大田软海绵酸的毒性、检测及应用的研究进展

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摘　要：大田软海绵酸（Okadaic Acid，OA）属于腹泻性贝毒（Diarrhetic shellfish poisons，DSP）的 1 种，具有分布广泛、危害大等特点。它可以引起人体的腹泻、呕吐等症状，除此之外，越来越多的研究表明 OA 具有多种毒性，包括细胞毒性、神经毒性、胚胎毒性、肝毒性等。其致毒机理多与其可以特异性抑制几种丝氨酸 / 苏氨酸蛋白磷酸酶有关。基于 OA 的这些危害，对 OA 进行快速、灵敏的检测显得尤为重要，目前应用最多的检测方法有液相色谱 - 串联质谱法、高效液相色谱法、生物传感器法、酶联免疫吸附试验、蛋白磷酸酶抑制试验等。但这些检测方法都有自己的优缺点，需要进一步完善。虽然 OA 属于海洋生物毒素的 1 种，但其在生物医学领域也有很好的应用，在治疗阿尔茨海默病、肿瘤等疾病的研究中发挥着重要作用。本文对近年来 OA 毒性的研究，OA 的检测方法以及 OA 在科研工作中的应用进行综述，为该毒素更深层次的研究提供参考。

关键词：大田软海绵酸（OA）；毒性；海洋生物毒素；阿尔茨海默病
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Research progress on the toxicity, detection and application of okada acid

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Abstract: Okadaic acid (OA) belongs to a type of diarrhetic shellfish poisons, which is widely distributed and harmful. It can cause diarrhea, vomiting and other symptoms in humans. In addition, a growing number of studies show that OA has a variety of toxicity, including cytotoxic, neurotoxic, embryotoxic, hepatotoxic, and so on. The mechanism of its toxicity is mostly related to its ability to specifically inhibit several serine/threonine protein phosphatases. Based on these hazards of OA, the rapid and sensitive detection of OA is particularly important. The most commonly used assays are Liquid chromatography-tandem mass spectrometry, high performance liquid chromatography, biosensor method, enzyme-linked immunosorbent assay, protein phosphatase inhibition tests, etc. However, these assays have their own advantages and disadvantages and need further improvement. Although OA is a kind of marine biotoxin, it also has a good application in the field of biomedicine and plays an important role in the research of Alzheimer's disease, cancer and other diseases. In this paper, we reviewed the recent studies on OA toxicity, the detection methods of OA and the application of OA in scientific research, and provided an overview of the toxicity of this toxin and deeper research provides references.

Key words: Okadaic acid (OA); toxicity; marine biotoxin; Alzheimer's disease

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大田软海绵酸（Okadaic Acid，OA）是一类亲脂性聚醚类化合物，属于腹泻性贝毒（Diarrhetic shellfish poisons，DSP）的 1 种，主要是由利玛原甲藻产生 [1]，这些藻类会被一些贝类或鱼类食用，之后在其体内积累和转化 [2]。OA 的特性不会因烹饪或冷冻而改变，也不会改变被污染有机体的味道，因此人们很难察觉到 OA 的存在，容易被人类误食而导致食物中毒 [3-4]，使人产生腹泻、恶心、呕吐、腹痛和发冷等症状，并且 OA 对人体造成这些中毒现象的最低不良反应水平在 1.0~1.6 μg/kg 体质量 [5]。OA 在全球的分布非常广，甚至在亚北极和北极水域都有关于 OA 中毒事件的报道 [6]。OA 主要作用于丝氨酸 / 苏氨酸蛋白磷酸酶（serine/threonine protein phosphatases）PP2A、PP5、PP1、PP2B，并且对这些蛋白磷酸酶的抑制程度是依序递减的 [7-9]。OA 具有多种毒性，除急性毒性外还具有细胞毒性 [10]、遗传毒性 [11]、胚胎毒性 [12]、肝毒性 [13]、免疫毒性 [14] 以及神经毒性 [15]。

近年来 OA 中毒事件的发生愈发频繁，OA 的检测技术也在迅速发展。主要包括：小鼠生物测定法（mouse bioassay，MBA）[16]、液相色谱 - 质谱（LC-MS）[17]、高效液相色谱（HPLC）[18]、酶联免疫吸附试验（ELISA）[19]、蛋白质磷酸酶抑制分析（Protein phosphatase inhibition assays，PPIA）[20]、生物传感器 [21] 等方法。这些方法各有利弊，随着研究的深入在被不断改进。建立快速、准确、灵敏的 OA 检测方法是非常必要的。

