茶叶儿茶素的癌症化学预防增效机制研究进展

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摘要：研究证实，茶叶中儿茶素对预防癌症起到重要的作用，其中表没食子儿茶素没食子酸酯（EGCG）具有比较强的抗氧化、抑制癌细胞增殖和诱导细胞的凋亡能力，是化学预防癌症最具潜力的天然产物之一。作者归纳了儿茶素的生物活性、EGCG与天然抗癌产物和临床药物的增效机制研究进展，为更加深入地开展EGCG癌症化学预防机制研究提供参考。

关键词：茶；EGCG；化学预防；增效

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Advances in Synergistic Mechanism of Tea Catechins on Cancer Chemoprevention

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Abstract: Experiments have confirmed that tea is effective in preventing cancer, and catechins play the important role, among which EGCG has strong anti-oxidation to inhibit cancer cell proliferation and induce cancer cell apoptosis. EGCG is also one of the most potential natural products for cancer chemoprevention. In this paper, the biological activities of catechins were reviewed. Synergistic mechanism of EGCG with natural anticancer products and clinical reagents was summarized, to provide a reference for further research on cancer chemoprevention mechanism.

Keywords: EGCG, chemopreventive, synergistic effect

癌症是因细胞生长调控机制失控而引起的疾病，全球每年有超过1 000万人被确诊为癌症，超过600万人的死亡与癌症相关，约占全世界总死亡人数的12%[1]。传统的治疗手段之一是通过化学药物有效灭杀癌细胞和阻止癌细胞增殖，但往往会带来毒副作用、大面积创伤和多药耐药等不良结果。研究表明，30%~40%的癌症是可以预防的[2]，其中20%的癌症可通过合理的植物性膳食来预防[3]。流行病学和前瞻性研究也证实植物性膳食（水果、蔬菜和茶叶等）与降低癌症发病率存在一定的相关性[4-5]。

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因此,利用膳食营养或安全有效的天然产物抑制癌症的发生发展是预防癌症的有效手段之一,也是癌症化学预防研究的热点。

类黄酮化合物广泛存在于蔬菜、水果和茶叶等植物性膳食中,从蔬菜和水果中摄入高含量类黄酮化合物可降低胃癌的发生率[6]。茶叶是世界三大无酒精饮料之一,茶叶中含有丰富的类黄酮化合物,其中儿茶素占绿茶干质量的20%,远高于其他的植物性膳食[7]。据现存最早的药物典籍《神农本草》和《本草拾遗》记载,茶叶最早是被作为药物来使用,目前在湖南江华、广东阳山、广东龙门和广东梅州等山区仍保留有这一习惯。儿茶素属于黄烷3-醇,是茶叶中最重要的类黄酮化合物。流行病学、体内外实验和临床研究均证实绿茶具有化学预防癌症的功效,儿茶素是主要的活性成分[8]。作者对茶叶中儿茶素组分的生物学活性进行比较分析,重点对表没食子儿茶素没食子酸酯(EGCG)化学防预癌症的增效机制研究进展进行归纳总结,以期为天然产物应用于癌症化学预防提供参考。

