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# Nutraceutical use in late-stage cancer

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## Abstract

Access to a wealth of information on the internet has led many cancer patients to use complementary methods as an adjunct to traditional therapy for cancer, with, and more often, without informing their primary caregiver. Of the common complementary modalities, the use of dietary supplements appears to be highly prevalent in patients in active treatment for cancer, and later in cancer survivors. Emerging research suggests that some plant-based agents may, indeed, impact late-stage cancer, influencing molecular processes corrupted by tumor cells to evade detection, expand clonally, and invade surrounding tissues. The intent of this article is to review some of the current science underpinning the use of nutraceuticals in the latter stages of cancer.

### Keywords

Dietary supplements; Nutraceuticals; Cancer treatment; Metastasis

## 1 Use of nutraceuticals and nutritional challenges in the late-stage cancer patient

There is little doubt that the diagnosis of cancer, its treatment, and surviving cancer present a challenge to the cancer patient. Current treatment for cancer including chemotherapy, radiotherapy, and biologically based therapies each contribute unintended side effects


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compromising the maintenance of health and nutritional well-being. Among these complications are nausea and vomiting, changes in taste and smell, pain and fatigue, and changes in bowel habits [1]. All or some of these symptoms can result in weight loss, dysregulated satiety, and food aversions that can lead to loss of weight, muscle mass, and low energy. In some cases, chemotherapy may actually cause an increase in weight.

As the course of therapy abates, some of these symptoms resolve while others persist, especially prolonged aversion to certain foods due to altered taste and smell and changes in bowel habit. The intent of this review is not to offer dietary advice as reasonable sources of information exist on the topic. The overriding principle seems to maintain healthy and adequate nutritional intake, averting weight loss, but taking advantage of dietary advice that is concordant with that prescribed for the prevention of cancer. A general consensus is to maintain adequate and balanced intake of protein and whole-grain sources of carbohydrates with good amounts of fresh fruit and vegetables [2].

However, to be expedient and to work around certain dietary restrictions and aversions, many cancer patients turn to dietary supplements and nutraceuticals to augment their sense of well-being while undergoing cancer therapy. These patterns often follow into the period of cancer survivorship.

## 2 Uses of dietary supplements and nutraceuticals in the cancer patient

The number of people who have successfully dealt with cancers in the US is increasing constantly, with about 11 million people currently claiming they are “cancer survivors” [3, 4]. In a recent survey of use across 13 countries, it was estimated that 30% of cancer patients employ some type of complementary and alternative medicine practice [5]. Individual studies estimate the use at a much higher prevalence rate of 69% of US patients in one study, 76% of patients in a study of Midwestern cancer patients, and 95% of radiation oncology patients in another study [6–8]. In the latter study, of the 95% of patients using some form of CAM, almost half were taking dietary supplements in the form of multivitamins. It is also believed that about half of the users of CAM modalities, especially those using supplements, do not reveal this information to the primary oncological caregiver [9]. The most common reasons for self-medication with dietary supplements lies in a perceived effort to control the symptoms of cancer, alleviate the unwanted side effects of certain therapies, to prevent future disease, as well as aid in the treatment of current disease. A belief system that use of dietary supplements gives patients a sense of control over their cancer treatment is commonly cited as the raison d’être for use [6]. The possibility always exists for herbal-based dietary supplements (or nutraceuticals) to antagonize therapy, and the most common interactions will be discussed in the following section. However, recent basic research has illuminated the promise for certain natural compounds of phytochemical origin to also have the potential to interfere with the late-stage cancer, and perhaps alter the course of metastatic spread of cancer. This topic will be addressed in the penultimate section of this review.

