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综述

5-脂氧合酶抑制剂的研究进展

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摘要：脂氧合酶是一种含铁的氧化还原酶，存在于动植物的组织和细胞中。脂氧合酶主要分为1、3、5、8、12、15-脂氧合酶6种亚型。5-脂氧合酶(5-lipoxygenase，5-LOX)是LOX同工酶中研究较为深入的非血红素铁蛋白氧化代谢酶，是许多高活性氧化脂质生物合成中的关键酶，参与多种炎症性疾病，如炎症、哮喘、脑缺血、部分恶性肿瘤及阿尔茨海默症等疾病的发生和发展过程。因此，开发有效的5-LOX抑制剂对治疗上述疾病至关重要。本文介绍了5-LOX抑制剂的研究成果，并对其分类、来源、治疗药效和优缺点进行了讨论，为深入研发创新型5-LOX抑制剂提供理论依据。

关键词：5-脂氧合酶；5-脂氧合酶抑制剂；脂氧合酶

Research progress of 5-lipoxygenase inhibitors

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Abstract: Lipoxygenases are an iron-containing oxidoreductases which found in the tissues and cells of plants and animals. Lipoxygenases are mainly divided into 6 subtypes of 1, 3, 5, 8, 12 and 15-lipoxygenase. 5-lipoxygenase (5-LOX) is a non-heme ferritin oxidative metabolic enzyme which has been studied deeply among LOX isoenzymes, and it is a key enzyme in the biosynthesis of many highly active oxidative lipids. The key role of the 5-lipoxygenase in formation of inflammation, asthma, cerebral ischemia, some malignant tumors and Alzheimer's disease had been demonstrated. Therefore, the development of effective 5-LOX inhibitors is crucial for the treatment of these diseases. This article, reviews the research findings introducing 5-LOX inhibitors, by focusing on the classification, and discusses on their sources, therapeutic efficacy, advantages and disadvantages of them. It can provide a theoretical basis for further research and development of innovative 5-LOX inhibitors.

Key Words: 5-lipoxygenase; 5-lipoxygenase inhibitor; lipoxygenase

脂氧合酶是一种含铁的氧化还原酶，存在于动、植物的组织和细胞中[1,2]。脂氧合酶主要分为1、3、5、8、12、15-脂氧合酶6种亚型[3]。5-脂氧合酶(5-lipoxygenase，5-LOX)作为脂氧合酶同工酶中是最常见的、研究较为深入的非血红素铁蛋白氧化代谢酶，是许多高活性氧化脂质生物合成中的关键酶，通过催化花生四烯酸(arachidonic acid，AA)变成5-羟过氧化二十碳四烯酸(5-hydroperoxyeicosatetraenoic acid，5-HPETE)后被氧化成白三烯(leukotriene，LT)。LT是哮喘、慢性阻塞性肺疾病、炎症性肠病、关节炎、动脉粥样硬化、皮炎和癌症等多种慢性炎症性疾病相关的促炎性脂质介质，通过进一步的双加氧作用和对外源化学物的协同氧化作用，在炎症[4]、哮喘[5]、脑

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缺血[6]、部分恶性肿瘤[7]及阿尔茨海默症[8]等疾病的发生和发展中具有极其重要的作用。5-LOX抑制剂通过阻断LT的产生，抑制AA转变为LT，从而减少炎症的产生。因此，开发有效的5-LOX抑制剂对治疗上述疾病至关重要。

近年来，5-LOX抑制剂的开发和研究已经越来越受到关注[9,10]。本文对5-LOX的特性及在疾病中的作用，5-LOX抑制剂的分类、来源、治疗性能和优缺点进行了综述。

1 5-LOX的特性与疾病

1.1 5-LOX的特性

人类*5-LOX*基因定位于10号染色体上，包括了14个外显子和13个内含子。转录的起始位点在转录起点位置的上65 bp，可以与转录因子Sp1结合。5-LOX有1个单一的多肽链，它被折叠成2个主要的结构域：C-端催化结构域和N-β-桶结构域，它的活性位点有一个催化金属(高度自旋的亚铁离子和铁离子)和一个酰基链，被蛋白质外壳包围。在C-端催化结构域中，有一个很深且特殊的富含赖氨酸的区域，底物可以停靠在其中。实际上，5-LOX特定的-kkk-序列导致其倾向于非翻转失活，这可能是它本质上不稳定的原因。5-LOX的独特特性是Lys在2肽或3肽的位置上取代了Leu[11]。

