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Synergistic anti-colon cancer effects and mechanisms by combined phytochemicals

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Abstract: Colon cancer is the second leading cause of cancer-related mortalities worldwide and the third in the United States. Current colon cancer treatments, including surgery, chemotherapy, and radiotherapy, have adverse effects and significantly decrease patients' quality of life. Developing treatments without side effects is critical in helping American colon cancer patients have a healthy life. Phytochemicals are non-nutritious compounds present in plants, exert various health benefits with low side effects, particularly cancer. However, the required dosages to exert anti-colon cancer effects of the phytochemicals are too high to be achieved by dietary intake. Increasing evidence supports that combining two or more phytochemicals synergistically inhibits cancer cell proliferation and tumor growth in cells and animals. This mini-review focused on two phytochemical curcumin and luteolin, combined or the individual on the anti-colon cancer effects and mechanisms in cells, animals, and humans. We conclude that combining phytochemicals may be a practical approach to treat colon cancer in humans after more extensive investigations.

Keywords: Colon cancer; Phytochemicals; Combination; Synergistic; Curcumin; Luteolin

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1.Introduction

Cancer is a major cause of death globally, with a record of about 9.6 million mortalities in 2018 [1]. Colon cancer also called colorectal cancer, is the second leading cause of all cancer-related deaths in the world across all age and both sexes owing to the prolonged precancerous stage [2]. Evidence from the American Cancer Society (ACS) reported that colon cancer is the second most common cancer in the United States. Colon cancer is expected to cause about 53,000 deaths in 2021 [3]. Colon cancer incidence and mortality rates are approximately 30 percent and 40 percent greater in males than females (ACS, 2017). Rationalities for the gender discrepancies are not well understood but partially show the changes in risk factors exposure levels (e.g., smoking, heavy alcohol use) and sex-related hormones, and complex relationships between these factors [137]. Manifestations of colon cancer incorporate weight reduction, diarrhea, constipation, anorexia, anemia, fatigue, and bloody excrement. Generally, most of these symptoms do not appear in the early stages of cancer and are only apparent after cancer progresses to a later stage. The 5-year relative survival rates of people diagnosed with colon cancer between 2009 and 2015 at the time of diagnosis at localized, regional, and distant stages are 90%, 71%, and 14%, respectively [3].

Phytochemicals are non-nutritional compounds naturally occurring in plants (spice, vegetables, grains, herbs, and fruits), have been reported in the treatment and actions toward colon cancer with low cytotoxicity. However, very few clinical studies confirm that single phytochemicals prevent/treat colon cancer, mainly through oral intake.

2. Epidemiology and risk factors of colon cancer

There are projections of 104,610 newly diagnosed colon cancer cases in the US 2020, 58% of colon cancer cases in the US are aged 65 and above, the lifetime risk is similar in men and women, but the incidence is 31% greater in men [134]. Colon cancer is known to be environmental cancer, having its major incidences in industrialized countries, and it is highly attributed to diet [135]. Risk factors, including unhealthy diets, excessive body weight smoking, high alcohol consumption, physical inactivity, are attributable to more than half of the incidence cases and mortality in colon cancer [136]. Notwithstanding, there has been an uprise in cases among individuals less than 50 years of age [4]. Studies have linked an ample consumption of plant-based diets with reduced risks of developing various cancers [5]. Colon cancers have the metastatic ability and invasive potential to invade surrounding tissues and organs, thereby migrating from the primary site of origin; this has been associated with about 90% of colon cancer mortality [6]. The normal colonic epithelium is transformed into colon adenocarcinomas via the accumulation of genetic alterations [7]. There is an increase in DNA methylation of gene promoters in the colonic mucosa of colon cancer patients, an important driving factor for cancer progression and metastasis [8].

