International Journal of Nutritional Sciences

Open Access

Austin Publishing Group

Review Article

Role of Epigallocatechin, Resveratrol and Curcumin as Anti-Inflammatory and Anti-Tumoral Agents

Giordano F, Mauro L, Naimo GD and Panno ML*
Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Italy

***Corresponding author:** Panno ML, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Cubo 4C, Via ponte P. Bucci, 87040 Arcavacata di Rende, Cosenza, Italy

Received: March 01, 2018; **Accepted:** April 09, 2018; **Published:** April 20, 2018

Abstract

Inflammatory microenvironment plays a critical role in tumorigenesis process as well as in chemoresistance. In response to tissue injury, inflammatory cytokines help to start and maintain carcinogenesis over time. Epidemiological investigations have shown that the consumption of polyphenol-rich food reduces the oxidative cellular damage and in such way, it can exert protective effects against degenerative diseases and cancers. In addition, these compounds reduce proliferation, trigger apoptosis, modulate signal transduction and have anti-inflammatory action. In this review we have focused the study on three polyphenolic compound-derivatives (EGCG, RES, CUR), going to show the molecular mechanism through which they antagonize the cancer – associated inflammation and the stem-cell chemoresistance.

Keywords: Polyphenols; Chemoresistance; Inflammation; Citokines

Introduction

The assumption that the "right nutrition" keeps a healthy life is quite known and mostly reiterated in traditional medicine. In recent years, natural compounds are getting increasing interest suggesting that their consumption, perpetuated over time, offers good defense for the onset of certain serious ailments such as cancer, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases. The phytochemicals, which include phenolics, carotenoids, alkaloids, nitrogen containing compounds, organosulfur compounds [1] have shown to possess anti-inflammatory, antioxidant and anti-tumoral effects, so they possess beneficial properties for human health. Acute inflammation is a transient reaction of the immune system against infection, which is self-regulating, while chronic inflammation is a prolonged response in which the persistent production of pro-inflammatory mediators, has been associated to the onset of chronic degenerative diseases and, very often, to the consequent tissue functional impairment.

The chronic inflammatory diseases are characterized by an enhanced state of oxidative stress, which may result from the overproduction of reactive species and/or a decrease in antioxidant defense.

Many studies have shown how it is necessary to keep under control the inflammatory process and ROS production in order to prevent the pathogenic processes such as cancer, cardiovascular and neurodegenerative diseases, and premature aging [2,3].

The conventional therapeutic approach, based on Non-Steroid Anti-Inflammatory Drugs (NSAID), used to counteract the pain and inflammation has represented, over the years, a real breakthrough. However, the widespread use of NSAIDs has also recorded numerous side effects and contraindications, especially if consumed for a long time or in combination with other drugs, with which they can interact. The role of natural products, as a remedy in the treatment and prevention of inflammatory diseases has long been known since ancient times. Today, they represent a valid alternative, especially in some conditions, since many products, due to technological innovation, are meticulously studied and tested in their biological effects at the cellular and molecular level. This has made their use more targeted and successful. The mechanism by which many natural products exert their beneficial effect is to reduce the proinflammatory mediators and to modulate immune response.

It is the case for the phenolic compounds, which decrease cytokine productions, down-regulate COX-2, TNFalpha, NF-κB, and IL-8 with minimal or null side effects [4].

The list of substances with these characteristics is always growing and, among these, it is worth mentioning the micronutrients e.g., Cu, Mn, Zn present in medical herbs that possess antioxidant action [5-7].

In recent years, particular attention has been paid to the antioxidant activity of algae, as they contain vitamin C and E, which display radical scavenging activities [8-10].

A balanced diet, rich in fruits and vegetable that contain many polyphenols, offers health guarantees, reduces the risk of heart disease, lowers the incidence of cancer and contrasts neurodegenerative disorders. The Mediterranean diet is a good example of this; it includes also the consumption of olive oil, a source of monounsaturated fat acids that can help reduce LDL cholesterol levels.

Many of phenolic compounds, such as isoflavones, quercetin, lignans, catechins, flavanones, resveratrol and curcumin have been studied due to their anticancer activity, even if their mechanisms of action is different. Generally, in tumoral cells, they reduce proliferation, trigger apoptosis, modulate signal transduction, and have antioxidant property and anti-inflammatory action [11,12].

The present review will focus on the protective effects of some polyphenols in the tumor pathogenesis and on their responses aimed

Panno et al. © All rights are reserved

Citation: Giordano F, Mauro L, Naimo GD and Panno ML. Role of Epigallocatechin, Resveratrol and Curcumin as Anti-Inflammatory and Anti-Tumoral Agents. Int J Nutr Sci. 2018; 3(1): 1022.

to antagonize the chemoresistance and the inflammatory process in the cells.

Cancer and inflammation

Cancer development is a complex and multistage process in which the mechanisms that control cell growth are subverted. Genetic changes, inherited or arisen during lifetime, that contribute to cancer development mainly affect three categories of genes: proto-oncogenes, tumor suppressor genes and DNA repair genes. The right functional balance of the first two categories of genes ensures the normal control of cell growth. However, the presence of mutations at their levels allows cells to growth and survive in an uncontrolled manner. The DNA repair genes, through their enzymatic products, represent an additional mechanism for monitoring chromosomes to correct damaged nucleotide. A defective to these enzymes would allow accumulation of mutations that might cause the cells to become cancerous.

During neoplastic growth, cancer cells are able to influence the nearby normal cells to form blood vessels that provide the nutrients necessary to ensure proliferative activity. In this way, neoplastic cells may spread through the connective tissues and begin the metastatic process.

Only 5–10% of all cancer cases can be attributed to genetic defects, while the remaining 90-95% are related to the environment and lifestyle [13,14].

