Cancer Chemoprevention by Polyphenols and Their Potential Application as Nanomedicine

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Today cancer is a leading cause of death among the developed countries. Its highly complex nature makes it difficult to understand as it entails multiple cellular physiological systems such as cell signaling and apoptosis. The biggest challenges faced by cancer chemoprevention/chemotherapy is maintaining drug circulation and avoiding multidrug resistance. Overall there is modest evidence regarding the protective effects of nutrients from supplements against a number of cancers. Numerous scientific literatures available advocate the use of polyphenols for chemoprevention. Some groups have also suggested use of combination of nutrients in cancer prevention. However, we have yet to obtain the desired results in the line of cancer chemotherapy research. Nanotechnology can play a pivotal role in cancer treatment and prevention. Moreover, nanoparticles can be modified in various ways to prolong circulation, enhance drug localization, increase drug efficacy, and potentially decrease the chances of multidrug resistance. In this communication, we will cover the use of various polyphenols and nutrients in cancer chemoprevention. The application of nanotechnology in this regard will also be included. In view of available reports on the potential of nanoparticles, we suggest their usage along with different combination of nutrients as cancer chemotherapeutic agents.

Key Words: cancer; chemoprevention/chemotherapy; polyphenols; nanotechnology; nanomedicine

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INTRODUCTION

Cancer is a major public health concern worldwide. Despite the enormous amount of research and rapid developments that have proceeded in the past few decades, cancer incidence and mortality have still been increasing [1–3]. According to recent statistics, cancer accounts for about 23% of the total deaths in United States and is the second most common cause of death after heart disease [4].

Cancer is a dynamic process that involves many complex factors [5], which may explain why a "magic bullet" cure has not yet been found [6]. The lack of such a cure has led to an increased interest in using chemoprevention as an alternative approach to the control of cancer progression.

Chemoprevention is defined as pharmacological approaches used to arrest or reverse the process of cancer development before invasion and metastasis occur [7]. Carcinogenesis may span over a period of 20 years or more. Since it has a very short initiation stage, the promotion stage and possibly also the progression stage could be considered as the rate-limiting steps in cancer development, which renders both these stages ideal and logical targets for intervention. The understanding of the cell signaling pathways and the molecular events leading to carcinogenesis will provide more insight into the identification and development of potent chemotherapeutic agents that specifically target these pathways. Strategies for the prevention of cancer suggest that targeting intracellular cascade and their individual components could be more beneficial.

An ideal chemopreventive agent should be nontoxic to normal cells, highly effective against multiple sites, have a known mechanism of action, economical to use, appropriate for oral consumption, and should be acceptable to the human population [8]. According to the conventional classification originally proposed by Lee Wattenberg [9], chemopreventive agents can be divided into two main categories: blocking agents and suppressing agents. Blocking agents prevent carcinogens from reaching the target sites, from undergoing metabolic activation, or from subsequently interacting with crucial cellular macromolecules such as DNA, RNA, and proteins. On the other hand, suppressing agents inhibit the malignant transformation of initiated cells, either at promotion or progression stage [10].

Although great efforts have been made to prevent the development of various types of cancers, but still we are far from creating any reliable and promising therapeutic agent. Moreover, cancer is a class of diseases so it is unlikely to have a single cure for all the varieties. Evidence from various laboratory and population-based research supports that a variety of natural products interfere with all three stages of cancer development [11]. The present review intends to recapitulate the researched polyphenolic chemotherapeutic agents. The scope of nanoparticles in this regard is also highlighted.

POLYPHENOLS: THE NUTRIENTS CONFERRING CHEMOPREVENTION

Polyphenols are a group of chemical substances found in plants that are characterized by the presence of more than one phenol unit or building block per molecule with one or more hydroxyl groups [12]. They are generally conjugated with sugars and organic acids and can be grouped into flavonoids and nonflavonoids. The polyphenols are annexed with diverse biological properties including but not limited to antioxidation, induction of detoxification enzymes and inhibition of bioactivation enzymes, estrogenic and anti-estrogenic activity, antiproliferation, cell cycle arrest and apoptosis, and promotion of differentiation. This makes them versatile chemopreventive agents enabled naturally, which interfere with each stage of carcinogenesis: initiation, promotion, and progression [13–15]. Specifically they regulate growth factor-receptor interactions and cell signaling cascades, including kinases and transcription factors, that determine the expression of genes involved in cell cycle arrest, cell survival and apoptosis, activities of antioxidant enzymes [3,16–17]. They can enhance the body's immune system to recognize and destroy cancer cells as well as inhibit the development of new blood vessels (angiogenesis) that is necessary for tumor growth. They also attenuate adhesiveness and invasiveness of cancer cells, thereby reducing their metastatic potential [18]. The inhibitory effects of phenolics on the stress activated NF-kB and AP-1 signal cascades in cancer cells have been in focus recently.

Most of the polyphenols encompass antioxidant activity, which often contributes to their anticancer effects [19]. Polyphenols may act as antioxidants terminating free radical chain reactions, activating nuclear factor-erythroid-2-related factor 2, which stimulates the activities of antioxidant enzymes such as glutathione peroxidase (GPx), glutathione S-transferase, catalase, NAD(P)H: quinone oxidoreductase-1 (NQO1), and/or phase II enzymes effectively chelating redox-active metals capable of catalyzing lipid peroxidation [20–21].

