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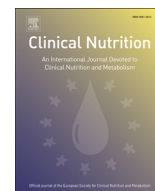
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## Review

## Green tea polyphenol epigallocatechin-3-gallate (EGCG) as adjuvant in cancer therapy

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## SUMMARY

**Background & aims:** Green tea catechins, especially epigallocatechin-3-gallate (EGCG), have been associated with cancer prevention and treatment. This has resulted in an increased number of studies evaluating the effects derived from the use of this compound in combination with chemo/radiotherapy. This review aims at compiling latest literature on this subject.

**Methods:** Keywords including EGCG, cancer, chemotherapy, radiotherapy and side effects, were searched using PubMed and ScienceDirect databases to identify, analyze, and summarize the research literature on this topic. Most of the studies on this subject up to date are preclinical. Relevance of the findings, impact factor, and date of publication were critical parameters for the studies to be included in the review.

**Results:** Additive and synergistic effects of EGCG when combined with conventional cancer therapies have been proposed, and its anti-inflammatory and antioxidant activities have been related to amelioration of cancer therapy side effects. However, antagonistic interactions with certain anticancer drugs might limit its clinical use.

**Conclusions:** The use of EGCG could enhance the effect of conventional cancer therapies through additive or synergistic effects as well as through amelioration of deleterious side effects. Further research, especially at the clinical level, is needed to ascertain the potential role of EGCG as adjuvant in cancer therapy.

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## 1. Introduction

Green tea, the second most consumed beverage all over the world after water, is characterized by being rich (30% of dry weight) in non-oxidized catechins among which epigallocatechin-3-gallate (EGCG) stands out as the most abundant and active.<sup>1</sup> The use of this catechin has been shown to inhibit cancer process *in vitro* and in animal models, not only during the initiation but also during progression and metastasis, in a high variety of cancer types including skin, breast, prostate, colorectal, liver and lung cancer.<sup>2</sup>

Moreover, its potential use as chemo/radiosensitizer of cancer cells has been proposed, and synergistic effects with different cancer treatments have been shown.<sup>3</sup> In addition, antioxidant and

anti-inflammatory properties of EGCG have been associated with the amelioration of adverse side effects derived from cancer therapy.<sup>4</sup> (Fig. 1).

Nevertheless, it should be noted that most of the studies published to date on this topic are preclinical, and that undesirable interactions of EGCG with some anticancer drugs have been described. Therefore, further research, especially at the clinical level, is needed to support the potential role of EGCG as adjuvant in cancer therapy.

## 2. EGCG as adjuvant for cancer therapy

Time-dependent resistances to chemo- and radiotherapy, as well as treatment discontinuation caused by side effects, are major problems in cancer treatment. Consequently, the development of new strategies, including combination of conventional therapies with bioactive dietary compounds such as EGCG, has gained considerable interest in last years. These new cancer treatment strategies have been shown to exert additive or synergistic activities, and to decrease therapy-induced toxicity, when combined with chemo- or radiotherapy. As explained in detail below, EGCG has been proposed as potential adjuvant for cancer therapy.<sup>3</sup>

**Abbreviations:** 5-FU, 5-fluorouracil; ATO, arsenic trioxide; CP, cisplatin; DNR, daunorubicin; DNROL, daunorubicinol; DOX, doxorubicin; EGCG, epigallocatechin-3-gallate; HBMEC, human brain microvascular endothelial cells; HRPc, hormone refractory prostate cancer; HNE, hydroxynonenal; IL, interleukin; IR, ionizing radiation; ROS, reactive oxygen species; TSA, trichostatin A.

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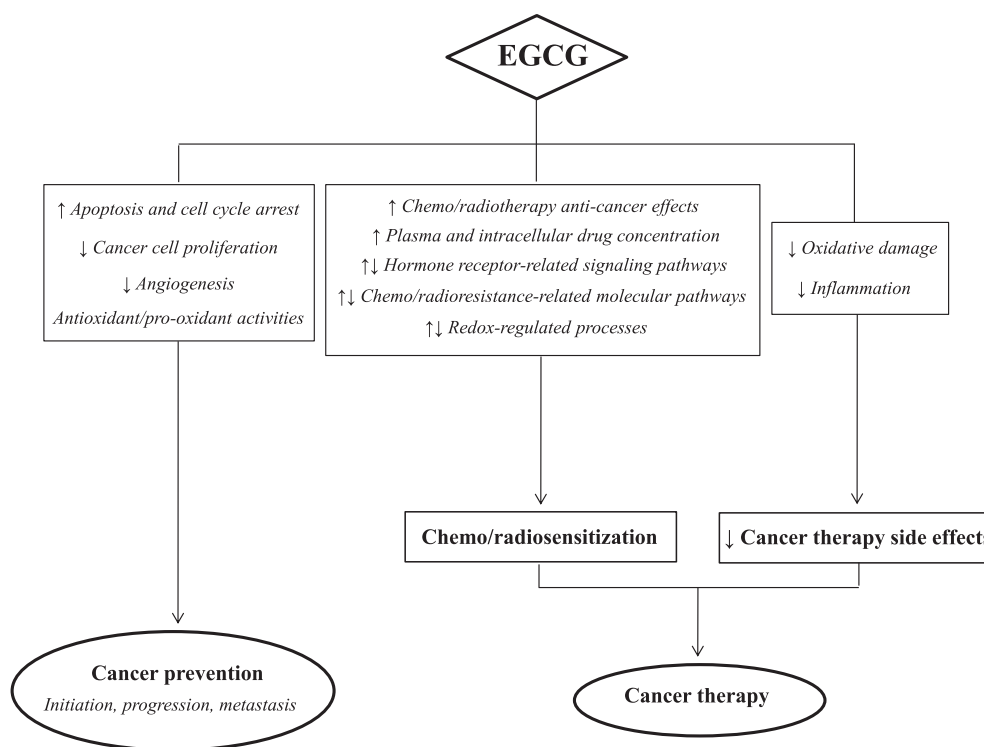


Fig. 1. Role of EGCG in cancer prevention and treatment. ↑, Increase; ↓, decrease; ↑↓, modulation.

### 3. EGCG as chemosensitizer

EGCG-induced chemosensitization of cancer cells through additive or synergistic effects with anticancer drugs have been evidenced in a number of preclinical, *in vitro* and *in vivo* studies. The effect of drugs such as 5-fluorouracil (5-FU), temozolomide, cisplatin or tamoxifen has been shown to be significantly increased when combined with EGCG, in a variety of cancer types. Different mechanisms of action have been proposed to explain the improvement of anticancer drugs by EGCG as shown in Table 1. More than one might contribute to the overall effect and different molecular events could be involved depending on the drug and the type and stage of cancer. Chemosensitization of cancer cells could imply decreases in drug doses and, as a consequence, reduced risk of undesirable side effects.

