Review Article

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Phytochemicals in cancer prevention and management?

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Abstract
Phytochemicals are compounds found in plants, which are responsible for the colour, taste and aroma of foods. Over and above these pleasant attributes, they protect us from environmental and ingested carcinogens by arming our antioxidant enzymes, enhancing DNA repair pathways and have direct effects on the fundamental hallmarks of cancer progression and metastasis. It is not a surprise then that analysis from the World Cancer Research Fund and other academic bodies, report that individuals eating phytochemical-rich foods have a lower risk of cancer or relapse after treatments. The debate lies in whether concentrating these foods, or elements of these foods, into nutritional supplements may boost their health attributes. One notable randomised controlled trial (RCT) has demonstrated benefits for men with prostate cancer, but other trials of extracted chemicals have shown no benefit or even an increased cancer risk. This article provides a clinical overview, for medical practitioners, of the major classes of phytochemicals with examples of their common food sources. It reviews the international evidence for their anti-cancer mechanisms of action and their clinical benefits, as well as discussing the pros and cons of concentrating them into nutritional supplements.
Keywords: Cancer, diet, phytochemicals, polyphenols

Introduction

Phytochemicals, are not regarded as essential nutrients in humans although an increasing number of well-conducted studies are linking higher intake with a lower risk of developing cancer, as well as lower relapse after initial treatment completion [1,2,3]. There is a wide range of dietary phytochemicals, but one of the largest and well-known groups being the polyphenols [Table.1]. The average total dietary intake of polyphenols is reported to be over 1g per day, which is up to ten times higher than that of all other classes of phytochemicals and known dietary antioxidants[4]. The health benefits of phytochemical rich foods or concentrated nutritional supplements are often being highlighted in the medical and popular media and hence they are an increasing topic of conversation between medical practitioners and their patients especially those with cancer who have a particular interest in over the counter self help strategies [5,6]. This article provides an overview of the major classes of phytochemicals with examples of their common food sources. It highlights the international evidence for their anti-cancer mechanisms of action, their clinical benefits, as well as discuss the pros and cons of concentrating them and, into nutritional supplements in an attempt to harness and boost their health benefits. Hopefully this review will provide some useful learning points to aid communication between patients and clinicians [Table. 2].

Classification

There are three major groups of phytochemicals: the polyphenols which can be subcategorized as the flavonoids, phenolic acids and other non-flavonoid polyphenols; the terpenoids, which can be subcategorized as the carotenoids and non-carotenoid terpenoids; and the thiols, which includes the glucosinolates, allylic sulfides and non-sulphur containing indoles (Table. 1). There are other phytochemical group, which although have some properties within these groups, have been classified within a miscellaneous category and examples of these include the betaines, chlorophylls and capsaicin.

Table.1 Classification of phytochemicals with notable food rich sources

Polyphenols
1. Flavonoids
o Flavonols:quercetin, kaempferol (onions, kale, leeks, broccoli, buckwheat, red grapes, tea, apples)
o Flavones: apigenin, luteolin (celery, herbs, parsley, chamomile, rooibos tea, capsicum pepper)
o Isoflavones: genistein, daidzein, glycitein (soya, beans, chick peas, alfalfa, peanuts)
o Flavanones: naringenin, hesperitin (citrus fruit)
o Anthocyanidins (red grapes, blueberries, cherries, strawberries, blackberries, raspberries, tea)
o Flavan-3-ols (tannins): catechins, epicatechin, epigallocatechin gallate (tea, chocolate, grapes)
o Flavanolols: silymarin, silibinin, aromadedrin (milk thistle, red onions)
o Dihydrochalcones: phloridzin, aspalathin (apples, rooibos tea)
2. Phenolic acids
o Hydrobenzoic acids: gallic acid, ellagic acid, vanillic acid (rhubarb, grape seed, raspberries, blackberries, pomegranate, vanilla, tea)
o Hydroxycinnamic acids: ferulic acid, P-coumaric acid, caffeic acid, sinapic acid (wheat bran, cinnamon, coffee, kiwi fruit, plums, blueberries)
3. Other non-flavonoid polyphenols
o Other tannins (cereals, fruits, berries, beans, nuts, wine, cocoa)
o Curcuminoids: curcumin (turmeric)
o Stilbenes: cinnamic acid, resveratrol (grapes, wine, blueberries, peanuts, raspberries)
o Lignans: secoisolariciresinol, enterolactone, sesamin (grains, flaxseed, sesame seeds)