The polyphenols are nonselective, that is, they can suppress the growth of variety of cancer cell through various mechanisms. This complexity is further extended by the fact that thousands of polyphenols exist making the identification of their specific targets difficult though in silico approaches have very recently tracked some of the molecular targets [22]. Various excellent reviews have elaborated on the processes affected by polyphenols exerting chemoprevention [21,23–27].

Briefly, the tumor promoters (stimuli) differentially activate various mitogen activated protein kinase (MAPK) signaling pathways. MAPK on translocation to nucleus get activated and phosphorylate target transcription factors (AP-1, Activator Protein-1, NFκB), which then activate the downstream cancer transcription factors. AP-1, a homo- or heterodimer of Jun, Fos, activating transcription factor, and musculoaponeurotic fibrosarcoma protein families is crucial to cell transformation, tumor progression, and metastasis [28].

Inhibition of AP-1 can block the tumor progression. MAPK are extracellular signal regulated protein kinases (ERKs), c-Jun-terminal kinases (JNKs), stress activated protein kinases, and p38 kinases. Upon activation these signaling pathways can result in apoptosis, proliferation, development, differentiation, and inflammation [28]. Almost all the components of tumor induction machinery previously mentioned are targeted by polyphenols. Apoptotic machinery (caspases, growth factors, etc.) and matrixmetalloproteinases are also modulated by the polyphenols.

Some compounds have been reported to inhibit carcinogenesis at early stages through mechanisms that alter the profile of both phase I and phase II drug-metabolizing enzymes as well as the rates of DNA repair and scavenge reactive oxygen and other free radical species. Phenolic and sulfur-containing compounds are two major groups of dietary components that induce detoxifying enzymes. In addition to these compounds, other natural chemical entities, such as indoles, diterpenes, coumarins, lactones, and selenium, can also induce detoxifying enzymes [10].

The risk of initiation of cancer is decreased by the administration of chemopreventive agents through altering carcinogen metabolism via phase I enzymes and/or increasing conjugation and detoxification of activated metabolites via phase II enzymes. Ultraviolet radiation (UVR) can induce DNA damage, which is one of the mechanisms of tumor formation. It was found that pre-incubation with epigallocatechin gallate (EGCG) significantly decreased DNA damage induced by UVR in human skin fibroblasts, lung fibroblasts, and epidermal keratinocytes cell lines [29].

In one study, Umemura and colleagues [30] reported anticancer potential of green tea at initiation stage. The anticarcinogenic activity of tea is accredited to its ability to modulate the activity of carcinogen metabolizing enzyme systems. Treatment of rats with tea was shown to stimulate the deactivation of heterocyclic aromatic amines, a major group of food borne carcinogens [31]. Green and black tea polyphenols have antimutagenic effects. Cacao polyphenols have also been shown to be antimutagenic (against heterocyclic aromatic amines) in bacterial and mice [32]. Green tea extract has been shown to reduce the carcinogenicity of tobacco by inhibiting the in vitro nitrosation (due to interaction of sodium nitrite with methyl urea) [33]. Polymeric black tea polyphenols prevent cancer initiation. They were shown to prevent Benzo(a)pyrene-DNA adduct formation in vitro as well as in rat epidermal DNA and reduced the activity of CYP 1A1 and 1A2 [34]. Moon and associates [35] have detailed the anti-initiating effects of polyphenols on cancer. Flavonoids alter the activities of CYP enzymes, as mentioned previously; either through binding to the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor, acting as either AhR agonists or antagonists or inhibiting (CYP 1A1, 1A2, 2E1, and 3A4) by competitive mechanisms. Aromatase (CYP19) activity may also be inhibited by certain flavonoids

preventing estrogen formation, an important step in prostate and breast cancers. Phase II detoxifying enzymes, such as UDP-glucuronyl transferase, glutathione S-transferase, and quinone reductase, are activated and sulfotransferase 1A1 is noncompetitively inhibited by flavonoids, ultimately preventing carcinogenesis.

Flavonoids effectively scavenge various free radicals (like superoxide anion and peroxynitrite) possibly preventing DNA damage and tumor promotion [36–37]. They also regulate oxidative stress-mediated enzyme activity and signaling pathways involved in carcinogenesis [38–39]. Various phenolics are also capable of attenuating ROS generation through inhibition of redox-sensitive transcription factors such as NF-kB and AP-1, which are responsible for the expression of the ROS-induced inflammatory enzyme cascade. Xanthine oxidase, cyclooxygenase-II (COX-II), and lipooxygenase (LOX) were reported to be depleted by dietary phenolics like curcumin, silymarin, and resveratrol [3,40–41].

They can interact with proteins that control cell cycle progression depending on p53 [42], apoptosis induction by activation of caspase-9 and caspase-3 [43], and general inhibitors of cytokine-induced gene expression [44]. Flavonoids have also been recognized as modulators of the Wnt signaling pathway, providing yet another means of cancer prevention where conventional therapeutics are still ineffective [45].

Quercetin is one of the most studied anticancer phenolic compounds known to date [46]. In vitro and in vivo studies have shown that quercetin exerts a dose-dependent inhibitory effect on cell growth [47–48] in numerous types of cancer [49–51]. Anticancer effects of quercetin on tumor cells are exerted through inhibition of cell division by interference with cell cycle components, like cyclin D1 and induction of apoptosis and necrosis [46].

