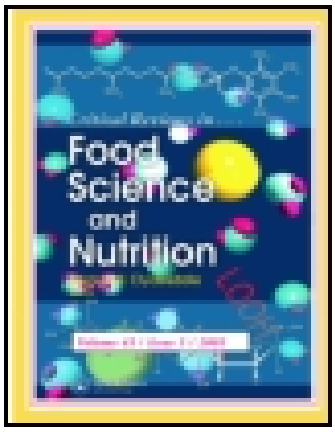

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Mohammad F. Ullah[a], Showket H. Bhat[a], Eram Husain[a], Faisel Abu-Duhier[a], S.M. Hadi[b], Fazlul H. Sarkar[c] & Aamir Ahmad[c]

[a] Prince Fahad Research Chair, Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, University of Tabuk, Tabuk-71491, KSA

[b] Department of Biochemistry, Faculty of Life Sciences, AMU, Aligarh-202002 U.P, India

[c] Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201, USA

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Pharmacological Intervention through Dietary Nutraceuticals in Gastrointestinal Neoplasia

Mohammad F. Ullah[1], Showket H. Bhat[1], Eram Husain[1], Faisel Abu-Duhier[1], S.M.Hadi[2], Fazlul H. Sarkar[3] and Aamir Ahmad[3*]

[1]*Prince Fahad Research Chair, Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, University of Tabuk, Tabuk-71491, KSA*

[2]*Department of Biochemistry, Faculty of Life Sciences, AMU, Aligarh-202002 (U.P.), India*

[3]*Department of Pathology, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI 48201, USA*

[*]Correspondence should be addressed to:

Aamir Ahmad, Ph.D

Department of Pathology, Karmanos Cancer Institute, Wayne State University

707 HWCRC, 4100 John R St, Detroit, MI 48201

Email: ahmada@karmanos.org

Abstract

Neoplastic conditions associated with gastrointestinal (GI) tract are common worldwide with colorectal cancer alone accounting for the third leading rate of cancer incidence. Other GI malignancies such as esophageal carcinoma have shown an increasing trend in the last few years. The poor survival statistics of these fatal cancer diseases highlight the need for multiple alternative treatment options along with effective prophylactic strategies. Worldwide geographical variation in cancer incidence indicates a correlation between dietary habits and cancer risk. Epidemiological studies have suggested that populations with high intake of certain dietary agents in their regular meals have lower cancer rates. Thus an impressive embodiment of evidence supports the concept that dietary factors are key modulators of cancer including those of GI origin. Preclinical studies on animal models of carcinogenesis have reflected the pharmacological significance of certain dietary agents called as nutraceuticals in the chemoprevention of GI neoplasia. These include stilbenes (from red grapes and red wine), isoflavones (from soy), carotenoids (from tomatoes), curcuminoids (from spice turmeric), catechins (from green tea) and various other small plant metabolites (from fruits, vegetables and cereals). Pleiotropic action mechanisms have been reported for these diet-derived chemopreventive agents to retard, block or reverse carcinogenesis. This review presents a prophylactic approach to primary prevention of GI cancers by highlighting the translational potential of plant-derived nutraceuticals from epidemiological, laboratory and clinical studies, for the better management of these cancers through consumption of nutraceutical rich diets and their intervention in cancer therapeutics.

Key words: Gastric neoplasm; Colon cancer; Aberrant cryptic foci; Chemoprevention; Pharmacological intervention; Nutraceutical; Clinical trials; Curcumin; Resveratrol; Gamma-amino butyric acid; Lycopene; Epigallocatechin-3-gallate.

Introduction

Cancer is a growing health problem around the world particularly with the steady rise in life expectancy (Adhami and Mukhtar, 2013). Despite the efforts to limit the incidence of this global disease, cancer has been one of the leading causes of death for the last 50 years (Jemal et al., 2010). It is responsible for approximately 13% of deaths worldwide (WHO, 2011) and remains the second leading cause of death in the United States, accounting for nearly one in every four deaths. GI neoplasia refers to the malignant disorders of GI tract and its accessory organs including esophageal neoplasm, gastric carcinoma, GI lymphoma, scirrhous neoplasm of stomach, ulcerating antral neoplasm, cecal lipoma, carcinoid tumors, colorectal cancer, and pancreatic cancer along with other metastatically invaded malignant conditions. Colorectal cancer alone is estimated to be the third common cancer in both men and women. Recently in its report on "Cancer Facts & Figures-2012", American Cancer Society noted with concern the increasing incidence of esophageal adenocarcinoma and cancers of the pancreas and liver, particularly because of their poor survival rates, thus highlighting the need for multiple treatment options for these highly fatal cancers (ACS, 2012). The concept that cancer can be prevented, or its onset postponed, by certain diet-derived substances, has in the recent years attracted considerable interest (Vainio and Weiderpress, 2006). Thus, as the experts believe, the concept of "slowing the process of carcinogenesis'' appears to be a viable approach for cancer control and is valid for most solid malignancies (Mukhtar H, 2012). Chemoprevention using dietary factors is an effective approach to extend the latency period of carcinogenesis in humans which will mean a better quality life before death by some other cause (Sporn and Suh, 2002). In this

regard dietary agents interfering with tumor development are of potential clinical value as also due to their elevated margin of safety and desired range of efficacy. It has been estimated that more than two-third of human cancers could be prevented through appropriate lifestyle modification including dietary habits as the chances of developing cancer are significantly affected by the choice of our lifestyle (Khan et al, 2010). For colon cancer alone, 70 % of cases can be prevented through appropriate modifications in the diet and lifestyle risk factors (Platz et al., 2000). Plant-derived small metabolites which are component of human diet and possess pharmacological benefits are termed as nutraceuticals. Nutraceutical is a term first coined by Stephen DeFelice in 1989 from ‘‘nutrition’’ and ‘‘pharmaceutical’’. According to DeFelice, nutraceutical can be defined as, ‘‘a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease’’ (Brower, 1998). **Figure 1** shows the chemical structures of some major plant derived nutraceuticals that possess the potential to be used as chemopreventive agents and are useful in pharmacological intervention in cancer therapeutics. Unlike pharmaceuticals (drugs) which usually act on single molecular target, nutraceuticals have been shown to exert their pharmacological effects at multiple molecular and cellular targets. **Figure 2** depicts some of the important mechanisms for few of the candidate dietary nutraeuticals that have been implicated for their cancer chemopreventive properties and are now well established in preclinical studies. It is well known that cancer cells display malfunction because of multiple molecular alterations in cellular signaling network. Thus in comparison to conventional chemotherapeutics, the four distinct advantages of these agents are their diverse structure, pleiotropic action mechanism to simultaneously influence multiple targets, significantly lower toxicity and selective killing of cancer cells (by certain dietary

agents). Studies have been reported where nutraceuticals were shown to target tumor specific microenvironment such as elevated serum and cellular copper levels in cancers of different origin including stomach and colorectal cancer (Gupte and Mumper, 2009). Many of such dietary molecules have been shown to be strongly associated with chemopreventive and therapeutic properties against cancer. These include stilbenes such as resveratrol (from red grapes and red wine) (Jang et al., 1997)**,** isoflavones such as genistein and daidzein (from soy) (Adlercreutz, 2002), carotenoids such as lycopene (from tomatoes) (Clinton, 1998), curcuminoids such as curcumin (from spice turmeric) (Tayyem et al., 2006), catechins such as epigallocatechin-3-gallate (from green tea) (Yuan et al., 2011) and other small plant metabolites such as gamma-aminobutyric acid (from fruits, vegetables and cereals) (Al-Wadei et al., 2011). Gamma-aminobutyric acid (GABA), which is a non-protein amino acid and a nutraceutical present in high quantities in plant-derived food, has been reported to possess effective anti-cancer properties against GI and pancreatic cancers mediated through interference with key cancer cell signaling pathways (Al-Wadei et al., 2011)**.** Lycopene, the principal carotenoid present in tomato, has been strongly implicated as chemopreventive dietary agent in a number of human population based case-control studies related to cancers of GI tract (Giovannucci, 1999). Epidemiological studies demonstrated a protective role of tea, in particular green tea, against the development of cancers in the upper GI tract including oral cavity, esophagus, and stomach (Yuan et al., 2011)**.** Polyphenolic nutraceuticals from green tea such as epigallocatechin-3-gallate (EGCG) have been linked to chemopreventive actions against a number of cancers including gastric and colorectal malignancies with diverse mechanistic viewpoints (Surh, 2003; Khan and Mukhtar, 2008)**.** Green tea nutraceuticals such as EGCG have also been shown to interfere with

metastatic process which involves tumor cell invasion from the primary tumor, intravasation, arrest, and extravasation of the circulatory system, followed by angiogenesis and growth at a distant site (Khan and Hasan, 2010). Evidence in literature suggests that cancer preventative nutraceuticals might be combined with standard chemotherapy or radiotherapy for the more effective treatment of GI cancers. Genistein has been shown to enhance radiosensitivity in human esophageal cancer cells (Akimoto et al., 2001)**.** Similarly, Hwang et al. reported that the combination of genistein and 5-fluorouracil (5-FU) synergistically induced apoptosis in chemoresistant HT-29 colon cancer cells (Hwang et al., 2005)**.** Furthermore, there is suggestive evidence that inflammation may have a role in the three phases of carcinogenesis (Balkwill et al., 2005). Certain nutraceuticals like curcumin have been shown to be effective against colorectal cancer and their effect on carcinogenesis is believed to be through inhibition of pro-inflammatory cytokine NF-κB as well as other molecular targets (Park and Conteas, 2010). Additionally, these agents inhibit the cell survival pathways or augment the cell death pathways thereby arresting the growth potential of cancer cells. In one of the studies the genotoxic activity of resveratrol was tested in primary cell cultures derived from gastric adenocarcinoma, obtained by mucosal biopsy at upper digestive endoscopy (Mitrut et al., 2009)**.** The adenocarcinoma cells were analyzed for the presence of micronuclei at different concentrations of resveratrol at 48 hours and at 72 hours. The results showed that resveratrol induced micronuclei dose-dependently and the frequency of micronuclei increased progressively with the dose of resveratrol.