## 3 Dietary supplements and nutraceuticals—potential interactions with cancer therapies

That certain herbal supplements have the potential to interfere with drug therapy is well known. For example, in addition to warnings about disuse of non-steroidal anti-inflammatory drugs prior to surgery, anti-coagulant properties have also been documented for ingestion of garlic supplements and warfarin interactions have been shown for ginger and gingko [10–12]. Although the data are mixed for the immunomodulatory effects of echineacea and its products in humans, a theoretical interaction could arise in patients who

are undertaking immunotherapy for cancer [13]. Probably the most well-documented drug–herb interaction is the potential for St. John's Wort to induce cytochrome P4503A4, a major cytochrome involved in the metabolic activation of certain cancer drugs [14]. As well, garlic and its constituent organosulfides may interact to suppress the function of cytochrome P4502E1, a pathway of lesser importance in terms of number of human drugs, but the major form involved in the metabolism of the commonly used analgesic, acetaminophen [11].

Antagonism of selective estrogen receptor modifiers such as tamoxifen has been shown for the isoflavones characteristic of soy, and these will be addressed in the individual section on soy.

## 4 Dietary supplements and nutraceuticals—promising research for late-stage cancers

Apart from fundamental basic research investigating mechanisms by which the latter stages of cancer can be inhibited, there are no nutraceuticals that have advanced to the point of clinical trial testing. However, this is a promising area of basic research in cell lines and in animal models. The current status of selected phytochemicals that have undergone some development are surveyed below. The review of these agents is limited to their existing use as nutraceutical supplements.

### 4.1 Chile pepper (*Capsicum* sp.)

The active compound accounting for the pungency of red chilies, capsaicin, is biologically active [15]. Capsaicin *in vitro* retards the proliferation of cancer cells, suppresses the inflammatory response, and may mediate apoptosis through influence on the GSKβ3 component of the beta-catenin pathway, corrupted in many human cancers [16, 17]. Of interest is the finding that oral capsaicin can inhibit the proliferation of human pancreatic cancer grown as xenografts in nude mice [18]. In very different studies, the efficacy of capsaicin as a pain reliever has been offered as a potential treatment of one of the major side effects of chemotherapy or radiotherapy—oral mucositis [19].

### 4.2 Cloves (*Syzygium aromaticum*)

Eugenol (4-allyl-1hydroxy-2-methoxybenzene) is found in oil of cloves, basil, cinnamon, and other aromatic spices [20]. Tumor growth suppressive effects of eugenol were noted in studies of human cancer cell lines and in the MNNG-rat model of gastric cancer [21, 22]. In the latter study, cell proliferation was inhibited via suppression of nuclear factor kappa beta (NFκβ), in keeping with many other nutraceuticals that appear to be both anti-inflammatory and growth inhibitory. More recent studies by the same group in the rat gastric cancer model have amplified the anti-inflammatory effects of eugenol by down-regulating the expression of MMPs, VEGF, TIMP-2, and RECK, all associated with invasion [23].

While there are no known data to suggest that cloves or eugenol antagonize standard cancer therapy, the idea to inhibit VEGF by pharmacological means (*i.e.,* avastin), while showing early promise, may require some rethinking. As in other agents that inhibit VEGF, a combination of a natural VEGF inhibitor with lower doses of pharmacological agents may prove helpful in reducing unwanted side effects of therapeutics.

### 4.3 Ginger (*Zingiber officinale*)

Gingerol (6-gingerol) is one the active compounds in ginger [24]. It also has pronounced anti-inflammatory activity and has been found to have the ability to inhibit invasion, motility, and adhesion in human breast cancer cell lines, human hepatocarcinoma cells, and other cell lines [24–28]. However, one recognized use for ginger lies not in its anticancer

activity, but its ability to offset one of the major side effects of cytotoxic chemotherapy, nausea and vomiting [29]. In a Phase 2 trial conducted in 162 patients receiving cancer chemotherapy, encapsulated ginger did not add to the efficacy of 5-HT3 receptor antagonists and/or aprepitant which all subjects were receiving [30]. Other phase 2/3 trials are underway to further define the use of ginger in this setting.

