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·综述·

岩藻黄质及其活性

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[摘 要] 岩藻黄质(fucoxanthin，FX)是一种广泛存在于藻类和无脊椎的动物中的海洋活性物质，它的特点是分子质量小，化学活性强，易氧化，容易被生物体吸收，对皮肤细胞、肝、肾、脾和组织没有毒性。自从FX被发现后，它的安全性得以证实，其在体内和体外的代谢、不同的提取工艺及活性被研究，FX因其显著的活性，目前已经被用于临床试验和产品开发。研究表明FX具有开发为临床用药的潜力。

[关键词] 岩藻黄质；药理活性；海洋活性物质

Fucoxanthin and its activity

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Abstract Fucoxanthin is a marine active material, which it's widely found in algae and invertebrate animals. It is characterized by small molecular weight, intense chemical activity, easy oxidation, easy to be absorbed by the organism body. Fucoxanthin is not toxic to human skin cells, liver, kidney, spleen and glandular tissue. Since its discovery, its safety has been verified, and in vivo and in vitro, different extraction processes and activities have been studied. Because of the significant activity of fucoxanthin, clinical trials and product development have been started. Evidence of fucoxanthin activity suggests that it also offers the opportunity to be developed for other clinical applications. In this essay, it will provide an overview of the above content. It provides a better basis for development as products, which are used to treat more diseases.

Keywords fucoxanthin; pharmacological activities; marine active substances

岩藻黄质(fucoxanthin，FX)是一种广泛存在于藻类、海洋浮游植物、水生贝壳类和无脊椎动物中的含氧类胡萝卜素。研究[1]证实FX具有光保护、抗血管生成、抗脑损伤、抗肿瘤、抗炎、抗氧化、抗阿尔茨海默病、减肥和神经细胞保护等药理活性，此外由于FX对肝、肾、脾和性腺组织无毒副作用，目前已被广泛应用于护肤美容产品及保健品中[1]。本文对FX的特性、代谢、合成、提取工艺、

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药理活性、安全性及应用的进展进行综述，为后期FX更好地应用于临床提供依据。

1 FX的发现和特性

FX分子式是$C_{42}H_{58}O_6$，分子质量是658.91，化学结构如图1所示，是一种含氧的胡萝卜素，因其呈淡黄色至褐色的粉末又被称之为褐藻黄素、岩藻黄素。1914年首次[2]从海洋棕色海藻中分离出FX，此后又确定了FX的手性的完整结构[3]，由于其结构中包含5个共轭双键的发色基团[4]、丙二烯键、单环氧基、羰基和羟基等特殊分子[5]，使得FX具有3种同分异构体[6]：9'Z-、13'Z-和13Z-。已从Cystoseira hakodatensis、厚叶解曼藻、海带、褐藻类、冈村枝管藻、岩藻、墨角藻、Hijikia fusiformis、铁钉菜、长角马尾藻、黄藻、四迭团扇藻、褐藻纲、马尾藻、鼠尾藻、铜藻、裙带菜等多种褐藻中分离得到FX。FX约占生物源类胡萝卜素总量的10%，不溶于水，易溶于乙醇等有机溶剂中，极其不稳定，主要表现为光不稳定和热不稳定[7]，易发生氧化还原反应[8]。