The lifestyle factors include cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity. The correlation between diet and cancer is documented by the great variation in incidence rates of specific tumors in different countries and by the observed changes in populations following migration. The concept that hereditary factors tend to justify only a small part of the pathogenesis of tumors, while lifestyle has a profound influence, has postulated that tumors can be prevented. An important aspect to be considered is the contribution of inflammatory cytokines, in response to a tissue injury, in initiating and maintaining the tumor process. While acute inflammation is rarely linked to cancer, chronic inflammation is rather associated with tumorigenesis. Epidemiological studies heavily link chronic inflammation with cancer initiation, promotion, including progression, invasion and angiogenesis [15-17]. Inflammatory markers such as TNF, IL-1, IL-6, chemokines, eicosanoids, ROS, different Matrix Metalloproteases (MMPs) and elastases share various molecular targets and transductional pathways with the tumorigenic process. Indeed, they may affect apoptosis, proliferation and angiogenesis. Virus infections like those induced by human papillomavirus (HPV-cervical carcinoma), herpes virus (lymphoma), hepatitis B and C (hepatocarcinoma), cytomegalovirus (glioblastoma), and *Helicobacter pylori* (gastric cancer), by chronic inflammation, might trigger the tumorigenic process [18]. Other types of cancers associated with chronic inflammation are colorectal cancer, cholangiocarcinoma, lung cancer, prostate cancer, melanoma and many others. In a study conducted in USA on a population-based cohort of 692 inflammatory bowel disease patients the colorectal cancer risk was increased among those with extensive colitis. The incidence of colorectal cancer resulted to be slightly increased among Crohn's disease patients, who also had a 40-fold excess risk for small-bowel cancer [19]. Similarly, in liver diseases, like cholangiocarcinoma, characterized by a background of chronic inflammation, the high milieu of cytokines and growth factors allows a high rate of cell turnover, the accumulation of genetic alterations and growth of mutated cells. In same patients affected by cholangiocarcinoma, the over expression of EGFR or defective down regulation, correlated with the activation of MAPK or Akt, has been reported to trigger the tumorigenesis process. [20]. p53 mutation is seen in 20-61% of cholangiocarcinoma cases [21,22], together with dysregulation of cell cycle, and suppression of apoptotic response [23]. In addition, abnormal activation of inflammatory mechanisms induced by environmental factors might create dangerous conditions for the onset of different kinds of cancer. In fact, an important source of risk for lung, bladder, mouth, colon, kidney, throat cancers is habitual tobacco smoking and other irritants. For example, asbestos, silica, cadmio when inhalated, directly or indirectly, can trigger inflammation at the level of the respiratory parenchyma that builds a tumor-favorable microenvironment. Amplification of the Fibroblast Growth Factor Receptor 1 (FGFR1) is a frequent alteration found in lung carcinoma and it has been reported to correlate with a high incidence and mortality in lung cancer patients. In the recent paper, the authors addressed how the block of this receptor, through FGF monoclonal antibody, abrogated cell survival and the metastatic signaling pathways in lung cancer cells [24]. Another mechanism, related to the inflammatory process, that deserves attention, is the enrichment of the stem cell population supported by the cytokines and growth factors. The main characteristic of stem cells is their capacity for self-renewal, which gives them a lifetime existence. Chen et al in 2008 indicated that STAT3 is able to address both stem cell reprogramming and stem cell renewal [25]. In another study, it has been suggested that, in response to progastrin, IKKα, β/NFκB pathway may activate beta-catenin in colonic crypts, leading hyper proliferative and anti-apoptotic effects [26]. In fact, NFκB and STAT3 represent the cell-signaling molecules correlate with both inflammation and tumorigenesis. They are activated by growth factor signaling, hypoxia, hyperglycemia, flogistic mediators (IL-1, IL-6, TNF alpha). Many tumors have constitutively NFκB active and, on the other hand, its down regulation makes the cells more sensitive to chemotherapy treatments and regresses tumor growth in "*in vivo*" experiment [27-29]. NFκB is a pro-survival factor that, similarly to Akt, activates antiapoptotic responses in opposition to p53. Indeed, an inverse correlation exists between NFκB and p53, since they are antagonized each other. NFκB is able to suppress p53 expression by up regulating MDM2, which in turn addresses p53 to proteasomal degradation [30]. On the other hand, activated p53 induces NFkB DNA binding with a blockage of its transcriptional activity, suggesting a novel p53-mediated suppression system for tumorigenesis [31]. The complex functional antagonism between p53 and NFκB also includes the physical interaction with multimerisation domains of the transcription factors [32]. Therefore, the constitutive activation of NFkB, such as that which occurs as a result of persistent inflammation, may drive tumorigenic signal, especially when the suppressor brakes are weakened. In addition, it has been documented how NFkB might play a role in chemoresistance, since it results to be up regulated by many chemotherapy agents and by irradiation. In contrast, inhibition of the transcription factor increases sensitivity of cancer cells to the apoptotic action of chemotherapeutic agents and to radiation

exposure [33,34]. The inflammatory microenvironment itself plays an important role in promoting and maintaining the characteristics of cellular resistance. Overall, this is drived by secreted factors, cancer-associated fibroblasts, and host immune response and by stroma function. In Chronic Lymphocytic Leukemia (CLL), Stromal cell-Derived Factor 1 (SDF1) and its membrane-bound receptor, Chemokine (C-X-C motif) Receptor 4 (CXCR4), sustain ERK1/2 and Akt signal promoting tumor cell survival [35-37]. In human Colon Cancer (CRC) the above mentioned chemokine and its receptor CXR4 were enriched in chemotherapeutic-resistant CRC cells and inhibition of this signal reduces tumor formation and angiogenesis [38]. The pluripotency of cancer stem cells is dependent of many signaling factors such as nanog, oct4, sox2, Wnt , notch and Sonic hedgehog . The expression of nanog signal in ovarian cancer is essential for maintaining self-renewal and pluripotency in stem cells. It controls cell invasion and migration along with decreased expression of E-cadherin, caveolin-1 and FOX proteins [39]. Over expression of nanog is reported in breast, cervix, prostate, gastric and ovary cancers. In esophageal adenocarcinoma cells that express higher Notch pathways the tumors were partly or fully refractory to treatment. In contrast, suppression of Notch inhibits tumor growth in xenograft models, providing evidence that blocking of this signal will have efficacy for the treatment of this type of adenocarcinoma [40]. Stem/cell progenitor cells, as revealed in the literature, are involved in inflammation-mediated tumorigenesis [41,42] The data reported in Nasopharyngeal Carcinoma (NPC) show a greater expression of stem markers CD44v6 and ALDH1A1 compared to chronic nasopharyngitis tissues, as well as to normal nasopharyngeal epithelial cell line. Therefore, chronic inflammation can represent an etiological factor for human tumors and for stem cells enrichment [43]. Therefore, there is current opinion in the literature that inflammatory signaling cascades within the tumor microenvironment can promote, in differentiated tumor cells, the increased expression of stem cell markers, thus exacerbating tumor evolution. Since phytochemical compounds, as before mentioned, are able to counteract pro-inflammatory signals, it will be important to examine whether their implementation, alone or in combination with chemotherapeutics, can also help to decrease Cancer Stem Cell (CSC) populations and to promote better responses to standard therapy.

