

Review

Cancer Chemoprevention by Phytochemicals: Nature's Healing Touch

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Academic Editor: Santosh K. Katiyar

Received: 24 January 2017; Accepted: 28 February 2017; Published: 3 March 2017

Abstract: Phytochemicals are an important part of traditional medicine and have been investigated in detail for possible inclusion in modern medicine as well. These compounds often serve as the backbone for the synthesis of novel therapeutic agents. For many years, phytochemicals have demonstrated encouraging activity against various human cancer models in pre-clinical assays. Here, we discuss select phytochemicals—curcumin, epigallocatechin-3-gallate (EGCG), resveratrol, plumbagin and honokiol—in the context of their reported effects on the processes of inflammation and oxidative stress, which play a key role in tumorigenesis. We also discuss the emerging evidence on modulation of tumor microenvironment by these phytochemicals which can possibly define their cancer-specific action. Finally, we provide recent updates on how low bioavailability, a major concern with phytochemicals, is being circumvented and the general efficacy being improved, by synthesis of novel chemical analogs and nanoformulations.

Keywords: phytochemicals; cancer chemoprevention; tumor microenvironment; inflammation; pro-oxidant; nanotechnology

1. Introduction

Cancer is currently the second leading cause of death worldwide and a major health problem throughout the world. It is estimated that in 2017, the United States alone will have 1,688,780 new cancer diagnoses and 600,920 cancer-related deaths [1]. While significant progress has been made to improve diagnosis and surveillance, this has not helped much to improve the overall cancer survival rates. This had led to a surge in molecular targeted therapies to develop better clinical outcomes for cancer patients [2]. Unfortunately, these strategies have also not provided substantial improvement due to the development of resistance against therapies [3], reviving an interest in the prospects of phytochemicals, natural anticancer agents from plants, due to the multitude of effects of these agents on diverse molecular signaling pathways, with no or minimal toxicity in normal cells [4].

It is believed that the number of new cancer cases can be reduced and many cancer-related deaths can be prevented. The studies focused on 'cancer prevention' are a step in this direction. The overall aims of cancer prevention are broad. The *primary aim* is to completely prevent or at least delay the onset of cancer through maintenance of healthy lifestyle, avoidance of exposure to toxicants/carcinogens, and dietary consumption of chemopreventive agents and drugs. The *secondary aim* depends on the early detection of cancer in the precancerous or early stage tumors, thereby helping in the better management

and treatment of these tumors, and the *tertiary aim* of cancer prevention involves reducing the risk of metastases, development of secondary tumors and recurrence, using preventive agents. Natural products (from botanicals, herbs, etc.) as well as minerals and vitamins have been demonstrated to affect all three areas of cancer prevention [5,6]. Among natural products, phytochemicals represent the class of compounds that have been extensively studied for their biological effects.

Consumption of fruits and herbal medicines in the diet is a convenient and effective method of administering phytochemicals in a cost-effective manner [7,8]. Overall, at least 20% of all cancers can be prevented by consumption of diets rich in vegetables and fruits (>400 g/day) [9]. According to an analysis, of all the 175 small molecules approved for cancer therapy from 1940s to the year 2014, 85 (49%) were natural products or directly derived therefrom [4]. Phytochemicals continue to enter clinical trials or provide leads for the synthesis of semi-synthetic medicinal agents. However, the laboratory success of phytochemicals has not been reproduced in the clinic. This is partly due to the inherent differences between *in vitro* laboratory experiments and the human physiological conditions. As with other drugs, improvements in formulation of compounds with potential anticancer properties are being made for better therapeutic outcomes. In this article, we briefly discuss the mechanism of action of phytochemicals and, instead of touching upon the classical activities such as induction of apoptosis/cell cycle arrest, we discuss the effect of phytochemicals on reactive oxygen species (ROS) production and the tumor microenvironment (TME), along with updates on current studies to improve the efficacy of these compounds.

2. Preventive and Therapeutic Mechanisms of Phytochemicals

The proposed mechanisms by which vegetables and fruits affect human cancers are multiple and complex. Various stages of carcinogenesis may be inhibited, and various *in vitro* or *in vivo* systems are used to model these inhibitory effects in preclinical studies. Therefore, characterizing the active chemical components of these plant products and accumulation of compelling *in vitro* and animal study data prior to clinical studies is necessary. Phytochemicals, due to their dietary origin, are presumed safer and are better tolerated with relatively low toxicity. For the ease of discussion and to keep the discussion focused, we have chosen five representative phytochemicals, *viz.* curcumin, epigallocatechin-3-gallate (EGCG), resveratrol, plumbagin and honokiol. Chemical structures of these phytochemicals are provided in Figure 1.


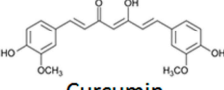

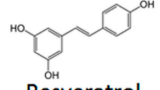



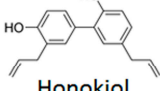


Source	Phytochemical
 Turmeric	 Curcumin
 Grapes	 Resveratrol
 Tea	 EGCG
 Magnolia	 Honokiol
 Pumblago	 Plumbagin

Figure 1. Phytochemicals and their sources. EGCG: Epigallocatechin gallate.

