

Keeping cancer at bay the natural way

Jonathan Hill, Zoey Hanstock and Brian Lockwood discuss nutraceuticals that appear promising in the prevention and treatment of cancer

The World Health Organization estimates there are more than 10 million cancer cases around the world each year. The increase in cancer incidence is thought to be caused in part by the increase in life expectancy and lifestyle factors.¹ The American Institute for Cancer Research and the World Cancer Research Fund give a figure of 30–40 per cent for the proportion of cancers that can be prevented by lifestyle modification, including diet.²

Hence, the role of nutraceutical supplementation and dietary factors is more relevant than ever. Much research has, therefore, been carried out into nutraceuticals and their role in cancer prevention. They may, in the future, be used to enhance current conventional drug regimens, ameliorate some of the toxic side effects associated with chemotherapy and prevent cancer incidence in the first place.

This review considers seven nutraceuticals: lycopene, flaxseed, polyunsaturated fatty acids, coenzyme Q10, melatonin, conjugated linoleic acid and resveratrol. All of these are either endogenous in the body, available in the diet or both; it is thus interesting that these natural compounds exhibit anticancer effects.

Lycopene

Tomatoes and tomato-based products, which are the major source of many of the dietary carotenoids, especially lycopene, have shown promise for the prevention of some cancers.³ Figure 1 shows the structure of lycopene.

It is the ability of lycopene to act as an antioxidant and free radical scavenger that is considered by the majority of researchers to be the most likely mechanism that could account for its beneficial effects on human health.⁴ Reactive oxygen species are the main source of oxidative damage that can generate structural alterations in DNA and decrease DNA repair by damaging essential proteins, and ultimately cause cancer.⁵

Lycopene in animal model studies

Animal model studies have reported positive results after using lycopene in mouse lung, rat bladder, rat colon cancer, rat aberrant colon crypt formation and rat hepatic preneoplasia models. However, its use in rats with mammary tumorigenesis produced conflicting results.⁶ Unfortunately, the data from these



Tomatoes contain lycopene — a likely force in the battle against cancer

animal studies are not comparable because in each case different lycopene preparations, doses and routes of administration were used.

As well as supporting the anticancer activity of lycopene, these animal studies have provided information about the pharmacokinetics of lycopene and also have highlighted several methodological issues relevant to future studies on the chemopreventive effects of lycopene. The animal studies have shown that a large proportion of ingested lycopene is excreted in the faeces and that 1,000-fold more lycopene is absorbed and stored in the liver compared with what accumulates in other target organs.⁶ However, physiologically significant levels of lycopene have also been measured in other key organs such as the breast, prostate, lung and colon, and there is an approximate dose-response relationship between lycopene intake and blood levels.⁷ Findings also revealed that the general diet of the individual can affect the uptake and distribution of lycopene and provided evidence that tomatoes are absorbed more efficiently than lycopene alone, making them the more effective form.⁶

Lycopene and the digestive tract

A series of clinical experiments have shown a consistent inverse relationship between tomato consumption and the risk of digestive tract neoplasms. Preliminary case-control studies carried out in Italy during the early

1990s found a high frequency of tomato intake to reduce the risk of developing cancers of the oral cavity, pharynx, oesophagus, stomach and colon. A later, much larger study, also carried out in Italy, used patients below the age of 80 with incident, histologically confirmed cancer of the oral cavity and pharynx (n=754), oesophagus (n=304), colorectum (n=1,953), breast (n=2,529) and ovary (n=1,031) who had been admitted to hospital. The comparison group, in total, included approximately 5,000 patients, also below the age of 80, with acute, non-neoplastic, non-hormone-related diseases, unrelated to long-term diet modifications and admitted to the same network of hospitals. Information regarding the patient's diet was collated. The trials provided supportive evidence that tomato consumption (the major source of lycopene) is inversely related to the risk of upper digestive neoplasms. Levels of cancer of the oral cavity, pharynx and oesophagus decreased with increasing levels of lycopene intake. A similar relationship was also found in colorectal cancers. The association with lycopene, however, was less consistent in cancers of the ovary and breast.⁸

Lycopene and the lung

The human lung is continually being exposed to oxidative stresses, the risk of damage being increased due to the large volumes of oxygen that pass through the lung each day, so that without numerous mechanisms of antioxidant protection the lung would become susceptible to damage. In addition, ozone, which is present in the lung, can promote oxidative damage and, in addition to other activities, it has been shown to affect the lung capacity.⁵ For protection, the lung has developed multiple antioxidant defences that are present in both the lung epithelial fluids and the lung cells themselves.⁹

An autopsy study and bronchial lavage carried out on the lung has provided evidence for the presence of lycopene and other carotenoids in lung tissue.⁹ Although only low concentrations were found, their presence suggests they may have an important role as a lung defence mechanism, protecting both lung integrity and lung function. Researchers have attempted to assess whether elevated levels of lycopene and other carotenoids in the lung will provide a greater degree of protection against oxidative and ozone-induced damage.