Anti-cancer and anti- inflammatory effects of polyphenols

Phenolic compounds are elements which possess an aromatic ring bearing one or more hydroxyl substituents. They include flavonoids (flavonols, flavones, isoflavones, anthocyanins, flavanols, flavanones, and others) and non flavonoids compounds (Benzoic acid, cinnamic acid, stilbenes, tannins and lignins) [44].

Daily consumption, over time, of food rich in these compounds preserves many diseases and chronic inflammatory processes. Nowadays, a lot of attention is paid to dietary habits, since it has revealed that a diet consisting of vegetables, fruits and grains has beneficial health effects.

Their efficiency is mainly due to the anti-inflammatory and antioxidant activity, therefore, capable of modulating cell signals, gene expression and essentially the cell behavior.

Here we focus on some specimens of polyphenols (Epigallocatechin gallate, Resveratrol, Curcumin) that show protective effects in many cancers and able also to counteract chemoresistance.

Epigallocatechin gallate (EGCG)

Epigallocatechin Gallate (EGCG), also known as epigallocatechin-3-gallate, is the ester of epigallocatechin and gallic acid. EGCG, mainly present in green tea, is the polyphenol catechin that feels antioxidant properties and for this, it may counteract inflammatory processes, associated with tumorigenesis. On hepatocellular carcinomas it inhibits proliferation in vitro and *in vivo*, induces apoptosis by the down regulation of Bcl-2 and Bcl-xl, through inactivation of NF-k, indicating that EGCG may be useful to improve clinical prognosis [45]. Doses of either green tea polyphenol mix or EGCG between 40 to 80μg/ml decreased the growth of estrogen receptor-negative breast cancer cell lines, inhibited the Her-2/neu signaling pathway and tumor cell survival [46]. In human thyroid carcinoma cell lines, EGCG inhibits growth, by affecting cyclin D1, p21 and p53, reduces metalloprotease activity and epithelial to mesenchymal transition [47]. Analogously, in HT-29 human colon adenocarcinoma cells, EGCG induces mitochondrial damages and apoptotic responses, by JNK activation [48]. The anti-cancer effect associated with green tea in human colorectal cancer cell lines HT-29 and HCA-7 was due to the inhibition of COX-2 and NF-kappaB expressions, and down regulation of the ERK1/2 and Akt pathways. The results point that inhibition of COX-2 is responsible for the anti-proliferative effect of green tea and this underscores the protective role that dietary factors have as anti-cancer agents [49]. Another recent study conducted in HCT116 human colon cancer cells, evidenced that tea polyphenol epigallocatechin inhibits Met signaling, proliferation and invasiveness, being more effective than Met inhibitor SU11274 [50]. In UV-induced skin tumors EGCG increases the numbers of cytotoxic T-lymphocyte and down regulates angiogenesis by decreasing VEGF production [51]. Furthermore, EGCG could directly scavenge ROS. The antioxidant activity results from the transfer of hydrogen atom or single-electron transfer reactions, involving hydroxyl groups of the B and/or D rings. In fact, due to the presence of the 'catechol' structure, Epicatechin (EC), Epigallocatechin Gallate (EGCG) and theaflavins are strong metal ion chelators. These molecules are able to prevent ROS formation, and, through this effect, they inhibit adhesion and invasion of hepatoma cells in culture [52]. By contrast, it has been reported that EGCG may act as pro-oxidant. The production of ROS by auto-oxidation of EGCG is important for its cytotoxic effects in cancer cells. As revealed, green tea catechin reduces cell growth an induces apoptosis in the presence of low-dose H (2) O (2) treated colon carcinoma cells. Under this condition, EGCG exerts its cytotoxic effect through ROS-mediated mechanisms [53]. These dual and contrasting responses depend on the cell culture conditions, on EGCG concentration, temperature and pH [54]. EGCG inhibits human Prostate Cancer cell (PC-3) proliferation by antagonizing the PI3-K-dependent signalling pathway and by blocking the androgen receptor [55,56]. The effect of EGCG, alone or in combination with curcumin, was investigated against breast Cancer Stem Cells (CSCs). Treatment of MDA-MB-231 and MCF7-HER2, with both compounds significant reduces the tumorigenicity and cell invasiveness. Since STAT3 is the oncogenic pathway involved in growth and self-renewal, in breast cancer cells curcumin and EGCG treatment was reported to clearly inhibited STAT3 activation and to reduce stem cell properties [57]. More recently, Fujiki H et al, reported that EGCG and green tea

extracts prevent carcinogenesis process at different levels [58]. The EGCG is active against drug-resistant human CSCs since it inhibits the transcription and translation of genes encoding stemness markers and furthermore the expression of the epithelial-mesenchymal transition phenotypes of human CSCs. The combinaton of EGCG with anticancer drugs has been pointed out to be a promising therapeutic agent to attack CSCs [58].

