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Review

Physiological Effects of Green-Colored Food-Derived Bioactive Compounds on Cancer

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Featured Application: This review paper represents the anti-cancer activities and molecular mechanisms of chemicals derived from green-colored food and suggests the direction for developing chemotherapeutic agents from green-colored food.

Abstract: Green-colored foods, such as broccoli, sprouts, soybean, and green leafy vegetables are considered one of the representative healthy foods for containing various functional ingredients that can combat chronic diseases, including diabetes, obesity, and cancer. Herein, we reviewed the anti-cancer activities and the underlying mechanisms of some important bioactive compounds, such as sulforaphane, catechins, chlorophyll, isoflavone, indole dervatives, and lutein, present in green-colored foods. In vivo and clinical studies suggest that sulforaphane, a sulfur-containing compound found in cruciferous vegetables, can ameliorate prostate and breast cancer symptoms by arresting cell-cycle progression and modulating Ki67 and HDAC expression. A green tea compound, known as epigallocatechin-3-gallate (EGCG), has shown remarkable anti-cancer effects against prostate cancer and lung adenocarcinoma in human trials through its antioxidative defense and immunomodulatory functions. Chlorophyll, a natural pigment found in all green plants, can regulate multiple cancer-related genes, including cyclin D1, CYP1A, CYP1B1, and p53. Epidemiological studies indicate that chlorophyll can substantially reduce aflatoxin level and can mitigate colon cancer in human subjects. Remarkably, the consumption of soy isoflavone has been found to be associated with the lower incidence and mortality of breast and prostate cancers in East Asia and in Canada. In vivo and in vitro data point out that isoflavone has modulatory effects on estrogen and androgen signaling pathways and the expression of MAPK, NfκB, Bcl-2, and PI3K/AKT in different cancer models. Other green food bioactive compounds, such as indole derivatives and lutein, also exhibited suppressing effects in rodent models of lung, liver, stomach, cervical, and prostate cancers. In addition, some micronutrients, such as folate, riboflavin, retinoic acid, and vitamin D3 present in green foods, also showed potential cancer suppressing effects. Taken together, these data suggest potential chemopreventive functions of the bioactive compounds from green-colored foods. This paper could be beneficial for further research on the anti-carcinogenic effects of green-colored food-derived compounds, in order to develop green chemotherapeutics for cancers.

Keywords: anti-cancer; green-colored food; sulforaphane; catechin derivatives; chlorophyll; isoflavone; indole derivatives; lutein

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1. Introduction

Traditionally, it is accepted that regular consumption of green-colored foods, such as spinach or cruciferous vegetables, can alleviate the risk of chronic diseases [1,2]. Several trials have attempted to prove a negative correlation between green-colored food intake and the risk of chronic illnesses (e.g., cancer and type 2 diabetes) [1–3]. A former study reported an inverse association between fruits and vegetable intake and the risk and mortality of coronary heart diseases, cardiovascular disease, and cancers [4]. In that paper,

the authors demonstrated that the consumption of cruciferous vegetables (a representative green-colored vegetable) and green and yellow vegetables could reduce total cancer risks. The study showed that the total cancer risk was inversely associated with cruciferous vegetables (RR = 0.88) and green leafy vegetables (RR = 0.84) intake. In particular, the risk of prostate cancer was found to be staggeringly decreased with the intake of cruciferous vegetables [5–7]. The same tendency was also presented in hazard ratios (HR) for lung cancer in a previous paper [8]. In that report, the subjects who served with 77.5% green leafy vegetable were identified with lower risk of lung cancer (HR = 0.70; 95% CI = 0.51–0.98; *P*-trend = 0.05). Hence, it is worth concluding that the constituents in green-colored food, such as cruciferous or green leafy vegetables, could be associated with lower incidence and mortality of cancer.

Diverse compounds in green-colored foods have well-known anti-cancer benefits. Chlorophyll is one of the representative green compounds, which exist in green-colored foods. Chlorophyll is a photosynthetic pigment present in the thylakoid membrane of chloroplast in plants [9]. On a dry weight basis, chlorophyll is estimated to comprise 0.6–1.2% of the total mass of higher plants [10]. Besides its use as a coloring agent, chlorophyll has been extensively studied for its potential anti-cancer benefits. In this article, we will focus on the anti-cancer activities of chlorophyll and other bioactive constituents, such as sulforaphane, isoflavone, lutein, and indole derivatives found in green-colored foods, and touch upon the anti-carcinogenic trace elements available in green foods. As green-colored foods contain various bioactive compounds, it is worth studying the individual compounds' actions and their molecular mechanisms for understanding the anti-cancer activities of green-colored foods.

