NATURALLY OCCURRING SUBSTANCES AND THEIR ROLE IN CHEMO-PROTECTIVE EFFECTS

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SUMMARY

Cancer chemoprevention is defined as the use of natural, synthetic or biological chemical agents to reverse, suppress or prevent carcinogenic progression of invasive cancer. Carcinogenesis is a complex multi-step process; therefore, it is necessary to attack cell proliferation, stimulate apoptosis and inhibit angiogenesis. There have been more than 60 randomised trials using chemopreventive potential agents.

The success of several recent clinical trials in preventing cancer in high-risk populations suggests that chemoprevention is a rational and appealing strategy. In this review, we describe the conceptual basis for the chemoprevention of cancer, proven concepts of efficiency and current trends in the use of chemopreventive agents according to place and mechanism of action. We classify chemopreventive substances into seven groups based on their chemical structure and their effects, namely, deltanoids (paracalcitriol), retinoids (13-cis retinoic acid), non-steroidal anti-rheumatics (Deguelin), antiestrogens (genistein), polyphenols (curcumin), sulphur containing compounds (sulforaphane) and terpenes (lycopene). Chemoprevention is one of several promising strategies for reducing the incidence of malignant tumours or helping to prolong the time before recurrence.

Key words: chemoprevention, cancer, malignant transformation, inhibitors of metastasis

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INTRODUCTION

Chemoprevention is understood to mean the use of natural or synthetic substances to slow, inhibit or insult the start of carcinogenesis – the change in the genetic and regulation system of the cell induced by carcinogens. In respect to the individual phases of carcinogenesis, anti-initiating, anti-promoting and anti-progressive strategies play a role in chemoprevention. Anti-initiating strategies include scavenging DNA-reactive electrophilic compounds and free radicals, intensive carcinogen detoxification or stimulating DNA repair mechanisms. Inhibiting proliferation and angiogenesis, supporting apoptosis and scavenging ROS – *reactive oxygen species* represent anti-promoting and anti-progressive approaches.

Phytochemicals are substances present in fruit, vegetables and different plants, and some phytochemical have a modulation potential that is very beneficial regarding cancer chemoprevention. Naturally occurring chemopreventive compounds can be divided, according to their chemical structure and biological activity, into a few groups: terpenes, sulphides, phenols, organic acids and other macromolecules. The mechanism of phytochemical action is set on anti-oxidative effects, carcinogen detoxification through cytochrome P450 activation, carcinogen modification by inhibition of specific enzymes, regulation of gene expression during cell proliferation and apoptosis as well as modification of hormone receptors and inhibitory effects on the vascularisation of a tumour. All of the following – deltanoids, retinoids, rexinoids, antiestrogens, aromatase inhibitors, 5-alfa reductase, COX-2 inhibitors, non-steroidal anti-inflammatory drugs, some fruits or plants substances like epigalocatechin-3-galat, curcumin, resveratrol, lycopene as well as the other antioxidants like vitamin E, N-acetylcysteine, L-carnitine and selenium – are among chemopreventives.

Deltanoids

Deltanoids are derivates of vitamin D. The active form of vitamin D is calcitriol (1, 25-dihydroxycholecalciferol), which is synthesised in the skin from 7-dehydrocholesterol after UV-B irradiation followed by hydroxylation in the hepatocytes and oxidation in the kidneys (Fig. 1.A). In many studies calcitriol is believed to be a chemopreventive substance with anti-proliferative, anti-angiogenic, anti-metastatic and pro-apoptotic effects (1–5). Chemopreventive and anti-carcinogenic effects are caused by binding to a specific nuclear vitamin D receptor – VDR. Activated VDR influences the transcription of many genes associated with differentiation, proliferation, neo-angiogenesis, and metastasis.

Different studies have shown this chemopreventive effect in carcinoma of the breast, prostate, bladder, and colorectum as well as in bone cancer or myelodysplastic syndrome, especially when using calcitriol and paracalcitriol (19-nor-1, 25-dihydroxyvitamin D2) (Fig. 1.B), but thus far these findings have not been supported by randomised controlled trials (4, 6, 7). In essence, the implication resulting from the Institute of Medicine (IOM) report concerning the non-osseous roles of vitamin D is that there may be a biological plausibility and/or an epidemiological association.