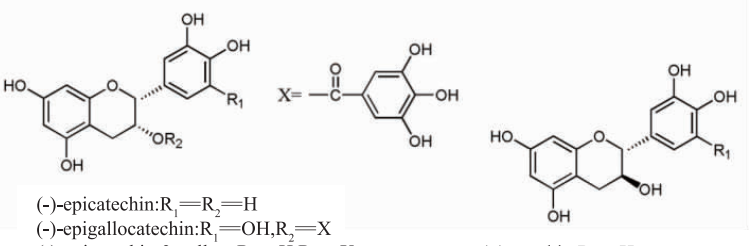
1 茶叶儿茶素生物学活性

2008年,Song和Chun通过分析8 809名美国成年人膳食结构发现[9],人体摄入的类黄酮中83.5%为儿茶素,其中96.9%的儿茶素来自于茶叶。茶叶中儿茶素有6种组分,分别是EGCG、表没食子儿茶素(EGC)、表儿茶素没食子酸酯(ECG)、没食子儿茶素(GC)和儿茶素(C)和表儿茶素(EC),其分子结构式见图1。Wang等[10]对绿茶水提物的HPLC分析表明,水提物中EGCG占11.16%,ECG占2.25%,EGC占10.32%,EC占2.45%,C占0.53%。EGCG是绿茶中占比最高的儿茶素组分。Zamora-Ros等[11]通过分析8个欧洲国家的340 234名成年人的儿茶素摄入量进一步发现,儿茶素平均摄入量为41.4 mg/d,其中EGCG的贡献最大(45.6%),其余依次为ECG(14.2%)、EGC(13.8%)、EC(13.2%)、C(9.2%)、CG(2.5%)和GC(1.5%)。ABTS、FRAP和DPPH试验表明,抗氧化活性依次为EGCG≥GCG≥ECG>EGC≥GC≥EC≥C,EGCG抗氧化活性最高[12]。Du等[13]以EGCG、ECG、EGC、EC、C、CG和GC分别处理人类大肠癌HCT-116和SW480细胞,EGCG、ECG、EGC、CG和GC均可抑制癌细胞分化且表现出剂量依赖性,其中EGCG抑制癌细胞分化和诱导细胞凋亡的能力最强。体外细胞试验表明,EGCG是儿茶素中预防癌症最有效的成分。EGCG的临床实验表明,90名感染宫颈子宫瘤病毒(HPV)的女性口服EGCG 400 mg/d 12周之后,超过50%的患者宫颈癌病变的损伤程度显著下降,活体检测病变组织完全消失,没有出现副作用[14]。60名有高度前列腺上皮瘤变(HG-PIN)的男性患者口服600 mg/d绿茶提取物(51.88% EGCG)1年后,呈阳性的男性患者患前列腺癌的几率降低了90%,没有出现明显的副作用[15]。因此,EGCG可预防宫颈癌和前列腺癌。

因此,EGCG是儿茶素组分中最有潜力的预防癌症的天然产物。大量的研究表明,EGCG癌症化学预防作用主要分为抑制癌细胞增殖、诱导癌细胞凋亡和抑制血管生成3个方面[16]。EGCG不仅在单独使用有预防癌症的功效,与其它潜在的天然抗癌成分和临床药物联用时具有增效作用。

2 EGCG与天然产物的协同增效作用

水果、蔬菜和茶叶等含有很多抗氧化化合物,如染料木黄酮、番茄红素、白藜芦醇和芦丁等,这些天然化合物具有化学预防癌症的功效[17]。EGCG被认为是最具潜力的化学预防癌症的药物前体,体内



(-)-epicatechin:R_1=R_2=H
(-)-epigallocatechin:R_1=OH,R_2=X
(-)-epicatechin-3-gallate:R_1=H,R_2=X
(-)-epigallocatechin-3-gallate:R_1=OH,R_2=X
(+)catechin:R_1=H
(+)-gallocatechin:R_1=OH

图1 儿茶素化学结构式

Fig. 1 Chemical structures of catechins

和体外试验证明,EGCG 有协同增强或加成天然产物抑制癌细胞增殖、促进癌细胞凋亡的作用,详细信息见表 1。

Wnt/β-链蛋白(Wnt/β-catenin)和音猬因子(Sonic hedgehog)信号通路是保持癌细胞干性的重要通路[38]。EGCG 通过下调肺癌 A549 和 H1299 干细胞中的 Wnt/β-catenin 信号通路来抑制干细胞分化,诱导细胞凋亡[39]。EGCG 也可通过调节 Hedgehog 信号通路,抑制胃癌 MGC-803 细胞增殖,诱导其凋亡[40]。茶黄素具有与儿茶素类似的酚羟基结构[41],茶黄素通过抑制人白血病 U937 和 K562 细胞中蛋白激酶 B 的信号来抑制 Hsp90 和Wnt/β-catenin 信号转导,上调细胞周期转录因子FOXO1,最终诱导细胞凋亡[42]。当 EGCG 与茶黄素联用时,可协同调节 Wnt/β-catenin 和 hedgehog 两条信号通路,减少肝癌 SMMC-7721 干细胞数量,有效抑制大鼠肝癌细胞增殖,诱导细胞凋亡[43]。

