg	乌鳢	提高对嗜水气单胞菌的抵抗	[55]
荷荷巴	2 g/kg	罗非鱼	改善血液学指标,增强抗嗜水气单胞菌能力	[56]
生姜	10 g/kg	虹鳟	提高抗氧化和免疫力,降低死亡率	[57]
山茶花	200 mg/kg	鲮	提高血液免疫指标	[58]
芦丁	50 μg/g	凡纳滨对虾	提高酚氧化酶活性,提高存活率	[59]
薄荷	1~5 g/kg	花鲈	提高血液免疫指标,增强对哈氏弧菌的抗性	[60]
大蒜	1.0 g/100 g	尼罗罗非鱼	有效预防链球菌感染	[61]
水葫芦	2.5%~5%	鳊	抗哈氏弧菌	[62]
辣木	40%	鲫	提高抗氧化和免疫反应,增强对嗜水气单胞菌的抗性	[63]
银杏叶	10 g/kg	鲤	改变免疫相关基因的表达,提高对嗜水气单胞菌抗性	[64]
辣木	40%	鲫	提高抗氧化和免疫反应	[65]

化能力并激活其免疫系统,增强对嗜水气单胞菌抗性,降低死亡率^[54, 63-65]。在对罗非鱼(*Oreochromis niloticus*)抗嗜水气单胞菌的研究中发现,膳食补充罗望子(*Tamarindus indica* L.)和天鹅绒豆(*Mucuna pruriens* L.)粗提物增强了其抗嗜水气单胞菌感染能力,其中当罗望子粗提物添加剂量为 15 g/kg 时效果最佳^[66-67]。研究表明,辣木(*Moringa oleifera* Lam.)经发酵后替代饲料中 40% 的鱼粉可以促进鲫(*Carassius auratus*)生长,同时提高了其抗氧化和免疫反应,增强对嗜水气单胞菌的抗性^[63]。研究还发现,虹鳟(*Oncorhynchus mykiss*)膳食补充 40 mg/kg 蒙古韭(*Allium mongolicum* Regel)对嗜水气单胞杆菌有明显抵抗作用^[55]。0.5% 剂量的槲寄生(*Viscum album*)粗提物还能增强日本鳗鲡(*Anguilla japonica*)的非特异性免疫,提高感染嗜水气单胞菌后吞噬细胞的活性,导致活性氧中间体(ROI)的产生增加^[68]。穿心莲(*Andrographis paniculata*)提取物通过提高血红蛋白水平和红细胞-白细胞总数以及吞噬指数来增强露斯塔野鲮(*Labeo rohita*)对嗜水气单胞菌的抗性^[69]。

深入研究发现,从中草药中分离得到的单体成分也展现了令人欣喜的活性。例如,Vijayaram 等^[52]指出从梔子花等中草药中分离得到的一种具有生物活性的环烯醚萜苷——京尼平苷在体内、体外均展现了抗炎、抗菌、抗氧化和免疫调节等多种药理作用,养殖时在膳食中补充京尼平苷可增强鲫鱼抗嗜水气单胞菌感染的能力。药用植物大黄(*Rheum palmatum* L.)、虎杖(*Reynoutria japonica* Houtt.)等含有的白藜芦醇(resveratrol)能有效降低嗜水气单胞菌毒力并减弱机体炎症反应,腹腔注射 25 ~ 100 mg/kg 白藜芦醇对感染病原菌的异育银鲫(*Carassius auratus gibelio*)有一定保护作用^[70]。资料显示,从大黄中提取的活性蒽醌化合物被证实具有抗嗜水气单胞菌的作用^[71]。牛国一等^[72]试验发现,厚朴酚(magnolol)和黄藤素(palmatine)2 种植物源单体对嗜水气单胞菌有显著抑制作用,且随黄藤素质量浓度降低,抑菌圈直径减少。此外,杜仲叶提取物绿原酸(chlorogenic acid)、板蓝根(*Isatis tinctoria* Linnaeus)多糖和五味子(*Schisandra chinensis*)多糖等多糖类均展现出惊人的抑菌活性,可以被进一步研究^[73]。