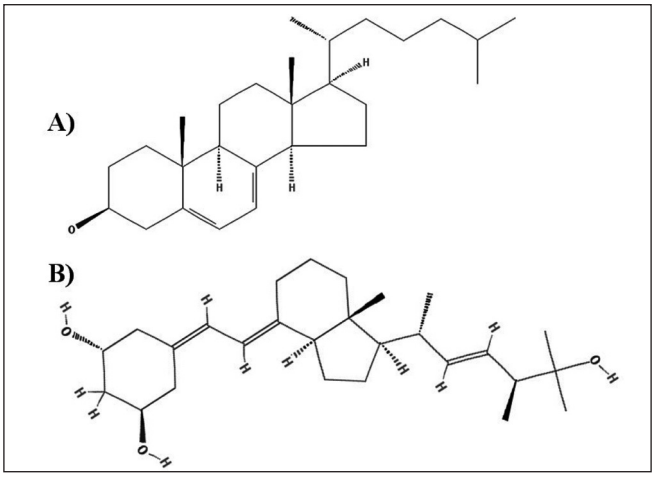

Fig.1. *Deltanoids: A) 7-dehydrocholesterol, B) 19-nor-1, 25-dihydroxyvitamin D2.*

However, there is no consistent, conclusive or sufficient evidence to support a daily dose or a range of serum 25-(OH)D concentrations associated with the non-osseous functions of the vitamin (8).

Retinoids, Rexinoids

Natural or synthetic derivatives of retinol – vitamin A (3, 7-dimethyl-9-(2, 6, 6-trimethyl-1-cyclohexenyl)-nona-2, 4, 6, 8-tetraen-1-ol) – are called retinoids. The main supply of naturally occurring retinoids occurs in form of retinyl esters from animal foods. Due to the activity of isomerase in cells, specific isomerase derivatives are created; these bind to specific nuclear receptors RAR (retinoid acid receptor) or RXR (retinoid X receptor). Each of them comprises three isotypes encoded by separate genes, designated α, β and γ (9). Rexinoids are defined as agents that bind selectively to RXR receptors. In general, retinoids with a selective effect on RAR have different biological properties than rexinoids with a selective effect on RXR. Retinoid receptors are homo or heterodimeric. Once activated, retinoid receptor dimers bind to DNA at retinoic acid response elements and act as transcription factors that regulate the expression of genes which control cellular differentiation and proliferation. Retinoid agonists can activate the expression of retinoid-regulated genes by removing negative transcription control or by facilitating positive transcriptional activity. They exert anti-cancer action by interfering with the growth of tumour cells (10). Differentiation therapy of acute promyelocytic leukemia (APL) is based on the ability of retinoic acid to induce differentiation of leukemic promyelocytes. All cases of APL are associated with chromosomal translocations involving RARα (retinoic acid receptor). More than 99% have a characteristic chromosomal translocation which produces a fusion protein between RARα and a protein called promyelocytic leukemia protein (PML) (11). PML–RARα is responsible for the initiation of leukemogenesis in humans (12).

13-cis retinoic acid (RA) was used as chemopreventive agent after bone marrow transplantation in neuroblastoma via blockade of p21, p27, cyclin E and cyclin A during the cell cycle (13) (Fig. 2). Upregulated p21 by RA accompanies caspase-3 activation and precedes the occurrence of apoptosis, p21 induction leads to increased p21 complex formation with cyclin E/CDK2, which occurs when cyclin E and CDK2 levels remain constant. CDK2

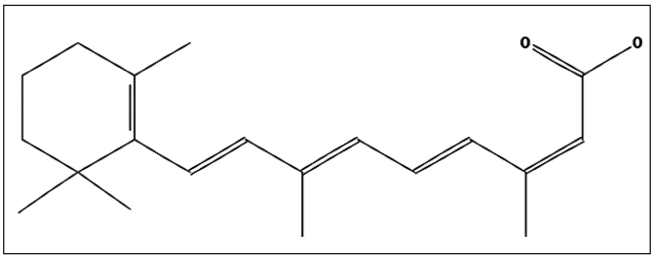

Fig. 2. *Retinoids, 13-cis retinoic acid.*

can alternatively promote apoptosis, but the mechanisms remain unknown. These data suggest a novel RA-signaling, by which RA-induced p21 induction and complex formation with cyclin E/CDK2 diverts CDK2 function from normally driving proliferation to alternatively promoting apoptosis (14).