#### 3.1. Alteration of anticancer drug pharmacokinetics

Increased intracellular drug concentration is one of the proposed events related to the enhancement of chemotherapy by EGCG. Some recent studies have described this effect for 5-FU,<sup>5</sup> doxorubicin (DOX),<sup>6,7</sup> or tamoxifen.<sup>8</sup> To explain EGCG-induced increased intracellular drug concentration, different mechanisms have been suggested. Modulation of dihydropyrimidine dehydrogenase (DPD), a rate-limiting enzyme in the elimination of 5-FU, has been recently proposed as underlying event for the significantly increased 5-FU plasma concentration in rats treated with 5-FU and EGCG.<sup>5</sup> The redox activity exerted by EGCG could modulate DPD through its NADPH binding site. This modulation could result in a reduction of 5-FU catabolism thus leading to increased plasma concentrations. In the same study, *in vitro* experiments showed no additive effects of EGCG-5FU co-treatment in different cancer cell lines. The absence of effects *in vitro* could be explained by the low doses of EGCG tested (0.1 µg/mL), markedly lower than those usually included in similar *in vitro* studies.

EGCG-induced increase in intracellular DOX concentration, leading to synergistic effects, has been shown in a chemoresistant hepatocellular carcinoma model *in vitro* and *in vivo*.<sup>7</sup> EGCG, at non-toxic doses (14 µg/mL), increased DOX-dependent cell death and enhanced cancer cell sensitivity to this drug. EGCG-induced drug resistance reversal to a greater extent than verapamil, a well-known chemosensitizer. The proposed mechanism of action was the inhibition of P-glycoprotein (P-gp) efflux pump activity in cancer cells and significantly reduced expression of multidrug resistance MDR1 protein. Inhibition of P-gp induced by EGCG has also been related to modified pharmacokinetics of tamoxifen and to chemosensitization in tamoxifen-resistant breast carcinoma cells, through down-regulation of P-gp and breast cancer resistant protein (BCRP).<sup>8</sup>

#### 3.2. Effects of EGCG on cell cycle, apoptosis and angiogenesis

Increased cell cycle arrest and apoptosis, as well as down-regulation of pro-angiogenic and pro-invasive molecular pathways have been proposed to contribute to the enhancement of anticancer drugs effect by EGCG. Co-administration of this catechin with taxanes (*i.e.* paclitaxel, docetaxel) has been shown to induce an additive effect by blocking PC-3ML prostate cancer cells growth *in vitro* and *in vivo*.<sup>9</sup> These results were associated with increased expression of apoptotic genes including p53 and caspase 3. Significantly reduced metastasis and increased disease-free survival rate to greater than 90% were also observed. In the same way, EGCG has been shown to sensitize cancer cells to apoptosis and cell cycle arrest induced by vorinostat in human melanoma cell lines,<sup>10</sup> and by SU5416, an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) in an *in vitro* model of neuroblastoma.<sup>11</sup> EGCG-SU5416 co-treatment led to a synergistic increase in cell cycle arrest and apoptosis and inhibition of angiogenic pathways. Increased expression of some Bcl-2 family proteins, caspase 3, and cleaved poly-ADP-ribose polymerase (PARP), and suppression of

**Table 1**

Experimental studies evaluating the modulation of anticancer drugs effect by epigallocatechin-3-gallate.

| Main mechanism                                    | Drug                                                                                                                                       | Cancer type                                                                                                                                                                                                | Effects of EGCG-drug combination                                                                                                                                                                                                                                                                                                                             | EGCG-induced underlying events                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alteration of drug pharmacokinetics               | Doxorubicin <sup>6,7</sup><br>5-fluorouracil <sup>5</sup><br>Tamoxifen <sup>8</sup>                                                        | Prostate <sup>6</sup><br>Colon <sup>5</sup><br>Bladder <sup>5</sup><br>Stomach <sup>5</sup><br>Chemo-resistant hepatocellular carcinoma <sup>7</sup><br>Tamoxifen-resistant breast carcinoma <sup>8</sup>  | ↑ Oral drug bioavailability.<br>↑ Drug concentration in tumor cells.<br>Chemosensitization of cancer cells to drug.<br>Synergistic antitumor effect.                                                                                                                                                                                                         | Inhibition of drug efflux. <sup>6</sup><br>↑ ↓ Enzymes involved in drug metabolism. <sup>5</sup><br>↓ P-gP efflux pump activity in cancer cells. <sup>7,8</sup><br>↓ Expression of MDR1. <sup>7</sup><br>Down-regulation of BCRP. <sup>8</sup>                                                                                                                                                                         |
| Effects on cell cycle, apoptosis and angiogenesis | Taxane <sup>9</sup><br>Gemcitabine <sup>12</sup><br>Vorinostat <sup>10</sup><br>SU-5416 <sup>11</sup><br>Celecoxib <sup>13</sup>           | Prostate <sup>9</sup><br>Melanoma <sup>10</sup><br>Neuroblastoma <sup>11</sup><br>Pancreas <sup>12</sup><br>Urothelial carcinoma <sup>13</sup>                                                             | ↑ Cell cycle arrest and apoptosis.<br>Additive/synergistic effect blocking tumor cell growth.<br>Additive/synergistic inhibition of angiogenesis.<br>Significantly reduced metastasis.<br>Increased disease-free survival.                                                                                                                                   | ↑ Expression of pro-apoptotic genes. <sup>9,10</sup><br>↑ ↓ Bcl-2 family proteins. <sup>9</sup><br>↑ ↓ Cell cycle and apoptosis molecular pathways. <sup>11–13</sup><br>Suppression of proangiogenic and prometastatic proteins. <sup>11</sup><br>Inhibition of GRP78. <sup>7,15,16</sup><br>↓ Expression and activity of multidrug resistance proteins. <sup>7,8</sup><br>Blockage of CBR1 active site. <sup>17</sup> |
| Modulation of chemo-resistance-related proteins   | Temozolomide <sup>15</sup><br>Paclitaxel <sup>16</sup><br>Doxorubicin <sup>7</sup><br>Tamoxifen <sup>8</sup><br>Daunorubicin <sup>17</sup> | Glioblastoma <sup>15</sup><br>Breast <sup>16</sup><br>Tamoxifen-resistant breast carcinoma <sup>8</sup><br>Hepatocellular carcinoma <sup>17</sup><br>Chemo-resistant hepatocellular carcinoma <sup>7</sup> | Overcoming of chemoresistance in cancer cells.<br>Sensitization to chemical antitumor agents.                                                                                                                                                                                                                                                                | ER binding. <sup>18,19</sup><br>Epigenetic restoration of ER through histone modifications. <sup>20</sup><br>↓ expression of AR in hormone responsive prostate cancer. <sup>21</sup><br>Interaction with AR in hormone sensitive and hormone resistant prostate cancer. <sup>22</sup>                                                                                                                                  |
| Interaction with hormone receptors                | Tamoxifen <sup>19</sup><br>TSA <sup>20</sup>                                                                                               | Breast <sup>18–20</sup><br>Prostate <sup>21,22</sup>                                                                                                                                                       | ↓ Estrogen-induced cancer proliferation in hormone responsive tumors.<br>Tumor sensitization to drugs targeted to steroid receptors.<br>Synergism with TSA in ER-negative breast cancer cells in restoration response to endocrine therapy.<br>Suppression of tumor growth and relapsing of tumors in hormone responsive and non-responsive prostate cancer. | ER binding. <sup>18,19</sup><br>Epigenetic restoration of ER through histone modifications. <sup>20</sup><br>↓ expression of AR in hormone responsive prostate cancer. <sup>21</sup><br>Interaction with AR in hormone sensitive and hormone resistant prostate cancer. <sup>22</sup>                                                                                                                                  |
| Redox-mediated modulation of cancer chemotherapy  | 5-fluorouracil <sup>5,26</sup><br>Cisplatin <sup>24</sup><br>ATO <sup>25</sup><br>Etoposide <sup>26</sup>                                  | Colon <sup>5</sup><br>Bladder <sup>5</sup><br>Stomach <sup>5</sup><br>Ovary <sup>24</sup><br>Leukemia <sup>25</sup><br>Chemo-resistant colon cancer <sup>26</sup>                                          | Pro-oxidant mediated chemosensitization to antitumor drugs.<br>↑ Plasma concentration of anticancer drugs.<br>Synergistic pro-apoptotic and antiangiogenic effect with anti-cancer drugs.                                                                                                                                                                    | Interaction with NADPH/NADH binding site of DPD. Reduced catabolism of antitumor drugs. <sup>5</sup><br>Hydrogen peroxide production. <sup>24</sup><br>Oxidative-mediated induction of mitochondrial-dependent apoptosis. <sup>25</sup><br>AMPK activation as a result of ROS production. <sup>26</sup><br>Direct interaction with the drug. <sup>27,28</sup>                                                          |
| Antagonistic interaction                          | Proteasome inhibitors <sup>27</sup><br>Sunitinib <sup>28</sup>                                                                             | Prostate <sup>27</sup>                                                                                                                                                                                     | Antagonism with boronic acid-based proteasome inhibitors (e.g. bortezomib).<br>↓ Bioavailability of anticancer drugs.                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                        |