随着对 OA 的深入研究，其在生物医学领域的作用也逐渐凸显，其最主要的应用就是构建阿尔茨海默病（Alzheimer disease，AD）的病理模型。阿尔茨海默病是当今社会比较严重的疾病之一，目前为止，还没有合理的治疗手段和有效的药物可以治愈阿尔茨海默病。所以需要构建合理的 AD 模型对阿尔茨海默病进行更深入全面的研究。而 OA 为 AD 模型的建立提供了条件，是研究阿尔茨海默病神经退变和再生调节机制的工具 [22]。除了阿尔茨海默病，OA 对肿瘤的功效研究也在逐渐深入，作为蛋白磷酸酶的强效抑制剂，OA 被看作是肿瘤促进因子 [23]，但也有关于 OA 抑制肿瘤细胞的研究报道 [24-25]，关于这类问题，还需要进一步进行实验验证。所以还需要更加深入全面地去研究这种毒素，进一步开发 OA 在生物医疗领域的价值。

1 OA 的毒性

1.1 急性毒性

OA 是蛋白磷酸酶 PP2A 的强效抑制剂，可导致人体腹泻，但具体机制尚不清楚。在动物实验中，OA 会导致胃肠上皮损伤和胃肠道积液，口服 OA 还导致小鼠胃水肿和黏膜糜烂，并伴有黏膜下层的急性炎症，小鼠肠道绒毛结构塌陷，微绒毛脱落 [26]。在高剂量时，会导致死亡 [27]，其口服致死剂量是腹腔注射的 2~10 倍 [28]。OA 在小鼠肠道的毒性是复杂多样的，除蛋白磷酸酶外，还有其他多种蛋白质参与了腹泻过程。绒毛蛋白 Villin-1 和核不均一核糖核蛋白 F 可能是引起小鼠小肠腹泻的关键蛋白 [26]。在 OA 对斑马鱼的急性毒性实验中，高剂量 OA 不仅通过抑制 PP1 和 PP2A，而且通过调节关键细胞防御系统如 ABC 转运蛋白和热休克蛋白的表达对斑马鱼的肝脏造成严重的损伤 [29]。

早在 1990 年，Cohen 等 [30] 就提出 OA 导致的腹泻可能和其抑制蛋白磷酸酶的特性有关，但并没有提供有效的证明。由于其他有效的磷酸酶抑制剂并没有显示出腹泻作用，因此腹泻与蛋白磷酸酶抑制之间的联系尚未确定 [31]。目前关于 OA 的急性毒性又有新的见解，即 OA 不直接刺激肠道分泌，而是增加肠上皮细胞的细胞旁通透性，这种变化是 OA 引起腹泻的最有可能的原因 [32]。除此之外 Departamento 提出 OA 通过影响神经肽 Y 的分泌导致腹泻的发生 [33]。

1.2 细胞毒性

OA 可诱导人骨肉瘤 MG63 细胞 [34-35]、结肠癌 Caco-2 细胞和 HT29-MTX 细胞 [36] 等细胞的凋亡。OA 通过线粒体介导的 Caspase 途径来刺激机体产生活性氧（Reactive Oxygen Species，ROS）、激活 P38 丝裂原活化蛋白激酶和 c-Jun 氨基末端激酶 3 来诱导细胞死亡 [37]。在 OA 诱导 MG63 细胞凋亡过程中，还有双链 RNA 依赖性蛋白激酶、核转录因子 -κB 的参与 [34]。除此之外，OA 可以破坏细胞骨架，刺激细胞运动，使粘着斑失稳 [38]，也可以激活一般的细胞信号通路，导致皮质肌动蛋白细胞骨架的破坏和细胞脱落 [39]。并且 OA 可以通过改变细胞骨架结构，引起跨膜电阻降低进

而影响细胞通透性 [40]。OA 还可以影响细胞周期，在白细胞和神经细胞中导致细胞周期中断 [41]，OA 对细胞周期的影响不仅具有浓度依赖性，不同的细胞对 OA 的敏感程度也不尽相同 [42-44]。