2.1. Modulation of Oxidative Stress

Healthy cells maintain an intricate balance of redox homeostasis wherein the levels of ROS and reactive nitrogen species (RNS) are fine-tuned by the antioxidant defense system [10]. ROS/RNS are by-products of normal cell metabolism with physiological roles at moderate and low concentrations [10]. Oxidative stress is induced as a result of imbalance in the redox status of the cells, and has been suggested to be responsible for the pathophysiology of several diseases, including cancer. In cancer, oxidative stress by physical and chemical agents, inflammation and infection can give rise to direct DNA damage inducing tumorigenesis [11]. Oxidative stress also alters protein conformation and function, thus affecting regular functions of affected proteins. Phytochemicals are generally known for their antioxidant activity and have been demonstrated to counteract the damaging effects of oxidation *in vitro* by a direct quenching of ROS. In addition, phytochemicals also upregulate the expression of genes that detoxify reactive species, metabolize toxic compounds, and maintain cellular homeostasis.

The ability of phytochemicals to inhibit chemically-induced carcinogenesis in mice models has been a cornerstone for their chemopreventive property. A delay in tumor promotion has been shown, upon concurrent topical application of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and phenolic compounds such as caffeic acid, chlorogenic acid, curcumin and ferulic acid [12], or resveratrol and ursolic acid [13]. TPA is a commonly used phorbol diester, a known tumor promoter, employed to over-activate the PKC signaling, and is a potent generator of superoxide anions [14]. Thus, the ability of phytochemicals to inhibit/delay the progression of TPA-induced carcinogenesis is indicative of their antioxidant effects. Plumbagin [15] and honokiol [16] have also been reported to inhibit TPA-induced effects. In addition, the promotion and progression of 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis in rats was inhibited by these polyphenols when administered in the diet [17]. 4-NQO is a carcinogenic agent that introduces DNA damage through the production of ROS [18]. Curcumin, the most bioactive constituent of turmeric and an integral part of the Indian diet, inhibits diethylnitrosamine (DEN)-induced hepatocarcinogenesis in mice at a concentration of 0.2% in the diet [19]. DEN specifically induces carcinogenesis of the gastrointestinal tract, especially liver, through the downregulation of ROS-detoxifying enzymes [20]. Green tea and black tea constituents have also demonstrated potential inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-treated UVB-induced skin carcinogenesis [21]. Administration of decaffeinated green or black tea to mice has been reported to significantly reduce 4-(methylnitrosamine)-1-(3-pyridyl)-1 butanone-induced tumor formation in mice [22].

2.2. Inhibition of Inflammation

The persistent inflammation and inflammatory mechanisms have been implicated as the basis of several diseases, such as chronic conditions of old age [23]. Studies have also provided significant evidence to demonstrate a positive relation between inflammation and cancer [24,25]. Chronic inflammatory states are triggered by multiple factors such as microbial infections, obesity, autoimmune diseases, etc. [26]. Underlying infections or inflammatory responses have been linked to nearly 15%–20% of cancer-associated deaths [27]. A number of phytochemicals have been suggested to interfere with inflammation-related pathways, partially explaining their anti-cancer potential [28] (Table 1). Curcumin is a well-known anti-inflammatory agent [29]. Its effect on inflammation is mediated by multiple mechanisms, such as transforming growth factor beta1 (TGF- β 1) up-regulation and down-regulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2) [30], as well as by modulation of toll-like receptors (TLR)/interleukin-1 receptor (IL-1R) pathway [31]. Resveratrol, another known anti-cancer agent [32,33], also works as an anti-inflammatory agent [34]. It inhibits the production of pro-inflammatory cytokines [interleukin (IL)-6/8 and tumor necrosis factor-alpha (TNF- α)] and pro-inflammatory miR-155, while also inducing the anti-inflammatory cytokines and miR-663 [35]. Resveratrol has also been shown to interfere with pro-inflammatory events triggered by IL1- β [36].

Table 1. Inflammation-influencing signaling factors/pathways modulated by phytochemicals.

Signaling Factor/Pathway	Phytochemical	Reference
COX2	Curcumin	[30]
IL-1 β	Resveratrol	[36]
IL-6	Resveratrol	[35]
IL-8	Resveratrol	[35]
iNOS	Curcumin	[30]
TLR/IL-1R	Curcumin	[31]
Keap1/Nrf2	Curcumin	[30]
	EGCG	[37,38]
	Honokiol	[39]
	Plumbagin	[40]
NF- κ B	Resveratrol	[41]
	Curcumin	[42]
	EGCG	[43,44]
	Honokiol	[45,46]
	Plumbagin	[47]
	Resveratrol	[48]

A number of signaling pathways play a critical role in inflammation, and often connect inflammation with cancer onset and progression. Signaling through nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is one well studied pathway that links inflammation with cancer [49]. It also happens to be the pathway that has been investigated in detail, with respect to the anticancer effects of phytochemicals [45,50–52]. Almost all phytochemicals have been shown to affect NF- κ B signaling, including curcumin, resveratrol, EGCG, plumbagin and honokiol [42,44–48,53]. The Kelch-like erythroid cell-derived protein with Cap'n'collar homology-associated protein (Keap1)/NF-E2 p45-related factor 2 (Nrf2) pathway is another pathway that regulates inflammation-related gene expression [54]. Nrf2 coordinates antioxidant response to several stimuli, thereby preventing oxidative damage and onset of inflammation-responsive diseases, including cancer. Keap1, under normal conditions, keeps Nrf2 sequestered in the cytoplasm thus preventing Nrf2 from discharging its antioxidant functions. It is therefore proposed that targeting of Keap1 by phytochemicals can favorably induce the antioxidant activity of Nrf2. Indeed, several phytochemicals are well known to target Keap1/Nrf2 pathway [30,37,39–41,55].