### 4.4 Fenugreek (*Trigonella foenum-graecum*)

Diosgenin is a steroid saponin found in fenugreek seeds and has been found to be safe at very high doses when tested in rats [31]. It has anti-inflammatory activity, but its cancer preventive attributes have not been fully tested in chemo-prevention animal models. In terms of utility as a factor in mitigating the biology of established tumors, activity has been found in suppressing the proliferation of human myelogenous leukemia cells, colon cancer cell lines, and breast cancer cell lines [32–34]. Diosgenin inhibits NFκβ activity, COX enzymes, and has possible effects on 5-LOX as well, but LOX suppression studies remain to be confirmed [35].

### 4.5 Grape and muscadine (*Vitis vinafera* and *Vitis rotundiflora*)

The table grape of commerce and the muscadine, a wild-grape adapted to the Southeastern US, are sources of proanthocyanadins, but are also found in other red/purple pigmented fruits such as cranberries [36–38]. In keeping with other phytochemicals that might influence the propensity for small clones to metastasize, proanthocyanadins have pronounced anti-tumor activity. Of these diverse compounds, the most well studied is resveratrol [39]. The release of various cytokines, TNFα, iNOS, and down-regulation of COX enzymes have been reported for resveratrol both in cell culture and animal models [40]. Because resveratrol has been found to inhibit both forms of COX, COX-1 and COX-2, its activity has been compared with non-steroidal anti-inflammatory drugs (NSAIDs). NSAID compounds, highly cancer preventive in their own right, have the potential to produce severe side effects, especially those NSAIDS that have mixed COX specificity [41]. This might portend that resveratrol in high doses may have the same profile of unintended side effects. Recently, a clinical trial of resveratrol in patients with multiple myeloma was suspended because of concerns over nephropathy in subjects taking the supplement [42]. The intent of this trial was to determine if resveratrol acts similarly to a new class of therapeutic agents called sirtuins. Whether the kidney damage observed in this trial might be related to its COX-1 interference remains to be clarified.

In spite of this clinical setback, the experimental evidence for resveratrol as a potential inhibitor of late-stage cancer can be attributed to its antiangiogenic effects [43, 44]. Malignant gliomas are a form of brain tumors which are difficult to treat clinically. They are highly vascular in nature, and interventions with resveratrol both in cell culture and *in vivo* have indicated promise for suppressing neovascularization [45]. Further, resveratrol treatment significantly inhibits MMPs involved in invasion and metastasis of glioblastoma cells. Grapes are not the only available source of proanthocyandins. Muscadine grapes, which have a different antioxidant profile from that of the table grape, are relatively new to the nutraceutical market. Cranberries also are rich sources of proanthocyandins [46]. Proanthocyandin-rich extracts of the American cranberry have been found to efficiently suppress MMP-2, MMP-9, and TIMP-2 activity in the DU145 human prostate cancer cell line [47].

### 4.6 Green tea (*Camellia sinensis*) and green tea polyphenols

Aside from the pluripotent effects of green tea polyphenols in an ever increasing list of molecular processes, the ability of green tea constituents to inhibit aspects of neovascularization and angiogenesis is suggestive that they might influence the development

of existing cancers. Of the compounds in green tea, epigallocatechin gallate (EGCG) has been the most thoroughly researched [48–50]. EGCG inhibits the proliferation of many tumor types in culture but has also been shown to inhibit neovascularization promoted by VEGF in colon, breast, and head and neck cancer cell lines [48, 51–54]. Probably influencing VEGF and many other growth factors is the well-known interference of EGCG with aberrant cell signaling pathways, notably, the Akt and ERK 1 and 2 signaling systems [55, 56]. EGCG has been shown to inhibit pathways involving NFκβ, MMPs, and COX-2, all implicated in tumor cell expansion and survival [57, 58]. It remains to be seen whether non-physiological doses of EGCG (*i.e.*, pharmacological doses) could be used to impact angiogenesis and thwart the expansion of incipient metastatic lesions in humans.