Because of structural similarity to estradiol and their binding to estrogen receptors, genistein is suggested to contribute to the putative breast and prostate cancer-preventive activity of soy [52]. It can inhibit the growth of various cancer cell lines including leukemia, lymphoma, prostrate, breast, lung, and head and neck cancers mainly through modulation of cell cycle and metastasis events [53–57].

Apigenin has gained particular interest over the years as a beneficial and health-promoting agent because of its low intrinsic toxicity and its striking effects on normal versus cancer cells compared with other structurally related flavonoids [58]. It restricts tumor promotion by inhibiting ornithine decarboxylase and cell growth through various mechanisms like altering Bax/Bcl2 ratio, MAPK, and PI3/Akt signaling, etc. [59–64]. Exposure of a wide array of malignant cells to apigenin induces a reversible G2/M and G0/G1 arrest by inhibiting p34 (cdc2) kinase activity accompanied by increased p53 protein stability [42,64].

Luteolin prevents cancer mainly by affecting the signal transduction pathways, ROS levels, and DNA replication enzymes [65–68]. Elangovan and colleagues [65] reported that diets containing 1% luteolin reduced the incidence of fibrosarcoma in mice by reducing the elevated levels of lipid peroxides and cytochrome P450. Luteolin was also found to exert chemopreventive effects against colon cancer in rats [66–67]. Modulation of ROS levels, inhibition of topoisomerases I and II, reduction of NF-kB and AP-1 activity, stabilization of p53, and inhibition of PI3K, STAT3, IGF1R, and HER2 are possible mechanisms involved in the biological activities of luteolin [68].

Oleuropein has been reported to induce cell cycle arrest and apoptosis in various cancer cells [69–70]. Oleuropein, aglycone, and hydroxytyrosol have also been shown to deplete the overexpressed HER2/neu receptor in breast cancer cells. It also displays a synergistic augmentation of herceptin induced down-regulation of Her2/neu expression [71].

Caffeic acid (CA) possess antitumor and antimetastatic properties [72–74]. CA attenuates tumor promotion by inhibiting oxidative and inflammatory responses thereby diminishing the expression of NF-κB and COX-2.

The anticarcinogenic activities of ellagic acid are similar to apigenin [75–78]. It also takes part in various DNA maintenance reactions and prevents genomic instability, which could lead to cancer progression [79].

Umesalma and Sudhandiran [80] reported prevention of PI3K/Akt activation by ellagic acid, which resulted in modulation of Bcl-2 family proteins. Bax expression and caspase-3 activation were also found to be modulated in response of ellagic acid supplementation leading to elevation of cytochrome c levels and finally cell death. Nandakumar and associates [81] highlighted anticancer potential of proanthocyanidins, which modulate various molecular targets in vitro and in vivo tumor models.

Genistein and quercetin were found to inhibit protein tyrosine kinase, which is also involved in cell proliferation [42,82]. Marchand [83] reported that apigenin, luteolin, and quercetin cause cell cycle arrest and apoptosis by a p53-dependent mechanism. Dietary intake of genistein and daidzein in soy products has also been implicated in a reduction in rates of incidence of prostate and breast cancer in humans. They compete with the natural hormone receptor and suppress the growth and progression of the tumors [3,16].

Green tea polyphenols have been known to modify the activities of various receptor tyrosine kinases and particular pathways of signal transduction, thereby altering the expression of genes involved in cell proliferation, angiogenesis, and apoptosis [8]. The chief catechin substances present in green tea are epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin gallate (EGCG).

EGCG has great potential in cancer prevention because of its safety, low cost, and bioavailability. Various studies have demonstrated that EGCG can

inhibit carcinogenesis and also the growth of established cancers at various organ sites such as liver, stomach, skin, lung, mammary gland, and colon [84–87]. EGCG exhibits both antimatrix metalloproteinase and antiangiogenesis activities [88–89]. EGCG has been shown to inhibit several critical signal transduction pathways as well the activation of the redox-sensitive transcription factors, NF-κB, and AP-1 in cultured cells [90–92]. EGCG was reported to inhibit TPA-induced DNA binding of NF-κB and CREB in mouse skin in vivo [93]. In vitro studies have demonstrated that EGCG blocks carcinogenesis by affecting a wide array of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt, and Notch [10,15,93]. EGCG also stimulates telomere fragmentation by the inhibition of telomerase activity.

EGCG inhibits the phosphorylation of JNK, JUN, MEK1, MEK2, ERK1, ERK2, and ELK1 (Ets-like protein 1) in KB6 epidermal cell lines and lung cancer model [95–96]. In one study, EGCG was suggested to inhibit MEK1 phosphorylation by decreasing its association with the kinase RAF1 [97]. Cyclin-dependent kinase 2 (CDK2) and CDK4 were also reported to be inhibited by EGCG in MCF-7 breast cancer cell lines and this was associated with cell cycle arrest in G0 and G1 phases [98].