The underlying sections provide an overview of some major dietary nutraceuticals for their clinical potential in GI cancers based on *in vitro* and *in vivo* models of carcinogenesis as well as clinical studies. **Table 1** provides a list of ongoing and recently completed clinical trials for these

candidate molecules. It is believed that standard treatment regimens of GI cancers could be potentiated with complementary or adjuvant therapy using these pharmacologically relevant dietary agents and their regular intake might be advised as a prophylactic protocol of clinical nutrition against high risk populations.

Curcumin

Epidemiological studies have indicated that curcumin may be responsible for the lower rate of colorectal cancer in Asian countries in the form of dietary spice turmeric (Chauhan, 2002). Curcumin is well tolerated in humans even at doses as high as 12 g but it has a poor systemic bioavailability (Vareed et al., 2008; Anand et al., 2007). In an earlier phase I trial 8 gm of curcumin through oral administration was well tolerated in patients with premalignant neoplasia, and the authors suggested its biologic effect in the chemoprevention of cancer (Cheng et al., 2001). It has been hypothesized that a higher systemic availability of curcumin may not be essential for chemoprevention of target GI cancers and in particular colon/colorectal cancers because GI mucosal tissues come in direct contact with such pharmacological agents when given orally. A recent Phase IIa cancer prevention trial demonstrated a significant reduction in the number of rectal ACF with curcumin at successive doses of 2 g or 4 g per day for 30 days. There was no change in normal mucosal proliferation by curcumin treatment which was assessed by Ki-67 immunohistochemistry (Carroll et al., 2011). It should be noted that preclinical studies in animal models have demonstrated that the reduction in the number of ACF are mostly time associated with decreased proliferation in surrounding normal mucosa in the colon (Carroll et al., 2009). A combination treatment with curcumin 480 mg and quercetin 20 mg orally 3 times a day

was studied in five familial adenomatous polyposis (FAP) white patients with previous coloectomy for a period of 6-9 months. Over a time period of 3-6 months there was a significant decrease in the number as well as the average size of the polyps. The mean decrease in polyp number from baseline was 60.4 % and the average size from baseline reduced to 50.9 % (Cruz-Correa et al., 2006). Interestingly, one patient showed complete regression (**figure 3**). Twelve patients with confirmed colorectal carcinoma at different stages of invasion were given oral curcumin capsules (3,600, 1,800, or 450 mg daily) for 7 days. Colorectal cancer and normal mucosal tissue biopsy specimens were analyzed for curcumin after treatment. Curcumin parent molecule levels in normal and malignant colorectal tissue ranged from 7 to 20 nmol/g tissue though in cancerous tissue the concentration decreased 2-3 folds with respect to normal colonic mucosa. COX-2 protein and M_1G adduct levels were also compared among surgical colorectal tissue samples and biopsy specimens that were obtained at the time of diagnosis. Post-treatment, the levels of M_1G were 2.5 fold higher in malignant tissues compared with normal tissues (Garcea et al., 2005). Oral curcumin administration of 8 g daily dose up to 18 months has been found to benefit at least some pancreatic cancer patients that had participated in a phase II trial. Patients who appeared to benefit most had a gradual decrease in plasma cytokine levels (Dhillon et al., 2008). Curcumin is on the path of becoming an agent of choice to potentiate the anti-tumor activity of conventional chemotherapeutic drugs against advanced pancreatic cancer. It has been reported that the antitumor effect of certain standard chemotherapeutic drugs against advanced pancreatic cancer can be potentiated by treatment with curcumin/analogs, *in vitro* as well as *in vivo* and multiple mechanisms have been put forth (Ali et al., 2010). Gemcitabine is one of the best standard chemotherapeutic drugs currently available for pancreatic cancer patients, but

patients develop résistance over time against the drug. The safety and feasibility of gemcitabine-based chemotherapy plus curcumin for gemcitabine resistant cancers has been already evaluated. No dose-limiting toxicities were observed in the patients in phase I and in phase II; 8 g/day along with gemcitabine chemotherapy regime was well tolerated (Kanai et al., 2011). Such combination therapies for pancreatic cancer are based on encouraging results from previous *in vivo* studies. For example, the effects of curcumin 1g/kg and gemcitabine 25 mg/kg, alone or in combination were evaluated on the growth of orthotopically implanted pancreatic tumors in nude mice. After 5 weeks of treatment the tumor volumes in the group (curcumin + gemcitabine) were significantly lower than the gemcitabine alone or the control groups (Kunnumakkara et al., 2007). Other curcumin based combination therapies have also been evaluated in xenograft animal models. A preclinical study in mice showed that dietary administration of curcumin with omega-3-fatty acids had a significant synergetic and suppressive effect on pancreatic tumor xenograft compared with either treatment alone. There was a delay in tumor latency in mice fed with the combination diet compared to PUFA-rich diet or curcumin alone. Mice fed with fish oil and curcumin diets showed 25% and 43% reduction in mean tumor volumes, respectively, while mice fed with a combination of n-3 PUFAs with curcumin decreased the formation of tumor xenograft by approximately 72% compared to tumors of the mice fed with the control diet. Based on the supporting results with pancreatic cancer cell lines, it was suggested that the observed synergetic effects could be, at least in part, due to inhibition of COX-2, 5-LOX, and iNOS activities, leading to the activation of $p21^{waf1/cip}$ (Swamy et al., 2008). Curcumin as 2-5 % turmeric diet has been shown to have protective effects against benzo[a]pyrene induced forestomach cancer in Swiss mice (Azuine and Bhide, 1992) **(35)**. Curcumin affords such

protection by affecting both the activation as well as inactivation pathways of benzo[a]pyrene metabolism in the liver (Singh et al., 1998**).** Dietary 0.5-2.0% curcumin decreased the number of benzo[a]pyrene-induced forestomach tumors per A/J mouse by 51-53% when administered during the initiation period and 47-67% when administered during the post-initiation period (Huang et al., 1994). It has been observed that in long-term assessments the success of chemotherapeutic strategies is impeded by chemoresistance. Curcumin has been shown to reverse such chemoresistance in gastric cancer cell lines by suppressing NF-κB and NF-κB-regulated anti-apoptotic genes (Yu et al., 2011). Curcumin potentially inhibited the growth of 65 H. pylori strains *in vitro* that were isolated from infected patients suffering from GI disorders. Curcumin eradicated H. pylori from H. pylori-infected mouse stomach (De et al., 2009). In connection with this study, it should be noted that epidemiological studies and randomized trials have established that eradication of H. Pyllori infection reduces gastric cancer risk (Fuccio et al., 2009).Moreover, curcumin inhibited N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in male F344 rats when fed on diet containing 500 ppm curcumin during the post-initiation as well as initiation phase (Ushida et al., 2000). Based on results in preclinical studies with cancer cell lines, multiple mechanisms have been put forward by various investigators that may be responsible for the chemopreventive action of curcumin against esophageal cancer in animals, including modulation of Notch signaling (Suramaniam et al., 2012) and by suppressing the formation of lipid raft-associated Rac1/PI3K/Akt signaling complexes (Lin et al., 2012).