A new vista for green tea research and potential use as therapy may result from the ability of EGCG to reactivate tumor suppressor and other regulatory genes by inhibiting DNA methyltransferases or acting as histone deacetylase inhibitors [59, 60]. This is an exciting area of research that may well extend to other nutraceuticals.

At present, there has been little research to support the notion that green tea polyphenols could interfere with cancer therapy. Limited research has bolstered the hypothesis that tea polyphenols could help in the sensitization of chemoresistant cells to therapeutics. And, there is evidence to suggest that these agents could make tumor cells more vulnerable to chemotherapeutics by concomitant targeting of the same cellular processes as a given drug or by generally impacting on aberrant cell signaling and inhibiting proliferation.

### 4.7 Pepper (*Piper nigrum*)

One biologically active principle in black pepper is piperine [61]. Piperine has been widely studied for its ability to offset one common liability in the use of natural products of plant origin as medicinal—they are poorly absorbed. Piperine enhances the uptake and bioavailability of curcumin and tea polyphenols through its modulation of drug metabolism isoforms in the liver [62]. Both the *in vitro* and *in vivo* anticancer efficacy of the commonly used therapeutic, 5-flurouracil, were enhanced in the presence of piplartine, another alkaloid found in *Piper* species [63]. Piperine has been shown to have anticancer activity in a number of tumor models and notably, was found to suppress lung cancer metastases in an animal model [64]. But perhaps the most intriguing activity reported for piperine was a direct effect on the development of breast stem cells, inhibiting mammosphere formation [65]. It remains to be seen whether piperine would also modulate breast cancer stem cell biology.

### 4.8 Soy (*Glycine max*)

Soybeans are a biologically diverse source of anticancer agents. Generally, research has mostly focused on soy isoflavones, the signature flavonoids found in soybeans and in edible soyfoods [66]. Attention has been drawn to the isoflavones in soy due to their ability to modulate the estrogen receptor (ER). ER status is one of three important metrics known to anyone diagnosed with breast cancer, the others being progesterone receptor status and expression of the HER-2/neu oncogene [67]. Of the soy isoflavones, genistein has been widely studied because of potential safety concerns [68]. Certain soy isoflavones can bind to and transactivate ERs. For this reason, the potential could exist, that if soy were consumed in large quantities, compounds such as genistein could have an untoward effect on breast cancers, and feed into the ER+ tumor cells, causing breast cancers to progress [69]. The other concern is that the binding of phytoestrogens to the receptor could offset the therapeutic and preventive effects of SERM drugs and their efficacy, tamoxifen, being an example [70]. While these findings have been demonstrated in animal models for breast cancer, there has not been a randomized, controlled trial on breast cancer recurrence especially in regard to ER status.

The experimental evidence for soy isoflavones in influencing the metastatic process is very mixed, and if anything, supports a possible deleterious outcome. In experimental models, genistein has been shown to increase the propensity for metastatic spread of xenografted human breast cancer in animals, to have both beneficial and harmful effects in prostate cancer metastasis in animals, and to have no effect in enhancing the therapeutic effects of gemcitabine and erlotinib in advanced pancreas cancers [71–73]. Yet, potentially therapeutic effects have been observed for genistein in mouse melanoma models and in bladder cancer [74, 75]. Taken together, the issue of soy use in the cancer patient cannot be resolved at the level of basic research, and caution should be recommended until more definitive conclusions can be reached.

### 4.9 Turmeric (*Curcuma longa*)

The underground rhizome of the turmeric plant has been an essential part of the Indian pantheon of spices for thousands of years [20, 76]. The yellow color of curry powder is due to the fact that commercial turmeric contains 5–6% curcumin, a diferuloylmethane [77]. Curcumin is under intensive investigation because of its known anti-inflammatory activity that could impact on risk for cancer, but in addition for risk of diabetes, obesity, metabolic syndrome, and atheroschlerosis—diseases driven by chronic, unresolved inflammation [78]. Research has shown that curcumin has an effect in modulating the effects of TNF-α and for its ability to suppress a constellation of molecular signals mediated by the nuclear transcription factor, NFκβ. Inhibition of NFκβ can have profound consequences for a tumor cell. Among the proteins modulated by curcumin are: COX-2, VEGF, the chemokines MCP-1 and MCP-4, the interleukins IL-1 and IL-6, and IGF [79–83].