The regression of disease after targeted administration of ATRA (all-trans retinoid acid, tretinoin) has been observed. N-4-hydroxyfenyl-retinamid is able to induce apoptosis in carcinoma of the breast, bladder and prostate, especially after oxygen radical injury. Bexarotene, the selective antagonist of RXR receptor, is believed to be an effective chemotherapeutic for cutaneous T-cell lymphomas. This is why RARs and RXRs expression and their role in chemoprevention and cancer therapy are among the leading topics of scientific study. In the past two decades, a number of experimental and clinical studies have been performed with retinoids showing the inhibition or reversion of the carcinogenic process in some organs, including hematological malignancy as well as premalignant and malignant lesions in the oral cavity, head and neck, breast, skin, and lung (9). Although Bettoli (15) in his review notes that despite numerous studies in the literature concerning retinoids in the chemoprevention of NMSC (non-melanoma skin cancer), the type of retinoid, dosage and duration of preventive treatment and management of side effects in the case of long-lasting treatment are still not uniform and comparable. Moreover, neither guidelines nor approval by the Food and Drug Administration exist to regulate the use of retinoids in chemoprevention (15).

COX2 Inhibitors, Non-steroid Anti-rheumatics

COX (cyclooxygenase) inhibitors play a role in the chemoprevention of several types of tumours. Cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1) as well as lipooxygenase (LOX) are key enzymes in the synthesis of eicosanoids – signalling molecules derived from arachidonic acid. COX-2 is stimulated by oxidative stress, growth factors (EGF) and cytokines IL-6 or TNF. COX-2 is not expressed in healthy breast tissue, but there its over-expression has been described in hyperplasia and carcinoma tissue (16).

Over-expression of COX-2 leads to over-production of eicosanoids. Since it produces prostaglandin E2 (PGE2), COX-2 plays a role in the regulation of estrogen. PGE2 increases the expression of the cytochrome P-450 enzyme complex known as aromatase, which catalyzes androgen to estrogen conversion. COX-2 could be induced by many factors, such as mitogens, cytokines, and hormones (17). Molecular studies suggest that COX-2 is related to mutagenesis, angiogenesis, inhibition of apoptosis and aromatase-catalyzed estrogen biosynthesis. There is also a hypothesis that local estrogen levels induced by elevated

aromatase activity stimulate tumour growth; thus the development and role of COX-2 seems to be essential in breast cancer. COX-2 is known to be expressed in several cancers, including colorectal, prostate, lung, pancreas, and breast cancer (18).

The effect of NSAIDs (non-steroid anti-inflammatory drugs), which work as selective COX inhibitors, is based on the same principle. There is a huge decrease in the incidence of breast and colorectal carcinoma during chronic intake of NSAID. But long-term usage of some NSAIDs leads to health problems (19, 20). In lung carcinoma chemoprevention, several studies have been done with deguelin, giving hopeful results. Deguelin is a rotenoid from the flavonoid group present in legume family plants, and it inhibits COX-2. Additional effects are that it is a strong pro-apoptotic, via the reduction of anti-apoptotic molecules expression (XIAP − x-linked inhibitor of apoptosis proteins, HSP90 − heat shock proteins), and it has anti-proliferative and anti-angiogenic potency (21). Another member of NSAIDs from flavonoids is quercetin which inhibits the cyclooxygenase pathway. The effect of quercetin-induced apoptosis in neuro2a cells by the activation of intrinsic caspase cascade pathway was assessed by the expression of caspases 3 and 9, bax, cytochrome-c, which led to the induction of apoptosis (22).