2.2 抗弧菌

弧菌(*Vibrio* sp.)属于革兰氏阴性菌,常在海洋和河口环境中被检测到,多为海水养殖对象的条件致病菌。Yilmaz 等^[74]统计分析表明弧菌病是最为常见的水

产动物细菌性疾病之一,其中,溶藻弧菌(*Vibrio alginolyticus*)、副溶血性弧菌(*Vibrio parahaemolyticus*)和哈维氏弧菌(*Vibrio harveyi*)是诱发弧菌病最常见的病原菌。Yilmaz 等^[74]还表示长期使用多种抗生素等化学合成药物对弧菌病进行防控带来了一些负面影响,如耐药菌、药物残留和环境污染等,这对人类健康产生了不良影响。同时,Abdel-Latif 等^[75]预计 2030 年全球人口总数将超过 90 亿,伴随着全球市场需求的不断增加水产养殖业得以迅速发展,然而在水产养殖业快速发展的过程中由弧菌诱发的病害问题频发,如在 2009 ~ 2018 年亚洲对虾养殖业每年因弧菌诱发的疾病损失高达 40 亿美元。因此,有必要快速寻找安全、有效和环保的抗生素替代品,以避免由弧菌造成的严重经济损失。

近年来,已有研究人员使用中草药对水产养殖过程中暴发的弧菌进行防治并取得了令人振奋的结果。Zhu 等^[76]在自己的论述中总结了当前使用中草药成功防治弧菌的案例,如肉桂(*Cinnamomum cassia* Presl)、金银花(*Lonicera japonica* Thunb.)、苦味叶下珠(*Phyllanthus amarus* Schumacher)和红葱(*Eleutherine plicata* Herb.)等中草药及其粗提物均可以通过提高对虾(*Litopenaeus vannamei*)体内酚氧化酶和白细胞的吞噬活性来增强其非特异性免疫,进而有效阻断弧菌的侵染,降低病虾死亡率^[76-79]。Ghosh 等^[59]在已发表的论著中也表明,中草药及其有效化合物可以发挥免疫刺激作用,同时其施用方法多样且简便。例如,中草药的根茎叶粉碎后可以直接施用,作为单一提取物或混合物施用,甚至还可以与其他免疫刺激剂共同使用等,中草药将是水产养殖过程中替代化学合成药物使用的最有潜力对象。

其他研究还发现,水葫芦(*Eichhornia crassipes*)和薄荷(*Mentha piperita*)的提取物分别可有效阻断哈维氏弧菌对鳊(*Channa punctata*)和花鲈(*Lates calcarifer*)的感染^[60-62]。以 1.0 g/kg 剂量的大黄(*Rheum officinale*)提取物饲喂石斑鱼(*Epinephelus coioides*)对副溶血弧菌有较好的抵抗能力^[80]。Ng'ambi 等^[81]研究发现,皂树中提取的皂苷(saponin)可以激活三疣梭子蟹(*Portunus trituberculatus*)的免疫反应,包括吞噬活性、血细胞总数、超氧化物歧化酶和酚氧化酶活性,增强三疣梭子蟹对溶藻弧菌的抵抗能力。Sivaram 等^[82]筛选得到了 10 种中草药的甲醇提取物可以有效抑制石斑鱼养殖过程中哈维氏弧菌的暴发,其中圣罗勒(*Ocimum sanctum*)