AP-1 是癌症预防中最重要的靶向目标,体内和体外实验均证实,AP-1 在正常细胞发育或肿瘤向癌症发展的过程中起关键作用[44],其中核因子 kappa B(NFκB)转录激活蛋白 AP-1,在细胞的转化和肿瘤的发生中起关键作用。Sen 等[45]用 EGCG 处理乳腺癌 MDA-MB-231 细胞,一方面下调粘着斑激酶(FAK)和细胞外调节激酶(ERK)活性,导致 FAK/ERK 诱导的 MMP-9 分泌中断;另一方面核因子 kappa B(NFκB)的表达和 NFκB 和激活蛋白 1(AP-1)与 MMP-9 启动子的 DNA 结合活性显著降低,MMP-9 转录失调,抑制癌细胞增殖,促进细胞凋亡。萝卜硫素(SFN)是西兰花中分离得到一种异硫氰酸盐化合物,具有预防癌症的功效[46]。Nair 等[34]将 SFN(25 mmol/L)和 EGCG(100 mmol/L)同时处理人结肠癌 HT-29 细胞,AP-1 显著激活并抑制细胞增殖,但 AP-1 启动子下游基因或细胞周期调节基因表达不显著。SFN 和 EGCG 联用后可减缓 EGCG 诱导的细胞程序性死亡。当 SFN (10 μmol/L)和 EGCG(20 μmol/L)处理卵巢癌 SKOV3 细胞,EGCG 协同增强 SFN 对紫杉醇敏感性细胞(SKOV3-ip1)和紫杉醇耐药性细胞(SKOV3TR-ip2)的抑制作用,通过下调 hTERT 和 Bcl-2 表达,诱导细胞凋亡。与 SKOV3-ip1 相比,EGCG/SFN 对 SKOV3TR-ip2 的抑制作用和诱导细胞凋亡的能力更显著,SFN/EGCG 特异性增强 SKOV3TR-ip2 DNA 损伤,阻滞细胞停留在 S 期[34]。

表 1 EGCG 与天然产物的协同增效作用

Table 1 Synergistic effect of epigallocatechin-3-gallate combined with natural products

编号	天然产物	英文名	类别	分子式	增效作用
1	[6]-姜酚	[6]-Gingerol	多酚	$C_{17}H_{26}O_4$	协同诱导神经胶质瘤 1321N1 和 LN18 细胞凋亡[18]
2	姜黄素	Curcumin	多酚	$C_{21}H_{20}O_6$	协同抑制口腔上皮 KB 细胞[19]、乳腺癌 MDA - MB - 231 细胞[20]、胃癌 A549 和 NCI-H460 细胞[21]、前列腺癌 PC-3 细胞增殖[22]
3	白藜芦醇	Resveratrol	多酚	$C_{14}H_{12}O_3$	协同诱导前列腺癌 PC-3 细胞凋亡[23],抑制头颈癌细胞增殖[24]
4	染料木黄酮/白藜芦醇	Genistein/ Resveratrol	黄酮/多酚	$C_{15}H_{10}O_5$ / $C_{14}H_{12}O_3$	协同减缓乳腺癌 MCF-7 和 MDA-MB-231 细胞增殖[25] 加成抑制前脂肪细胞 3T3-L1 和 HPAs.细胞分化[26]
5	茶黄素	Theaflavin	多酚	$C_{29}H_{24}O_9$	抑制肿瘤 JB6 细胞转变[27]
6	茶黄素-3-3'-双没食子酸/维生素 C	Theaflavin-3-3'-Digallate/ Ascorbic Acid	多酚/维生素	$C_{43}H_{32}O_{20}$/ $C_6H_8O_6$	协同诱导胃癌 SPC-A-1 和 Eca-109 细胞凋亡[28]
7	槲皮素	Quercetin	黄酮醇	$C_{15}H_{10}O_7$	协同抑制前列腺癌 PC-3 细胞侵袭、迁移和分化[29-30]
8	木犀草素	Luteolin	黄酮	$C_{15}H_{10}O_6$	协同诱导头颈部和肺癌细胞凋亡[31]
9	维生素 C	Ascorbic Acid	维生素	$C_6H_8O_6$	协同抑制肺腺癌 SPC-A-1 细胞增殖[32]
10	紫檀芪	Pterostilbene	二苯乙烯类	$C_{16}H_{16}O_3$	增强抑制胰腺癌 MIA PaCa-2 和 PANC-1 细胞增殖[33]
11	萝卜硫素	Chemoprevention	异硫氰酸酯类	$C_6H_{11}NOS_2$	协同诱导结肠癌 HT-29 细胞[34],卵巢癌 SK-OV-3 细胞凋亡[35]
12	人参二醇	Panaxadiol	皂苷	$C_{30}H_{52}O_3$	协同抑制大肠癌 HCT-116 细胞分化[36]
13	百里香醌	Thymoquinone	醌类	$C_{10}H_{12}O_2$	协同抑制胰腺癌 PANC-1 细胞增殖[37]