Terpenoids
1. Carotenoid terpenoids
o Alpha, beta and gamma carotene (sweet potato, carrots, pumpkin, kale)
o Lutein (corn, eggs, kale, spinach, red pepper, pumpkin, oranges, rhubarb, plum, mango, papaya)
o Zeaxanthin (corn, eggs, kale, spinach, red pepper, pumpkin, oranges)
o Lycopene (tomatoes watermelon, pink grapefruit, guava, papaya)
o Astaxanthin (salmon, shrimp, krill, crab)
2. Non-carotenoid terpenoids
o Saponins (chickpeas, soya beans)
o Limonene (the rind of citrus fruits)
o Perillyl Alcohol (cherries, caraway seeds, mint)
o Phytosterols: natural cholesterols, siosterol, stigmasterol, campesterol (vegetable oils, cereal grains, nuts, shoots, seeds and their oils, whole grains, legumes)
o Ursolic acid (apples, cranberries, prunes, peppermint, oregano, thyme)
o Ginkgolide and bilobalide (Ginkgo biloba)

Thiols
o Glucosinolates: isothiocyanates (sulforaphane) and dithiolthiones (cruciferous vegetables such as broccoli, asparagus, brussel sprouts, cauliflower, horseradish, radish and mustard)
o Allylic sulfides: allicin and S-allyl cysteine (garlic, leeks, onions)
o Indoles: Indole-3-carbinol (broccoli, Brussel sprouts)

Other phytochemicals
o Betaines found in beetroot
o Chlorophylls found in green leafy vegetables
o Capsaicin found in chilli
o Peperine in black peppers

Table. 2 learning points

- Higher intake of phytochemical-rich foods such as colourful fruit, vegetables, herbs, pulses, spices and teas is associated with a lower risk of cancer and relapse after treatments.
- Their anti-oxidant properties help to protect our DNA from ingested or environmental carcinogens.
- Phytochemicals, particularly polyphenols have direct anti-cancer mechanism of action via inflammation, modulation of cellular and signalling events involved in growth, invasion and metastasis.
- Concentrating element of foods such as minerals, vitamins and phytoestrogenic polyphenols to potentially boost their health effects have largely been unsuccessful in preventing cancer in clinical trials.
- Whole food phytochemical-rich supplements have demonstrated significant benefits in phase II and well conducted RCT and their true potential is been evaluated in ongoing studies.

Clinical evidence for cancer prevention.

Although not all, many studies have linked a higher intake of phytochemical-rich foods, such as vegetables, fruit, legumes, nuts, herbs and spices, with a lower incidence of cancer as highlighted in the latest comprehensive review from the World Cancer Research Fund and other systemic reviews[2,3].

More specifically, certain elements of food have been addressed within a number of cohort studies. Carotenoids found in leafy green vegetables and carrots have been linked with a lower risk of breast cancer in a recent meta-analysis demonstrated[7] and a lower risk of ovarian and pancreatic cancers, especially among smokers in either questionnaire or serum-based studies[8, 9, 10]. Higher intake of cruciferous vegetables such as cabbage, cauliflower, Brussel sprouts, radishes and broccoli have been associated with a lower prostate cancer risk[11], as have foods rich in isoflavones such as pulses and soy products[12], lycopene rich colourful fruits and tomatoes[13]. Foods with abundant levels of flavonoids such as onions, rich in quercetin, have been shown to reduce the incidence of numerous cancers particularly those arising from the lung, especially amoung smokers[14, 15]. The anthoxanthins, in dark chocolate, have been reported to lower the risk of colon cancer[16] and higher green tea intake lowers the risk of breast, prostate, ovarian and oesophageal cancer, again particularly among smokers and alcoholics[17, 18]. Finally, coffee consumption has been shown to reduce the risk of non-melanomatous skin cancers and melanoma, even after removing other factors such as ultraviolet radiation exposure, body mass index, age, sex, physical activity, alcohol intake and smoking history[19,20].