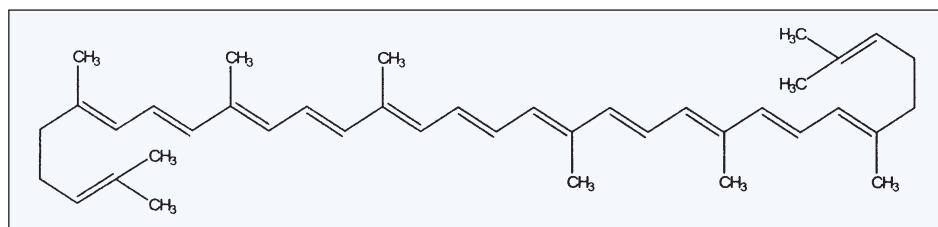


Figure 1: The structure of lycopene

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The Antioz study A randomised clinical trial looked at the effects of supplementation of carotenoid-rich vegetable juice (V8) on lung macrophage levels of carotenoids and in moderating ozone-induced lung damage. Lycopene was the predominant carotenoid in the vegetable juice, representing 88 per cent of total carotenoids. The dose of lycopene that the subjects received equated to 23mg per day. Healthy young adults were exposed to 0.4ppm ozone for two hours after either two weeks of antioxidant supplementation (one can of V8 juice daily) or placebo. Mean lung concentrations of lycopene increased by 12 per cent in supplemented subjects. The decreases in forced expiratory volume in one second and forced vital capacity were 30 per cent and 24 per cent, respectively, in the supplemented subjects compared with the placebo subjects. However, there was no difference in markers of inflammation in the lung between both sets of subjects. This may be because antioxidants have a role in protecting the lung from damaging ozone and maintaining lung function but play no part in mediating the inflammatory response. Although the study showed no significant change in peripheral blood lymphocyte DNA damage in either supplemented or placebo subjects, the lung epithelial cell DNA damage, as measured by the Comet assay, was 20 per cent lower in supplemented subjects. This provides evidence that antioxidants do, in fact, protect the lung from DNA damage caused by oxidative stresses, in particular, those associated with ozone exposure.⁹ The study demonstrated the presence of lycopene in the human lung following supplementation and provided preliminary evidence that an increased intake of lycopene might provide an additional level of protection against oxidative damage. This study is supported by epidemiological literature that has found that diets rich in tomatoes are associated with lower lung cancer rates.^{6,8,9}

Lycopene and prostate cancer Prostate cancer is the most common of all male cancers,¹ yet preventive measures for this malignancy are not well established.³ Recent epidemiological studies have shown that a high intake of lycopene in the diet lowers the risk of developing prostate cancer.¹⁰ Lycopene outperformed a number of tested carotenoids and vitamin E in several *in vitro* antioxidant systems, especially those that generate singlet oxygen, but it is more likely to be a pro-oxidant in peroxide-generating systems.¹¹ Three mechanisms have been put forward to explain how lycopene may help to prevent prostate cancer: inhibition of growth and induction of differentiation in prostate cancer cells, up regulation of the tumour suppressor protein, Cx43, alongside improved intercellular communication and prevention of oxidative DNA damage.¹²

One of the studies providing the strongest evidence concerning tomatoes and prostate cancer prevention was published in 1995. The dietary habits of over 47,000 men

enrolled in the "Health professionals follow-up study" were examined. This is the only dietary study that showed estimated concurrent plasma lycopene levels in a sample of participants.¹³ Of the participants, 773 were diagnosed with prostate cancer during the follow-up period. The only foods found to be associated with a reduced risk of prostate cancer were raw tomatoes, tomato sauce and pizza. In men who had more advanced prostate cancer consuming 10 servings of tomato products per week compared with less than 1.5 servings per week, lycopene was found to be significantly protective. The study identified a correlation between plasma and dietary lycopene. In addition, a high intake of tomatoes and tomato products, which accounted for 82 per cent of the lycopene, was associated with a 35 per cent lower risk of total prostate cancer and a 53 per cent lower risk of advanced prostate cancer. Tomato sauce had the strongest inverse association with prostate cancer and a slightly weaker inverse association was found with tomatoes and pizzas. This decline in protective effect from tomato sauce to tomatoes and pizza corresponded with a mirrored decline in plasma lycopene levels.⁴ This study showed an association between intake of tomato products and a lower risk of prostate cancer.

A pilot study was conducted to investigate the biological and clinical effects of lycopene supplementation in patients with localised prostate cancer. Newly diagnosed prostate cancer patients were given either tomato extract containing 30mg of lycopene, or no supplementation, for three weeks before radical prostatectomy.

Prostatic tissue lycopene levels were 47 per cent higher in the intervention group. However, plasma lycopene levels were not significantly different between the groups, nor did they change significantly within each group. Mean plasma prostate-specific antigen levels (a clinical parameter of prostate cancer burden) decreased by 18 per cent in the supplemented patients and increased by 14 per cent in the control group. Of patients in the intervention group, 73 per cent had involvement of surgical margins and/or extra-prostatic tissues with cancer, compared with 18 per cent of patients in the control group. Additionally, the intervention group was found to have smaller tumours. Of those who took the lycopene, 80 per cent had tumours that measured 4ml or less, compared with only 45 per cent in the control group.¹²

Intake of tomato products, equating to 30mg lycopene per day over a three-week period, was shown to cause a decrease in lipid peroxides, a reduction in DNA strand breaks in circulating lymphocyte DNA and a decline in nucleoside damage in the form of 8-OH-deoxyguanosine/deoxyguanosine (8OHdG/dG) in circulating leukocytes, indicating antioxidant activity.¹¹ It is probable that the prostate, because of greater chronic inflammation of prostate epithelial cells and faster cell turnover, together with reduced levels of DNA repair enzymes compared with

Guide to abbreviations

AA	Arachidonic acid
ALA	Alpha-linolenic acid
CLA	Conjugated linoleic acid
Co Q10	Coenzyme Q10
COX	Cyclo-oxygenase
DMBA	7,12-Dimethylbenz(a)anthracene
EL	Enterodiol
ED	Enterolactone
ER +/-	Oestrogen receptor positive/negative
IGF-I	Insulin-like growth factor-I
NSAIDs	Non-steroidal anti-inflammatory drugs
PGE ₂	Prostaglandin E ₂
PUFAs	Polyunsaturated fatty acids
SDG	Secoisolariciresinol diglycoside
SHBG	Sex hormone binding globulin
TNF	Tumour necrosis factor-alpha
VEGF	Vascular endothelial growth factor

other tissues, may be more susceptible to oxidative damage. After the three week intervention, the patients' serum and prostate lycopene concentrations had increased 1.97- and 2.92-fold, respectively. There was a positive correlation between leukocyte and prostate 8OHdG/dG, which may allow leukocyte 8OHdG/dG measurement to be used as a prognostic biomarker of oxidative stress in clinical practice. However, there was no inverse linear correlation between plasma or prostate lycopene concentrations and 8OHdG/dG in leukocytes or prostate tissue.¹¹

Staining of the biopsy and resected tissue samples showed that there had been a decrease in DNA damage in cancer cells after tomato sauce consumption, mean cancer cell nuclear density had decreased by 40 per cent and by 36 per cent in mean area. Mean serum PSA concentrations decreased by 17.5 per cent and apoptotic index was higher in hyperplastic and neoplastic cells in the resected tissue following supplementation. It is probably the decreased DNA damage in these neoplastic cells that leads to the induction of apoptosis (and therefore fewer viable cancer cells), thus producing an elevated apoptotic index.¹¹