↑ Increase; ↓ decrease; ↑ ↓ modulation; AMPK, AMP-activated protein kinase; AR, androgen receptor; ATO, arsenic trioxide; BCRP, breast cancer resistant protein; CBR1, carbonyl reductase 1; DPD, dihydropyrimidine dehydrogenase; ER, estrogen receptor; GRP78, glucose-regulated protein 78; MDR1, multidrug resistance protein; P-gP, P-glycoprotein; ROS, reactive oxygen species; TSA, trichostatin-A.

VEGFR-2 expression, were proposed as underlying mechanisms.<sup>11</sup> Additive and synergistic effects between anticancer drugs and EGCG have also been related to the modulation of different molecular pathways (e.g. signal transducer and activator transcription-3 (STAT-3) pathway) and protein expression (e.g. glucose-regulated protein 78, GRP78) with key roles in cell survival and tumor progression and metastasis.<sup>12,13</sup>

### 3.3. Modulation of chemoresistance-related proteins

The effect of EGCG in the expression of certain proteins (e.g. Bcl-2 family, matrix metalloproteinases MMPs) and molecular pathways (e.g. nuclear factor kappa B, NF-κB pathway) has been proposed to contribute to the role of EGCG as chemosensitizer, since those pathways and proteins have been proved to be involved in the development of drug resistance in cancer cells.<sup>14</sup>

Decreased expression and activity of multidrug resistance proteins have been associated with administration of EGCG. As

previously described, this catechin has been shown to act as chemosensitizer for DOX and tamoxifen in chemoresistant hepatocellular and breast cancer models, through decreased P-gP efflux pump activity and reduced expression of proteins involved in drug resistance such as MDR-1 and BCRP.<sup>7,8</sup> Expression of GRP78, which is over-expressed in chemoresistant cancer cells, has been shown to be decreased after drug-EGCG co-treatment, and has been proposed to mediate EGCG-induced sensitization of glioblastoma cells to temozolomide,<sup>15</sup> and breast cancer cells to paclitaxel.<sup>16</sup> In both cases, increased apoptosis and reduced tumor growth were described as a consequence of the co-treatment.

Finally, EGCG has been shown to interact with human carbonyl reductase 1 (CBR1). CBR1 limits the use of daunorubicin (DNR) as it converts DNR into the alcohol metabolite daunorubicinol (DNROL) thus reducing DNR antitumor activity. EGCG has been shown to block the active site of CBR1 and induce chemosensitization to DNR in hepatocellular carcinoma cells and corresponding xenografts.<sup>17</sup>

### 3.4. Receptor interaction in hormone-related cancers

Hormone-related cancers, namely breast and prostate cancer, are characterized by an initial hormone responsive stage, followed by a non responsive to hormone stage. The latter is more resistant to treatment, more aggressive, and has worse prognosis. EGCG has been proposed to interact with hormone receptors, delay the development of hormone refractory tumors, and induce chemosensitization in all stages of breast and prostate cancer *in vitro* and *in vivo*.

In the case of breast cancer, EGCG has been shown to interact with estrogen receptor (ER) function and inhibit estrogen-induced breast cancer cells proliferation, sensitizing hormone responsive tumors to drugs that target steroid receptors (e.g. tamoxifen).<sup>18,19</sup> Moreover, restoration of ER has been proposed as a valuable mechanism contributing to the potential use of EGCG as enhancer for cancer chemotherapy in breast cancer. Chemosensitization and synergistic anti-tumor effects were shown as a result of co-treatment with EGCG and histone deacetylase inhibitor trichostatin A (TSA). TSA was administered in combination with EGCG to ER-negative breast cancer cells. EGCG was shown to restore ER by regulating epigenetic mechanisms through histone modifications. EGCG synergistically increased anticancer effects of the drug and sensitized ER-negative breast cancer cells to TSA.<sup>20</sup>

Regarding the effect of EGCG in prostate cancer, EGCG could enhance the effect of androgen deprivation-based treatments improving the hormonotherapy outcome. EGCG has been shown to antagonize androgen action and decrease androgen receptor (AR) expression in hormone responsive prostate cancer cells.<sup>21</sup> Moreover, EGCG could play a role as cancer treatment enhancer in hormone refractory prostate cancer (HRPC), more aggressive, resistant to androgen deprivation and with high metastatic potential. HRPC still expresses AR and depends on AR signaling axis for growth and progression. EGCG has been shown to functionally antagonize AR in HRPC, resulting in inhibition of prostate cancer growth and increased disease-free survival rates in xenograft models. This effect of EGCG in HRPC could lead to sensitization of advanced stages of prostate cancer.<sup>22</sup>

