

Review Article

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

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***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; Cytokines**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, TNF α , NF- κ B, 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

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 grow 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 some 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 inhaled, 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, IKK α , β /NF κ B pathway may activate beta-catenin in colonic crypts, leading hyper proliferative and anti-apoptotic effects [26]. In fact, NF κ B 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 NF κ B 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]. NF κ B is a pro-survival factor that, similarly to Akt, activates antiapoptotic responses in opposition to p53. Indeed, an inverse correlation exists between NF κ B and p53, since they are antagonized each other. NF κ B 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 NF κ B 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 NF κ B also includes the physical interaction with multimerisation domains of the transcription factors [32]. Therefore, the constitutive activation of NF κ B, 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 NF κ B 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 driven 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 CXCR4 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 and induces apoptosis in the presence of low-dose H₂O₂ 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 significantly 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 combination 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 50 μ M 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 (DEN)-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-1 β) 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 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 antimetabolic 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 I κ B as reported in Burkitt lymphoma cells and it addresses apoptosis.

In human myeloid leukemia and human embryonic kidney cells curcumin suppressed TNF-induced NF- κ B dependent reporter gene expression and Akt activation. Moreover, it affects the NF- κ B 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 inhibit 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-angiogenic 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.

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