Meta-analysis A meta-analysis of observational studies, regarding the role of tomato products and lycopene in the prevention of prostate cancer, supported the protective effect of lycopene also. Again, data suggested that the protective effect of lycopene is somewhat better when tomatoes are consumed rather than when lycopene is taken alone.¹⁰ This combination may compose an efficient system that keeps lycopene in an antioxidant state in cell membranes.¹¹ In addition, the protective effect is slightly stronger for high intakes of cooked tomato products than for high intakes of raw tomatoes. This may be due to either higher concentrations of lycopene in tomato-based products or a difference in lycopene bioavailability in processed tomato products compared with raw tomatoes.¹⁰

Conclusions These preliminary studies have provided us with evidence to suggest that tomato consumption, lycopene intake and serum lycopene levels are associated with a reduced risk of developing cancer, most notably prostate and lung cancer. The beneficial effects of lycopene, owing to its ability to act as an antioxidant, may allow it to be used as an adjunct therapy in the treatment of some cancers. Due to the lack of information we have on its mechanism of action and safety in homogenous patient populations, larger clinical trials would be needed to warrant the use of lycopene in the prevention of cancer. A problem arises in ascertaining the most suitable tomato-based product, since lycopene content varies immensely between formulations and brands. The lycopene content of tomatoes themselves can vary significantly with variety and ripening stage.⁴ Lycopene concentrations in the red strains approach 50mg/kg compared with only 5mg/kg in yellow varieties. High quality supplements are one alternative. Also, the form in which lycopene would be delivered to patients poses the greatest subject for deliberation, since this appears to have a profound impact on its effectiveness.^{10,11}

Flaxseed

Flaxseed is an oilseed that contains two principal substances of possible therapeutic application: the phytoestrogen lignans and alpha-linolenic acid (ALA). Flaxseed has several plant lignans, including matairesinol, pinoresinol, isolariciresinol and secoisolariciresinol diglycoside (SDG), which is the major lignan. Figure 2 shows the structures of SDG and ALA.

The lignans are metabolised by resident bacteria in the colon to mammalian lignans, namely enterodiol (ED) and enterolactone (EL). These lignan metabolites undergo enterohepatic circulation, are conjugated with glucuronides and subsequently excreted in the urine. ALA, a constituent of flaxseed oil, is an n-3 fatty acid.¹⁴

It has been proposed that both the phytoestrogen lignans and ALA have anticancer properties. Breast and prostate cancer is rarer in Asian countries than in the western world and this could be due to dietary differences. Indeed, those living in low cancer areas have

greater concentrations of phytoestrogens in their plasma and urine.¹⁵ This begs exploration of a link between flaxseed and cancer.

Anticancer activity Studies have shown that flaxseed has anticancer properties, which have largely been attributed to the lignan component, but a recent study has been conducted to elucidate the contribution of both the lignans and the flaxseed oil to anticancer activity. In this experiment, different groups of mice with oestrogen receptor-negative breast cancer were given either flaxseed, flaxseed oil, or both SDG and flaxseed oil. Tumour growth and metastasis was reduced in all cases but the groups did not differ in their effects, suggesting that both the SDG and flaxseed oil contribute to the anticancer behaviour of flaxseed. Furthermore, the lung and total metastasis incidences were significantly lowest in the group given SDG and flaxseed oil, indicating that SDG and flaxseed oil complement each other against metastasis.¹⁶ Nevertheless, evidence for the anticancer effects of ALA is somewhat limited and doubtful. Beneficial effects from ALA in studies may be due to the overall fatty acid profile of the flaxseed oil rather than ALA specifically.¹⁷

In a study in Finland it was found that there was a significant inverse relationship between the metabolite serum EL level and breast cancer incidence.¹⁸

Mode of action of flaxseed lignans ED and EL, the lignan metabolites, are structurally similar to the natural oestrogen, 17 β -oestradiol. It is the aromatic hydroxylated phenyl ring that confers oestrogenicity or anti-oestrogenicity to the lignans. This structural similarity may provide lignans with the ability to interfere with the activity of 17 β -oestradiol.¹⁹

Lignans are thought to be weakly oestrogenic and/or anti-oestrogenic.¹⁹ Therefore, they may be of use against hormone-dependent cancers.

One study looked at the anti-oestrogenic effect of flaxseed and its principal lignan SDG on the oestrous cycle in rats. Rats given 3.0mg SDG or a high fat diet of 10 per cent flaxseed had acyclic or irregular oestrous cycles. Similar results were shown with tamoxifen, an anti-oestrogenic drug.

Reduced breast cancer risk is linked to irregular or prolonged cycles, possibly because of reduced oestrogen exposure.²⁰

In another study, rats were given flaxseed. Epithelial cell proliferation was reduced by about 40–50 per cent, the effect being most striking in the terminal end buds of the rats' mammary glands. Since hormone changes affect the terminal end buds and alter their proliferation, the reduction in proliferation here suggests that the lignans may be acting anti-oestrogenically, by inhibiting 17 β -oestradiol's effects. The greatest anti-proliferative effect was achieved with a high fat diet consisting of 5 per cent flaxseed flour. The decreased proliferation in this study was matched by an increase in urinary lignan excretion, evidence that the lignans are responsible for the anticancer properties.²¹

Endogenous oestrogen is linked to breast cancer risk. Therefore, the influence of flaxseed on biosynthesis or metabolism of oestrogen may contribute to its putative anticancer activity.