Clinical evidence for a benefit after cancer

The benefits of healthy foods do not stop after a diagnosis, especially if combined with other healthy lifestyle habits. For example, breast cancer survivors who regularly consumed more than the government recommended five portions of fruit and vegetables a day, had a third lower breast cancer recurrence risk if combined with regular physical activity[21]. In another study, women with breast cancer who had the highest serum lignan levels, reflecting good intake of legumes, cereals, cruciferous vegetables and soya, were reported to have the lowest risk of death[22]. Likewise, a lignan and polyphenol rich diet was associated with a lower colorectal cancer relapse rate[23].

The large Shanghai Breast Cancer Survival Study demonstrated that women with the highest intake of the phytoestrogenic polyphenols isoflavones and flavanone found in soya and other beans, had a 29% lower risk of relapse and death[24]. Similar findings were seen for green tea after breast[25] and colorectal cancer[23]. Green tea also decreased the abnormal white cell count in 30% of patients with chronic leukaemia and reduced the levels of several markers of proliferation, as well as serum Prostate Specific Antigen (PSA) among men with prostate cancer[26]. A slowing of PSA progression has similarly been observed in other dietary studies, most notably the randomised trial involving a plant-based diet together with other lifestyle changes[27] and a phase II study of pomegranate juice[28].

Another cancer influenced by nutrition is skin cancer, as highlighted by a study of individuals who have been treated for basal cell carcinoma or squamous cell carcinoma, and who have a high risk of further lesions due to their on-going solar damage.

Those who consumed the highest levels of lutein and zeaxanthin-rich foods, such as leafy green vegetables, had the lowest levels of new cancer formation[29].

A number of other studies evaluating the impact of phytochemicals are underway, the largest and probably most comprehensive is the UK's DietCompLyf prospective trial involving 3159 women treated for breast cancer[30].

What are the likely anti-cancer mechanisms of phytochemicals?

The precise biochemical mechanisms through which phytochemicals exert their anti-cancer effects are still being explored, as their actions are wide-ranging and complex but significant advances have been made of late in the understanding the mode of action. The most quoted cancer prevention mechanism is via their antioxidant activity, elicited either through direct free radical absorption or through induction of antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione via a variety of molecular mechanisms[31, 32]. One of these mechanisms is activation of Nrf2, which switches on genes that code for antioxidant as well as detoxification enzymes[31, 32]. Phytochemicals, particularly the thiol class such as sulforaphane,have also been shown to inhibit the conversion of procarcinogens to their electrophilic, DNA damaging, chemicals[32,33].

A number studies involving known, common carcinogens have highlighted the antioxidant properties of phytochemicals. A good example of their protective effect was an experiment involving the known house-hold carcinogen triclocarban, commonly found in detergents and cleaning agents. Healthy cells exposed to triclocarban tend to mutate into pre-malignant cells, however, the amount and rate of carcinogenesiswas significantly reduced byadding curcumin to the petri dish culture feeds[34]. In another study, volunteers who ate a diet rich in kaempferol were found, on serum and urine analysis, to have improved SOD activity and higher urinary concentration of these polyphenols[35]. Rats exposed to cigarette smoke given indole-3-carbinol, a phytochemical rich in cruciferous vegetables, had a lower lung cancer rate than those not given idole-3-carbinol[36]. Subjects eating a meal of onions, which increased their serum levels of quercetin, demonstrated decreased levels of oxidative metabolites including 8-hydroxydeoxyguanosine (8-OHdG) a marker of DNA damage and repair16[18, 37]. Quercetin supplementation has also been shown to improving mitochondrial dysfunctions induced by the toxin 3-nitropropionic acid[38]. A clinical study in Singapore gave Chinese smokers 170g of watercress a day, rich in the indole-3-carbinol, and found a similar effect on urinary markers of DNA damage[39]. Finally, marinating meat in rosemary and thyme, has been reported to reduced the serum levels of carcinogenic heterocyclic amines (HCA) by 87% compared to subjects who eat the meat unseasoned[40].