Gamma amino-butyric acid (GABA)

In the recent years there has been special interest in GABA as a health-related compound because it is a bioactive constituent of various fruits (such as strawberries and grapes), vegetables (such as tomato and soy), and cereals (such as rice and barley) (Deewatthanawong et al., 2010; Saito et al.,2008). GABA is believed to play a role in defense against stress in plants. In animals, it acts as an inhibitory neurotransmitter in brain while also expressed in non-neuronal cells. Evidence emerging from laboratory studies have implicated β-Adrenergic receptors (β-ARs) signaling cascade, as mediators of cancer growth and progression in *in vitro* and *in vivo* models of pancreatic, gastric and colon malignancies (AL-Wadei et al., 2011)**.** These β-ARs are constitutively expressed in most mammalian cells and are associated with regulatory pathways operating under conditions of stress (Lefkowitz et al., 1990). Their stimulation is thought to be related to the growth and differentiation of tumor cells Marchetti et al., 1991), thus making β -ARs a promising target for the prevention and treatment of all of these cancer types. It has been observed that nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) significantly enhanced cell proliferation in human gastric cancer cells. Treatment of cells with propranolol (β-AR antagonist) blocked NNK-induced cell proliferation (Shin et al., 2008). This may explain why smokers have twice the risk of getting gastric cancer than non-smokers (Unakami et al., 1989). In one study, colon cancer HT-29 cell growth was reported to be stimulated by the nonselective adrenergic agonist noradrenaline, and more effectively by the β-selective agonist isoproterenol (Wu et al., 2005). The level of cyclic AMP, the second messenger for β-adrenoceptor activation, was elevated by isoproterenol treatment. The β2-adrenoceptor blockade with ICI 118 551, in contrast, significantly decreased cell proliferation. Studies have shown

marked up-regulation (44-fold) of the β2-adrenergic receptor mRNA in Kupffer cells being implicated for the metastatic potential of colorectal cancer to liver, suggesting that β-AR signaling pathway serves as a modulatory mechanism in cancer growth and metastasis (Thomas et al., 2004). Epinephrine or its precursor norepinephrine has also been shown to stimulate the migration of adenocarcinoma of colon (Masur et al., 2001) and stomach (Shin et al., 2007). It hence appears that hyper-stimulation of cAMP mediated signaling in response to β-AR stimulation might contribute to the aggressive behavior of these solid human cancers. As shown in **figure 4,** GABA acts by neutralizing the excitatory effects of cAMP signaling by inhibiting adenylyl cyclase *via* activation of the inhibitory G-protein ($G\alpha_i$)-coupled γ-aminobutyric acid receptor (GABABR) (Franek, 2004)**.** In an earlier study it was reported that prolonged alternate-day injections of GABA after treatment with N-Methyl-N'-nitro-N-nitrosoguanidine (for chemical induction of gastric carcinogenesis) significantly reduced the incidence and the average number of gastric cancers in the glandular stomach in Wistar rats (Tatsuta et al., 1990)**.** It was also shown that long-term administration of baclofen (a $GABA_B$ receptors agonist) significantly reduced the incidence and number of gastric cancers (Tatsuta et al., 1990). In a similar study 100 μM of baclofen completely inhibited the noradrenaline-induced migration of SW480 colon carcinoma cells (Joseph et al., 2002). These findings indicated that GABA inhibits the development of gastric cancers, and that this effect of GABA may be mediated *via* metabotropic $GABA_B$ receptors (Tatsuta et al., 1990)**.** An interesting study was carried out by Kawabata et al. (1999) in which the effect of dietary administration of GABA-enriched, defatted rice germ was investigated on azoxymethane-induced colon carcinogenesis in rats. The results from the study demonstrated that GABA-enriched rice germ significantly inhibited the growth of colonic

aberrant crypt foci (ACF) and suppressed the progression of pre-neoplasia to a malignant neoplasm. Moreover some studies have shown that GABA inhibited cAMP signaling, cAMP-dependent transactivation of the EGFR pathway, cell proliferation, and cell migration in immortalized human pancreatic duct epithelial cells and in human pancreatic ductal adenocarcinoma (PDAC) cell lines Panc-1 and BXPC-3 (Al-Wadei et al., 2009: Shuller et al., 2008). GABA significantly inhibited base-level and β-adrenoreceptor-stimulated pancreatic ductal adenocarcinoma cell growth and migration *in vitro* and in xenograft models (Shuller et al., 2008). These findings strongly suggest that GABA may also have tumor suppressor function for pancreatic cancer. Accumulation of GABA is a metabolic response of plant systems to stress such as salinity, anoxia, hypoxia, drought, heat, and chilling (Kinnersley and Turano,2000; Zushi and Matsuzoe, 2007). Many researchers are following the strategy to use this inherent mechanism of plants to accumulate GABA under stressful conditions to develop GABA-rich foods for humans (Deewatthanawong et al., 2010). GABA tea has been produced on a commercial basis for people with hypertension (Wang et al., 2006). GABA is an FDA-approved dietary supplement. Moreover, several *in vivo* studies have indicated that pharmacological value of a GABA-enriched diet has been utilized for stimulation of immune system (Oh and Oh,2003) and prevention of disorders such as hypertension (Hayakawa et al., 2004) and diabetes (Hagiwara et al., 2004). Thus the above noted data are indicative that consuming a GABA-rich diet and other dietary factors that possess the ability to modulate β-adrenergic signaling in gastric, colon and pancreatic cancer, as adjuvants to standard cancer therapy, may have significant beneficial effects on the outcome of these cancers by inhibiting the proliferation and migration of cancer cells.

Lycopene

Lycopene belongs to a class of plant-derived pigments called carotenoids and has been reported to be the major phytochemical constituent of variety of fruits and vegetables including tomatoes, guava, apricot, papaya and watermelon (Scort and Hart, 1995; Mangels et al., 1993). Lycopene has the highest antioxidant activity among all dietary carotenoids and contributes to a reduction in the risk of several experimental cancers (Clinton, 1998; Rao and Aggarwal, 1999). The possibility of preventive effects of lycopene on the development of colorectal cancers is well supported by a number of case-control studies. The pharmacological benefits of lycopene was thus realized following the epidemiologic studies implicating lycopene in the prevention of cardiovascular disease and cancers of GI tract including oral, laryngeal, esophageal, gastric and colorectal cancer (Girster, 1997; Tsugane et al., 1992; Zheng et al., 1993; Nomura et al., 1997). In an earlier case-control study carried on a high risk population of Iran where esophageal cancer had a significant rate, it was observed that tomato consumption was associated with a 40% reduction in the risk (Cook-Mozaffari et al., 1979). Another association correlating high tomato consumption with a 50% reduction in gastric malignancy and esophageal cancer was reported in a case-control study in Italian population (Franceschi et al., 1994). In addition to gastric cancer (Tsugane et al., 1992) cohort studies have shown an inverse association of serum lycopene concentrations with a reduced risk of pancreatic cancer (Burney et al., 1989). Similarly several studies have reported an inverse relationship for colorectal cancer and high intake of lycopene-rich tomato diet (Madon et al., 1981; Macquart-Moulin et al., 1986; Benito et al., 1990). Although the relationships among estimated carotenoid intake and their bioavailable

concentrations in serum and tissues may vary depending upon the structural specificities of different carotenoids, lycopene plasma concentrations have been reported to be correlating well with the lycopene in gastric biopsies (Sanderson et al., 1997). Human metabolism of lycopene has been recently examined in a study which showed the time to maximum concentration (t_{max}) of lycopene in plasma as 0.5 d and the elimination half-life ($t_{1/2}$) as 48 d (Ross et al., 2011). In a preclinical study using rodent model of *N*-methylnitrosourea-induced colonic ACF, lycopene in relatively small doses demonstrated efficacy against these premalignant lesions (Narisawa et al., 1996). A clinical study assessed the relation between plasma lycopene concentrations and colorectal adenomas, the precursors for most colorectal cancers on subjects undergoing a complete colonoscopy (73 with adenomas, 63 without any polyps, and 29 with hyperplastic polyps) (Erhardt et al., 2003). The median plasma lycopene concentration was found significantly lower in the adenoma group than in the control group (-35%; P =0.016) and the multiple logistic regression presented a plasma lycopene concentration < 70 µg/L (odds ratio: 2.31; 1.12, 4.77; P =0.023) as a risk factor for adenomatous polyps. As clinically classified, the two main tumor sites of gastric adenocarcinoma are proximal (cardia) and distal (noncardia). In a prospective cohort study carried by Nouraie et al., (2005), the association of dietary intake of fruits, vegetables, antioxidants, and baseline serum levels of antioxidants with subsequent incidence of the two anatomic subtypes of gastric malignancy i.e. gastric cardia cancer (GCC) and gastric noncardia cancer (GNCC) was reported. During a median follow-up of 12 years, 243 incidents of gastric adenocarcinomas (64 GCC and 179 GNCC) were diagnosed in the cohort and the statistical data showed a protective association of lycopene on GNCC (95% CI). Studies examining the mechanisms of anticancer action of lycopene have reported its ability to

negatively affect the development of cancer by modulating cell cycle progression and cell proliferation. It was shown to have an inhibitory effect on DNA synthesis, initiating up-regulation of gap-junction proteins and a reduction of local androgen signaling, impact on IGIF-1 signaling, antioxidant activity and induction of apoptotic cell death (Wertz et al., 2004; Kumar et al., 2008). In a recent study using cellular model of colon cancer (HT-29 cells), Teodoro et al. (2012), highlighted the capacity of lycopene to inhibit cell proliferation, arrest cell cycle in different phases and increase apoptosis of colon cancer cells in a dose-dependent manner. Lycopene also inhibited cellular proliferation of HT-29 cells *via* suppression of major survival signaling pathways such as Akt signaling and inhibiting the phosphorylation of the retinoblastoma tumor suppressor protein along with increased expression of nuclear cyclin-dependent kinase inhibitor p27(kip) (Tang et al, 2008**).** Studies from the same laboratory presented the *in vivo* anticancer effects of lycopene against colon cancer demonstrating the role of lycopene in preventing the growth and progression of colorectal tumor in a mouse xenograft model (Tang et al., 2011). The chemopreventive effects of lycopene were associated with suppression of COX-2, PGE(2), and phosphorylated ERK1/2 proteins and showed an inverse correlation with the plasma levels of matrix metalloproteinase 9 (MMP-9) in tumor-bearing mice. Earlier, another anti-cancer mechanism was reported using N-methyl-N′-nitro-N-nitrosoguanidine and saturated sodium chloride (S-NaCl)-induced gastric carcinogenesis model (Bhuvaneswari et al., 2001). The results suggested that lycopene blocks experimental gastric carcinogenesis by up-regulating GSH-dependent hepatic detoxification systems (reduced glutathione (GSH), glutathione peroxidase (GPx), glutathione S-transferase (GST) and glutathione reductase (GR)) thereby protecting against carcinogen-induced oxidative damage.