EGCG inhibits oxidative stress-mediated phosphorylation of MAPK signaling pathways as has been found in human skin cells, human fibrosarcoma HT1080 cells, and breast cancer cell line T47D [99–101]. Khun and colleagues [102] reported that EGCG potently inhibits the proteasomal activity in HeLa cells, which was confirmed by accumulation of ubiquitinated proteins and three natural proteasome targets (p27, IκB-α and Bax). EGCG has been reported to exert anti-invasive effect in gastric cancer by controlling MMP expression through the suppression of MAPK and AP-1 activation [103]. Manna and associates [104] suggested that the tea polyphenols can restrict lung cancer by differential modulation of the expression of p53 and its associated genes such as bax, bcl-2, mdm2, p21, and p27 along with H-ras, c-myc, and cyclin D1 in mice models. Harakeh and coauthors [105] reported that EGCG administration at nontoxic concentrations to leukemia cells (Jurkat and C91Cl) and HTLV-1 infected leukemia cells (HUT102 and CEM) inhibits cell proliferation and triggered cell apoptosis. EGCG also exerts inhibitory effect on class I histone deacetylase in prostate cancer cell lines [106].

Epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein with intrinsic tyrosine kinase activity that regulates cell proliferation and differentiation and has become a novel molecular target of cancer therapies. EGCG was found to inhibit EGFR autophosphorylation in YCU-N861 and YCU-H891 head and neck carcinoma cells and MDA-MB-231 breast carcinoma cells [107–108]. EGCG was also shown to inhibit the activation of the EGFR, HER2, and multiple downstream signaling pathways in colon cancer cell lines [109].

Increasing evidences indicate an association of carcinogenesis and chronic inflammation. Interleukin-1 (IL-1) plays a crucial role in inflammation-associated carcinogenesis. Hoffmann and colleagues [110] analyzed the biological effects of IL-1 and its modulation by EGCG in the human pancreatic adenocarcinoma cell line. They reported down regulation of the IL-1RI expression and NF-kB inhibition in response to EGCG exposure.

Black tea has been found effective against lung and liver tumorigenesis [111–112]. Polymeric black tea polyphenols such as theaflavins modulate the PI3-K mediated signal transduction affecting proliferation, inflammation, and apoptosis in mouse model [113]. Theaflavins also inhibit chymotrypsin like activity of tumor proteasome exerting antitumor effects in human multiple myeloma cells [114].

Curcumin (and its derivatives) suppress all the 3 stages of carcinogenesis [13]. Anti-invasive and/or antimetastatic potential of curcumin and its derivatives has been reported on variety of cancers [115–118]. Oral administration of curcumin has also shown to prevent cancer in the colon, skin, stomach, duodenum, and breasts of rodents [119–120]. Inhibition of NF-κB-related proinflammatory pathways [121], c-Jun/AP-1 activation [122–123], phosphorylation reactions [124], and expression of matrix metalloproteases and cyclooxygenase-2 [125] appear to be primary targets of curcumin.

Compounds that can attenuate growth factor (GF) binding and the attendant signal cascade are generally regarded as excellent chemopreventive agents. Curcumin inhibits epidermal growth factor receptor (EGFR) action and reduces the invasive potential of cancer cells [126–127]. Curcumin was also reported to inhibit EGF kinase activity in A431 cells and EGF expression in Ishikawa endometrial cancer cells [126,128].

Recently Prasad and colleagues [129] showed that the up-regulation of a serine protease inhibitor expression by curcumin might contribute to the inhibition of invasion of breast carcinoma cells. Curcumin exerts a strong anti-invasive effect through the down-regulation of NF-κB/AP-1 dependent MMP-1 and -2 expression, the up-regulation of tissue inhibitor metalloproteinase protein - 1 and the inhibition of vascular endothelial growth factor and basic fibroblast growth factor (b-FGF) in breast cancer [115,130]. Curcumin also inhibits cell migration of Colo205 cells through the inhibition of NF-κB and the down-regulation of COX-2 and MMP-2 expression [131]. It suppressed the expression of human epidermal growth factor receptor (HER) 2 and the activity of p21-activated kinase (PAK) 1 to inhibit the proliferation and invasion of gastric cancer cells [118]. A decrease in migration and invasion of osteosarcoma cells was also reported after treatment with curcumin and the observed reduction was correlated with the activity and protein level of MMP-9 [132].

Curcumin was found to inhibit MMP-9 secretion, migration, and invasion of CBO140C12 cells and the formation of actin stress fibers in hepatoma [133]. The suppression of the migration and invasion of A549 cells by curcumin took

place via mitogen-activated protein kinase kinase (MEKK) 3 and ERK signaling pathway, which results into inhibition of MMP-2 and 9 expressions [134]. Curcumin has also been reported to reduce cell migration and invasion of CL1–5 cells via suppression of several invasion-related genes [135–136].

Resveratrol is one of the most versatile phytochemicals present in many plant tissues in both the cis- and trans-configuration [137]. It has been reported to exhibit potent chemopreventive properties [138] by virtue of its unique ability to influence multiple cellular modules involved in tumor progression, such as Fas pathway, Rb-E2F/DP pathway, NF-κB and AP-1 transcriptional factors, MAPK, and many others [139]. It is a potent inhibitor of cycloxygenase-1 [140]. It is an excellent scavenger of hydroxyl, superoxide, and other radicals [141]. It is reported to inhibit the induction of JNK, protein kinase C (PKC)-delta, and their downstream target MMP-9 [142].