2.3. Prooxidant Activity

While antioxidant activity of phytochemicals has traditionally been at the forefront of investigations into their putative anticancer action, interestingly, many of these agents also exhibit prooxidant action, particularly in the presence of transition metal ions, especially copper [33,56,57]. There seems to be enough evidence to support phytochemicals-mediated production of ROS, a prooxidant action that is responsible for their ability to induce apoptosis in cancer cells [58,59]. Several phytochemicals that are antioxidants at some concentrations become prooxidants at other concentrations. The relevance of copper in the prooxidant action of phytochemicals stems from the observation that preneoplastic and neoplastic cells have elevated copper levels, compared to normal cells [60]. Such cancer cells with endogenously elevated copper levels are much more sensitive to electron transfer, and generation of ROS, presumably through redox recycling of copper ions [32,56]. Therefore, the prooxidant action of phytochemicals, in the presence of redox active transition ions, represents an important pathway through which transformed cells are selectively targeted by phytochemicals while normal cells survive. Such prooxidant action has been demonstrated for many phytochemicals, including curcumin [61,62], EGCG [59], plumbagin [63] and resveratrol [32]. Copper is not the only metal ion with associated prooxidant activity. Iron [64] and zinc ions [65] have also been reported to generate ROS leading to prooxidant activity. Interestingly, the anticancer activity

of vitamin C [66,67] has also been reported to involve prooxidant production of ROS. Further, a role of vitamin C in Fenton reaction type production of ROS, involving redox recycling on iron ions, is well known [68]. An investigation into prooxidant activity of known antioxidants and vitamins reported prooxidant potential of vitamins A and C in synergy with iron and copper ions, with combination of vitamin C and copper being the most effective [69]. Based on these evidences, it is conceivable that the prooxidant mechanism of induction of apoptosis better explains the anticancer effects of phytochemicals, through generation of ROS close to the DNA. It also helps explain how anticancer agents with diverse chemical structures function similarly, and exhibit preferential cytotoxicity against cancer cells.

2.4. Modulation of Tumor Metabolism

Metabolism in tumor cells is intricately connected with ROS production [70]. Cancer cells extensively alter their metabolic activity to meet the growing needs associated with survival and growth [71]. The two most important metabolites supporting tumor growth are glucose and glutamine [72]. Breakdown of glucose supports energy demand and the generation of biosynthetic metabolites for the growth of cancer cells. In addition, glutamine, the most abundant amino acid in human plasma, not only contributes to the energy pool, but also provides nitrogen for the biosynthesis of nitrogen-containing compounds. Thus, targeting the altered tumor cell metabolism can yield therapeutic outcomes.

A number of studies have now identified the regulation of glucose and glutamine metabolism by phytochemicals through different mechanisms [73,74]. Phytochemicals have been observed to directly inhibit the basal transport of glucose in cancer cells to improve their response to chemotherapy [75]. Curcumin, in addition to glucose uptake, has been shown to alter glutathione as well as lipid metabolism in association with docetaxel [76]. The ability of curcumin to interfere with glucose transport can be explained by its direct binding [77] and inhibition of glucose transporter 1 (GLUT1) [78]. Similar to curcumin, resveratrol [79] and plumbagin [80] can also down-regulate GLUT1. As a proof that glucose metabolism can be effectively targeted in cancer cells, particularly in the cancer cells with metastatic mesenchymal phenotype, glucose-coated magnetic nanoparticles were observed to be preferentially taken up by mesenchymal cells, as opposed to epithelial cells [81]. Blocking of GLUT1 affected the uptake of nanoparticles, suggesting an important role of glucose shell on the nanoparticles. In addition to curcumin [82,83] and resveratrol [83,84], EGCG [85,86], plumbagin [87] and honokiol [88] have also been reported to alter glucose metabolism leading to anti-cancer effects. Given the relevance of glutamine metabolism in cancer cells, phytochemicals have also been tested for their ability to modulate glutamine metabolism. It was reported that resveratrol-induced cell death in castration-resistant C4-2 prostate cancer cells depends on glutamine metabolism [89]. Further, curcumin's cytotoxicity against colorectal cancer stem cells was suggested to involve blocking of glutamine's entry into the cells through coupling of curcumin to the CD44 receptors [90]. Thus, there is evidence in literature to support an effect of phytochemicals on glucose and glutamine metabolism as a mechanism for their anti-tumor properties.