Synergistic studies using combination of dietary agents also showed lycopene to be an effective anti-cancer agent against gastric cancers. One such study showed that the combination of S-allylcysteine (derived from garlic) and lycopene induce apoptosis by modulating Bcl-2, Bax, Bim and caspases during experimental gastric carcinogenesis (Velmurugan et al., 2005). In another study concomitant supplementation of lycopene and eicosapentaenoic acid inhibited the proliferation of human colon cancer cells by suppression of phosphatidylinositol 3-kinase/Akt signaling pathway, blocking the activation of downstream mTOR molecule and up-regulating the expression of apoptotic proteins such as Bax and Fas ligand to suppress cell survival (Feng et al., 2009).

Resveratrol

Resveratrol (RVT) has been well evaluated in animal models as a chemopreventive agent in colon cancers. Most studies have focused on its effects on ACF which are most of the time induced by a carcinogen in rodents. ACF are also present in humans and such lesions are at high risk of transforming into a malignant state. In mice with azoxymethane-induced colon carcinogenesis, RVT pre-treatment reduced the number of ACF, their multiplicity and also abolished large sized ACF. Further investigations implicated that the underlying mechanisms may at least involve changes in the expression levels of bax and p21 in the cryptic foci and surrounding intestinal mucosa (Tessitore et al., 2000). Resveratrol similarly reduced the number of adenomas in the colon of mice challenged with benzo(a)pyrene (Huderson et al., 2012). In Min mice which are genetically predisposed to develop intestinal tumors, resveratrol treatment prevented the formation of colon cancers and also reduced their number by 70% with respect to untreated controls. Such effective reduction in intestinal tumors could be achieved at such low

doses as 0.3 mg/day/mouse. Gene expression studies revealed that resveratrol lead to down-regulation of genes such as cyclin D1 and D2, Y-box binding protein among others involved in cell cycle regulation while at the same time it down-regulated the expression of genes involved in tumor progression and expansion (Schneider et al., 2001). Another study demonstrated that RVT was more effective in inhibiting colon carcinogenesis in wistar rats challenged with 1,2-dimethyhydrazine if given at tumor promotion and progression stages. The prolonged treatment with resveratrol led to reduced colon tumor incidence, rate, size and multiplicity and as well as a decrease in the number of ACF in the colon tissues (Sengottuvelan et al, 2006; Sengottuvelan et al., 2006). Resveratrol in drinking water reduced the formation of colon and small intestine tumors in $Apc^{Min/+}$ by decreasing the expression of genes involved in cell cycle progression or cell proliferation (Schneider et al., 2001)**.** A recent human intervention study demonstrated that resveratrol is well tolerated at daily oral doses of 0.5-1 gm in colorectal cancer patients. Such oral doses produce and sustain resveratrol levels in GI tract sufficient to elicit chemopreventive effects (Patel et al., 2010). Novel approaches to enhance the bioavailability of this agent has shown promising potential. An interesting study demonstrated that piperine, an alkaloid derived from black pepper significantly improves the in vivo bioavailability of resveratrol (Johnson et al, 2011). In a phase I pilot study effects of low doses of resveratrol formulation and resveratrol-containing freeze-dried grape powder (GP) were evaluated in eight colon cancer patients. Cancerous colonic and surrounding normal mucosa was analyzed for WNT pathway by microarray and quantitative real-time polymerase chain reaction. In colon cancerous tissues resveratrol/GP treatments lead to no change in most WNT target gene expression. However, in normal colonic mucosa, resveratrol/GP treatment lead to a decrease in the expression of most of

the WNT target genes including myc, jun, TCF7, axinII and cyclinD1. Based on such results, the authors conclude that resveratrol and possibly along with some additional active components in GP may be beneficial in colon cancer prevention (Nguyen et al., 2009). Intestinal microbiomes vary considerably from individual to individual and their association to cancer risk is markedly influenced by interaction with phytonutrient in the intestines and potential of chemopreventive efficacy against colon cancer. There exist significant observations relating to mechanisms whereby dietary components can interact with the microbiota to influence colon cancer risk (Davis CD and Milner JA, 2009). It has been shown that polyphenolic nutraceuticals such as resveratrol may alter bacterial metabolizing enzymes and thus influence overall cancer risk. Resveratrol supplementation (8 mg/kg body weight/day, intragastrically) significantly reduced activities of fecal and host colonic mucosal enzymes, such as β-glucoronidase, β-glucosidase, β-galactosidase, mucinase, and nitroreductase activities (21%, 45%, 37%, 41% and 26% respectively) compared to control animals. The reduced bacterial enzyme activity was associated with a significant reduction in colonic tumor incidence in the resveratrol fed compared to control rats (Sengottuvelan M and Nalini N, 2006)

Genistein

The pharmacological significance of soy as an anti-cancer constituent of human diet was highlighted when in 1987 Akiyama et al., (1987) reported that genistein, the principal isoflavone in soy, was a potent and specific *in vitro* inhibitor of the of the epidermal growth factor receptor tyrosine kinase. Since the protein products of most of the oncogenes were previously shown to be either membrane bound receptors with tyrosine kinase activity or intracellular proteins catalyzing tyrosine phosphorylation (Hunter, 1984), the role of genistein as tyrosine kinase

inhibitor provided a potential approach to cancer chemoprevention. Such an approach was supported by the epidemiological studies indicating that a high intake of isoflavonoids are frequently associated with lower risks of various types of cancers including those of GI tract such as colon and gastric cancers (Adlercreutz**,** 1998). It is well established that almost all colorectal cancers arise from benign, neoplastic adenomatous polyps and if untreated about 5% to 10% of adenomatous polyps are estimated to become malignant in five to ten years (American Society for Gastrointestinal Endoscopy, 2006)**.** A case-control study aimed to evaluate the role of a variety of foods in contributing to the risk of colorectal adenomas (CRA) in Malaysian subjects demonstrated soy bean and soy products to be associated with a reduced risk for CRA (OR = 0.38, 95% CI = 0.15-0.98) (Ramadas and Kandiah,2009) . In a recent study using rat model, the administration of genistein was shown to reduce proliferation in ileal and colonic mucosa cells thus suggesting its protective role in the ileal and colonic epithelium from tumor development *via* modulation of tissue homeostasis (Schleipen et al., 2011). In human colon cancer cells the expression of EGF has been observed to be elevated and is considered critical for the progression of cancer which is mediated by loss of tumor suppressor FOXO3 activity (Rego et al., 2010; Fichera et al., 2007). A recent study examined the effect of genistein on proliferation stimulated by EGF-mediated loss of FOXO3 in human colonic cancer HT-29 cells (Qi et al., 2011)**.** The results showed that genistein inhibited EGF-induced proliferation, while favoring dephosphorylation and nuclear retention of FOXO3 (active state) which in turn promoted cell cycle arrest in colon cancer cells. Genistein can also decrease cell invasion and angiogenesis in various cancers such as pancreatic cancer (Wang et al., 2010) and colon cancer (Ogasawara et al., 2007). In pancreatic cancer, the protein Forkhead box protein M1 (FoxM1),

which is normally associated with cell cycle progression through the G2/M-phase checkpoint was revealed as the target of genistein action (Wang et al., 2010). The inhibition of FoxM1 resulted in a decrease in MMP-9, as well as decreases in proteins that regulate the cell cycle and angiogenesis. Similarly, genistein was shown to inhibit invasion of colon cancer and its metastatic growth to lungs and in this case antioxidant properties were shown to be dominant (Ogasawara et al., 2007). The anti-cancer action of genistein against colon cancer has also been attributed to its ability to attenuate WNT signaling pathway by up-regulating sFRP2 (a WNT pathway antagonist) (Zhang et al., 2011) and also interfering with Insulin-Like Growth Factor-I Receptor (IGF-1R) signaling (Kim et al., 2005). In one of the study, morphological characterization of genistein treated human colon cancer cells (SW480) using light microscopy showed cancer cells were shrunken, disrupted and show cytoplasmic vacuolization whereas electron microscopic examination demonstrated cell shrinkage, nuclear fragmentation and pronounced chromatin condensation, the hallmark of cells undergoing apoptosis (Fan et al., 2010). Genistein also induced topo II-mediated DNA damage in HT-29, SW-620 and SW-1116 colon cancer cells and induced apoptosis through a topo II-independent mechanism (Salti et al., 2000). Consistent with the observations in human colon cancer cells, genistein has also been reported to cause apoptotic cell death of primary gastric cancer cells in dose- and time-dependent manner by down-regulating the expression of anti-apoptotic inflammatory cytokine NF-κB while up-regulating pro- apoptotic factor such as Bax and caspase-3 (Zhou et al., 2004;Liu et al., 2011). Further, suppression of COX-2 protein was also reported to be important for the anti-proliferative and pro-apoptotic effects of genistein in gastric cancer BGC-823 cells, and these effects are believed to be mediated through the NF-κB pathway (Li et al., 2011). In a study by

