DEVELOPMENTS IN NUTRACEUTICALS FOR CHEMOPREVENTION: A REVIEW
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Abstract
In recent years there is a growing interest in nutraceuticals which provide health benefits and are alternative to modern medicine. Nutrients, herbals and dietary supplements are major constituents of nutraceuticals which make them instrumental in maintaining health, act against various disease conditions and thus promote the quality of life. Epidemiological and clinical studies have demonstrated the relationship between diet and health status. It is well known that populations consuming a large proportion of plant-based foods, including fruits, vegetables, whole grains and cereals or those with a high intake of seafoods, have a lower incidence of cardiovascular diseases and certain types of cancer. Functional foods and nutraceuticals may provide a means to reduce the increasing burden on the health care system by a continuous preventive mechanism Therefore; interest has been expressed in functional foods, nutraceuticals and dietary supplements. Functional foods are defined as being similar in appearance to conventional foods, are consumed as part of a usual diet, and are known to improve health status and render physiological effects beyond basic nutritional function expected of conventional foods. Chemoprevention is the use of small molecules, including dietary or herbal chemicals, to prevent diseases, as opposed to chemotherapeutics, where chemicals, mostly synthetic, are used to remove or alleviate the symptom of diseases. However, nutraceuticals are products produced from foods, but sold in the medicinal form of capsule, tablet, powder, solution, or potion. They are not generally associated with food and have demonstrated physiological benefits and/or provide protection against chronic diseases; these are now referenced as “natural health products”.

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Introduction: In the past five years, the world has witnessed the explosive growth of a multibillion dollar industry known as nutraceuticals. The term “nutraceutical” combines the word “nutrient” (a nourishing food or food component) with “pharmaceutical” (a medical drug). Conventional cancer treatment has been in place for over 50 years with little change in the overall strategy. Tumors are removed surgically, while remaining inoperable sites are treated with radiation, chemotherapy or both. These latter modalities nonspecifically target all tissues, the only differentiation being their rapidity of growth and the focusing possible with directed radiation and certain methods of chemotherapy delivery. As a result, collateral damage and adverse side effects are the rule. The severity of these adverse effects has stimulated a continuing search for ways to reduce them. As the research has progressed, there has developed a growing consensus that a variety of nutraceuticals can complement the effects of standard cancer treatment. Their contributions are several [Fig.1]:

- Nutraceuticals can decrease the side effects of conventional cancer treatment.
- Nutraceuticals can protect normal cells from the indiscriminate damage done by cancer treatment.
- Nutraceuticals can enhance the effects of cancer treatment.
- Nutraceuticals can abrogate or delay the onset of cancer.
- Nutraceuticals can destroy cancer after it appears.

A single admonition and three specific caveats accompany such recommendations. There is a fear that the antioxidant supplements that protect normal cells from chemotherapy will also protect cancer cells. Research has identified only three potential antagonistic interactions among the many nutraceutical and chemotherapeutic agent combinations studied. [Fig.2] Beyond these three, the results have been universally benign, both in the laboratory and in clinical trials.

Carotenoids

Recent epidemiologic studies have shown good correlation between dietary intake of tomato and reduced risk of cancer and cardiovascular diseases. Tomato is rich in various carotenoids. Lycopene is the precursor of carotene in
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tomato, which accumulates after the lycopene cyclase gene is down regulated during ripening\(^5\). Lycopene and carotene can induce apoptosis in prostate cancer cells\(^6\) and malignant lymphoblast cells at a concentration range of 3 to 30 M within 24 h. The carotenoid-induced apoptosis shows typical DNA fragmentation, poly ADP-ribose polymerase (PARP) cleavage, and caspase-3 activation\(^7\). However, in the case of insulin-like growth factor-1–stimulated growth of MCF-7 mammary cancer cells, the inhibitory effect of lycopene may be independent of apoptosis\(^8\). Although it is certain that carotenoids have antiproliferative activity, it is unclear what the direct molecular targets of lycopene and carotene. Carotene has been shown to affect NF-\(\kappa\)B binding activity\(^9\), whereas lycopene causes an increase in connexin-43 mRNA and stimulates gap junction communication at a concentration (0.1 M) much lower than that required for apoptosis\(^10\). Thus, it is likely that the biological effects of carotenoids are pleiotropic, and their chemopreventive activity may not be solely due to apoptosis.

