Curr Pharmacol Rep (2016) 2:11–20
DOI 10.1007/s40495-016-0047-0

CANCER CHEMOPREVENTION (R AGARWAL, SECTION EDITOR)

Natural Agents Used in Chemoprevention of Aerodigestive and GI Cancers

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Published online: 16 January 2016

Abstract Aerodigestive cancers are on an increasing level in both occurrence and mortality. A major cause in many of these cancers is disruption of the inflammatory pathway, leading to increased cell proliferation and epigenetic silencing of normal regulatory genes. Here, we review the research on several natural products: silibinin, silymarin, quercetin, neem and nimbolide, gingerol, epigallatecatechin-3- gallate, curcumin, genistein, and resveratrol conducted on aerodigestive cancers. These types of cancers are primarily those from oral cavity, esophagus/windpipe, stomach, small and large intestine, colon/rectum, and bile/pancreas tissues. We report on the utilization in vivo and in vitro systems to research these dose effects on the inflammatory and epigenetic pathway components within the aerodigestive cancer. To follow up on the basic research, we will discuss the remaining research questions and future directions involving these natural products as putative stand alone or in combination with clinical agents.

Keywords Natural product · Quercetin · EGCG · Genistein · Resveratrol · Aerodigestive cancer

This article is part of the Topical Collection on *Cancer Chemoprevention*

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Introduction

Cancers of the upper aerodigestive tract constitute approximately 4 % of all malignancies [1]. The combined organs and tissues of the respiratory tract and the upper part of the digestive tract (including the lips, mouth, tongue, nose, throat, vocal cords, and part of the esophagus and windpipe) are referred as aerodigestive tract. There are a number of factors that can increase a person's risk for developing cancers of the upper aerodigestive tract which includes smoking, moderate to heavy alcohol consumption, exposure to asbestos, and other toxic substances, genetic/family history, previous occurrence of upper aerodigestive cancer, pulmonary diseases, including chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, etc. (www.cancer.gov). Within the lower aerodigestive tract the, stomach, small intestine, colon, and rectum are the major tissue sites of deleterious effects [2–5], encompassing approximately 11 % of all cancers.

One of the major corrupted components within aerodigestive cancers is the disruption of normal inflammatory signaling pathways. Pathways involved in JAK/STAT, MAPK, prostaglandin synthesis, and NF-κB signaling have all been implicated as therapeutic intervention strategies [6–17]. Diet and lifestyle are major contributing factors to increased cancer risk in these tissues [18, 19]. Numerous studies show that dietary intake antioxidants and/or polyphenols have an inverse risk effect on several aerodigestive cancers by mitigating the increase in inflammation [20–24]. Curcumin, a compound from turmeric, along with several other natural agents, silibinin, silymarin, quercetin, neem and nimbolide, gingerol, epigallatecatechin-3-gallate (EGCG), genistein, and resveratrol, all have been heavily research in aerodigestive cancers as preventive agents, front line therapy and/or in combination with more traditional therapeutics agents in the clinic

[6, 9, 25–33]. In this review, we will focus on these compounds, their effects on inflammatory signaling pathways, and effects on epigenetic regulators and discuss how these natural products (NPs) can enhance clinical treatments.

Inflammatory Effectors

JAK/STAT Signaling

The JAK/STAT is the principal signaling pathway including transcriptional factors responding to extracellular ligands, cytokines, and growth factors; it affects various cellular functions, such as metastasis, proliferation, growth, and immune response [34]. Upon activation, STAT family proteins translocate into the nucleus, where it dimerizes and binds specific regulatory sequences, activating downstream target genes, e.g.,cyclins D1/D2, Myc, Bcl-xL, and Mcl-1 [35]. Therefore, activation of JAK/STAT pathway plays important role in activating cell cycle and inhibiting apoptosis [36]. In recent publications, gastric [37], pancreatic [17], colon [16], rectal [38], and cancer cells were shown to express high levels of STAT proteins, which is interesting given the implications for blockage of JAK/STAT pathway to inhibit tumor progression.