3 EGCG 与临床药物的协同增效作用

5-氟尿嘧啶、卡培他滨、顺铂和阿霉素等是临床常用的癌症预防药物,长期使用后人体会产生耐药性并产生毒副作用,严重者引起血液及实质脏器毒性。减少药物使用量和逆转癌细胞耐药性是癌症化学预防中亟待解决的问题。研究表明,EGCG 可与许多床抗癌药物联用,协同抑制多种癌细胞增殖并诱导其凋亡,也可增强癌细胞的敏感性,缓解细胞毒性,见表 2。

Cisplatin 是临床上使用广泛的抗肿瘤药物,Cisplatin 通过与 DNA 交联,阻断 DNA 转录和复制来达到抑制肿瘤生长[68]。肾脏毒性是 Cisplatin 临床应用时最显著的副作用,当单独使用 Cisplatin 时,小鼠细胞中核基因 Nrf2 和血红素加氧酶-1(HO-1)表达显著降低,NFκB 表达增加,引起小鼠肾脏毒性。当 EGCG 与 Cisplatin 联用时,Nrf-2 和 HO-1 表达增强,NFκB 表达降低,小鼠肾毒性减弱[69],EGCG 可通过抑制 Fas-l、Bax 和 p53 表达来增加 Bcl-2 的表达,从而增加细胞血清肌酐和 BUN,改善 Cisplatin 诱导的肾脏细胞凋亡[70]。EGCG 与 Cisplatin 可以抑制宫颈癌细胞中环氧化酶-2(COX-2)表达,增强 Nrf-2 和 HO-1 蛋白积累,降低 mTOR 途径相关基因表达,减弱 Cisplatin 细胞毒性,诱导癌细胞凋亡[50]。

Celecoxib 是 COX-2 的选择性抑制剂,可以预防多种癌症。GADD153 是 Celecoxib 诱导宫颈癌细胞细胞凋亡的关键因子[71]。EGCG 与 Cisplatin 联用,专一性地协同上调肺癌 PC-9 细胞中 GADD153 基因的高表达及蛋白质合成,诱导癌细胞凋亡[62]。单独使用 Celecoxib 时,Celecoxib 可诱导尿路上皮癌细胞停滞于 G1 期和内质网应激反应,促进细胞凋亡。当与 EGCG 联用时,EGCG 通过抑制内质网分子伴侣葡萄糖调节蛋白 78(GRP78)表达来增强细胞凋亡[72]。5-fluorouracil 是一种胃癌常用的预防药物,临床上有超过 50%的病人会出现耐药性[73]。转录因子

表 2 EGCG 与临床药物联用的增效作用

Table 2 Synergistic effect of epigallocatechin-3-gallate combined with clinical reagents

编号	临床药物	英文名	药物类型	增效作用
1	紫杉醇	Paclitaxel	抗肿瘤药物	协同抑制乳腺癌 MDA-MB-231 细胞增殖[47]
2	氮烯唑胺	Dacarbazine	抗肿瘤药物	协同抑制黑色素瘤的生长和转移[48]
3	紫杉烷	Taxane	抗肿瘤药物	协同诱导恶性前列腺癌 PC-3 凋亡[49]
4	顺铂	Cisplatin	抗肿瘤药物	协同增强对宫颈癌细胞的敏感性和诱导凋亡[50]
5	5-氟尿嘧啶	5-fluorouracil	抗代谢药物	逆转 5-fluorouracil 的耐药性[51]
6	雷洛昔芬	Raloxifene	抗癌药物	协同抑制乳腺癌细胞的增殖、诱导凋亡[52]
7	他莫昔芬	Tamoxifen	抗癌药物	协同诱导乳腺癌 MDA-MB-231 细胞凋亡[53]
8	厄洛替尼	Erlotinib	抗癌药物	协同抑制头颈部鳞状细胞癌增殖[54]
9	舒林酸	Sulindac	抗癌药物	协同增强大鼠结肠癌细胞凋亡[55]
10	卡培他滨	Capecitabine	抗癌药物	协同抑制小鼠血管生成和肿瘤生长[56]
11	帕纳替尼	Ponatinib	抗癌药物	协同诱导慢性粒细胞白血病 K562 细胞凋亡[57]
12	柔红霉素	Daunorubicin	抗癌药物	增强对肝癌 SMMC7721 细胞的敏感性,诱导细胞凋亡[58]
13	恩他卡朋	Entacapone	高选择性 COMT 抑制剂	协同抑制肺癌 H1299 和 CL-13 细胞增殖[59]
14	比卡鲁胺	Bicalutamide	非甾体类抗雄激素药物	协同抑制前列腺癌 LNCaP 细胞增殖,诱导凋亡[60]
15	塞来昔布	Celecoxib	非甾体抗炎药	协同诱导肺癌 A549[61]、ChagoK[61]和 PC-9[62]细胞凋亡
16	布洛芬	Ibuprofen	芳基丙酸类抗炎药物	协同诱导乳腺癌 DU-145 细胞凋亡[63]
17	阿霉素	Doxorubicin	蒽环类抗生素	协同杀死肝癌 Hep3B 细胞[64];抑制骨肉瘤细胞增殖,杀死癌细胞,逆转骨肉瘤细胞耐药性[65]
18	4-羟基他莫昔芬	4-Hydroxytamoxifen	雌激素受体调节分子	增强 4-羟基他莫昔芬对乳腺癌 MDA-MB-231 细胞毒性,诱导细胞提早凋亡[66]
19	西妥昔单抗	Cetuximab	EGFR 特异性抑制剂	加速乳腺癌 231DXR 和 HCCDXR 细胞凋亡[67]