A study has shown that 10g of flaxseed significantly increases the 2-hydroxylated metabolite of oestrogen (2- α -OH-oestrogen) excretion by 30.7 per cent compared with the control and significantly increases the 2- α -OH-oestrogen:16- α -OH-oestrogen ratio by 25.2 per cent compared with a wheat bran diet. This effect on the premenopausal women in the study suggests that flaxseed alters the 2-hydroxylation pathway more than the 16-hydroxylation pathway. Thus, by influencing the metabolism of oestrogen, one can increase the proportion of the more desirable 2-hydroxylated metabolite, which has anticancer activity, while the 16-hydroxylated metabolite is oestrogenic. The authors of this study proposed that flaxseed's lignan metabolites, ED and EL, may induce cytochrome P450 enzymes, which catalyse the oestrogen 2-hydroxylation step.²²

There is some evidence that lignans may stimulate liver production of sex hormone binding globulin (SHBG) and thus reduce the free-sex-hormone concentration and prolong the menstrual cycle, leading to reduced breast cancer risk; although this evidence is controversial since SHBG only appears to be increased by lignans in women who have low SHBG in the first place.¹⁵

Therefore, lignans may reduce oestrogen exposure by being anti-oestrogenic, by decreasing 17 β -oestradiol in cancer cells or by provoking the production of less oestrogenic metabolites. In effect, the bioavailability of 17 β -oestradiol to cancer cells is reduced. Furthermore, lignans have been shown to inhibit tumour growth of oestrogen receptor positive (ER+) MCF-7 cells with already low oestrogen concentration and also inhibit growth of oestrogen receptor negative (ER-) tumour cells, showing that flaxseed has non-hormonal anticancer roles too.²³

Reduction in growth factors High plasma insulin-like growth factor I (IGF-I) concentrations are linked to a higher breast

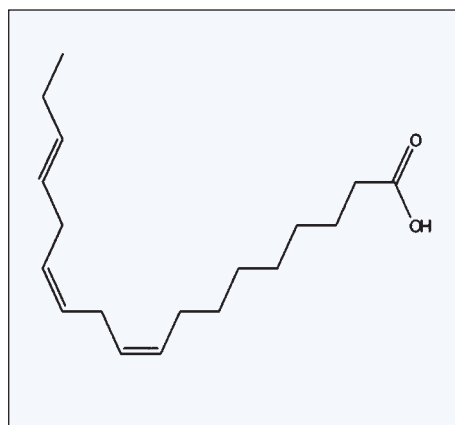
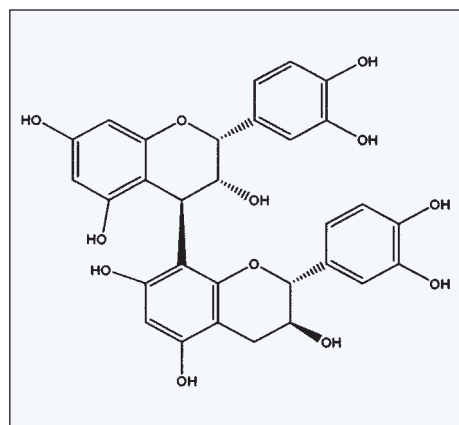


Figure 2: Structure of SDG (left) and ALA

cancer risk — the factor has mitogenic and antiapoptotic effects.

A study showed that a diet supplemented with 5 per cent flaxseed or 1.5mg SDG daily for four weeks can decrease rats' IGF-I plasma levels, so the anticancer activity of flaxseed and SDG may be partly due to this effect.²⁴ Cancer cells, in their growth and metastasis, employ angiogenesis, whereby new capillaries are made to allow further blood supply to the developing tumour. Vascular endothelial growth factor (VEGF) is important in this process and levels are higher in breast cancer patients. A study in mice has shown that, in large tumours, a diet of 10 per cent flaxseed significantly reduces extracellular levels of VEGF. It is possible that the flaxseed influences VEGF production and angiogenesis directly by acting on cells and indirectly by reducing free oestrogen.²⁵

Other modes of action Many more sites of action, such as membrane ATPase, ornithine decarboxylase, tyrosine protein kinase and DNA topoisomerases, appear to be targets, their inhibition resulting in inhibition of growth and proliferation. Lignans may inhibit the enzyme that produces primary bile acids from cholesterol. This means there are fewer primary bile acids to be converted in the colon to secondary bile acids, which correlate with colon cancer. Antioxidant properties have also been linked to lignans.²⁶

Conclusions The experimentally observed anticancer effects of flaxseed are mainly due to the lignan fraction.² Flaxseed oil is less likely to be the major active anticancer agent, although it is likely to have some contribution. More information is needed on the bioavailability of lignans. Even when the same amount of lignan is ingested by humans, there is large variability in plasma and urine levels between individuals. Lignan bioavailability is thought to be associated with gender, age and an individual's bacterial flora.²⁷ The latter is responsible for ED and EL production; young women who frequently suffer urinary tract infections and therefore regularly use antibiotics have been shown to be at increased risk of breast cancer because the bacterial flora have been eradicated.¹⁵

The metabolism of flaxseed lignans is highly important since it is the metabolites that are active and not the parent compound. As with bioavailability, metabolism also varies and there is a wide range of ED and EL excretion in humans.²⁷

Flaxseed could be used not only to prevent cancer or its metastasis, but also alongside conventional therapy. It has been claimed that flaxseed could be employed to reduce the menopausal-like side effects of tamoxifen, and, in combination with this anti-oestrogenic drug, flaxseed could help overcome the problem of tamoxifen resistance. Indeed, flaxseed has been shown to enhance tamoxifen's inhibitory actions.²³

The effects of lignans are more striking in premenopausal women than in post-

menopausal women, implying a mechanism involving endogenous hormone levels. More research needs to be done, especially distinguishing between men, and premenopausal and postmenopausal women.¹⁴

Lignans have so far been well tolerated in animal studies but safety data are still lacking. ED and EL have not been found to be mutagenic in bacteria, animals or humans,²⁷ but more rigorous long-term data is required.

Polyunsaturated fatty acids

The amount and type of fat that we consume in our diet may affect our risk of developing cancer. Several influential organisations, such as the World Cancer Research Fund, have advised that we limit our intake of fat, particularly animal fat, in an attempt to decrease the incidence of cancer. Dietary fat is known to be able to affect changes in genetic structure and genetic expression, both of which have been linked to the cause of cancer.

High dietary fat intake has been identified as a causative factor in the development of colon, breast, prostate and pancreatic cancer, particularly when there is evidence of a high intake of meat and monounsaturated fat in the diet. Saturated fat has been found to be a risk factor for ovarian cancer, as have polyunsaturated fats for hepatic cancer.

A meta-analysis of experimental animal studies found n-6 polyunsaturated fatty acids (PUFAs) to significantly enhance carcinogenesis, saturated fatty acids to slightly enhance carcinogenesis, monounsaturated fatty acids to have no effect and n-3 fatty acids to inhibit carcinogenesis.²⁸

Nutritionists have long accepted the association between a high dietary intake of long-chain n-3 fatty acids found in fish and a reduced risk of death from coronary heart disease. However, it has only more recently come to light that consumption of ALA, the parent compound of all n-3 fatty acids, may be linked to an increased risk of developing prostate cancer.