A clinical study found that in the nucleus of 40 cancer cells in human gastric cancer specimens, 11 (27.5 %) showed activated form of STAT3, Tyr-705 phospho-stat3. Signal transduction and activator of transcription 3(STAT3) signaling is constitutively activated in various tumors and is involved in cell survival and proliferation during oncogenesis [15]. A number of studies have shown that the quercetin, the major constituent of the flavonol subclass of flavonoids, inhibits the expression of STAT3 with drug treatment at the dosage of 40 μmol/L for 48 h, thereby resulting in the suppression of gastric cancer cell's growth [37]. In addition, dietary supplementation of quercetin attenuated the growth of orthotopically transplanted pancreatic xenografts [39]. Moreover, a study of Velázquez group showed that when $Apc^{Min/+}$ mice were treated with 25 mg/kg of quercetin daily for 3 weeks, tumor burden of these mice was attenuated compared with control groups [40•]. Silibinin, the major biologically active compound of the milk thistle (S*ilybum marianum*), has been reported to inhibit the migratory and invasive potential of human tongue squamous cell carcinoma cells in vitro [41] and human colorectal carcinoma (CRC) HT29 xenograft growth [42]. Clear mechanism of its chemoprevention effects on oral and CRC cancer was not shown, but Alpna Tyagi's study on lung cancer found that silibinin decreased phosphorylation STAT3 (ser727) (16 %, $p<0.01$) in lung cancer cells [42], suggesting that silibinin may block the constitutive and inducible activation of STAT3, resulting in reduction in expression of STAT3 target genes, such as JAK2, v-src, and cyclin D1. Many clinical studies have explored the effect of curcumin on colorectal and pancreatic cancer prevention or treatment and have reported no toxicity with moderate dose (440 and 2200 mg/day) of curcumin over a few months [43–45]; phase II trial conducted by Dhillon et al. showed decreased phosphorylated signal transducer and activator of transcription 3 in peripheral blood mononuclear cells from patients [44].

MAPK Pathway

Mitogen-activated protein kinases (MAPK) are serine/threonine (proXser/ThrPro) kinases, and they can convert various extracellular signals into intracellular responses through serial phosphorylation cascades [46]. When extracellular mitogen binds to extracellular signal-regulated kinase (ERK), it will activate GTPase (Ras) by converting its GDP to GTP, then phosphorylates downstream MAP3K (e.g., Raf), which in turn activates ERK, JNK, and p38 [47]. When all these MAPKs are activated, a lot of downstream transcription factors, such as c-myc, c-jun, activating transcription factor-2 (ATF2), GADD153, myocyte enhancer factor-2C (MEF2C), and Sin1-associated protein (SAP-1), will get phosphorylated, leading to a variety of cellular responses including inflammation, cell proliferation, differentiation, and migration [48, 49]. Several natural dietary phytochemicals have been found to inhibit MAPK pathway, suggesting their abilities to be chemoprevention therapy for cancer progression.

6-Gingerol, a major component of ginger (*Zingiber officinale*), incubated with human hepatoma Hep3B cells human pancreatic duct cell-derived cancer PANC-1 cells with concentration of ≥10 μM downregulation of the extracellular signal-regulated kinase (ERK); thus, significantly reduced MAPK signaling [29, 50] Gingerol was also found to suppress PMA-induced IκBα degradation and translocation of p65 to nucleus in mouse skin by blocking of upstream kinase p38 MAPK [51]. Moreover, a recent study by Weng CJ et al. found that HepG2 and Hep3B cells with ginerol treatment (≥10 μM for 24 h) showed MMP-9 suppression, TIMP-1 induction, and reduced invasion or metastasis [52].

Nimbolide, a component of neem (*Azadirachta indica*) inhibited phosphorylation of ERK1/2 of colon cancer cell lines (WiDr and HCT116) in a time-dependent manner with dosage of 1.25 μM. As a result, downstream MAPK proteins, including p38 and c-Jun amino-terminal kinases (JNK), are activated and correlated to the activation of ERKs [53]. This result might be able to explain the beneficial effect of Nimbolide on animal model of oral oncogenesis conducted by G. Harish Kumar research group [54]. Another phytochemical silibinin was found to inhibit SNU216 and SNU668 gastric cancer cell growth and migration by inhibiting phosphorylation of MER/ERK pathway [12]; silibinin also inhibits the growth of SW480 xenograft tumors carrying the mutant APC gene [55]. Resveratrol has also been shown to inhibit growth in human oral cancer cell line (SCC-

9) in a dose-dependent manner by inhibiting phosphorylation of MAPK response element targets [56].