1.3　神经毒性

OA 可以引起严重的记忆障碍，其关键因素是 OA 造成的线粒体功能的损害，以及参与学习记忆的受体亚单位基因的改变 [45-47]。OA 还会导致海马细胞 [48]、大鼠肾上腺嗜铬细胞瘤（PC12）细胞等神经细胞的损伤和丢失 [46]，影响神经细胞的细胞周期 [11]，但不同的神经细胞对 OA 的敏感程度是不同的 [49]。除此之外，OA 还会影响海马神经递质的活性 [50]。Tau 蛋白是最丰富的微管相关蛋白，OA 可影响蛋白磷酸酶的活性从而引起 Tau 过度磷酸化，并从微管解离进而聚集成不溶性神经原纤维缠结（Neurofibrillary tangles，NFTs）积聚在胞体中 [51]，这也是阿尔茨海默病的主要病理学特征 [52]。

1.4　肝毒性

肝脏是人体的解毒器官，肝脏中可能存在不同的 OA 代谢机制。虽然肝脏可以保护机体免受低剂量 OA 的侵害，但 OA 同样会对肝脏造成一定的伤害 [53]。在 OA 感染小鼠实验中，组织病理学检查显示肝组织内有坏死灶和脂质空泡 [54]。OA 对肝癌 HepG2 细胞也有细胞毒作用 [13]。OA 和虾夷扇贝毒素（yessotoxins，YTXs）联合暴露比单独暴露有更强的肝毒性 [55]。Ikema 等 [56] 认为 OA 可能是肝细胞特异性摄取转运蛋白 1B1/B3 的底物，可能与不明原因的肝功能衰竭和肝癌有关。

1.5　免疫毒性

免疫细胞是研究海洋毒素免疫调节潜能的相关靶点，因为免疫系统已被报道为海洋藻毒素的靶标之一。OA 可以使小鼠 T 淋巴细胞株 EL-4 细胞受体复合物下调，从而影响 EL-4 细胞活性 [57]，且呈时间和浓度依赖性，这与 OA 对蛋白磷酸酶的抑制有关 [58]。巨噬细胞是激活炎症反应的主要细胞，亚致死剂量的 OA 能刺激炎症因子的分泌 [59]。除了哺乳动物，OA 对软体动物和节肢动物同样有免疫毒性，暴露于 OA 的海湾扇贝其免疫系统功能遭到破坏，增加了氧应激，其体内的新陈代谢也被扰乱 [60]。受 OA 影响的贻贝，血液免疫学参数血细胞发生很大的变化 [61]。同样 OA 可以影响利马对虾的细胞周期调控和免疫系统相关基因的 mRNA 调控表达 [62]。

1.6　胚胎毒性和遗传毒性

OA 具有胚胎毒性，OA 可通过诱导过多活性氧 ROS 的生成，干扰发育中的鸡胚胎的血管生成 [63]。一定浓度的 OA 使黑鲷鱼卵的死亡率和孵出仔鱼的畸形率升高，但对孵化率的影响较弱 [64]。OA 还会导致长鳍黄尾鱼的卵有高死亡率 [65]。在哺乳动物中，OA 可以影响小鼠胚胎细胞的分化过程 [66]。OA 还具有遗传毒性，OA 对遗传物质具有断裂效应，最显著的表现是 DNA 断裂和 DNA 修复机制的改变 [67]。同样，OA 对不同类型细胞的遗传物质的影响程度也是不同的 [24,68]。OA 还会导致重要的染色体损伤和其他可能导致严重病理（包括肿瘤）的遗传损伤 [69]。不仅是在动物体中，在植物体中 OA 同样可以使 DNA 断裂，引起前期细胞周期阻滞，导致玉米幼苗生长受到抑制 [70]。

2　检测

2.1　生物检测

OA 的生物检测法中应用最广泛的是小鼠生物检测法（MBA）。然而由于小鼠个体之间的差异性比较大，此方法重复性、灵敏性都不太高，不同品系的小鼠对 OA 的易感性可能存在显著差异 [16]，甚至不同性别的小鼠也存在显著差异 [71]。正因为此方法暴露出的缺点越来越多，并且还涉及到伦理问题，许多国家已不再使用 MBA 法。Coates 等 [72] 提出利用蜡蛾幼虫 *Galleria mellonella* 来代替啮齿动物，这即不违背伦理也节约经费，并且其检测结果与啮齿动物模型发表的数据大致相符。