Another key anti-cancer mechanism of phytochemicals appears to be their ability to reduce inflammation. It is now well established that inappropriate inflammation is intimately involved in the cancer process, particularly in the promotion and progression stages of cancer. Inflammation is closely associated with oxidative stress and activation of NF-kappa B family of transcription factors. These factors regulate more than 150 genes involved in mechanisms of cell survival and these target genes are not just pro-inflammatory but also oncogenic. Numerous phytochemicals have been shown to inhibit NF-kappa B signalling, particularly the green tea polyphenol epigallocatechin-3-gallate (EGCG), quercetin, curcumin, caffeic acid and caffeic acid phenethyl ester and the phytochemicals within bilberries[31,41].

More recently, it has been reported mainly from laboratory studies that phytochemicals have an affect on several cancer process through modulation of cellular and signalling events involved in growth, invasion and metastasis[32]. Pomegranate, for example, rich in the polyphenol ellagic acid, has been shown to directly inhibit cell growth and induce apoptosis in androgen sensitive and aggressive human prostate cancer cells[42]. Pomegranate extract has also been reported to inhibit processes involved in cancer metastasis in a study involving oestrogen sensitive and resistant breast cancer cell lines, showing increased markers of cell adhesion and migration in cancer but not normal cells[43]. In another study it inhibited a chemokine that attracts breast cancer cells to the bone[44]. Curcumin slows cancer cell growth by blocking the cell cycle, increasing the rate of apoptosis and preventing the invasion and migration of cells[45, 46, 47, 48]. It has also been found to halt the growth of stem cells that give rise to breast cancer without harming normal breast stem cells[49]. Curcumin has been shown to modulate miRNA expression in breast cancer cells leading to a reduced expression of Bcl-2[50] and stabilisation of tumour suppressor gene in colorectal cancer cell lines[52]. Green tea, rich in epigallocatechin gallate (EGCG), has demonstrated significant reduction of several factors that promote cancer cell proliferation by inhibiting DNA synthesis, de-differentiation and angiogenesis[26, 52, 53]. It has also been shown to block ornithine decarboxylase, an enzyme which signals cells to proliferate faster and bypass apoptosis[50, 54]. Resveratrol has demonstrated epigenetic regulatory properties which influence regulate proliferation, cell survival and apoptosis in prostate cancer by global modulation of gene expression through deacetylation of FOXO transcription factor[46]. Caffeic acid and phenethyl ester, as well as inhibiting NF-κB signaling, also have been shown to inhibit cell motility in vitro and inhibit metastasis of tumour models in vivo[47]. Luteolin, as well as inhibiting tumour growth and metastasis, inhibits epithelial mesenchymal transition which is a basic biological process related to cancer initiation and development[47].

Finally some polyphenols and other phytochemicals are also able to influence cancer via a hormonal mechanism.

Phytoestrogenic compounds, most notably isoflavones and lignans found in soy products, legumes and some cruciferous vegetables, weakly bind to the oestrogen receptor without stimulating proliferation of the cells, yet at the same time blocking the binding of more harmful oestrogens, including those produced endogenously[39]. This explains why in the previously mentioned Shanghai Breast Cancer Survival Study, women with the highest intake of isoflavones and flavanones-rich foods had a lower risk of death[24]. In men, phytoestrogenic compounds have been shown to affect 5 alpha reductase lowering endogenous testosterone levels. This may partly explain why men who eat phytoestrogenic foods such as beans and pulses have a lower risk of prostate cancer.

Can concentrating foods into supplements enhance their anti-cancer effect?