Zhou et al on *in vivo* model, the effect of genistein was evaluated against implanted tumor of human gastric cancer SG7901 cells in nude mice (Zhou et al, 2008). The results showed genistein was able to induce apoptosis of transplanted tumor cells, mediated by down-regulation of the apoptosis-regulated gene Bcl-2 and up-regulation of apoptosis-regulated gene bax. The cytotoxic effect of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is limited in some cancer cells, including AGS gastric adenocarcinoma cells. However, study has shown that treatment with TRAIL in combination with subtoxic concentrations of genistein sensitizes TRAIL-resistant AGS cells to TRAIL-mediated apoptosis (Jin et al., 2007). Moreover genistein has been shown to enhance radiosensitivity in human esophageal cancer cells (Akimoto et al., 2001) and the combination of genistein and anti-cancer drug 5-fluorouracil (5-FU) synergistically induced apoptosis in chemoresistant HT-29 colon cancer cells (Hwang et al., 2005). In a recent study, a series of genistein analogues were prepared by difluoromethylation and alkylation, and their effect was tested against human gastric cancer cell lines AGS and SGC-7901 cultured *in vitro* (Xiang et al., 2012). Interestingly nine of the genistein analogues were reported to have more effective antitumor activity than genistein with 7-difluoromethoxyl-5, 4'-di-n-octylgenistein (DFOG) appearing to be the most potent anti-cancer analogue. Thus the anti-cancer potential of genistein may also be significant in the context that it could sensitize the cancer cells to the existing radio- and chemo-therapeutic regimens and further it may act as a lead compound for the synthesis and development of novel anti-cancer drugs.

Epigallocatechin-3-gallate (EGCG)

Polyphenolic compounds, which represent 30% of dried leaf extract in brewed green tea, are found to have profound health effects (Lin et al., 1999)**.** These compounds include flavonols, flavandiols, flavonoids, and phenolic acids; however, most of the polyphenols found in green tea are monomeric flavan-3-ols, better known as catechins, including: epicatechin (EC), epicatechin-3-gallate, epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG) (McKay et al., 2002). Among the catechins EGCG gained immense interest and pre-dominated scientific scrutiny for promising anticancer potential (Khan and Mukhtar, 2007; Baba et al., 2012). Plasma bioavailability of green tea polyphenols (GTPs) also appears to be quite inconsistent. For example, although EGCG concentration is five times more abundant than EGC in green tea, plasma levels of EGC were higher as compared to EGCG in rats given 0.6% GTPs in their drinking water over a period of 28 days. On the contrary, a similar dose when given to mice resulted in EGCG levels much higher in plasma as compared to EGC, indicating that bioavailability of catechins may vary with species **(**Okushio et al., 1996**).** In humans, a pharmacokinetics study of catechins showed average peak plasma concentrations of 223, 124 and 78 ng/mL for EGC, EC and EGCG, respectively after oral administration of 20 mg tea solids/kg (Lee et al., 2002). Rationally, organ sites that are accessible directly to orally administered tea, such as digestive tract, are thought to represent good targets for potential chemoprevention by tea because of the high bioavailability (Lambert et al., 2005).

The antitumor effects of GTPs and EGCG have been investigated in a variety of cancer cell lines, animal models, and clinical studies (Khatiwada et al., 2011;Okello et al., 2011;Yang et al., 2011). EGCG has been found to block the growth of human colon carcinoma cells HT-29

(Valcic et al., 1996) and also inhibit the proliferation and migration of human colon cancer cells SW620 *via* inhibition of the extracellular signal-regulated kinase 1 and 2 (ERK1/2) and nuclear NF-kB pathways, indicating its potential to serve as a preventive and therapeutic agent for colon cancers (Zhou et al., 2012). Synergistic anticancer activity of curcumin and catechin was evaluated in human colon adenocarcinoma HCT 15, HCT 116, and human larynx carcinoma Hep G-2 cell lines. A cumulative enhanced effect was observed due to cytotoxicity, nuclear fragmentation as well as condensation, and DNA fragmentation associated with the appearance of apoptosis (Manikandan et al., 2012). In a recent study, the chemopreventive effect of green tea on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis was studied in male Wistar rats. The significant reduction of serum tumour necrosis factor, C-reactive protein levels, inhibition of tumour incidence, and nearly normal survival rate and colonic architecture was observed with EGCG treated group (Sadik et al., 2012). In another study investigating the chemopreventive effect of EGCG on the development of azoxymethane-induced colonic pre-neoplastic lesions in F344 rats, EGCG was found to suppress the occurrence of colonic pre-neoplastic lesions (Ogawa et al., 2012). Using a similar model Ju et al., (2003) observed that green tea extract inhibit ACF formation even in mice fed a high corn oil diet, suggesting the potential to inhibit colon carcinogenesis in population such as those in the Western countries that consume a high fat diet. Ju et al., (2005) reported that administration of EGCG at 0.02%–0.32% in drinking fluid dose-dependently inhibited small intestinal tumorigenesis in *Apc*Min/+ mice. The alteration of vital signaling proteins was revealed by Western blot analysis which indicated that the EGCG administration resulted in increased levels of E-cadherin as well as decreased levels of beta-catechin in the nucleus, c-Myc, phospho-Akt, and phospho-Erk in the tumor tissue.

Interestingly in related studies green tea administration (0.6% in drinking fluid) inhibited the formation of azoxymethane (AOM)-induced aberrant crypt foci in CF-1 mice on a high-fat diet (Ju et al., 2003) and EGCG (0.1% in drinking fluid) administration decreased tumor incidence and the number of tumors per tumor-bearing mouse in AOM-treated CF-1 mice (Ju et al., 2007).

A recent large prospective cohort study investigated the association of tea consumption with incidence of all digestive system cancers (stomach, esophagus, colorectal, liver, pancreas, and gallbladder/bile duct cancers) in 69,310 non-smoking and non-alcohol-drinking middle-aged and older Chinese women. An inverse association was found primarily for colorectal, stomach and esophageal cancers (Nechuta et al., 2012). Another similar study with 74,942 women aged 40-70 years from seven urban communities of Shanghai found that regular consumption of green tea was inversely associated with the risk of colorectal cancer, particularly among women who maintained drinking habit over time. The longer the duration of lifetime tea consumption, the lower was the risk of colon cancer. The risk also decreased as the amount of tea consumption increased (Zheng et al., 2005)**.** In a large population-based case control study conducted in Shanghai, newly diagnosed cancer cases - 931 colon, 884 rectum and 451pancreas, during 1990-1993, among residents 30-74 years of age were compared to controls (n = 1,552) selected among Shanghai residents and frequency-matched to cases by gender and age. An inverse association with each cancer was observed with increasing amount of green tea consumption. Importantly, the time and type associated with the consumption and differences among and between populations also need to be addressed (Hakim et al., 2011). In the western societies the consumption of black tea is predominant. Reduced risks for digestive tract cancers were attributed to regular consumption of black tea in the Iowa Women's Health Study (for colorectal

cancer) (Dora et al., 2003;Arts et al., 2002; Arts et al., 2002)**,** in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up study (for colon cancer) (Su and Arab, 2002), and in the Nurses Health Study (for rectal cancer) (Michels et al., 2005).

Green tea catechins show protective effect on the pancreas from oxidative damage (Kim et al., 2003) and also have dose-dependent inhibitory effects on growth rate on AR42J cells, a rat pancreatic tumor cell line (Kim et al., 2011). Black and green tea extracts, GTPs and EGCG decreased the expression of the K-ras gene, and inhibited growth of pancreatic cancer cells (Lyn-Cook et al., 1999). EGCG induces suppressive effect on human pancreatic cancer cell lines by inducing cell cycle arrest and apoptosis. It causes Bax oligomerization, generates reactive oxygen species (ROS), and depolarizes mitochondrial membranes to facilitate cytochrome c release into cytosol. EGCG may also activate c-Jun N-terminal kinase (JNK) in pancreatic carcinoma cells (Qanungo et al., 2005; Tan et al., 2006). Thus, EGCG may be a potent biologic inhibitor of human pancreatic carcinomas, reducing their proliferative and invasive activities. Recently a population-based case-control study conducted in urban Shanghai, 908 cases of pancreatic cancer and 1067 healthy controls examined the association of multiple tea drinking habits with the risk of pancreatic cancer. In women, regular green tea drinking was associated with 32% reduction of pancreatic cancer risk (OR 0.68, 95% CI 0.48–0.96), compared to those who did not drink tea regularly (Wang et al., 2012). Among other epidemiological studies regarding tea intake and risk of pancreatic cancer, four have reported inverse associations (Ji et al., 1997; Shibata et al., 1994; Whittemore et al., 1983; Zatonski et al.,1993)**.**

EGCG has been shown to induce cell death in gastric cancer cells NUGC-3 by apoptosis *via* inhibition of survivin expression downstream of p73 (Onada et al., 2011) and also inhibit the growth of AZ521 human gastric cancer cells (Tanaka et al., 2011). Epidemiologic studies have shown the progression of chronic gastritis to atrophy to intestinal metaplasia, subsequently to dysplasia and to the intestinal type of stomach cancer (Correa**,** 1992). Studies have shown that green tea drinkers have reduced risk of chronic gastritis (Borrelli et al., 2004) with another investigation suggesting 51% lower risk to green tea drinkers than nondrinkers and 48% reduced risk of stomach cancer than non-drinkers after adjusting for potential confounders (Setiawan et al., 2001). Furthermore, this relationship has also been explored in Chinese (Mu et al., 2005;Yu et al., 1995) and Japanese populations, providing supporting evidence of reduced risk of stomach cancer with green tea extract (Sasazuki et al., 2012).