### 3.5. Redox modulation of anticancer drugs effect

EGCG has been shown to exert both antioxidant and pro-oxidant activities. The concentration of EGCG in the cell environment seems to be a major factor to explain this dual role. Thus, this catechin has been shown to act as an effective antioxidant when used at low doses (within the range of high nanomolar and low micromolar levels) and to induce the production of reactive oxygen species (ROS) and oxidative damage at higher doses. Antioxidant activity of EGCG has been associated with the prevention of cancer whereas its pro-oxidant activity has been proposed to induce cancer cell death.<sup>23</sup>

Redox activities exerted by EGCG have been proposed to contribute to overcome drug resistances and to the synergistic interaction of EGCG with some anticancer drugs. EGCG may alter the pharmacokinetics of some anticancer drugs through redox interactions. As previously described, increased plasma 5-FU concentration in rats was related to redox activities exerted by EGCG leading to the modulation of the enzyme DPD through its NADPH binding site.<sup>5</sup> Regarding EGCG-induced generation of ROS, hydrogen peroxide production induced by EGCG has been associated with 3- to 6-fold enhancement of cisplatin efficacy in ovarian cancer cells, even in some cell lines highly resistant to the treatment with the drug alone.<sup>24</sup> In leukemia cancer cells, co-treatment with arsenic trioxide (ATO) and EGCG showed oxidative-mediated induction of mitochondrial-dependent

apoptosis.<sup>25</sup> EGCG increased intracellular hydrogen peroxide in cancer cells and ATO-induced heme oxygenase-1 (HO-1) provided ferrous iron thus increasing Fenton reaction and, as a consequence, oxidative damage to cells. Moreover, EGCG was shown to inhibit expression of ferritin thus increasing ferrous iron available for Fenton reaction. Another study carried out in chemoresistant human colon adenocarcinoma HT29 cell line, showed a synergistic pro-apoptotic and antiangiogenic effect of EGCG with 5-FU or etoposide, mediated by EGCG-induced oxidative damage. The proposed mechanism was the EGCG-induced upregulation of 5' adenosine monophosphate-activated protein kinase (AMPK) pathway and the subsequent down-regulation of cyclooxygenase-2 (COX-2) and VEGF. Production of ROS was proposed as upstream for AMPK activation.<sup>26</sup>

### 4. Limitations to the use of EGCG as chemosensitizer for anticancer drugs

Inhibition of the anticancer effect of bortezomib by EGCG was recently evidenced in a xenograft mouse model of prostate cancer. Low concentrations of EGCG, corresponding to those achieved by dietary intakes or supplements, had no effect on bortezomib activity. However, higher concentrations of EGCG effectively antagonized the anticancer effect of this proteasome inhibitor.<sup>27</sup> Bortezomib is not the only drug that could be antagonized by EGCG. Reduced bioavailability of the anticancer drug sunitinib has been recently related to co-administration with EGCG.<sup>28</sup> These observations show the need to conduct further studies to ascertain the interaction between EGCG and different anticancer drugs, for each particular type and stage of cancer. The possibility of antagonistic interactions must be taken into account in the development of new cancer therapy strategies based on drug-EGCG co-treatments.

### 5. EGCG as radiosensitizer

Research aimed at evaluating the effects induced by co-administration of EGCG with ionizing radiation (IR) in cancer cells is still limited, but promising results obtained up to date, mainly in preclinical studies, support the need of further investigation. Radiosensitization and synergistic anticancer effects were shown after pre-treatment of a glioblastoma multiforme (GBM) radio-resistant cell line with EGCG.<sup>29</sup> Pre-treatment with EGCG reduced in a dose-dependent manner IR-induced expression of survivin leading to a significantly increased radiosensitive state and decreased cell proliferation.<sup>29</sup> Improvement of the anticancer effect of IR when combined with EGCG has also been evidenced through decreased cell proliferation and increased apoptosis and necrosis in leukemic (K-562), cervix (HeLa), and multiple myeloma (IM-9) cell lines.<sup>30</sup> Different responses to the co-treatment depending on the cell line were reported showing different sensitivities to IR and to the effect of EGCG in the modulation of cell response to IR. Another interesting study, based on the role of the microvasculature in the evolution of brain tumors and its potential use as a target for IR treatment, was carried out on human brain microvascular endothelial cells (HBMEC).<sup>31</sup> HBMEC were treated with EGCG and IR, and the results showed that EGCG significantly increased IR-induced cell death. A clinical trial was conducted recently in breast cancer patients undergoing radiotherapy showing that EGCG could potentiate the effect of IR.<sup>32</sup> After two to eight weeks of EGCG (400 mg thrice daily, orally) plus radiotherapy administration, serum levels of angiogenic factors VEGF, hepatocyte growth factor (HGF), and active MMP-2 and MMP-9 were lower compared to those from patients receiving only radiotherapy. Furthermore, the addition of these sera to MDA-MB-231 breast cancer cells, led to

decreased cell proliferation and invasion and downregulation of molecular events related to radioresistance as expression of Bcl-2/Bax and NF- $\kappa$ B, or activation of MMP-9. Moreover, 5–10  $\mu$ M EGCG significantly increased  $\gamma$ -radiation-induced apoptosis in MDA-MB-231 cells. Thus, not only EGCG but also its metabolites may potentiate the effects of radiotherapy.<sup>32</sup>

## 6. EGCG as protective agent against chemo- and radiotherapy side effects

Adverse effects derived from the use of chemo- and radiotherapy constitute a major problem in cancer treatment. The development of unwanted side effects may yield to discontinuation of the treatment thus reducing its effectiveness.

As shown in this review, sensitization and synergistic effects of EGCG when used in combination with radio- or chemotherapy may imply reductions in the required doses and, as a consequence, decreased risk of toxicity. In addition, antioxidant and anti-inflammatory activities of this tea catechin have been suggested to contribute to the potential protective role of EGCG against chemo- and radiotherapy side effects. Latest studies in this regard, most of them preclinical, are summarized in Tables 2 and 3, and discussed below.

