查尔酮类化合物抗肿瘤作用靶点的研究进展

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摘要 查尔酮是一种天然化合物, 为多种药用植物的有效成分, 国内外已经陆续报道了其抗肿瘤活性。查尔酮类化合物抗肿瘤作用靶点较为广泛, 但缺乏系统性的文献综述。因此, 该文将针对查尔酮类化合物作为潜在的抗肿瘤药物靶向抑制IκB激酶、硫氧还蛋白还原酶、微管蛋白、血管表皮生长因子、p53通路来发挥抗肿瘤作用的研究进行综述, 以期为肿瘤的治疗提供更多的理论参考。

关键词 查尔酮; 抗肿瘤; 靶点

Research Advance in Anti-Tumor Targets of Chalcone Compounds

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Abstract Chalcone is a natural compound, which is an active ingredient in a variety of medicinal plants, and its anti-tumor activity has been successively reported at home and abroad. Chalcone compounds have a wide range of anti-tumor targets, but there is a lack of systematic literature review. Therefore, the article reviews chalcone compounds as potential anti-tumor drugs to inhibit IκB kinase, thioredoxin reductase, tubulin, vascular epidermal growth factor and p53 pathway in order to provide more theoretical reference for tumor treatment.

Keywords chalcone; anti-tumor; target

查尔酮是一种天然化合物, 是黄酮类化合物和异黄酮类化合物的前体, 属于类黄酮家族。以查尔酮为母体的天然化合物存在于水果、蔬菜、香料、茶和豆类食品等中[1]。查尔酮的化学结构为1,3-二苯基丙烯酮[2](图1A), 附在羰基上的苯环被定义为A环, 另一个苯环被称为B环。查尔酮存在反式和顺式两种同分异构体, 其反式异构体在热力学上更稳定[3]。目前, 有数个查尔酮类药物如利胆药美托查酮(图1B)和抗溃疡及黏膜保护药索发酮[4](图1C), 已经被批准用于疾病的临床治疗。随着对查尔酮类化合物药理作用研究的不断深入, 科研工作者对查尔酮类化合物抗肿瘤作用的研究也日渐增多[5]。本文通过查阅近年来查尔酮类化合物在抗肿瘤方面的相关文献, 对其抗肿瘤作用中的靶点进行总结, 旨在为后续肿瘤治疗提供思路。

1 与迈克尔反应受体分子相关的抗肿瘤作用

据文献报道, 迈克尔受体具有亲电性, 能够参与许多生物反应并调节重要信号通路[6]。查尔酮中的α,β不饱和羰基官能团被认为是迈克尔受体, 它通过迈克尔加成与亲核试剂形成共价键, 参与多种生物反应[7](图2)。因此, 多种查尔酮类化合物的抗肿瘤活性可能均与查尔酮中的α,β不饱和羰基官能团相关。

1.1 以IκB激酶为靶点抑制肿瘤的发生及发展

IκB激酶(IκB kinases, IKKs)是NF-κB信号通路的关键调控因子之一。NF-κB信号通路通过上调肿

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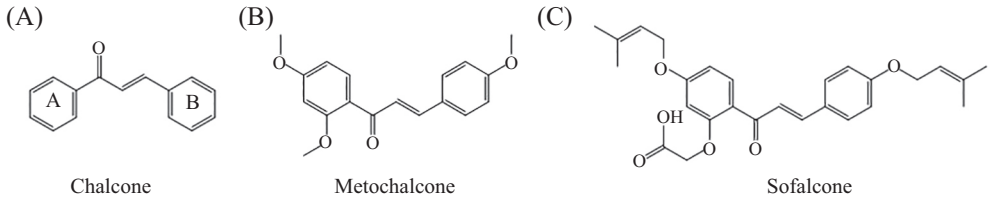
瘤细胞因子、抑制细胞凋亡、促进血管生成等参与肿瘤的发生[8]。NF-κB信号通路的激活主要由IKKs调控, 抑制IKKs活性可阻止NF-κB蛋白向细胞核转位, 从而阻止肿瘤的发生与发展[9]。