AKT/PI3K Pathway

The Akt/PI3K (phosphatidylinositol 3-kinase) pathway plays a very important role in the regulation of cell proliferation and survival. It can enhance cell survival by activating cell proliferation and inhibition of cell metastasis [13], and the dysregulation of a lot of components of the Akt/PI3K pathway has been found in many human cancers' cases [14]. PI3K can be activated by receptor tyrosine kinases when they are bound by a ligand, and the PI3K activation can activate AKT which activates mTOR and has a lot of downstream effects, like cell growth, cell renewal, and resistance to chemotherapy [30]. Therefore, it is important to explore the therapeutic target in this pathway, and it can become a promising target for therapy.

Recently, it has shown that quercetin can reduce tumor cell proliferation and the growth of orthotopically transplanted pancreatic xenografts was decreased when quercetin was used as dietary supplementation [10,39]. Park JH group reported that quercetin downregulated ErbB2/ErbB3 signaling and the Akt pathway, thus inducing apoptosis in SW480 and HT-29 colon cancer cell and inhibited cell growth in a dose-dependent manner when cells were treated with 25, 50, or 100 μmol/L quercetin for 72 h [31].

6-Gingerol treatment to in vitro neonatal rat cardiomyocytes and H9c2 cell line suppresses doxorubicin-triggered oxidative stress and apoptosis through activating PI3K/Akt pathway [6]-GR upregulated expression of PI3K and p-Akt in DOX-induced NRCs in a dose-dependent manner, and the optimal dose is 100 μM. Moreover, the cytoprotection of higenamine plus [6] gingerol could be abrogated by a PI3K inhibitor LY294002 [57]. All of the studies show that dietary agents target the PI3K/Akt signaling pathway to inhibit cell proliferation, highlighting a potential target for therapy of cancer.

NF-κB Pathway

The NF-κB family of transcription factors has an essential role in inflammation and innate immunity, and this has been increasingly recognized as a crucial player in many steps of cancer initiation and progression [58]. This NF-κB is a nuclear factor that binds to the enhancer element of the immunoglobulin kappa light chain of activated B cells [59]. The proteins harboring this specific DNA binding activity are expressed in almost all cell types and regulate many target genes with a variety of functions [11]. There are five members of this transcription factor family, p65 (RelA), RelB, c-Rel, NF-κB1, and NF-κB2, of which NF-κB1 and NF-κB2 are synthesized as pro-forms (p105 and p100) and are proteolytically processed to p50 and p52, respectively [60]. In contrast to the other members of the NF-κB family, p50 and p52 do not contain a transactivation domain [61]. So dimers of p50 and p52, which bind to NF-κB elements of gene promoters, act as transcriptional repressors [62]. However, when p50 or p52 is bound to a member containing a transactivation domain, such as p65 or RelB, they constitute a transcriptional activator [63]. The fact that different NF-κB dimers have differential preferences for variations of the DNA-binding sequence enhances the complexity of this transcriptional regulation system [64]. Thus, different target genes are differentially induced by distinct NF-κB dimers. Besides, the sites for phosphorylations and other post-translational modifications in the NF-κB subunits are important for activation and crosstalk with other signaling pathways [65]. NF-κB in the blood stream is usually bound to the inhibitory protein IκB which renders it inactive. However, during an inflammatory response, the IκB kinase phosphorylates the IκB protein, thus releasing NF-κB. NF-κB activation then leads other inflammatory cytokines such as TNF-α and interleukin-1 (IL-1) to bind to their receptors and become activated [10].

Silymarin is a polyphenolic flavonoid derived from the fruits and seeds of the milk thistle, also called artichoke *S. marianum*, which has anti-inflammatory, cytoprotective, and anticarcinogenic effects. Silymarin may involve suppression of NF-κB, a nuclear transcription factor, which regulates the expression of various genes involved in inflammation, cytoprotection, and carcinogenesis, to produce these effects [9]. Another flavonoid, silibinin, has shown strong preventive and therapeutic efficacy in different pre-clinical models through various mechanisms in colorectal cancer [66]. Studies have shown that silibinin strongly inhibits TNF-α-induced NF-κB activation in human CRC cells [67]. Silibinin treatment (50–200 μM) of human CRC SW480, LoVo, and HT29 cells strongly inhibits tumor necrosis factor-α-induced NF-κB activation together with decreased nuclear levels of both p65 and p50 sub-units. Silibinin also significantly increased IκBα level with a concomitant decrease in phospho-IκBα, without any effect on TNFR1, TRADD, and RIP2, indicating its inhibitory effect on IκBα kinase α activity [67]. In the same study, the effect of oral silibinin feeding on NF-κB pathway in SW480 (cycloxygenase (COX) COX-2 negative) and LoVo (COX-2 positive) tumor xenografts in nude mice were determined. Together with its inhibitory efficacy on tumor growth and progression, silibinin inhibited NF-κB activation in both xenografts [67].