**Antioxidants**

Antioxidants protect the body from destructive free radicals, which are generated when the body uses oxygen to make energy and from exposure to environmental factors, such as cigarette smoke. Left unchecked, free radicals cause uncontrollable chemical reactions that damage the body\(^11\). Radiotherapy and some forms of chemotherapy function by creating oxidizing free radicals that damage malignant cells. The chemotherapeutic agents most noted for creating cellular damage by generating free radical oxidants are the alkylating agents (e.g., cyclophosphamide, ifosamide), the tumor antibiotics (e.g., doxorubicin, bleomycin), and the "platinum" compounds (e.g., cisplatin).

Since antioxidants are free-radical scavengers, their use in combination with these agents must be explored before being recommended. Sufficient evidence from research has justified the practice, although the mechanism by which these nutraceuticals exert opposite effects on normal and malignant cells has yet to be fully elucidated. Two theories have been proposed, both of which require an exploration of the mechanisms of action of cancer treatments\(^12\).

Traditionally it has been thought that DNA damage leading to cell necrosis is the way radiation and chemotherapy kill cancers.[Fig.3] More recently evidence suggests, however, that damage of a lesser severity, perhaps to cell membranes by lipid peroxidation, arrests mitosis and initiates apoptosis\(^13\). Since many antioxidant treatments
stimulate apoptotic pathways, such an effect might override any potential antagonism\textsuperscript{14,15}. This effect is likely to be further enhanced by an intrinsic deficit in malignant cell repair mechanisms. A dramatic deficiency of catalase has been identified in many cancers.

When cells with this deficiency are treated with vitamin C, hydrogen peroxide accumulates, and the cells die. Adding catalase to these cell cultures completely nullifies the effect\textsuperscript{16,17}. In the laboratory, cancer cell cultures have demonstrated a variety of beneficial results from the addition of a mixture of antioxidants. Numerous tumor growth inhibitory signals have been generated, among them inhibited expression the activity of protein kinase C and increased expression of transforming growth factor (TGF) mRNA, TGF protein and its secretion, and the expression of p21 and wild-type p53. Specific nutraceuticals have by themselves generated many other beneficial effects, although the results have not been entirely benign. Certain individual antioxidants at low doses have been shown to stimulate the growth of some cancers. Others, given individually even at high doses, have had no effects whatsoever. And the effects of many agents at both low and high doses have yet to be defined. Therefore, carefully designed regimens, usually involving multiple agents at tested dosages, have been advocated, rather than individual supplements used alone or indiscriminate combinations in poorly controlled doses\textsuperscript{18}. One clinical study compared standard paclitaxel and carboplatin chemotherapy for non-small-cell lung cancer with and without ascorbic acid 6100 mg/day, dl-alpha-tocopherol (vitamin E) 1050 mg/day and beta-carotene 60 mg/day. A tendency to favor the combined regimen appeared but was statistically insignificant at p = 0.20\textsuperscript{19}. Most of the research that has evaluated the effects of antioxidants on cancer has been conducted in a laboratory and because of this it is considered experimental. But it nonetheless serves important roles in the research process: It helps determine the activity of a compound and directs future clinical trials.

**Flavonoids**

Flavonoids are plant compounds known to have antioxidant properties \textit{in vitro} and \textit{in vivo}. Flavonoids are a group of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin. These compounds possess a common phenylbenzopyrane structure (C6-C3- C6), and they are categorized according to the saturation level and
opening of the central pyran ring, mainly into flavones, flavonols, isoflavones, flavonols, flavanone, and flavanonols. Many of the thousands of flavonoids in nature have been studied for anticancer properties. The most well characterized anti-tumor flavonoids are epigallocatechin gallate (from green tea), genistein (from soy and red clover), curcumin (from turmeric), silibinin (from milk thistle). Among them, tea polyphenols, quercetin, and genistein have been widely studied for their potential chemopreventive applications. Although epidemiologic studies have not yielded a clear positive correlation between tea consumption and cancer risk reduction, there is no doubt that tea extracts or tea polyphenols have promising anticancer effects in animal models. In addition to cancer, tea polyphenols may have protective effect for cardiovascular and inflammatory diseases. Epigallocatechin gallate (EGCG; Figure 2B) and other catechins were first shown to be apoptotic in human lymphoid leukemic cells and human carcinoma cells. Similar observation has since been extended to lung tumor cell lines, colon cancer cells, breast cancer cells and virally transformed human fibroblasts, prostate cancer cells, stomach cancer cells, brain tumor cells, head and neck squamous carcinoma, and cervical cancer cells. The effective dosages of EGCG for apoptosis in these cells are in the range of 20 to 100 µM, and the time course varies from 10 to 30 h. Based on the study of using p53-dominant negative mutant or p53 knockout cells, it is thought that intrinsic and extrinsic apoptotic pathways are involved in the action of EGCG.