The predominance of aerobic glycolysis in cancer cells, the 'Warburg effect [91]' has generated a lot of attention in last several decades. Interestingly, phytochemicals have been shown to reverse this phenomenon. Curcumin could reverse inflammatory TNF- α mediated Warburg effect in breast cancer cells [92]. Resveratrol was recently shown to partially reverse Warburg effect resulting in increased cell death through increased oxygen consumption, hyperpolarization of mitochondrial membrane and ROS generation [93]. While the contribution of 'Warburg effect' to tumorigenesis has been challenged in recent years [94], particularly with the realization that a number of tumor cells have functional mitochondria, the overall role of altered metabolism in tumor cells still remains an attractive target for therapy [95]. With multi-targeted effects against different metabolic pathways, phytochemicals are prime candidates for further testing in clinical settings.

3. Modulation of Tumor Microenvironment

The tumor microenvironment (TME) refers to the immediate vicinity of tumor cells that is populated by many different types of cells/factors: immune cells, fibroblasts, cytokines, blood vessels, etc. The dynamic interactions between several components within the TME are now considered drivers of cancer progression [96]. The bi-directional talk between tumor cells and the surroundings in the TME facilitates their proliferation, invasion and metastasis, in addition to bestowing upon them the ability to evade therapeutic insults. In view of the important role that the TME plays in tumor progression, it is critical for any putative therapy to be able to modulate the TME favorably, countering the many advantages that the TME confers to the tumor cells. There are reports documenting the effects of phytochemicals on the TME as basis of their anti-cancer activity [97,98].

In pancreatic cancer the TME is particularly marked by severe hypoxia, which, in turn, triggers the activation of hedgehog (Hh) signaling [99,100]. The cross-talk between tumor cells and the surrounding stroma in the hypoxic TME has a profound dependence on Hh signaling [100] making Hh signaling an attractive target for therapy. A recent report has documented the inhibitory action of curcumin against Hh signaling in hypoxic pancreatic cancer cells Panc-1 TME [101]. In addition to its action against Hh signaling, curcumin was also demonstrated to reverse hypoxia-induced epithelial to mesenchymal transition (EMT). Resveratrol is also a potent inhibitor of Hh signaling, as revealed by its action in hypoxic TME of pancreatic cancer cells BxPC-3 and Panc-1, through a mechanism that involved suppression of ROS [102]. Similar to these effects of curcumin and resveratrol, our own investigations have revealed an effect of honokiol against Hh signaling in pancreatic cancer TME [103]. In addition to Hh signaling, we found a potent effect of honokiol against C-X-C chemokine receptor type 4 (CXCR4), another important factor that mediates tumor-stromal cross-talk. Further, EGCG can decrease hypoxia in non-small cell lung cancer (NSCLC) A549 cells through a rebalance of angiopoietins, resulting in sensitization of these cells to cisplatin [104].

In addition to induction of EMT, there is also evidence for enrichment of cancer stem cells (CSCs) in the TME, which can be effectively targeted by curcumin [105]. Not just in a pancreatic cancer model, CSCs are also enriched in the TME of colorectal cancer as well, where curcumin is able to interfere with the cross-talk between CSCs and stromal fibroblasts, resulting in reversal of EMT and the associated metastasis [106]. In the colorectal TME, the therapeutic potential of curcumin is underlined by its ability to potentiate 5-FU activity [106,107]. The same research group has reported a very similar action of resveratrol as well [108] which also involves potentiation of 5-FU activity in a 3D-alginate microenvironment, through reversal of EMT and inhibition of NF- κ B signaling.

There is also evidence for immunomodulatory potential of phytochemicals within the TME. For example, curcumin, when delivered as polyethylene glycol (PEG) conjugate along with Trp2 peptide vaccine, resulted in reduced IL-6 levels and down-regulation of immunosuppressive factors (regulatory T cells, myeloid-derived suppressor cells) in a melanoma-bearing mouse model [109]. Resveratrol, however, in a renal cell carcinoma model, could only reduce regulatory T cells, but had no effect on myeloid-derived suppressor cells [110]. Further, COP9 signalosome 5 (CSN5) stabilized programmed cell death-ligand-1 (PD-L1) plays important role in TNF- α -induced cancer immunosuppression in TME, and curcumin can inhibit CSN5, leading to sensitization of cancer cells to immunotherapy [111].

Plumbagin seems to be a promising phytochemical to target bone metastasis of breast cancer [112] because of its ability to target tumor-bone microenvironment [113]. It specifically disrupts association of receptor activator of nuclear factor of κ B (RANK) with TNF receptor-associated factor 6 (TRAF6), thus abrogating mitogen-activated protein kinases (MAPK) and NF- κ B signaling [113]. IL-6 levels can be reduced by EGCG in breast cancer TME, as part of regulation of tumor-associated macrophages (TAMs) [114], and IL-18 can be inhibited by resveratrol in melanoma TME, leading to reduced metastasis [115]. Also, plumbagin has been demonstrated to inhibit the activity of c-MYB [116], an important modulator of tumor-stromal cross-talk and pancreatic cancer signaling [117]. In addition, EGCG has been shown to inhibit prostate cancer-associated myofibroblast differentiation [118]. Thus,

there seems to be ample evidence in support of an action of phytochemicals against various components of the TME (Table 2).