除了动物个体，体外实验也可用来检测 OA。小鼠神经元细胞（Neuro-2a）生物测定法被认为是最有前途的基于细胞的体外生物测定法之一，Neuro-2a 细胞对所有化合物均表现出良好的敏感性 [73]。除此之外，人肝脏细胞（HepG2）和 Caco-2 细胞也被用于检测 OA 的研究 [74]。

2.2　基于色谱法的检测

液相色谱 - 串联质谱法（LC-MS/MS）是欧洲检测 OA 的官方分析方法 [75]，具有操作简单、灵敏度高的特点。但在操作之前必须要对检测样品进行纯化 [71]。人们在此方法基础上进行了改进，Chen 等 [76] 建立了 1 种免疫磁珠液相色谱 - 串联质谱法测定贝类中 OA 的方法，报道的检测和定量

限分别为 3 和 10 μg/kg。Fang 等 [77] 建立了 1 种线湍流色谱与 LC-MS/MS 相结合的新方法。Yan 等 [78] 通过免疫亲和色谱与 LC-MS/MS 联用测定 OA，具有基体干扰小、灵敏度较高的特点。除此之外，液相色谱 - 高分辨质谱（LC-HRMS）这种高通量方法已经被成功验证，符合欧盟立法的要求，并已作为常规方法在公共卫生实验室实施 [79]。

高效液相色谱同样是常用的方法，具有灵敏度高、准确度高、校正方便、适用范围广、所需样品量小等特点。但不足之处是不能同时检测大量样品，毒物标准产品昂贵，预处理要求高，设备昂贵复杂，需要操作人员有较高的素质 [18]。Chen 等 [80] 通过制备磁性氮掺杂碳纳米管笼来萃取水中 OA，并用高效液相色谱法来检测样品中的 OA。高效液相色谱 - 串联质谱（HPLC-MS/MS）的方法也可测定 OA，通过对该方法的改进，回收率有所提高 [81]。Bosch 等 [82] 在固 - 液超声辅助萃取和固相萃取的基础上，采用高效液相色谱 - 高分辨质谱联用的方法对 OA 检测同样有不错的效果。超高效液相色谱也可用于 OA 检测，Xu 等 [83] 在用超高效液相色谱 - 串联质谱（UPLC-MS/MS）分析亲脂性海洋生物毒素实验中，采用磁性固相萃取作为 1 种降低基质效应的方法，检测效果有很大优化。验证后的 QuEChERS（quick，easy，cheap，effective，rugged and safe） 与 UPLC-MS/MS 联用方法，被成功地用于新鲜和加工贝类样品中亲脂性海洋毒素的测定 [84]。

2.3 基于传感器的检测

2.3.1 生物传感器

不断发展的生物传感器是非常有前景的，它有可能被开发出易用、经济有效、快速和准确的海洋生物毒素检测方法 [21]。Li 等 [85] 提出了 1 种基于心肌细胞的双功能生物传感器，通过监测心肌细胞的活力和电生理来检测 OA 毒素，表明基于心肌细胞的双功能复合生物传感器将成为贝类毒素检测的 1 种很有前途的实用工具。Wang 等 [86] 以人支气管上皮细胞株为敏感元件，制作了检测 OA 细胞毒性的高灵敏度细胞阻抗生物传感器。Pan 等 [87] 构建的电生物传感器能有效检测 OA，表明生物传感器有很大的潜力替代传统的分析和免疫学方法。根据 OA 抑制 PP2A 活性的原理，Sun 等 [88] 建立了检测 OA 的固定化酶生物传感器，并对时间、pH、温度等参数进行了优化。电化学生物传感器具有省时、简便、灵敏度高、检测限低、成本低等特点，为准确分析海洋毒素提供了 1 种新技术 [89]。Eissa 等 [90] 将亲和力最高的适配子用于制备检测 OA 的电化学生物传感器。