脂氧合酶是一类非血红素含铁双加氧酶，可催化AA、二十二碳六烯酸和各种多不饱和脂肪酸(polyunsaturated fatty acid，PUFA)的氧化反应。5-LOX作用于AA氧化通过两步完成：第一步使5-LOX氧化成5-HPETE再转化为5-HETE。第二步催化5-HPETE生成白三烯A4(leukotriene A4，LTA4)。LTA4既可转化为致炎物白三烯B4(leukotriene B4，LTB4)，也可生成白三烯C4(leukotriene C4，LTC4)进而生成白三烯D4(leukotriene D4，LTD4)、白三烯E4(leukotriene E4，LTE4)等导致过敏反应的反应物质[12]。

1.2 5-LOX和疾病

1.2.1 5-LOX和癌症

癌症主要是由不正常和不受控制的细胞增殖引起的。高脂肪饮食与癌症的发展有关。脂肪酸的代谢物质会形成不同的生物活性分子，这些衍生物质参与了癌症的发病机制，现在普遍认为在肿瘤进展、转移、血管生成等方面发挥着重要作用。5-LOX直接参与不同类型癌症的发展，包括前列腺癌、肺癌、结肠癌和结直肠癌。5-LOX激活蛋白催化AA代谢为LTB4或者LTC4，5-HETE、LTs的氧化形式通过与G蛋白偶联的跨膜受体OXER1结合，促进细胞增殖和癌细胞的活力[13]。5-LOX抑制剂可以抑制肿瘤细胞的增殖和分化，并且能诱导细胞的凋亡。这种显著的抑制活性可在一定程度上作为治疗癌症这一疾病的关键因素发挥重要作用[14]。

1.2.2 5-LOX和代谢性疾病

肥胖是代谢综合征相关合并症的主要危险因素，例如胰岛素抵抗、2型糖尿病和非酒精性脂肪肝病(nonalcoholic fatty liver disease，NAFLD)等[15]。有证据表明，代谢综合征的相关病理因脂肪组织中慢性低级别炎症状态的发展而加剧[15,16]。在肥胖和胰岛素抵抗患者和动物的脂肪组织中，5-LOX常过表达[17]。Horrillo等[18]的研究表明，高脂饮食(high-fat diet，HFD)诱导肥胖小鼠的脂肪组织样本显示5-LOX酶产物的形成增加。该研究还发现，LTB4明确地增加了核转录因子p50(NF-κB p50)和p65(NF-κB p65)，因而诱导了该转录因子在脂肪组织中的活性。此外，继发于LTB4诱导的NF-κB激活，肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)、脂肪因子-1(monocyte chemoattractant protein-1，MCP-1)和白介素-6(interleukin-6，IL-6)的释放增强。这些炎性因子与具有胰岛素抵抗和肝脏脂肪变性的脂肪组织炎症直接相关。除了炎症，5-LOX途径也被证明有助于调节来源于脂肪组织的游离脂肪酸的增加。选择性5-LOX抑制剂能够降低循环中游离脂肪酸浓度，减轻胰岛素抵抗和肝脏脂肪变性。综上，肥胖过程中伴随着5-LOX依赖的脂肪组织炎症发生，发炎的脂肪组织中游离脂肪酸和胰岛素抵抗性脂肪因子(TNF-α、IL-6和MCP-1)的大量释放导致胰岛素抵抗并导致NAFLD的发展。因此，对这些脂质介质生成途径进行药理调控将为代谢性肝病、2型糖尿病提供新的保护和治疗策略[19]。

1.2.3 5-LOX和痛风

痛风是40岁以上男性最常见的炎症性关节炎[20]，是由关节内及周围的尿酸钠晶体沉积引发

的的炎症性疾病。有研究表明，由5-LOX代谢AA产生的LTB4能够促进白介素-1β(interleukin-1β，IL-1β)的产生，是痛风发作的重要介质[21]，而且敲除5-LOX或阻断LTB4的产生会下调IL-1β，从而减少痛风模型小鼠中的功能性关节损伤[22]。因此，靶向5-LOX抑制剂可能在缓解痛风炎症方面具有重要的作用。