Resveratrol was reported to suppresses constitutively active NF-κB through the inhibition of IκBa kinase and thus down-regulating a number of pro-proliferation and anti-apoptotic gene products viz, Akt, cyclin D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TRAF2; thereby suppressing cell proliferation and potentiating the pro-apoptotic effects in human multiple myeloma cells [143]. It is reported to inhibit STAT3, which also indicates its anti-proliferative and pro-apoptotic potential [143]. Resveratrol can regulate cell cycle by transiently and reversibly blocking its S-phase [144–145]. Resveratrol is also reported to inhibit IL-6 and IL-8 expression in various cells by down-regulating EGF effects [3].

Avenanthramides, the oat polyphenols, attenuate cell proliferation of colonic cancer cells. Studies conducted on various human colon cancer cell lines have indicated that such effects are mediated by COX-2 independent antiproliferative mechanisms [146]. Olive oil polyphenols also have proven antitumor effects in vivo and in vitro [147].

OTHER DIETARY NUTRIENTS

Cancer can be prevented by different nutrients that can counteract genetic damage and modulate the acquisition of a neoplastic phenotype [148]. Vitamins are essential nutrients for human metabolism, playing an important role as coenzymes or enzymes in many vital processes for the normal functioning of the body. Currently, it has been proposed that vitamins can have an important role in the prevention and treatment of cancer [149]. Numerous dietary nutrients, such as carotenoids and selenium along with vitamins C and E, have been reported to possess antioxidant properties [150–151] and may also inhibit tumor development by stimulating the immune system and regulating cell growth [152–153]. Several studies are in support of this notion. In a case

control study, Williams and colleagues [154] demonstrated that dietary antioxidants (vitamin C, vitamin E, β-carotene, selenium) and DNA methylation-related nutrients (folate, vitamin B6, vitamin B12) are associated with reduced risk of colorectal cancer. Yeon and associates [155] reported the beneficial potential of vitamin A intake against oxidative stress-mediated breast cancer.

Antioxidative, anti-inflammatory, and anticarcinogenic activities of tocopherols were reported by Yang and coauthors [156]. They reported inhibition of inflammation, cancer formation, and growth in lung and colon in response to treatment with tocopherol mixture. Ascorbate has been the most commonly used nutrient in cancer treatment for more than two decades. It is also branded as a "miracle nutrient" and is reported to be useful in the treatment of almost all types of cancers [157]. It was presumed that the anticancer potential of vitamin C is due to its antioxidant activity. However, it is now clear that vitamin C exercises its effects in several other ways too.

In the search of an effective solution to cancer treatment, Rath and colleagues [158] proposed a new perspective in the therapeutic use of nutrient synergy as an effective way to control the critical processes of cancer, including metastasis, angiogenesis, cell proliferation, and apoptosis [159–163]. The nutrient synergy proposed by Rath research group consists of a mixture of: ascorbic acid, l-lysine, l-proline, l-arginine, N-acetyl cysteine, epigallocatechin gallate (EGCG), selenium, copper and manganese [164].

All types of cancers can be controlled by optimum therapeutic dosage of certain essential nutrients especially in combination. This view is supported by the use of nutrient synergy, which has been found to be effective in a variety of cancer cell types, including solid tumors, leukemias, HTLV-1 virus-derived leukemia, breast and prostate cancers [159–163, 165–166]. The pro-apoptotic effect of nutrient synergy on cancer cells was indicated by the up-regulation of p53, p21, and Bax protein expression and the decrease in Bcl-2a, as well as cell cycle arrest, up-regulation of TGF-beta, and the decline in TGF-alpha cytokine expression [167]. Harakeh and associates [164] reported the inhibition of proliferation and induction of apoptosis in both HTLV-1-infected and noninfected cell lines in the presence of nutrient synergy. Treatment with a diet containing lysine, proline, arginine, ascorbic acid, and green tea extract to athymic nude mice implanted with human melanoma A2058 cells strongly suppressed tumor growth with inhibition of MMP-9 and VEGF secretion [168]. Roomi and colleagues [169] reported therapeutic potential of a novel nutrient mixture (consisting of ascorbic acid, lysine, proline, and green tea extract) in the treatment of hepatocellular carcinoma in vitro as well as in vivo.

Mukhtar and Ahmad [170] also proposed a certain phytococktail, in which various natural and synthetic products can be mixed in concentrations that could easily be consumed by humans. Different agents in the cocktails

should preferably act on different molecular pathways and through this the possibility of producing lasting cancer chemopreventive effects in humans might be achieved.

POSSIBLE ADVERSE EFFECTS OF POLYPHENOLS

Disease preventive effects of polyphenols, the antioxidative and the free radical scavenging activities are often cited in scientific literature. However, under certain conditions (high concentrations of phenolic antioxidants, high pH, presence of iron) phenolic antioxidants can initiate an auto-oxidation process and behave like pro-oxidants [50,171].

There is a considerable amount of evidence to suggest the pro-oxidative potential of polyphenols, the hepatic, intestinal and renal toxicities of high doses of polyphenols and the potential DNA damaging effects and leukemiogenic activities of flavonoids [172–177].

Weisburg and colleagues [178] and Hong and associates [179] demonstrated that the tea catechins, including EGCG, are unstable under cell culture conditions and undergo oxidative polymerization with cogeneration of H_2O_2. This oxidative stress may have implications regarding potential toxicity of these compounds. Galati and coauthors [175] reported that treatment of rat hepatocytes with 200 μM EGCG reduced cell viability by increased production of reactive oxygen species and depletion of reduced glutathione.