2.3.2 免疫传感器

免疫传感器同样拥有不错的应用前景，用于 OA 检测的电化学免疫传感器验证了免疫传感器在实际贻贝样品检测中有很好的应用 [91]。新型石墨烯伏安型免疫传感器被用于 OA 的检测，其在 PBS 缓冲液中的检出限为 19 ng/L[90]。Pan 等 [92] 研制了 1 种基于磁珠和量子点的新型高灵敏荧光免疫传感器，可用于 OA 的检测。Zou 等 [93] 研制了 1 种用 Love 波传感器结合免疫金染色法测定 OA 的免疫传感器。制备免疫传感器后，引入金纳米颗粒放大相位信号，采用间接竞争免疫分析的方法检测 OA。基于石墨烯场效应晶体管的免疫传感器可用于实际海水样品中 OA 的检测，并可推广到其他海洋环境污染毒素或制剂的检测 [94]。Pan 等 [95] 基于荧光免疫传感器和流式细胞技术发展了 1 种新的有效的 OA 检测方法，用藻红蛋白染料标记的免疫球蛋白 G 作为二抗进行荧光检测，采用便携式流式细胞仪进行原位荧光定量来检测 OA。

2.4 酶联免疫法

酶联免疫吸附试验（ELISA）是最常用的检测方法。ELISA 试剂盒可用于 OA 的筛查 [19]，此方法也一直被完善。Pang 等 [96] 建立了 1 种基于环氧功能化磁珠检测 OA 的快速竞争性 ELISA 方法，其检测 OA 水平在 0.35~25.0 μg/L 范围内具有良好的线性关系。Zhang 等 [97] 建立了毛细管电泳酶联免疫分析和电化学检测系统。Wang 等 [98] 建立了贻贝肌肉中 OA 的间接竞争酶联免疫吸附化学发光法。Wang 等 [99] 通过骨髓瘤（Sp2/0）细胞与免疫小鼠脾细胞的细胞融合，筛选到 1 株单克隆抗体，命名为 10E8，以该单克隆抗体为基础建立的 ELISA 和胶体金免疫法可用于 OA 的检测。

2.5 蛋白磷酸酶抑制法

蛋白磷酸酶抑制法（PPIA）是 1 种敏感、可靠的检测方法。OA 对 PP2A 有很强的抑制作用，因此可以通过测量 OA 对酶的抑制程度来检测 OA。Sun 等 [20] 对加酶量、反应条件等参数进行了优化，使其有更好的准确性和重复性。Chen 等 [100]

建立了以对硝基苯磷酸（p-NPP）为底物的蛋白磷酸酶抑制比色法来检测 OA。Eberhart 等 [101] 将 ELISA 与 PPIA 相比较，认为在华盛顿州贝类毒素检测中 PPIA 更加可靠。

2.6　其他方法

胶体金免疫层析技术是 1 种新型快速检测方法，Ling 等 [102] 用胶体金免疫法同时检测海鲜样品中的 OA 和河豚毒素。基于胶体金 - 单克隆抗体（monoclonal antibody，McAb）偶联物的侧向流免疫层析试纸，可用于现场快速检测贝类中 OA[103]。适配体的发展也可用于 OA 检测，基于滚环扩增（rolling circle amplification，RCA）的 OA 竞争性荧光团连接适配体分析法有较高的特异性和重复性 [104]。随着科学的进步，各个技术之间相互交集，基因工程技术 [105]、人工智能技术 [106]、固相吸附毒素跟踪技术 [107]、纳米颗粒的发光技术 [108]、定量核磁共振 [109]、发光共振能量转移概念 [110]、盐析辅助液液萃取技术 [111] 等都可被用来建立检测 OA 的新方法。

3　应用 - 诱导 AD 模型

OA 虽然是 1 种海洋生物毒素，但近年来其在生物医学领域的作用也逐渐被发掘出来，比如 OA 通过抑制 PP1 和 PP2A，对 Hippo 信号通路的核心组成部分 MST1/2 进行负向调节。因此，OA 已被广泛用于实验激活 Hippo 信号通路 [112]。OA 在大鼠星形胶质细胞培养中也显示出促进神经生长因子（nerve growth factor，NGF）的分泌等活性，显示出良好的保健应用前景 [113]。OA 还可以通过促进脂肪细胞中几种蛋白质的磷酸化来刺激脂肪分解 [114]。依靠 OA 的促凋亡作用，可以更好地诱导唐氏综合征（down syndrome，DS）成纤维细胞的凋亡 [115]。在植物中，OA 抑制了胞质外体途径的放射性分子摄取及其在细胞间的分布，被用于研究蔗糖的代谢和运输 [116]。但最主要的还是 OA 在 AD 中的研究。