Table 2. Tumor microenvironment components affected by phytochemicals.

TME Component	Phytochemical	Cancer Model	Reference
CSCs	Curcumin	Pancreatic	[105]
		Colorectal	[106]
Hh signaling	Curcumin	Pancreatic	[101]
	Honokiol	Pancreatic	[103]
	Resveratrol	Pancreatic	[102]
CXCR4	Honokiol	Pancreatic	[103]
IL-6	Curcumin	Melanoma	[109]
	Resveratrol	Renal	[110]
	EGCG	Breast	[114]
IL-18	Resveratrol	Melanoma	[115]
Microvasculature	EGCG	NSCLC	[104]
Myofibroblast Differentiation	EGCG	Prostate	[118]
RANK	Plumbagin	Breast	[113]
Regulatory T-cells	Curcumin	Melanoma	[109]
	Resveratrol	Renal	[110]

4. Challenges for Phytochemicals in Cancer Therapy and Emerging Alternatives

Despite many promises and the demonstrated success in *in vitro* and pre-clinical studies, there has been little to no progress in the transition of phytochemicals to the clinic as the first line therapy. The limitations of *in vitro* testing models are well known. A direct exposure of cancer cell lines during *in vitro* testing causes an acute presentation of phytochemicals, inducing significant anticancer and antiproliferative action at concentrations usually not achieved under normal physiological conditions even upon consumption of the pure compound extract. While these *in vitro* studies provide significant insights into the cellular signaling mechanisms, they do not provide information on the effect of test agent on the organism as a whole. However, the obvious practical and ethical limitations of involving human studies without substantial laboratory evidence still makes it mandatory to rely on such *in vitro* models as the first step. Thus, there is a pressing need for *in vitro* and/or preclinical models that can mimic systemic exposure to phytochemicals, with resulting metabolomic and pharmacokinetic changes.

The first and foremost challenge is the problem of bioavailability [119–121]. Since a majority of these phytochemicals are part of normal human diet, they are efficiently metabolized and cleared by body. They do not persist in physiological systems and the therapeutic effects are usually short-lived [119]. The other aspect of using phytochemicals in cancer therapy is the lack of target specificity. While this is viewed by some as a limitation, it is increasingly being realized that such lack of specificity, and the multi-targeted effects of phytochemicals, the ‘pleiotropic’ effects, underline the very essence of these anticancer agents [51,122], particularly in view of the knowledge that when challenged with targeted therapies, tumor cells often activate alternate pathways which results in failure of targeted therapy. Under such circumstances, a multi-targeted therapeutic agent is likely to be a comparatively more effective because of its ability to check the activation of alternate survival pathways.

While the issue of bioavailability cannot be resolved just by increasing the administered dose or the frequency of administration, there are certain alternate ways which are being pursued to circumvent this problem. These include: (a) chemical syntheses of novel analogs of phytochemicals to increase the efficacy and bioavailability; (b) novel formulations to selectively and more effectively deliver the phytochemicals to their intended target organs; and (c) formulation of novel delivery systems that modulate the pharmacokinetics of the anticancer agent. In this section, we will highlight some recent

advancements in these fields, particularly related to the phytochemicals discussed so far, to provide an overview of the broader research field.

4.1. Synthesis of Chemical Analogs

Curcumin is an exemplary phytochemical that has shown lots of potential in pre-clinical studies, only to fail in clinical settings. It also remains one of the most extensively modified phytochemicals, with so many reported analogs that it will be beyond the scope of this article to comment on every single curcumin analog that has been tested and reported for its enhanced anticancer activity. Just to put this into perspective, some curcumin analogs (Table 3) reported within the past two years include C-150 (inhibits NF- κ B in glioblastoma cells [123]), Da0324 (inhibits NF- κ B in gastric cancer cells [124]), 2,2'-fluoromonocarbonyl analog (modulates ROS in lung cancer cells [125]), A17 (induces ER stress in lung cancer cells [126]), MC37 (induces cell cycle arrest in colorectal cancer cells [127]), HO-3867 (STAT3 inhibitor in pancreatic cancer cells [128]), BDMC-A (inhibits NF- κ B in breast cancer cells [129]), GO-Y078 (inhibits invasion of endothelial cells [130]), DM-1 (induces apoptosis in melanoma cells [131]), FLLL12 (induces apoptosis in lung cancer cells [132]), BHBA (activates Nrf2 in lung cancer models [133]) and L49H37 (induces apoptosis in pancreatic stellate cells [134]). Other than these, there are a few other curcumin analogs that have been investigated in comparatively more detail. These include difluorinated curcumin (CDF, inhibits MMP2 in lung cancer cells [135], restores PTEN in colorectal cancer cells [136] and inhibits cancer stem cells in pancreatic and colorectal cancer models [137,138]), WZ35 (modulates ROS in gastric cancer [139,140] and prostate cancer cells [141]) and EF24 (inhibits src phosphorylation in hepatocellular carcinoma cells [142], suppresses EMT through miR-33b in melanoma cells [143], induces ROS-dependent apoptosis in colorectal cancer cells [144], suppresses NF- κ B in cholangiocarcinoma [145] and induces apoptosis in pancreatic cancer cells [146]).