The highest proportion of our daily ALA intake is from plants and vegetable oils. Its intake in wealthy countries is 5–10 times higher than that of n-3 fatty acids from fish. Unfortunately ALA is incorporated into foods much more readily than is the long chain n-3 fatty acid from fish. This is because ALA does not carry with it the distinct taste and smell of fish, as does the long-chain n-3 fatty acid from fish.²⁹

Meta-analysis A meta-analysis was carried out to estimate quantitatively the association between ALA intake, mortality from heart disease and occurrence of prostate cancer in observational studies. Data from nine observational studies investigating the relationship between prostate cancer incidence and intake or blood levels of ALA were identified and reviewed. These studies all suggested that a high intake or blood level of ALA increased the incidence of prostate cancer.²⁹

These data raise the question as to whether we should consume high levels of

ALA for its protective effect on coronary heart disease or avoid it because of its association with an increased risk of prostate cancer. For men with a predisposed increased risk of developing heart disease the benefits of ALA probably outweigh the risks.

The n-3 PUFAs found mainly in fish oils are promising molecules in both cancer prevention and possibly cancer treatment.³⁰

Effects of PUFAs on tumour growth

It has been reported that certain types of fish (oil) might protect against colorectal cancer because n-3 PUFAs are able to inhibit some of the steps in colon carcinogenesis. This has been confirmed by a variety of experimental animal systems which found colon cell proliferation, an intermediate biomarker for colon carcinogenesis, to be lower in rats that had been fed fish oil. Alternatively, other experiments have shown that it is increasing apoptosis and differentiation rather than decreasing proliferation that gives n-3 PUFAs their antitumour effect. Other experiments carried out in hepatocarcinogenesis and mammary carcinogenesis rat models also found n-3 PUFAs to have an antitumour effect. In addition, diets containing n-3 PUFAs, such as those that contain fish oil, have been found to reduce both mammary and lung tumour metastasis.³⁰

Interaction with antioxidants

Experiments have shown that the inhibitory effect of fish oil on tumour growth is suppressed by vitamin E and is actually a function of increased lipid peroxidation. Further investigations have also shown oxidised PUFAs to have an inhibitory role on tumour growth. The ability of n-3 PUFAs to induce lipid peroxidation has been demonstrated in a variety of *in vitro* and *in vivo* systems and this leads to the conclusion that n-3 PUFAs may inhibit tumour growth by promoting apoptosis of tumour cells.³¹

Following on from this, further studies have found n-3 PUFAs to be an outstanding substrate for lipid peroxidation in cytotoxic agents where oxidative stress is involved. Therefore, n-3 PUFAs have been shown to enhance the activity of anticancer drugs that work by inducing apoptotic cell death in tumour cells, as well as those that expose tumour cells to oxidative stresses. The ability of n-3 PUFAs to enhance tumour sensitivity to several cytotoxic drugs shows that they would possibly be an excellent adjunct to use in chemotherapy.³⁰

Clinical data A number of clinical trials have reported effects of n-3 fatty acids in many types of cancers, with varying success. One large meta-analysis of clinical trials investigating the incidence of cancers after supplementation with n-3 fatty acids has been published. Overall 20 cohorts from seven countries have been studied for incidence of 11 different types of cancers. No significant benefits were detected for supplementation for aerodigestive, bladder, ovarian,

pancreatic or stomach cancer, or lymphomas. Statistically significant associations were found with four studies on breast cancer, one study on colorectal cancer, two for lung cancer, and two for prostate cancer. Unfortunately there were found to be both increased and decreased risks for breast, lung and prostate cancers, and there was an increased risk with skin cancer.³²

Coenzyme Q10

Coenzyme Q10 (Co Q10) is one of the most heavily advertised alternative therapies for cancer on the internet. Figure 3 shows the structure.

Co Q10 is an essential part of the electron transport chain in mitochondria which enables ATP synthesis.³³ The reduced form of Co Q10 is a powerful antioxidant and as oxidative damage to DNA, proteins and lipids is associated with carcinogenesis,³⁴ there is great interest in Co Q10 as a potential chemopreventive or chemotherapeutic agent in cancer. In addition, a deficiency in Co Q10 has been shown to be significantly higher in cancer patients than in healthy people.³³

Coenzyme Q10 as an antioxidant The relationship between Co Q10 and cancer can be shown by measuring Co Q10 levels in cancer tissue. Normal blood levels of Co Q10 are $0.9 \pm 0.2 \mu\text{g/ml}$. Two studies in the US and Sweden showed that about 20 per cent of breast cancer patients in those studies had Co Q10 levels of $0.5 \mu\text{g/ml}$ or lower.³⁵

A clinical trial of 200 breast cancer patients showed that plasma Co Q10 levels were reduced both in cancer and non-malignant lesions compared with the control. Large volume tumours and patients with poor prognoses exhibited more dramatic reduction in Co Q10 levels.³⁶ Breast cancer may, in part, be attributed to the lack of Co Q10's antioxidant defence activity.

In another study, a patient with high-risk breast cancer, who showed partial tumour regression on treatment with antioxidants, fatty acids and 90mg of Co Q10 daily, was stepped up from 90mg to 390mg of Co Q10. Within two months, a mammograph showed no sign of the patient's tumour. The investigators were so encouraged by this that they treated another patient who had residual tumour post-surgery. For this patient, 300mg of Co Q10 daily left no tumour tissue remaining after three months.³⁵ Unfortunately clinical trials are lacking in the area.

Other modes of action Co Q10 has been shown to have the ability to enhance the immune system and regression of breast cancer may be partly attributed to this.³⁷

An *in vitro* model of cervical cancer was used in the investigation of Co Q10 to treat HeLa cells. In this study $30 \mu\text{mol/L}$ of Co Q10 showed 40 per cent cell growth inhibition after three days. An increase in apoptosis was observed along with increased induction of lipid-related genes and subsequent lipid accumulation in the HeLa cells.