Many risk factors are believed to increase the rate at which genetic mutations occur in various oncogenes and

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tumor suppressor genes and/or result in growth-promoting epigenetic modifications. These factors are germline genetic mutations, environmental exposures, personal or family history of colon cancer and its associated diseases, and demographic considerations. Environmental exposures associated with an increased risk of colon cancer include a history of abdominal radiation, smoking, alcohol use, and a western-style diet [9,10]. There is a direct interaction between colonic cells and dietary components. Colon cancer is highly sensitive to lifestyle, especially western-style diet, and environmental factors [11]. Increasing epidemiologic studies indicate that a western-style diet is associated with a high incidence of colon cancer [12]. It was observed that a high dietary intake of fiber was associated with a low incidence of colon cancer in the African population [13].

Colon cancer involves a series of genetic and morphological changes in the colonic epithelium, emerging from the formation of aberrant crypt foci (ACF), superseded by polyps and adenomas, till the occurrence of adenocarcinomas occurs [14]. Most colon cancer is caused by chromosomal instability, which defects the various genes related to cell proliferation, survival, cell cycle, apoptosis, and DNA repair mechanisms, such as adenomatous polyposis coli, Tp53, Kirsten rat sarcoma virus oncogene (Kras), and B-raf proto-oncogene (Braf) [15]. The dormancy of the adenomatous polyposis coli (APC) gene and activation of the K-Ras proto-oncogene are two early events of colon tumorigenesis [16]. Indeed, about 80% of patients with sporadic colon cancers carry APC mutation, while half of colon cancer patients with wild-type APC carry mutations in β-catenin [17]. Epithelial-mesenchymal transition (EMT) is implicated in the metastasis of cancers [18]. Chronic inflammations drive colon cancer initiation and progression via different mechanisms, including pro-inflammatory mediators like chemokines, cytokines and reactive oxygen species (ROS), intracellular signaling pathway mediators, overexpression of oncogenes, matrix metalloproteinases, to promote transformation, the proliferation of tumor cells, angiogenesis, invasion, and metastasis [19].

3. Shortcomings of current cancer treatment

Common colon cancer treatments have adverse effects on the quality of life of patients. Colectomy causes adhesion, secondary infection or blood clotting [20], chemotherapy causes pancytopenia, hair loss, sores, fatigue, and diarrhea [21] radiation therapy causes skin and bladder irritation, sexual problems, and fatigue and immunotherapy; fatigue, cough, nausea, itching, skin rash, decreased appetite, constipation, joint pain, and diarrhea [22].

Cancer growth treatments include a medical procedure of tumor, chemotherapy, and radiation therapy. Treatment strategy relies on the stage and area of the tumor. Chemotherapy includes cytostatic and cytotoxic medications and ends up being proficient when utilized in blend with different treatments. Legitimate chemotherapeutics incorporate alkylating specialists. Paclitaxel has been demonstrated powerful cancer-suppressing medication to treat several diseases. It occurs in endophytes present in Taxus brevifolia bark [23]. Bevacizumab represses vascular endothelial development factor receptors and has been utilized to treat metastatic malignancies [24]. Rituximab targets CD20 in lymphoma, imatinib targets Bcr/Abl, gefitinib follows up on epithelial development factor receptor, and bortezomib is endorsed as proteasome inhibitor [25]

4. Phytochemicals have the potentials for the prevention and treatment of colon cancer

Phytochemicals are naturally occurring compounds present in plants [133]. It has been shown that a significant dietary intake of phytochemicals plays crucial role in the promotion of human health. They are classified based on their function and Physico-chemical characteristic [26]. Major categories of phytochemicals include phenolics (flavonoids, phenolic acide, and polyphenols), steroids and alkaloids. Phytochemicals are known for their antioxidants, anti-inflammatory, anti-microbial, and anti-cancer effect. They also act as sedatives, strengtheners, and immunostimulants [27].

Phytochemicals have come a long way in their use against diseases. Novel bioactive compounds of plant origin may be considered a reliable therapeutic element to treat different malignancies based on their selective molecular targets [28,29]. Several biological mechanisms are involved in the antitumorigenic properties of phytochemicals, including anti-angiogenesis, inhibition of invasion, and cell adhesion [30]. Oxidative stress plays a vital role in different cancer types; due to this, antioxidants have emerged as a new therapy for cancer [31].