Maitake Mushrooms

Amazing cancer cure case studies with maitake mushroom has been clinically proven to prevent and heal cancer, as well as decrease and even eliminate cancerous tumors. Maitake (grifola frondosa) is a polypore mushroom that is native to Japan. It grows in clusters at the base of trees, particularly oaks, and has been prized for its medicinal properties for centuries. It is commonly known as Hen of the Woods, Ram’s Head and Sheep’s Head, and its Japanese name, maitake, literally means “dancing mushroom,” a term derived from Japanese folk medicine. Maitake is best known for its cancer-fighting properties. In 2009, a phase I/II human trial was conducted by Memorial Sloan-Kettering Cancer Center, and it showed that maitake extract stimulates the immune systems of breast cancer patients. A particular mushroom native to Japan has generated substantial interest for its ability to
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inhibit tumor growth. Maitake (Grifola frondosa) is so rare and so delicious that folks dance when they find it, hence the literal translation "dancing mushroom." It was singled out after 15 years of mushroom research by one investigator using MM46 mice with breast cancer.

Mice receiving either oral or intraperitoneal Maitake extract had either complete or >75% remission of their tumors. Powders and extracts of this mushroom, identified as Maitake D-fraction (Maitake Products, Inc.) and Maitake crude powder, have produced remarkable improvements in advanced breast, lung and liver cancers and some suggested benefits in leukemia, stomach and brain cancer patients. It appears to increase immune cell activity, generating increases in TNF-alpha and IFN-gamma from spleen cells and TNF alpha expressed in NK cells. It also increases macrophagederived interleukin-12, which serves to activate NK cells. In the laboratory, D-fraction, a heta-glucan, was tested in combination with carmustine (BCNU), 5-fluorouracil (5-FU), methotrexate (MTX), etoposide, cisplatin and mitomycin C on prostate cancer cell cultures. BCNU, 5-FU and MTX produced a 50% reduction in cell viability. Only the combination of BCNU and D-fraction increased the death rate to -90%. The increased death rate was accompanied by -80% reduction in the activity of glutathione-dependent detoxifying enzyme glyoxalase-I, suggesting a mechanism for the observed effect. Other laboratory studies involving Maitake D-Fraction (MDF), a standardized form of maitake mushroom containing grifolan — an important beta-glucan polysaccharide, show evidence of MDF’s therapeutic value. It exhibits anti-cancer activity, has the ability to block the growth of cancer tumors and boost the immune function of mice with cancer.

**Stilbenes**

The distribution of stilbenes in the plant kingdom is wide. Resveratrol, for example, is found in small fruits such as grapes and Vaccinium berries, peanuts and in Polygonum species. Stilbenes structurally related to resveratrol have been found in a variety of foods as well as in medicinal plants. Similar to resveratrol, these phytochemicals have a multitude of biological activities [Fig. 5]. Resveratrol (3,5,4-trihydroxy-trans-stilbene), a phytoalexin present in grapes, peanuts, and pines, has antioxidant and anti-inflammatory activities and is the active ingredient in Leguminoseae that inhibits cellular events associated with tumor initiation, promotion, and progression in a mouse.
In vitro mechanisms of action of the most representative stilbene, resveratrol, have been extensively discussed in numerous reports and reviews. Its potential as a cancer chemopreventive agent has been extensively reviewed recently. The possible role of resveratrol, a phytoestrogen, in cardiovascular protection has been reviewed recently. Resveratrol and other related stilbenes suppress the proliferation of a wide variety of cultured cancer cells, including colon, prostate, breast, pancreas, ovary, melanoma, head and neck, and others. In vitro, resveratrol induces apoptosis and inhibits the growth of various human tumor cells, including oral squamous carcinoma, promyelocytic leukemia, human breast cancer cells, prostate cancer cells, esophageal carcinoma cells, pancreatic cancer cells, and monocytic leukemia cells. Several key mechanisms of action include inhibition of the transcription factor NF-κB, regulation of cytochrome P450 enzymes, activation of nuclear receptors such as estrogen receptors (ERs), and peroxisome proliferator-activated receptors (PPARs), inhibition of expression and activity of inflammation-related enzymes such as cyclooxygenases, and regulation of sirtuins. The dosage of resveratrol used in various studies has varied between 10 and 300 µM, with apoptosis appearing between 24 and 96 h. Induction of p53 at the mRNA and protein levels is the most commonly observed effect of resveratrol and is considered the major cause for apoptosis. We found that resveratrol does not exhibit a clear differential growth inhibitory effect toward transformed human fibroblasts. Interestingly, a resveratrol analog, 3,4,5,4-tetrahydroxystilbene, is more potent than resveratrol in inducing apoptosis of transformed cells, but has no effect on normal counterparts at much higher concentrations.