Resveratrol (RES)

Resveratrol is a plant polyphenol found prevalently in the skin of red grapes (50–100 mg of resveratrol per gram wet weight), but it is also present in peanuts, berries, and in other traditional medicines. Many epidemiological studies have demonstrated an inverse relationship between consumption of red wine and incidence of cardiovascular diseases. A phenomenon which is known as "French Paradox", since French populations has a low incidence of cardiovascular disease, while having a diet relatively rich in saturated fats [59]. Resveratrol induces phase II drug-metabolizing enzymes in order to act as anti-initiator, it mediates anti-inflammatory actions and inhibits hydroperoxidase and COX enzymes, thus antagonizing promotion activity. Furthermore, it retrieves anti-progression activity since it induces cell differentiation in human promyelocytic leukemia [60]. Different studies have indicated the anti-carcinogenic effects of resveratrol, given that it may affect cell cycle progression, protein kinase cascades, oxidative status of the cells, angiogenesis, metastatic process and inflammatory response. As concerning breast cancer, its anti-tumoral effect depends on concentrations used in experimental investigations. The molecule has structural similarities with Diethylstilbestrol (DES), so it acts as a selective estrogen modulator (SERM) capable of acting both as estrogen and anti-estrogen [59].

In fact, in MCF-7 cells low concentrations below 50μM promote cell growth, while high doses induced growth arrest and apoptosis [61]. In MDA-MB 231 xenograft tumors, resveratrol inhibits angiogenesis and increases apoptotic response [62].

The efficacy of this polyphenol has also been shown in androgen-dependent and androgen-independent prostate cancer cells. Treatment with resveratrol decreases prostate cancer cell survival signalings, blocks cell cycle at the G1-S phase and elevates the expression of pro-apoptotic proteins [63-65].

In xenograft mouse model, resveratrol counteracted pancreatic cancer by inhibiting leukotriene A4 hydrolase, which stimulates the production of inflammatory mediators and increased cancer cell growth [66].

In mice, the oral administration of RES, suppresses the UV-induced skin tumor progression. This effect is mainly linked to a down-regulation of TGF-Beta2 signaling, which sustains tumorigenesis in the experimental model [67]. This polyphenol decreases the inflammatory response by acting at different levels: it inhibits the synthesis of pro-inflammatory mediators, antagonizes the action of Kupffer cells, downregulates the expression of the adhesion molecules and counteracts the activation of immune cells. Mbimba T et al. reported that resveratrol prevents Diethylnitrosamine (DENA)-initiated hepatocarcinogenesis in rats by inhibiting inflammatory response and ROS production. In this study, resveratrol treatment reversed the DENA induced proinflammatory cytokines (TNF alpha, IL-1Beta, IL-6) and the oxidative stress, emphasizing its chemoprevention action against rat liver carcinogenesis [68]. Indeed, it is an excellent scavenger of hydroxyls and superoxides, as well as radicals generated in the cells by metals/enzymes. In a chronic colitis model, resveratrol caused a substantial reduction of pro-inflammatory cytokines (TNF-α and IL-1β) and an increase of anti-inflammatory IL-10 mediator, concomitantly with a reduction of the metabolism of arachidonic acid and eicosanoids. For these characteristics resveratrol diet represents a useful support for the treatment of chronic intestinal inflammation [69]. It had also been reported that this polyphenol could reverse drug resistance in cancer cells by sensitizing them to chemotherapeutic agents such as sorafenib and cisplatin [70,71]. The natural phytoalexin RES strengthened the pro-apoptotic effects of the drugs bortezomib and thalidomide and in addition it lowered the IL-6 release together with an inhibition of the STAT3, NF-kB pathway in myeloma cells. Overall, RES results an efficient strategy to overcome drug resistance [72]. In breast Cancer Stem Cells, RES suppressed the proliferation and decreased the size and number of mammospheres [73-75].

Curcumin (CUR)

The polyphenolic compound Curcumin (1,7- bis[4- hydroxy- 3-methoxyphenyl]- 1E, 6E- heptadiene- 3, 5-dione) is a derived from the ginger family *Curcuma longa* [76].

It has long been known in Asian medicine for its anti-inflammatory, antioxidant and anti-microbial properties [77].

Studies in this regard have highlighted its anti-tumor effects, since curcumin inhibits tumor initiation and tumor progression [78,79].

The anticancer effects occur because the molecule contrasts the metastatic process, the invasion, the proliferation and angiogenesis. In vivo animal models it has been assessed the anti-growth effect of CUR alone, or in combination with chemotherapeutic agents [80].

In cancer cells, CUR inhibits cell cycle progression and cell survival by affecting the cyclin D1, c-myc expressions, and the signaling mTOR, AkT, Bcl-2, Bcl-x [81]. The block of cell cycle in breast tumor cells was associated with the suppression of dynamic instability of microtubules, thus disturbing the mitotic spindle structure. This event may enhance nuclear translocation of p53, since antimitotic drugs address apoptosis by inhibiting microtubule dynamics [82]. In human lung carcinoma cells curcumin causes DNA damage and apoptosis, through the activation of caspases. Moreover, reports suggest that curcumin is able to induce apoptosis through extrinsic and intrinsic pathways [83,84].

Another mechanism through which curcumin antagonizes cell proliferation is the inhibition of growth factor signaling. EGFR, HER2, FGF, PDGF, IGF-1 are mainly affected by this compound in cancer cells, thus leading to a decreased activation of their downstream substrates ERK1/2 and p38 MAPK [85-87].

Curcumin's anticancer effect is also related to its anti-inflammatory response. It inhibits NF-kB stimulator Lipopolysaccharide (LPS)-induced inflammation and the expression of different NF-kB-targets such as c-myc, c-fos, c-jun, NIK, involved in oncogenic signals [88].

This polyphenol inhibits IKK- mediated phosphorylation of IκB as reported in Burkitt lymphoma cells and it addresses apoptosis.