Increasing studies show that phytochemicals exert an anti-colon cancer effect. For instance, morin, a flavonoid primarily presents in guava, onion, and almond leaves, results in activation of intrinsic and extrinsic apoptosis pathway in SW480 cells [32]. Phytochemicals exert an anti-cancer effect through the regulation of multiple cellular signaling pathways [33].

The flavonoid scutellarin is used to treat colon cancer, cardiovascular, inflammatory, and neurological disease in Korea and south China [34]. Apigenin exerts anti-proliferative and anti-metastatic effects in colon cancer, lung cancer, and osteosarcoma via inhibition of Wnt/β-catenin signaling pathway [35,36]. Kaempferol pres-

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ent in fruits and vegetables, including green and black tea has been found to reduce the risk of colon cancer [37]. Additionally, kaempferol induces apoptosis of HT-29 colon cancer cells via activation of the extrinsic and intrinsic apoptosis pathways while decreasing the expression of the anti-apoptotic protein Bcl-xl [38]. Quercetin is widely known for its antioxidant, anti-proliferative, and anti-inflammatory properties [39]. It has been reported to suppress the Wnt/β-catenin and NF-κB pathways in colon cancer cells [40]. Piperine; an alkaloid in black and long pepper plant induces apoptosis by inhibiting the cell survival PI3K/Akt signaling pathway and upregulating endoplasmic reticulum stress response proteins [41]. Sesamol in sesame seeds exhibits pro-oxidant activities at higher concentrations by decreasing the viability of HCT116 colon cancer cells via interruption of the cell cycle at the S-phase – it also induces apoptosis via mitochondrial dysfunction [42]. Moreover, A phase I clinical trial with resveratrol relayed that Wnt target gene expression in the normal colonic mucosa of colon cancer patients was downregulated while Wnt target genes, including myc and cyclin D1, in the colon was upregulated [43].

The specific mechanism by which phytochemicals perform anti-cancer capacities is as yet a subject of examination. They apply the wide and complex scope of activities on atomic and cytosolic variables of tumor cells. They can straightforwardly retain the responsive oxygen species (ROS) or advance exercises of cancer prevention agent compounds (e.g., superoxide dismutase, glutathione, and catalase) in a changed cell [44]. A phyto-molecule can impede harmful change of a started pre-neoplastic cell, or it can impede the metabolic transformation of the supportive of cancer-causing agent. Likewise, they can adjust cell signaling involved in the development, intrusion, and metastasis of tumor cells [45]. Ellagic acid of pomegranate incites apoptosis in prostate and breast cancer cells and restrains metastasis cycles in different tumor growths [46]. Apigenin, the flavone found in parsley, celery, and chamomile, targets the leptin/leptin receptor pathway and promotes apoptosis in lung adenocarcinoma cells [47]. It initiates caspase subordinate extraneous apoptosis in human epidermal development factor receptor 2 (HER-2) over-communicating BT-474 breast malignancy cells through the suppression of STAT3 signaling [48]. Curcumin, the polyphenol of Curcuma longa hinders the development of human glioblastoma cells by tweaking a few sub-atomic parts. It upregulates the outflows of p21, p16, p53, early development reaction protein 1 (Egr-1), extracellular sign managed kinase (Erk), c-JunN-terminal kinase (JNK), ElK-1 (individual from ETS oncogenic family), Bcl-2 related X protein (Bax) and Caspase-3, 8, 9 proteins; and downregulates the degrees of B cell lymphoma 2 (Bcl-2), the unthinking objective of rapamycin (mTOR), p65, B cell lymphoma extra-huge protein (Bcl-xL), protein kinase B (Akt), epidermal development factor receptor (EGFR), NF-κB, cell division cycle protein 2 (cdc-2), retinoblastoma protein (pRB), cell myelocytomatosis oncogenes (c-myc) and cyclin D1 proteins [49].