2 FX的生物代谢与合成

关于FX体内代谢的研究经历了一个漫长的过程。FX在肠道中很容易代谢为顺式FX和岩藻黄质醇，在肝中代谢为amarouciaxanthin A (Amx A)和顺式Amx A，其中岩藻黄质醇和顺式岩藻黄质醇是人类摄入褐藻或褐藻提取物的主要血浆代谢物[9]。蛤蜊体内发现FX的代谢产物为岩藻黄质醇和梳黄质，并且存在于生殖腺中[10]，因此推测在双壳动物中，FX可能是先代谢为岩藻黄质醇而后再代谢为梳黄质。当FX进入小鼠体内后，会被代谢成多种成分排出体外，这些代谢产物同时也具有很强的药理活性。研究[11]发现：在小鼠灌胃40 nmol的岩藻黄素1 h后血浆中未发现FX原型成分，却发现了岩藻黄质醇和Amx A。当FX进入小鼠消化道之后，通过酶促作用降解为岩藻黄质醇，此外，胃肠上皮细胞也能吸收一部分FX，随后FX经淋巴系统和血液循环系统被运送到肝，最后降解为Amx A。值得关注的是，在人体试验[12]中却没有发现这2种代谢产物，可能原因是某种成分阻碍了小肠对FX的吸收。但是FX却能被Caco-2人体肠道细胞更好地吸收，并且会将其转化为岩藻黄质醇[13]，抑制B淋巴细胞瘤-2基因(B-cell lymphoma-2，Bcl-2)蛋白的水平，诱导DNA片段断裂[14]。而在人类肝癌细胞HepG2细胞中加入FX会被降解为Amx A[15]，具体原因却还未知。这可能与其抗癌的作用机制相关，但具体机制还未知。相较于FX复杂的代谢过程，其合成途径较为简单，相关研究[16]报道了FX的合成途径是：一种新的紫黄质脱环氧化物酶负责将紫黄质转化为新黄质，紫黄质又用作二叠黄素生物合成的前体，然后二叠黄素转化为FX。

3 FX的提取工艺

由于FX自身理化性质的特殊性，其化学合成至今未取得突破性进展。各国研究者从原料种属、采集季节、提取方法及纯化等方面对FX的提取工艺进行了大量的研究(表1)，但至今仍未从根本上大幅度提高FX的产率，对其提取工艺的研究仍是研究的热点。

4 FX的药理活性

4.1 抗肿瘤活性

大量的研究[28-31]发现：FX可通过多种不同的作用机制抑制肿瘤的生长。FX能明显抑制由1-乙基-3-硝基-1-亚硝基胍诱导的十二指肠癌变现象[32]，对右旋糖酐硫酸钠导致的炎症小鼠的结直肠癌有预防作用[33]，该预防作用可能与改变粪便微生物群有关[34]。细胞周期与肿瘤细胞增殖息息相关，FX能将GOTO肿瘤细胞、HepG2细胞的细胞周期阻滞在G_0~G_1期，从而发挥其抑制生长的作用[35]。此外，包括Snail、Twist、Fibronectin、N-cadherin、MMP-2、PI3K、p-AKT和NF-κB等在内的多条信号通路也参与了FX的抗肿瘤作用[29,36-40]。即将发表的文章也证实，FX在体内外能抑制非小细胞肺癌的增殖、迁移和侵袭，而使用PI3K/AKT信号通路激动剂可逆转FX对非小细胞肺癌的作用(前期研究数据，在投中)。值得注意的是，不同来源的FX其抗肿瘤作用机制也不尽相同。从海藻Petalonia bingamiae 中提取的FX能有效地抑制哺乳动物DNA聚合酶[37]，从而诱导细胞凋亡；而首次从褐藻中分离出来的FX则是通过降低*N-myc*基因表达来抑制GOTO肿瘤细胞生长[41]。此外，FX除自身具有抑制肿瘤生长的作用外，其代谢产物halocynthiaxanthin也被发现有同样的活性[42]。