L.) 和肉豆蔻 (*Myristica fragrans*) 对该菌的抑制效果最佳。

2.3 抗链球菌

链球菌 (*Streptococcus* spp.) 是一种广泛存在于水产养殖系统中的条件致病菌, 暴发时可导致养殖对象的大规模死亡。罗非鱼饲料中添加阿萨姆茶 (*Camellia sinensis*)、黄芪 (*Astragalus membranaceus*)、大蒜 (*Allium sativum*)、蜂巢草 (*Leucas aspera*)、迷迭香 (*Rosmarinus officinalis*)、马兜铃 (*Aristolochia debilis*)、人参 (*Panax ginseng*) 和鸡血藤 (*Spatholobus suberectus*) 等中草药及其粗提物均可以提高其免疫力, 增强其对无乳链球菌 (*Streptococcus agalactiae*) 感染的抵抗。其中, 迷迭香作为一种抗菌和抗肿瘤的常用中草药, 可抑制罗非鱼体内无乳链球菌的增长并降低染病罗非鱼的死亡率^[53], 而兜铃、人参和鸡血藤的提取物对感染无乳链球菌的尼罗罗非鱼有显著治疗作用, 10 g/kg 剂量的川香菊 (*Chamaemelum nobile* L.) 就可降低罗非鱼感染无乳链球菌的发生概率^[61, 83-88]。同时, Verma 等^[89]研究发现银合欢 (*Leucaena leucocephala*) 的豆荚籽提取物对铜绿假单胞菌 (*Pseudomonas aeruginosa*)、哈维氏弧菌、鳃弧菌 (*Vibrio anguillarum*)、无乳链球菌和嗜水气单胞菌均有抑制作用, 在不影响胡子鲶 (*Clarias gariepinus*) 生长性能的情况下提高了其免疫水平。另一项研究表明, 在虹鳟饲料中添加的薄荷提取物具有抗致病性鲁氏耶尔森菌 (*Yersinia loghem*) 活性^[90]。同时, 饲料中添加生姜 (*Zingiber officinale*)、杜松 (*Juniperus excelsa*) 和胡荽 (*Coriandrum sativum*) 均可提高虹鳟对鲁氏耶尔森菌的抗性^[57, 91-92]。

2.4 抗其他细菌

研究发现, 防己科 (*Menispermaceae* Juss.) 种子的不同溶剂提取物对多种细菌均表现出显著的抑菌活性^[93]。另一项研究表明, 从中草药精油中提取的各种活性成分被证明对绝大多数细菌具有抗菌活性^[94-95]。例如, 从鼠尾草 (*Salvia officinalis*)、麝香草 (*Thymus vulgaris*)、薄荷和蓝桉树 (*Eucalyptus globulus*) 提取的混合精油对铜绿假单胞菌、大肠杆菌 (*Escherichia coli*) 和金黄色葡萄球菌 (*Staphylococcus aureus*) 具有协同作用^[96]。Hai^[94]也总结展示了三叶龙葵、穿心莲和补骨脂三种中草药的甲醇提取物可以有效阻断枯草芽孢杆菌、普通变形杆菌、伤寒沙门氏菌、铜绿假单胞菌、假单胞菌、弧菌、金黄色葡萄球菌和嗜水气单胞菌对对虾的侵染。膳食补充黄芩 (*Scutellaria baicalensis*) 可显著提

高条石鲷 (*Oplegnathus fasciatus*) 的免疫参数, 并有效降低感染爱德华菌 (*Edwardsiella tarda*) 后的死亡率^[97]。Kakoolaki 等^[58]研究发现, 膳食补充 200 mg/kg 山茶花 (*Camellia sinensis*) 提取物可提高鲮 (*Mugil cephalus*) 血液免疫指数和溶菌酶活性, 增强对美人鱼发光杆菌 (*Photobacterium damsela*) 的抗性。

3 中草药抗病毒活性

病毒性疾病的肆意暴发给水产养殖业带来了毁灭性打击, 严重束缚了水产养殖业的可持续发展, Zhang 等^[98]认为目前多数抗生素等化学药物均不能有效预防和治疗多种水产动物的病毒性疾病, 而疫苗是防治病毒性疾病暴发的有效方法, 但因其成本高、无法大规模使用限制了疫苗的发展。幸运的是大量中草药在水产动物中展现了非凡的抗病毒活性, 中草药毒副作用小、不易产生耐药性和安全等特点, 在鱼类病毒防治等方面备受关注。中草药及其活性分子的使用可有效降低农药、抗生素等化学合成药物的使用量, 并改善水产品的质量和品质。目前, 对水产养殖业造成严重危害的病毒主要有弹状病毒、虹彩病毒、呼肠孤病毒和白斑病毒等^[99], 利用中草药及其活性分子来防控各种病毒性疾病的暴发显得尤为重要。