5. Luteolin

Luteolin (3',4',5,7-tetrahy-droxyflavone), is a flavonoid found in high content in vegetables, radicchio, green peppers, celery, broccoli, thyme, lettuce, and pumpkin. Luteolin is known to have anti-inflammatory, anti-allergic, anti-cancer, antioxidant, and reacting oxygen species (ROS) scavenging activities [50]. Luteolin is a flavonoid that has a potent anti-cancer therapy in several cancer cells and animal studies as it has been demonstrated to induce apoptotic cell death and inhibit cancer cell proliferation [31].

The pharmacological functions of luteolin as an anti-inflammatory agent have been linked to its anti-cancer function [51]. Luteolin induces apoptosis in cancer cells which involves DNA damage and protein kinases in the suppression of proliferating cancer cells [51]. Luteolin induced G1 phase cell cycle arrest via the suppression of CDK2 activity in colorectal cancer in HT-29 cells and melanoma OCM-1 cells [52,53].

Luteolin-rich plants have been used in the treatment of hypertension, cancer, and inflammatory-related disorders in Chinese traditional medicine [54]. Luteolin induces growth arrest by suppressing the Wnt/β-catenin/GSK-3β signaling pathway and induces apoptosis by caspase-3 in human colon cancer cells [55]. A recent study shows that luteolin induced apoptosis by activating the mitochondria-mediated caspase pathway in HT-29 cells and caused loss of the mitochondrial membrane action potential, upregulated Bax, downregulated Bcl-2, induced mitochondria release of cytochrome C into the cytosol , and expands the levels of the active forms of caspase-9 and caspase-3 – thereby indicating that luteolin initiates apoptosis by advancing cancer prevention agent movement and enacting MAPK motioning in human colon malignant growth cells [56]. Oral and intraperitoneal administration of luteolin (50mg/kg/day) to mice with experimental autoimmune encephalomyelitis (EAE) suppressed behavioral deficits, prevented relapse, and reduced inflammation and axonal damage [57]. The anticarcinogenic properties of luteolin have effects on cell proliferation, metastasis, angiogenesis, and apoptosis induction [58,59]. Be that as it may, the molecular components underlying these activities remain vague.

With several documented studies, luteolin is expected to be a putative anti-cancer therapy [58]. Long-term

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treatment of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary carcinogenesis in Wistar rat model with luteolin (30mg/day for 20 days) showed no apparent cytotoxicity in the rats. Additionally, luteolin reduced tumor volume and tumor incidence significantly with no apparent change in the body weight of the rat [60]. With insufficient nutrition and oxygen, tumors cannot grow past 1-2mm in diameter [61]. Angiogenesis, a physiological process of developing new blood vessels, is essential for tumor growth, metastasis, and invasion. Angiogenic factors like vascular endothelial growth factor (VEGF) and matrix metalloproteases (MMPs) are secreted by tumor cells to promote angiogenesis [62]. In cancer studies, VEGF is over-expressed [63]. Luteolin can inhibit hypoxia-inducible factor-1α (HIF-1α) through proteasomal degradation to suppress VEGF expression [64]. Luteolin was shown to effectively block the activation of the VEGF receptor and its downstream phosphatidylinositol 3′-kinase activity (PI3K/Akt kinase pathways), thereby inhibiting VEGF-induced proliferation and survival of human umbilical vein endothelial cells (HUVEC) [65]. In a study that demonstrated the proliferation inhibitory effect of luteolin in human hepatoma cells, luteolin inhibited proliferation and induced apoptosis in HLF cells in a dosage and time-dependent fashion. 2 x 10 4 HLF cells had a 43.6% reduction in cell number after treatment with a concentration of 10μmol/L for 72 hours. A treatment of HLF cells with 50μmol/L of luteolin showed apoptosis in cells within 12 hours of treatment. The study also investigated the anti-tumor effect of luteolin in nude mice, after 5 weeks of the dietary intake of luteolin containing food, tumor volume decreased significantly even in mice fed 50ppm luteolin containing food [66]. 60μmol/l of luteolin decreased cell viability in Human colon cancer cells HT-29 in a dose dependent manner with about 83+- 2% decrease in number after 72hrs [58]. A low dosage (1 mg/kg bodyweight) and high (25 mg/kg bodyweight) dosage of luteolin significantly reduces the occurrence of large mammary tumor in Sprague-Dawley rats [67]. Luteolin at 100μM in colon cancer cells Caco-2 exerts no evidence of cytotoxicity in the cells while inducing a dose-dependent decrease in cell viability [68]. Oral administration of luteolin at 1.2mg/kg body weight in mice decreased the expression of nitric oxide synthase (iNOS) and cyclooxygenase 2 in azoxymethane induced colon carcinogenic mice [69]. Oral administration of luteolin (1.2mg/kg body weight /day also remarkedly lowered tumor markers and decreased the expression of matrix metalloproteinase 2 and 9 [69]. Luteolin treatment at 8.5μM showed a slight inhibitory effect of about 15% inhibition in vitro invasion of MDA-MB-231 breast cancer cell, luteolin also reduced colon cancer liver metastasis by 24% in CT26 mouse model (Balb/C nude mice) after injection of luteolin at 20mg/kg by vein tail on alternate days for 11 days period [70]. There are only a few documented clinical trials with luteolin, but most have no known results. Luteolin at 30μM was effective against prostate carcinoma in LNCaP cells [71].

