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Review Article

DIETARY ANTI-OXIDANTS IN CHEMOPREVENTION

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Abstract

External agents like carcinogens, pollutants, ionizing radiations produce oxidative stress in living cells generating reactive oxygen species [ROS]. Cells have built in defense against these reactive species and keep a balance between generated ROS and their neutralization by endogenous antioxidants [AO]. In addition, many antioxidants present in our diets react with the ROS and make them inactive. The maintenance of balance is a continuous process inside cells to keep them functioning normally. When generation of ROS exceeds the level of endogenous and externally added AOs , cells are driven to pathogenic state leading to diseases. A variety of dietary AOs are available from various sources of fruits and vegetables. This paper aims to review the molecular mechanisms of oxidative stress, generation and reactions of ROS with vital molecules such as DNA, Protein and membrane and involvement of ROS in the induction of cancer and other diseases. An attempt is made to suggest ways to reduce cancer incidence risks , need to modify dietary foods by consuming vegetables, fruits for chemo prevention. An example has been given to emphasize the role of curcumin as an antioxidant in the mechanism of chemoprevention.

Keywords: Oxidative stress, Carcinogens, ROS, Antioxidants, Chemoprevention.

Introduction

Exposure of living cells to external stressors initiate oxidation reactions producing free radicals which cause damage to cellular targets like DNA, membrane, proteins etc. Free radicals derived from oxygen, sulphur, nitrogen molecules with unpaired electrons e.g. ROS, RNS are highly reactive and damage cellular molecules [1, 2]. Living cells are equipped with endogenous antioxidant machinery to neutralize induced ROS produced by metabolic reactions and due to external stressors. When ROS produced exceed the level of antioxidant inside cells, they begin producing a variety of damages in cellular molecules resulting in loss of cell function and eventually diseased state is produced e.g. cancer, ageing neurodegenerative and cardiovascular ailments [3, 4]. Over production of ROS creates imbalance in cytosol and initiates numerous processes driving cells to apoptotic death .

Cancer is known to arise from oxidative stress related processes. It involves initiation, propagation and progression steps in cancer induction. Consequent to oxidative stress ROS are induced leading to cancer by reaction of radical with vital cellular bio- molecules, The radical so generated can lead to aberration of cell function including cancer induction.

Initiation and Propagation reactions

Carcinogen (or ROS) + RH $\longrightarrow$ $R^{\cdot}$ +ROSH Initiation
$R^{\cdot} + O_2 \longrightarrow RO_2^{\cdot}$ (peroxy radical)
$RO_2^{\cdot}$ + RH $\longrightarrow$ ROOH + $R^{\cdot}$ Chain reaction

Branching reactions

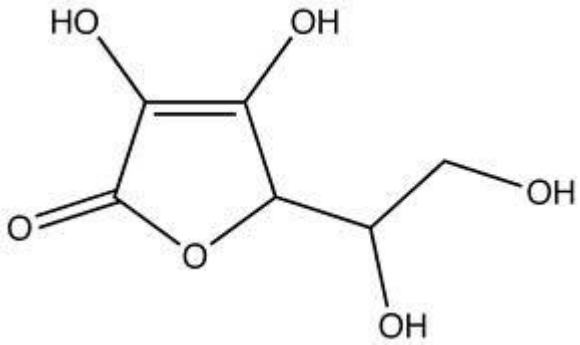
ROOH $\longrightarrow$ $RO^{\cdot} + HO^{\cdot}$
2ROOH $\longrightarrow$ $ROO^{\cdot} + RO^{\cdot} + H_2O$ Branching

Termination reactions

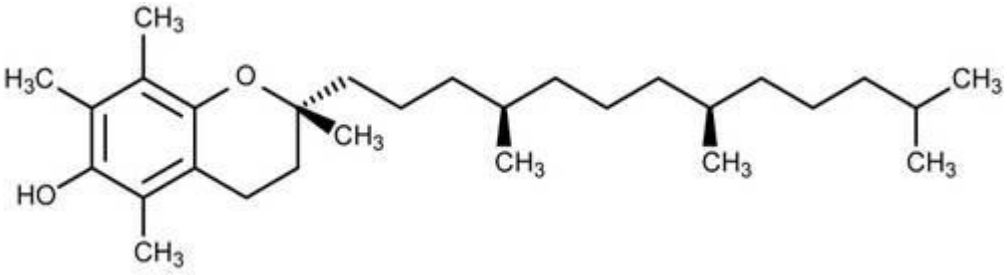
$R^{\cdot}$ +AH $\longrightarrow$ RH + $A^{\cdot}$
$ROO^{\cdot}$ +AH $\longrightarrow$ ROOH + $A^{\cdot}$
$RO^{\cdot}$ +AH $\longrightarrow$ ROH + $A^{\cdot}$ Termination

Extensive search of antioxidants for prevention of cancer has succeeded in identifying compounds which can neutralize initial radical formed. Another class of AOs are identified which are capable of breaking the chain reaction and thereby causing prevention of promotion steps. A number of AOs are known which are commonly taken as food by people. Most prominent among them are vit. C, carotene and vit .E.

Vit. C acts as the first line of antioxidant defense and neutralizes the initiation step of the radical formation.On the other hand, vit E is known to be involved in the chain breaking reaction and, therefore, inhibits the propagation step of cancer induction. Chemical structure of these vitamins are given below:



Structure of vit. C [ascorbic acid]



Structure of vit. E [α- tocopherol]

Dietary AOs are obtained from fruits and leaves of several medicinal plants.[16] Vit. C is water soluble and localizes in the cytosolic compartment of the cell. Sources of vit. C include cantaloupe, citrus fruits, kiwi, mango, strawberries and watermelon.

