vitro, although other agents may induce apoptosis via the death receptor pathway [9].

Chemotherapy aims to kill cancer cells, in the hope of preventing further cancer progression. Chemoprevention, on the other hand, involves administering non-toxic agents to individuals who may be at an increased risk for cancer. Moreover, surgical and traditional therapeutic approaches (chemotherapy and radiation) are, at present, unable to control most cancer types. Thus, the development of new chemopreventive strategies is required [10,11,92,93]. Chemopreventive compounds can be classified into two major groups: 1) blocking agents, which prevent carcinogens from reaching or reacting with critical target sites, and 2) suppressing agents, which stop the evolution of the pre-neoplastic process. Given that the initiation and progression phases are relatively transient and irreversible events, it seems logical that chemopreventive agents should intervene at the prodromal promotion phase. Three decades of research suggest that chemoprevention is a promising strategy to reduce the incidence of cancer, both in well-defined high-risk groups and in the general population [10-12,92,93].

Of great importance, aberrant NF-κB regulation and Akt activation has been observed in many cancers. To prevent the development and progression of cancers, the strategy should target the cell signaling pathways that are deregulated in malignant tumors. Aberrant regulation of NF-κB and the signaling pathways that control its activity are involved in cancer development and progression, as well as in drug resistance, especially during chemotherapy and radiotherapy [94]. Blocking NF-κB can cause tumor cells to cease proliferation or become more sensitive to the action of antitumor agents [95]. Changes in Akt activator expression observed in human precancerous tissues that might be targeted for chemoprevention [96]. Inhibition of Akt signaling has been associated with the biological actions of numerous chemopreventive compounds. Thus far, several chemopreventive agents including, green tea polyphenols, curcumin, and quercetin have shown their various activities in the inhibition of carcinogenesis through the regulation of major cell signaling pathways such as Akt and NF-κB. Therefore, those are the subject of intense study. Agents capable of suppressing Akt and/or NF-κB activation have therapeutic promise and potential to inhibit carcinogenesis. We currently review dietary cancer chemopreventive compounds include EGCG, curcumin, and quercetin, capable of functioning in this capacity.

Representative dietary cancer chemopreventive compounds include EGCG, curcumin, and quercetin.

4.1. EGCG

Cancer prevention by green tea and its constituents been studied in different animal models of carcinogenesis [97]. The major catechins (a group of polyphenols) in green tea are EGCG, (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallete (ECG) and (-)-epicatechin. EGCG, the most abundant and most studied catechin, exhibits significant growth inhibitory effects in cancer cells. More importantly, after treatment of a primary cell line such as normal epithelial cells with EGCG, there is no observable toxicity at doses that are used for cancer inhibition studies [98,99]. A collection of reviews have commented on the possible mechanistic effects of EGCG in multiple cell lines and have noted similarities in regard to growth inhibition and cell cycle arrest [100-102].

EGCG reportedly affects the transcription factors p53 and NF-κB leading to a change in the ratio of Bax/Bcl-2 in a manner that favors apoptosis [103]. The induction of apoptosis by other green tea catechins has been evaluated in a dose dependent manner (*i.e.* ECG > EGCG > EGC > EC) [104].

EGCG treatment may lead to a significant dose- and time-dependent inhibition of activation and translocation of NF-κB to the nucleus by suppressing the degradation of IKBα in the cytoplasm [105,106]. EGCG may also inhibit the ATP- and IL-1β-induced activation of NF-κB [107].

EGCG has been found to inhibit PI3K/Akt activation, resulting in the modulation of Bcl-2 family proteins and leading to the enhanced apoptosis of bladder cancer cells [108]. EGCG has also been shown to inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis *in vitro* through suppression of VE-cadherin phosphorylation and inactivation of Akt, suggesting that EGCG has an inhibitory effect on the Akt signaling pathway [109, 110]. Further studies have also demonstrated that constitutive activation of Akt, EGFR and Stat3 was inhibited in both YCU-H891 head and neck squamous cell carcinoma and MDA-MB-231 breast carcinoma cell lines treated with EGCG [111].

A dose-dependent increase in p53 was observed after EGCG treatment of LNCaP cells, which carry WT p53, but not in DU145 cells carrying mutant p53 [112]. EGCG was also shown to stabilize p53 and cause up-regulation of its transcriptional activity, resulting in the activation of its downstream targets such as $p21^{WAF1}$ and Bax, and the induction of apoptosis [113]. In human liver cancer cells, a significant increase in the expression of p53 and $p21^{WAF1}$ protein that lead to cell cycle arrest was reported after EGCG treatment [114]. **Table 1** summarizes the action/mechanisms of three selected compounds that affect NF-κB and Akt-phosphatidylinositol 3-kinase (PI3K) activity *in vivo* system.