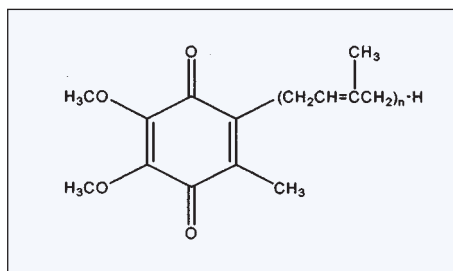


Figure 3: Structure of Co Q10

This lipid response to Co Q10 treatment may be part of the reason for HeLa cell growth inhibition.³⁸

Conclusions Many studies have exhibited Co Q10's potent antioxidant nature and this fact warrants more widespread evaluation of this nutraceutical's potential in cancer treatment.

Melatonin

Melatonin is a chronobiotic agent produced by the pineal gland that is released in accordance with the light/dark daily cycle. The release of melatonin is thus a method of conveying the temporal context to the body.³⁹ The structure is shown in Figure 4.

Inhabitants of industrialised countries have lifestyles that tend not to follow the day and night cycle as closely as in the past. Shift work, involving light exposure at night, thus suppressing melatonin secretion, has been blamed for contributing to increased cancer risk. Melatonin has been shown to be anti-oestrogenic *in vitro* and *in vivo* and many studies have linked a lack of melatonin to increased cancer risk or growth. One such experiment looked at the effect of light at night on the growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary adenocarcinomas in rats. Corresponding to reduced melatonin levels and increased oestradiol levels, light significantly increased the tumour growth rate and reduced survival rates compared with the controls.⁴⁰

To further the link between melatonin and oestrogen levels, another study has shown that oestrogen receptor-positive tumours had a much lower melatonin peak at night compared with oestrogen receptor negative tumours. The higher the tumour oestrogen receptor concentration, the lower the melatonin peak, thus indicating that a low or no nocturnal melatonin peak may predict an increased risk of hormone-dependent cancer.⁴¹

Observational studies show that light pollution at night increases the risk of breast cancer. The longer women work night-time shifts, the greater the breast cancer risk.⁴² A meta-analysis, looking at the relationship between shift work and breast cancer, concluded that night-time shift work, including the work of flight attendants, increased breast cancer risk by 48 per cent. This figure is strikingly significant and attenuates the idea that female flight attendants are at increased risk of

breast cancer because of increased exposure to radiation. Instead, melatonin deficiency may well be involved in tumour development.⁴³ The reduced risk of breast cancer in blind women, who cannot perceive light and therefore do not have reduced melatonin levels, also strengthens the argument for the anticancer nature of melatonin.⁴²

The increased cancer risk associated with reduced melatonin levels may be explained by associated increased oestrogen levels, but melatonin does not appear to act entirely by that mechanism since light at night seems to increase the risk of other non-hormonally dependent cancers too. For example, women doing night-time shift work for more than 15 years are at increased risk of colorectal cancer.⁴²

In 2005, the first meta-analysis looking at the impact of melatonin on various cancers, either on its own or along with conventional chemotherapy, was published. It considered 10 randomised controlled trials between 1992 and 2003 and entailed 643 patients. Melatonin was found to reduce the death risk at one year, with similar effects in different cancers. No severe side effects were reported, and this combined with melatonin's apparent anticancer efficacy and low cost, indicates that melatonin may have good potential in cancer treatment.⁴⁴

Melatonin is a potent antioxidant and it acts as a direct free radical scavenger and is involved in oxidative defence by stimulating enzymes which metabolise and inactivate free radicals.⁴⁵

Melatonin is pro-apoptotic although it also appears to inhibit apoptosis in immune cells and neurones. Therefore, while melatonin may be considered for cancer therapy, melatonin's activity in relation to apoptosis may depend on both the type of the cell and the functional state of the cell.⁴⁶

Melatonin and the immune system

An *in vivo* study has shown that optimal immune function in mammals relies on an evening "dose" of melatonin. Melatonin helps to develop haemopoietic and lymphoid cells in the bone marrow, thymus, spleen and lymph node and also enhances lymphocyte- and phagocyte-mediated immunity.⁴⁷

Not only can melatonin revert metabolic changes and enhance lymphocyte and macrophage response to tumours but it can also, by acting at G-protein-coupled membrane receptors, stimulate cytokine release and thus help mount an immune response.

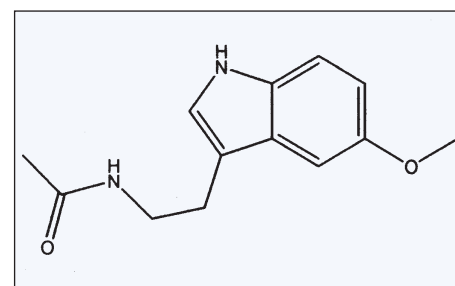


Figure 4: Structure of melatonin



Richard Jones/Rex Features

Shift work involving light exposure at night has been linked with cancer

For example, melatonin administered with the cytokine interleukin-2 might act synergistically to prolong survival of a cancer patient.⁴⁸

Use of melatonin in chemotherapy It has been shown that melatonin exhibits anticancer properties but, in clinical practice, it is more realistic that it will be used as an adjunct to conventional chemotherapy.

Various studies have shown that melatonin may enhance chemotherapy efficacy and reduce the toxic side effects that cancer patients suffer. One such study looked at one-year survival status in advanced cancer patients with poor clinical status. Chemotherapy, when used along with 20mg/day of melatonin, significantly increased the number of patients surviving at one year (63 out of 124 patients compared with 29 out of 126 for chemotherapy without melatonin). Also, the tumour regression rate was significantly increased. This is probably because of melatonin's performance as a powerful antioxidant, shown to enhance the cytotoxicity of chemotherapeutic agents, and its pro-apoptotic nature. The increased survival rate of patients may be due to the ability of melatonin to reduce the immunosuppression induced by chemotherapy. Melatonin also reduced incidence of thrombocytopenia, cardiotoxicity, neurotoxicity and other adverse effects induced by chemotherapy. Chemotherapy often entails generating free radicals. Melatonin, being the most active natural antioxidant, can help counteract the toxicity from such therapy. No side effects owing to melatonin itself were noticed. Therefore, in patients with advanced cancer, efficacy and toxicity of chemotherapy may be increased and decreased respectively by melatonin.⁴⁹

To further these findings, another longer-term study was carried out that investigated the five-year survival in patients with metastatic non-small cell lung cancers. The results further the evidence that melatonin should be used in cancer treatment. Chemotherapy alone (cisplatin and etoposide) left no patients alive after two years, whereas the same chemotherapy, plus 20mg/day melatonin, resulted in 6 per cent of patients living after five years. Not only does

melatonin prolong survival but it increases the quality of the patient's life during that extended survival period,⁵⁰ probably due to its anticachetic effects.