2. Physiological Effects and Mode of Actions (MoA)

2.1. Sulforaphane

Sulforaphane is a sulfur-containing amino acid derivative belonging to a group of phytochemicals known as isothiocyanate [11]. Chemically, sulforaphane is composed of an isothiocyanate functional group and a methylsulfonyl butyl group as a side chain [12]. Sulforaphane is generally found in broccoli sprout, kale, cabbage, and other cruciferous vegetables [13]. This phytocompound was first discovered in the 1950s in red cabbage and in a rangeland weed as an antibiotic [13]. Later, sulforaphane was isolated from broccoli by Talalay and Zhang, and was identified as a cancer preventing agent [14]. The most abundant source of sulforaphane is known as broccoli sprout, in which it is stored in its chemically stable form, called glucoraphanin [15]. Its biosynthesis begins with the formation and the elongation of the methionine side chain, followed by the generation of the glucosinolate structure and the modification of its side chain [13]. While processing, an endogenous enzyme called myrosinase hydrolyzes glucoraphanin to produce sulforaphane, which is metabolized in the gut through the mercapturic acid pathway [16]. Sulforaphane enters the circulation through passive diffusion and reaches the highest concentration within 1~3 h after consumption [17]. Chemically, sulforaphane is composed of an isothiocyanate functional group and a methylsulfonyl butyl group as a side chain, and it has very high pharmacological activity in the intestinal ambiance due to its electrophilic structure and water solubility [17]. Although sulforaphane has been described as a highly bioavailable compound, its bioavailability can be hindered by the presence of epithiospecifier protein present in the plant, which can be eliminated with mild heating [18]. The role of erucin in the bioavailability of sulforaphane has also been mentioned elsewhere [18,19].

Sulforaphane is the most prominent isothiocyanate that shows anti-carcinogenic effects against various forms of cancers, including prostate, ovarian, lung, bladder, stomach, and oral cancers in preclinical and clinical studies [20]. Sulforaphane can block or attenuate the proliferation, maturation, and migration of human cancer cells by targeting multiple cellular signaling pathways [21]. Primarily, sulforaphane's anti-cancer effects are attributed to its ability to suppress the phase 1 metabolizing enzymes and to activate the phase 2 detoxification/antioxidant enzymes [22]. Sulforaphane can also regulate the

inflammatory responses and activate the genes associated with apoptosis and cell cycle arrest, including p21 and cyclin D1 [22]. In addition, the role of sulforaphane as an epigenetic regulator and a HDAC inhibitor in cancer prevention cannot be overemphasized [23]. According to the literature, the critical mechanism that sulforaphane exerts its chemopreventive effects is the Nrf2-mediated activation of the metabolizing enzymes, which can detox or neutralize the carcinogens and their metabolites [24]. In preclinical studies, sulforaphane-enriched diet increased the detox enzymes, such as GST and NQ01 in plasma, and the carcinogens, including acrolein and benzene in urinary excretion [13,25,26]. Thus far, clinical trials have focused mainly on sulforaphane's preventive effects on prostate cancer [27]. Recurrent prostate cancer patients, when treated with Prostphane® (400 µmol sulforaphane), experienced a drastic reduction of the serum PSA level [27]. A more extended treatment (5 months) with 200 µmol sulforaphane showed very similar results [27]. Remarkably, supplementation of GFN BroccoMaX^{TM} (30 mg glucoraphanin) to women with breast cancer showed promising results by modulating the expression of Ki-67 and HDAC3 [28]. Clinical studies regarding the effects of sulforaphane against the other forms of cancer should be conducted to utilize the potential anti-cancer benefits of sulforaphane (Table 1). The application of sulforaphane also demands further studies to determine its appropriate doses and the suitable vehicle in order to get the maximum benefits out of it to fight cancers. Alternatively, combination therapies of sulforaphane and the available cancer drugs should be considered to develop more effective strategies to combat cancers. Several combined treatments involving sulforaphane have been reviewed by Mokhtari et al. (2018), where sulforaphane significantly enhanced the efficacies of cancer therapeutics, such as cisplatin and doxorubicin, in cancer stem cells [18]. A few of the studies pointed out that sulforaphane could selectively sensitize cancer cells for the cancer drugs to better perform [18,29].