Green tea extract is regarded as a protective factor for esophageal cancer by a number of studies (Singh et al., 2011). Fluidic intake of decaffeinated green tea or decaffeinated black tea extracts resulted in reduced esophageal tumor incidence and multiplicity by ~70% in both groups of N-nitrosomethylbenzylamine-induced esophageal tumor model of Sprague-Dawley rats (Wang et al., 1995). Significant inhibitory effects of similar tea extracts were also seen in a similar model of esophageal carcinogenesis in Wistar rats (Maliakal et al., 2011) and F-344 rats (Li et al., 2002). Polyphenon E (Poly E), a well-defined green tea-derived catechin mixture inhibited growth of Barrett's and adenocarcinoma cells by suppressing cyclin D1 expression through both transcriptional and posttranslational mechanisms (Song et al., 2009). Barrett's esophagus develops as a consequence of chronic gastroesophageal reflux (GORD) and patients with Barrett's have a 40 fold increased risk of oesophageal adenocarcinoma (Gordon et al., 2011). The

literature provides ample rationale for further evaluation to use EGCG as a potential chemopreventive and therapeutic agent for esophageal adenocarcinoma and its precursor, Barrett's esophagus. A large case-control study indicated the green tea showed protective effect on esophageal cancer (Gao et al., 1994). However evidence suggests very hot green tea consumption results in an increased risk of esophageal cancer (Ghadirian, 1987). A comparative case-referent study conducted using Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) comprising of 1,706 histological diagnosed cases of digestive tract cancers (185 esophagus, 893 stomach, 362 colon, 266 rectum) suggested decreased risk for all these cancers (Inoue et al., 1998). Other population studies also supported high consumption of green tea to increased protective effect for esophageal cancer with warm tea rather than hot intakes (Gao et al., 1994; Chen et al., 2011).

The National Cancer Institute of the National Institute of Health has sponsored numerous studies to evaluate the pharmacokinetics and safety of oral green tea, Polyphenon E and EGCG (Chen et al., 2011;Chow et al., 2005; Jatoi et al., 2003; Laurie et al., 2005; Shanafelt et al., 2012). In a Phase I trial of oral green tea extract (caffeine-free) in adult patients with solid tumors, Pisters et al.,(2001) reported that a safe dose of green tea extract was equivalent to 7-8 Japanese cups (120 ml) of green tea three times daily for six months. In other prospective cohort studis, preclinical safety trials (with tablets of green tea extract), double-blind randomized clinical phase II prevention trial (for recurrence of colorectal adenomas), and synergistically enhanced inhibition by the combination of green tea catechins and anticancer drugs was analyzed. From the results obtained, Fujiki et al., (2012) suggested the consumption of 10 Japanese-size cups of green tea per day as a significant factor in primary cancer prevention for the general population. The study

also proposed the preventive effect on recurrence of colorectal adenomas in patients as vital evidence in tertiary cancer prevention by green tea and its constituents.

Conclusion & future perspectives

There is an impressive collection of preclinical data along with epidemiological and dietary intervention studies in literature, accumulated over the years showing the chemopreventive and chemotherapeutic potential of dietary nutraceuticals against most gastrointestinal cancers. Dietary nutraceuticals have attracted much attention in cancer chemoprevention primarily due to the four distinct advantages associated with these agents; their diverse structure, pleiotropic action mechanism, significantly lower toxicity and selective killing of cancer cells (by certain dietary agents). Studies have put forward interesting observations with regard to the clinical outcome of cancer patients when treated with nutraceuticals and thus strongly encourage the utilization of these chemopreventive agents towards realizing their translational potential. For an instance, in patients with advanced colorectal malignancy refractory to standard chemotherapy, 5 of 15 individuals administered oral curcumin daily had stable disease during follow up evaluation (Sharma et al., 2001)**.** Multiple molecular mechanisms are responsible for such cancer chemopreventive and cancer therapeutic effects of dietary nutraceuticals which have been well demonstrated in preclinical cancer models. Laboratory studies in different in vitro and in vivo systems have shown that many natural compounds possess the capacity to regulate response to oxidative stress and DNA damage, suppress angiogenesis, inhibit cell proliferation and induce autophagy and apoptosis (Mukhtar et al., 2012). However there appears a vacuum regarding whether such molecular mechanisms come into play when these studies are translated into human intervention studies. As of yet, very few studies have attempted the underlying molecular

mechanisms for the chemopreventive action of dietary nutraceuticals in humans. It also appears that cancer patients may respond differentially towards the chemopreventive effects of the nutraceuticals; some are more sensitive and responsive than others. Possibly genetics as well as pre-neoplasm lifestyle may be critical factors for the biased responses of the patients. It is believed that precise mechanistic details can lead to tailoring of nutraceutical/adjuvant regimes and help design future clinical trials in cancer patients. As depicted in **figure 5,** a mechanism-based model of treatment is proposed which could assume significance as these dietary agents have diverse chemical structure and pleiotropic actions. It is envisaged that different cocktails of structurally diverse nutraceuticals having the ability to interfere with the stage specific impairment of proteins and pathways could be utilized to intervene and derail the progression to the next advanced cancer stage. Many plant-derived dietary nutraceuticals, and in particular polyphenols/flavonoids, have limited systemic bioavailability when administered orally even at high doses due their fast metabolism and systemic clearance. However, it needs a mention that the higher systemic concentration may not necessarily reflect the actual concentrations of the nutraceuticals in the target tissues. It is observed that the local concentration of these agents in the major parts of the gut is readily bioavailable due to direct access to mucosal epithelia and could thus target the neoplastic tissues originating in GI sites. Moreover increasing the systemic concentrations through novel strategies will have an additive effect over local tissue concentrations in the gut and thereby enhance the chemopreventive effects of dietary nutraceuticals against GI cancers. Recently a novel approach of "nanochemoprevention" was proposed to enhance the efficacy of dietary nutraceuticals in cancer chemoprevention (Siddiqui et al., 2010; Siddiqui and Mukhtar 2010). The study examined the efficacy of tea polyphenol

epigallocatechin-3-gallate (EGCG) encapsulated in polylactic acid (PLA) and polyethylene glycol (PEG) nanoparticles and findings showed that the nano-EGCG was able to retain its biological effectiveness, with over 10-fold dose advantage compared to non-encapsulated EGCG for exerting its cell growth inhibition, proapoptotic, and angiogenic inhibitory effects. Nano-EGCG was also observed to be effective in inhibiting tumor cell growth in athymic nude mice, with over 10-fold dose advantage compared to non-encapsulated EGCG. In addition pharmacological synergism among dietary nutraceuticals which enhance their chemopreventive activity has strong potentials for developing cocktails of such agents for cancer patients. Such synergistic phenomenons are supported by studies reporting anticancer effects of whole food rather than a specific constituent. For an instance, the cancer preventive efficacy of pomegranate juice and avocado fruit which could be consumed in regular routine has been documented for both *in vitro* and *in vivo* animal models (Syed et al., 2007; Adhami et al., 2009; Ding et al., 2007). Similarly, dietary freeze-dried berries were shown to inhibit chemically induced cancer of the rodent esophagus by 30–60% and of the colon by up to 80% (Stoner et al., 2007). In view of these observations it is believed that the conceptualization of the molecular mechanisms and targets as well as nutraceutical-based standalone custom-tailored treatment regimens or adjuvant therapies would lead to closer steps towards an efficient management and clinical outcome in patients with GI cancer diseases.

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Conflict of Interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of this manuscript.