Proteolytic Enzymes

Proteolytic enzymes (or proteases) refer to the various enzymes that digest (break down into smaller units) protein. These enzymes include the pancreatic proteases chymotrypsin and trypsin, bromelain (pineapple enzyme), papain (papaya enzyme), fungal proteases, and Serratia peptidase (the “silk worm” enzyme). Among the proteolytic enzymes of interest to oncology, trypsin and chymotrypsin from cattle or pigs, papain from papaya sap, and bromelain from pineapple stems are the most studied.
Bromelain contains nine active proteases. They reduce the adverse effects caused by radiotherapy and chemotherapy and, prolong survival. One study of patients with inoperable lung cancer treated with fluorouracil, vinblastine, methotrexate and cyclophosphamide found a reduction in leukopenia, mucusitis and uremia in patients who received in addition a combination of papain, trypsin and chymotrypsin. The mean survival also increased by 25%. The same combination reduced the elevation in liver enzymes caused by carboplatin, epirubicin and prednimustine treatment of ovarian carcinoma and prolonged survival by 76% in patients treated with a variety of regimens for multiple myeloma [Table 1]. Several studies augmenting radiotherapy with the same combination of proteolytic enzymes produced improvements in radiation side effects or disease progress [Table 2]. The effects of proteolytic enzymes are not well understood as yet, but they appear to be based on induction of antiproteinases and on alterations of cytokine composition inducing anti-inflammatory effects. Among patients who have pancreatic cancer, those who chose gemcitabine-based chemotherapy survived more than three times as long (14.0 vs 4.3 months) and had better quality of life than those who chose proteolytic enzyme treatment.

Curcumin

Curcumin is a diferuloylmethane derived from the Indian spice, turmeric (popularly called “curry powder”) that has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF-jB, TNF, IL-6, IL-1, COX-2, and 5-LOX).[Fig.6] The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets. Thus an “old-age” disease such as cancer requires an “age-old” treatment. Curcumin (diferuloylmethane), a polyphenol derived from the turmeric plant, is a potent antioxidant and anti-inflammatory agent. During 50 years of research it has shown an ability to suppress initiation, proliferation and metastasis of a wide variety of tumor cell lines. Its many mechanisms of action include down-regulating the
expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules, cyclin DI and growth factor receptors (such as EGFR and HER2). It also inhibits the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases.[Fig.7]

Even at high doses it has demonstrated no dose-limiting toxicity and thus offers considerable promise as a cancer treatment, although human cancer studies should be completed and published to further validate its effects and initiate widespread implementation of this cancer treatment strategy. Extensive research for decades has made the clear conclusion that curcumin appears beneficial therapeutic effects on inflammation-related diseases including cancer. Marked by chronic inflammation modulator, NF-κB is the major molecular target of curcumin treatments. Since blocking of IκB degradation and its control by IKK are essential steps in down-regulating NF-κB activation, targeting this point by curcumin for NF-κB-specific blockage without safety concern is worth exploring in future.

Quercetin

Quercetin is a flavonoid molecule ubiquitous in nature. A number of its actions make it a potential anti-cancer agent, including cell cycle regulation, interaction with type II estrogen binding sites, and tyrosine kinase inhibition. Quercetin appears to be associated with little toxicity when administered orally or intravenously. Quercetin, a flavonoid antioxidant present in many yellow vegetables, has been studied extensively in the laboratory and occasionally in human cancer trials. It is able to alter the concentration of chemotherapeutic agents inside cancer cells, affect cell cycle regulation, interact with type II estrogen binding sites, and inhibit tyrosine kinase, frequently, but not always, generating an anticancer effect. It is also able to overcome anti-apoptotic mutations that result in drug resistance in human tumors. It is proposed that quercetin could be used in both the prevention and treatment of cancer and that diet would likely fulfill the concentration requirements for prevention, but supplementation or another form of delivery could be necessary for therapeutic responses. Enzymatic modification of quercetin could further lower the threshold necessary for anti-tumor activity.
Graviola (*Annona Muricata*)