### 6.1. Gastrointestinal disorders

Among adverse effects induced by chemo- and radiotherapy, gastrointestinal disorders are some of the most commonly reported. Oxidative damage to rapidly dividing cells of the mucosa has been suggested as one of the underlying mechanisms. Green tea polyphenols, including EGCG, have been shown to reduce oxidative damage and inflammation induced by chemo- or radiotherapy in small intestine.<sup>4,33</sup> Furthermore, the effectiveness of EGCG in this regard has been shown in murine models of oxidative-induced colitis. Thus, EGCG (10 mg/kg) administered intraperitoneally twice a day prevented from trinitrobenzenesulfonic acid-induced diarrhea, weight loss, colonic bleeding, ulcers, and edema. Inhibition of NF- $\kappa$ B and activator protein AP-1 was proposed as molecular mechanism for the protection of the intestinal mucosa.<sup>34</sup> Finally, an *in vitro* model of inflamed human intestinal epithelium was developed to evaluate the antioxidant properties of dietary phenolic compounds, including EGCG. The pro-inflammatory treatment caused attenuation of the transepithelial electrical resistance and over-expression of pro-inflammatory markers interleukin 6 (IL-6) and interleukin 8 (IL-8). EGCG down-regulated the inflammatory response by a significant decrease in IL-6 and IL-8.<sup>35</sup>

### 6.2. Declination of hematological parameters and immune system

Immunosuppression and myelosuppression have been described as major side effects induced by cancer therapies and correlate with higher risk of serious infection and mortality. Low blood cell count including anemia, thrombocytopenia and neutropenia can be induced by chemo- and radiotherapy. The protective role of EGCG against radiation-induced changes in hematological parameters has been recently proposed. Oral administration of green tea polyphenols, including EGCG, to irradiated mice, significantly counteracted radiation-induced changes in hematological parameters. EGCG treatment was related to amelioration of leukocytopenia, reduction of inflammatory cytokines in serum and improved antioxidant defense.<sup>36</sup> Moreover, EGCG administered intraperitoneally to mice after cecal ligation and puncture, was shown to protect against lethal endotoxemia and rescued animals from lethal sepsis.<sup>37</sup> This effect could be

explained by EGCG-induced decrease in systemic concentration of high mobility group box 1 (HMGB1), a critical proinflammatory mediator of lethal sepsis.

### 6.3. Development of secondary tumors

Antiangiogenic effects of EGCG may contribute to the prevention of secondary tumors induced by cancer therapies. To illustrate this potential, an interesting study was carried out to evaluate the effect of EGCG in the radiation-induced tubulogenesis in endothelial cells. Single doses of irradiation stimulated cell migration and *in vitro* tubulogenesis in human umbilical vein endothelial cells. Pre-treatment with EGCG prevented radiation-induced proangiogenic molecular events as expression of membrane type-1 matrix metalloproteinase (MT1-MMP), caveolin-1 and cell surface beta (3) integrin.<sup>38</sup> Another recent study evaluated the antimutagenic effect of different dietary antioxidants, including EGCG in green tea extract, against genotoxic damage induced by IR in human lymphocytes. The results showed a significant decrease in X-ray-induced chromosomal damage to levels higher than those obtained by amifostine, a well-known radioprotective compound.<sup>39</sup>

### 6.4. Radiation-induced dermatitis

Dermatitis constitutes one of the most important symptoms of discomfort in patients undergoing radiotherapy. Radiation-induced oxidative damage and inflammation have been proposed as underlying events and both could be reduced by EGCG. Panjonk and co-workers carried out a study to evaluate the effect of topically applied black and green tea extracts on radiation-induced skin toxicity. Data from 60 patients with cancer of head and neck or pelvic region were analyzed retrospectively. Topical application of tea extracts contributed to the restitution of skin integrity after acute radiation-induced damage. Inhibition of proteasome and suppression of cytokine release as well as modification of NF- $\kappa$ B activity were investigated as potential underlying mechanisms.<sup>40</sup>

### 6.5. Nephrotoxicity

Several anticancer agents may lead to different degrees of renal damage as a side effect. Nephrotoxicity constitutes the major complication derived from the use of platinum derivatives as cisplatin (CP). Moreover, the induction of nephrotoxicity limits the long-term use of this anti-neoplastic agent. Increased oxidative stress and inflammation have been associated with CP-induced renal injury. Khan et al. carried out an *in vivo* study in rats to assess the protective effect of green tea against CP-induced nephrotoxicity. After 25 days of co-treatment, green tea was shown to prevent the deleterious effects of CP as evidenced by measurements of various serum parameters, enzymes of carbohydrate metabolism, and antioxidant defense system in renal cortex and medulla.<sup>41</sup> Another recent study evaluated the effect of the pre-treatment with EGCG prior to CP injection in rats. CP led to a significant downregulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2)/HO-1 signaling pathway and increased levels of NF- $\kappa$ B and hydroxynonenal (HNE), a biomarker for oxidative stress. EGCG significantly reduced the nephrotoxic effect of CP and attenuated the CP-induced modification of abovementioned parameters. Moreover, renal antioxidant defense was significantly improved in EGCG-treated animals in contrast with the depletion registered in CP-controls.<sup>42</sup> The association between antioxidant and anti-inflammatory activities of EGCG and its protective role against CP-induced nephrotoxicity has been shown by El-Mowafy and co-workers in mice bearing Ehrlich ascites carcinoma (EAC).<sup>43</sup> This study showed that EGCG administered in combination with CP

**Table 2**

Experimental studies showing green tea and its major phenolic compound, epigallocatechin-3-gallate, as protective agents against chemotherapy side effects.