2.2. Catechin Derivatives

Catechins are a group of natural flavonoids found in fresh tea leaves, fruits, vegetables, and wine [30]. In total, eight catechins have been identified so far, and among them, only four catechins, such as (-)-Epigallocatechin-3-galate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC), are considered highly bioactive for showing numerous health benefits [31]. Green tea is known as the most plentiful source of catechins, where the majority of the catechins (50–80%) is represented by EGCG [32]. Basically, catechins are formed when a 3-carbon chain is attached to two aromatic rings containing several hydroxyl groups [33]. Depending on the arrangement of the hydroxyl groups in the aromatic rings, catechins can be of cis and trans isomers; and each isomer can have two optical isomers, such as (+)-catechin and (-)-catechin [34]. Catechin derivatives, including EGCG, are formed with the esterification of the optical isomers. Notably, due to the presence of hydroxyl groups, catechins can donate hydrogen and bind with water molecules to form larger molecules barring them from being easily absorbed [35]. Therefore, the bioavailability of catechins largely depends on their size and polarity and follows Lipinski's Rule of Five [36]. Reportedly, EC with a molecular weight of 290 has remarkably higher bioavailability than the EGCG with a molecular weight of 458. It has been suggested that the significant amount of catechins enter the cells through passive diffusion and later efflux to the intestinal lumen [37,38]. In the gut, catechins undergo biotransformations, including methylation, glucuronidation, and microbial degradation, before being excreted in the feces [38].

Green tea and green tea catechins have shown promising efficacies against various forms of cancers, including lung, prostate, ovarian, liver, intestinal, bladder, and skin cancers in cellular and animal cancer models [39]. A formulation of tea catechins, known as Polyphenon E (65% EGCG), remarkably attenuated breast cancer, aberrant crypt foci, and lung adenocarcinoma [37,39,40]. In vivo studies have reported that the consumption of green tea could improve malignant cancers, such as stomach, colorectal, liver, and lung cancer [40]. Based on previous findings, multiple molecular mechanisms of how EGCG

and other catechins exert anti-cancer effects have been proposed, including the modulation of the inflammatory responses, antioxidant defense, inhibiting angiogenesis, facilitating apoptosis, promoting the tumor suppressor genes, such as p53, arresting the cell cycle, and activating the phase II detoxifying enzymes [41].

Although the data from the epidemiological studies regarding the effects of green tea and green tea catechins are so far inconclusive, a few of the trials have shown positive results (Table 1). In Japan, patients with colorectal cancer supplemented with 1.5 g green tea extract per day noticeably reduced the recurrence of the tumor cells [42]. Another study in Italy found that the supplementation of 300 mg of green tea catechins could produce substantial effects against prostate cancer [43]. A green tea formulation containing 400 mg of EGCG could significantly reduce the symptoms of chronic lymphocytic leukemis [44]. A cohort study involving 8000 participants with breast cancer showed that the daily intake of green tea resulted in the lower recurrence of the disease [45]. Based on these results, the prospect of EGCG as an anti-cancer agent is worthy of further research attention. Considering its wide-ranging biological activities, including its anti-carcinogenic effects, EGCG is being recommended to be incorporated into functional foods [46].

2.3. Chlorophyll

Chlorophyll is a green pigment present in all plants, cyanobacteria, and algae and is responsible for the photosynthesis process for plants to make their foods. As a component of vegetables and fruits, chlorophyll has been a part of human diet since time immemorial [47]. Chlorophyll has mainly been used as a natural coloring agent, and its bioactive functions have only been discovered in recent years [48]. Chlorophyll is produced and resides in the interior of a cellular structure called chloroplast, and it is primarily composed of a tetrapyrrole ring containing a magnesium ion (Mg^{+}) in the center and a hydrophobic chain [49]. While there are five forms of chlorophylls found in nature, only two forms, namely chlorophyll a and chlorophyll b, are widely available in plants and various photosynthetic algae [50]. Both chlorophyll a and b are structurally similar to each other, except for the constitution of a side chain at the C-7 position, where chlorophyll a contains a –CH3 and chlorophyll b contains a CHO group [51].