研究发现, 天然查尔酮类化合物异甘草素[10-11](图3A)、licochalcone A[12](图3B)和cardamonin[13](图3C)都具有较好的抗肿瘤活性, 它们可能因为其结构中具有迈克尔受体活性α,β不饱和结构单元, 能够与IKKβ的179位半胱氨酸残基共价修饰, 从而抑制IKK的活性, 发挥抗肿瘤作用。3-羟基-4,3',4',5'-四甲氧基查尔酮(图3D)可以与IKKβ的半胱氨酸残基共价结合, 抑制NF-κB信号通路的核转位, 从而在体内外显示出较强的抗肿瘤活性[14]。这表明, IκB激酶可能是查尔酮类化合物的作用靶点之一。

1.2 以硫氧还蛋白还原酶为靶点诱导细胞凋亡

硫氧还蛋白还原酶(thioredoxin reductase, TrxR)能够调节肿瘤细胞的增殖、凋亡、转移, 以及血管生成等[15]。TrxR的498位硒半胱氨酸残基是TrxR抑制剂的作用靶点[16]。许多以TrxR为靶点的化合物, 特别是α,β-不饱和酮(如查尔酮及其类似物)已被开发成为潜在的TrxR抑制剂, 用于肿瘤治疗[17]。

GAN等[18]报道, 具有迈克尔反应受体型药效团的查尔酮类化合物4A(图4A)和查尔酮类化合物4B(图4B)表现出对TrxR的抑制活性。质谱(mass spectrometry, MS)分析表明, 查尔酮类化合物4B(图4B)具有抗肿瘤活性, 其通过共价修饰TrxR的498位硒半胱氨酸残基, 抑制TrxR活性。此外, 研究发现一系列类似于黄腐酚的查尔酮类化



A: 查尔酮的化学结构; B: 美托查酮的化学结构; C: 索发酮的化学结构。

A: chemical structure of chalcone; B: chemical structure of metochalcone; C: chemical structure of sofalcone.

图1 查尔酮的化学结构式和两种临床获批的查尔酮类药物的化学结构式

Fig.1 Chemical structures of chalcone and two clinically approved chalcone-based drugs

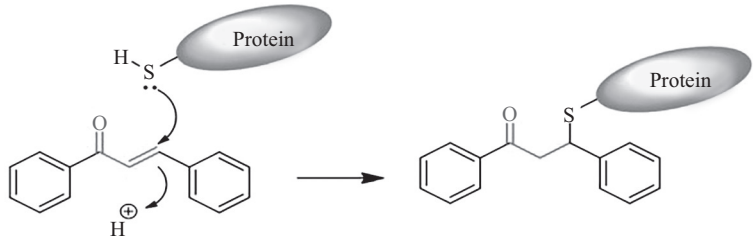
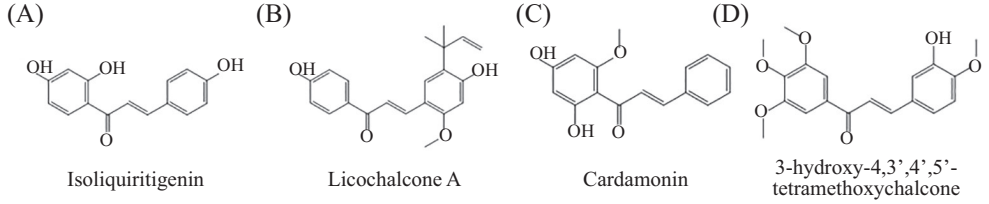


图2 查尔酮的迈克尔加成反应(根据参考文献[7]修改)

Fig.2 Michael addition reaction of chalcone (modified from the reference [7])