| Side effect                | Drug              | Aims of the study                                                                                                                                                                                               | Study outline                                                                                                                                                                                                                                                     | Drug-induced deleterious effects                                                                                                                                                                                                              | Effects of combined treatment drug-green tea/EGCG                                                                                                                                                                                                                                                                                                                     | Ref      |
|----------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Gastrointestinal disorders | Irinotecan, IT    | -IT-induced inflammation and oxidative stress in mice small intestine.<br>-Protective role of GTP.                                                                                                              | IT treatment: 0.17 g/kg BW, IP, 2d.<br>GTP treatment: 1 g/L in drinking water. 7d before and 3d after IT treatment (pre + post-treatment).                                                                                                                        | ↑ Oxidative stress and inflammation. Mucosal damage.<br>↓ Ileum glutathione concentration.<br>↑ Lipid peroxidation and NF-kB levels.                                                                                                          | -Protection against IT-induced oxidative damage.<br>-Improvement of GSH levels.<br>-No modification on lipid peroxidation or NF-kB activation.                                                                                                                                                                                                                        | 4        |
| Nephrotoxicity             | Cisplatin, CP     | -CP-induced deleterious effects and nephrotoxicity in a rat model.<br>-Preventive role of GT.<br>-CP-induced nephrotoxicity in rats.<br>-Underlying mechanisms.<br>-Effects of EGCG pre-treatment.              | CP treatment: 3 mg/kg BW/d, IP, every 5 d, 25d.<br>GT treatment: 3% w/v GT extract in drinking water, 25d (co-treatment).<br>CP treatment: 7 mg/kg BW, IP, single dose.<br>EGCG treatment: 100 mg/kg BW/d <i>p.o.</i> , 2 d, before CP injection (pre-treatment). | ↑ Serum creatinine, blood urea nitrogen, LDH, ACP.<br>↓ Antioxidant defense system.<br>↓ SOD, CAT.<br>↓ MDH, G6Pase, Pi transport.<br>↓ Nrf2 and HO-1 expression.<br>↑ NF-kB and HNE.<br>↓ Activity of antioxidant enzymes and GSH in kidney. | -Protection against CP-induced nephrotoxicity. -Prevention from enzymatic and biochemical CP-induced alterations.<br>-Reinforced antioxidant defense.<br>-Counteraction of CP-induced nephrotoxicity-associated biochemical parameters.<br>-Increased renal activity of antioxidant enzymes and GSH.                                                                  | 41<br>42 |
| Nephrotoxicity             | CP                | -CP-induced nephrotoxicity in rats.<br>-Impact on oxidative damage and inflammation.<br>-Protective role of EGCG.                                                                                               | CP treatment: 5 mg/kg BW, IP, single dose.<br>EGCG treatment: 20 mg/kg BW/d or 40 mg/kg BW/d, IP, 20 days, after CP injection (post-treatment).                                                                                                                   | ↑ Serum urea and creatinine.<br>↓ GSH.<br>↑ MDA (lipid peroxidation).<br>↑ Renal TNF- $\alpha$ .<br>-Disrupted renal glomerular filtration rate.<br>-Lethal renal crisis.                                                                     | -Prevention of oxidative damage and inflammation.<br>-Enhancement of antioxidant defense.<br>-Prevention of lethal CP-induced nephrotoxicity.                                                                                                                                                                                                                         | 43       |
| Cardiotoxicity             | Doxorubicin, DOX  | -DOX-induced toxicity in cardiomyocytes of neonatal rats.<br>-Effect of EGCG treatment.<br>-DOX-induced toxicity in rat cardiomyocytes.<br>-Effect of co-treatment with EGCG.                                   | DOX treatment: 0.1–1 $\mu$ M.<br>EGCG treatment: 3–200 $\mu$ M for 1 h previous to DOX administration (pre-treatment).<br>DOX treatment: 10 $\mu$ M, 12 h.<br>EGCG treatment: 12.5–50 $\mu$ M, 12 h (co-treatment).                                               | ↑ Apoptosis.<br>↑ ROS.<br>↑ Oxidative damage.<br>↑ Lipid peroxidation.<br>↓ Cell viability.<br>↑ ROS and apoptosis.<br>-Impaired contractile function.<br>-Impaired $\beta$ -adrenergic function.                                             | -Dose-dependent increased cell viability.<br>↑ Activity and expression of antioxidant enzymes.<br>↓ ROS, ↓ lipid peroxidation, ↓ oxidative-induced apoptosis.<br>-EGCG dose-dependent<br>↑ Cell viability, ↓ ROS.<br>-Prevention of DOX-induced impairment of contractile function, $\beta$ -adrenergic function and calcium handling.                                | 44<br>45 |
| Cardiotoxicity             | Daunorubicin, DNR | -DNR antitumor activity and induced cardiotoxicity.<br>-Effect of EGCG on DNR antitumor activity and cardiotoxicity in hepatocellular carcinoma cells and corresponding xenografts.<br>-EGCG modulation of CBR1 | <i>In vitro</i><br>DNR treatments: 0.03–0.4 $\mu$ M, 48 h; 100 $\mu$ M, 30 min.<br>EGCG treatment: 10 $\mu$ M, 20 $\mu$ M, 48 h; 20–80 $\mu$ M, 30 min (co-treatment).<br><i>In vivo</i> EGCG-DNR co-administration, 15d (co-treatment)                           | <i>In vitro</i><br>↓ Cell viability.<br>↑ Apoptosis.<br>-Cell cycle arrest in G2/M phase.<br><i>In vivo</i><br>↑ MDA ↑ cTnT<br>-BW loss.<br>-Cardiotoxicity.                                                                                  | <i>In vitro</i><br>-Sensitization of cancer cells to DNR.<br>-Synergistic increased effect of DNR-induced cell cycle arrest and apoptosis.<br>-Reversion of CBR1-mediated resistance to DNR.<br><i>In vivo</i><br>↑ Antitumor effect of DNR.<br>↓ BW loss.<br>↓ Metabolization of DNR into cardiotoxic metabolite.<br>-Restoration of MDA and cTnT to control levels. | 17       |
| Ototoxicity                | CP                | -CP-induced ototoxicity in mice utricular hair cells.<br>-Phosphorylation of STAT1 as underlying molecular event.<br>-Preventive role of EGCG.                                                                  | CP treatment: 10–80 $\mu$ g/mL<br>EGCG treatment: 10–200 $\mu$ M, 1 h before and 1 h, 4 h, 8 h or 24 h after CP (pre + post-treatment).                                                                                                                           | -Dose-dependent cell death induction.<br>-Phosphorylation of STAT1.                                                                                                                                                                           | -EGCG dose-dependent<br>↑ Survival of hair cells.<br>↓ Activation of STAT1.                                                                                                                                                                                                                                                                                           | 46       |

(continued on next page)

Table 2 (continued)

| Side effect                    | Drug          | Aims of the study                                                                                                                                                                  | Study outline                                                                                                                                                                                                                                                                  | Drug-induced deleterious effects                                                                                                                                                                                                                                                                                                                                | Effects of combined treatment drug-green tea/EGCG                                                                                                                                                                                                                                                                                                                                                                  | Ref    |
|--------------------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| Dysfunction of salivary glands | CP            | -Impact of EGCG in CP-treated human acinar and ductal salivary cells and oral squamous carcinoma cells.                                                                            | CP treatment: 5–50 $\mu$ M, 48 h<br>EGCG treatment: 12.5–200 $\mu$ M, 24 h before CP (pre-treatment).                                                                                                                                                                          | ↓ Cell viability in a dose-dependent manner.                                                                                                                                                                                                                                                                                                                    | -Protection of normal salivary gland cells from CP-induced damage.<br>-Protection of oral squamous carcinoma cells only in the lowest concentrations of EGCG.                                                                                                                                                                                                                                                      | 48     |
| Pulmonary fibrosis             | Bleomycin, BM | -Effect of EGCG in the progression of BM-induced pulmonary fibrosis in rats.<br>-Antioxidant and anti-inflammatory activities of EGCG after BM-induced pulmonary fibrosis in rats. | BM treatment: 6.5 U/kg BW, ITT, single dose.<br>EGCG treatment: 20 mg/kg BW/d, 28d from 6 h after BM administration (post-treatment).<br>BM treatment: 6.5 U/kg BW, ITT, single dose.<br>EGCG treatment: 20 mg/kg BW/d, 28d from 6 h after BM administration (post-treatment). | ↑ Histopathological parameters.<br>↑ Glycoconjugates.<br>↑ Activity of pathophysiological enzymes.<br>↑ Activity of matrix degrading lysosomal enzymes.<br>↑ MPO, ↑ lipid peroxidation ↑ ROS.<br>↓ Phase II enzymes.<br>↑ NF- $\kappa$ B, TNF- $\alpha$ , IL-1 $\beta$ .<br>-Induction of inflammation.<br>-Alveolar damage.<br>-Increased collagen deposition. | -Attenuated modification of glycoconjugates and histo-pathological parameters.<br>-Reduced activity of matrix degrading lysosomal enzymes and ultrastructural changes in lung.<br>-Restoration of MPO, Phase II enzymes and oxidative markers to normal values.<br>↓ Inflammation.<br>↓ NF- $\kappa$ B, TNF- $\beta$ , IL-1 $\alpha$ .<br>↓ Alveolar damage and collagen deposition.<br>-Modulation of NrF2-Keap1. | 49, 50 |