Quercetin, a flavonol, is the most common flavonoid in nature and is often linked to sugars such as rutin (quercetin-3-rutinoside) and quercitrin (quercetin-3-rhamnoside) [68]. Quercetin is reported to have antioxidant properties [28] associated with antithrombotic, antihypertensive, anticarcinogenic, and anti-inflammatory effects [69]. Quercetin downregulates Bcl-2 through inhibition of NF-κB [70]. Clinical trials of quercetin effect on CRC are lacking and evidence

of efficacy of quercetin comes from preclinical studies. Thus, further research in this field is needed.

Resveratrol is a polyphenol derived from grapes, berries, and other plant sources. It is a natural compound that aids in suppressing the risk of obesity-induced cancer. Resveratrol has a role in suppressing inflammatory responses through decreasing nitric oxide levels and inhibiting the phosphorylation of the IKB complex, thus interfering with the activation of NF-κB-dependent mechanisms [71]. Resveratrol suppresses the activity of NFkB by interfering its DNA-binding ability. Resveratrol at doses of 0.5 or 1.0 g reduced CRC tumor cell proliferation by 5 % ($p = 0.005$) and are enough to induce anticarcinogenic effects in colon tumors [72].

A. indica (neem) containing various bioactive components is a promising candidate for chemoprevention. Studies have shown that neem leaf extract acts on different levels of the NF-κB pathway, and it induced apoptosis in colorectal cancer cells [27]. Several groups reported anticancer, anti-inflammatory, and antioxidant activities of neem tree extracts without providing in-depth analysis of the molecular mechanisms leading to NLE-induced inhibition of NF-κB activation. Phytochemicals such as nimbolide, derived from Neem, can target multiple steps along the NF-κB signaling circuit are promising candidates for future phytochemical-based mechanistic pathway-targeted anticancer regimens [73]. One study has shown that Nimbolide inhibits the NF-κB activation pathway induced in carcinogenesis through direct interaction with Cys^{179} of IKK-β, leading to suppression of IκBα phosphorylation and degradation, inhibition of p65 nuclear translocation, downregulation of NF-κB-regulated gene products, inhibition of cell proliferation, and potentiation of apoptosis induced by TNF-α and chemotherapeutics in oral squamous tumor cells [74].

Gingerol is the chief phenolic compound from ginger, a spice of Southeast Asia, with antioxidant, anti-inflammatory, and anti-tumor properties. Gingerol suppresses inflammation by blocking the movement of NF-kB into the nucleus, with the resulting downregulation of such inflammatory cytokines as TNF-α, as well as inducible nitric oxide synthase (iNOS). Pretreatment with [6] gingerol resulted in a decrease in both TPA-induced DNA binding and transcriptional activities of NF-κB through suppression of IκBα degradation and p65 nuclear translocation. Phosphorylation of both IκBα and p65 was substantially blocked by [6] gingerol. In addition [6], gingerol inhibited TPA-stimulated interaction of phospho-p65-(Ser-536) with cAMP response element binding protein-binding protein, a transcriptional coactivator of NF-κB [8].

Cyclooxygenase Pathway

Cyclooxygenase (COX), also known as prostaglandin synthase, is the rate-limiting enzyme responsible for the conversion of arachidonic acid (AA) into the various prostaglandins (PGs), a family of lipid mediators that have widespread and diverse biological functions [75]. There are two isoforms of COX, with distinct tissue distributions and physiological functions. COX-1 is constitutively expressed in many tissues and cell types, whereas the inducible isoenzyme COX-2 is pro-inflammatory in nature and expressed only in response to certain stimuli such as mitogens, cytokines, and growth factors. COX-2 is upregulated in a number of epithelial cancers, including in upper aerodigestive tract (UADT) premalignant and malignant lesions [7].