Based on the polarity of the chlorophyll derivatives, their bioavailability depends on their chemical structure, release, and stability in the gut ambiance and the composition of the food matrix [49,52]. Therefore, the efficient absorption and metabolism of the lipophilic chlorophylls often require the co-consumption of lipids for their efficient absorption. On the other hand, hydrophilic derivatives, such as chlorophyllides and pheophorbides, would not require any lipid consumption.

Although the use of chlorophyll as an anti-carcinogenic agent is a recent phenomenon, the anti-cancer potential of chlorophyll was first mentioned in the 1940s by Figge et al. [53]. Accumulating evidence suggests that chlorophyll and its derivatives can prevent different forms of cancer, including skin, liver, and colorectal cancers in in vitro and in vivo conditions [54]. Chlorophyll is considered one of the essential natural dietary anti-carcinogenic agents for its wide range of biological functions, including antigenotoxic, mutagen engulfing, anti-inflammation, antioxidative, and apoptotic activities [55]. Based on previous studies, the anti-carcinogenic effects of chlorophyll could be attributed to its modulatory actions on CYP1A1 and CYP1B1 expression, cell cycle arrest, cyclin D1, and Bcl-2, DNA adduct formation, and apoptosis [56]. According to a report, chlorophyll can also increase p53, cyclin A and B, and suppress CDK1 and CDK2 in melanoma cells [57]. Chlorophyll has a unique capacity to bind with toxic and carcinogenic substances in the intestinal lumen. Based on this characteristic, a human trial was conducted among the residents in the Qingdong province in China, where the participants were subjected to 100 mg of daily chlorophyll intake for four months [58]. At the end of the trial, a staggering 50% reduction of urinary aflatoxin was found in the subjects. In another study, a group of patients in the Netherlands, under a chlorophyll-deficient diet, experienced a higher incidence of colon cancer [59]. The authors proposed that chlorophyll could be instrumental in blocking the

carcinogenic agents in the intestine. Even though chlorophyll has low bioavailability in the lumen, a significant portion of chlorophyll and its derivatives might be active in the intestinal lumen to bind with the mutagens. Although the epidemiological evidence of the chemopreventive effects of chlorophyll is still inadequate, promising effects of chlorophyll and its synthetic derivatives have been reported in several in vivo cancer models [60].

Chorophyll's anti-cancer potential is making it increasingly popular as a dietary intervention through green or processed foods for cancer prevention. In the EU, chlorophyll and chlorophyllins are being used in the formulation of medicines and as a food colorant and bioactive ingredient in different food products to enhance their functionalities [61]. However, in order to help preserve its stability, chlorophyll should be processed with some precautionary measures, such as using a controlled atmosphere and applying mild processing treatments [61].

2.4. Isoflavone

Isoflavone is a group of plant-origin natural flavonoids belonging to the Fabaceae family. For showing structural similarity to 17ß-estradiol as well as its binding capacity to estrogen receptors and showing weak estrogenic activities, isoflavone is often called phytoestrogens [62]. The estrogen receptor binding properties of isoflavone are attributed to the positions of its hydroxyl groups (7 and 4′), which are identical to those in estradiol [62]. Its benzopyran ring, located in position 3, is what differentiates it from other flavonoids [62]. The positions of the hydroxyl groups on benzene rings are responsible for the biological activities of isoflavone [62]. Soybean and soy products are the predominant source of isoflavone, containing approximately 1~3 mg isoflavone per 1 g of fresh weight [63]. The major isoflavones found in soybean are genistein (50%), daidzein (40%), and glyceitein (10%) [64]. Among the major isoflavones in soybean, genistein has been studied the most against cancer and other illnesses through in vivo and preclinical studies [65]. Isoflavone is present in the intestine as glycosides, which are broken down by ß-glucosidase and the gut microbiota. In general, Isoflavone is readily absorbed in the intestine, however, their bioavailability may vary in different circumstances [66] A recent study demonstrated that the bioavailabilities of daidzein and genistein in Japanese women after ingestion were 66.9% and 33.7%, respectively [64]. Based on the preclinical and clinical data, it has been suggested that the bioavailability of isoflavone in the human intestine can rely on the type and origin of the isoflavone, population group, dose, and the concurrent meal taken [65,66].