Administration of EGCG to $Apc^{min/+}$ mice, an animal model of human intestinal carcinogenesis, via their drinking fluid was found to significantly decrease small intestinal tumor formation [115]. Shimizu *et al.* have recently re-

ported that EGCG prevents obesity-related colonic and liver tumorigenesis by inhibiting the phosphorylation of the insulin like growth factor-1 receptor (IGF-1R), extracellular signal-regulated kinase (ERK), Akt, glycogen synthase kinase-3beta (GSK-3β), signal transducers and activators of transcripton 3 (Stat3), and c-Jun NH_2-terminal kinase (JNK) proteins, and improving hyperinsulinemia in carcinogen-induced mouse model [116,117]. EGCG suppressed the growth of melanoma cells in nude mice with impaired angiogenesis by inhibiting PI3K/Akt signaling specifically in tumor-associated endothelial cells and peripheral blood-derived endothelial cells [118]. Continuous feeding with EGCG to mice prior to and during establishment of bladder carcinoma xenografts *in vivo* revealed >50% reduction in mean tumor volume without detactable toxicity [119].

4.2. Curcumin

It is widely accepted that curcumin, a yellow pigment found in the rhizome of the spice turmeric, has potent cancer chemopreventive activity in various animal carcinogenesis models [120]. Curcumin is known to be a strong inhibitor of NF-κB. Curcumin has been shown to inhibit IKK, suppress both constitutive and inducible NF-κB activation, and potentiate tumor necrosis factor (TNF)-induced apoptosis [121]. Recent studies have shown that curcumin suppresses the constitutive activation of NF-κB [122] and sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting NF-κB regulated gene products [123]. Treatment with a liposomal formulation of curcumin resulted in a dose-dependent growth suppression of cancer cells and decreased activation of NF-κB [124]. The findings that expression of NF-κB target genes, including cyclin D1, cyclooxygenase (COX)-2, matrix metalloproteinase-9, Bcl-2, Bcl-xL, Mcl-1L and Mcl-1S, was reduced by the treatment with a liposomal formulation of curcumin indicate that curcumin acts the NF-κB pathway which is involved in carcinogenesis. Al-Hujaily *et al.* have demonstrated that a novel curcumin analogue, PAC, significantly reduced tumour size, and triggered apoptosis in breast cancer tumor xenografts by inhibiting expression of survivin, NF-κB and its downstream effectors, and strongly up-regulated p21 (WAF1) [125]. Moreover, clinical trials have shown that curcumin down-regulates the expression of NF-κB and COX-2 in peripheral blood mononuclear cells from patients with pancreatic cancer [126]. These results clearly indicate that curcumin inhibits tumor growth by affecting the NF-κB signaling *in vitro* and *in vivo*.

Curcumin also exhibits an inhibitory effect on Akt signaling. Recent studies have shown that curcumin dose- and time-dependently inhibits the phosphorylation of Akt and mammarian trget of rapamycin (mTOR), and their downstream targets in prostate cancer cells [127]. Inhibition of the Akt/mTOR pathway by curcumin results in suppression of the growth of SCC40 xenografts, and curcumin at 15 mg significantly increases in survival in the 4-nitroquinoline 1-oxide--induced head and neck squamous cell carcinoma survival study [128].

Curcumin has also been shown to inhibit the proliferation of cisplatin-resistant ovarian cancer cells via the inhibition of Akt activation [129]. It has also been reported that an analog of curcumin, 4-hydroxy-3-methoxybenzoic acid methyl ester (HMBME), targets the Akt signaling pathway, inhibits the proliferation of cancer cells and induces apoptosis [130]. Likewise, HMBME was shown to decrease the level of phosphorylated Akt, inhibit Akt kinase activity, and reduce the DNA-binding activity of NF-κB [130]. Several reports also suggest that curcumin has molecular targets within the Akt signaling pathways and that the inhibition of Akt activity may facilitate inhibition of proliferation and induction of apoptosis in cancer cells [131,132]. A curcumin derivative, diphenyl difluoroketone, significantly inhibited the colon cancer xenograft Akt and ERK phospholyration in mice [133]. In other study, solubilized curcumin effectively blocked brain tumor formation in the mice that had already received an intracerebral bolus of mouse melanoma cells (B16F10) by suppressing p-Akt, Cyclin D1, p-NF-κB, Bcl-xL and VEGF [134].