Angiogenesis in tumor cells depends highly on matrix metalloproteinases (MMPs), particularly MMP-9, oral intake of luteolin (1.2mg/kg of body weight/day) lowered the expression of cathepsin markers, MMP2 and MMP-9 in azoxymethane (AOM) induced colon carcinogenesis in Balb/C mice [70]. Perhaps, the main variables directing angiogenesis is the vascular endothelial development factor (VEGF). VEGF controls key angiogenic reactions of endothelial cells (ECs), for example, expansion, relocation, and separation, just as security from apoptosis [72]. In malignant growth, VEGF is overexpressed after hypoxia [63] and additionally as an outcome of the hereditary changes of cancer, for example, transformations of oncogenes and tumor silencer qualities [73]. Most tumors express undeniable degrees of VEGF, while the neighboring ECs express VEGF receptors 1 and 2 [74], setting up an angiogenic circle. Along these lines, in a broad scope of malignancies, VEGF levels in plasma or in biopsy have fundamental prognostic significance for the result of tumor development and impact the treatment utilized [75]. The significance of VEGF in the incitement of tumor angiogenesis is clear from the reality that it addresses one of the main focuses of antiangiogenic anti-cancer treatments. Thus, numerous techniques have been created for hindering VEGF movement. These medications include the utilization of hostile to VEGF antibodies, solvent receptors, peptides that meddle with VEGF signaling [75]. Antiangiogenic quality treatment of malignant growth with adenoviruses communicating dissolvable VEGFRs in mice gave prevalent outcomes looked at with different methods of antiangiogenic treatment [76]. VEGF is found in numerous isoforms (VEGF-A, - B, - C, - D, and - E) that get from the elective grafting of similar quality [72]. These isoforms transduce their signs to the core principally through three receptors, VEGFR-1, - 2, and - 3 [77]. Of these receptors, VEGFR-2 seems to assume a fundamental part in the guideline of angiogenesis [77], though VEGFR-1 additionally appears to take part in obsessive angiogenesis [78]. VEGFR-2 receptor has tyrosine kinase action, which seems to manage epithelial cells (EC) multiplication through the activation of ERK1/2, mitogen-activated protein kinases (MAPKs) and p70 S6 kinase [79].

6. Curcumin

Curcumin, scientifically known as 1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-di-