Resveratrol has also generated considerable interest because of its anti-cancer potential, and consequently, a number of groups have synthesized analogs of resveratrol with an aim to enhance its efficacy [147–153] (Table 3). The DMU-212 analog of resveratrol has not just been reported to exhibit enhanced anti-tumor effects, but, interestingly, its mechanism of action has been reported to be distinct from the parent compound, resveratrol [154]. DMU-212 has also been suggested to suppress pro-inflammatory factors, especially NF- κ B [155], a mechanism which happens to be similar to resveratrol. The interest in DMU-212 has led to synthesis of its own analogs that have been tested against a panel of 60 human cancer cell lines with mixed results [156]. HS-1793 is another synthesized analog of resveratrol with multiple reported properties ([157–162]).

In contrast to curcumin and resveratrol, only a handful of studies have reported synthesis of EGCG analogs. The D-ring analog of EGCG was one of the first to be made, and it was observed to target VEGF in breast cancer cells [163]. Such VEGF-targeting activity of another EGCG analog, a methylated one, has also been reported [164]. Other analogs of EGCG include the fluoro-substituted analogs that have shown promise in inhibiting proteasomal activity of leukemia [165] and breast cancer cells [166,167]. There is evidence for synthesis of novel plumbagin analog [168] but it has not yet been tested in pre-clinical cancer models. For the phytochemical honokiol, a dichloroacetate ester has been synthesized which inhibits androgen receptor signaling in prostate cancer cells [169] and re-sensitizes vemurafenib-resistant melanomas [170].

Table 3. Chemical analogues of phytochemicals and their reported effects.

Phytochemical	Analogue	Reported Activity	Reference
Curcumin	C-150	Inhibits NF- κ B	[123]
	Da0324	Inhibits NF- κ B	[124]
	2-2'-fluorine mono-carbonyl analog	Modulates ROS	[125]
	A17	Induces ER stress	[126]
	MC37	Induces cell cycle arrest	[127]
	HO-3867	Inhibits STAT3	[128]
	BDMC-A	Inhibits NF- κ B	[129]
	GO-Y078	Inhibits invasion of endothelial cells	[130]
	DM-1	Induces apoptosis	[131]
	FLLL12	Induces apoptosis	[132]
	BHBA	Activates nrf2	[133]
	L49H37	Induces apoptosis in pancreatic stellate cells	[134]
	CDF	Multiple pathways affected	[135–138]
	WZ35	Modulates ROS	[139–141]
	EF24	Multiple pathways affected	[142–146]
EGCG	D-ring analog	Targets VEGF	[163]
	Methylated analog	Targets VEGF	[164]
	Fluoro-substituted	Inhibits proteasomal activity	[165,166]
Honokiol	Dichloroacetate ester	Inhibits AR, chemosensitizes	[169,170]
Plumbagin	Isoniazid analog	Multiple pathways affected	[168]
Resveratrol	DMU-212	Inhibits NF- κ B	[155]
	HS-1793	Multiple pathways affected	[157–162]

4.2. Novel Formulations

Nanotechnology has expanded the horizon of anti-cancer therapy in general [171], and the activity of several phytochemicals in particular [172]. Due to the overwhelming interest in curcumin in pre-clinical studies, a number of reports are available on the nanoformulations of curcumin as well as its analogs, all with the premises of recapitulating the pre-clinical success of curcumin in clinical settings [173–175]. Again, similar to the sub-section above, we will list here reports from only last two years, to keep the discussion meaningful.

Poly(D,L-lactic acid)-glycerol (PDLLA)-G-based curcumin nanoparticles have been reported to be as effective as free curcumin in in vitro assays, and their in vivo clearance was comparatively lower [176]. Such delayed clearance of curcumin nanoparticles can result in enhanced in vivo activity, as confirmed in a cervical cancer model [177]. Curcumin-loaded monomethoxy polyethylene glycol (mPEG)- poly(ϵ -caprolactone) (PCL) micelles showed increased plasma retention [178] while curcumin's oligosaccharide of hyaluronan conjugate nanoparticle has been shown to be more stable and less toxic, relative to curcumin [179]. Similarly, curcumin-cyclodextrin/cellulose nanocrystal complexes kill colorectal and prostate cancer cells at IC₅₀ values lower than curcumin [180]. Poly(lactic-co-glycolic acid) (PLGA)-curcumin particles have been demonstrated to deliver active curcumin directly to the cells' cytosolic compartment, resulting in enhanced therapeutic activity [181]. This is similar to amphiphilic polyaspartamide polyelectrolytes that increase cellular uptake of curcumin [182]. Targeted delivery to prostate cancer tissue has been reported via lipid-polymer hybrid nanoparticles that encapsulate curcumin as well as docetaxel [183]. Conjugating curcumin on the hydrophilic terminals of pluronic F68 chains through *cis*-aconitic anhydride linkers is proposed to improve delivery of curcumin [184] while curcumin micelles have been shown to overcome multidrug resistance [185].