Many bioactive compounds and phytochemicals have been found in graviola, as scientists have been studying its properties since the 1940s. Its many uses in natural medicine have been validated by scientific research. Several studies by different researchers demonstrated that the bark as well as the leaves had hypotensive, antispasmodic, anticonvulsant, vasodilator, smoothmuscle relaxant, and cardiodepressant activities in animals\(^69,70\). The leaves, bark, and stems of Graviola, an evergreen indigenous to tropical areas in South and North America including the Amazon, show remarkable cytotoxicity and selectivity against cancer cells. The phytochemical group, *Annonaceous acetogenins*, seems to play a significant role in this tree's antitumor properties\(^71-74\) [Fig.10]. In 1976 plant screening program by the National Cancer Institute, graviola leaves and stem showed active cytotoxicity against cancer cells and researchers have been following up on these findings since\(^75\). Much of the cancer research on graviola focuses on a novel set of phytochemicals called *Annonaceous acetogenins*. Graviola produces these natural compounds in its leaf and stem, bark, and fruit seeds. Three separate research groups have isolated these acetogenin compounds in graviola which have demonstrated significant antitumorous and anticancerous properties, and selective toxicity against various types of cancer cells (without harming healthy cells) publishing eight clinical studies on their findings\(^76-83\). Many of the acetogenins have demonstrated selective toxicity to tumor cells at very low dosages—as little as 1 part per million. Four studies were published in 1998 which further specify phytochemicals and acetogenins which are demonstrating the strongest anticancerous, antitumorous, and antiviral properties\(^84-87\). Thus far, specific acetogenins in graviola have been reported to be selectively toxic to these types of tumor cells: lung carcinoma cell lines; human breast solid tumor lines; prostate adenocarcinoma; pancreatic carcinoma cell lines; colon adenocarcinoma cell lines; liver cancer cell lines;\(^88,89\) human lymphoma cell lines;\(^90\) and multi-drug resistant human breast adenocarcinoma\(^91\).

The group of compounds found in Graviola are potent inhibitors of NADH: ubiquinone oxidoreductase, which is an essential enzyme in complex I leading to oxidative phosphorylation in mitochondria. They also inhibit the ubiquinone-linked NADH oxidase enzyme, which is specific to the plasma membranes of cancerous cells. Much of
the recent research done on extracts of this tree has been conducted by Purdue University, supported by grants from the National Cancer Institute and the National Institutes of Health. What they have found is that Annonaceous acetogenins can selectively inhibit the growth of cancerous cells and also inhibit the growth of adriamycin and other drug-resistant tumor cells. Not only are the compounds effective in killing tumors that have proven resistant to anti-cancer agents, but they also have a special affinity for such resistant cells. And we know the mechanism of action of at least one compound in the Annonaceous acetogenin group, bullatacin, which preferentially kills multi-drug resistant cancer cells by inhibiting ATP production, and thus removing the cancer's energy source.

Conclusion

Nutraceuticals are destined to play an important role in future therapeutic developments but their success will be governed by control of purity, safety and efficacy without inhibiting innovation. Nutraceuticals will continue to appeal because they are convenient for today’s lifestyle. Over 50 years of research has shown that cancer is easier to prevent than cure. Whether preventing cancer or treating it once it has occurred, it is clear that this disease is multifactorial and that treatment necessitates the modulation of multiple pathways and targets. The targeted actions of chemopreventive nutraceutical agents, such as those present in fruits and vegetables, are increasingly being recognized as useful in the therapy of cancer. Among the targets subject to modulation by these agents are activation of apoptosis; suppression of growth factor expression or signaling; down regulation of antiapoptotic proteins; and downregulation of angiogenesis through inhibition of vascular endothelial growth factor expression, cyclooxygenase-2, matrix metalloproteinase-9, urokinase-type plasminogen activator and adhesion molecules. Furthermore, phytochemicals can modulate these molecular targets with considerably greater safety than standard radiation and chemotherapeutic agents. This article has covered some of these chemicals but there are more. Genistein, resveratrol, dially sulfide, isothiocyanates, S-aiiy cysteine, allicin, lycopene, capsaicin, 6-gingerol, ellagic acid, ursolic acid, betulinic acid, flavopiridol, silymarin, anethol, catechins and eugenol, are among the many naturally occurring agents being studied for use in cancer treatment. Recent work has shown that these and other phytochemicals work synergistically with chemotherapy regimens and can reverse chemoresistance. Because of their
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Pharmacological safety, select antioxidants, Maitake mushrooms, fruits, vegetables, curcumin, quereetin, Graviola, and other well-researched phytochemical agents can be used alone or in combination with standard chemotherapy to treat cancer, and alone, to prevent its onset. Chemopreventive agents are much sought after as an early interventional approach to prevent tumor development or to lower the incidence risk of cancers. Given that the current available methods of treatment are chemotherapy, radiation, and surgery, all of which can induce significant side effects, an urgent need for alternate or adjuvant therapies has arisen. Phytochemicals are relatively safe and abundantly available from dietary sources. Therefore, alternate medicine aims at harnessing the protective properties of these nonessential nutrients toward cancer prevention and treatment.