Dietary intake of soy isoflavone has shown remarkable anti-carcinogenic activities against breast and prostate cancers in epidemiological studies [67]. It has been reported that the lower incidence of breast and prostate cancers in Asian countries is associated with the high consumption of soy products [68]. In Canada, an ethnically diverse cohort study involving 6235 women with breast cancer revealed that the consumption of dietary isoflavone was associated with decreased mortality [69]. A population-based cohort study in Japan showed that the isoflavone consumption from soy products resulted in a lower incidence of postmenopausal breast cancers [70]. The positive effects of soy isoflavone have also been documented by a case-control study from a large group of Chinese breast cancer patients [71]. Multiple clinical trials reviewed by Mahmoud et al. showed that soy isoflavone consumption was associated with lower incidence and recurrence of prostate cancer among the patients of different ethnic groups [35]. Remarkably, a significant correlation was found between the dietary soy isoflavone intake and the suppression of the prostaglandin pathway among prostate cancer patients [72]. In addition, the potent efficacy of isoflavone and soy products on colorectal cancer has been reported by a case-control study [73].

Following the epidemiological evidence, potent anti-cancer effects of isoflavone have been reported by preclinical, in vivo, and in vitro studies (Tuli, 2019). Based on those studies, it has been suggested that the anti-cancer effects of isoflavone could be linked with its modulation of estrogen and androgen-mediated signaling pathways, MAPK, NFκB, PI3K/AKT signaling pathways, as well as Bcl-2 and ERK protein levels (Table 1) [74,75].

While the evidence on the chemopreventive functions of isoflavones is plentiful, there were also a few instances claiming some adverse health consequences of isoflavone consumption, such as reproductive toxicity, impairing children's growth, and deteriorating natural immunity, which need to be addressed [76]. Currently, soy milk and tofu yogurt enriched with isoflavone are available, further studies are needed in order to expand the use of isoflanones in functional foods.

2.5. Indole Derivatives

Indole has also known as benzypyrrole, is an aromatic organic compound composed of benzyl and a pyrrole ring [77]. The aromatic properties of indole originate from the mobilization of its 10 π electrons throughout the indole structure [77]. Although the presence of indole has been confirmed in various plant species, the primary natural source of this compound has been identified as cruciferous vegetables, such as cabbage, cauliflower, and broccoli [78]. The biosynthesis of this compound begins with the attachment of tryptophan and other amino acids or through microbial activities [79]. Indol-3 carbinol (I3C) is the most popular indole derivative that has been widely investigated for its strong anti-cancer benefits [80]. I3C is highly bioavailable, and upon the actions of the acidic gastric juice, I3C is converted into its principal metabolite, known as diindolylmethane (DIM) [81]. It has been reported that the anti-carcinogenic activities of I3C could largely be attributed to its oligomeric products [82]. According to earlier reports, I3C demonstrates anti-cancer effects by targeting multiple signaling pathways and receptors, such as estrogen receptor signaling, Akt-Nfkb signaling, endoplasmic reticulum stress, BRCA gene expression, and caspase activation (Table 1) [82].

Although anti-carcinogenic effects of I3C have been shown against various forms of cancer, including breast, cervical, prostate, and endometrial cancers, the therapeutic effects of I3C against breast and prostate cancers have been noteworthy, and hence drew remarkable research attention over the last decade [83]. Epidemiological studies have found a clear association between the consumption of cruciferous vegetables and the lower incidence of breast and prostate cancers [81]. A clinical study conducted in 2018 reported that women with stage III-IV breast cancers treated with combined therapy of I3C and catechin experienced a lower recurrence of the disease [84]. This study suggested I3C and catechin as maintenance therapy for breast cancer. Meng et al. reported that I3C showed anti-tumor activity by regulating estrogen activity and metabolism in human tumor cells [78]. The same group of researchers later found that I3C exerted anti-carcinogenic effects by modulating the BRCA genes in human breast and prostate cancer cells [85]. Remarkably, I3C suppressed the prostate cancer cells by inhibiting the telomerase activity and the gene expression [86]. Positive effects of I3C in several in vivo cancer models, including breast, lung, liver, and stomach cancers, have also been reported [81]. Based on these studies, it is worth suggesting that I3C has all the potential to be among the forefront of the natural medicinal agents in anti-cancer therapy. Even though the food applications of indole and its derivatives have yet to begun, the pharmaceutical applications of them are now a commonplace. However, for their safe and effective food and pharmaceutical applications, green synthesis technologies, such as microwave- or ultrasound-assisted synthesis are being proposed [87].

