Chapter 4

Plant Phenolics in the Prevention and Treatment of Cancer

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Abstract

Epidemiological studies indicate that populations consuming high levels of plant derived foods have low incidence rates of various cancers. Recent findings implicate a variety of phytochemicals, including phenolics, in these anticancer properties. Both monophenolic and polyphenolic compounds from a large variety of plant foods, spices and beverages have been shown to inhibit or attenuate the initiation, progression and spread of cancers in cells in vitro and in animals in vivo. The cellular mechanisms that phenolics modulate to elicit these anticancer effects are multi-faceted and include regulation of growth factor-receptor interactions and cell signaling cascades, including kinases and transcription factors, that determine the expression of genes involved in cell cycle arrest, cell survival and apoptosis or programmed cell death. A major focus has been the inhibitory effects of phenolics on the stress-activated NF-κB and AP-1 signal cascades in cancer cells which are regarded as major therapeutic targets. Phenolics can enhance the body's immune system to recognize and destroy cancer cells as well as inhibiting the development of new blood vessels (angiogenesis) that is necessary for tumour growth. They also attenuate adhesiveness and invasiveness of cancer cells thereby reducing their metastatic potential.

Augmentation of the efficacy of standard chemo- and radiotherapeutic treatment regimes and the prevention of resistance to these agents is another important effect of plant phenolics that warrants further research.

Plant phenolics appear to have both preventative and treatment potential in combating cancer and warrant further, in-depth research. It is interesting that these effects of plant phenolics on cancer inhibition resemble effects reported for specific fatty acids (omega-3 PUFA, conjugated linoleic acids).

Although phenolic effects in cells in vitro and in animal models are generally positive, observations from the less numerous human interventions are less clear. This is surprising given the positive epidemiological data and may relate to mixed diets and synergistic interactions between compounds or the bioavailability of individual compounds. Much of the work in vitro with phenolic compounds has utilized concentrations higher than the amount that can be obtained from the diet suggesting a role of fortified, functional foods in cancer suppression.

Introduction: Epidemiology of Plant Foods and Disease Incidence

The role of nutrition in the prevention of disease has been recognised for centuries. Hippocrates, some 25 centuries ago, stated "Let food be thy medicine and medicine be thy food", thereby recognizing the importance of food in determining the health of an individual. He also highlighted

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the fact that, since time immemorial, plants and plant extracts have been used as treatments of the various ailments known to man. This tenet is further supported by numerous population-based studies that show clear differences in incidence rates of various diseases, including cancers, in different countries throughout the world. For example, there is a distinct North-South divide in Europe with the incidence rates of most types of cancer being significantly lower in populations from Southern European and particularly Mediterranean countries, compared with those from Northern European countries.[1,2] Similarly, populations in South East Asian countries have a much lower risk of developing numerous cancers, including colon, gastrointestinal, prostate, breast compared to their more industrialized, Western counterparts.[1-6] Epidemiological studies have also revealed that certain, specific cancers appear to be more prevalent in people from some cultures than from others.[3-6] As already stated, cancers of the lung, colon, breast and prostate are very common in populations from Western compared to Eastern countries whereas cancers of the head, neck and cervix are more common in Indian populations and stomach cancer is significantly more prevalent in Japanese populations.

That these variations in cancer risk were probably not the result of genetic variations between populations from different countries was also evident from a number of migration studies where people migrating from their native country to an adopted country (mainly the USA) developed the risk profile and cancer incidence of their adopted country within one or two generations.[3-6] Similarly, the heritability of breast cancer was investigated in a study with identical twins (100% homology in DNA) in Sweden and showed that if one twin developed the disease the likelihood of the second twin also developing the disease was only 15-20%, suggesting that the inheritance of faulty genes only made a small contribution to the overall pathogenesis of the disease within a population.[7] This agrees with the known percentage distribution of inherited/mutated breast cancer genes like BRCA1, BRCA2, Her-2/neu.[8]

Since the genetic composition of individuals and populations can only account for a small proportion of their cancer risk, other factors external to the individual must play a major role. It has been estimated that 75%-85% of chronic illnesses and diseases appear to have significant lifestyle factors in their aetiology and chief amongst these are smoking, lack of exercise and poor nutrition.[9] Doll and Peto[10] suggested that a majority of cancers diagnosed in the USA in 1970 might have been prevented if lifestyle factors like diet and smoking had been modulated. A large number of studies have since supported these suggestions and it has been estimated that circa 30% of cancer deaths could be attributed to inadequate diet, which is on a par with cancer deaths attributable to smoking; i.e., poor diet and smoking can account for circa 60% of cancer deaths.[9-11] Clearly, a combination of heavy smoking, high alcohol intake and inadequate diet, a common occurrence in lower socio-economic groups in Western societies, would be expected to elicit an even greater risk profile.[9-11]

Epidemiological studies have also shown that, those populations with significantly lower incidence of various types of cancer common in industrialized Western populations tended to consume diets that were high in foods of plant origin, namely fruits-including berries, nuts, vegetables, whole-grains, legumes, seeds, various types of tea and a bewildering array of spices, but also low in red meat and animal fats. Such diets are exemplified by the classical Mediterranean diet of Southern Europe and the highly vegetarian diets of South East Asian populations.[11-18] An analysis of results from 206 human epidemiological studies and 22 laboratory animal studies also supported an inverse relationship between the consumption of fruit and vegetables and the risk of developing various cancers.[13] Such compelling evidence of cancer prevention by dietary plants has resulted in great deal of research over the past two decades to identify the specific components of dietary plants responsible for these beneficial effects and the mechanisms by which they elicit these effects. It should be noted here that the quest for natural, plant-derived phytochemicals that express anticancer properties is not restricted to food plants. Pharmaceutical companies are currently isolating and assessing the anticancer potential of numerous phytochemicals from all regions of the World in order to discover more efficient treatments for various types of cancer. The validity of such an approach is evident from the widely used taxanes, first extracted from

the bark and leaves of the Pacific and European yew tree, in chemotherapy of various cancers, particularly breast and prostate cancer.[19] Consideration must be given to the possibility that although individual components of plants may have significant, specific anti-cancer effects, these effects may be even greater when these components are consumed in various combinations, as occur naturally in foods. The interactions and synergisms between compounds occurring within a food matrix should be given greater consideration than at present.