↑ Increase; ↓ decrease. ACP, acid phosphatase; BW, body weight; CAT, catalase; CBR1, carbonyl reductase 1; cTnT, cardiac troponin (marker for myocardial cell death); EGCG, epigallocatechin-3-gallate; G6Pase, glucose-6-phosphatase; GSH, glutathione; GT, green tea; GTP, green tea polyphenols; HNE, 4-hydroxynonenal (oxidative stress marker); HO-1, heme oxygenase-1; IL-1 $\beta$ , interleukin-1 beta; IP, intraperitoneal; ITT, intratracheal; Keap1, Kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; MDA, malondialdehyde; MDH, malate dehydrogenase; MPO, myeloperoxidase; NF- $\kappa$ B, nuclear factor-kappa B; NrF2, NF-E2-related factor-2; Pi, inorganic phosphate; *p* (*per os*), oral administration; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT1, signal transducer and activator of transcription 1; TNF- $\alpha$ , tumor necrosis factor-alpha.

reduced CP-induced nephrotoxicity and markedly increased CP effectiveness. Administration of EGCG (50 mg/kg) together with CP (10 mg/kg) prevented from CP-induced nephrotoxicity and their consequences, including death. Significantly lower concentrations of tumor necrosis factor-alpha (TNF $\alpha$ ) and malondialdehyde (MDA) together with higher levels of reduced glutathione in EGCG-treated animals showed the correlation between the observed effects and redox and inflammatory status.

#### 6.6. Cardiotoxicity

DOX treatment has been strongly associated with the development of cardiotoxicity. The induction of cumulative and irreversible cardiomyopathy limits the use of this chemotherapy drug. Oxidative damage has been suggested to be the main underlying mechanism to DOX-induced cardiotoxicity. It urges to develop new approaches to prevent or delay the cardiotoxic effect and improve the efficacy of the treatment. Some recent studies showed the protective role of EGCG against this side effect of DOX. Dose-dependent increased viability in DOX-treated cardiomyocytes after EGCG treatment has been evidenced. Decreased ROS and MDA levels together with increased expression and activity of antioxidant enzymes showed that induction of the antioxidant defense contributed to the protective effect.<sup>44,45</sup> Moreover, EGCG was shown to improve Ca<sup>2+</sup> handling in DOX-treated cells.<sup>45</sup> Hence, this green tea polyphenol may reverse DOX-induced intracellular Ca<sup>2+</sup> depletion and contribute to the maintenance of contractile function. EGCG could also reduce cardiotoxicity induced by daunorubicin (DNR), as shown by Huang et al.<sup>17</sup> The proposed underlying mechanism was EGCG inhibition of CBR1, the protein involved in the conversion of DNR into DNROL. DNROL is directly associated with DNR-induced cardiotoxicity thus contributing to limit the use of this drug. In this study, EGCG was shown to significantly decrease cardiotoxic side effects in a xenograft mouse model of human hepatoma treated with DNR.

#### 6.7. Ototoxicity

Auditory impairment has been recognized as an adverse effect derived from the use of some cancer chemotherapeutic agents and has been associated with the use of CP. This drug has been proposed to cause hearing loss due to the death of mechanosensory hair cells as a result of oxidative damage and inflammatory processes. Schmitt and co-workers used utricles from mature Swiss Webster mice to evaluate the effect of EGCG in CP-induced ototoxicity. Activation of pro-inflammatory signal transducer and activator of transcription 1 (STAT1) was shown as key factor for the development of the toxic effect since STAT1-deficient mice were resistant to CP toxicity. In this study, EGCG led to a dose-dependent increase in hair cell survival through inhibition of STAT1.<sup>46</sup>

#### 6.8. Dysfunction of salivary glands

Dysfunction of salivary glands has been associated with the use of radio- and chemotherapy. A recent *in vivo* study showed the protective effect of tea polyphenols against radiation-induced injury in submandibular glands. Rats were intragastrically administered tea extracts during 14 days previous to 15-Gy dose radiation in head and neck areas. Morphologic changes in submandibular glands and apoptosis indexes were evaluated. Both parameters were improved in the groups pretreated with tea extracts, containing EGCG, showing the protective role and the contribution of anti-apoptotic mechanisms to the overall effect.<sup>47</sup> Another study evaluated the effect of EGCG against the toxicity induced by radiation or CP treatment in human immortalized salivary acinar and

**Table 3**

Experimental and clinical studies showing tea and tea polyphenols, including epigallocatechin-3-gallate, as protective agents against radiotherapy side effects.