3.1 抗弹状病毒

弹状病毒是一类引起鱼及其他水生动物大规模死亡的主要病原体之一。目前发现引起鱼类重要疾病的弹状病毒主要有五类: 鲤春病毒血症病毒 (*Pring viremia of carp virus*, SVCV)、梭子鱼苗弹状病毒 (*Pike fry rhabdovirus*, PFRV)、病毒性出血性败血症病毒 (*Viral hemorrhagic septicemia virus*, VHSV)、传染性造血器官坏死病毒 (*Infectious hematopoietic necrosis virus*, IHNV) 和大口黑鲈弹状病毒 (*Micropterus salmoides rhabdovirus*, MSRV)。研究发现, 黄芪多糖、连翘、金银花和白芍均能够对 MSRV 表现出良好的抗病毒作用, 其中黄芪多糖的效果最为显著^[100]。另外, 饲料中添加 0.01% 黄芪多糖可以改善斑马鱼的生长性能、肠道健康和抗病毒能力^[101]。作为补骨脂的主要成分之一, 补骨脂甲素对 SVCV 糖蛋白和核蛋白表达的半抑制浓度 (half maximal inhibitory concentration, IC_{50}) 分别为 0.46 mg/L 和 0.31 mg/L^[102]。浓度为 6 mg/kg 的柴胡皂苷 D 能够有效治疗感染 SVCV 的斑马鱼和鲤, 可使其存活率分别提高 36% 和 32%^[103]。Shen 等^[104]利用胖头鱼鳞上皮瘤

(epithelioma papulosum cyprini, EPC) 细胞研究了 12 种天然化合物和 7 种常用抗病毒药物的抗 SVCV 活性,发现 1.6 mg/L 的牛蒡子苷元对 SVCV 复制的抑制作用最高,对 SVCV 的最大抑制率 >90%,并阻断 SVCV 诱导的活性氧(ROS)生成和细胞凋亡。

棕榈酸作为油棕榈果实的主要成分,可降低体内和体外 SVCV 感染引起的死亡率^[105]。除此之外, Ren 等^[106]从香菇菌丝体中提取的一种新香菇多糖(LNT-I)经分离纯化后发现, LNT-1 在 MOI 分别为 0.05 和 0.10 时对 IHN 具有显著抗性,其抗病毒机制主要涉及直接灭活和抑制病毒复制。为了寻找更好的抗 IHN 药物,

Li 等^[107]利用 EPC 细胞研究了 32 种药用植物的抗 IHN 活性,发现夏枯草对 IHN 复制的抑制效果最佳,当使用浓度为 100 mg/L 时,抑制率达到 99.3%。也有研究发现,漆树树皮中分离得到的黄酮类化合物对鱼类 IHN 和 VHSV 表现出显著的抗性,其 EC₅₀ 分别为 5.0 μg/mL 和 3.6 μg/mL^[108]。Park 等^[109]将鸡冠花和萝卜提取物混合后进行抗 VHSV 活性分析,结果发现该混合物处理 EPC 细胞后可增强其对 VHSV 的抵抗能力。