2.6. Lutein

Lutein, belonging to the family of xanthophyll, is one of the 600 carotenoids found in nature. This oxycarotenoid is generally found in green leafy vegetables, fruits, egg yolk, marigold flowers, and brown algae [88,89]. The most abundant natural lutein sources are dark green vegetables, marigold flowers, and microalgae [90]. Currently, lutein comprises 23% of the carotenoid market worldwide [90]. Lutein is a lipophilic compound composed of a 40 carbon backbone with a methyl group attached to it [89]. The carbon–carbon double bonds present in the molecule give it a yellow-orange color by allowing it to absorb light. Unlike most other carotenoids, lutein has two hydroxyl groups at both ends of the carbon

chain. In the plant system, lutein is synthesized by the melvonate pathway through an enzymatic breakdown of mevalonate [91]. As a lipophilic compound, the bioavailability of lutein is mainly dependent on the food matrix. After entering the intestine, lutein is transformed as a lipid droplet and eventually as a micelle complex absorbed through the enterocyte [92]. The presence of fat in the carrier food is therefore essential for lutein absorption in the gut. Reportedly, the bioavailability of lutein highly increases when it is fortified in milk and other high-fat foods [93].

Lutein has been widely discussed in the scientific literature for exhibiting numerous health benefits, including eye disease, neurological dysfunctions, cardiac problems, skin irritation, and so on [91]. Recent studies suggest that lutein also shows potential anti-cancer properties in vivo and in vitro studies [94]. Gunsukh et al. reported that lutein obtained from marigold flowers triggered caspase-3-mediated apoptosis in cervical cancer cells [95]. The effects of lutein against prostate, breast, and cancer cells have been reported elsewhere [96,97]. It has been shown that lutein could suppress the phosphorylation of protein kinase B, ERK 1/2, and NFkB in breast cancer cells [98]. Lutein has been shown to inhibit breast cancer cells and increase the efficacy of a chemotherapeutic [99]. The results from several epidemiological studies also suggest that the daily intake of lutein could positively affect various types of cancer, including esophageal, breast, lung, colorectal, and pancreatic cancers [100]. These data indicate that lutein has a great potential to be included in the list of natural anti-cancer agents for which more data and extensive evidence from preclinical and human trials are required. Lutein already has a wide application as functional food and medicinal ingredient. Since lutein is easily degradable, the companies are using sophisticated production technologies to preserve the integrity and functions of lutein [90].

Green chemoprevention is a relatively new phenomenon, and it has received a breakthrough at the onset of the twenty-first century with a great deal of research, identifying green foods as a source of potential anti-cancer compounds. Numerous studies point out that the chemotherapeutics agents from green foods are effective, safe, and cost-efficient. Green food compounds, including chlorophyll, sulforaphane, isoflavone, and catechins, have shown promising results against different forms of cancer in human trials and in in vivo models. In addition, these compounds have been shown to reverse cancer progression by modulating important biomarkers, such as phase I and phase II enzymes, p53, HDAC inhibitors, and multiple signaling pathways, including PI3K/Akt ERK, BCl-2, and wint signaling. Green foods also contain a number of anti-carcinogenic trace elements, such as folate, riboflavin, retinoic acid, and vitamin D3 (Table 2). The wide application of lutein as pharmaceutical and functional food ingredient makes us believe that other compounds in green-colored foods will follow suit and will be available as chemotherapeutics. However, for their successful application as green chemotherapeutic agents, determining the appropriate and safe doses of these compounds through preclinical and clinical studies is necessary. In addition, an interdisciplinary approach involving pharmacology, medicinal chemistry, and epidemiology would solve many of the challenges, in order for green food compounds to be at the forefront of cancer therapy.

Table 1. Anti-cancer activities of green-colored food-derived bioactive compounds and their mechanisms.