2 5-LOX抑制剂的研究进展

目前，5-LOX抑制剂根据抑制剂的作用机制可将其分为直接抑制剂和间接抑制剂。直接抑制剂是根据5-LOX的结构进行研发，导致其活性降低；间接抑制剂是抑制5-LOX活化蛋白从而阻断5-LOX代谢通路。直接5-LOX抑制剂可以根据抑制作用方式分为：(1)含羟肟酸或N-羟基脲基团的铁配体抑制剂，可螯合活性部位的铁；(2)非氧化还原型抑制剂，与AA竞争与5-LOX结合而不具有氧化还原性质；(3)氧化还原活性5-LOX抑制剂，通过还原活性位点铁，从而解偶联酶的催化循环。间接抑制剂根据化合物来源进行进一步细分，如基于已知结构的修饰、筛选、虚拟筛选和合理设计等。

2.1 直接抑制剂

2.1.1 尿素、N-羟基脲和羟肟酸衍生物

羟肟酸衍生物BWA4C和羟基脲衍生物Zileuton是有效的口服5-LOX抑制剂，这些化合物属于铁配体型抑制剂。BWA4C是溃疡性结肠炎患者结肠组织中LTB_4合成的有效选择性抑制剂，以BWA4C为代表的乙酰异羟肟酸5-脂氧合酶抑制剂可能有助于评价LTB_4在溃疡性结肠炎中的临床意义，并为该病的治疗提供新的途径。Zileuton使急性和慢性气道功能得到了改善，也减少了β受体激动剂或糖皮质激素的需求，并在美国被批准用于治疗哮喘，但是对于变应性鼻炎、类风湿关节炎和炎症性肠病的治疗潜力较低，并且它有许多缺点，如肝毒性和不良药代动力学特征等[23]。以Zileuton结构为基础设计出了一种新型抑制剂VIA-2291，可以在支气管痉挛动物模型中表现出比Zileuton高5倍的效力，口服半衰期为16 h，对哮喘患者的运动性支气管收缩有一定的疗效[24]。VIA-2291已成功完成动脉粥样硬化和心血管疾病的Ⅱ期临床试验，成为临床开发中领先的5-LOX抑制剂之一[25-27]。

LDP-977是另一种N-羟基脲衍生物，可口服，其效力是Zileuton的5~10倍，作用时间更长因此，LDP-977不再被认为是临床候选[28]。RBX-7796是一种具有十二烷基链的尿素衍生物，可抑制大鼠血液中LTB4的体外合成，并对各种炎症和支气管收缩动物模型有活性[29](图1)。

2.1.2 四氢吡喃衍生物

ZD-2138、L-739,010、CJ-13,610和PF-419183是非氧化还原型5-LOX抑制剂，在细胞测定中显示IC50的低纳摩尔范围[30]。Kusner等[31]报道了ZD2138能够抑制豚鼠体内中抗原诱导的肺阻力增加。L-739,010可以减少LT介导的炎症反应，且其抗痛觉亢进活性与炎症大脑中LT水平降低有关在急性卡拉胶模型和慢性炎症模型中表现出优异的药效和药代动力学，但难以形成共价蛋白结合代谢物[32]。CJ-13,610在大鼠内侧半月板横切面模型上对骨关节炎疼痛有抑制作用，口服CJ-13,610可逆转该动物模型的两种疼痛模式，包括触觉异位痛和负重差异[33]。

Masferrer等[34]通过大鼠气囊模型证明了PF-4191834对LTB4产生的抑制作用，PF-4191834也完成了哮喘的Ⅱ期临床试验，但其用于膝骨关节炎的Ⅱ期临床试验因出现晕厥、急性肝炎和胃溃疡出血等严重不良事件而被终止[35](图2)。

2.1.3 苯醌衍生物

1982年，1,4-苯醌AA-861作为第一批氧化还原型5-LOX抑制剂首次被提出[36]，并经多项研究证实其在体内可产生抗炎作用，这种化合物已经通过了预防季节性过敏性鼻炎的临床试验[37]。有研究发现，苯醌衍生物在人类单核细胞、中性粒细胞和整个人类血液中可作为5-LOX的有效活性抑制剂，对两种LT相关炎症标准化动物模型的实验研究表明，新型1,4-苯醌RF-Id能够通过抑制LT的产生，在体内抑制导致抗炎反应的5-LOX[38-40]。在另一项研究中，对苯醌和十一烷基残基进行了依次修饰，证明1,2-苯醌RF-22c对乙酰胆碱刺激的卵白蛋白致敏小鼠的支气管收缩、卡拉胶诱导的足水肿渗出液形成和酶沙诱导的气囊白细胞浸润均有损害。总之，在完整的人类白细胞中RF-22c是一种高效的5-LOX抑制剂，在不同的炎症模型中具有