Curcumin is a phytochemical derived from the spice turmeric and has a potential in decreasing inflammation and inhibiting the growth of neoplastic cells through cell cycle arrest and promoting apoptosis by activating the mitochondria-mediated pathway. Curcumin has a role in anti-inflammation where it targets and inhibits COX-2 gene expression, nitric oxide synthase, NF-κB, and PGE_2 [26, 76]. In a phase IIa clinical trial, curcumin at a dose of 2 or 4 g was administered over a 30-day period to 44 eligible smokers with 8 or more ACF. Results showed that curcumin at a dose of 4 g significantly reduced the ACF number by 40 % ($p < 0.005$) whereas the ACF number was not reduced by the 2 g dose [77•]. It has been shown that curcumin enhances the effect of chemotherapy against colorectal cancer cells by inhibition of NF-κB and Src protein kinase signaling pathways [25]. Curcumin has a role in anti-inflammation where it targets and inhibits COX-2 gene expression. In a study, the combined effects of hexahydrocurcumin (HHC) with 5-FU exhibit a synergistic inhibition by decreasing ACF formation mediated by downregulation of COX-2 expression [78].

Clinical trials of COX-2 inhibitors have shown that inhibition of this enzyme can prevent the formation of colonic adenomas and potentially carcinomas; however, concerns regarding the potential toxicity of these drugs have limited their use as a chemopreventive strategy. Curcumin, resveratrol, and quercetin are three chemopreventive agents that are able to suppress multiple signaling pathways involved in carcinogenesis including COX and, hence, are attractive candidates for possible clinical intervention research.

Resveratrol (RSVL; 3,5,4′-trihydroxy-trans-stilbene) demonstrates nonselective COX-2 inhibition. We report herein that RSVL directly binds with COX-2, and this binding is absolutely required for RSVL's inhibition of the ability of human colon adenocarcinoma HT-29 cells to form colonies in soft agar. It has been shown that RSVL inhibited COX-2-mediated PGE(2) production in vitro and ex vivo. HT-29 human colon adenocarcinoma cells expressing high levels of COX-2 and RSVL showed suppressed anchorage-independent growth of these cells in soft agar. RSVL suppressed growth of COX-2(+/+) cells by 60 to 80 %, respectively. Notably, cells deficient in COX-2 were unresponsive to RSVL or RSVL-2 [6].

It has been shown that [6]-gingerol inhibits TPA-induced COX-2 expression in vivo by blocking the p38 MAP kinase-NF-kB signaling pathway [8]. In another study, 6-gingerol effectively suppressed tumor growth in vivo in nude mice [79]. Specifically, in CRC, [6]-gingerol has been shown to reduce the incidence of CRCs in a rat azoxymethane (AOM) model [80] and to inhibit CRC cell proliferation and endothelial cell tube formation [81]. While we have focused on a few pathways within aerodigestive cancers (Table 1), these compounds have shown to have effects in other cancer types and tumorigenic pathways.

Epigenetic Effectors

Genetic mutations have long been a central theme in the causality of cancer. Recently, Hanahan and Weinberg [82] expanded their previous tenets on the origins of human cancer to now include epigenetic events in the pathway of carcinogenesis. Across the paradigm of cancer, recent data suggest that epigenetic events are of central importance in regulation of tumor formation and progression, possibly creating a new avenue for prevention and treatment [82–84]. There are many intrinsic and extrinsic factors that encompass epigenetic changes, and these can involve diet, heritability, and the environment. Regulation of the epigenome is under the control of DNA methyltransferases (DNMTs), histone deacetylases (HDACs), histone acetyltransferases (HATs), and associated modifier proteins [83, 85, 86]. Compounds regulating these proteins or altering their function is an emerging field for drug development. Some pharmacologic inhibitors such as 5-Aza-2′-deoxycytidine (5aza-dc) and suberoylanilide hydroxamic acid (SAHA) have entered clinical testing, but off-target toxicity has limited its progress [87].

Targeting epigenetic regulators is a new paradigm for cancer prevention [87–90]. Within this field, NPs such as resveratrol (from grapes), genistein (from soy), and sulforaphane (broccoli) are reported to modulate cancer risk while modifying epigenetic pathways [88, 91–93]. One extensively studied NP is epigallocatechin gallate (EGCG), the major polyphenolic compound from green tea [89, 94, 95••, 96–100]. In methylation-sensitive human colon cancer cells, EGCG at 100 μ has been shown to decrease DNMT3a protein levels and increased DNMT3a protein degradation [101]. Sulforaphane, on the other hand, had little effect on DNMT transcripts levels in human colon cancer cells [102]. In terms of aerodigestive cancers, little research outside of in vitro cell studies has been conducted using these NPs. This dearth of information suggests an open avenue for future basic research to possibly advance these compounds towards clinical testing.