In human myeloid leukemia and human embryonic kidney cells curcumin suppressed TNF-induced NF-kB dependent reporter gene expression and Akt activation. Moreover, it affects the NF-kB downstream targets such as COX-2, cyclin D1, c-myc as well as IAP, IAP2, XIAP, Bcl-2, which are involved in cell proliferation and antiapoptosis responses respectively. In addition, it down-regulates VEGF and metalloproteinases and in such way, it inhibits the carcinogenic process by acting at different levels [89].

Reports have indicated that CUR is also effective in endocrine-resistant mammary tumors since it sensitizes cancer cells to chemotherapy and target therapy [90-93].

Among the mechanisms that determine drug resistance, is the over-expression of drug efflux pumps such as P-glycoprotein and multidrug resistance protein 1. Therefore, molecules that could be used as potential and well-tolerated inhibitors of MDR proteins are being investigated in clinical trials.

In this regard, it has been reported that curcumoids are effective MDR modulators since they are able to inhibits MDR–mediated transport. In fact, these phytochemical molecules increased the sensitivity of vinblastine,mitoxantrone and etoposide in many drug resistance cancer cells. The suppressive effect of curcumin against cytokines was shown to reverse the multi-drug resistance and stemness. In fact, one mechanism by which curcumin targets CSCs is the inhibition of IL-6 release from cells and the STAT-3 phosphorylation. At the same time, it has been observed that curcumin suppresses Notch/Hedgehog pathways which, as well known, sustain CSCs and chemoresistance [94].

Overall, these findings suggested that curcumin alone and in combination with other drugs may be useful to increase the therapeutic benefit and to be effective also in the chemoresistant tumors.

Conclusion

Cancer chemoprevention with dietary phytochemicals is arousing considerable interest.

Natural polyphenolic products have profound antioxidant, anti-inflammatory, anti-antiangiogenic and pro-apoptotic actions with no side effects, when compared with the classic NSAID.

Research in this regard has been going on, many molecular mechanisms of natural compounds have been studied and, more recently, their antagonistic actions towards stemness has been highlighted.

This last aspect is very interesting since it is well known that enrichment of the stem component within the tumor mass, directs it towards the pharmacological resistance. Based on current scientific knowledge, foods rich in polyphenols offer protection for human health and their frequent use in the diet may represent a great opportunity for the prevention and treatment of many malignancy diseases, even in cases of cellular resistance.

References

1. Budisan L, Gulei D, Zanoaga OM, Irimie AI, Chira S, Braicu C, et al. Dietary Intervention by Phytochemicals and Their Role in Modulating Coding and Non-Coding Genes in Cancer. 2017; 18: 1178.
2. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MNVR. Role of Antioxidants in Prophy-laxis and Therapy: A Pharmaceutical Perspective. Journal of Controlled Release. 2006; 113: 189-207.
3. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free Radicals and Antioxidants in Normal Physiological Functions and Human Disease. International Journal of Biochemistry & Cell Biology. 2007; 39: 44-84.
4. Herrera-Carrera E, Moreno-Jiménez MR, Rocha-Guzmán NE, Gallegos-Infante JA, Díaz-Rivas JO, Gamboa-Gómez CI, et al. Phenolic composition of selected herbal infusions and their anti-inflammatory effect on a colonic model *in vitro* in HT-29 cells. Cogent Food & Agriculture. 2015; 1: 1059033.
5. Frei B, Higdon JV. Antioxidant Activity of Tea Polyphenols *in Vivo*: Evidence from Animal Studies. Journal of Nutrition. 2003; 133: 3275s-3284s.
6. Higdon JV, Frei B. Tea Catechins and Polyphenols: Health Effects, Metabolism, and Antioxidant Functions. Critical Reviews in Food Science and Nutrition. 2003; 43: 89-143.
7. Czinner E, Hagymasi K, Blazovics A, Kery A, Szoke E, Lemberkovics E. The *in vitro* effect of Helichysi flos on microsomal lipid peroxidation. Journal of Ethnopharmacology. 2001; 77: 31-35.
8. Li YX, Li Y, Lee SH, Qian ZJ, Kim SK. Inhibitors of Oxidation and Matrix Metalloproteinases, Floridoside, and D-Isofloridoside from Marine Red Alga Laurencia undulate. Journal of Agricultural and Food Chemistry. 2010; 58: 578-586.
9. Li K, Li XM, Ji NY, Wang BG. Natural Bromo-phenols from the Marine Red Alga Polysiphonia Urceo-lata (Rhodomelaceae): Structural Elucidation and DPPH Radical-Scavenging Activity. Bioorganic and Medicinal Chemistry. 2007; 15: 6627-6631.
10. MacArtain P, Gill CIR, Brooks M, Campbell R, Rowland IR. Nutritional Value of Edible Seaweeds. Nutrition Reviews. 2007; 65: 535-543.
11. García-Lafuente A, Guillamón E, Villares A, Rostagno MA, Martínez JA. Flavonoids as antiinflammatory agents: implications in cancer and cardiovascular disease. Inflamm Res. 2009; 58: 537-552.
12. Cojocneanu Petric R, Braicu C, Raduly L, Zanoaga O, Dragos N, Monroig P, et al. Phytochemicals modulate carcinogenic signaling pathways in breast and hormone-related cancers. Onco Targets Ther. 2015; 6: 2053-2066.
13. Stein CJ, Colditz GA. Modifiable risk factors for cancer. Br J Cancer. 2004; 90: 299–303.
14. Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008; 25: 2097–2116.
15. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860–867.
16. Philip M, Rowley DA, Schreiber H. Inflammation as a tumor promoter in cancer induction. Semin Cancer Biol. 2004; 14: 433–439.
17. Blaylock RL. Cancer microenvironment, inflammation and cancer stem cells: A hypothesis for a paradigm change and new targets in cancer control. Surg Neurol Int. 2015; 6: 92.
18. Read SA, Douglas MW. Virus induced inflammation and cancer development. Cancer Lett. 2014; 345: 174–181.
19. Jess T, Loftus EV Jr, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, et al. Risk of Intestinal Cancer in Inflammatory Bowel Disease: A Population-Based Study From Olmsted County, Minnesota. GASTROENTEROLOGY. 2006; 130: 1039– 1046.
20. Leone F, Cavalloni G, Pignochino Y, Sarotto I, Ferraris R, Piacibello W, et al. Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma. Clin. Cancer Res. 2006; 12: 1680-1685.
21. Khan SA, Carmichael PL, Taylor-Robinson SD, Habib N, Thomas HC. DNA adducts, detected by 32P post labelling, in human cholangiocarcinoma. Gut. 2003; 52: 586-591.
22. Nault JC, Zucman-Rossi J. Genetics of hepatobiliary carcinogenesis. Semin liver dis. 2011; 31: 173-187.