Antiestrogens and Phytoestrogens

Antiestrogen is a substance that keeps cells from making or using estrogen. Antiestrogens may stop some cancer cells from growing and are used to prevent and treat breast cancer. They are also being studied in the treatment of other types of cancer. The effect of estrogen on other tissues like bone, endometrial or fat is also being studied. An antiestrogen is a type of hormone antagonist. There are differences in mechanism of action within hormonal chemotherapeutics. SERMs (selective estrogen response modifiers), which include therapeutics such as raloxifen, arzoxifen and tamoxifen, decrease breast-tumour incidence in women with a genetic predisposition (23, 24). SERM have both estrogen agonist and antagonist actions. The most important anti-cancer effect is estrogen receptors (ER) blocking and elimination of the stimulating effect on mammary gland epithelium proliferation. They inhibit the formation of a tumour by stopping the G1 phase of the cell cycle following the inhibition of pRb (retinoblastoma protein) and CDK2 (cyklin-dependent kinase 2). SERDs (selective estrogen receptor down regulators) are pure estrogen antagonists and probably decrease the number of ER by degradation after binding (e.g. fulvestrant) (25). Both preclinical and clinical studies show SERDs to have bigger potency when compared with SERMs in breast cancer cells growth inhibition. They are devoid of any estrogen-agonist action on the uterus and vagina but lack the beneficial effects of SERMs on the bone and serum lipid profile (24, 26–28).

The last from this group are AIs (aromatase inhibitors). After menopause, most circulating estrogens originate from androgen-estrogen conversion by the activity of enzyme aromatase. The development progressed from non-selective to selective non-steroid inhibitors of aromatase, such as letrosol and anastrosol, which block estrogen production (29). The importance of aromatase quantity in tumours was evaluated by Miller et al (31). They observed that most tumours obtain estrogen thanks to both local and peripheral aromatase. If the local aromatisation is crucial for the mammary gland, then in situ blockade of estradiol biosynthesis by aromatase inhibitors is possible and can be effective in mammary gland carcinogenesis suppression. Geisler et al. (32) described the suppression of intratumoural estrogen levels after application of aromatase inhibitors. Mackay et al. (33) described very variable responses after application of aromatase inhibitor YM511, and intratumoural inhibition of aromatase was not sufficient to provide an antiproliferative effect. The expression of the aromatase gene in tumour tissue is controlled by different transcription promoter areas when compared with normal tissue. The importance of chemoprevention or adjuvant hormonal therapy by aromatase inhibition lies in mammary-carcinogenesis inhibition and depression of relapse risk and mortality in patients (34). In comparison with chemotherapy, hormonal therapy had an identical effect considering their relapse risk (35). It is necessary to evaluate the effects of aromatase inhibitors, NSAID and COX-2 inhibitors, in terms of effectiveness and toxicity (raloxifen).

Phytoestrogens are bioactive, naturally occurring plant compounds with a structure similar to that of estrogen resulting in the ability to cause estrogenic and/or antiestrogenic effects through binding to estrogen receptors or modulating the concentration of endogenous estrogens via binding or inactivating some enzymes. Plants serving as food sources of phytoestrogens are nuts, oilseeds, legumes, soya, cereals, and many others. Phytoestrogens are part of a plant's defence mechanism (isoflavones, lignans, coumestanes). Isoflavones are the source of the aglycanes genistine, daidzine and glycetine, which are transformed in the body into active forms as genistein, daidzein, glycetein. Daidzein and genistein behave primarily as weak estrogen agonists (bone, brain), but they can also have an anti-estrogen effect (breast, uterus) (Fig. 3. A and B). Genistein inhibits androgen-dependent and androgen-independent prostatic oncocells *in vitro* and *in vivo* (36–38).

Polyphenols

Polyphenols are a group of chemical compounds contained in plants. They are characterised by the presence of large multiples of phenol units. The properties of particular polyphenols depend on the number and characteristics of phenol structures. Polyphenols are generally divided into phenolic acids, stilbenes, lignans, flavonoids, and other unclassified polyphenols. Phenol phytochemicals