TFAP2A 在癌细胞增殖中有关键作用,TFAP2A 可靶向调控癌细胞中 VEGF/VEGFR2 信号通路[74]。MDR-1 和 P-gp 通过调控信号通路抑制癌细胞凋亡和增强癌细胞耐药性[75]。当 EGCG 和 5-fluorouracil 联用时,EGCG 一方面通过抑制TFAP2A/VEGF 信号通路来抑制癌细胞增殖;另一方面下调胃癌 SGC7901 和 MGC803 细胞中耐药性相关蛋白MDR-1 和 P-gp 表达,逆转 5-fluorouracil 的耐药性[51]。

由上述可知,EGCG 对大部分临床癌症预防药物有协同增效作用。也有研究指出,EGCG 与硼替佐米(Bortezomib)和舒尼替尼(Sunitinib)联合使用时,则表现出拮抗作用。Bortezomib 是 26S 蛋白酶选择性抑制剂,可抑制多发性骨髓瘤和套细胞淋巴瘤细胞的增殖,促进癌细胞凋亡[76]。体外试验表明,Bortezomib 与 EGCG 联合使用时,EGCG 与 Bortezomib 反应形成复合物,5.0 nmol/L EGCG 可 100% 抑制 Bortezomib 对 RPMI/8226、U266 和 MM1 细胞的凋亡作用。小鼠试验进一步表明,EGCG 可显著减弱 Bortezomib 对多发性骨髓瘤细胞的凋亡作用。EGCG 也可有效拮抗 Bortezomib 对套细胞淋巴瘤细胞 LN229 和 U251 的毒性[77]。Sunitinib 是治疗胃癌的临床抗癌药物,体外和体内研究证实,EGCG 与 Sunitinib 可在胃中形成黏性复合体,阻碍 Sunitinib 的吸收,临床表现为患者的治疗症状不明显[78]。

4 展 望

EGCG 是植物中最有潜力的可预防癌症的天然产物之一。EGCG 是通过调控多靶点协同增强临床癌症药物的功效来促进癌细胞凋亡。EGCG 也可与癌症药物直接发生化学反应[77-78],通过调节药物代谢酶和药物转运体的活性[79-83]来影响药物吸收和生物活性起到降效作用。因此,EGCG 与抗癌药物在联合使用时增效或降效机制还需要更加深入研究,才能有效发挥 EGCG 在临床应用中的优势和潜力。

茶叶是人体摄入 EGCG 的重要来源,高剂量摄入 EGCG 会对肝脏产生毒性。流行病学和临床研究表明,饮用绿茶和茶饮料不会对人体肝脏产生毒性,EGCG 摄入量建议每人不超过704 mg/d[84-85]。动物试验表明,EGCG 以膳食补充剂(胶囊和药片)的形式摄入会产生肝脏毒性[86],人体对 EGCG 最大安全摄入量为每人 300~338 mg/d[85,87-88]。通过合理且科学的摄入 EGCG,可促进人体产生活性氧,激活 Nrf2 依赖性酶系统,发挥自身细胞的保护作用,可达到对癌症的预防作用[89],这也正是精准营养的实质,通过精准化的营养补充来预防和干预慢性疾病(癌症)。因此,EGCG 或儿茶素类作为膳食补充剂,在实现个体化精准营养中有很大的应用前景。

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