| Side effect                                                | Radiation therapy | Aims of the study                                                                                                                                                                            | Study outline                                                                                                                                                                                                                                            | Radiation-induced deleterious effects                                                                                                                               | Effects of radiation combined with GT/EGCG                                                                                                                                                                     | Ref |
|------------------------------------------------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| Gastrointestinal disorders                                 | Gamma radiation   | -Radioprotective role of GT extract and GTP in jejunal crypts of irradiated mice.<br>-Comparison with the radioprotector DDC.                                                                | Radiation therapy: 2–12Gy single dose. GT, GTP treatment: Single dose, 50 mg/kg BW, IP, 24 h before IR (pre-treatment).<br>DDC treatment: Single dose, 1000 mg/kg BW, IP, 30 min before IR (pre-treatment).                                              | ↑ Intestinal crypt cells death.<br>↓ Number of endogenous spleen colonies.                                                                                          | ↑ Jejunal crypt cells survival.<br>↑ Formation of endogenous spleen colonies.<br>-Antioxidant activity proposed as underlying mechanism.                                                                       | 33  |
| Declination of hematological parameters and immune system. | Gamma radiation   | -TP combinations (including EGCG) as radioprotective agents against radiation-induced damage in mice.                                                                                        | Radiation therapy: Total body sublethal dosage at 400 cGy/min dose rate. IR time 110.7 s.<br>TP treatment: 50 mg/kg BW/d or 100 mg/kg BW/d, 28 d, IG, after IR (post-treatment).                                                                         | ↓ BW, total white blood count, Hb concentration.<br>↓ Thymus and spleen indices.<br>↓ SOD activity.<br>↑ Lipid peroxidation<br>↑ TNF- $\alpha$ IL-1 $\beta$ , IL-6. | ↑ Antioxidant defense.<br>↓ Inflammatory cytokines.<br>-Reversal of IR-induced decreases in BW, hematological parameters, and thymus and spleen indices.                                                       | 36  |
| Development of secondary tumors                            | Gamma radiation   | -Proangiogenic effects of IR on human umbilical vein endothelial cells.<br>-Protective role of EGC and EGCG                                                                                  | Radiation therapy: 10Gy single dose<br>GTP treatment: EGCG 5 $\mu$ M or EGC 5 $\mu$ M. 7 h previous to IR (pre-treatment).                                                                                                                               | ↑ Endothelial cell migration.<br>↑ Production of proangiogenic molecules.<br>↑ Tubulogenesis.<br>-Induction of neovascularization.                                  | -Prevention of IR-induced proangiogenic molecular events.<br>-Antagonization of IR-induced tubulogenesis in a more efficient manner than antiangiogenic drugs.                                                 | 38  |
| Development of secondary tumors                            | X-radiation       | -Protective effect of GT against X-ray-induced genotoxic damage in human lymphocytes.                                                                                                        | Radiation therapy: 2Gy single dose.<br>GT treatment: GT extract 5 min before exposure to irradiation (pre-treatment).                                                                                                                                    | ↑ Micronuclei frequency.<br>↑ Chromosomal damage.                                                                                                                   | -Frequency of micronuclei maintained at non-IR control level.<br>-Prevention from X-ray induced genotoxic damage.<br>-Degree of protection higher than that obtained from the radioprotective drug amifostine. | 39  |
| Radiation-induced dermatitis                               | Gamma radiation   | -Effect of IR and BT, GT, or EGCG on cell viability in RAW 264.7 murine macrophages.<br>-Effect of IR and BT, GT, or EGCG in the release of pro-inflammatory cytokines from human monocytes. | Radiation therapy: 2–8Gy single dose. BT/GT/EGCG treatment: BT/GT extract (0.00004%–4%) or EGCG (40 $\mu$ M, 400 $\mu$ M).<br>4 h before irradiation (pre-treatment).                                                                                    | ↓ Cell viability.<br>↑ Pro-inflammatory cytokines secretion from human monocytes.                                                                                   | ↓ Radiation-induced macrophages death.<br>↓ Pro-inflammatory cytokines secretion from human monocytes.                                                                                                         | 40  |
| Radiation-induced dermatitis                               | Gamma radiation   | -Effect of topically-applied BT and GT extracts on radiation-induced skin toxicity in patients under radiation treatment.                                                                    | Patients: 60 inpatients with radiation-induced skin toxicity RTOG score grade 2 and higher (grade 2+).<br>Radiation therapy: Daily fractions 1.8–2Gy.<br>BT/GT treatment: BT/GT extract (25–100 $\mu$ g catechins/mL) topically applied for 10 min, 3/d. | -Skin toxicity RTOG score grade 2+.                                                                                                                                 | -Tea extracts contributed to restore skin integrity.<br>-Shorter duration of grade 2 + skin toxicity during radiation therapy in GT-treated patients.                                                          | 40  |
| Dysfunction of salivary glands                             | Gamma radiation   | -Protective effect of TP against radiation-induced damage in submandibular glands in rats.                                                                                                   | Radiation therapy: Single dose 15Gy in the head and neck regions.<br>TP treatment: TP extract ( $\geq$ 40% EGCG) 0.2 g/kg BW/d, IG, from 14 days before radiation (pre-treatment) until the 3rd, 6th, or 30th day after IR (post-treatment).             | ↑ Cell death.<br>-Pathohistological changes in sub-mandibular glands.                                                                                               | ↓ Radiation-induced cell injury and apoptosis<br>-Amelioration of radiation-induced morphologic and ultramicroscopic changes in submandibular glands                                                           | 47  |
| Dysfunction of salivary glands                             | Gamma radiation   | -Effect of EGCG on IR-treated salivary cells and oral squamous carcinoma cells.                                                                                                              | Radiation therapy: 5Gy or 10Gy, single dose.<br>EGCG treatment: 12.5 $\mu$ M–200 $\mu$ M, 24 h before irradiation (pre-treatment).                                                                                                                       | ↓ Cell viability.<br>-Induction of cell cycle arrest.                                                                                                               | -Protection of normal salivary gland cells from the damage induced by IR.<br>-Protection of oral squamous carcinoma cells only in the lowest EGCG assayed concentrations.                                      | 48  |

↑ Increase; ↓ decrease; BT, black tea; BW, body weight; DDC, diethyldithiocarbamate; EGC, epigallocatechin; EGCG, epigallocatechin-3-gallate; GT, green tea; GTP, green tea polyphenols; Hb, hemoglobin; IG, intragastric; IL-1 $\beta$ , interleukin-1 beta; IL-6, interleukin-6; IP, intraperitoneal; IR, ionizing radiation; RTOG, Radiation Therapy Oncology Group; SOD, superoxide dismutase; TNF- $\alpha$ , tumor necrosis factor-alpha; TP, tea polyphenols.

ductal cells. In this case, cells were pretreated with growing concentrations of EGCG before gamma-radiation or CP-treatment. Physiologically achievable salivary concentrations of EGCG protected normal salivary glands from the toxicity induced by both treatments.<sup>48</sup>

### 6.9. Pulmonary fibrosis

Pulmonary fibrosis and associated impaired lung function are serious complications that have been related to bleomycin, a drug used for the treatment of different types of cancer including Hodgkin's lymphoma and testicular cancer. Excessive deposition of extracellular matrix components in the alveolar space as well as depleted antioxidant defense and increased concentration of inflammatory cytokines have been described in bleomycin-induced pulmonary fibrosis. EGCG has been shown to act as antifibrotic agent in a rat model of bleomycin-induced pulmonary fibrosis. Administration of this green tea polyphenol to bleomycin-treated rats led to prevention of body weight loss and enhanced enzymatic and non-enzymatic antioxidant defense. EGCG was also shown to reduce the activity of matrix degrading lysosomal enzymes and to attenuate bleomycin-induced increased activities of pathophysiological enzymes. When the underlying molecular events were investigated, bleomycin-induced increased levels of NF- $\kappa$ B, TNF- $\alpha$  and interleukin-1 beta (IL-1 $\beta$ ) were significantly attenuated by EGCG. Nrf2-Keap1 signaling pathway played a key role in the development of bleomycin-induced pulmonary fibrosis. Interestingly, EGCG was shown to effectively induce Nrf2 and, as a consequence, enhance antioxidant activities of Phase II enzymes, and to reduce inflammation.<sup>49,50</sup>

## 7. Conclusion and perspectives

Latest cancer research is focused on new therapeutic approaches that combine natural compounds with synthetic drugs or radiotherapy to enhance treatment outcome and to prevent adverse side effects. A number of preclinical studies have recently shown that EGCG, the major phenolic compound in green tea, could exert anticancer activity and act as chemo/radiosensitizer when combined with conventional therapies. Moreover, its protective role against cancer therapy side effects has been proposed. However, clinical studies are still scarce, and some studies describe antagonism with some anticancer drugs. Further research, especially at the clinical level, is needed to define the use of EGCG as adjuvant for cancer treatment.

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### Conflict of interest statement

The authors declare no potential conflicts of interest.

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