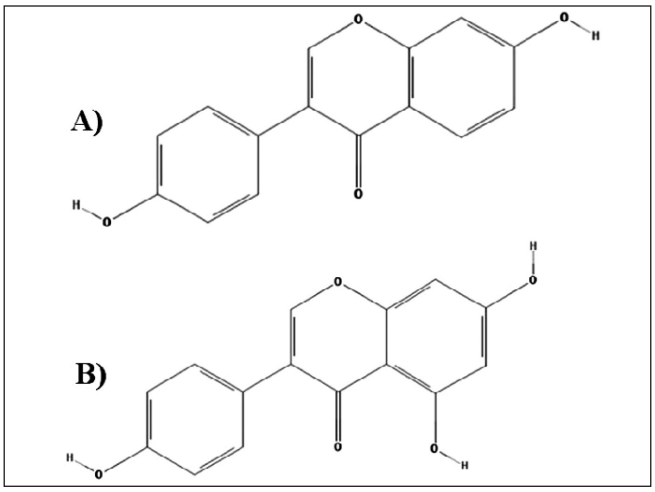

Fig. 3. *Phytoestrogens, A) daidzein, B) genistein.*

are present everywhere in the plant kingdom (green tea, berries, wine, olive oil, walnuts, coffee) (39–44). Structures of individual polyphenols are shown in Fig. 4.

Ellagic Acid

Ellagic acid (Fig.4.A) is a polyphenolic antioxidant present in raspberries, strawberries, cranberries, and many other plant foods. It is a dimer of gallic acid. The anticancer properties of ellagic acid are based on the direct ability to direct the inhibition of the binding of some carcinogens (e.g. nitrosamines, polycyclic aromatic hydrocarbons) to DNA. Like other polyphenolic antioxidants, ellagic acid has in cell models a chemo-protective effect by limiting oxidative stress (45, 46).

Caffeic Acid

Phenol acids and their derivatives show the effects of primary antioxidants. Activity depends on the number hydroxyl groups in the molecule. Antioxidants are generally more active derivatives of cinnamic acid and o-diphenols (e.g. caffeic acid and its ester chlorogenic acid) (47). Caffeic acid is formed from 4-hydroxycinnamic acid and its derivatives, such as caffeic acid phenethyl ester (CAPE), are key intermediates in the biosynthesis of lignins. Caffeic acid (Fig. 4.B) is contained in coffee, potatoes, apples, and pears. It has been shown to inhibit carcinogenesis, although other experiments have revealed possible carcinogenic effects. It is known as an antioxidant *in vitro* and also *in vivo*. In addition, caffeic acid shows immunomodulatory and anti-inflammatory activities (48).

Curcumin

Plant extracts usually have more than one chemopreventive mechanism. It has been experimentally shown that the light-yellow flavonoid present in *Curcuma longa* roots is able to inhibit initiation, promotion and progression of the cancer genetic process. Curcumin (Fig. 4.C) suppresses and inverts carcinogenesis via multifaceted molecular targets. Experimental studies and experimental models have revealed that curcumin regulates several molecules in the cell-signal transduction pathway, including NF-κB, Akt, MAPK, p53, Nrf2, Notch-1, JAK/STAT, β-catenin and AMPK. The cell-signalling pathways modulation, through the pleiotropic effects of curcumin, likely activates cell death signals and induces apoptosis in cancer cells, thereby inhibiting disease progression (49, 50). Plummer et al. (51) reported the inhibition of NF-κB activation by curcumin, leading to the inhibition of COX-2 expression. The COX-2 gene is induced by tumour promoters and tumour necrotic factor alpha (TNF-alpha) in intestine epithelial cells. Curcumin, like another polyphenols, shows significant antitumour synergism when compared with normal cytostatics, e.g. vincristine, gemcitabine or 5-phlourouracil (52).