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Legends to figures

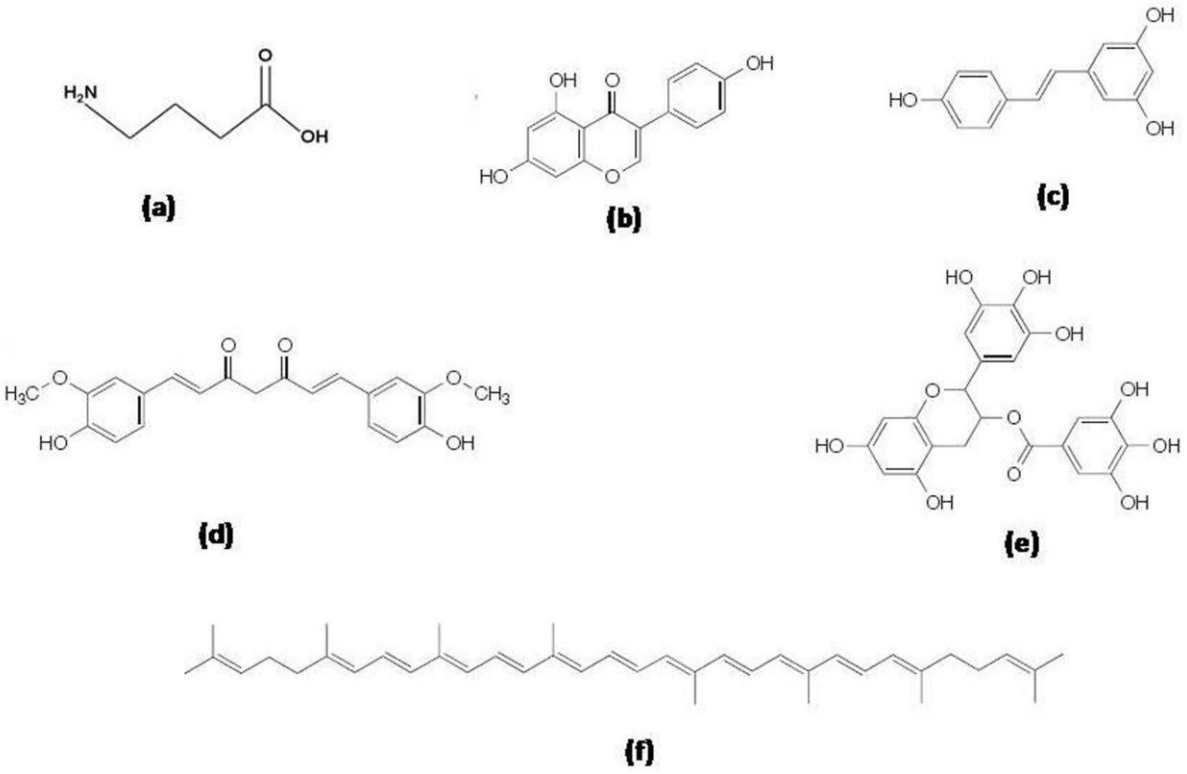

Figure 1. Chemical structures of dietary nutraceuticals useful in pharmacological intervention of gastrointestinal cancers: (a) Gamma-amino butyric acid (b) Genistein (c) Resveratrol (d) Curcumin, keto form (e) Epigallocatechin-3-gallate (f) Lycopene.

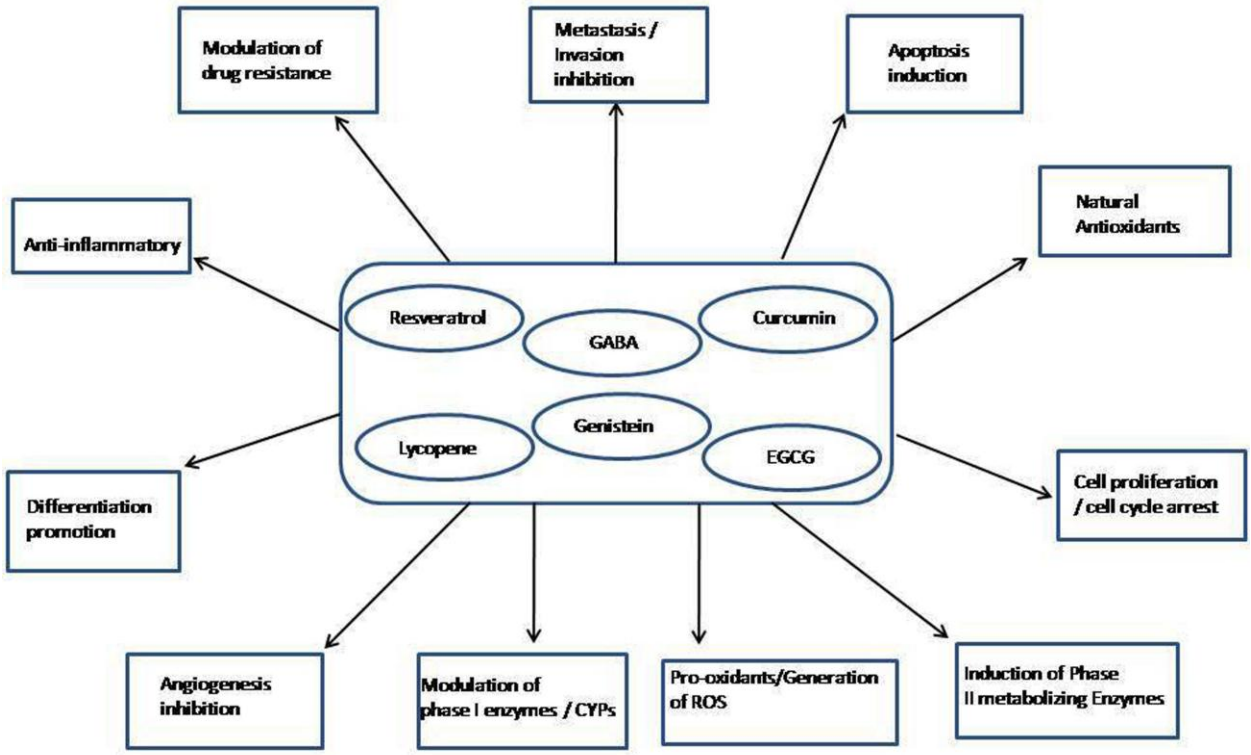

Figure 2. Dietary nutraceuticals hit multiple cellular and molecular targets to interfere with the process of carcinogenesis.

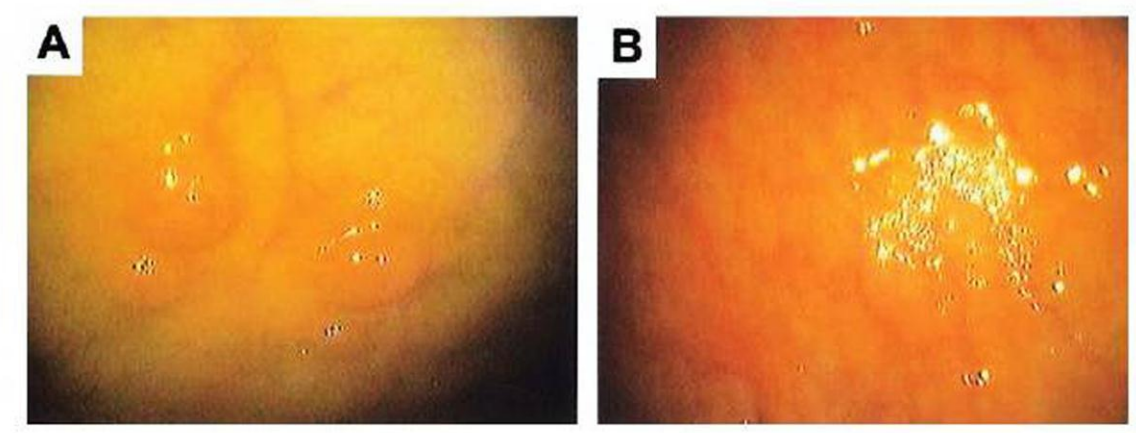

Figure 3. Endoscopic photographs of the retained rectal segment of a patient before and during treatment with curcumin and quercetin: (*A*) Before treatment, the patient had 11 adenomas averaging 4 mm in size ;(*B*) At 3 months of treatment, the rectum was polyp free. Reproduced from the original source (Cruz-Correa et al., 2006) with the permission of Elsevier Ltd.