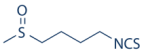
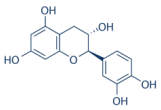
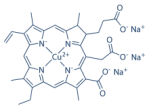
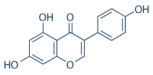
NO	Chemical Name	Structure	Source	Cancer Site	Mechanism or Target Marker	Reference
1	Sulforaphane		- Broccoli sprout - Kale - Cabbage	- Prostate - Ovarian - Lung - Bladder - Stomach - Oral - Breast	- Suppress phase 1 metabolizing enzyme - Activate the phase 2 detoxification/antioxidant enzyme - Nrf2-mediated signaling - p53 - Arrest cell cycle - Epigenetic regulation - HDAC inhibition - Modulate Ki-67	[22–24,26,27]
2	Catechin derivatives		- Fresh tea leaves - Green tea - Fruits - Vegetables	- Prostate - Lung - Ovarian - Liver - Intestinal - Colorectal - Bladder - Skin	- Modulate inflammatory cytokines - Upregulate antioxidant enzymes - Activate the phase 2 antioxidant enzyme - p53 - Arrest cell cycle - Suppress IGF1R, phosphor-GSK3ß, - Decreases MMP2 and 9	[38,41]
3	Chlorophyll (Sodium copper salt)		- Green pigment present in all plants - Cyanobacteria - Algae	- Skin - Liver - Colorectal - Lung	- Inhibits heme oxygenase (HMO) - Upregulate p53 and cyclin A and B - Downregulate CDK1 and CDK2	[57,59]
4	Isoflavone (genistein)		- Soybean - Soy product	- Prostate - Breast	- Suppression of prostaglandin pathway - MAPK signaling pathway - NFkB signaling pathway - PI3k/Akt signaling pathway - BCl-2 signaling pathway - ERK signaling pathway - Wint signaling	[74,75,101]
5	Indole derivatives		- Cabbage - Cauliflower - Broccoli	- Breast - Cervical - Prostate - Endometril	- Estrogen receptor signaling pathway - Akt/NFkB signaling pathway - Endoplasmic reticulum stress - BRCA gene expression - Caspase activation	[82,102]
6	Lutein		- Dark green vegetables - Marigold flower - Fruits - Egg yolk - Brown algae	- Breast - Prostate - Esophageal - Lung - Colorectal - Pancreatic	- Caspase-3-mediated apoptosis - Block phosphorylated protein kinase B - Suppress phosphorylated ERK 1/2 ad NFkB - Downregulate HES1	[95,98,103]

Table 2. Anti-cancer activities of other bioactive compounds-derived from green colored food.

NO	Bioactive Compounds	Green Color Food	Anti-Cancer Type	Reference
1	Folate	- Green beans - Lentils - Asparagus - Spinach - broccoli - Lettuce	- Colorectar - Breast - Ovarian - Esophageal - Gastric - Pancreatic - Lung	[104,105]
2	Riboflavin	- Spinach - Broccli	- Breast	[106]
3	Retinoic acid	- Kale - Broccoli	- Lung - Breast - Prostate	[107]
4	Vitamin D3	- Broccoli - Bok Choy - Leeks - Celery - Green beans - Kale - Cabbage	- Colorectal - Prostate - Breast	[108]

3. Conclusions

Previous literatures have demonstrated the habitual intake of green-colored food prevent or retard carcinogenesis step. Indeed, many epidemiological studies reported an adverse relationship between the administration of natural compounds derived from green-colored food and cancer incidences or death rates. According to the human trials, an increased incidence of colon cancer was detected in a chlorophyll-deficient group. Furthermore, daily intake of green tea revealed the lower recurrence of breast cancer. The mode of actions of these compounds, which originated from green-colored foods, are similar to anti-cancer drugs or immunologic adjuvants against cancers. To develop green chemotherapeutic agents, it is required for widely and thoroughly studying the anti-cancer activities and mechanisms of green bioactive compounds. This review article would be a milestone for the development of green chemotherapeutic agents.

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Abbreviations

MAPK, mitogent-activated protein kinase; Nf-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; ERK, extracellular signal-regulated kinases; EGCG, Epigallocatechin-3-gallate; EC, Epicatechin; ECG, Epicatechin-3-gallate; HDAC, histone deacetylase; CDK, cyclin dependent kinase; CYP1A1, Cytochrome P450, family 1, subfamily A, polypeptide 1; DIM, Diindolylmethane; I3C, Indole-3-carbinol.

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