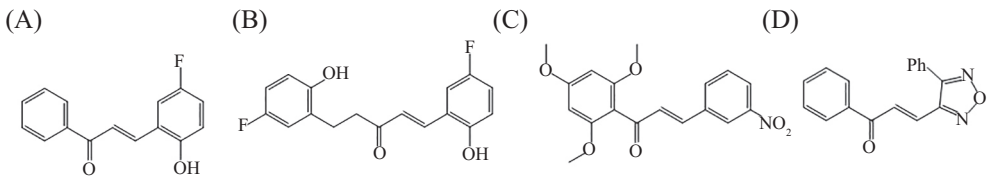


A: 异甘草素的化学结构; B: 甘草查尔酮A的化学结构; C: 小豆蔻明的化学结构; D: 3-羟基-4,3',4',5'-四甲氧基查尔酮的化学结构。

A: chemical structure of isoliquiritigenin; B: chemical structure of licochalcone A; C: chemical structure of cardamonin; D: chemical structure of 3-hydroxy-4,3',4',5'-tetramethoxychalcone.

图3 查尔酮类化合物包括异甘草素、甘草查尔酮A、小豆蔻明、3-羟基-4,3',4',5'-四甲氧基查尔酮的化学结构式

Fig.3 Chemical structures of the chalcone compounds including isoliquiritigenin, licochalcone A, cardamonin, and 3-hydroxy-4,3',4',5'-tetramethoxychalcone



A: 查尔酮类化合物4A的化学结构; B: 查尔酮类化合物4B化学结构; C: 查尔酮类化合物4C的化学结构; D: 呋喃芳基查尔酮的化学结构。
A: chemical structure of chalcone compound 4A; B: chemical structure of chalcone compound 4B; C: chemical structure of chalcone compound 4C; D: chemical structure of furoxanyl chalcone.

图4 查尔酮类化合物包括查尔酮类化合物4A、查尔酮类化合物4B、查尔酮类化合物4C、呋喃芳基查尔酮的化学结构式

Fig.4 Chemical structures of the chalcone compounds including chalcone compound 4A, chalcone compound 4B, chalcone compound 4C, and furoxanyl chalcone

表1 与迈克尔反应受体分子相关的抗肿瘤作用靶点

Table 1 Targets of anti-tumor action associated with the Michael response receptor molecules

查尔酮类化合物 Chalcone compound	作用靶点 Target of action	参考文献 References
Isoliquiritigenin, licochalcone A, cardamonin	Covalent modification with the cysteine 179 of IKKβ inhibited the IKK activity	[10-13]
3-hydroxy-4,3',4',5'-tetramethoxychalcone	Covalently binding to the cysteine residues of IKK inhibited the nuclear translocation of NF-κB signaling, thus demonstrating strong anti-tumor activity *in vitro* and *in vivo*	[14]
Chalcone compound 4A, 4B	Covalently modified the selenocysteine residue at position 498 of the TrxR to inhibit the TrxR activity	[18]
Chalcone compound 4C	Selective inhibition of TrxR showed good cytotoxicity to HeLa cells (IC_{50}=1.4 μmol/L) and induced apoptosis	[19]
Furoxanyl chalcone	Induce ubiquitination and degradation of Keap1, and promote transcription and expression of target genes	[24]

合物4C(图4C)对HeLa细胞表现出良好的细胞毒性(IC_{50}=1.4 μmol/L), 可选择性抑制TrxR, 诱导细胞凋亡[19]。

1.3 以Keap1-Nrf2-ARE通路中的Keap1为靶点抑制肿瘤细胞生长

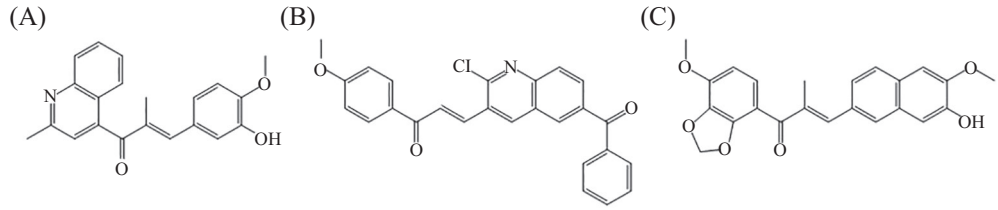
Nrf2(nuclear factor erythroid 2 related factor 2)是细胞氧化应激反应中的关键因子[20], 在正常条件下, Nrf2与Keap1(kelch-like ech-associated protein 1)结合, 且存在于细胞之中。发生氧化应激时, Keap1的半胱氨酸残基被修饰, 构象发生改变导致Nrf2被释放出来并进入细胞核中, Nrf2与ARE结合后, 促进靶基因的转录与表达, 避免了肿瘤的发生[21]。