The catalogue of plants, their specific derivatives, their health benefits and the cellular mechanisms by which these benefits are elicited is far too extensive for the somewhat eclectic remit of the present review which will focus mainly on specific phenolic phytochemicals derived mainly from food, beverage and spice plants, although many of these compounds are ubiquitous in the plant kingdom. For a more comprehensive treatise the reader is directed to the many excellent reviews on the different aspects of phytochemicals and human health, some of which are referenced in the current text below.

Anticancer Phytochemicals in Foods, Beverages and Spices

Fruits, vegetables, nuts and whole grains are major sources of fibre, trace metals, essential oils and vitamins all of which are important for the maintenance of human health, including the prevention of cancer, through their effects on numerous cell mechanisms.[1,2,10-18] They also contain a bewildering array of secondary metabolites (micronutrients) including flavonoids and allied monophenolic and polyphenolic compounds, terpenoids, nitrogen-containing alkaloids, phytosterols and sulphur-containing compounds, to name a few, that have been implicated in a reduced cancer incidence. The compounds that have been most cited as being cancer protective include the various catechins from green and, to a lesser extent, from black tea, diallyl sulphides and allicin from garlic and onions; sulforaphanes and indole-3-carbanols from brassica vegetables; genistein from soya; delphinidine and ellagic acid from soft fruits and various nuts; curcumin and resveratrol from turmeric and red grapes respectively; anthocyanins in berries, grapes, cherries and many other fruits.[1,2,10-18,20] This short review will be limited to considering certain aspects of the reported anticancer benefits derived from plant phenolic compounds and the putative cellular mechanisms by which these benefits are derived.

Classification and Occurrence of Plant Phenolic Compounds

The phenolics under consideration are secondary plant metabolites characterized by having one (monophenolic) or more (polyphenolic) aromatic rings with one or more hydroxyl groups attached. Over 8000 different plant phenolics have been identified and they are widely distributed throughout the plant kingdom.[1,2,20-26] The nature, synthesis and distribution of plant phenolics can vary significantly and depends on the plant species, growing conditions and tissue type. The major route of synthesis of mono- and polyphenolic compounds is from carbohydrates by way of the shikimic acid, phenylpropanoid and flavonoid biosynthetic pathways.

Their structure ranges from simple, low molecular weight compounds with a single aromatic ring to the large, complex, multi-ringed tannins. They can be classified by the number and arrangement of their carbon atoms (see Fig. 1 and structures), are generally conjugated with sugars and organic acids and can be grouped into flavonoids and nonflavonoids.

For a more complete description and classification of the major plant phenolics the reader is referred to references.[2,24-26] The following is a brief outline of the salient aspects of phenolic classification and occurrence.

Flavonoids

The polyphenolic flavonoids are the most abundant and numerous plant phenolics with a ubiquitous distribution. They can be categorized into 13 classes comprising more than 5,000 compounds. They are found in high concentrations in leaf epidermis and fruit skins and have important roles to play in the plants as secondary metabolites in such diverse processes as pigmentation, protection against UV radiation and disease resistance.[2,24-26] The major sub-classes

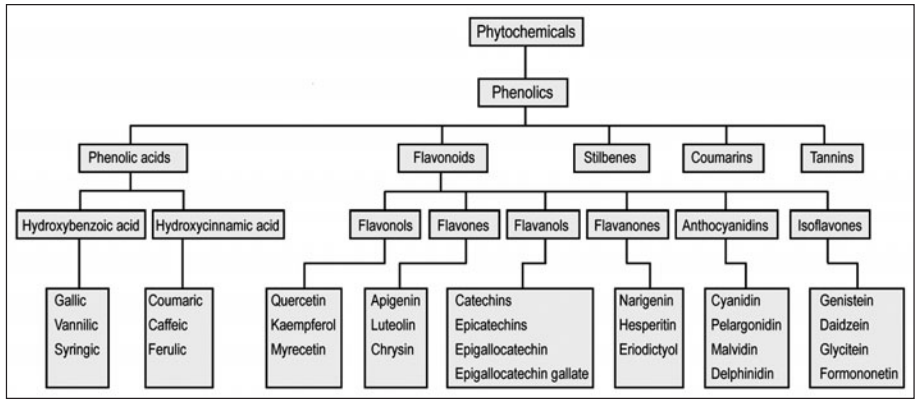

Figure 1. A brief classification of some phenolic phytochemicals reported to have health benefits.

of flavonoids are the flavones, flavonols, flavan-3-ols, isoflavones, flavanones and anthocyanidins (Fig. 1). Other sub-groups are of less importance in nutrition such as dihydroflavones, flavan-3,4,-diols, coumarins, chalcones, dihydrochalcones and aurones but they may still have anticancer effects.[2,24-26]