If certain foods have anti-cancer effects, then it is not unreasonable to hypothesise that concentrating them into a pill may be a good way to supplement individuals with poor diets or further enhance the benefits in those whoes diets are already adequate. People living with and beyond cancer (PLWBC) are certainly attracted to the potential health benefits of food supplements, as over 65% report regular intake[5,6]. There are two main categories of supplements commercially available: the first involves chemicals extracted from food, or made synthetically, such as minerals and vitamins; the second involves purifying and concentrating whole foods:

Vitamins and mineral supplements: The majority of studies, to date, have evaluated extracted chemicals such as vitamins and minerals. Some have shown a benefit. For example, a recent meta-analysis of studies reported that women who took supplements providing an average daily intake of vitamin C over 100mg had a reduced risk of breast cancer relapse[57]. The SU.VI.MAX study randomised French adults to a single daily capsule of ascorbic acid, vitamin E, beta carotene, selenium and zinc, or a placebo, and found no reduction in mortality or cancer-specific mortality overall[58], although a further analysis in men found a reduction in the risk of prostate cancer. The authors postulated that this difference between the sexes was related to French men having a lower baseline micro-nutrient status[59]. A major trial of selenium and vitamin supplements in a poor region of China, demonstrated reduced risks of oesophageal cancer; at the time this population was known to have widespread micro-nutrient deficiencies[60].

Unfortunately, most other studies of vitamin, minerals and other extracted nutrients have shown no benefit, or have actually shown an increased risk of cancer. For example, the CARET study found that beta carotene and retinol increased the risk of lung cancer[61]. The Health Professionals Follow-up study (HPFS) which followed the lifestyle habits of 51,529 male professionals for over 15 years found that men who took very high doses of zinc (>100mg/day), or took it for long durations were more than twice as likely to develop advanced prostate cancer compared with controls[62]. The randomised SELECT study demonstrated an increased prostate cancer incidence with vitamin E and selenium supplementation[63]. A further analysis of the HPFS found that of the 4,459 men who had developed prostate cancer, those who took selenium supplementation of ≥ 140 μg/d after diagnosis were associated with a 2.60-fold greater risk of prostate cancer mortality[64].

The negative effects of vitamin E and beta carotene were once again demonstrated in the ATBC study which found them to increase lung cancer risk, although subsequent analysis showed that men with pre-intervention low plasma levels of beta-carotene had a lower prostate cancer risk following supplementation, and that those with high levels had a higher risk, particularly in smokers[65]. This u-shaped distribution of risk was also observed in the EPIC study where those with folate-deficient diets and those with the highest intake both had a higher risk of cancer[66]. These data have prompted organisation such as the National Cancer Institute to issue statements stating that long term vitamin and mineral supplements should ideally be given to correct a known deficiency[67], which is rarely routinely detected unless individuals have self funded micro-nutrient analysis (cancernet.co.uk).

Whole food supplements: More recently academic attention has turned towards the evaluation of concentrated whole food supplements, particularly foods rich in polyphenols and other phytochemicals such as herbs, spices, green vegetables, teas and colourful fruits which have appeared to be beneficial in environmental cohort studies. Despite some initial encouragement from smaller evaluations, studies of extracted lycopene or genistein given on their own in more scientifically robust analyses have not demonstrate a benefit for either prostate cancer or benign prostatic hypertophy[68, 69, 70] neither were there links with the reduction in the risks of breast cancer with regular intake[5]. Of more concern, a randomised study from Memorial Sloan Kettering reported that serum taken from women who had take very high dose soy supplementation (25.8 g twice a day) added to laboratory tumour cells caused them to proliferate faster (Increased K67 expression) and overexpress the tumorigenic growth factor receptor FGFR2[71]. This supports the notion that phytoestrogen foods are healthy, but concentrating them into strong supplements is not recommended.