HDACs decrease the open conformation of DNA shutting down gene transcription, and their increased activity has been implicated in numerous cancers [103]. EGCG at 100 μM decreased HDAC3 protein levels in HCT116 colon cancer cells and in combination (EGCG 10 μM) with sodium butyrate decreased HDAC1 activity in both HT29 and HCT116 colon cancer cells [101, 104]. In pancreatic cancer cell line AsPC-1, ECGC treatment can disrupt invasive metastatic by perturbing epigenetic modification of Snail 1 expression, thus shutting off the downstream target activation [105]. In HT29 colon cancer cell line, both EGCG and genistein decreased HDAC1 protein levels [106]. EGCG (20 μM) with sulforaphane (25 μM) treatment of HT29 human colon cancer cells decreased cell viability, suggesting a synergistic effects of multiple NP treatment in cancer cells [107•]. With the expansion of epigenetic research tools, further basic research in aerodigestive cancers using NP as individual or in combination therapies will allow better understanding of their future role as clinical agents.

Questions to Answer and Future Directions

These natural constituents tend have less aggressive side effects than standard clinical therapies and present another or additional avenue of cancer prevention/treatment [108–113].

Table 1 Natural product and aerodigestive cancer targets

Natural product	Colo/Rectal	Gastric	Pancreas	Oral
Silymarin	↓ NFkB			
Quercetin	↓ APC/$^{min+}$ tumors,	STAT3	↓Xenograft tumors, ↓ ErbB2/B3	
Silibinin	↓ cell migration	↓ ERK phosphorylation		↓cell migration
Curcumin	↓ NFkB, ↓ COX2			
Gingerol	↓ NFkB, ↓ MAPK		↓ ERK phosphorylation	
Nimbolide/neem	↓ ERK1/2 phosphorylation			↓ NFkB
Resveratrol	↓ NFkB			↓ MAPK phosphorylation
EGCG	↓ DNMT3a, HDAC1, HDAC3		↓ Snail 1	
Genistein	↓ HDAC1			

However, several questions remain: (1) Is dietary consumption of the foods containing these or a supplement with the isolated single compound a better strategy? (2) Will limited in vitro research suggest that bioavailability of these compounds might limit their effectiveness before they even research preliminary human trials? (3) Will research be better focused using these compounds in combination with conventional therapies instead of development as standalone therapeutic agents?

Epidemiological data suggests that green tea consumption can reduce CRC despite conflicting evidence that circulating serum levels of the tea constituents is much lower than those reported in the in vitro studies, and concentrations of active agents may be magnitude less in serum compared with cell line studies [114–124]. Several options are currently under exploration. Co-administration with other polyphenols enhances cellular absorption [125–127]. Piperine has been shown to enhance the anticancer effects of curcumin, cocoa flavanols enhance quercetin uptake by Caco-2 cells, and nanoparticle encapsulation has been shown to increase absorbed Np levels [125–127]. This enhancement is not without concern. When EGCG and genistein are given to mice, EGCG concentration were increased 50 %; however, when the EGCG was placed in the drinking water during the co-administration with genistein (contained in the diet), an increase in tumorigenesis occurred [128]. This type of research using combinations, delivery methods, and in vitro models highlights just how many unanswered questions remain.

Conclusion

All these issues aside, the use of NP as preventive or therapeutic agents still has a promising future in cancer chemotherapy. Lifestyle changes are one of the most readily adaptable factors one can implement to improve health. Dietary changes to increase bioactive dietary compounds can be a defense against chronic diseases, such as cancer. These compounds have the ability to alter numerous pro-cancer pathways to either slow down or halt tumor progression. Given the high cost and high toxic side effects of conventional therapies, the addition of NP into the treatment regime could have multiple benefits from cost reduction to enhanced efficacy of drugs and/or lower treatment dose. The ability to deliver these compounds in countless ways, their relatively safe side effects, and co-treatment flexibility with current standard therapies gives reason to continue exploration with these relevant NPs as therapeutics in future management strategies.

Compliance with Ethical Standards

Conflict of Interest Jay Morris, Yuan Fang, Keya De Mukhopdhyay, and Michael J. Wargovich declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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