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东莨菪内酯的生物活性研究进展

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摘 要: 本文就近年来国内外对东莨菪内酯这一天然活性化合物的生物活性研究进行了综述。东莨菪内酯是植物体内的一种重要的酚类植物抗毒素,属于香豆素类化合物,在临床上具有抗肿瘤、降血压血脂、解痉等多种药理活性,同时还具有良好的杀虫、抗菌杀菌、杀螨、化感等农用生物活性。但目前其研究主要集中在药理活性方面,药动力学方面的研究报道相对较少,同时其杀虫杀螨作用机理也有待进一步研究。

关键词: 东莨菪内酯; 生物活性; 进展

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Advances in Studies on Biological Activities of Scopoletin

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Abstract: The biological activities of scopoletin were reviewed in this paper. Scopoletin is an important coumarin phytoalexin in plants, which exhibited a lot of pharmacological activities in medicine including antitumor, hypolipidemic, spasmolysis and agricultural biological activity with insecticidal, antibacterial sterilization, acaricidal, allelopathy and so on. Whereas, its research mainly concentrated in pharmacological activities, the medicine dynamics research is rarely reported, and its insecticidal and acaricidal mechanism should be carried out in the future work.

Key words: scopoletin; biological activities; advances

东莨菪内酯(scopoletin)又称东莨菪素、莨菪亭、莨菪酚,是一种重要的香豆素类化合物,其化学名称为7-羟基-6-甲氧基香豆素(化学结构式见图1)。其在氯仿或乙酸中的结晶体为浅黄色或白色针状,熔点为205~207 ℃[1],易溶于氯仿、热乙醇、热乙酸、N-甲基吡咯烷酮、二甲基亚砜等高极性有机溶剂中,微溶于水,其溶液在365 nm的紫外光下显示蓝色荧光[2]。由于东莨菪内酯的良好杀螨活性,全国农药标准化技术委员会于2012年正式将其通用名称定为"甲氧香螨酯"(农标字2012第005号)。

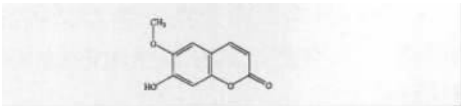

图1 东莨菪内酯化学结构式

Fig. 1 Chemical structural formula of scopoletin

植物受到外界生物及非生物不良环境的刺激后,会产生一些次生代谢物抵御干扰。东莨菪内酯是植物体内的一种重要的酚类植物抗毒素,当植物受到病原菌、害虫或其他植物及环境变化等因素的干扰时,能够大量合成和累积东莨菪内酯,用于防御不良因素的干扰。东莨菪内酯存在于多个科的110000余种[3,4]植物中,主要分布于菊科(Asteraceae)、旋花科(Convolvulaceae)、十字花科(Cruciferae)、杜鹃花科(Ericaceae)、大戟科(Euphorbiaceae)、豆科(Fabaceae)、楝科(Meliaceae)、桑科(Moraceae)、茜草科(Rubiaceae)、芸香科(Rutaceae)、茄科(Solanaceae)、伞形科(Umbelliferae)等多个科的多种植物中,其中在黄花蒿(*Artemisia annua*)茎叶、茵陈蒿(*A. capillaris*)叶、丁公藤(*Erycibe obtusifolia*)茎、拟南芥(*Arabidopsis thaliana*)全株、诺丽(*Morinda citrifolia*)果实、苦楝(*Melia azedarach*)种子等多种植物中的含量相对较高。因此,东莨菪内酯也被赋予了多种药理活性以及杀虫、抗菌杀菌、杀螨、化感等农用生物活性。现就近年来国内外对东莨菪内酯这一天然活性化合物的生物活性研究进展进行综述。