The bioactivity of flavonoids is also dependent on the various structural sub-constituents such as hydroxyl groups, usually present at the 4-, 5- and 7-positions in the ring. Sugar attachments are common and the majority of flavonoids exist naturally as glycosides. Methyl and isopentyl groups are also present, thereby conferring lipophilicity (lipid solubility) to these compounds; sugars and hydroxyl groups increase the water solubility of the compounds.[2,24-26]

Flavonols

Flavonols are the most widespread of all the flavonoids and are found throughout the plant kingdom with the exception of fungi and algae. Compounds such as myrecetin, quercetin, kaempferol and isorhamnetin most commonly occur as O-glycosides. Numerous flavonol conjugates exist with over 200 different sugar conjugates of kaempferol alone. This emphasizes the complexity of the flavonol profile occurring in fruit, vegetables and beverages as well as their activity levels in relation to health benefits in mammalian systems. This complexity is compounded further by the marked differences in concentration of these compounds that can occur in apparently similar produce which is possibly due to seasonal changes, growing regions and different varieties of the same produce.[2,24-26]

Flavones

Flavones are structurally very similar to flavonols (Fig. 1, ia) but they lack the hydroxyl group at position 3 of the C-ring. As with the flavonols, a large number of substitutions are possible including hydroxylation, methylation, as well as alkylation and glycosylation. Flavones, unlike flavonols, are not widely distributed in nature and occur mainly in parsley, celery and certain herbs. Polymethoxylated flavones like nobiletin and tangeretin occur in citrus fruits.[2,24-26]

Flavan-3-Ols (Flavanols)(Catechins)

Flavanols are structurally the most complex of the flavonoids. They occur as simple monomers of (+)-catechin and (–)-epicatechin and range in complexity to oligomeric and polymeric proanthocyanidins which constitute the condensed tannins. Proanthocyanidins can occur as polymers of circa 50 catechin units. Flavanols can be hydroxylated to form gallocatechins and can be esterified to gallic acid. These compounds are abundant in black grapes (oligomeric proanthocyanidins) and consequently in red wine. Green tea is a rich source of flavanols, mainly

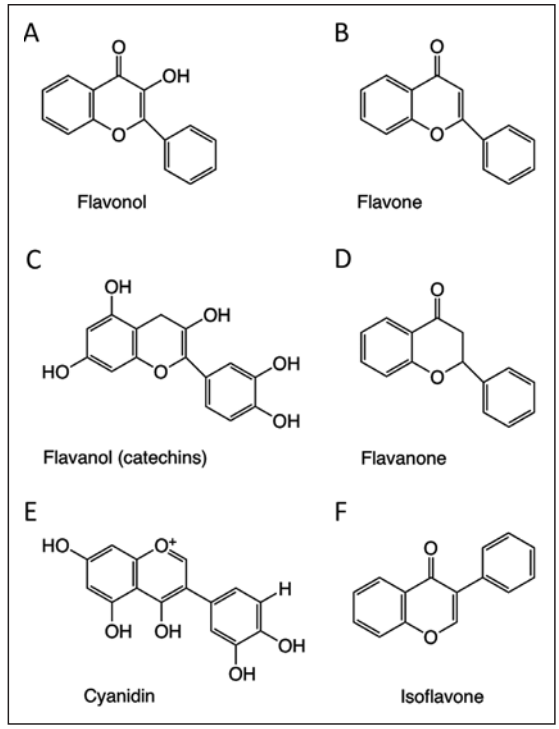

Figure 2. General structures of common flavonoids. In order A) Flavonols; B) Flavones; C) Flavanols; D) Flavanones; E) Anthocyanidins; F) Isoflavones.

(−)-epigallocatechin, (−)-epigallocatechin galate and (−)-epicatechin gallate. Fermentation of the green tea leaves results in a decline in the levels of catechins and consequently black tea contains mainly high molecular weight thearubigens, which are also flavanoids, but their structures have not been clearly elucidated.[2,24-26] A number of intervention and epidemiological studies have shown that the consumption of flavanols can confer health benefits in animals and man, including anticancer benefits (vide infra).

Flavanones

Flavanones are highly reactive compounds and can readily undergo hydroxylation, glycosylation and methylation reactions. They are present in high concentrations in citrus fruits, particularly in the peel (i.e., hesperidin-a flavanone rutiside; naringin from grapefruit peel). For detailed structures see reference.[2,24-26]

Anthocyanidins

Anthocyanidins occur widely in the plant kingdom, principally as their sugar-conjugated derivatives, anthocyanins, where they are responsible for the red, blue and purple colours in a variety of fruits and flowers. They are also found in leaves, stems, seeds and roots of numerous plant species where they are involved in protecting sensitive plant tissues from excessive light and in attracting insects for pollination. The most common anthocyanidins are pelargonidin, cyanidin, delphindin, peonidin, petunidin and malvidin.[2,24-26] Anthocyanins have also been reported to have anticancer effects (see below).

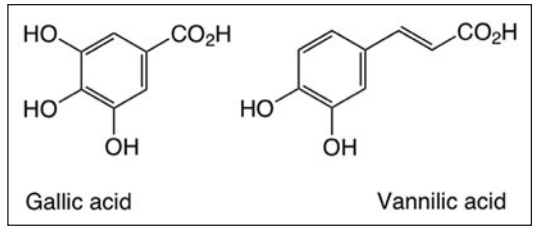

Figure 3. Structure of common phenolic acids; gallic and vannilic acids.