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one is a yellow polyphenol and the dynamic segment of the perpetual spice Curcuma longa, typically known as turmeric [80]. It contains 80% curcuminoid mind-boggling, 17% dimethoxy-curcumin, and 3% bis-demethoxycurcumin [81]. Curcumin is likely the most promising phytochemical in cancer prevention research [82]. Ayurvedic medicine states curcumin as an effective treatment for a vast number of disorders such as bronchial asthma, loss of appetite, bronchial hyperactivity, cough, chronic respiratory disease, allergy, sinusitis, and liver diseases [83]. The National Cancer Institute of the United States has listed curcumin as a third-generation cancer drug. Studies have shown that the anti-apoptotic effect of curcumin is associated with inhibiting tumor cell autophagy, which can induce autophagy in leukemia K562 cells glioma cells. Studies conducted on the small digestive system and liver of mice have shown that curcumin can stifle or initiate the statement of numerous qualities related to the guideline of the cell cycle, apoptosis, cell attachment, phosphatases, and kinases. The adjustments in a few stage II cell reinforcement/detoxification catalysts that are constrained by Nrf2 show the potential parts of curcumin and Nrf2 in bringing down the danger of malignancy [84]. The downregulation of miR-27a (oncogenic), yet the upregulation of miR-34a were prompted by curcumin joined by a tweak of downstream targets, prompting cell cycle capture and apoptosis in colon cancer cells [85]. It has been reported that Curcumin mediated the downregulation of miR-130a, leading to the activation of Wnt/β-catenin in colon cancer [86]. Curcumin inhibits proliferation and promotes colon cancer cell autophagy of HCT116 and SW620 cell lines, and reversed the effect of Yes Associated Protein in colon cancer cells [87], the anti-apoptotic effect of curcumin is associated with inhibiting tumor cell autophagy, which can induce autophagy in leukemia K562 cells glioma cells [88]. Curcumin inhibited cell growth via downregulating Yes Associated Protein in pancreatic carcinoma cells [89]. Clinical trials have proven that curcumin is safe at a dose of 12g/day in humans but exhibits poor bioavailability [90].

Curcumin induced apoptosis in HCT-166 colon cancer cells by inhibiting Wnt and cell-cell adhesion pathways [91]. In human colon cancer cells HCT-116, curcumin at 10-25μM, prevented the release of calcium from the endoplasmic reticulum, thereby inhibiting the activation of Protein Kinase C (PKC) [92]. It was reported that in cervical cancer cells curcumin down-regulated Activated Protein-1 [93]. Curcumin suppresses Wnt/β-catenin pathway via the downregulation of transcription co-activator p300 in colon cancer cells [94]. Curcumin also inhibited colon carcinogenesis in mice and suppressed lipopolysaccharide (LPS)-induced expression of iNOS and cyclooxygenase 2 [95]. In pancreatic cancer cells, curcumin inhibited the Notch signaling pathway [96]. In prostate cancer cell lines, curcumin downregulated the expression of cyclin D1 [97]. Curcumin induced cell cycle held in G2/M phase in HCT116 cells and downregulated the expression of cyclin D and E while cyclin B levels remain unaffected [98]. It was shown that obsessive angiogenesis is a characteristic of cancer and a few ischemic and fiery infection [99]. During the previous years, incredible advancement has been made in understanding the system of angiogenesis in various pathophysiological conditions, the anti-angiogenesis impact of curcumin is among them. Angiogenesis inhibitors can fall into two classifications. The immediate angiogenesis inhibitors allude to those inhibitors, which are generally sensitive to endothelial cells than tumor cells. The circuitous inhibitors, which may have no immediate consequences for endothelial cells, yet may control angiogenesis through downregulating an angiogenesis trigger [100]. Curcumin is a direct inhibitor of angiogenesis; meanwhile, it can likewise downregulate a few proangiogenesis factors [101]. Curcumin influences the entire interaction of angiogenesis through downregulating record factors like NF-κB and proangiogenesis factors, for example, VEGF, bFGF, and MMPs, which are all intently and straightforwardly connected with tumorigenesis, including in the muddled managing cycle of curcumin.

Curcumin at 16μM suppressed growth in colon cancer cell lines SW620 by about 70% after 72h of treatment [87]. The treatment of liver cancer cell with 1.2-9.6ug/ml of curcumin on the vHepG2 cells revealed a dose-dependent reduction in cell viability after 24h and 48h of treatment. Also, curcumin at 240mg/kg bodyweight/day in HepG2 xenograft mouse model significantly decreased tumor volume associated with a marked reduction in tumor weight [102]. Curcumin at 10 mg/100 μL by oral gavage reduced tumor growth by 49% and 55% in SKOV3ip1 and HeyA8 human ovarian cancer mice respectively [103]. Curcumin at 25 μM inhibits growth in T24 and RT4 bladder cancer cells by about 75% after incubation for 72h. It also suggested that curcumin inhibited growth in the bladder cancer cells in a time-dose-dependent fashion (Zhang et al., 2018).