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1 东莨菪内酯的药理活性及药动学研究

1.1 抗肿瘤活性

东莨菪内酯的抗肿瘤活性一直备受医学界的关注,狗骨柴(*Tricalysia dubia*)[5]、红果小芸木(*Micromelum minutum*)[6]、黄花蒿[7]等植物中具有较强细胞毒素活性的物质即为东莨菪内酯。目前报道较多的是东莨菪内酯对前列腺癌 PC3 细胞以及 T 淋巴瘤细胞的抗肿瘤活性[8,9]。东莨菪内酯能阻断肿瘤细胞血管内皮生长因子受体-2 的自身磷酸化及下游信号通路,抑制纤维母细胞生长因子(FGF-2)及细胞外信号调节激酶(ERK1/2)的活性,从而使肿瘤细胞血管生成受阻,抑制原发肿瘤细胞的生长和转移,并诱导肿瘤细胞凋亡[10]。研究表明,东莨菪内酯的抗肿瘤活性位点主要为 C-6 的酚羟基和 C-7 的甲氧基,对其 C-6 的酚羟基引入烷氧基后,其衍生物对乳腺癌细胞 MCF-7 和 MDA-MB231 及结肠癌 HT-29 的抑制活性比东莨菪内酯提高 10 余倍[11,12]。此外,其 4-烷氧基衍生物也具有显著地细胞毒素活性[13]。目前,Khuda-Bukhsh 等[14]研制了东莨菪内酯聚合物纳米胶囊,可增强人体黑色素肿瘤细胞 A375 对东莨菪内酯的吸收和利用,显著提高其抗肿瘤活性。

1.2 降血压、血脂活性

东莨菪内酯能够调节 Fe^{3+} 与活性氧(ROS)螯合,减弱及清除 ROS 产生,从而表现出调节心血管疾病的作用[15]。高甘油三酯血症是重要的心血管疾病,其中脂蛋白脂酶(LPL)是重要的致病因素,而东莨菪内酯具有提高 LPL 活性的作用,从而表现出治疗高甘油三酯血症的作用,其机制是在通过增加 LPL 的 mRNA 的合成,从而增加了 LPL[16]。此外,在心血管疾病方面,东莨菪内酯具有诱导人体骨髓性白血病细胞的凋亡,并激活细胞核因子 κB 及抗血小板凝聚的作用[17]。Olivera 等[18]报道,东莨菪内酯具有抑制大鼠离体主动脉环收缩的作用,很可能缓解动脉粥样硬化所导致的心肌缺血。

1.3 解痉活性

Ca^{2+} 在痉挛中具有重要的作用,东莨菪内酯可调控 Ca^{2+} 平衡而具有解痉挛活性[19]。0.1 μM 东莨菪内酯能显著激活红细胞膜的 Ca^{2+}-ATP 酶和 Mg^{2+}-ATP 酶,0.25 μM 东莨菪内酯能显著激活 Na^+-K^+-ATP 酶,可有效调节机体的离子平衡[20],且对 GH_4C_1 细胞诱导的 Ca^{2+} 上调抑制率为 15.2%,即东莨菪内酯具有调节 Ca^{2+} 平衡的作用[21]。Oliveira 等[22]发现东莨菪内酯能有效抑制苯肾上腺素的活性,增强肌钙蛋白与 Ca^{2+} 的亲和力,从而起到解痉挛的作用。

1.4 抗炎及镇痛活性

东莨菪内酯是药用植物藏药雪莲(*Saussurea involucrata*)[23]、紫花前胡(*Angelica decursiva*)[24]、月桂(*Litsea guatemalensis*)[25]等抗炎和镇痛的主要活性物质。东莨菪内酯主要通过抑制一氧化氮(NO)合酶和环氧化酶(COX-2)的活性,抑制炎症过程中产生的 NO 对机体的危害[26]。Mahattanadul 等[27]的东莨菪内酯对小鼠反流性食管炎和慢性胃溃疡的调控作用研究也证明了这一点。中药丁公藤注射液的主要活药理活性物质为东莨菪内酯,临床上用于治疗风湿性关节炎。研究表明,东莨菪内酯可降低大鼠的关节炎指数,减少滑膜组织中血管的生成[28]。此外,东莨菪内酯能够竞争性的抑制高尿酸血症小鼠中黄嘌呤氧化酶的活性,减少尿酸的产生,进而对抗由高尿酸血症引起的痛风性关节炎[29]。

1.5 保肝作用

含有东莨菪内酯的药用植物对肝炎、肝硬化及肝脏损伤具有良好的保护作用[30]。Chang 等[31]发现芙蓉菊(*C. chinensis*)水提取物对 CCl_4 致损的小鼠肝脏具有显著地保护和治疗作用的活性物质为东莨菪内酯;Han 等[32]报道在胆汁导管结扎的小鼠模型中,东莨菪内酯使淤胆型肝纤维化变弱,保护肝脏的功能;Yin 等[33]发现刺天茄(*S. indicum*)种子提取物中具有抗乙型肝炎病毒及细胞毒素活性的活性成分为东莨菪内酯;Noh 等[34]报道日本栗(*Castanea crenata*)内壳提取物含有东莨菪内酯,其对乙醇诱导慢性氧化效应的小鼠肝脏细胞具有较强的保护作用,可抑制乙醇诱导产生的氧化酶(CAT、SOD、GPx、GR)活性。另外,日本栗内壳提取物对饲喂高脂肪的小鼠的肝脂质沉着症也具有较强地抑制作用[35]。