Although consumption of polyphenols has been suggested to have beneficial biological effects in cancer chemoprevention, there is considerable evidence that suggest that such compounds are not without risk of adverse effects. Clearly, more research is needed to better understand the effects of polyphenols, whether positive or negative, particularly in the context of dose, timing, duration, and susceptibility of consumer to disease.

NANOMEDICINE IN THE TREATMENT OF CANCER

Nanoscience and nanotechnology have witnessed a significant progress during past decades and today their applicability is widespread in every field. Basically, nanotechnology involves the tailoring of materials at atomic level to attain unique properties, which can be suitably manipulated for the desired applications [180].

The role of nanotechnology in cancer prevention is an extensive field and for this article we have restricted the discussion only to the use of nanoparticles (NPs) along with various nutrients (especially polyphenols) in cancer chemoprevention.

The advent of nanoparticles in cancer research could not have come at a more opportune time. Their small size and subsequent larger surface area endows them with some highly useful characteristics for various applications

that can remove current obstacles in cancer therapies [164,181]. Nanoparticles may have properties of self-assembly, stability, specificity, drug encapsulation, and biocompatibility as a result of their material composition [182]. The foremost challenges for cancer chemotherapy is maintaining drug circulation and avoiding multidrug resistance. Due to chemical compositions and lack of targeting, many current therapeutic agents are removed from the body's circulation by immune system [183]. Besides these hydrophobicity and poor bioavailability of most of the bio-polyphenolic chemotherapeutic agents also create deadlock to their usage.

The National Cancer Institute (NCI) has recognized nanotechnology as an emerging field with the potential to revolutionize modern medicine for detection, treatment, and prevention of cancer [184]. Cancer related nanodevices include but are not limited to injectable nanovectors, such as liposomes; biologically targeted, nanosized magnetic resonance imaging contrast agents; and novel, nanoparticles-based methods [185].

The properties of nanoparticles essential to be ideal carriers for various anticancer drugs are:

(a) **Size** (10–100 nm as recommended by NCI) is critical for biodistribution of circulating NPs (due to restraints from various physiological processes like hepatic filtration, tissue extravasation, tissue diffusion, kidney excretion etc.) [186]. Disease targeting NPs must resist immediate clearance, degradation, biotransformation, biophysical/biochemical barriers [187].

(b) **Surface characteristics** of the NPs are major determinants of their solubility, stability and of course bioavailability. The surfaces must be minimally interactive with self or nonself moieties [188–189]. The surface properties can be modulated by conjugation with antibodies, polyethylene glycol, aptamer, etc., improving the pharmacokinetics of the drug NPs [190].

(c) **Targeting** of the drug to the cancer cells ensures that the cells receive optimal dose and that there are minimal off target effects. Manipulating the physicochemical properties like pH or hydrophobicity of the NPs (passive targeting) [191] or attaching tumor specific stable functional moieties on to the NP surface (active targeting) increases selective cellular binding and internalization through receptor-mediated endocytosis [192–193].

(d) **Various formulation methods** have been devised for the efficient delivery and targeted therapy like nanoprecipitation, nanoemulsion, and reverse phase evaporation [189,194–197].

The structure and surface of a nanoparticulate system is flexible and can be easily manipulated. This allows encapsulation/conjugation of single or multiple entities either in the core or on the surface and renders them as suitable

vehicle for anticancer drug [198]. The use of nanocarriers allows for the preparation of low water soluble cancer medications as solid or liquid formulations. Nanoparticles made up of biodegradable and biocompatible polymers such as polylactic acid (PLA), poly (DL-lactide-co-glycolide acid; PLGA), starch, and chitosan, and so forth have been extensively utilized for the delivery of various drugs [199–200]. The PLA/PLGA NPs usually suffer from the disadvantage of being cleared by the macrophage system. This has been countered by attachment of hydrophilic moieties like polyethyleneglycol (PEG) (referred to as PEGylation), which increases the circulation time and improves the pharmacokinetic and pharmacodynamic properties of the drugs encapsulated in the NPs [199]. PEGylated NPs encapsulating anticancer polyphenols have been analyzed by Siddiqui and associates [198]. The PEGylated nanoformulations exhibit significantly high accumulation in the tumor tissue due to the enhanced permeation and retention effect (EPR) arising because of the leaky endothelial lining that allows the easy infiltration of the NPs into the tissue as compared to the normal tissue. Siddiqui and colleagues [201] have enumerated various nanotechnology approaches, which are currently being explored or proposed for preparation of therapeutics for nanochemoprevention.
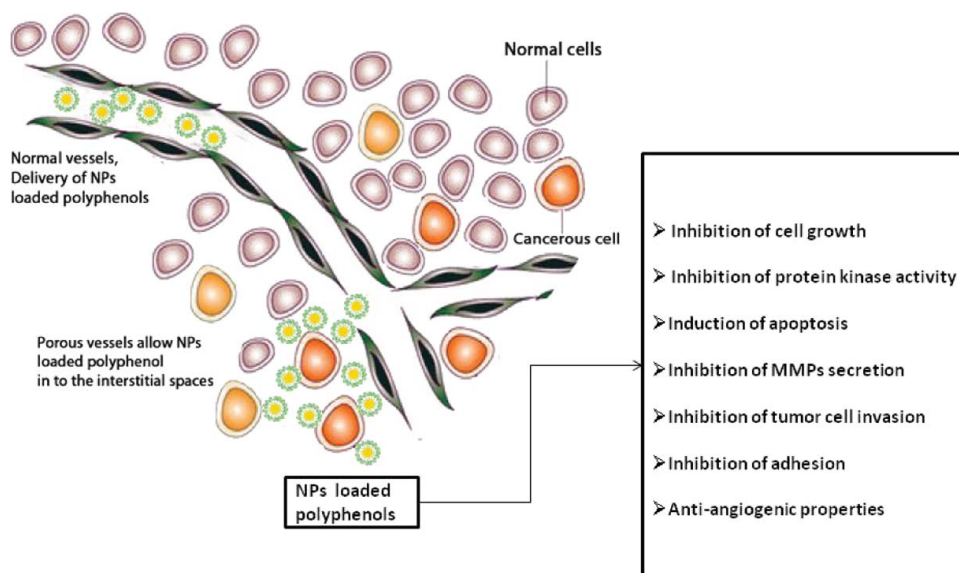
NANO-POLYPHENOLS