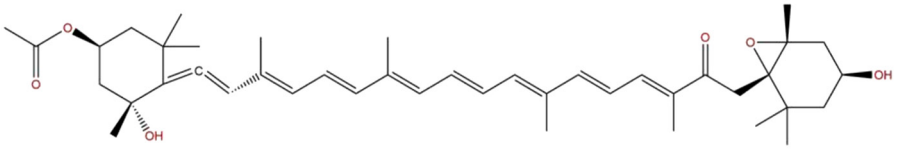

图1 FX的化学结构

Figure 1 Chemical structure of FX

表1 FX的提取工艺

Table 1 Extraction process of fucoxanthin

提取方法	原料	条件	产率
有机溶剂提取	羊栖菜[17]	溶剂：90%乙醇:丙酮=3:1；液料比：40:1；温度：65 ℃；次数：2；时间：80 min	1.067%
	海带[18]	溶剂：80%甲醇；液料比：10:1；温度：40 ℃；时间：1 h；次数：2	0.556 mg/g
	海带粉[19]	溶剂：无水乙醇:丙酮:石油酸=4:1:1；液料比：40:1；温度：40 ℃；次数：2，每次1 h	0.06%
	裙带菜[20]	溶剂：丙酮:乙醇=95:5；液料比：40:1；时间：24 h；次数：3	0.1202%
酶提法	海带[21]	7.5%纤维素酶和2.5%果胶酶，pH 4；温度：40 ℃；时间：37 min	1.0068 mg/g
	裙带菜[22]	温度：37 ℃，pH 6.2；酶：0.05%褐藻酸裂解酶；时间：2 h，溶剂：乙二醇二甲醚:乙醇=1:1	0.7 mg/g
超临界萃取	褐藻[23]	夹带剂：3%乙醇；温度：323 K；压力：20 MPa	0.00753 μg/g
	海藻[24]	夹带剂：超临界CO_2；温度：40 ℃；压力：40 MPa	1.22 g/100 g
微波萃取[25]	鲜海带	提取溶剂：乙醇；料液比：1:15；温度：60 ℃；时间：75 min，微波强度：300 W	0.83 mg/25 g
	干裙带菜		1.09 mg/25 g
	马尾藻		0.2 mg/15 g
超声波提取	海带[26]	温度：60 ℃中超声，1%抗氧化剂；料液比：1:45；时间：30 min；次数：2	0.382 mg/g
	海带[21]	溶剂：无水乙醇，1%的抗坏血酸；料液比：1:45；温度：60 ℃超声；时间：30 min；次数：2次	0.4417 mg/g
加压溶剂萃取	棕藻[27]	溶剂：90%乙醇；温度：110 ℃；时间：15 min；压力：1 000 psi	0.42 mg/g

1 psi=6.895 kPa。

4.2 抗肥胖活性

FX具有显著的抗肥胖的活性。FX及其代谢产物可以减少三酰甘油进入淋巴液中，抑制淋巴对三酰甘油的吸收和降低其在血液中浓度，其原因可能是抑制了胃肠道中胰脂肪酶的活性[43]。此外，其代谢产物可以通过减少过氧化物酶增殖激酶受体水平，抑制3T3-L1前成细胞系向脂肪细胞系的分化过程来抑制肥胖的进程[44]。解偶联蛋白(uncoupling protein，UCP)对肥胖起着多种调控作用，研究发现FX对调控UCP家族的表达起着重要作用[45]。在体内实验中，0.2%浓度的FX会增加通过高脂饮食造成的肥胖小鼠中UCP1、UCP2的表达，0.05%浓度的FX则只会提高UCP1 mRNA在附睾白色脂肪组织中的含量[46-47]，说明FX可能只是对小鼠肥胖发展过程中的脂肪组织有抑制作用[45]。主要在白色脂肪组织中和棕色脂肪组织中表达的β3肾上腺素受体(β3-adrenergic receptor，β3-AR)也受FX调控，在分别灌胃高脂肪和正常脂肪食物10周后的小鼠中给予富含FX的裙带菜，结果发现在富含FX的裙带

菜组中白色脂肪组织中的β3-AR与对照组相比有所提升[48]。FX还能够通过转录因子NF-E2相关因子2(nuclear factor erythroid-2 related factor 2，Nrf2)诱导脂肪细胞中β3-AR而刺激UCP1的表达，并增加高脂饮食喂养的肥胖小鼠的氧消耗[49]。FX可降低KK-A(y)小鼠的血糖和血浆胰岛素浓度，和鱼油结合比单独食用FX更能有效减轻白色脂肪组织(white adipose tissue，WAT)的体重增加[50]。此外，FX被认为还可以抑制脂肪吸收从而具有减肥的效果[51]，食物中添加的FX补充剂会显著降低血压和肝脏脂肪储存和肝酶值，但目前其作用机制还不明确。