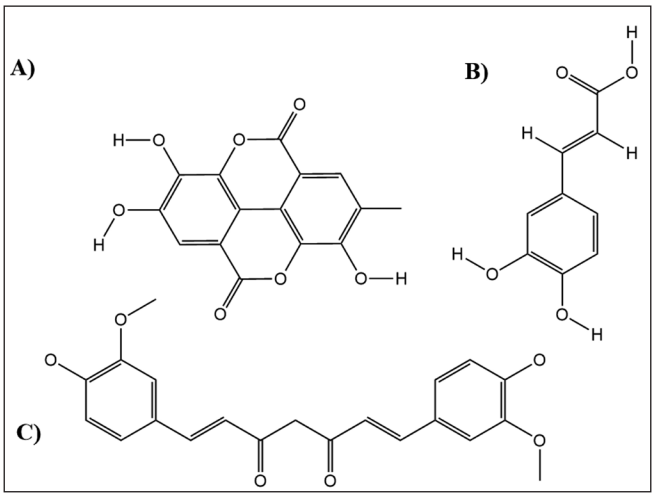

Fig. 4. *Polyphenols, A) Ellagic acid, B) Caffeic acid, C) Curcumin.*

Ferulic Acid

In plants, caffeic acid (Fig. 5.A) is transformed into ferulic acid ((E)-3-(4-hydroxy-3-methoxy-phenyl) prop-2-enoic acid). Ferulic acid is usually associated with food and the fibre in it. The main sources of ferulic acid are foods such as wheat bran, but also coffee, apples, artichokes, peanuts, oranges, and pineapples. Animal studies and *in vitro* studies suggest that ferulic acid may have direct antitumour activity against breast and colon cancer (53–55). Ferulic acid has a significant role in the inhibition of abnormal cell proliferation in cancer cells occurring in induced carcinogenesis due to its modulatory effect on pro-apoptotic genes p53 and bcl-2 expression (56).

Resveratrol

Resveratrol (3, 5, 4-trihydroxy-trans-stilben) (Fig. 5.B) is a natural phenol and phytoalexin produced by many different plants (e.g. grapevine, currants, juniper, grapefruit) when attacked by pathogens (bacteria, mushrooms). Its antioxidant effects and DNA damage inhibition have been described in many studies. The effects on surviving periods of living organisms are very controversial. In mice and rats, several positive effects were described: e.g. anticancer, anti-inflammatory, glycaemia reduction and different cardiovascular benefits (57−59). Clinical studies on humans are currently taking place. It is assumed that due to its ability to inhibit androgen receptor it has a positive effect on the prevention of prostate cancer (60, 61).

Catechins

The polyphenols present in green tea neutralising O_2 radicals (ROS) that are produced endogenous or by chemical carcinogens are currently very popular. Catechins present in green tea (epicatechine – EC, epigalocatechine – EGC, epicatechine gallate – ECG, and epigalocatechine gallate – EGCG) belong to the green tea polyphenol group (*Camellia sinensis*). Epicatechine (Fig. 5.C) inhibits the formation and progression of oncologic disease. It has a synergic action together with other specific experimental chemopreventive substances and is used in lung and colorectal carcinoma therapy (60–65).

Sulphur-containing compounds

Isotiocyanates

Vegetable foods with typical flavours such as wasabi, horseradish, watercress, mustard, radish, broccoli, cabbage, kale, or Brussels sprouts contain compounds called glucosinolates. When plant cells are destroyed, the glucosinolates released are converted by the enzyme myrosinase (present in plants and also in the bowel) into isothiocyanates. Isothiocyanates such as phenethyl isothiocyanate (PEITC) and sulforaphane are potent inhibitors of hydrolase enzyme CYP2E4, which oxidises compounds such

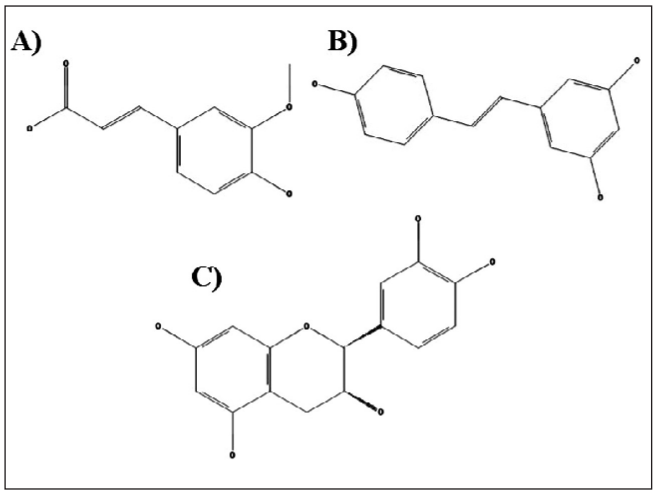

Fig. 5. *Other polyphenols, A) Ferulic acid, B) Resveratrol, C) Epicatechine.*

as benzo[a]pyrene and other polycyclic aromatic hydrocarbons (PAHs) into more polar epoxy-diols, which can induce mutation and cancer development. By this mechanism isothiocyanates prevent the potential activation of carcinogens (66). They also occur in raspberries, blackberries, licorice, blackberry, cocoa, and tomato. A study by Traka et al. showed that an increased level of dietary sulforaphane is able to modulate gene expression and alternative gene splicing in a PTEN null preclinical murine model of prostate cancer (67, 68).