表 3 中草药抗水生病毒活性

Table 2 The anti-aquatic virus activity of Chinese herbal medicine

中草药	活性物质	剂量	病毒原	物种	使用方式	参考文献
鸡冠花、萝卜	提取物	10 μg/mL, 167 ng/g	VHSV	EPC 细胞、比目鱼	浸泡/口服	[99]
	黄芪多糖	12.5 mg/mL	MSRV	草鱼卵巢细胞	浸泡	[100]
	黄芪多糖	0.01%	SVCV	斑马鱼	饲料添加	[101]
补骨脂	补骨脂甲素	5 mg/mL	SVCV	EPC 细胞	浸泡	[102]
柴胡	柴胡皂苷 D	6 mg/kg	SVCV	斑马鱼、鲤	腹腔注射	[103]
	牛蒡子苷元	1.6 mg/L	SVCV	EPC 细胞	浸泡	[104]
	棕榈酸	1 mmol/L	SVCV	斑马鱼、斑马鱼成纤维细胞样 ZF4 细胞	浸泡	[105]
香菇	香菇多糖	100 μg/mL	IHN	EPC 细胞	浸泡	[106]
夏枯草	熊果酸	100 mg/mL	IHN	虹鳟	注射	[107]
漆树	黄酮类化合物	10 μg/mL	IHN/VHSV	牙鲆脾脏细胞/鲑胚胎细胞	浸泡	[108]
没食子	没食子儿茶素没食子酸酯	20 μg/mL	GCRV	CIK 细胞	浸泡	[110]
远志	甲醇提取物 1、甲醇提取物 2	100 mg/L, 5 mg/L	GCRV	CIK 细胞	浸泡	[111]
厚朴	厚朴酚	1.5 μg/mL	GCRV	CIK 细胞	浸泡	[112]
槲皮	槲皮素	100 μmol/L	GCRV	CIK 细胞	浸泡	[113]
紫花地丁	水提取物	10 mg/mL	GIV	GS 细胞	浸泡	[114]
金银花	木犀草素	500 μg/mL	GIV	GS 细胞	浸泡	[115]
鳄嘴花	乙醇提取物	5 mg/mL	KHV	锦鲤	口服	[116]

3.2 抗呼肠孤病毒

草鱼出血病毒(Grass carp reovirus, GCRV)是水生动物呼肠病毒 C 型的代表性毒株,能够导致幼鱼出现极高的死亡率,造成不可估量的经济损失^[117]。在过去的几十年里,研究人员开发了一系列抗生素等化学药物去应对该病毒带来的危害,然而长期使用化学药物会导致药物残留和耐药菌等诸多负面影响^[118]。因此,为探寻安全有效的防治剂, Wang 等^[110]对没食子儿茶素和没食子酸酯的抗病毒活性进行了分析,发现二者

均以剂量依赖的方式抑制 GCRV 颗粒黏附到草鱼肾(Ctenopharyngodon idellus kidney, CIK)细胞表面,从而抑制草鱼呼肠病毒感染。另有研究表明,从远志中分离纯化得到的化合物通过调节草鱼肾细胞的免疫基因,以此提高其感染 GCRV 后的存活率^[111]。厚朴酚在体内可以有效抑制草鱼肾细胞中 GCRV 的复制,提高血清中超氧化物歧化酶和总抗氧化能力,同时能够增强草鱼肾细胞先天免疫相关基因的表达以增强其抵抗 GCRV 感染的先天免疫信号反应^[119]。还有研究发现,

植物来源的槲皮素以剂量依赖性的方式抑制草鱼呼肠孤病毒的复制,主要表现为降低子代病毒产量和提高鱼类存活率(表3)^[120]。

3.3 抗白斑综合征病毒

白斑综合征病毒(White spot syndrome virus, WSSV)是迄今对虾养殖业危害最大的一种病毒^[114]。为了保证对虾养殖业的健康发展,研究人员利用中草药的不同部位(如叶、花和根茎)和成分(如粗品、提取物和活性成分)进行抗病毒研究(表4)。目前,在中草药抗 WSSV 中的研究多集中于粗提物,如马尾藻中提取的粗岩藻胶^[115],杜氏藻提取物^[116],双尾马尾藻和重尾马尾藻的水提物^[121],紫齿龙、马尾鹿、堇孢草、黑水藓和旱莲的甲醇提取物^[122],半叶马尾藻粉的水提物^[123],江蓠的水提物^[124],角果木的水提物^[125],黄细心的乙醇提取物^[126]。类似的,马缨丹、苦味叶下珠、木橘、马尾藻、紫锥菊、毛钩藤、大花唐棣、番石榴、红凤菜、紫背草、狗牙根和栀子花的提取物也有良好的抗 WSSV 活性^[127-135]。但因上述中草药粗提物成分复杂、用量大、成本高等无法推广。