Bioactive natural products (bioflavonoids, polyphenols), which have miraculous antitumor properties, remain underutilized as cancer drugs because of their poor water solubility, low oral bioavailability, and inefficient systemic delivery. These problems can be meted out with the application of nanotechnology. Nano formulations of nutraceuticals are based on the general principles of nanotechnology. Some of them have showcased their potential in experimental/human studies. The potential molecular targets of nanopolyphenols have been demonstrated in Figure 1.

Genistein covalently attached to iron oxide NPs coated by cross-linked carboxymethylated chitosan has been studied as novel multifunctional, tumor-targeting drug delivery system [189]. This nanoconjugate inhibited SGC-7901 cancer cells more significantly than the free genistein, seemingly provision for a multifunctional chemotherapeutic application combining drug release and magnetic hyperthermia [189].

Nigella sativa active component thymoquinone possesses anti-inflammatory and anticancer activity. Thymoquinone NPs prepared by nanoprecipitation have shown improved effectiveness (potency for antiproliferative and proapoptotic effects on various cancer cell lines) and bioavailability [189].

Nanoemulsion of caffeine (found in tea leaves, coffee, cocoa, guarana, and kola nuts) has been widely studied for its tremendous potential against ultraviolet light-induced skin cancer [189].

Figure 1: Illustration of potential molecular targets of cancerous cells by nano-polyphenols. (Color figure available online).

Clinical trials of curcumin in various human cancers revealed its low oral bioavailability in vivo as a major limitation [202–207]. Curcumin low bioavailability is attributable mainly to poor oral absorption and rapid metabolism in the intestines and liver. In contrast curcumin NPs (prepared by nanoprecipitation) exhibit higher half-lives and low serum clearance in vivo and enhanced cellular uptake and bioactivity in vitro [189].

Various nanoformulations of curcumin analyzed to date have shown efficacy and dose advantage over free curcumin in different cancer cell lines [201,208]. Encapsulated/entrapped/emulsified or self-assembled in (a) the micellar aggregates of cross-linked and random copolymers of N-isopropylacrylamide, with N-vinyl-2-pyrrolidone and PEG monoacrylate; (b) the polymeric methoxy poly(ethylene glycol) (mPEG) and palmitic acid aggregates; (c) prostate membrane-specific antigen-specific antibodies coated liposomes; (d) biocompatible polymers, that is, alginate, chitosan, and Pluronic®; (e) a PEGylated conjugate; (f) PLGA-PEG NPs/PLGA NPs stabilized by polyvinyl alcohol and poly (L) lysine; (g) nanocrystal solid dispersion, amorphous solid dispersion, and nanoemulsion; (h) a poly(oxyethylene) cholesteryl ether (PEGChol), curcumin has exhibited significantly increased bioavailability, cellular intake, antiproliferative, and anticell growth properties [209–217].

Nanoparticle encapsulation of anticancer polyphenols causes a several-fold increase to their oral bioavailability. A 9-fold improvement in oral bioavailability has been shown for nano-encapsulated curcumin compared to curcumin

administered with piperine as an absorption enhancer [218]. Nanopowders of poorly soluble natural products with wide variety of antitumor activities (for example for ursolic acid) have also been prepared and are underway studies [219].

Polyphenol-loaded nanoparticles can combat the low bioavailability and shorter half-lives of free polyphenols [220]. However, nano-encapsulation of polyphenols is challenging itself because of their varying and oxidation labile structures [221–222], and only few combinations have been tried [223].

Nano-EGCG (PLA-PEG NPs encapsulated EGCG), when used against the human prostate cancer cell lines (also in relevant tumor xenograft mouse model), exercised comparable anticancer, proapoptotic, and antiangiogenic effects at 10-fold lower dose as non-nano-EGCG [224]. The same group further extended their observation of enhanced efficacy of nano-EGCG by reporting its longer half-life. This nano-EGCG cannot withstand the acidic environment and hence cannot be delivered orally. To overcome this disadvantage chitosan-based NPs are now being tried. Hu and colleagues [225] have used caseinphosphopeptides/chitosan (CS-CPP) NPs for encapsulation of EGCG as a strategy for nano-chemoprevention. The CS-CPP loaded EGCG prepared by self-assembly method has high biocompatibility, pH stability (2.5–7.0, mimicking the oral delivery route), intestinal permeability (studied in CaCo-2 cells and compared with EGCG permeability), and lower cytotoxicity. Thus it offers a better alternative for nutrient loaded PLA-PEG NPs [225].