On the other hand, no study of non-phytoestrogenic foods supplements has shown any detrimental effects on cancer outcomes and some have beneficially influenced progression rates. For example, a study carried out at John Hopkins involving pomegranate seed extract, found that men taking the supplements had a reduction in PSA progression rate[72]. A study conducted at the Mayo Clinic found that green tea concentrate decreased the abnormal white cell count in 30% of patients with chronic leukaemia, and a small study from Louisiana University reported that green tea concentrate significantly reduced levels of several cancer-promoting growth factors as well as PSA levels in participants[26]. In the Vitamins and

Lifestyle (VITAL) cohort study, a regular intake of grapeseed extract was shown to be linked with a lower risk of prostate cancer[70], and another small RCT found that a dietary supplement containing isoflavones, plus other phytochemicals and anti-oxidants delayed PSA progression[73]. Interestingly one of the most popular supplements, Saw Palmetto, despite an effect in early small studies, showed no benefit for prostate cancer or benign prostatic hypertrophy in the largest randomised evaluation[74]. Likewise, another popular supplement, lycopene, despite similar suggestions from smaller non-randomised trials[68, 69], demonstrated no benefits in a more robust evaluation.

So far, the largest trial analysing phytochemical-rich food extracts was the National Cancer Research Network adopted Pomi-T study[75]. This study combined four different food types (pomegranate, green tea, broccoli and turmeric) in order to provide a wide spectrum of synergistically acting nutrients, whilst at the same time avoiding over-consumption of one particular phytochemical. It involved two hundred men, with localised prostate cancer managed with active surveillance or watchful waiting experiencing a PSA relapse, following initial radical interventions.

The results, presented as an oral presentation at the American Society of Clinical Oncology Conference (ASCO), Chicago, showed a statistically significant, 63% reduction in the median PSA progression rate compared to placebo in both men on active surveillance and experiencing a PSA relapse post-treatment. A further analysis of MRI images, demonstrated the cancers size and growth patterns correlated with PSA changes, excluding the possibility that this was just a PSA rather than tumour effect[75]. It was well tolerated, apart from some mild loosening of the bowels in 10% of men, and there was no effect on testosterone levels. At 6 months, significantly more men opted to remain on surveillance rather than proceeding to expensive radiotherapy, surgery or medical castration which can cause unpleasant effects such as depression, hot flushes, weight gain, osteoporosis and erectile dysfunction[75].

A number of other RCT's involving whole food phytochemical-rich supplement have demonstrated benefits for some of the distressing symptoms common after cancer treatments, such as fatigue[76] and urinary infections[77]. There are currently over ten, on-going studies registered with the National Institute of Health. In the UK, the Institute of Preventative Medicine has plans to include the Pomi-T supplement into the next national prostate cancer prevention study. This study will be recruiting men with a higher genetic risk of prostate cancer identified in the national RAPPER study, co-ordinated by the Institute of Cancer Research. Further trials are being designed involving men with prostate cancer already on androgen deprivation therapy and individuals with skin, colorectal and bladder cancer. In the meantime, a trial is passing through the regulatory process to investigate whether the natural anti-inflammatory properties of these ingredients could help joint pains after breast cancer.

Conclusion

There is increasingly convincing evidence to show that plant phytochemicals, particularly polyphenols have significant benefits for humans. Not only do they improve our daily lives by helping our food taste, smell and look appetising, they also reduce our risk of cancer and help people living with and beyond treatments. Living well programmes, slowly being introduced in the UK, are beginning to highlight the importance of phytochemical-rich diets, along side other lifestyle factors, largely being driving by the National Survivorship Initiative and guidelines from influential organisations such as ASCO. Going a step further and concentrating these foods, or extracted elements of these foods, into nutritional supplements gives an opportunity to boost their beneficial anti-cancer effects, but have their pitfalls. Studies of concentrated minerals, vitamins and phytoestrogenic supplements have reported detrimental effects. No study has reported detrimental effects of whole, non-phytoestrogenic food supplements and some have reported significant advantages. Despite these potential benefits and reports that over 60% of patients living with and beyond cancer take nutritional supplements, oncologists have been reluctant to discuss their pros and cons due to a lack of RCTs from academic institutions[55, 56]. Hopefully this trend will change, particularly following the success of the Pomi-T study[75] and ongoing studies registered with the National Cancer Institute.

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