为了进一步分离和鉴定活性物质, Wongprasert 等^[136]利用核磁共振和红外光谱等技术从红海藻江蓠分离鉴定了硫酸半乳聚糖具有良好的抗 WSSV 活性。也有研究者从红海藻龙须菜中分离鉴定出的硫酸半乳聚糖以 WSSV 包膜蛋白为靶点,保护虾血细胞免受病毒感染^[137]。此外, Velmurugan 等^[138]经初步筛选, 曲浒苔乙酸乙酯提取物能有效抑制 WSSV 增殖,并通过硅胶柱层析进一步纯化得到不同成分。薄层色谱和气相色谱分析表明, FIII 馏分中含有抗病毒的酚类化合物为 2-(2-羟基苯氧基)-1-苯乙醇。在研究人员的不断努力下,越来越多的抗 WSSV 单体化合物被鉴定。绿茶中含量最丰富的儿茶素、没食子儿茶素和没食子酸酯能增强对虾的免疫力,提高其抗 WSSV 的能力^[139]。秦皮甲素在 100 $\mu\text{mol/L}$ 时能抑制对虾体内 WSSV 拷贝数超过 90%^[140]。类似地, 芍药苷在 100 $\mu\text{mol/L}$ 能提高感染 WSSV 对虾的存活率至 60%^[141]。此外, Huang 等^[142]报道了从栀子果实中提取的生物活性化合物京尼平具有潜在的抗 WSSV 活性。

表 4 中草药抗 WSSV 活性

Table 4 The anti-WSSV activity of Chinese herbal medicine

名称	活性物质	剂量	物种	参考文献
匍枝马尾藻	岩藻多糖	400 mg/kg	斑节对虾	[115]
杜氏藻	β -胡萝卜素	300 mg/kg	斑节对虾	[116]
双尾马尾藻和重尾马尾藻	水提物	750 mg/L	斑节对虾	[121]
紫齿龙、马尾鹿、堇孢草、黑水藓和旱莲	甲醇提取物	800 mg/kg	斑节对虾	[122]
半叶马尾藻粉	水提物	300 mg/L	凡纳滨对虾	[123]
江蓠	水提物	600 mg/L	凡纳滨对虾	[124]
角果木	水提物	500 mg/kg	斑节对虾	[125]
黄细心	乙醇提取物	10 mL/kg	斑节对虾	[126]
马缨丹和苦味叶下珠	水提物	150 mg/kg	斑节对虾	[127]
木橘	甲醇提取物	150 mg/kg	斑节对虾	[127]
马尾藻	岩藻多糖	400 mg/L	斑节对虾	[128]
紫锥菊和毛钩藤	水提物	4 g/kg	凡纳滨对虾	[129]
大花唐棣	乙酸乙酯和甲醇提取物	400 mg/kg	印度明对虾	[130]
番石榴	粉末	0.4%	斑节对虾	[131]
红凤菜	水提物	2 g/kg	凡纳滨对虾	[132]
紫背草	丙酮提取物	100 $\mu\text{g/mL}$	墨吉对虾	[133]
狗牙根	乙醇提取物	2%	凡纳滨对虾	[134]
栀子花	乙醇提取物	100 mg/kg	克氏原螯虾	[135]
红海藻江蓠	硫酸半乳聚糖	200 $\mu\text{g/mL}$	斑节对虾	[136]
红海藻龙须菜	硫酸半乳聚糖	1000 $\mu\text{g/mL}$	斑节对虾	[137]
曲浒苔	2-(2-羟基苯氧基)-1-苯乙醇	400 mg/kg	印度明对虾	[138]

3.4 抗其他病毒

石斑虹彩病毒(*Grouper iridovirus*, GIV)是一种重要的病原体,该病通常可在短时间内造成石斑鱼大量死亡,给石斑鱼养殖产业造成严重的经济损失^[143]。因此,为促进石斑鱼养殖的可持续绿色发展,开发抗石斑虹彩病毒的中草药及其活性成分极为重要。多项研究表明金银花和紫花地丁作为我国两种常用的药用植物具有抗病毒的功能,紫花地丁能够干扰 GIV 在宿主细胞中的结合、进入和复制过程,金银花也对 GIV 表现出良好的抗病毒活性,对石斑鱼脾脏(grouper spleen, GS)细胞中 GIV 复制的抑制率达到 90% 以上^[143-144]。锦鲤疱疹病毒(*Koi herpesvirus*, KHV)对普通鲤和锦鲤养殖场造成严重经济损失,至今仍没有理想的治疗手段。Haetrakul 等^[145]发现鳄嘴花的乙醇提取物具有抗鲤疱疹病毒感染的作用,在鲤疱疹病毒感染前和感染后的鱼中都显示出良好的抗病毒活性。