1.6 增强记忆活性

东莨菪内酯是一种有效的天然乙酰胆碱酯酶抑制剂[3],在老年性痴呆症模型小鼠中,东莨菪内酯可抑制大脑海马体突触体的 AChE 作用于烟碱乙酰胆碱受体,促进乙酰胆碱的释放,提高了老年性痴呆症患者的学习和记忆能力[4,36]。东莨菪内酯及其衍生物对 AChE 的抑制作用,主要通过 C-6 和 C-7 上的的官能团作用于 AChE 的 Trp286、Tyr124、Tyr341

和 Phe295 等氨基酸残基而发挥抑制活性[37]。此外,诺丽果的果实富含东莨菪内酯,其氯仿提取物对乙酰胆碱酯酶的抑制活性最强,对莨菪碱导致小鼠记忆损失的保护作用,且提取物与东莨菪内酯对小鼠的行为、生物化学及大脑血液流动的影响相似[38]。

1.7 其他药理活性

东莨菪内酯还具有其他药理活性,例如东莨菪内酯具有降温作用,能显著地降低正常活动家兔及由大肠杆菌内毒素致热的家兔的体温[39];东莨菪内酯可通过抑制酪氨酸酶活性,进而抑制黑色素的合成,具有美白功能;东莨菪内酯的乙酰胆碱酯酶抑制作用,在临床上有应用于缩瞳和降眼压[40]。

1.8 药动学研究

东莨菪内酯的药动力学研究主要集中在大鼠肠道、体胃的吸收和渗透方面。在大鼠体内,东莨菪内酯口服吸收快,在 10 min 左右即可达峰,口服后血浆半衰期 $t_{1/2}$ = (14.1 ± 0.6) min。东莨菪素在大鼠胃中 2 h 的吸收百分率为 76.31%,在结肠、十二指肠、回肠、空肠的吸收率分别为 46.25%,40.54%,38.21%,32.77%;不同质量浓度、pH 值对东莨菪素在大鼠全肠道的吸收没有显著性影响,药物的吸收呈一级动力学过程,吸收机制主要为被动扩散,这与体外试验相一致;东莨菪素在胃肠道均有较好的吸收[41]。Galkin 等[42]通过 Caco-2 模型对香豆素类口服药物的膜透性和细胞毒性进行了评估,结果表明该类药物的有很好的渗透性,在肠道内的吸收较好,但又不只局限于吸收,对线粒体功能也有一定影响。

2 东莨菪内酯的杀虫活性

东莨菪内酯对昆虫的生物活性主要表现为拒食、抑制生长、触杀、胃毒等方面,其中在拒食和抑制生长的研究较多。Leszcynski 等[43]发现小麦叶中东莨菪内酯等甲氧基酚类化合物对麦长管蚜(*Sitobion avenae*)具有显著的拒食活性。据此,有学者将小麦低温驯化后,使得小麦叶中东莨菪内酯等酚类化合物的含量显著提高,表现出良好的抗虫和抗病性[44]。甘薯(*Ipomoea batatas*)块根富含东莨菪内酯,对小菜蛾(*Plutella xylostella*)幼虫具有显著地生长抑制作用和胃毒作用[45],其块根被金针虫(*Conoderus* spp. 和 *Systena elongata*)、玉米根虫(*Diabrotica balteata*)、甘薯跳甲(*Chaetocnema confinis*)、白蛴螬(*Phyllophaga* spp.)等地下害虫的危害率与其东莨菪内酯的含量呈负相关关系[46]。Vera 等[47]报道了含 200 μg/g 的东莨菪内酯饲料对草地夜蛾(*Spodoptera frugiperda*)幼虫的选择性拒食率为 61%;源于黄花蒿的东莨菪内酯与人工饲料混合对尘污灯蛾(*Spilarctia oblique*)幼虫具有明显的拒食和抑制生长作用,东莨菪内酯(>100 μg/g)对尘污灯蛾幼虫的生物活性与印楝素(50 μg/g)无显著性差异[48]。