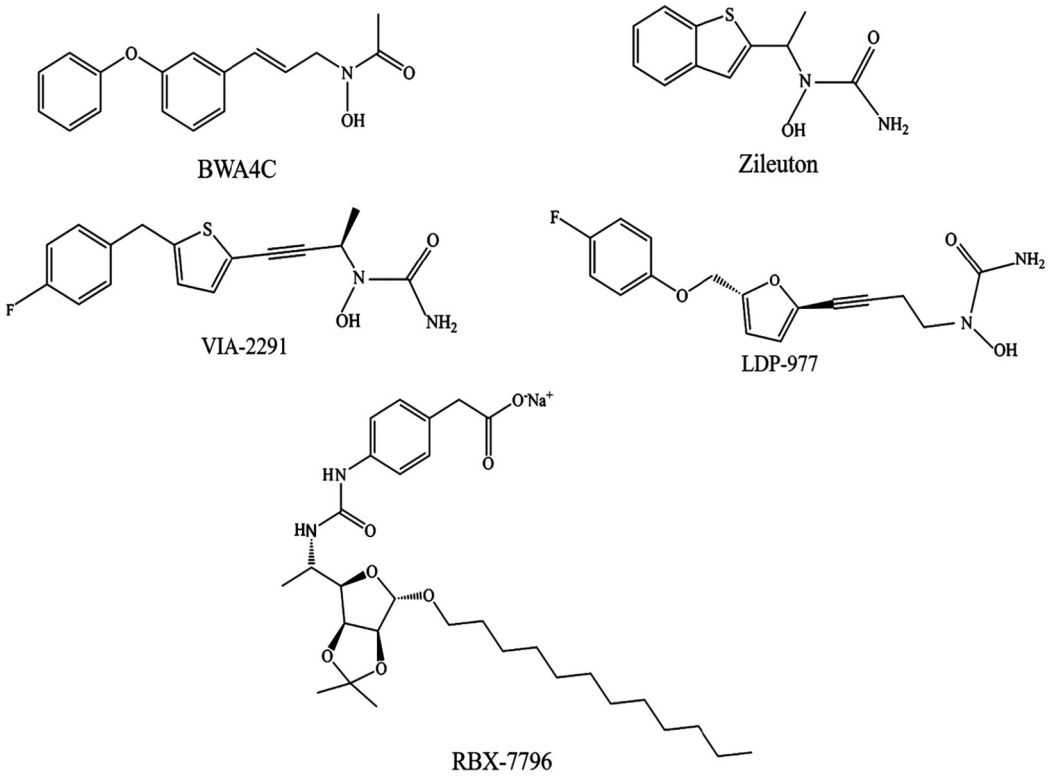

图1 化合物**BWA4C**、**Zileuton**、**VIA-2291**、**LDP-977**和**RBX-7796**的化学结构

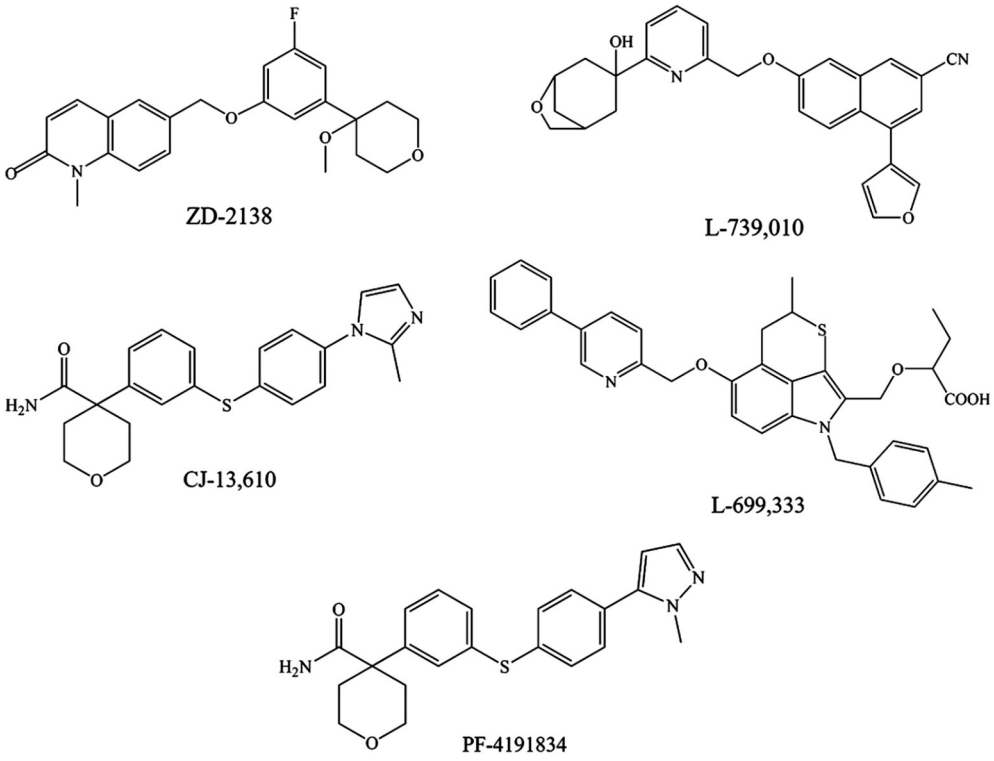

图2 化合物**ZD-2138**、**L-739,010**、**CJ-13,610**、**L-699,333**和**PF-4191834**的化学结构

显著效果，这证明了该化合物可作为消炎药进一步进行临床分析[41](图3)。

2.2 间接抑制剂

姜黄素Curcumin(来自姜黄根茎的黄色粉末)是

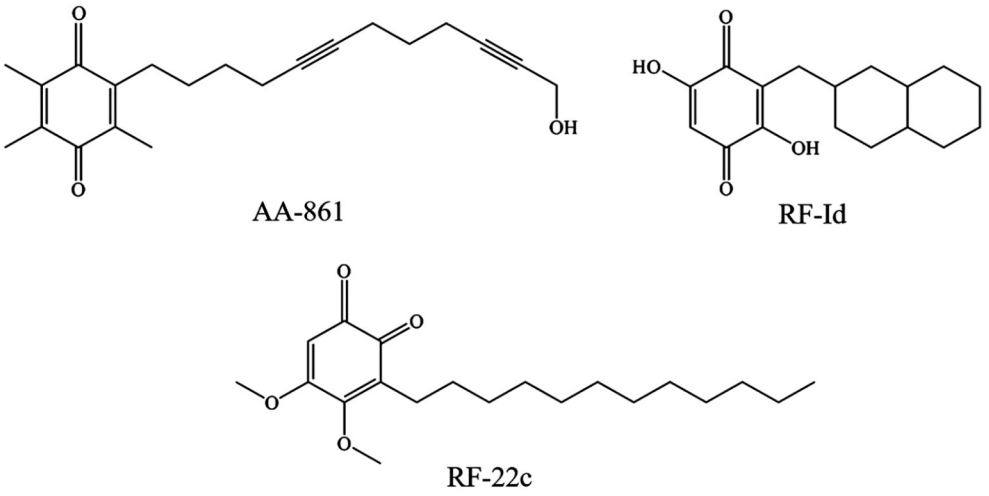

图3 化合物AA-861、RF-Id和RF-22c的化学结构

一种天然的多酚，可以阻断人类重组5-LOX的活性[42]。由于其抗氧化和抗炎机制，姜黄素可以帮助管理氧化和炎症条件[43]、代谢综合征[44]、疼痛[45]、退行性眼病[46]和糖尿病[47]等。咖啡酸(caffeic acid，CA)是酚酸家族中的一种多酚类化合物，广泛存在于各种水果中，如猕猴桃、蓝莓、樱桃等。CA的代谢转化发生在肝脏和肾脏，其最重要的保护作用是其抗凋亡活性，是一种有效的保护剂，并且可以表现出各种药理活性，包括抗氧化、抗炎、抗菌、神经保护和心脏保护[48]。Esculletin是一种天然香豆素，是有效的5-LOX抑制剂之一。Rzodkiewicz等[49]的研究发现，Esculetin在大鼠急性非炎症性疼痛和急性炎症性疼痛模型中的镇痛活性，以20 mg/kg为最佳剂量。2016年，他们在佐剂诱导关节炎模型的雄性Lewis大鼠身上测试了这种化合物，结果显示，与没有炎症的大鼠相比，佐剂诱导关节炎大鼠的血浆中LTB4水平显著降低[50]。