研究表明, 查尔酮类化合物分子中α,β不饱和结构单元作为亲电试剂与Keap1中的半胱氨酸残基结合, 促进Keap1泛素化且降解, 从而使与之结合的Nrf2游离出来并进入细胞核, 然后Nrf2与ARE相互作用, 启动第II相解毒酶和抗氧化应激蛋白基因的转录, 抑制肿瘤细胞的生长[22-23]。呋喃芳基查尔酮(图4D)是一种含有杂环的化合物, 可以使Nrf2游离出来并进入细胞核, 与ARE相互作用, 在肝脏中显著诱导第II相解毒酶和抗氧化应激蛋白基因的转录, 抑制肿瘤的发生[24]。

综上所述, 查尔酮类化合物的化学性质影响其生物活性。查尔酮类化合物因其具有迈克尔受体特性能与不同的生物受体结合, 从而起到抗肿瘤的作用(表1)。

2 查尔酮类化合物作为微管蛋白抑制剂干扰肿瘤细胞有丝分裂, 诱导细胞凋亡

微管是细胞内的丝状结构, 是α和β微管蛋白异源二聚体的普遍存在的动态聚合物, 在细胞中处于高度动态的聚合–解聚过程[25]。DUCKI等[26]认为, 查尔酮的靶点可能是微管蛋白, 因为查尔酮与β-tubulin抑制剂考布他汀A4(combretastatin A4)具有相似性。考布他汀A4通过与β-tubulin的秋水仙碱结合位点结合, 抑制微管蛋白聚合, 干扰肿瘤细胞有丝分裂, 从而起到抑制肿瘤细胞生长的作用。

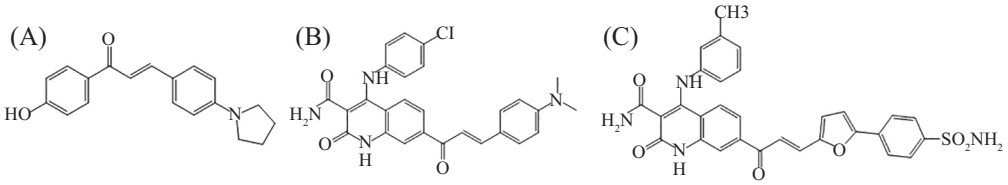


A: 喹啉–查尔酮类化合物5A的化学结构; B: 喹啉–查尔酮类化合物5B的化学结构; C: 查尔酮类化合物TUB092的化学结构。

A: chemical structure of quinoline-chalcone compound 5A; B: chemical structure of quinoline-chalcone compound 5B; C: chemical structure of chalcone compound TUB092.

图5 查尔酮类化合物包括喹啉–查尔酮类化合物5A、喹啉–查尔酮类化合物5B、TUB092的化学结构式

Fig.5 Chemical structures of the chalcone compounds including quinoline-chalcone compound 5A, quinoline-chalcone compound 5B, and TUB092



A: 查尔酮类化合物6A的化学结构; B: 4-苯胺喹啉-3-羧基酰胺的化学结构; C: 喹啉-3-羧酰胺呋喃的化学结构。

A: chemical structure of chalcone compound 6A; B: chemical structure of 4-anilinoquinoline-3-carboxamide; C: chemical structure of quinoline-3-carboxamidofuran.