东莨菪内酯不仅对同翅目、鞘翅目及鳞翅目的昆虫具有拒食及抑制生长作用,其对等翅目和双翅目的昆虫也具有拒食及毒杀活性。Adfa 等[49]发现东莨菪内酯对台湾乳白蚁(*Coptotermes formosanus*)表现出显著的拒食活性,同时发现,其抗白蚁的活性位点主要为 C-6 和 C-7 的烷氧基。据此,Adfa 等[50]将香豆素修饰为 6-烷氧基香豆素和 7-烷氧基香豆素,且不饱和烷氧基及环烷氧基能显著提高抗白蚁活性。Tunón 等[51]发现南木蒿(*A. abrotanum*)的细枝和叶的甲苯提取物对埃及伊蚊(*Aedes aegypti*)具有显著地驱避活性,其提取物中主要含有东莨菪内酯和香豆素。此外,东莨菪内酯为诺丽果叶甲醇提取物主要活性物质,提取物对斯氏按蚊(*Anopheles stephensi*)、致倦库蚊(*Culex quinquefasciatus*)及埃及伊蚊幼虫具有显著地触杀活性[52]。

3 东莨菪内酯的杀螨活性

东莨菪内酯对植食性螨类的生物活性研究起始于黄花蒿杀螨活性的研究,张永强等[53]系统研究了黄花蒿不同月份及其不同部位的不同溶剂提取物对朱砂叶螨(*Tetranychus cinnabarinus*)的触杀活性,结果表明:黄花蒿七月份叶的丙酮提取物中东莨菪内酯含量最高,对朱砂叶螨的 LC_{50} 值(48h)为 0.105 mg/mL,并且对柑桔全爪螨(*Panonychus citri*)和酢浆草岩螨(*Petrobia harti*)也表现出强烈的触杀活性,对朱砂叶螨还具有一定的产卵抑制活性[54]。Tunón 等[51]发现南木蒿地上部分乙醇提取物主要为东莨菪内酯和香豆素,对蓖子硬蜱(*Ixodes ricinus*)有较好的驱避作用。

东莨菪内酯的杀螨活性具有明显的温度效应和亚致死效应,其对朱砂叶螨雌成螨的最佳毒力温度为 23.2 ℃,在亚致死剂量下能使朱砂叶螨种群的发育和繁殖速率降低,且不易产生抗药性[55,56],原因可能与东莨菪内酯对朱砂叶螨的多靶标作用机理有关[56]。东莨菪内酯处理朱砂叶螨后,能够显著抑制螨体内超过氧化物岐化酶(superoxide dismutase,

SOD)和过氧化物酶(peroxidase,POD);对过氧化氢酶(catalase,CAT)、羧酸酯酶(carboxylesterase,CarE)和谷胱甘肽S-转移酶(gultathione S transferases,GSTs)表现为激活作用;对螨体的神经系统靶标——乙酰胆碱酯酶(acetylcholinesterase,AChE)、单胺氧化酶(monoamine oxidase,MAO)、Na^+-K^+-ATP酶及Ca^{2+}-Mg^{2+}-ATP酶的酶活性也表现为抑制作用,并推测东莨菪内酯可能是一种神经毒剂[53,57]。

4 东莨菪内酯的抑菌活性

4.1 东莨菪内酯的诱导抗菌活性

植物在受到病原菌或外来物质的刺激时,可诱导合成更多的东莨菪内酯,提高其抵抗能力[58]。2,4-D[59]、茉莉酸甲酯[60]、细胞分裂素[61]、阿氟曼链霉菌(*Streptomyces scabiei*)及其毒素thaxtomin A[62]等均可诱导烟草细胞中东莨菪内酯的含量增加,提高其抗菌活性。源于疫酶根腐病(*Phytophthora megasperma*)的无致病性糖蛋白也能诱导烟叶中东莨菪内酯含量的增加,显著增强烟株对烟草花叶病毒(TMV)的抗性[63]。东莨菪内酯在烟草中的抗菌活性需要通过转化为东莨菪苷,才能有效发挥作用[64],此过程需要烟草葡萄糖基转移酶(TOGTs)的协助,其主要调控基因是*Togt*1和*Togt*2,且基因的表达受水杨酸(SA)信号系统的调控[65,66]。但过度使东莨菪内酯转化为东莨菪苷,对烟草的组织也是有害的[67]。此外,核黄素(维生素B_2)也能诱导烟草细胞中东莨菪内酯的合成,其作用机理不属于水杨酸信号系统控制,而是依赖于磷脂酶C(PLC)和磷脂酶D(PLD)的表达[68]。