4.3. Quercetin

Quercetin, a powerful anti-oxidant, is consumed by humans as part of their diet [135]. Although the quercetin content of foods has not been systematically analyzed, it is found in many fruits, vegetables and beverages. The chemopreventive effects of quercetin against DNA damage and precancerous changes in cells were recently demonstrated both *in vitro* and *in vivo*. Quercetin was found to arrest the progression of cervical neoplasia in Swiss albino mice [136].

Quercetin may offer a defense against the detrimental effects of carcinogenic chemicals and can induce apoptosis via the mitochondrial pathway [137]. Although the anti-carcinogenic mechanisms of quercetin are not well known, quercetin specifically inhibits p21-Ras expression in human colon cancer cell lines and in primary colorectal cancers [138]. Reports suggest that quercetin has DNA-damaging and pro-oxidant property in cells [139]. One proposed mechanism involves the inhibition of Akt/protein kinase B (PKB) phosphorylation, an upstream kinase of the pro-survival protein kinase cascade involveing PI3K. Significant down-regulation of Bcl-2 and Bcl-xL along with Cu-Zn SOD, which could lead to an increase in ROS, has been reported after quercetin treatment in certain human cancer cell lines [43,140].

Survivin, which binds directly to and inactivates caspases

was inhibited by quercetin, resulting in the activation of caspases [43]. One promising therapeutical approach for the induction of apoptosis in cancer cells is using TNF-related apoptosis-including ligand (TRAIL) [141]. Quercetin has been shown to potentially arrest human prostate cancer cells and mediate activation of caspase and poly(ADP-ribose)polymerase (PARP) cleavage [142,143]. A combined treatment of TRAIL and quercetin was found to enhance TRAIL-induced cytotoxicity by activating caspases and inhibiting phosphorylation of Akt [144].

A principal approach for treatment of tumors is based on the fact that cancer cells are resistant to CD95-mediated apoptosis. Alterations in the CD95 system result in the escape of tumor cells from this defense system. Sensitivity to CD95 can be restored by treating the cells with quercetin, thus making the cancer cells susceptible to apoptosis [145]. One study has demonstrated the inhibitory effects of quercetin on H_2O_2-induced apoptosis via mediation of the AP-1-mediated apoptotic pathway. The mechanistic action of quercetin as an anti-apoptotic compound is attributed to its ability to inhibit MAPK pathways and reduce expression of genes participating in the JNK-c-JUN/AP-1 and ERK-cFOS/AP-1 pathways [146].

In an azoxymethane (AOM)-induced rat colon cancer model, dietary administration wirh quercetin and curcumin decreased the number of aberrant crypt foci (ACF), putataive precursor lesions for colonic adenocarcinoma, by 4- and 2-fold, respectively, compared with the controls [137]. Western blot analyses of caspase-9, Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) proteins from colon scrapings suggest that quercetin and curcumin induce apoptosis via the mitochondrial pathway. Sun *et al.* reported that quercetin significantly prevented *in vivo* growth of human salivary adenoid cystic carcinoma xenografts in nude mice, accompanied by induction of tumor cell apoptosis, suppression of NF-κB nuclear translocation, as well as down-regulation of Akt and IKB kinase-α activation. Thus, quercetin would be a promising chemotherapeutic agent through its function of down-regulating the PI3K/Akt/IKK-alpha/NF-κB signaling pathway [147].

5. COMBINATION THERAPY

Some naturally occurring chemopreventive compounds are known to act in synergy with other chemopreventive or anti-cancer agnets, as listed in **Table 2**. The anti-neoplastic agents have dose-limiting toxicity and drug resistance, thus limiting their clinical application. Development of novel strategies that overcome radio- and chemo-resistance and sensitize cancer cells to anti-neoplastic agent can enhance the therapeutic effect of these drugs. Combination treatment with EGCG and tamoxifen was synergistically cytotoxic and enhanced apoptosis in MDA-MB-231 human breast cancer cells and decreased tumor growth in a MCF-7 cell xenograft model [148,149]. The combined treatment with EGCG and curcumin also resulted in synergistic growth inhibition of MDA-MB-231 [150]. Curcumin and gemsitabin treatment decreased pancreatic tumor volume *in vivo* model [151,152]. Furthermore, combination of quercetin with sulforaphane, an isothiocyanate enriched in broccoli, exerted synergistic effects by improving apoptosis resistance [153]. Liposomal forms of curcumin plus resveratrol significantly decreased prostatic adeno-carcinoma in prostate-specific PTEN-knockout mice by effectively inhibiting cell growth and induceing apoptosis [154].