图6 查尔酮类化合物包括查尔酮类化合物6A、4-苯胺喹啉-3-羧基酰胺、喹啉-3-羧酰胺呋喃的化学结构式

Fig.6 Chemical structures of the chalcone compounds including chalcone compound 6A, 4-anilinoquinoline-3-carboxamide, and quinoline-3-carboxamidofuran

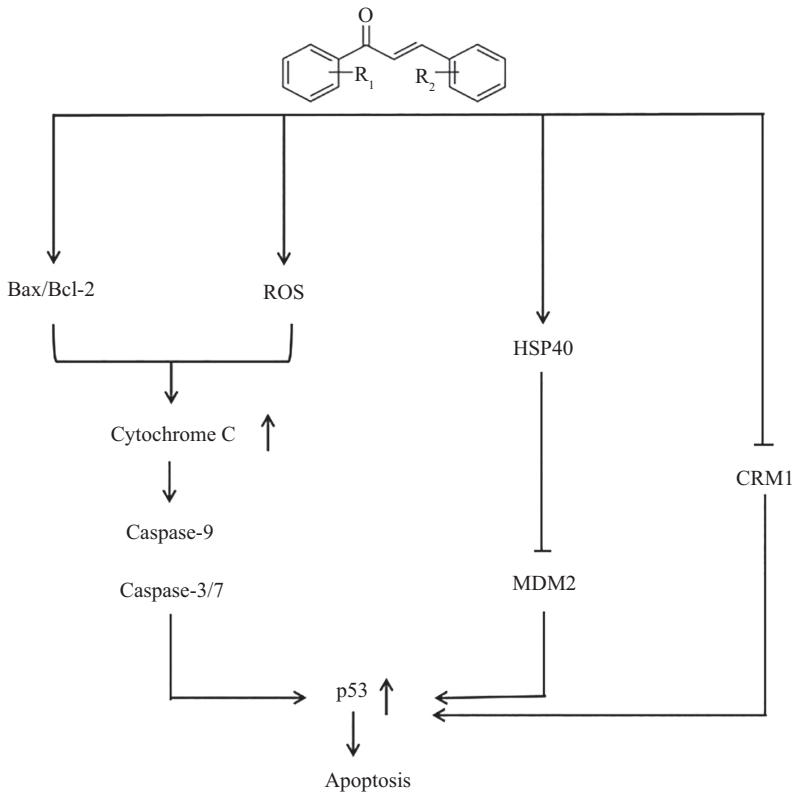
研究发现, 喹啉–查尔酮类化合物(图5A)通过与微管蛋白的秋水仙碱位点结合, 抑制微管蛋白聚合, 使K562细胞周期阻滞在G_2/M期, 诱导细胞凋亡[27]。MIRZAEI等[28]研究发现, 喹啉–查尔酮类化合物(图5B)也是微管蛋白抑制剂, 可诱使细胞周期阻滞在G_2/M期, 干扰肿瘤细胞有丝分裂。通过分子对接和机理研究, LIEKENS等[29]报道查尔酮类化合物TUB092(图5C)也可与秋水仙碱结合位点结合, 抑制微管蛋白聚合, 从而阻滞细胞周期于G_2/M期, 进而降低线粒体膜电位, 诱导细胞凋亡。综上所述, 微管蛋白也可能是查尔酮类化合物的作用靶点。

3 查尔酮类化合物作为血管生成抑制剂抑制细胞增殖和转移以及血管生成

实体瘤的生长及转移瘤的形成依赖于血管的形成。血管表皮生长因子(vascular endothelial factor, VEGF)可以特异性地促进血管内皮细胞增殖, 促进新血管的形成, 对肿瘤细胞的浸润和转移起到重要作用[30]。

研究发现, 异甘草素在体内外通过抑制VEGF/VEGFR-2信号通路来抑制乳腺癌细胞增殖和新血管生成[31]。天然查尔酮黄腐酚通过降低NF-κB的活性以及血管生成因子VEGF和IL-8的产生量, 在体内外抑制胰腺癌中新血管的生成[32]。JEONG等[33]研究发现, 一种新型查尔酮类化合物(图6A)可以调节上皮–间质转化(epithelial-mesenchymal transition, EMT)相关基因的表达, 降低人肺癌细胞A549中TGF-β1的表达量, 抑制A549细胞迁移和侵袭。STANOJKOVIC等[34]也报道了一系列蒽醌–查尔酮类化合物通过降低*MMP2*、*MMP9*和*VEGF*的基因表达抑制K562细胞侵袭和转移以及血管生成。