Cachexia is a wasting away of the human body with noticeable weight loss. This is not just due to malnutrition, but also partly due to increased release of tumour necrosis factor-alpha (TNF), which has anti-tumour effects but also metabolic side effects causing cachexia. Melatonin and TNF secretion are possibly related by a feedback mechanism and a study has shown that melatonin, when given along with supportive care, significantly decreases TNF levels compared with supportive care alone. Corresponding to this, weight loss in the group of patients receiving melatonin was 10 per cent less than in the group receiving only supportive care. This study thus provides evidence that melatonin may treat neoplastic cachexia by its effect on TNF levels. Furthermore, possibly by virtue of this inhibition of TNF secretion, respiratory problems due to cancer appear to be attenuated in the study.⁵¹

Conclusions The characteristic melatonin peak at night in healthy people is widely seen to be disrupted in cancer patients.⁵²

Especially lacking is information on the time of day melatonin might have its greatest benefit. The circadian nature of melatonin means it may have different effects at different times of the day, and this has been demonstrated in mice.⁴⁷ Linoleic acid, an n-6 PUFA, is known to stimulate tumour growth, particularly at night, when melatonin levels are lowest and melatonin supplementation has been shown to cause a dose-dependent reduction in linoleic acid uptake and tumour growth. Melatonin may also have an optimum time of day at which it inhibits fatty acid uptake, which itself exerts circadian rhythm.⁵³ It is known that cancers co-ordinate their cell cycles and vary in their susceptibility to chemotherapy throughout the day.⁵²

The clinical evidence for melatonin has shown increased survival times and amelioration of the toxicities of conventional chemotherapy.⁵² The safety of melatonin has been largely confirmed, with doses of 1–300mg or 1g melatonin daily for 30 days exhibiting no side effects. However, bone marrow toxicity has been shown to be worsened with melatonin use.⁴⁸ Also, the chief melatonin metabolite, 6-hydroxymelatonin, was found to be carcinogenic.⁵⁴

Not only has melatonin exhibited anticancer activity, the ability to reduce the side effects of conventional anticancer drugs and the antioxidant ability to minimise radiation therapy damage, but it has also been shown to

reduce levels of anxiety in patients and improved their overall quality of life.⁵⁵

Conjugated linoleic acid

Conjugated linoleic acid (CLA), chiefly found in meat and dairy products, comprises a set of geometric and positional isomers of linoleic acid.⁵⁶ Despite its structural similarity to linoleic acid, which stimulates carcinogenesis,⁵⁷ CLA has been found to be an anti-cancer agent, inhibiting initiation, promotion, progression and metastasis.⁵⁶ CLA was first shown to be useful against cancer when its discovery in grilled ground beef was found to be beneficial.⁵⁸ There are 15 isomers of CLA, arising from variations in the double bonds of its structure.⁵⁹ The *cis*-9, *trans*-11 (c9, t11) isomer is the main isomer found in dietary CLA. Most studies have used this isomer and the *trans*-10, *cis*-12 (t10, c12) isomer.⁵⁸ Figure 5 shows the structure of the t10, c12 isomer.

CLA inhibits chemically induced mammary tumours in rats and it has shown a strong relationship with cancer in humans. A study from Finland showed that CLA levels were significantly lower in women with breast cancer than in healthy people.⁶⁰

Mode of action There is a 40–50 per cent reduction in colorectal cancer relative risk in those people who use non-steroidal anti-inflammatory drugs (NSAIDs) continuously. This has led to the suggestion that inhibition of eicosanoid synthesis (NSAIDs block production of prostaglandins — an eicosanoid) may have anticancer effects.⁶¹ Arachidonic acid (AA) leads to eicosanoid production; it has been shown that these eicosanoid products, such as PGE₂, are involved in carcinogenesis and they can influence cell proliferation and tissue differentiation.⁶² Enzymes involved in eicosanoid manufacture include cyclo-oxygenase (COX) and lipoxygenase (LOX).⁶³

It is known that CLA is incorporated into phospholipids and, competing with AA, may thus displace it from cell membranes. This will alter subsequent eicosanoid production.⁶⁰ For example, CLA has been shown to reduce AA-derived PGE₂, and this is correlated to a reduction in tumorigenesis.⁶² Colon cancer is associated with increased expression of the COX-2 enzyme and enhanced synthesis of eicosanoids, especially prostaglandins. In a colon cancer study in rats, a diet consisting of 1 per cent CLA reduced AA levels in phospholipids. Leading from this was a significant reduction in PGE₂ and thromboxane, eicosanoid products of AA. The researchers concluded that eicosanoid levels were reduced by modulation of AA availability rather than involvement with COX-2 expression,

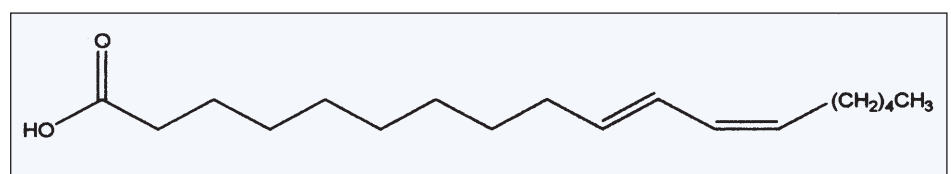


Figure 5: The structure of the trans-10, cis-12 (t10, c12) isomer of CLA

since levels of this enzyme were unchanged throughout the study. The reduced eicosanoid levels could contribute to increased apoptosis and reduced cell proliferation.⁶¹

CLA may oppose the tumour-inducing effects of LA because of their structural similarity.³⁸ CLA is metabolised by desaturation and elongation and it has been proposed that the enzymes involved may also be used by LA. A diet of 1 per cent CLA significantly reduced levels of AA and other LA metabolites in rat mammary tissue, indicating that there is competition for enzymes between CLA and LA and this can lead to reduced eicosanoid synthesis from AA.⁵⁷