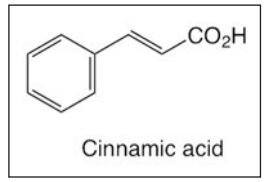

Figure 4. Structure of cinnamic acid (see also Figure 6, coumaric acid).

Isoflavones

Isoflavones are derived from the flavonoid synthetic pathway. Naringenin is converted to genistein via 2-hydroxyisoflavanone and removal of the hydroxy group on carbon 5- of the A ring yields daidzein. Isoflavones such as genistein and daidzein, like other members of the flavonoid family, can readily undergo hydroxylation, methylation and prenylation reactions to yield a range of isoflavonoids including coumestans, rotenoids and pterocarpins.[2,24-26] The isoflavones derived from soya and clovers (genistein, daidzein and the coumestan-coumesterol respectively), are known to have high oestrogenic activity and are termed phytoestrogens. Their structure resembles that of oestradiol, a mammalian steroid hormone that blocks ovulation and can seriously affect reproduction in grazing animals.

Dietary intake of genistein and daidzein in soya products has also been implicated in a reduction of prostate and breast cancer incidence rates in humans. The initiation and progression of these cancers involve androgen and oestrogen dependent mechanisms respectively and the isoflavones compete with the natural hormonal receptor mechanisms and suppress the growth and progression of the tumours.[2,24-27]

Nonflavonoid Phenolic Compounds

The major dietary nonflavonoid phenolics are: (a) the C_6-C_1 phenolic acids, namely gallic and ellagic acids and derivatives (hydrolysable tannins); (b) the C_3-C_3 hydroxycinnamates and their conjugated derivatives and (c) the polyphenolic C_6-C_2-C_6 stilbenes.[2,24-26]

Phenolic Hydroxybenzoic Acids and their Analogues

Gallic acid, one of the main phenolic acids, is formed primarily via the shikimic acid pathway. It is further converted to ellagic acid, another major phenolic acid. These compounds can then be further modified (sugar conjugations) to yield pentagalloylglucose or pentaellagoylglucose and a range of gallotannins and ellagitannins which together form the hydrolysable tannins which are more readily hydrolysed by dilute acids than the condensed tannins.[2,24-26]

Hydroxycinnamates

Cinnamic acid, a C_6-C_3 compound, is produced by deamination of the amino acid phenylalanine which is common to all plants. Hydroxylation of cinnamic acid then results in formation of

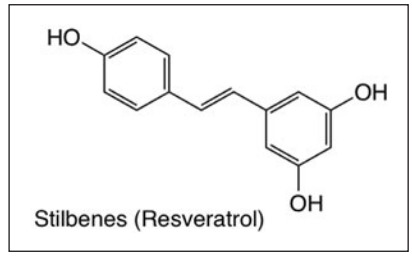

Figure 5. Structure of a common stilbene, resveratrol.

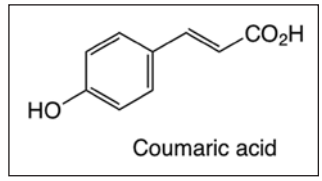

Figure 6. Structure of coumaric acid.

coumaric acid. The most common hydroxycinnamates are caffeic, 4-coumaric, ferulic and sinapic acids which are formed by a series of hydroxylation and methylation reactions. The quinic acid conjugate of caffeic acid, chlorogenic acid, is a common constituent of fruit and vegetables.[2,24-26]

Stilbenes

The stilbenes are polyphenolic compounds with a C_6-C_2-C_6 structure; two aromatic rings linked by an ethene bridge. They are produced by plants in response to various traumas like UV radiation and attack by fungal, bacterial and viral pathogens (infections). Resveratrol is a member of the stilbene sub-group of plant phenolics. It is present in many plant tissues in both the cis- and trans-configuration, often as the glucoside and it is the main phenolic in red wine that has been attributed with many health benefits in man and animals (vide infra).[2,24-26]

Coumarins

Coumarins are lactones derived by cyclisation of cis-ortho-hydroxycinnamic acid. They are characterized by their chemical/structural diversity due to the differing oxygenation in their benzopyrene ring. The majority of coumarins in nature are C7-hydroxylated derivatives. They occur in fruits, vegetables, olive oil, wine and beverages like tea and coffee. They have also been attributed with anti-oxidant and anti-cancer effects in cells and animal models.[2,24-26]

Tannins

Tannins are polyphenolic compounds in two classes characterized by their ability to be hydrolysed; nonhydrolysable tannins are the condensed forms. They are complex polyphenols that can be degraded to sugars and phenolic acids by both enzymatic and non-enzymatic hydrolytic processes. The basic units of hydrolysable, polyester tannins are gallic acid and its derivatives.

Tannins are high in many unripe fruits and levels decline as the fruit ripens. They also occur in nuts, food flavourings and red wine. Their astringent taste and adverse effects on gastric digestive enzymes makes them unpalatable to many mammalian species unless they are adapted to detoxify them. They have also been ascribed important antioxidant and anti-inflammatory effects in human cancer cells.[2,24-26]