在一项针对人脐静脉内皮细胞(human umbilical vein endothelial cell, HUVEC)的研究中, RIZVI等[35]发现喹诺–噻吩查尔酮类化合物可能抑制VEGFR-2激酶的活性, 从而抑制HUVEC细胞的增殖。GEORGE等[36]研究发现, 喹啉–查尔酮类化合物作为EGFR抑制剂能够抑制MCF-7、HeLa和DLD1细胞增殖, 具有良好的抗肿瘤活性。IBRAHIM等[37]报道, 4-苯胺喹啉-3-羧基酰胺(图6B)是潜在的抗肿瘤药物, 能够抑制EGFR活性。ALY等[38]认为, 喹啉-3-羧酰胺呋喃(图6C)是一种潜在的EGFR抑制剂, 对MCF-7细胞株具有良好的抗肿瘤活性。



CRM1: 染色体区域维持蛋白1; HSP40: 热休克蛋白40; MDM2: 双微体同源基因2; Bax/Bcl-2: 促凋亡蛋白/抑凋亡蛋白; ROS: 活性氧; ↑: 促进作用; ⊥: 抑制作用。

CRM1: chromosome region maintenance 1; HSP40: heat shock protein 40; MDM2: murine double minute 2; Bax/Bcl-2: pro-apoptotic protein/anti-apoptotic protein; ROS: reactive oxygen species; ↑: promotion; ⊥: inhibition.

图7 查尔酮类化合物靶向p53通路(根据参考文献[1]修改)

Fig.7 Chalcone compounds target the p53 pathway (modified from the reference [1])

4 查尔酮类化合物靶向p53通路抑制细胞增殖、促进细胞凋亡

转录因子p53在肿瘤细胞的凋亡中起着关键作用, 其失活是肿瘤发生的主要因素之一[39]。因此, 增强p53活性是治疗肿瘤的关键策略。

双微体同源基因2(murine double minute 2, *MDM2*)是E3泛素连接酶, MDM2是p53最主要的负调控因子, 通过介导p53发生泛素化来下调p53的表达[40]。因此, 靶向抑制p53-MDM2通路是重新激活p53的关键。SILVA等[41]研究发现, 在U2OS骨肉瘤细胞中, 反式查尔酮通过降解染色体区域维持蛋白1(chromosome region maintenance 1, CRM1)来促进热休克蛋白40(heat shock protein 40, HSP40)的表达, 而HSP40与MDM2的相互作用抑制了MDM2介导的p53泛素化, 从而增强p53活性并促进U2OS骨肉瘤细胞凋亡(图7)。SEBA等[42]研究发现, 4-氨基查尔酮类化合物不仅可以靶向抑制p53-MDM2通路, 上调p53的表达, 而且还可以抑制细胞外基质酶降解, 调节EMT相关基因的表达, 从而抑制骨肉瘤细胞迁移和侵袭。CABRAL等[43]报道了一种新型查尔酮类化合物LQFM064, 其可通过激活凋亡信号通路中肿瘤坏死因子受体1、Fas配体和Bax的表达诱使MCF7细胞的细胞周期阻滞在G_0/G_1期。综上所述, 这些研究表明, 查尔酮类化合物可通过p53通路抑制细胞增殖、促进细胞凋亡(图7)。

5 查尔酮类化合物作为多药耐药抑制剂逆转肿瘤耐药

肿瘤患者在使用药物治疗一段时间之后, 往往会产生耐药性, 肿瘤细胞对不同的抗癌药物产生耐药性称为多药耐药(multidrug resistance, MDR), 产生多药耐药的部分原因是P-糖蛋白(P-glycoprotein, P-gp)、多药耐药相关蛋白1(multidrug resistance associated protein 1, ABCC1)和乳腺癌耐药蛋白(breast cancer-resistance protein, ABCG2)这3种外排转运蛋白的过表达。它们主动将抗癌药物排出靶细胞, 降