4.3 抗血管生成

FX及其产物fucoxanthinol都被发现具有较好的抗血管生成的作用，尤其是在肿瘤的发生发展中对营养的需求上有重要的作用[52]。当FX浓度越大时，可以显著抑制人脐静脉内皮细胞(human umbilical vein endothelial cells，HUVEC)的增殖和管道的形成，但对HUVEC化疗没有显著影响[53]，其作用机制可能是抑制HUVEC中的管形成和迁移，促进血管紧张素2(angiotensin II，Ang2)表达[38]。人体由庞大的血管网络组成，血管从最大的心脏开始到最小的毛细血管都含有丰富营养，其中毛细血管是营养扩散的基石，由若干个内皮细胞构成了毛细血管，伤口愈合增殖阶段的一个标志是强大的血管生成[54]。尽管发现FX可以抗血管生成，却没发现FX对伤口愈合方面的报道。

4.4 抗糖尿病

FX降低血浆胰岛素浓度、胰岛素抵抗力和空腹血糖浓度的作用得到证实[55]。FX可以通过提高胰岛素的耐受度从而降低肥胖小鼠的血糖浓度[50,56]，其机制可能是与上调小鼠体内的葡萄糖载体有关[48]。

4.5 抗炎活性

FX具有抗炎活性，其作用机制可能与抑制炎症因子和炎症介质有关[57]。具体机制仍然存在很大的争议，研究人员发现FX是通过阻断氧化氮合酶(iNOS)和环氧化酶-2(cyclooxygenase 2，COX-2)蛋白的表达从而抑制内毒素炎症的作用，并且其对眼睛的抗炎作用与类似剂量的泼尼松龙的效果相当[58]。研究[59-62]表明：FX是通过显著降低单核细胞对BEAS-2B(bronchial epithelium transformed with Ad12-SV40 2B)细胞的黏附，抑制BEAS-2B细胞中促炎细胞因子、eotaxin和活性氧的产生，缓解气道高反应性(relieve airway hyperresponsiveness，AHR)、杯状细胞增生和非嗜酸性粒细胞浸润，并降低支气管肺泡(bronchoalveolar lavage fluid，BALF)中Th2细胞因子的生成，提高哮喘小鼠肺中谷胱甘肽和超氧化物歧化酶水平，降低丙二醛(malondialdehyde，MDA)、血管内皮生长因子(vascular endothelial growth factor，VEGF)、白细胞介素-6和肿瘤坏死因子-α和组胺水平，从而减轻炎症反应。此外FX对LPS和ATP联合诱导的骨髓源性免疫细胞和星形胶质细胞NF-κB和核苷酸结合寡聚结构域(nucleotide-binding oligomerization domain，leucine-rich repeat and pyrin domain-containing 3，NLRP3)炎性小体激活有抑制作用[63]，可负调控炎症小体信号[63]，改善非酒精性脂肪肝患者的肝脂肪变性、炎症、纤维化和胰岛素抵抗[64]。

4.6 抗氧化、抗衰老活性

抗光老化功能和抗氧化活性是类胡萝卜素类色素的一个最基本的特性[65]，其特性与分子内的氧原子数量正相关。作为类胡萝卜素的FX及其代谢产物，由于其结构中具有二烯键和末端环上有官能团[66-67]，同样具有抗氧化活性和清除自由基的作用[68-69]。研究[70]表明：FX可保护中波紫外线照射引起的光损伤。将FX加入抗坏血酸后可以增加其稳定性，阻止其氧化。此外，FX还能螯合铁，减缓β-胡萝卜素在亚油酸乳状液体系中的漂白作用[71]，还能保护细胞DNA损伤和过氧化氢诱导细胞凋亡[72]。