23. Zabron A, Edwards RJ, Khan SA. The challenge of cholangiocarcinoma: dissecting the molecular mechanisms of an insidious cancer. Disease Models & Mechanisms. 2013; 6: 281-292.

24. Hu P, Chen H, McGowan E, Ren N, Xu M, Lin Y. Assessment of FGFR1 Overexpression and Over-Activity in Lung Cancer Cells: A Toolkit for Anti-FGFR1 Drug Screening. Hum Gene Ther Methods. 2018; 29: 30-43.

25. Chen X, Xu H, Yuan P, Fang F, Huss M, Vega VB, et al. Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. Cell. 2008; 133: 1106–1117.

26. Umar S, Sarkar S, Wang Y, Singh P. Functional Cross-talk between beta-Catenin and NF{kappa}B Signaling Pathways in Colonic Crypts of Mice in Response to Progastrin. J Biol Chem. 2009; 284: 22274–22284.

27. Gasparian AV, Burkhart CA, Purmal AA, Brodsky L, Pal M, Saranadasa M, et al. Curaxins: anticancer compounds that simultaneously suppress NF-kappaB and activate p53 by targeting FACT. Sci Transl Med 2011; 3: 95ra74.

28. Vlantis K, Wullaert A, Sasaki Y, Schmidt-Supprian M, Rajewsky K, Roskams T, et al. Constitutive IKK2 activation in intestinal epithelial cells induces intestinal tumors in mice. J Clin Invest. 2011; 121: 2781–2793.

29. Gurova KV, Hill JE, Guo C, Prokvolit A, Burdelya LG, Samoylova E, et al. Small molecules that reactivate p53 in renal cell carcinoma reveal a NF-kappaB-dependent mechanism of p53 suppression in tumors. Proc Natl Acad Sci U S A 2005; 102: 17448–17453.

30. Vucic D, Dixit VM, Wertz IE. Ubiquitylation in apoptosis: a post-translational modification at the edge of life and death. Nat Rev Mol Cell Biol. 2011; 12: 439–452.

31. Kawauchi K, Araki K, Tobiume K, Tanaka N. Activated p53 induces NF-kappaB DNA binding but suppresses its transcriptional activation. Biochem Biophys Res Commun. 2008; 372: 137-141.

32. Ikeda A, Sun X, Li Y, Zhang Y, Eckner R, Doi TS, et al. p300/CBP-dependent and–independent transcriptional interference between NF-kappaB RelA and p53. Biochem Biophys Res Commun. 2000; 272: 375–379.

33. Wang CY, Cusack JC jr, Liu R, Baldwin AS jr. Control of inducible chemoresistance: Enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-κB. Nat Med. 1999; 5: 412-417.

34. Li F, Seth G. Targeting transcription factor NF-kappaB to overcome chemoresistance and radioresistance in cancer therapy. Biochim Biophys Acta. 2010; 1805: 167-180.

35. Martin M, Wei H, Lu T. Targeting microenvironment in cancer therapeutics. Oncotarget. 2016; 7: 52575– 52583.

36. Burger JA, Tsukada N, Burger M, Zvaifler NJ, Dell'Aquila M, Kipps TJ. Blood-derived nurse-like cells protect chronic lymphocytic leukemia B cells from spontaneous apoptosis through stromal cell-derived factor-1. Blood. 2000; 96: 2655–2663.

37. Nishio M, Endo T, Tsukada N, Ohata J, Kitada S, Reed JC, et al. Nurselike cells express BAFF and APRIL, which can promote survival of chronic lymphocytic leukemia cells via a paracrine pathway distinct from that of SDF-1. Blood. 2005; 106: 1012–1020.

38. Margolin DA, Silinsky J, Grimes C, Spencer N, Aycock M, Green H, et al. Lymphnode stromal cells enhance drug-resistant colon cancer cell tumor formation through SDF-1α/CXCR4 paracrine signaling. Neoplasia. 2011; 13: 874-886.

39. Siu MKY, Wong ESY, Kong DSH, Chan HY, Jiang L, Wong OGW, et al. Stem cell transcription factor NANOG controls cell migration and invasion via dysregulation of E-cadherin and FoxJ1 and contributes to adverse clinical outcome in ovarian cancers. Oncogene. 2013; 32: 3500–3509.

40. Wang Z, Da Silva TG, Jin K, Han X, Ranganathan P, zu X, et al. Notch signaling drives stemness and tumorigenicity of esophageal adenocarcinoma. Cancer Res. 2014; 74: 6364–6374.

41. Maitland NJ, Collins AT. Inflammation as the primary aetiological agent of human prostate cancer: a stem cell connection? Journal of Cellular Biochemistry. 2008; 105: 931–939.

42. Alison MR. Liver stem cells: implications for hepatocarcinogenesis. Stem Cell Reviews. 2005; 1: 253–260.

43. Wang S, Ma N, Zhao W, Midorikawa K, Kawanishi S, Hiraku Y, et al. Inflammation-Related DNA Damage and Cancer Stem Cell Markers in Nasopharyngeal Carcinoma. Mediators Inflamm. 2016; 9343460.