As an approach for the oral drug delivery, EGCG has been encapsulated in carbohydrate matrix of gum Arabic and maltodextrin [226]. Such entrapped EGCG retained its biological activity and was effective against Du145 prostate cancer cells. In another study, polymer-based nanoparticle of EGCG and theaflavin (TF) alone and in combination with the anticancer drug, cisplatin, when analyzed for their anticarcinogenic effects in human cancer lines A549 (lung carcinoma), HeLa (cervical carcinoma), and THP-1 (acute monocytic leukemia) exhibited a 20-fold dose advantage over EGCG/TF alone [227].

Table 1 summarizes the characteristics of some nano-nutraceuticals along with their possible cancer targets.

The in vivo usage of resveratrol has been limited by its high lipophilicity and rapidity of glucuronation and sulfonation. Various nanoformulations of resveratrol like with chitosan NPs have been shown to have increased bioavailability, proapoptotic, and antioxidative potency than the free resveratrol [201].

In the first of its kind study, Narayanan and colleagues [228] utilized liposome co-encapsulated curcumin and resveratrol in male B6C3F1/J and prostate-specific PTEN knockout mice. They found that such a combination had better cell growth inhibitory and proapoptotic activity than the free polyphenols in vitro. The usage significantly reduced the prostatic adenocarcinoma in vivo in PTEN mice. Solid lipid nanoparticles loaded with resveratrol have also been analyzed against skin cancer [229].

Table 1: Characteristics of Some Nano-Polyphenols Analyzed for Their Anticancer Effects

Phytochemicals	Materials	Size (nm; average)	Targets	References
EGCG	PLA-PEG	260	Pancreatic cancer	Siddiqui et al. 2009 (224)
	Gum-Arabic & maltodextrin	-	Prostate cancer cells	Siddiqui et al. 2012 (201)
	Gold		Prostate cancer cells	Rocha et al. 2011 (226)
			Bladder cancer (mouse model)	Hseih et al. 2011 (231)
EGCG, tannic acid, curcumin	Gelatin	-	Breast cancer	Shutava et al. 2009 (222)
β-Lapachone	Gold	47	Lung, colon cancer cells	Jeong et al. 2009 (232)
	PLA-PEG	29.6	Lung, prostate, breast cancer cells	Blanco et al. 2007 (233)
Curcumin	PLGA	80.9	Leukemia, colon, breast, prostate cancer cells	Nair et al. 2010 (188)
		45	Prostate cancer cells	Mukerjee et al. 2009 (234)
	Silk	100	Breast cancer cells	Gupta et al. 2009 (235)
	Casein	10~20	Cervical cancer cells	Sahu et al. 2008 (210)
	Bovine serum albumin	200	Prostate cancer cells	Zu et al. 2009 (236)
Epigallocatechin	PLGA	150~200	Leukemic cells	Nair et al. 2010 (188)
Thymoquinone	Solid-lipid	<180	Skin cancer	Teskac and Cristl, 2010 (229)
Resveratrol		~39	Non-Hodgkin's lymphoma cell line	Wang et al. 2012 (230)
Wogonin	Magnetic iron oxide coated with citric acid			

PLA-PEG = polylactic acid-polyethylene glycol.
PLGA = poly(lactic-co-glycolic acid).

In a recent study, Wang and colleagues [230] explored the potential of wogonin-magnetic nanoparticle conjugates (wogonin-MNPs) in as a therapy against lymphoma. Wogonin linked to magnetite Fe_3O_4 caused cell inhibition, apoptosis, and cell cycle arrest in Raji cells, a non-Hodgkin's lymphoma cell line by targeting caspases 3 and 8, survivin, and cyclin E.

Thus far, researches in cancer-nanotechnology have made remarkable advancements. Nanopolyphenols definitely pose to be attractive options for chemotherapy. Commercial nano-based drugs for the purpose have already been launched [201]. Nano-polyphenols, although extensively researched, are yet to arrive on such lists. The lack of information on in vivo fate of nano-carrier materials and their toxicity impedes the progress in the field. However, the data collected so far provides strong footage for appropriate animal and human clinical trials.

CONCLUSION

Most modern medicines currently available for treating cancers are very expensive, toxic, and less effective for the treatment of disease. The increasing magnitude of the cancer problem and the failure of conventional chemotherapy to bring about major reductions in the mortality rates indicate that new approaches to control cancer progression are urgently needed. Significant improvements in early detection of cancer and development of effective novel therapeutic strategies could improve the present scenario. Over the past three decades, polyphenols have emerged as one of the most promising naturally occurring compound with immense therapeutic potential. Moreover, consideration must also be given to the possibility that although individual components of plants may have significant, specific anticancer effects, these effects may be even greater when these components are consumed in various combinations. With a better understanding of the mechanisms underlying nutrient synergy, their anticancer potential should be further explored. In view of some interesting results on the use of various NPs along with nutrient mixture in cancer treatment, we also suggest use of different NPs along with combination of polyphenols/nutrients to increase the efficacy of cancer treatment.

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