黄酮类化合物是一种FDA监管的上市医疗产品，主要由黄酮类化合物黄芩苷Baicalin(从黄芩中分离出来)和儿茶素Catechin(从儿茶中分离出来)的混合物组成，可以抑制5-LOX[51]，已成功完成治疗膝骨关节炎的Ⅱ期临床试验[52]。然而，Chalasani等[53]报道了黄酮类化合物可以引起的急性但可逆肝损伤。Altavilla等[54]研究了黄酮类化合物对大鼠良性前列腺增生模型的抗炎作用，因为前列腺过度生长时5-LOX升高，黄酮类化合物减少前列腺重量和增生，增加PGE2和LTB4的产生。一些研究表明，黄芩苷在动物模型中具有抗氧化、抗炎和神经保护作用[55-57]，儿茶素具有心脏保护作用[58]，并在帕金森病[59]和阿尔茨海默病[48]等神经退行性疾病中具有降低神经毒性和氧化应激的能力(图4)。

3 总结与展望

5-LOX在某些疾病的形成和发展过程起着重要的作用，许多实验用于开发LOX抑制剂以达到治疗疾病的目的。尽管对5-LOX抑制剂的开发进行了多种策略以及长期的实验，但只有少数化合物获得了专利。例如，这类药物中唯一可用的药物是“Zileuton”，而临床开发中领先的5-LOX抑制剂是VIA-2291，这是一种由Zileuton结构优化而来的化合物。开发新型5-LOX抑制剂的主要方法之一是在不同的分析条件下对新化合物进行表征。值得值得注意的是，大多数研究的5-LOX抑制剂，特别是氧化还原抑制剂，是没有选择性的，其治疗效力可能是因为它们的脱靶效应，目前对它们的特性还有待深入研究。虽然我们在文章中介绍的5-LOX抑制剂可能都有体内研究，但在这里，我们试图只关注那些在动物模型上表现出治疗作用的化合物，这将为设计新型5-LOX抑制剂提供新的思路。药物的研发是一个漫长的过程，需要综合考虑各方面因素，从中选取最为合适的分子用于治疗5-LOX相关疾病是目前和未来一段时间研究的重点，希望在不久的将来能够研发出特异性靶向5-

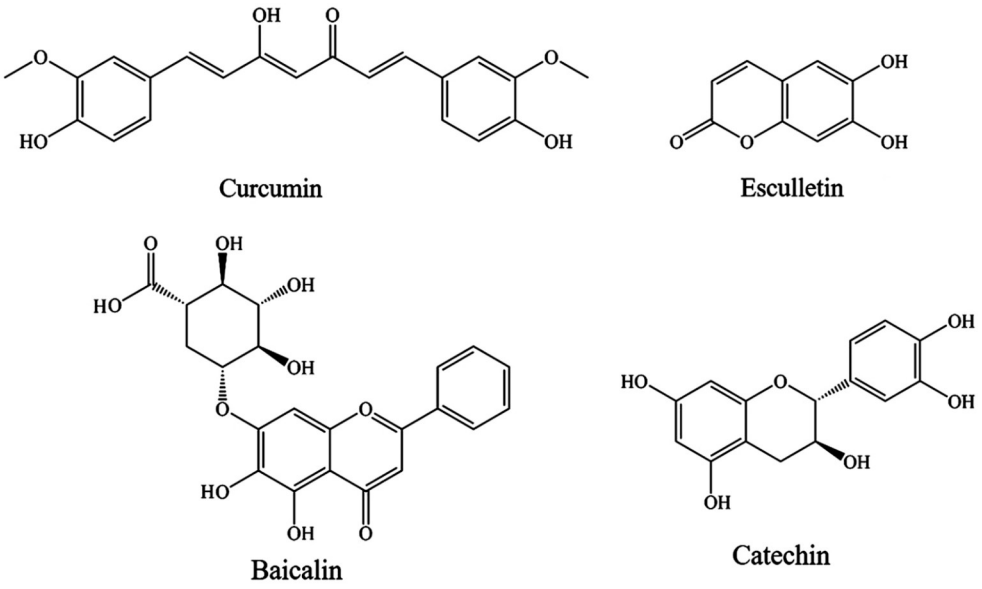

图4 化合物Curcumin、Esculletin、Baicalin和Catechin的化学结构

LOX的新型抗炎药物，用于治疗炎症相关性疾病，为患者带来新的希望。

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