Sulphides

Allicin, allyl sulphid and allyl mercaptocysteine are strong antioxidants that increase levels of glutathione in different body cells. As an enzyme substrate of glutathione peroxidise, it prevents cell destruction by peroxidase created during metabolism and other ROS reactions.

Diallyl sulphide – DAS present in garlic and onion is a very strong P45O 2E1 (CYP2E1) inhibitor. CYP2E1 is responsible for some carcinogens metabolism. DAS works as a CYP2E1 substrate and is very important in the inhibition of oncological disease prevalence caused by nitrosamines (69, 70).

Among other chemopreventive substances which content sulphur and stimulate glutathion-S-transferase, quinon-reductase and UDP-glucuronyl transferase in liver and colon are glutathione, allyl-sulphides and S-allyl-L-cysteine sulphoxide. They have inhibitory effect to carcinogenesis initiation.

Terpenes

Lycopene

Lycopene (Fig. 6.A) is a carotene without vitamin A activity and is found in red fruits and vegetables like carrots, watermelons, tomatoes, papayas, etc. The role of lycopene as a decreasing factor of lung, prostatic and colorectal carcinoma as well as cardiovascular disease has been discussed in many studies. Lycopene has positive antioxidant properties, such as positive modulation intercellular communication and hormonal and immune system changes. New evidence is emerging in regard to metabolic pathways mediating the anti-cancer activities of lycopene. In breast oncotic cells, lycopene blocks insulin-like growth factor1, which stimulates division in tumour cells (71, 72).

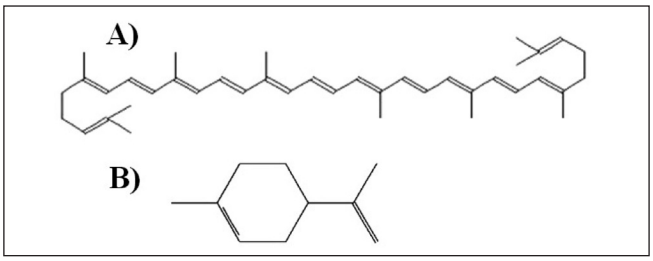

Fig. 6. *Terpenes: A) Lycopene, B) Limonene.*

Limonene

D-limonene (Fig. 6.B) is a colourless liquid compound giving a strong smell to citrus fruits. The anticarcinogenic activity of d-limonene has been well documented in the last few years. The anti-arcinogenic activity of d-limonene in N-nitrosodiethylamine (NDEA) induced hepatocarcinogenesis has been reported. The involvement of oncogenes which add to the mechanisms of d-limonene-mediated chemoprevention has also been suggested in the same model system. The over-expression of c-myc oncoprotein in different durations of NDEA-induced hepatocarcinogenesis has been observed and is inhibited completely when d-limonene was treated prior to and along with NDEA (73). D-limonene activated caspase-3 and -9 and PARP cleavage in a dose-dependent manner. Moreover, an increase in Bax protein and cytosol cytochrome c from mitochondria and a decrease in bcl-2 protein were observed following treatment with d-limonene, suggesting that d-limonene induced apoptosis via the mitochondrial death pathway and the suppression of the PI3K/Akt pathway (73). D-limonene is recognised as a potential chemotherapeutic agent, however, the details of this mechanism remain unclear (74).

CONCLUSION

Naturally occurring chemoprotective substances could provide optimal chemoprevention. Many experimental studies daily prove the strong potential of chemopreventive substances regarding the inhibition of progression and formation of metastasis together with their useful properties suitable for oncological therapy. This review described only small portion of the naturally occurring substances with chemopreventive effects, selected according to their efficiencies and healing potential. Research in this field has shown significant progress, because in addition to chemoprevention, natural chemoprotectives have recently been experiencing a huge boom in practical usage, mainly due to their minimal side effects, in place of synthetic drugs. Chemoprevention is one of several promising strategies to reduce the incidence of malignant tumours or help prolong the time of recurrence.

Acknowledgments

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Conflict of Interests

None declared

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