东莨菪内酯也是巴西橡胶树(*Hevea brasiliensis*)的一种重要植物抗毒素,棕榈疫霉分泌蛋白质激发子elicitin可诱导橡胶树叶东莨菪内酯的累积,能有效提高其对橡胶南美叶疫病菌(*Microcyclus ulei*)等的抗性[69]。

4.2 东莨菪内酯的杀菌活性

东莨菪内酯不仅可提高植物的抗菌作用,也具有杀菌或抑菌作用。0.5 mg/mL的东莨菪内酯能够完全抑制烟草灰霉病菌的孢子萌发和菌丝生长[70];东莨菪内酯(>0.4 mg/mL)能有效抑制腐皮镰刀菌(*Fusarium solani*)、尖孢镰刀菌(*F. oxysporum*)、根霉病菌(*Rhizopus stolonifer*)和焦腐病菌(*Lasiodiplodia theobromae*)的菌丝生长[45]。东莨菪内酯对梭形杆菌(*F. fusiformis*)、半裸镰刀菌(*F. semitectum*)和链格胞菌(*Alternaria alternata*)也具有显著的抑制作用[71]。此外,东莨菪内酯对苹果扩展青霉(*Penicillium expansum*)及其扩展青霉素的累积具有良好的控制作用[72];对侵染白榆(*Ulmus pumila*)的长喙壳科真菌*Ophiostoma ulmi*具有抑制孢子萌发和菌丝生长的活性[73]。Carpinella等[74]将东莨菪内酯分别与代森锌和萎锈灵复配,可有效减少两者的用量,显著提高了对镰刀菌(*F. verticillioides*)的抑制效果。

5 东莨菪内酯的化感作用

香豆素类化合物可作用于植物的细胞膜,致使胞内离子平衡紊乱、激素变化、代谢异常等,从而扰乱植物的平衡和光合作用,调控植物的生长[75]。Kim等[76]发现东莨菪内酯是多种入侵植物的化感物质。在多种杂草中,东莨菪内酯也发挥着化感作用的特性[77]。

东莨菪内酯可调节禾本科植物燕麦(*Avena sativa*)和梯牧草(*Phleum pratense*)幼苗根的生长,且高浓度表现为抑制作用,而低浓度则表现为促进作用,其调控作用主要作用于根尖,使根尖分生组织坏死,分泌黑色物质堵塞导管,进而调控植物的生长[78,79],其作用机理主要是保护吲哚乙酸(IAA)免受吲哚乙酸氧化酶的氧化作用,使生长点IAA含量过高[80]。此外,东莨菪内酯(>0.019 mg/mL)也能显著抑制红根苋(*Amaranthus palmeri*)和芥菜(*Brassica juncea*)根的生长,且破坏细胞胚植[81]。另外,东莨菪内酯对双子叶植物的幼苗根抑制较弱,但对叶的抑制作用也较为显著,其化感活性主要通过调节植物体内的相关酶系和气孔的开度,影响其光合作用,从而调节植物的生长[82,83]。

6 结语

东莨菪内酯存在于多个科的多种植物体内,其临床应用十分广泛,但是其研究主要集中在药理学方面,药动力学方面的研究报道较少。在农业应用上,东莨菪内酯对多种农业害虫及害螨具有作用方式多样性和作用靶标多样性的特点,能够减缓或者避免抗药性的产生,具有很好的开发利用价值。但是,现阶段对东莨菪内酯的研究还不是很深入,其杀虫杀螨作用机理尚不清楚,而且目前还没有一个成熟的剂型可以应用于实际生产。因此,要实现东莨菪内酯这一植物源物质的实际应用价值,首先,在医

学上需要对其药动力学进行进一步的研究; 第二,在农业应用上,需明确东莨菪内酯的杀虫杀螨作用机理,以期发现新的作用靶标,减缓抗性的产生; 第三,研究东莨菪内酯的毒力与药剂本身、受体生理代谢、环境条件等多方面因素的关系,为制剂的研发和有效利用提供理论依据。

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