Clinical trials with curcumin have been done on several illnesses, including cancer lesions, prostate cancer, breast cancer, colorectal cancer, multiple myeloma, and leukemia amongst others [19]. In 1937, the first clinical trials with curcumin against cholecystitis was done by Oppenheimer [19]. In a pilot study of colorectal cancer (familial adenomatous polyposis), curcumin administered at 480mg and quercetin at 20 mg, twice a day for 6 months was shown to reduce the number and size of polyps with no significant toxicity [105]. A clinical trial of curcumin was done in colorectal cancer patients before

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surgery, administration of 360mg twice a day for 10-30 days showed an increase in body weight of patients, increased expression of tumor suppressor protein p53 and the number of apoptotic cells, increased DNA fragmentation in colon cancer cells while reducing serum TNF-α levels. This suggests that curcumin improved the general health of colon cancer patients due to an increase in p53 expression [106]. An open, non-randomized clinical study was performed with curcumin at a dose of 2 or 4g in 44 smoking patients with ≥8 aberrant crypt foci (ACF) in a colonoscopic examination, curcumin at a 4g daily dose for 30 days reduced ACF by 40%, while no changes were observed in ACF level in the group treated with 2g of curcumin [107]. A pilot study on the effects of curcumin extract to lower cyclooxygenase 2 activity was conducted by Plummer et al., 15 patients with advanced colorectal cancer were given oral administration of curcuminoids between 40-200mg per day for 29 days. There was a significant reduction in the PGE2 levels with an increased dose of curcumin, suggesting a dose-dependent inhibition of COX 2 [108].

7. Combinations of phytochemicals in cancer prevention/treatment

Most phytochemicals have low bioavailability [132] which may be due to their molecular structure or physico-chemical properties like hydrophobicity and low solubility [109]. To overcome the low bioavailability, combining two or more phytochemicals at low concentrations may exert an anti-cancer effect. Indeed, increasing reports that dietary phytochemicals occur naturally and can be effective in malignancy chemoprevention in combinations [110]. For example, curcumin and quercetin, a flavonoid present in onions and apples, synergistically (several-fold decreases in IC50) suppressed proliferation in 4 different cancer cell lines, namely lung cancer cell line A549, colon cancer cell line HCT1116, melanoma cancer cell line A375 and breast cancer cell line MCF7 [111]. A combination of indole-3 carbinol (I3C) at 40, 50, and 100μg/ml and resveratrol at 50 and 100μg/ml reported a synergistic effect in inhibiting proliferation in SK-OV-3 ovarian cancer cells from day 2-4 [112]. Similarly, our recent report that a combination (I3C40) of luteolin at 30 μM and indole-3-carbinol 40μM synergistically constrains ERα+ breast cancer cell (MCF7 and T47D) proliferation only, but not in triple-negative breast cancer cells. At the same time, the individual LUT30 and I3C40 do not have this anti-proliferative effect in ERα+ breast cancer cells [113]

Emulsome nanoformulations of curcumin (25 μM CurcuEmulsome) and piperine (7μM PiperineEmulsome) effectively suppressed cell proliferation to about 50% viability in colorectal cancer HCT116 cells [114]. Combined curcumin and resveratrol each at 10μM inhibited proliferation in p53 positive and negative colon cancer HCT-116 cells by 40% when compared to the controls independent of p53 status also, gavage administration of the combination curcumin at 500mg/kg and resveratrol at 150mg/kg every day for 3 weeks caused a greater than 50% inhibition in tumor growth in mice xenograft [115]

A recent meta-analysis that included 13 prospective cohort studies found that the Mediterranean diet adherence is inversely associated with colon cancer incidence, which may result from the rich of dietary phytochemicals [116]. Mediterranean diet is characterized by a high intake of vegetables, fruits, legumes, nuts, and whole grains; a moderate intake of poultry, fish, and alcohol; and a low intake of red and processed meat. In fact, the Mediterranean diet contains a total of 290 different phytochemicals from 18 subclasses and intakes over 4mg phytochemicals per day [117]. Therefore, these hundred phytochemicals may synergistically exert anti-colon cancer effects.