CLA may also interfere with the LOX pathway, thus modulating cell proliferation and apoptosis. A study looking at this pathway found that the t10, c12 CLA isomer significantly reduced 5-hydroxyeicosatetraenoic acid (5-HETE — the normal 5-LOX metabolite) levels and tumour cell growth. This occurred by CLA competing with AA (5-LOX substrate) and by altering expression of a protein that enables 5-LOX to form 5-HETE. As malignant tissue shows increased expression of 5-LOX, treatment with t10, c12 CLA may be useful in anticancer therapy.⁶³

CLA may modulate eicosanoid production and therefore have anticancer activity by competing with the normal substrates in the pathway, by altering expression of enzymes and by inhibiting COX and LOX enzymes.⁵⁹

Other modes of action of CLA CLA may take part in the cellular response to TNF, which can decrease quality of life because of its link with cachexia. Mice were given CLA for 32 days and were then injected with TNF. They showed less weight loss than the control group, indicating that they were protected from TNF-induced cachexia.⁵⁸

In another study, mice fed CLA for six weeks had significantly lower TNF levels than the controls after lipopolysaccharide injection. Lipopolysaccharide stimulates TNF production by macrophages and so, again, CLA seems to have an effect on TNF-induced cachexia.⁶⁴

CLA was found to reduce angiogenesis significantly. Furthermore, CLA appears to be safe as there was no toxicity observed at high doses of CLA used long-term in the animal studies.⁵⁶

CLA was found to inhibit growth of oestrogen receptor-positive breast cancer cells *in vitro* but had no such effect on an oestrogen receptor-negative cell line, indicating that CLA works on the oestrogen pathway.⁶⁵

Conclusions The c9, t11 and t10, c12 CLA isomers differ in their mechanism of action. The isomers may also differ in the way they benefit different tissues. For example, the t10, c12 isomer works better against colorectal cancer proliferation.⁶⁶ The t10, c12 CLA appears to be the best isomer for use in androgen-dependent prostate cancer⁶⁷ and better than c9, t11 CLA in oestrogen receptor-positive breast cancer cell inhibition.⁶⁵ Another

isomer, cis-9, cis-11 CLA, has proven to be the best radiosensitiser and this could justify use in radiotherapy for breast cancer.⁶⁸ CLA should now be investigated more closely as its constituent isomers rather than as a mixture.

CLA has established anticancer properties existing at levels as low as 0.1 per cent by weight in the diet.⁵⁹ However, most studies have been carried out *in vitro* or on animals. Data on humans are rare.⁶⁰

Resveratrol

Resveratrol is a dietary stilbene, found in an array of edible plant products, in particular, peanuts, mulberry skins and grapeskins, and hence, in red wine.⁶⁹ The structure is shown in Figure 6.

Resveratrol has been shown to inhibit COX-1, an activity that correlates with anti-tumour promotion.⁷⁰ Several other mechanisms have been confirmed by experiment to account for its observed cancer chemoprotective activities.⁷¹ These include suppression of cellular proliferation, via inhibition of key steps in the signal transduction pathways and of cyclin-dependent kinases, promotion of cellular differentiation, scavenging or suppression of intracellular reactive oxygen intermediates, induction of apoptotic cell death via activation of mitochondria-dependent or -independent pathways, anti-inflammatory activity via down regulation of pro-inflammatory cytokines, and inhibition of androgen receptor function and oestrogenic activity.

Resveratrol and prostate cancer

Research using animal carcinogenesis models and cell cultures has shown the ability of resveratrol to prevent prostate cancer via three particular mechanisms: inhibiting each stage of multistage carcinogenesis, scavenging incipient populations of androgen-dependent prostate cancer cells through androgen receptor antagonism and scavenging incipient populations of androgen-independent prostate cancer cells by short-circuiting epidermal growth factor-receptor-dependent autocrine loops in the cancer cells. Individually, each of its activities may allow resveratrol to be used as a prophylactic therapy for prevention of prostate and other cancers, an adjuvant therapy for hormone-dependent prostate cancer and as an adjuvant therapy for treatment of advanced prostate disease.⁶⁹

Cell culture studies The mouse mammary gland culture of carcinogenesis was investigated for inhibition and development of 7,12-dimethylbenz(a)anthracene (DMBA)-

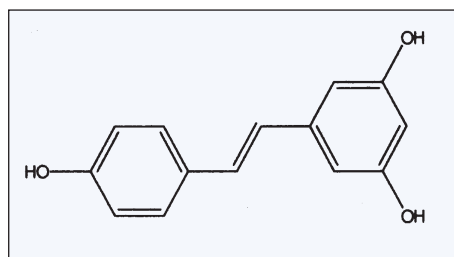


Figure 6: The structure of resveratrol

induced preneoplastic lesions. Also, tumorigenesis was studied in a two-stage mouse skin cancer model, again DMBA was used as an initiator and 12-O-tetradecanoylphorbol-13-acetate (TPA) was used as a promoter. In mice given 1, 5, 10, or 25 μmol of resveratrol, the number of skin tumours per mouse decreased by 68, 81, 76 and 98 per cent, respectively.⁷⁰ The study did not identify any resveratrol-induced toxicity in the mice, as judged by morphological examination of the glands.⁷¹

Conclusions In conclusion, resveratrol has anti-initiation, anti-promotion and anti-progression activity, enabling it to demonstrate chemoprotective activity in the three major stages of carcinogenesis.⁷⁰ Clinical studies using purified resveratrol are necessary to investigate its potential.

Overall conclusions

Cancer patients are increasingly turning to the use of preventive medication or nutraceuticals alongside their conventional chemotherapeutic drugs, either to enhance the anticancer effects, ameliorate the negative effects of conventional drugs or to improve their quality of life. Over the years, research has been devoted to unravelling the relationship between nutraceuticals and cancer, but there is still much work to be carried out before we may see compounds, such as these nutraceuticals, used regularly in therapy and side by side with cancer drugs.

Much of the available evidence for nutraceuticals is based on *in vitro* and *in vivo* studies in animals. To date, there are little epidemiological and clinical data for these nutraceuticals, but it is becoming evident that we can decrease the incidence of cancer through dietary selection.

Encouraging information from these nutraceuticals indicates that they have good safety profiles and are generally well-tolerated. However, there are conflicting data on the anticancer efficacy of these nutraceuticals.

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