Not only the parent compound curcumin, there has been interest in nanoformulation of curcumin analogs as well. Nanomicelles of curcumin analog curcumin difluorinated (CDF) with amphiphilic styrene-maleic acid copolymer (SMA) increased the solubility by 5%–15% and exhibited enhanced antitumor effect [186] while liposome encapsulation of CDF sensitized the cisplatin-resistant head and neck cancer stem cells [187]. The hyaluronic acid-SMA-CDF micelles were reported to specifically

target pancreatic cancer stem cells [188], similar to hyaluronic acid-PAMAM dendrimer formulation of CDF [189]. Another curcumin analog, EF24, has also been nanoencapsulated in pegylated liposomes resulting in enhanced anticancer effects against pancreatic cancer cells *in vitro* and in a pancreatic xenograft model [190]. Pegylated curcumin nanoparticles have also shown promise in real-time monitoring of drug release [191]. Another concept of embedding phytochemicals in the biopolymer PCL to continuously deliver the small molecule for extending periods of time has also been demonstrated for the delivery of curcuminoids [192]. The PCL-implant leads to the release of the agent in a two-step process. An initial burst releases the drug present on the surface into circulation. This initial burst-release can be controlled by coating an empty polymer; followed by the slow-steady release of the agent present in the matrix. Moreover, the site of implantation is hypothesized to increase drug accumulation at the site and a controlled release [192].

There are reports on nanoformulations of resveratrol as well. Resveratrol's PCL and PLGA-PEG-COOH nanoparticles have been shown to improve release of resveratrol in hypoxia-relevant acidic TME, with efficient take up by the prostate cancer cells [193]. One of the objectives of nanoformulations is to reduce effective toxicity and this was reported in case of lipid nanoparticles of resveratrol when tested in lung cancer cells exposed to cigarette smoke condensate [194]. Another objective is to increase solubility and this has been demonstrated by nanocomplexation of resveratrol with soy protein isolate [195]. The gold nanoparticles of resveratrol have been shown to be biologically active with activity against multiple signaling cascades [196].

Efforts have also been made to formulate EGCG nanoparticles. In an early report on the topic [197], EGCG was conjugated with FITC, and the complex could enter the cytoplasm as well as the nucleus. In another report, gelatinized EGCG was observed to retain its biological activity against breast cancer cells, and was as potent as EGCG [198]. Similarly, PLA-PEG-EGCG nanoparticles also retained their activity, and even reported a 10-fold dose advantage in *in vitro* as well as in *in vivo* assays [199,200]. While free EGCG was completely degraded in 4 hours, the EGCG nanoparticles had a significantly longer half-life [201,202]. Co-encapsulation of EGCG with paclitaxel within a targeted PLGA-casein nanoparticle has been reported to re-sensitize paclitaxel-resistant breast cancer cells [203].

For the phytochemical plumbagin, silver nanoparticles were synthesized to overcome the lack of sensitivity and selectivity towards cancer cells, and such formulation reduced the effective concentration required to induce apoptosis to half of the free compound [204] in addition to enhancing the cellular uptake [205]. The reduced toxicity in normal cells, and better bioavailability of nanoformulated plumbagin has been reported by another independent group as well [206]. There has been some interest in nanoformulations of honokiol as well. The PCL-PEG-PCL-honokiol nanoparticles were shown to release honokiol over extended time [207]. The MPEG-PLA-encapsulation also had similar effect on honokiol release [208] and, moreover, this formulation also made honokiol injectable [209]. The stability of honokiol was remarkably improved by MPEG, to the extent that whereas it took 2 h to release 20% honokiol from the formulation in plasma, it took more than 200 h to release the same amount of honokiol in PBS [210].

Recently nanoformulations of bioactive lipids have been described. These lipids, such as the fatty acid docosahexaenoic acid, have been observed to demonstrate potent anticancer properties against a variety of cancer types such as breast cancer, ovarian cancer, glioblastomas, etc. [211–214]. The nanocapsules, comprising shells of bioactive lipids, are able to deliver drugs and other biologically sensitive molecules to specific cells or organs, thus enhancing the potency and cancer therapeutic potential [211,215]. This represents a promising area of novel nanoformulation where some progress has been made in recent years [216,217]. As a whole, the developments in the field of nanotechnology have raised the hopes of using phytochemicals as chemotherapeutic anticancer agents in near future.

5. Conclusions and Perspectives

The action of phytochemicals against cancer cells, via inhibition of proliferation, invasion, angiogenesis and metastasis, is well documented. A number of derived analogs have also been

tested in different pre-clinical models. New investigations into phytochemicals' mechanism of action have suggested that many of the observed pre-clinical effects of phytochemicals can possibly be explained by their ability to regulate TME (Figure 2). The importance of TME in cancer progression is well recognized. However, the studies involving regulation of TME and its various components can get quite challenging, with unavailability of assay systems that can accurately mimic the complexities of TME. This is specially challenging for studies with phytochemicals, where often there is a need for quick and efficient screening of several novel phytochemicals or their synthetic analogs. As a step in this direction, a 3-dimensional microfluidic device has been reported, with a capability of assaying multiple compounds simultaneously for their anti-metastatic potential [218]. The co-culture of endothelial and cancer cells in this device, and their 3-dimensional morphology, better represents TME. Such advancements in experimental capabilities provide hope for possible use of phytochemicals in clinics in near future.