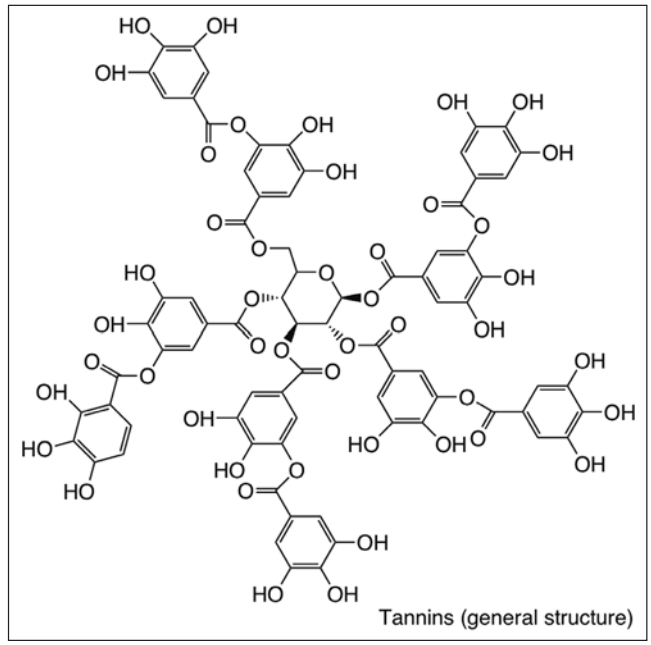

Figure 7. General structure of a tannin.

Other Important Dietary Mono- and Polyphenolic Compounds

Tyrosol and Hydroxyryrosol

These two monophenolic compounds are simple phenolic acid analogues and are important constituents of olive oil. Along with the high content of oleic acid (18:1), they have been implicated as major factors in the general health benefits of the "Mediterranean diet" including anti-cancer and anti-cardiovascular disease effects. They are also present in other edible oils and in wine. They are reported to have antioxidant and pro-apoptotic effects in various human cancer cells.[2,21-26]

Oleuropein

Another important phenolic compound found in olive oil, where it is present mainly as the glycoside esterified to a sugar moiety. As with the tyrosols, oleuropein is attributed with antioxidant and anti-inflammatory effects as well as inducing cell cycle arrest and apoptosis in various human cancer cells.[2,21-23]

Cellular Mechanisms Modified by Plant Phenolics That Can Reduce Carcinogenesis and Tumour Progression

Conventional therapeutic and surgical modalities have been responsible for the marked improvement in recent years in the survival and enhanced quality of life of patients with a variety of cancers. There is now a great need to prevent or attenuate the increasing incidence rate of various cancers in Western and industrialised populations. A judicious modification of diet with increased intakes of fruit and vegetables, with its increased availability of constituent phytochemicals, appears to be a strong lifestyle change that meets such a requirement.[1,2,10-18,20-27]

A wealth of epidemiological evidence suggests that one-third of cancers can be prevented through the consumption of appropriate diets containing adequate levels of fruit, vegetables and whole grains. Nutrition experts suggest that 5 or more helpings of fruit and vegetables would confer

significant benefit to the individual although it is difficult for people to assess what constitutes a helping and consequently such loose terminology needs to be clarified.[1,2,10-18,20-27]

The complex, multi-step processes leading to carcinogenesis can be activated by a number of environmental factors such as cigarette smoke, industrial pollutants, oxidative and inflammatory agents. The process of carcinogenesis can be broadly categorized into three distinct phases: tumour initiation, promotion and progression. Phytochemicals, including specific plant phenolic compounds, appear to play a significant role in suppressing all three stages of tumour formation and metastasis, including the transformative, hyperproliferative and inflammatory processes involved in initiation, the angiogenic processes required for tumour growth as well as the vascular adhesive properties necessary for metastasis or tumour dispersion.[1,2,16-18,20-27] In recent years, following the positive epidemiological evidence of phytochemical intake preventing cancer, a great deal of research has identified a variety of cellular signaling mechanisms that support this hypothesis and shows that numerous phytochemicals can modulate distinct cell receptors and signal transduction pathways to suppress the carcinogenic process, both in vitro and in vivo in animals and to a lesser extent in man.[1,2,20,22-25,28-30]

Effects of Phenolics on Growth Factors and Receptors (GFRs) Implicated in Cancer Initiation and Progression

Growth factors are proteins that bind to specific receptors on cell surfaces to elicit a signaling cascade responsible for the normal activation of cell proliferation/differentiation required for tissue growth and repair. Aberrant growth factor expression/availability results in a signaling cascade leading to uncontrolled cell proliferation and differentiation, suppression of apoptotic signals and ultimately in carcinogenesis, tumour growth/progression and metastasis.[2,20,22,24,25,29]

Major growth factors implicated in carcinogenesis are epidermal growth factor (EGF), plate-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors-α and -β (TGFs-α and -β), insulin-like growth factor (IGF), erythropoietin (EPO), as well as the inflammation-related cytokines interleukin1,-2,-6,-8 (IL-1,-2,-6,-8), tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and colony stimulating factors (CSFs).[24,25,29]

The binding of these factors to their specific receptors elicits powerful cell proliferation signals through the activation of signal cascades involving various receptor-regulated and cytosolic kinases and transcription factors which forms the basis of growth factor/receptor driven carcinogenesis and tumour progression.[24,25,29] Compounds that can attenuate GF binding and the attendant signal cascade are generally regarded as excellent chemo-preventive agents.