4 展 望

对水产病害的防控不仅要注重消除水产动物的各种安全隐患,而且还要避免药物对水环境的污染。当前中草药在水产养殖过程中的应用还存在有很大不足,特别是基础研究尚处于对中草药粗提物药效测定阶段,很少涉及中草药活性分子的药效、毒理、作用机制、代谢动力学和药残等方面的研究,这就导致生产上应用中草药很难在产品质量标准上建立相关的质量控制体系和保障水产品生产的安全。中草药符合当前水产养殖集约化、规模化生产的需要,便于对水产动物进行群体防治。同时,中草药还可以解决水产动物因使用化学药物而导致的药物残留问题,完全符合我国发展无公害养殖和绿色水产品的疾病防控方针。

中草药的研究是一个巨大的领域,至今仍存在许多研究空白。例如,在研究药理活性的同时,药用植物的毒理学和安全性有待进一步研究;一些配伍草药使用具有增效作用,效果远好于单一中草药的使用,但研究仍相对匮乏;目前中草药对水产动物免疫系统作用机制的认识还很有限,需要进一步研究,特别是多活性成分与宿主相互作用的分子机制。因此,随着研究不断深入,中草药的活性成分将得以明确,其作用机制将更加清晰。利用中草药活性分子作为前导化合物进行新药创制,是保障水产品安全 and 环境安全的有效方式,也是创制无公害绿色渔药的理论基础。

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Research Progress of Medicinal Plant Resources in Aquatic Animal Diseases Control

HU Yang^{1,2} ZHANG Xu^{1,2} WANG Huan^{1,2} SHAN Li-peng^{1,2} LIU Lei^{1,2} CHEN Jiong^{1,2}

(1 State Key Laboratory for Managing Biotic and Chemical Threats to the Quality and Safety of AgroProducts, Ningbo University, Ningbo 315211, China)

(2 School of Marine Sciences, Ningbo University, Ningbo 315832, China)

(3 Wuxi Tianxiangju Biotechnology Research Institute Co., LTD, Wuxi 214200, China)

Abstract With the continuous improvement of living standards, people's demand for aquatic products is increasing day by day, and the rapid development of the industry has become one of the fastest growing food production sectors worldwide. However, various diseases induced by parasites, bacteria and viruses have caused huge economic losses to aquaculture industry, which seriously restrict the rapid and stable development of the industry. As a traditional means of control, synthetic drugs such as antibiotics are often used in aquaculture processes. The abuse of a large number of chemosynthetic drugs induces drug residues, drug-resistant bacteria and other environmental pollution problems, endangering human health. Therefore, Chinese herbal medicine with a variety of effective active ingredients has become the research object for exploring new means of prevention and control of aquatic disease outbreak due to its natural, safe and small side effects. At present, Chinese herbal medicine is often used to regulate the immunity of aquatic animals, growth rate and prevent disease outbreaks. At the same time, it can also be used to improve the aquaculture environment and reduce the stress of environmental factors on aquatic animals. However, current studies mainly focus on obtaining compound active ingredients for disease outbreak prevention and control from Chinese herbal medicine, which are unstable in efficacy and unclear in active ingredients, and cannot meet the production needs of in-depth exploration of efficient, cheap and stable prevention and control agents. This paper discusses the application and mechanism of Chinese herbal medicine in prevention and control of aquatic animal disease outbreak, and reveals the insufficiency of the mechanism research on active molecules of Chinese herbal medicine. In conclusion, this paper highlights the potential of Chinese herbal medicine to be used as a more environmentally friendly and effective means of disease control and prevention in aquaculture, and the in-depth study of its resistance mechanism is particularly important.

Keywords Chinese herbal medicine Active ingredients Antibiotics Immunostimulants Aquatic diseases