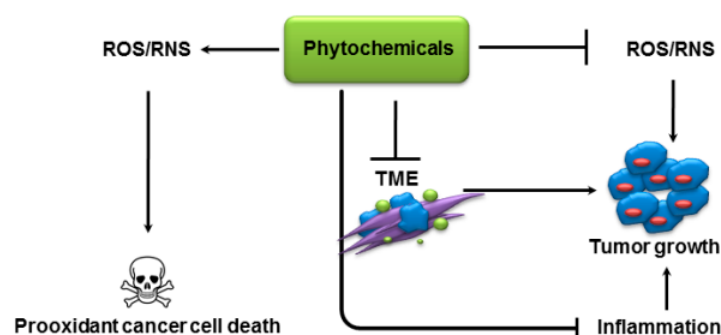


Figure 2. Role of phytochemicals in human malignancies. Phytochemicals potentially scavenge reactive oxygen species (ROS) or upregulate anti-oxidant signalling to combat ROS generation in cancer cells to inhibit growth. There are also context dependent evidences which advocate the prooxidant cell death inducing behaviour of phytochemicals. Phytochemicals have also been shown to inhibit inflammation via targeting NF- κ B pathway. Tumor micro environment (TME) plays a vital role in many solid tumors pathogenesis, and phytochemicals have been shown to target both tumor and stromal compartments.

Nanotechnology has been used to enhance chemoprevention outcome and the resulting 'nanochemoprevention' [219] seems to be relevant to enhancing the efficacy of phytochemicals [201]. However, nanoparticles themselves are often toxic, and often not suitable for oral consumption. This has led to novel ways to prepare nanoparticles, like for example chitosan-based nanoparticles [220]. Further, the individual chemicals used in nanoformulations are not alike, and differ in their ability to reinforce the intended biological effect. For example, silver-based nanoparticles are superior than zinc and titanium-based nanoparticles in protection against UV-induced DNA damage [221]. Thus, the promises of nanotechnology rest on fine tuning and careful characterization of the underlying materials and methods. Interestingly, the concept of 'green' nanotechnology, using biodegradable and eco-friendly materials, is gaining ground [222,223]. The combination of green nanotechnology and the natural phytochemicals sounds promising. By producing phytochemicals, nature has provided a healing touch to the very problems it frequently presents, including diseases such as cancer. Persistent and innovative methods to improve the anti-cancer efficacy of phytochemicals should not halt, until the pre-clinical success of these agents is realized in clinics.

Acknowledgments: This work was supported in part by NIH grants to A.P.S. (R01CA175772 and U01CA185490) and S.S. (R01CA204801 and R03CA186223). A.P.S. and S.S. also received funding and resource support from the University of South Alabama Mitchell Cancer Institute.

Author Contributions: H.Z., S.A., A.A. and A.P.S. conceived this work; H.Z., A.A., M.A.K. and G.K.P. helped in the writing and proof reading of article; S.S. and A.P.S. provided resources, infrastructure and oversight.

Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study or the writing of manuscript.

Abbreviations

The following abbreviations are used in this manuscript:

4-NQO	4-nitroquinoline-1-oxide
5-FU	5-FluoroUracil
CDF	Curcumin Difluorinated
COX2	CycloOxygenase2
CSC	Cancer Stem Cells
CSN5	COP9 Signalosome 5
CXCR4	C-X-C chemokine receptor type 4
DEN	DiEthylNitrosamine
DMBA	7,12-Dimethylbenz[a]anthracene
EGCG	EpiGalloCatechin Gallate
EMT	Epithelial-Mesenchymal Transition
FITC	Fluorescein IsoThioCyanate
Hh	Hedgehog
IL	InterLeukin
iNOS	inducible Nitric Oxide Synthase
Keap1	Kelch-like erythroid cell-derived protein with Cap'n'collar homology-associated protein
MAPK	Mitogen-Activated Protein Kinases
MMP2	Matrix MetalloProteinase2
MPEG	Mono methoxy Poly Ethylene Glycol
NF- κ B	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
Nrf2	NF-E2 p45-related factor 2
NSCLC	Non-Small Cell Lung Cancer
PCL	poly (ϵ -CaproLactone)
PD-L1	Programmed cell Death-Ligand-1
PDLLA-G	Poly(D,L-lactic acid)-glycerol
PEG	PolyEthylene Glycol
PKC	Protein Kinase C
PLA	Poly Lactic Acid
PLGA	Poly(Lactic-co-Glycolic Acid)
PTEN	Phosphatase and Tensin Homolog
RANK	Receptor Activator of Nuclear Factor of κ B
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SMA	Styrene-Maleic Acid copolymer
TGF- β	Transforming Growth Factor beta1
TLR	Toll-Like Receptors
TME	Tumor MicroEnvironment
TNF- α	Tumor Necrosis Factor-Alpha
TPA	12-O-tetradecanoylphorbol-13-acetate
TRAF6	TNF Receptor Associated Factor 6
UV	UltraViolet
VEGF	Vascular Endothelial Growth Factor

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