The combination of phytochemicals with other chemotherapeutic drugs has also been studied. For example, combined curcumin and cisplatin synergistically inhibited proliferation in hepatic cancer HA22T/VG cells [118]. A combination of curcumin and a pan-ERB inhibitor EGFR-related protein caused a greater inhibition of growth in colon cancer cells [119]. In colon cancer cells, a combination of curcumin and fluorouracil-oxaliplatin (FOL-FOX; a standard form of chemotherapy) showed significantly more significant inhibition of growth and apoptosis than the individual treatment [120]. Piperine, in combination with paclitaxel had a synergistic anti-cancer effect in MCF-7 cell line in a study [121]. Piperine in combination with doxorubicin caused a greater suppression in tumor growth in BALB/C mice that were injected subcutaneously with MDA-MB-231 breast cancer cells than either agent alone [122]. Also, piperine combined with another phytochemical thymoquinone present in volatile oil extracted from black seed induced apoptosis and inhibited angiogenesis in Balb/C mice inoculated with EMT6/P mouse mammary cells [123]. Thymoquinone in combination with paclitaxel; a chemotherapeutic drug induced a synergistic cytotoxicity in 4T1 breast cancer cell line [124]. In a study by Rajput et al., thymoquinone in combination with tamoxifen; a hormone therapy improves the anti-migratory activity of tamoxifen in MCF-7 and MDA-MB-231 cell lines [125]. Intraperitoneal injection of thymoquinone and resveratrol at 50mg/kg/day significantly reduced tumor sized by 60% in Balb/C mice inoculated with EMT6/P cells [126]. A combination of luteolin and celecoxib synergistically suppressed growth in three cell lines (MCF7, MDA-MB-231, SKBr3) compared with each treatment alone. The treatment also inhibited tumor growth in vivo [127].

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Curcumin and doxorubicin inhibited tumor migration in neuroblastoma SH-SY5Y cells [128]. Curcumin at 0-20 μM in combination with celecoxib 0-40 μM synergistically inhibited growth and induced apoptosis in osteoarthritis synovial adherent cells [129]. Curcumin 10-15 μM and celecoxib 5 μM induced a synergistic inhibitory effect on the growth of human colon cancer cell lines HT-29, SW-480, and Caco-2 [130].

Our recent studies confirmed that combined curcumin and luteolin exerts synergistic anti-cancer effect both in breast cancer and colon cancer. We found that combined luteolin and curcumin synergistically suppressed cell proliferation in triple-negative breast cancer (TNBC) BT-549 and MDA-MB-231 cells, but not in estrogen receptor-positive MCF7 cells, while the individual chemical did not inhibit cell proliferation at the selected concentration. Similarly, these combined luteolin and curcumin synergistically suppressed the xenograft tumor growth in mice (separate publication). Similarly, we found that the combination of luteolin and curcumin synergistically inhibited colon cancer CL-188 and DLD-1 cells and inhibited CL-188 cells-derived xenograft tumor growth (separate publication).

8. Conclusions

Based on the increasing studies, we recently summarized five mechanisms to understand how a combination of two or more phytochemicals exerts synergistic effects in cells, animals, and humans [131]: 1) enhance the bioavailability of phytochemicals; 2) increase antioxidant capacity; 3) interact with gut microbiome (change microbial profiles, reduce endotoxin and increase gut integrity); 4) target same and/or different signaling pathways, and 5) apply two or more of these four mechanisms simultaneously. Therefore, the combination of two or more phytochemicals may prevent/treat colon cancer through multiple approaches and mechanisms. In lieu, combining phytochemicals may enable their use at a low and safe concentration to create a novel treatment for malignancy in humans.

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