44. Ambriz-Pérez DL, Leyva-López N, Gutierrez-Grijalva EP, Heredia JB. Phenolic compounds: Natural alternative in inflammation treatment. A Review. Cogent Food & Agriculture. 2016; 2: 1131412.

45. Nishikawa T, Nakajima T, Moriguchi M, Jo M, Sekoguchi S, Ishii M, et al. A green tea polyphenol, epigalocatechin-3-gallate, induces apoptosis of human hepatocellular carcinoma, possibly through inhibition of Bcl-2 family proteins. J Hepatol. 2006; 44: 1074-1082.

46. Pianetti S, Guo S, Kavanagh KT, Sonenshein GE. Green tea polyphenol epigallocatechin-3 gallate inhibits Her-2/neu signaling, proliferation, and transformed phenotype of breast cancer cells. Cancer Res. 2002; 62: 652-655.

47. De Amicis F, Perri A, Vizza D, Russo A, Panno ML, Bonofiglio D, et al. Epigallocatechin gallate inhibits growth and epithelial-to-mesenchymal transition in human thyroid carcinoma cell lines. J Cell Physiol. 2013; 228: 2054-2062.

48. Chen C, Shen G, Hebbar V, Hu R, Owuor ED, Kong AN. Epigallocatechin-3-gallate-induced stress signals in HT-29 human colon adenocarcinoma cells. Carcinogenesis. 2003; 24: 1369-1378.

49. Peng G, Dixon DA, Muga SJ, Smith TJ, Wargovich MJ. Green tea polyphenol (-)-epigallocatechin-3-gallate inhibits cyclooxygenase-2 expression in colon carcinogenesis. Mol Carcinog. 2006; 45: 309-319.

50. Larsen CA, Dashwood RH. (-)-Epigallocatechin-3-gallate inhibits Met signaling, proliferation, and invasiveness in human colon cancer cells. Arch Biochem Biophys. 2010; 501: 52-57.

51. Mantena SK, Roy AM, Katiyar SK. Epigallocatechin-3-gallate inhibits photocarcinogenesis through inhibition of angiogenic factors and activation of CD8+ T cells in tumors. Photochem Photobiol. 2005; 81:1174-1179.

52. Zhang G, Miura Y, Yagasaki K. Suppression of adhesion and invasion of hepatoma cells in culture by tea compounds through antioxidative activity. Cancer Lett. 2000; 159: 169-173.

53. Park IJ, Lee YK, Hwang JT, Kwon DY, Ha J, Park OJ. Green tea catechin controls apoptosis in colon cancer cells by attenuation of H2O2-stimulated COX-2 expression via the AMPK signaling pathway at low-dose H2O2. Ann N Y Acad Sci. 2009; 1171: 538-544.

54. Min KJ, Kwon TK. Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate. Integrative Medicine Research. 2014; 3: 16-24.

55. Albrecht DS, Clubbs EA, Ferruzzi M, Bomser JA. Epigallocatechin-3-gallate (EGCG) inhibits PC-3 prostate cancer cell proliferation via MEK-independent ERK1/2 activation. Chemi. Biol. Interact. 2008; 171: 89–95.

56. Siddiqui IA, Asim M, Hafeez BB, Adhami VM, Tarapore RS, Mukhtar H. Green tea polyphenol EGCG blunts androgen receptor function in prostate cancer. FASEB J. 2011; 25: 1198–1207.

57. Chung SS, Vadgama JV. Curcumin and epigallocatechin gallate inhibit the cancer stem cell phenotype via down-regulation of STAT3-NFkB signaling. Anticancer Res. 2015; 35: 39–46.

58. Fujiki H, Sueoka E, Rawangkan A, Suganuma M. Human cancer stem cells are a target for cancer prevention using (-)-epigallocatechin gallate. J Cancer Res Clin Oncol. 2017; 143: 2401-2412.

59. Harikumar KB, Aggarwal BB. Resveratrol: A multitargeted agent for age associated chronic diseases. Cell Cycle. 2008; 7: 1020-1035.

60. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997; 275: 218–220.

61. Basly JP, Marre Fournier F, Le Bail JC, Habrioux G, Chulia AJ. Estrogenic/antiestrogenic and scavenging properties of (E) - and (Z)-resveratrol. Life Sci. 2000; 66: 769-777.

62. Garvin S, Ollinger K, Dabrosin C. Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts *in vivo*. Cancer Lett. 2006; 231: 113-122.

63. Scifo C, Cardile V, Russo A, Consoli R, Vancheri C, Capasso F, et al. Resveratrol and propolis as necrosis or apoptosis inducers in human prostate carcinoma cells. Oncol Res. 2004; 14: 415-426.

64. Kim YA, Rhee SH, Park KY, Choi YH. Antiproliferative effect of resveratrol in human prostate carcinoma cells. J Med Food. 2003; 6: 273-280.

65. Horvath Z, Marihart Fazekas S, Saiko P, Grusch M, Ozsuy M, Harik M, et al. Novel resveratrol derivatives induce apoptosis and cause cell cycle arrest in prostate cancer cell lines. Anticancer Res 2007; 27: 3459-3464.

66. Byrum RS, Goulet JL, Snouwaert JN, Griffiths RJ, Koller BH. Determination of the contribution of cysteinyl leukotrienes and leukotriene B4 in acute inflammatory responses using 5-lipoxygenase- and leukotriene A4 hydrolase-deficient mice. J. Immunol. 1999; 163: 6810–6819.

67. Kim KH, Back JH, Zhu Y, Arbesman J, Athar M, Kopelovich L, et al. Resveratrol targets transforming growth factor-β2 signaling to block UV-induced tumor progression. J Invest Dermatol. 2011; 131: 195-202.

68. Mbimba T, Awale P, Bhatia D, Geldenhuys WJ, Darvesh AS, Carroll RT, et al. Alteration of hepatic proinflammatory cytokines is involved in the resveratrol-mediated chemoprevention of chemically-induced hepatocarcinogenesis. Curr Pharm Biotechnol. 2012; 13: 229-234.