4.7 保护作用

FX具有多种保护作用[73]。FX可以通过抑制ERK1/2通路，防止甲状腺滤泡上皮细胞内质网应激，降低丙二醛水平，提高过氧化氢酶和抗坏血酸过氧化物酶水平来缓解氧化应激，增加细胞凋亡抑制来保护甲状腺损伤[74]。FX对神经退行性疾病的保护作用也得到证实。研究[75-76]表明：FX可穿透血脑屏障作用于淀粉样蛋白聚集、氧化应激、神经炎症、神经元缺失、神经传递失调、肠道菌群失调及Nrf2和NF-κB信号通路等多个靶点发挥其优于其他类胡萝卜素的神经保护作用。从裙带菜中提取的FX可显著减轻缺氧和复氧对神经细胞的损伤[77]，对UVB诱导的皮肤光老化也有保护作用[78]。FX也被发现可以抑制豆蔻酸-佛波醇-乙酸酯导致的肿胀和红疹[79]，促进血管、肝、骨骼、

大脑、皮肤和眼睛的健康发展[61]，是一个很好上市保健产品。

4.8 抗阿尔茨海默病

FX能抑制β-淀粉样蛋白(β-amyloid protein，Aβ)组装和减轻Aβ神经毒性来改善阿尔茨海默病(Alzheimer's disease，AD)[80]，其机制可能是激活PI3K/Akt级联反应和抑制ERK通路[81]。采用PLGA-PEG纳米颗粒可提高FX的生物利用度，增强其治疗AD的疗效，从而为其在AD治疗中的应用提供了可能[82]。在特应性皮炎模型中，FX因其对角质形成细胞有抗炎作用，可以通过调节淋巴细胞使免疫反应正常化来改善AD症状[83]。

5 FX 的生物安全

FX的安全性受到了很大关注，研究人员[84-85]分别给ICR小鼠喂食不同浓度的FX，未见大量死亡或其他异常反应，大鼠脾、肾、肝以及性腺组织等未出现变化。但是胆固醇浓度和胆红素的总量却明显升高，在血浆胆红素中发现了岩藻黄质醇，并且发现FX和岩藻黄质醇不具有诱变性。而在重建人类皮肤中使用FX也未发现其不良反应。因此，目前研究者[84]普遍认为FX是安全的，然而FX引起胆固醇升高的原因仍需进一步探究。

6 FX 的应用

FX自从发现以来备受关注，并且已经应用于临床实验[86]，因其具有抗炎、抗肥胖、抗糖尿病、抗癌等治疗作用，其中对肥胖和糖尿病的影响已在临床上得到了证实[87]。而被归类为营养品，如今已被广泛应用于化妆品和保健食品中[88]。FX可以抑制紫外线对表皮肥大细胞的损伤，发挥抗氧化活性、抑制酪氨酸激酶活性，抑制色素的沉积，因此被添加到多种护肤品中[78,89]。由于FX对眼睛具有保护作用，因此被用于预防或治疗后的白内障[90]。因其可以抑制破骨细胞的分化和诱导破骨细胞凋亡，因此被用于骨质疏松和风湿性关节炎的预防[75,91]。当FX与阿霉素联合使用时，可增强乳腺癌细胞对药物的敏感性，有可能成为乳腺癌治疗中阿霉素化疗方案的辅助剂[92]。

7 结语

FX作为类胡萝卜素的代表，是从海洋藻类中提取的小分子化合物，因其特殊的化学结构而具有多种药理活性，并且作用效果显著，如抗肿瘤、抗肥胖、抗血管生成、抗糖尿病、抗炎、抗氧化、抗衰老、保护作用、抗AD，因此具有广阔的应用前景和商业价值。然而其结构很不稳定，这给药物化学合成的研究人员提供了研究思路。它虽然广泛存在于各种海藻中，但对其大量开发仍然存在很大的挑战，提取率低、缺乏人工合成研究是导致其价格昂贵的根本原因。因此如何获取低廉且纯度高的FX，更深入的药效学和毒理学研究及如何取得更为广泛的应用是各国研究者需解决的关键问题。FX是一个很有潜力的海洋活性物质，希望今后能有更多的临床研究，明确它的作用机制，使其在医疗保健和制药市场中发挥更大的作用。

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