TABLES:

### Table-1: Clinical Studies of Proteolytic enzymes patients receiving chemotherapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Medication</th>
<th>Duration of therapy</th>
<th>Effects of enzyme therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoperable lung cancer</td>
<td>Prospective randomized</td>
<td>26 vs. 25</td>
<td>Pharmacal, vinblastine, cyclophosphamide vs. this combination plus enzymes</td>
<td>12 months</td>
<td>Improvement in general condition &amp; quality of life, some improvement in life expectancy, fewer side effects</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Prospective open</td>
<td>76 vs. 80 vs. 89</td>
<td>Mitomycin, fluorouracil, epirubicin vs. placebo vs. placebo plus enzymes</td>
<td>6-42 months</td>
<td>Increase in the ratio of T lymphocytes to total lymphocytes</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Prospective, randomised, placebo-controlled</td>
<td>23 vs. 36</td>
<td>Carboplatin, etoposide, prednisolone plus placebo vs. placebo plus enzymes</td>
<td>6 months</td>
<td>More rapid fall in tumor enzymes</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Retrospective parallel group cohort</td>
<td>99 vs. 166</td>
<td>Multidose chemotherapy plus enzymes</td>
<td>At least 6 months</td>
<td>Survival of patients with stage II multiple myelomas increased by 36 months</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Prospective, randomised, double-blind, placebo-controlled</td>
<td>30 vs 30</td>
<td>Thalidomide + leucovorin vs. plus enzymes</td>
<td>2-45 months</td>
<td>Reduction in adverse effects of chemotherapy, fewer patients with metastasis, more patients surviving &gt; 42 months</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Retrospective parallel group cohort</td>
<td>99 vs. 166</td>
<td>Combination chemotherapy plus enzymes</td>
<td>Up to 83 months</td>
<td>3-year increase in survival time in patients with stage III colon cancer</td>
</tr>
</tbody>
</table>

### Table-2: Clinical Studies of Proteolytic enzymes in patients receiving radiation therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Duration of therapy</th>
<th>Effects of enzyme therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal cancer</td>
<td>Prospective randomized</td>
<td>32 vs. 25</td>
<td>2-44 weeks</td>
<td>Delay in appearance of metastases, reduction in tumor size</td>
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<tr>
<td>Oral cancer</td>
<td>Open randomized</td>
<td>20 vs. 19</td>
<td>3 weeks</td>
<td>Shorter duration of radiation, less side effects</td>
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<tr>
<td>Head and neck cancers</td>
<td>Prospective randomised</td>
<td>42 vs. 58</td>
<td>At least 7 weeks</td>
<td>Significant reduction in tumors size, difficulty in swallowing, and skin reactions</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Prospective randomized</td>
<td>66 vs. 60</td>
<td>Not more than 10 weeks</td>
<td>Significant reductions in radiation-induced side effects</td>
</tr>
</tbody>
</table>

Table-1: Clinical Studies of Proteolytic enzymes patients receiving chemotherapy

Table-2: Clinical Studies of Proteolytic enzymes in patients receiving radiation therapy
FIGURES:

Fig. 1. Nutraceuticals: Safety and Efficacy

Fig. 2. Pathway influenced by Nutraceutical
Fig. 3. Role of antioxidants in cancer treatment

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Fig. 7. Role of Curcumin in cancer treatment
Fig. 8. Role of Quercetin in cancer treatment

Fig. 9. Role of Quercetin in cancer treatment
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