69. Sánchez-Fidalgo S, Cárdeno A, Villegas I, Talero E, de la Lastra CA. Dietary supplementation of resveratrol attenuates chronic colonic inflammation in mice. Eur J Pharmacol. 2010; 633: 78-84.

70. Mondal A, Bennett LL. Resveratrol enhances the efficacy of sorafenib mediated apoptosis in human breast cancer MCF7 cells through ROS, cell cycle inhibition, caspase 3 and PARP cleavage. Biomed. Pharmacother. 2016; 84: 1906–1914.

71. Lee YJ, Lee GJ, Yi SS, Heo SH, Park CR, Nam HS, et al. Cisplatin and resveratrol induce apoptosis and autophagy following oxidative stress in malignant mesothelioma cells. Food Chem. Toxicol. 2016; 97: 96–107.

72. Bhardwaj A, Sethi G, Vadhan-Raj S, Bueso-Ramos C, Takada Y, Gaur U, et al. Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-kappaB-regulated antiapoptotic and cell survival gene products in human multiple myeloma cells. Blood. 2007; 109: 2293-2302.

73. Dandawate PR, Subramaniam D, Jensen RA, Anant S. Targeting cancer stem cells and signaling pathways by phytochemicals: novel approach for breast cancer therapy. Semin Cancer Biol. 2016; 40–41: 192–208.

74. Fu Y, Chang H, Peng X, Bai Q, Yi L, Zhou Y, et al. Resveratrol inhibits breast cancer stem-like cells and induces autophagy via suppressing wnt/beta-catenin signaling pathway. PLoS One. 2014; 9: e102535.

75. Su YC, Li SC, Wu YC, Wang LM, Chao KS, Liao HF. Resveratrol downregulates interleukin-6-stimulated sonic hedgehog signaling in human acute myeloid leukemia. Evid Based Complement Alternat Med. 2013; 547430.

76. Bolton EE, Wang Y, Thiessen PA, Bryant SH. PubChem: integrated platform of small molecules and biological activities. In: Ralph AW, David CS, editors. Annual Reports in Computational Chemistry. Amsterdam, Netherlands: Elsevier. 2008; 4: 217–241.

77. Grynkiewicz G, Slifirski P. Curcumin and curcuminoids in quest for medicinal status. Acta Bioch Pol. 2012; 59: 201–212.

78. Huang MT, Wang ZY, Georgiadis CA, Laskin JD, Conney AH. Inhibitory effects of curcumin on tumor initiation by benzo[a] pyrene and 7, 12-dimethylbenz[a] anthracene. Carcinogenesis. 1992; 13: 2183–2186.

79. Conney AH, Lysz T, Ferraro T, Abidi TF, Manchand PS, Laskin JD, et al. Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. Adv Enzyme Regul. 1991; 31: 385–396.

80. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett. 2008; 269: 199-225.

81. Wanga H, Khorb TO, Shub L, Sub Z, Fuentesb F, Leeb J, et al. Plants Against Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability . Anticancer Agents Med Chem. 2012; 12: 1281–1305.

82. Banerjee M, Singh P, Panda D. Curcumin suppresses the dynamic instability of microtubules, activates the mitotic checkpoint and induces apoptosis in MCF-7 cells. FEBS J. 2010; 277: 3437-3448.

83. Bush JA, Cheung KJ Jr, Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase- 8 pathway independent of p53. Exp Cell Res. 2001; 271: 305–314.

84. Anto RJ, Mukhopadhyay A, Denning K, Aggarwal BB. Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: its suppression by ectopic expression of Bcl-2 and Bcl-xl. Carcinogenesis. 2002; 23: 143–150.

85. Squires MS, Hudson EA, Howells L, Sale S, Houghton CE, Jones JL, et al. Relevance of mitogen activated protein kinase (MAPK) and phosphotidylinositol- 3-kinase/protein kinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells. Biochem Pharmacol. 2003; 65: 361–376.

86. Chadalapaka G, Jutooru I, Chintharlapalli S, Papineni S, Smith R 3rd, li x, et al. Curcumin decreases specificity protein expression in bladder cancer cells. Cancer Res. 2008; 68: 5345–5354.

87. Lev-Ari S, Starr A, Vexler A, Karaush V, Loew V, Greif J, et al. Inhibition of pancreatic and lung adenocarcinoma cell survival by curcumin is associated with increased apoptosis, down-regulation of COX-2 and EGFR and inhibition of Erk1/2 activity. Anticancer Res. 2006; 26: 4423–4430.

88. Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, et al. Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway. Clin Cancer Res. 2007; 13: 3423–3430.

89. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol 2006; 69: 195-206.

90. Zhou QM, Wang XF, Liu XJ, Zhang H, Lu YY, Huang S, et al. Curcumin improves MMC-based chemotherapy by simultaneous sensitising cancer cells to MMC and reducing MMC-associated side-effects. Eur J Cancer. 2011; 47: 2240-2247.

91. Sen G, Mohanty S, Hossain DM, Bhattacharyya S, Banerjee S, Chakraborty J, et al. Curcumin enhances the efficacy of chemotherapy by tailoring p65 NFkappaB-p300 cross-talk in favor of p53-p300 in breast cancer. J Biol Chem. 2011; 286: 42232–42247.

92. Zhou Y, Eppenberger-Castori S, Eppenberger U, Benz CC. The NFkappaB pathway and endocrine-resistant breast cancer. Endocr Relat Cancer. 2005; 12: S37–S46.

93. Jiang M, Huang O, Zhang X, Xie Z, Shen A, Liu H, et al. Curcumin induces cell death and restores tamoxifen sensitivity in the antiestrogen-resistant breast cancer cell lines MCF-7/LCC2 and MCF-7/LCC9. Molecules. 2013; 18: 701-720.

94. Sordillo PP, Helson L. Curcumin and cancer stem cells: curcumin has asymmetrical effects on cancer and normal stem cells. Anticancer Research. 2015; 35: 599-614.