Plant phenolics such as curcumin, genistein, resveratrol and catechins are potent inhibitors of a number of growth factor binding and signaling pathways implicated in cancer. Thus, curcumin inhibits EGFR action and reduces the invasive potential of cancer cells.[31,32] Curcumin also inhibits EGF kinase activity in A431 cells[32] and EGF expression in Ishikawa endometrial cancer cells probably by inhibiting the tyrosine kinase activity.[33] This phenolic attenuates the Her2/neu receptor expression that is often over-expressed in breast, prostate, ovarian and lung cancer, indicating poor prognosis, by inhibiting the tyrosine kinase activity (e.g., c-Src) involved in activation of the G-protein-coupled receptor.[34] Similarly, the flavonoids apigenin and quercetin were shown to induce apoptosis by increasing the phosphorylation of Her2/neu via the PI3/Akt kinase pathway and subsequent proteosomal degradation in breast cancer cells over-expressing this receptor/transcription factor and suppress tumour growth in DMBA-induced rat mammary tumours in vivo by inhibiting the PTK pathway.[35,36] Consumption of olive oil, with its high oleic acid and phenolic content, has long been implicated in the reduced cancer incidence in Mediterranean compared with Northern European countries. The phenolics oleuropein aglycone and hydroxytyrosol have also been shown to deplete the over-expressed HER2/neu receptor expression (mRNA and protein) on breast cancer cells. Furthermore, oleuropein resulted in a synergistic augmentation of the Herceptin-induced down-regulation of Her2/neu expression indicating that such phenolics could be used as adjunct therapeutic agents to the standard chemotherapy in cancers expressing high HER2/neu.[36,37]

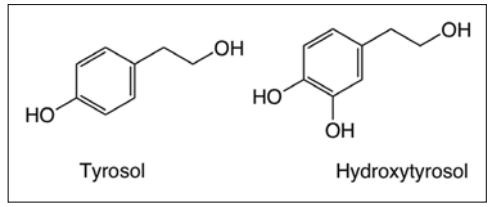

Figure 8. Structure of tyrosol and hydroxytyrosol from olive oil.

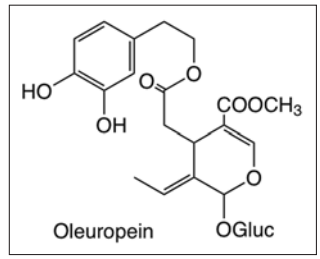

Figure 9. Structure of oleuropein from olive oil.

Resveratrol inhibited IL-6 and IL-8 expression in stimulated animal and human monocytic cells and suppressed proliferation of Ishikawa cells by down-regulating of EGF effects.[25]

The major green tea phenolic EGCG attenuates IL-6 and IL-8 expression, reduces VEGF production in breast cancer cells and inhibits VEGF-induced angiogenesis by suppressing VE-cadherin (an adhesin molecule) phosphorylation and inactivating the Akt pathway.[24,25] EGCG is known to inhibit activation of EGFR and human EGFR-2 signaling pathways in human colon cancer cells and this is thought to be through direct inhibition of the ERK1/2 and Akt kinases. Green tea also inhibits expression of other factors including FGF, VCAM-1 (an adhesion molecule) and HER-2/neu.[24,25] Flavonoids can also attenuate the expression of ICAM-1, E-selectin and E-cadherin, which possibly explains their attenuation of metastasis.[24,25,29,38]

Plant phenolics are regarded as potent antioxidants and their major beneficial effects on health, including anti-atherogenic and anti-cancer effects, appear to relate, in part, to their ability to down-regulate the oxidative and inflammatory signal cascades through such redox-sensitive transcription factors as NF-κB and AP-1 and subsequent modulation of down-stream gene expression.[20,24,25,29,39,40]

Attenuation by Phenolics of Oxidation and Inflammatory Processes

Oxidative and inflammatory stresses are now recognized as being closely involved in the initiation and progression of carcinogenesis. Excessive formation of reactive oxygen species (ROS) in cells can damage proteins, DNA and RNA and can oxidise membrane polyunsaturated fatty acids, thereby increasing the likelihood of deleterious mutations occurring in the genome.[20,24,25,29] ROS are regarded as major activators of the NF-κB and AP-1 transcription factor pathways.[20,24,25,29,41] Numerous dietary phenolics are potent antioxidants, capable of scavenging deleterious reactive species such as superoxide anions, singlet oxygen hydroxy radicals, nitric oxide and peroxynitrite.[20,24,25,29,42] Various phenolics are also able to attenuate ROS generation through inhibition of redox sensitive transcription factors such as NF-κB and AP-1 responsible for the expression of the ROS-induced inflammatory enzyme cascade. Xanthine oxidase, COX-II and LOX were shown to be reduced by dietary phenolics like curcumin, silymarin and resveratrol.[20,24,25,38,39,43,44]

Polyphenols can also induce detoxifying enzymes such as glutathione-S-transferase (GST) and quinone reductase (QR) which can protect cells from carcinogenic intermediates, exogenous or endogenous.[20,40,45]

Effects of Phenolics on Cell Cycle and Apoptotic Mechanisms

Disruption of normal cell cycling mechanisms and the over-expression of growth promoting mechanisms such as cyclin D1 and the cyclin-dependent kinases (CDKs) are major events in carcinogenesis.[20,24,25,46,47]

Phenolic compounds such as resveratrol have been shown to inhibit a variety of cells at different stages of the cell cycle, i.e., at G1, S, S/G2 and G2, both in vitro and in vivo in animal models of cancer.[20,24,25,47,48] ECGC elicits its effects by directly inhibiting CDKs or indirectly by inducing p21 and p27 gene expression and inhibiting cyclin d1 and Rb phosphorylation. Recently, resveratrol was shown to arrest HL-60 cells in the S/G2 transition phase, increase cell numbers in G1/S phase and induce apoptosis, possibly as a result of decreased Bcl-2 expression, a major anti-apoptotic oncogene.[20,24,25,29,47] Apigenin (celery, parsley), genistein (soya) and silymarin (milk thistle) have also been shown to modulate the effects of deregulated cell cycle checkpoints and are thereby believed to contribute to the prevention of cancer. They appear to elicit their beneficial effects not only through cell cycle arrest and the induction of cyclin-dependent kinase inhibitors (p15, Cip-1/p21 and Kip-1/p27) but also through down-regulation of anti-apoptotic gene products (Bcl-2, Bcl-xL) and induction of pro-apoptotic p53 and Bax.[24,25,29,47,49] Apoptosis, or programmed cell death, is an important mechanism in normal development and in anticancer surveillance. The process is regulated by various oncogenes/proteins, including the important pro-apoptotic p53, the anti-apoptotic and cell survival Bcl-2 and the caspase cascade.[24,25,29,47]