AD 是影响世界老年人口的主要神经退行性疾病，其特征是记忆力和认知能力的下降，语言退化，视觉和运动协调缺陷 [117]。为了更好对 AD 进行研究，首先需要建立合理的 AD 模型，依据 OA 的神经毒性，其可以作为诱导 AD 模型的有力工具。

OA 诱导的 AD 模型一般可分为体外模型和动物模型。对于体外模型，通常会选择 PC12 细胞 [118]、NG108-15 细胞 [119]、SH-SY5Y 细胞 [120]、HT22 细胞甚至是组织 [121] 经过不同浓度的 OA 以及不同时间的诱导来构建体外模型。在动物模型水平上，小鼠或大鼠脑内注射 OA 会导致 Tau 蛋白过度磷酸化，NFTs 的形成和淀粉样蛋白的沉积，并伴随着记忆丧失和神经变性。因此，通过脑内注射 OA 可提供 AD 模型。除此之外，通常还会选择鼻腔给药的形式构建 AD 动物模型 [122]。体外模型和动物模型有一定的差别，比如，经口服 OA 处理的大鼠海马体切片葡萄糖摄取减少，而在体外暴露于 OA 的海马体切片没有任何相关的葡萄糖摄取活性变化 [123]。目前这类动物模型还有一些缺陷，比如缺乏 AD 中观察到的淀粉样蛋白病理。Kaushal 等 [124-125] 根据有中风病史且发生过缺氧情况的患者更容易患上阿尔茨海默病这一结论，结合 OA 诱导和缺氧诱导 2 种不同的方法，建立了 1 种 AD 大鼠模型，模拟了 AD 中所观察到的大部分神经病理、神经行为和神经化学变化，这种散发性 AD 类型的大鼠，为新的治疗策略提供了有效工具。

尽管利用啮齿类动物模型研究 AD 已有很长时间，但大鼠 AD 模型和人体 AD 还是有一定区别的，比如在人类阿尔茨海默病患者中，胶质细胞表型与大鼠模型的明显不同 [126]。因此，有必要建立补充模型和改进现有模型来辅助 AD 的治疗。Koehler 等 [127] 通过对斑马鱼施用 OA 建立了 AD 模型，并证明了 OA 诱导的 AD 斑马鱼模型在药物发现过程中有不错的效果。但目前诱导斑马鱼 AD 模型的药理方法还不够成熟，同样不能代表该疾病的所有特征。所以对于 AD 来说，虽然现在存在很多模型，但没有 1 个现有的模型能概括 AD 的所有特征。AD 的发病机制多种多样，很难在动物模型中对 AD 进行概括 [127]。所以对于 OA 诱导的 AD 模型还需要进一步研究和完善。

4　展望

OA 作为世界上分布最广的海洋生物毒素之一 [5]，其潜在研究价值是非常巨大的，目前对 OA 的研究还不够充足。首先，虽然目前已经做了很多细胞水平和动物水平的 OA 毒理实验，但不同水平之间还没有做到能够相互联系地去探讨 OA

的毒性，即还没有一套系统的模型能够客观化、标准化地对 OA 毒性进行全面评价，只有把最基础的研究夯实才能更顺利地进行更深层次的研究。其次，目前对 OA 的检测方法有很多，但也各有利弊，还需要建立更加快速、精准、简便、低成本的检测方法来保障人们的身体健康。并且由于海洋环境复杂，还要考虑 OA 和其他因素的协同作用，比如要考虑到 OA 与某些真菌毒素的协同作用来完善监管方法 [128]。再次，OA 致病机理非常复杂，目前对该毒素还没有很好的解毒手段，需要进一步对 OA 的致病机理进行研究，找到对 OA 引起的症状的防护或者治疗方法。最后，虽然 OA 是 1 种毒素，并且会对人体造成一定危害，但越来越多的研究表明它可以成为生命科学研究中的有力工具。OA 不仅在 AD 和肿瘤的研究中发挥了作用，在治疗糖尿病、癫痫和艾滋病中的作用也应该得到重视 [48,129-130]。所以人们不仅要找到 OA 的解毒方法，还要更深刻全面地了解它，开发它的潜在价值，使其成为科研或者其他领域的有力工具。

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