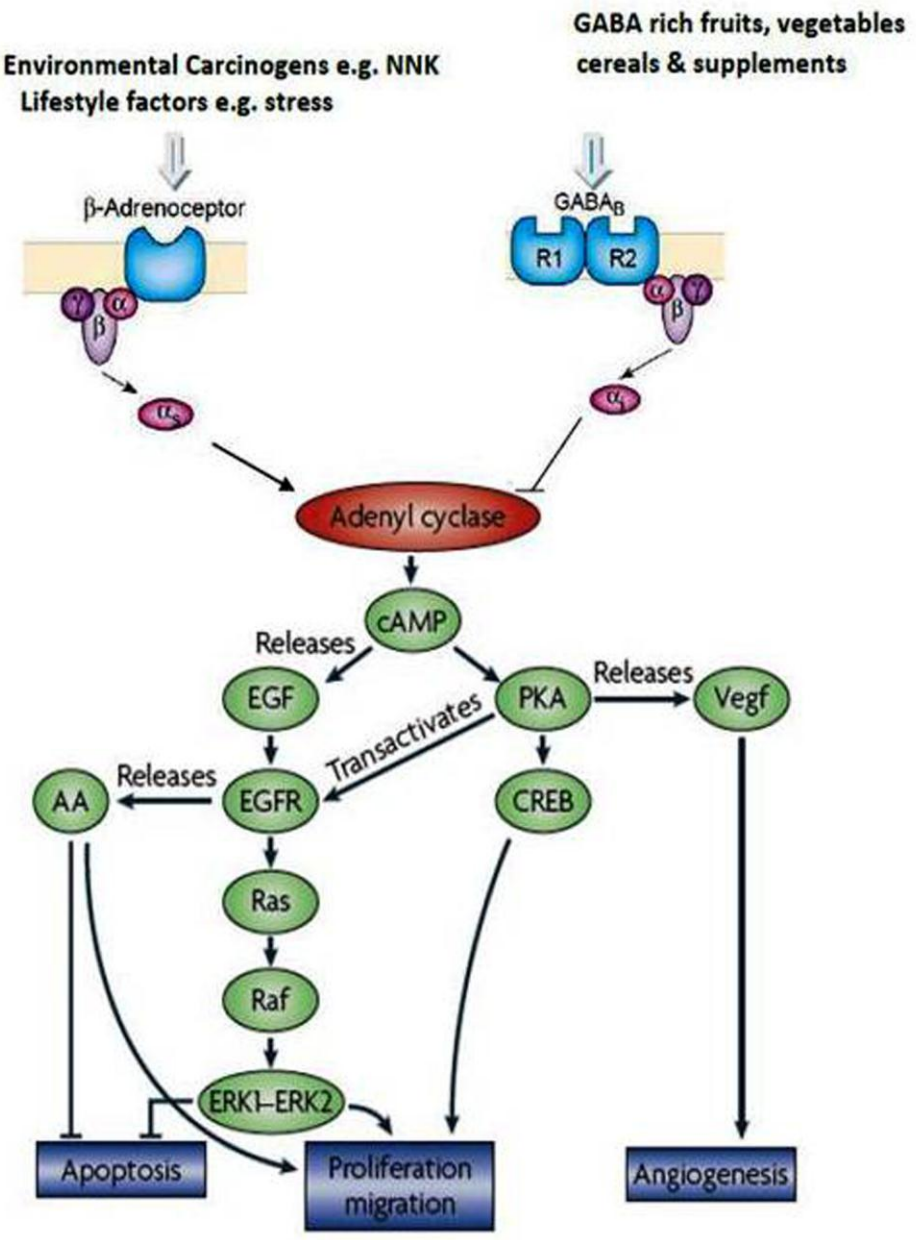

Figure 4. Schematic presentation of β-adrenergic pathway stimulation in cancer cells. Adenylyl cyclase activation downstream of β-AR induces the cyclic AMP–PKA–CREB pathway, transactivates EGFR, and induces the release of EGF, arachidonic acid (AA), and VEGF. The

nutraceutical GABA inhibits this signaling cascade at the level of adenylyl cyclase and thereby interfere with pro-oncogenic signaling. Reproduced from the original source (AL-Wadei et al., 2011) with the permission of John Wiley & Sons.

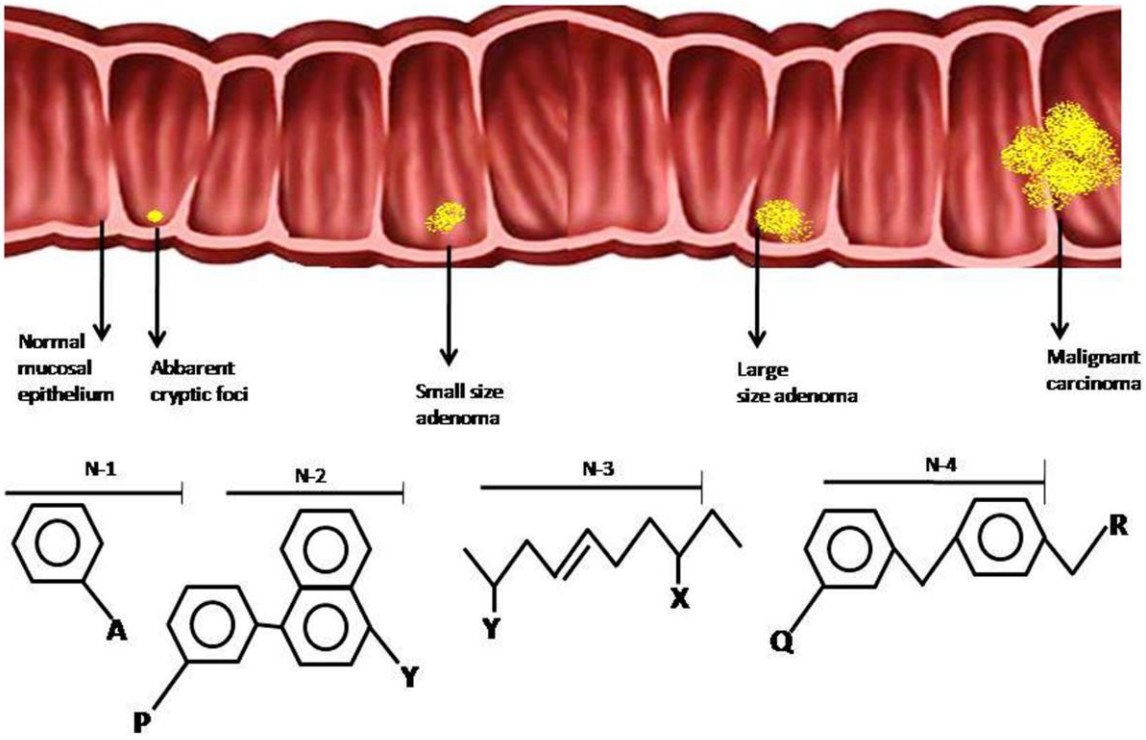

Figure 5. Colon Carcinogenesis is a multistage process wherein it takes 5-10 years for non-neoplastic aberrant cryptic foci to enter into a malignant state if left untreated. Different stages of cancer are well characterized in terms of carcinogenic events and involvement of impaired protein factors and oncogenic signaling. Structurally diverse dietary nutraceuticals can be evaluated for their chemopreventive and therapeutic effects since structurally divergent molecules are likely to have the ability to act on different cellular targets specific to a particular stage of carcinogenesis, thus each stage being treated by a cocktail of nutraceuticals specific to

the given stage. Note: Structures shown in the figure (N_{1-4}) are purely hypothetical and just depict the structural diversity required across different stages of cancer progression.

Table 1. A list of ongoing and completed clinical trials for the evaluation of few important dietary nutraceuticals as single agents /or as adjuvant in standard chemotherapies in different GI canc rs or otherwise in healthy conditions; Source: http://clinicaltrials.gov/ as 5th December 2012.

Nutraceutical/Identifier No.	Cancer Type/Condition	Status	Primary/secondary end point
Curcumin			
NCT00927485	Familial adenomatous polyposis	Recruiting	Safety/Efficacy
NCT01490996	Inoperable colorectal cancer	Not recruiting yet	Phase I/IIa; Dose escalation
NCT00365209	Colorectal/aberrant crypt foci	Active, not recruiting	Phase II A; % change in prostaglandin E2/5-HETE in ACF
NCT00973869	Colorectal cancer	Unknown	Phase I/Side effects/Preventive
NCT00181662	Healthy	Completed	Curcumin pharmacokinetics/Curcumin + piperine pharmacokinetics
NCT01333917	Colorectal cancer	Active, not recruiting	Phase I/Gene expression/Ribonucleic acid (RNA) level/Apoptosis
NCT01330810	Healthy	Active, not recruiting	Evaluation or bioavalibility of curcumin formulations

NCT00094445 Advanced pancreatic cancer Active, not recruiting Phase II/

Patient survival/ side efects/Pharmacokinetics

NCT00745134 Rectal cancer Active, not recruiting Phase II/

Evalvation of (curcumin + capecitabine+ radiation)

EGCG/Green Tea Extract

NCT00981292 Healthy young adults Completed Phase IV/

Cerebral blood flow/Cognitive performance

NCT01360320 Colorectal adenomas Recruiting Phase

II/Evaluation of EGCG for the incidence

Genistein

NCT00882765 Resectable Pancreatic cancer Withdrawn Phase II/

microvessel density in tumor tissues

NCT00376948 Advanced pancreatic cancer Completed Phase II/

Genistein +Gemcitabine + Erlotinib; patient survival

Nutraceutical/Identifier Cancer Type/Condition Status

Primary/secondary end point

NCT01182246 Pancreatic cancer Recruiting Phase I/II

Evaluation of Gemcitabine + Crystalline Genistein

Resveratrol/Resveratrol Supplement

NCT00256334 Colon cancer Completed Phase I/ modulation Wnt signaling

NCT01476592 Low grade gastrointestinal tumors Recruiting Notch1 activation in post-treatment tumor biopsy specimens

NCT00920803 Colorectal Cancer Completed Phase I/pharmacodynamics/ safety

NCT00433576 Reserectable colorectal cancer Completed Phase I/ Dose repeatability and tolerability

NCT00721877 Healthy adults Completed Phase I/ Safety/CYP enzyme and detoxification enzyme systems

NCT01640197 Healthy adults Completed Phase I/ cerebral blood flow and cognitive behavior

NCT00098969 Healthy adults Completed Phase I/ Single-Dose Safety and Phamacokinetics

NCT00578396 Healthy Adults Unknown Phase I/beta-catenin/wnt pathway; colon cancer prevention