低靶细胞内药物浓度, 从而限制其治疗效果[44]。大量研究表明, 查尔酮类化合物能够抑制这些外排转运蛋白的表达[45]。因此, 查尔酮类化合物作为临床耐药的化学增敏剂受到了广泛的关注。

YIN等[46]报道了一种新型查尔酮类化合物MY3, 其可通过抑制P-gp的表达逆转乳腺癌细胞MCF-7对阿霉素(adriamycin, DOX)的耐药性, 并且在MCF-7细胞异种移植模型实验中也具有明显的肿瘤耐药逆转作用。LI等[47]报道, 查尔酮类化合物FKA通过阻断PI3K/Akt通路抑制P-gp蛋白的表达, 查尔酮类化合物FKA联合紫杉醇(paclitaxel, PTX)可逆转A549细胞对PTX的耐药性。此外, 查尔酮类化合物对ABCG2介导的多药耐药的潜在调节作用已被研究多年。WU等[48]报道, 天然查尔酮Licochalcone A可通过抑制多药耐药癌细胞株中ABCG2的药物转运功能, 逆转ABCG2介导的多药耐药。LINDAMULAGE等[49]合成的新型喹诺酮查尔酮类化合物通过抑制ABCC1活性在三阴性乳腺癌细胞MDA-MB-231异种移植小鼠中显示出了明显的抗肿瘤活性。综上所述, 查尔酮类化合物可作为临床耐药的化学增敏剂逆转肿瘤耐药。

6 其他作用靶点

环氧合酶(cyclooxygenase, *COX*)是NF-κB的靶基因, 以不同方式影响肿瘤的发生和发展, 刺激肿瘤细胞增殖、迁移, 促进血管生成。布鲁索查尔酮已被证实能够抑制COX的活性从而起到抗肿瘤作用。OZDEMIR等[50]报道了一类吲哚查尔酮具有较强的COX抑制活性, 且可抑制肿瘤的生长。天然查尔酮Butein能够抑制COX-2进而诱导A549肺癌细胞凋亡[51]。

此外, 查尔酮类化合物也可以通过作用于如组蛋白去乙酰化酶(histone deacetylase, HDAC)[52]、拓扑异构酶II[53]、p38[54]等蛋白或者JAK/STAT(janus kinase/signal transducer and activator of transcription)[55]、Wnt[56]、ROS/MAPK(reactive oxygen species/mitogen-activated protein kinase)[57]和mTOR(mammalian target of rapamycin)[58]等信号通路来抑制肿瘤的生长, 但是其确切的靶点还未可知, 需要进一步的研究。为了探索查尔酮类化合物的作用靶点, 大量的研究人员通过定量结构活性关系(quantitative structure activity relationship, QSAR)评估、分子对接和虚拟筛选等计算机辅助技术进行筛选。

7 总结

查尔酮类化合物具有广泛的抗肿瘤活性及作用靶点, 能与不同的生物受体结合, 这可能与其分子具有较大的柔性和迈克尔受体特性有关。查尔酮类化合物因其具有与迈克尔受体相关的结构而能够靶向作用于IκB激酶、TrxR和Keap1, 并调控其下游相关基因, 抑制肿瘤细胞的生长。查尔酮类化合物也可以通过下调转移相关蛋白MMP2、MMP9和VEGF的表达抑制细胞增殖和转移以及血管生成, 从而起到抗肿瘤作用。另外, 查尔酮类化合物通过抑制p53通路中的*MDM2*基因, 从而激活促凋亡蛋白Bax表达并降低抑凋亡蛋白Bcl-2的活性, 进而引起细胞凋亡。

在肿瘤患者治疗过程中多药耐药的出现影响了肿瘤治疗的疗效, 给肿瘤临床治疗带来了巨大的挑战。研究表明, 查尔酮类化合物能够作为临床耐药的化学增敏剂下调P-gp、ABCC1和ABCG2这3种外排转运蛋白的表达, 进而逆转肿瘤多药耐药。这些都将成为查尔酮类化合物作为分子靶向剂的依据。在即将到来的分子靶向治疗和精准医疗时代, 查尔酮类化合物可能成为靶向肿瘤治疗的重要研究方向。

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