Bcl-2 family proteins are regulators of chemoresistance and radioresistance in cancer. *In vivo* treatment with quercetin and trans-3,5-dimethoxy-4'-hydroxystilbene (t-PTER) altered expression of molecules involved in regulating cancer cell resistance to drugs and radiations [155]. Combined administration with t-PTER+ quercetin, FOLFOX6 (oxaliplatin, leukovorin, and 5-fluorouracil, a first-line chemotherapy regimen), and radiotherapy eliminates colorectal cancer cells growing *in vivo* leading to long-term survival. Gene expression analysis of a Bcl-2 family of genes revealed that down-regulation of bcl-2 expression via inhibition of NF-κB activation. Curcumin also potentiates the antitumor effects of radiation therapy in colorectal cancer by suppressing NF-κB and NF-κB-regulated gene products, leading to inhibition of proliferation and angiogenesis [123].

In mouse cervical multi-stage squamous cell carcinoma model using 3-methylcholanthrene and a xenograft model of human cervical cancer in mice, the combined treatment with curcumin and paclitaxel induced a synergestic reduction in the tumor incidence as well as tumor volume compared with the individual treatment of paclitaxel or curcumin [156], suggesting that a sub-optimal concentration of curcumin augments the anti-tumor action of paclitaxel by downregulating the activation and downstream signaling of anti-apoptotic factors and survival signals such as NF-κB, Akt and MAPKs that have significant roles in proliferation, survival, angiogenesis and metastasis. By inhibition of NF-κB activity, curcumin augments the anti-tumor action of cisplatin enhancing growth suppression *in vivo* [157].

Recently, preclinical investigation revealed that combination therapy with curcumin and dasatinib to be highly effective causing an over 95% regression of intestinal adenomas in $Apc^{min/+}$ mice, which could be attributed to decrease proliferation and increased apoptosis [158].

6. SUMMARY AND PERSPECTIVES

The pathogenesis of many chronic diseases, including cancer, has been associated with aberrantly regulated apoptosis [14,75,77,78,159]. The synergistic combination of an undesirable proliferative stimulus and an associated

defect in the apoptotic pathway seems universal in cancer [76-80]. Epidemiological studies indicate that dietary habits contribute to, at least, one third of all human cancers [160], and suggest that certain dietary components can exacerbate or interfere with carcinogenesis. Apoptosis is likely to be a crucial mechanism in the chemopreventive properties associated with such dietary factors [14].

In addition to the conventional therapeutic agents, numerous dietary components and micronutrients are emerging, which possess considerable potential for hindering *in vivo* deleterious oxidative processes and inducing apoptosis of cancerous or pre-cancerous cells [160,161], and are therefore being considered as promising chemopreventive agents. A range of dietary compounds can modulate apoptosis and those with pro-apoptotic properties exhibit beneficial effects in animal and *in vitro* studies by eliminating cancerous cells [9,14,92]. Moreover, some dietary compounds have also shown beneficial effects in clinical trials [93].

A balance of cell proliferation and apoptosis normally maintains cellular homeostasis. However, apoptosis is a very complex process with numerous specific targets within each arm of the apoptotic pathways. Nevertheless, it is very encouraging that single bioactive dietary agents can directly and indirectly influence many of the targets within the apoptotic pathway. In additon, many of these dietary agents appear to exhibit some degree of specificity for neoplastic cells. Furthermore, the protective effects of single agents can be potentiated and/or synergized by other dietary factors suggesting the possibility of combinational approaches for chemoprevention. While dietary interventions seem encouraging for devising new chemopreventive strategies, there are several issues remaining that need to be fully understood. The dose of each agent, duration of exposure, relative bioavailability of each dietary compound and potentially adverse side effects and/or interactions should be considered.

Further research is required to identify the phytochemical-specific molecular mechanisms of the huge number of already recognized bioactive dietary chemopreventive agents. The potential benefits of cancer chemoprevention appear promising given the data obtained from clinical trials and pre-clinical studies.

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