Effects of Phenolics on Chemokines and Cytokines

Chemokines are small chemotactic cytokines responsible for leucocyte targeting and activation of inflammatory responses and they are involved in the regulation of tumour growth. Chemokines exert their migration- inducing effects on leukocytes through binding to specific chemokine receptors such IL-8/CXCL8 which stimulates endothelial chemotaxis, proliferation and angiogenesis in vivo and have been detected in high concentrations in a variety of tumours.[24,25,50]

Dietary phenolics like curcumin, resveratrol, quercetin, green tea polyphenols, black tea theaflavin, soya genistein and capsaicin from peppers have all been shown to attenuate chemokine and cytokine expression.[25,50-54]

Curcumin is a potent anticancer agent. It inhibits expression of inflammatory cytokines and chemokines (mRNA, protein) and their signal cascades in tumour cells but effects are reversible within 24hrs after removal of the phenolic.[25] This suggests that a constant intake of these compounds is necessary in order to inhibit carcinogenesis. Similarly, resveratrol inhibits phorbol ester-induced IL-8 expression in U937 cells, partly through inhibition of AP-1 activation.[51] Suppression of NF-κB activation by quercetin is also responsible, in part, for the inhibition of IL-1 induced expression of MCP-1.[52] Green tea EGCG inhibits the expression of chemokines IL-8, MIP3 and of prostaglandin E2 (PGE2), a down stream product of NF-κB transcriptional activity, in TNF-stimulated colon epithelial cells.[53] Theaflavin, from black tea, can inhibit TNF-stimulated IL-8 gene expression, probably at the transcriptional level (mRNA) and through inhibition of both IKK/NF-κB and AP-1 pathways.[54] Genistein and capsaicin have also been shown to inhibit expression of various growth factors/chemokines/cytokines in different, stimulated, cell types including melanoma cells through the suppression of the NF-κB pathway.[24,25,40]

Phenolic Suppression of Angiogenesis

As stated previously, angiogenesis, or new blood vessel formation, is vital for supplying nutrients and oxygen to the tumour and ensuring its growth and progression, its invasiveness and spread to other tissues. Prevention of angiogenesis would "starve" the tumour and prevent metastasis.[20,24,25,49,50] Consequently, angiogenesis inhibition is an active objective in current anticancer research.

Quercetin, genistein, resveratrol and various phenolic acids are capable of inhibiting angiogenesis in in vitro cell-based systems as well as in animal models. These effects appear to be due to attenuation of matrixmetalloproteinases (MMPs) inhibition of VEGF and their Src kinases.[24,49] These phenolics have also been shown to attenuate the expression of vascular adhesion molecules which would reduce the metastatic process.[25,38]

Epigenetic Modulation as a Novel Chemopreventive Role for Phenolics

DNA methylation state is regulated through the activity of DNA-methyltransferases (DNMTs) and demethylating reactions. Hypermethylation of reporter regions of specific genes results in their transcriptional silencing. Although hypermethylated genes can be inherited, the process of methylation is reversible and genes can be reactivated by removal of methyl groups.[24,25,29]

Numerous genes have been shown to be hypermethylated and consequently inactivated or hypomethylated and activated, in cancer cells.[55] These include genes involved in cell cycle regulation (p16, p21waf1/cip1, p151, Rb), genes associated with DNA repair (BRCA1 and 2, MGMT), redox enzymes (GPx1 and 4, MnSOD), apoptosis/tumour suppression (p53), drug resistance, detoxification, angiogenesis and metastasis, all of which are susceptible to hypermethylation and silencing. Various phenolics, including green tea polyphenols (epicatechin, catechin, EGCG) and flavonoids (quercetin, myricetin, fisetin) have been shown to reactivate silenced genes in cancer cells by inhibiting DNMT activity and reversing hypermethylation of their promoter DNA in a time and concentration manner.[55-57] Phenolics (e.g., EGCG) are also able to reverse hypomethylation that is observed in many cancers, presumably silencing pro-carcinogenic gene expression.[55]

Cancer Cell Sensitization and Reversal of Drug Resistance by Phenolics

Most chemotherapeutic agents and radiotherapy used in cancer treatment activate the NF-κB survival pathway which can eventually result in resistance to the treatment. Co-administration of phenolic chemopreventive agents such curcumin will tend to upregulate proapoptotic pathways (p53, p21waf1/cip1) whilst also downregulating the cell survival mechanisms (PI3K, AKT, NF-κB, AP-1) and changing the survival Bcl-2:Bax ratio to proapoptotic one.[29] Resveratrol was shown to enhance chemo-sensitisation by downregulating another cell survival gene, survivin.[58,59] EGCG from green tea also inhibits growth in human breast cancer cells by suppressing surviving expression; a member of the inhibitor of apoptosis proteins (IAP) highly expressed in cancer cells/tissues.[60]