In terms of cancer therapy, there is little to suggest that ingestion of curcumin from turmeric would have adverse effects on cancer drug efficacy, and it is likely, that in keeping with green tea, curcuminoids may aid cancer therapy in the chemosensitization of tumor cells or in co-influencing molecular processes that make tumor cells more amenable to therapy.

## 5 Conclusions and perspective

Clearly, research on phytochemicals and their influence on processes involved in the progression and metastasis of common cancers is lacking. Despite the dearth of experimental data, many cancer patients turn to nutraceuticals from a belief that they will not hurt and possibly benefit their clinical outcome. Caution is paramount when considering certain plant-based supplements as they may antagonize the activity of therapeutic agents, or, alter their metabolism from efficacious forms. Yet, there is promise on the horizon, and as shown in Table 1, there are some molecular targets in common for the natural agents that have inhibited, at least experimentally, some aspects of cancer spread and metastasis. And, as shown in Table 2, some phytochemical nutraceuticals may be generally safe to use during therapy, but this area of research is immature. At best, patients should carefully weigh the potential risks and potential benefits with their caregiver when ingesting nutraceuticals during cancer therapy and in a post-cancer lifestyle.

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## Abbreviations

| | |
|---|---|
| **CAM** | Complementary and alternative medicine |
| **COX** | Cycloxygenase |

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| **DNMT** | DNA methyltransferase |
| **EGFR** | Epidermal growth factor receptor |
| **ER** | Estrogen receptor |
| **IGF** | Insulin-like growth factor |
| **LOX** | Lipoxygenase |
| **MCP** | Monocyte chemoattractant protein |
| **MMP** | Matrix metalloproteinase |
| **RECK** | The reversion-inducing cysteine-rich protein with Kazal motifs |
| **TIMP** | Matrix metalloproteinase tissue inhibitor |
| **VEGF** | Vascular endothelial growth factor |

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**Table 1**

Selected molecular targets for nutraceuticals in late-stage cancer

| Molecular target | Agent identified with inhibition | Reference |
|---|---|---|
| COX-2 | EGCG, curcumin, resveratrol | [40, 57, 58, 81] |
| DNMTs | EGCG | [59] |
| EGFR | Curcumin, resveratrol | [62] |
| HDACs | EGCG | [60] |
| ERs | Genistein | [69] |
| MMPs | Eugenol | [23] |
| NFκβ | Curcumin, diosgenin, EGCG, eugenol | [20, 23, 56, 58] |
| TIMP-2 | Eugenol | [23] |
| VEGF | EGCG, curcumin, eugenol | [23, 51, 81] |

## Table 2

Benefits and risk for use of nutraceuticals by cancer patients

| Nutraceutical | Active agent | Potential benefit | Potential risk |
|---|---|---|---|
| Chile pepper | Capsaicin | Anti-inflammatory | Irritant |
| Cloves | Eugenol | Anti-inflammatory | Not clear |
| Ginger | Gingerol | Suppresses nausea | Not clear |
| Fenugreek | Diosgenin | Limited data but maybe anti-inflammatory | Not clear |
| Grapes and muscadines | Resveratrol | Anti-inflammatory | Kidney damage |
| Green tea | EGCG | Anti-inflammatory, antiangiogenic | Poor absorption may require high doses |
| Pepper (black) | Piperine | Stem cell behavior | Not clear |
| Soy | Isoflavones | Selective stimulus of ERβ | Antagonize SERMs |
| Turmeric | Curcumin | Anti-inflammatory and antiangiogenic | Poor absorption may require high doses |