Immune Response-Mediated, Anti-Cancer Mechanisms of Phenolics

The removal of cancer cells by the host immune response has long been regarded as the most desirable anti-cancer strategy. This is primarily because the immune system, due to its highly specific recognition mechanisms, has the potential to eradicate cancerous cells with the least damage to normal cells. The enhancement of immune cell responses that can specifically target cancer cells could prove to be a very effective preventive and treatment strategy. Thus, either nutrients or drug treatment modalities that enhance anti-tumour effector cell activities have naturally been perceived as an ideal mechanism in cancer treatment/prevention. The most simplistic perspective of enhanced immunity toward cancer cells is the direct enhancement of specific cell activities, particularly those that can kill tumour cells. T-cells are a potential target for any immunotherapeutic approach and enhancement of T-cell activity could enhance anti-tumour immunity. $CD8^+$ cytotoxic T-cells directly engage and kill appropriate target kills and one of the first T-cell responses to stimulation is the rapid clonal proliferative expansion of the T-cell population. The study of Gao et al,[61] showed that resveratrol at low concentrations (<12.5 μM) enhanced concanavalin-induced proliferation with no effect on IL-2-induced proliferation. This difference demonstrated that resveratrol does not enhance the proliferative response per se, rather it enhances the upstream mechanisms which signal for proliferation, most likely enhancing the T-cell receptor-mediated induction of IL-2, the major T-cell growth factor. However, resveratrol did not enhance the killing capability of these T-cells against lymphoma target cells. This study also showed that very high resveratrol concentrations (>20 μM) can suppress the effects, indicating a biphasic response to resveratrol which can have

implications for the use of this phenolic in human studies, i.e., high doses can have the opposite effect on immunity than intended.

A comparable study had also demonstrated similar results in human immune cells. Resveratrol was shown to increase the proportion of $CD8^+$ cells that produced interferon-gamma and IL-2 in response to activation of the T-cell receptor via CD3 and also costimulation via CD28.[62] These are cytokines that are important in the activation of T-cell receptor-mediated, cell killing capability; this was confirmed in the study when the authors also showed that specific cell killing (cytotoxicity) was enhanced. These effects were shown at low concentrations of resveratrol ($\leq$10 μM) whereas higher concentrations ($\geq$20 μM) had a suppressive action.[62] This study further showed that resveratrol enhanced natural killer (NK) cell cytotoxic activity against target human cancer cells at even lower concentrations ($\leq$1 μM). This is an extremely important observation since NK cells are a major mechanism whereby mutated cells can be eliminated in the earliest stages of cancer development. An example of this, with respect to specific cancers, is the control of melanoma by NK cells, where it has been confirmed that NK cells can directly lyse melanoma cells when the absence of self-antigens is detected.[63] These studies clearly indicate that low concentrations of resveratrol can enhance the profile of immune responses that are capable of suppressing/eliminating cancer cells in a specific and coordinated manner. Similarly, the flavonoid quercetin can also upregulate human antitumour mechanisms by selectively increasing the production of interferon-gamma thereby augmenting immune-cell mediated cell killing actions and downregulating suppressive cytokines such as IL-4.[64]

By contrast the flavonoid kaempferol has been shown to be suppressive toward $CD8^+$ cell activities including interferon-gamma production and may be counterproductive in cell-mediated cancer immunotherapy.[65] This polyphenol does attenuate adhesion molecule expression in vascular cells[25,38] and may thus be more effective in preventing metastatic spread of cancers.

A more recent consideration in our understanding of how immune responses control anticancer activity is the regulation of suppressor mechanisms in the ex vivo inhibition of suppressor/regulatory T-cell (Treg) which when switched-off can be permissive for a series of diverse immune cell responses. A recent study by Yang et al,[66] showed that resveratrol administration can regulate activities in tumour-derived cells, especially the release of cytokines (including transforming growth factor-beta), that inhibit the activation of many immune cells. Furthermore, the authors confirmed that this inhibition of cells also resulted in increased immune stimulatory activities, such as interferon-gamma production by $CD8^+$ cells, resulting in an unfavourable microenvironment for tumour cells to grow and proliferate by enhancing cell cytotoxic mechanisms. This gives an important insight into the possible mechanisms by which polyphenolic compounds such as resveratrol can modulate immune responses directly relevant to the elimination of cancer cells. They also show the importance of appropriate doses and that low doses, such as the ones that can be obtained from the diet, could be extremely beneficial in the immunotherapy of cancer.

Conclusion

This brief, eclectic review highlights the fact that plant phenolic compounds, consumed as part of a balanced diet, are able, not only to prevent cancer initiation, progression and metastasis through a variety of cell mechanisms, including immune cell functions and angiogenesis, but are also capable of enhancing standard chemo- and radiotherapeutic modalities by reversing the cell mechanisms that lead to desensitization. Such adjunct treatment with natural, dietary components would be expected to reduce the known debilitating side effects of standard treatments and should reduce the likelihood of cells/tissues becoming desensitized. The anticancer effectiveness of multi-matrices, as found in foods, should not be underestimated. Tumour cells utilize a multitude of survival mechanisms to remain viable and consequently preventative and treatment modalities that are capable of suppressing a number of pro-carcinogenic/pro-tumorigenic pathways, such as the ingestion of plant phenolics from our diet, have great potential in the future prevention and treatment of cancer.

Observations that omega-3 polyunsaturated fatty acids and conjugated linoleic acids appear to elicit similar anticancer effects on various cancer cells and animal models and that the same signaling cascades are affected suggests a common aetiology and warrants investigation.[67]

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