Vit E [α-tocopherol] is localized in the inner mitochondrial membrane which is the site of electron transport chain system. Sources of vit. E include wheat-germ oil, sunflower oil. Most of the external AOs are derived from plant kingdom and they can be used at higher concentrations without producing toxic effects. Synthetic AOs suffer from the fact that they cause toxic effects at higher concentrations and are, therefore, limited in their use in therapy. Herbs such as curcumin, green tea, grapes, ginger, garlic posses antioxidant activities in cellular and in animal systems. They are generally components of our diets which protect our body from oxidative damaging related injuries which lead to chronic ailments.[14,16]

The aim of this review is to discuss the role of AOs in chemoprevention mechanism and to delineate various pathways by which AOs act in the process of cancer radiotherapy. It has been discussed that AOs act by a complex mechanism in removing the ROS and save cells from harmful effects and work in enhancing the tumor toxicity together with other therapies. In the later process, AOs work as pro-oxidants and offer great potential to improve radiation and chemotherapy of cancer in hospital settings.

Report have appeared suggesting the pathways of chemoprevention employing natural agents to arrest and suppress carcinogenesis process [13,16]

Chemoprevention aims to reduce cancer risk in three main situations:

1. Primary prevention in high risk individuals
2. Cancer prevention in individuals having premalignant lesions
3. Pretreated patients undergoing second form of treatment.

It is commonly observed that increasing doses of chemotherapeutic drugs render many cancers resistance to therapies. Therefore, mechanism of chemo-resistance needs to be investigated.

ROS mediated chemical reactions

At the time of oxygen metabolism in mitochondria , oxygen is reduced to water. Some part of it gets converted into ROS [klaunig 2004].In enzymatic reaction, superoxide anion formed by NADPH oxygenase, lipoxy-oxygenase reacts with other molecules of the cell.

Reduction of molecular oxygen generating ROS

$$O_2 + e^- \longrightarrow O_2^{\cdot -}$$

SOD reduces superoxide anion to H_2O_2

$$2O_2^{\cdot -} + 2H^+ \longrightarrow H_2O_2 + O_2$$

Hydrogen peroxide generated is converted into hydroxyl radicals when metal ions are present (Fenton reaction)[17]

$$Fe^{2+} + H_2O_2 \longrightarrow Fe3+ + {}^{\cdot}OH + OH^{-}$$

Hydroxyl radicals are highly reactive and damage molecules of cell producing carbonyl [aldehydes and ketones] radicals and also initiate lipid peroxidation reaction. The hydroxyl radical scavenging is accomplished by their reaction with solutes.

ROS, Apoptosis and Antioxidants

ROS generation is increased in cells because of uncontrolled growth and proliferation abilities of cancer cells. Human cancers, therefore, become driven to more aggressive glycolytic states and shift to a metabolic stress state. Consequently, cancer cell becomes vulnerable to sudden lowering of ATP energy supply. This way the cells become sensitive to variations in the cell cycle. One important strategy to selectively kill cancer cell is through exploiting cancer specific metabolic and oxidative weaknesses. It is known that ROS participates in apoptotic program of tumor cell.killing. Therefore, sensitivity of tumor cell to therapies depends on the intrinsic AO capacity of the cell. ROS induced sensitivity of tumor cell is inversely related with respective AO capacities. Enhanced apoptotic killing can be obtained by using drugs that lower antioxidant level in the cell. [1,13,21]

Endogenous AO Enzyme Activation

Intracellular AO Enzymes have proved to be an important mechanism of protection against Oxidative stress. Due to production inside the cell , endogenous enzymes have proved to be a an efficient defense against induced free radicals.[9] For example, SOD, CAT, GSH, Glutathione- reductase, thioredoxin-reductase [TrXR] are some important antioxidant enzymes involved in the neutralization of ROS.[5,9] The mechanism of conversion of SOD shows the production of hydrogen-peroxide and oxygen molecule [6]. The oxidant formed is transformed into water and oxygen by [CAT]

H_2O_2 is further removed by using SOD to oxidize GSH into GSSG.[4]

$$M^{(n+1)+} - SOD + O_2^{\cdot -} \longrightarrow M^{n+} - SOD + O_2$$
$$M^{n+} - SOD + O2^{\cdot -} + 2H^{+} \longrightarrow M^{(n+1)+} - SOD + H_2O_2$$
$$2\ H_2O_2 \longrightarrow 2H_2O + O_2$$

Endogenous enzymes thus constantly remove ROS from inside of the cells.

Oxidative stress and gene expression

Apart from neutralizing free radicals, dietary AOs are known to be involved in the gene activation and expression. Based on the alterations in transcription factor, new proteins are synthesized which rescue cells from injurious damages, Cell damage by external agents are thus repaired by an array of newly synthesized proteins. It is now widely believed that AOs play multiple roles in saving cells from harmful damages. Among them, AO mediated neutralization reaction, repair of damaged molecules and activation of genes appear most prevalent mechanism of action in producing chemoprevention.

Vit.E has been known to cause gene expression and it is shown to modulate cell signaling.[4]. For example, CD36 is known to act as scavenger of free radical in oxidized low density lipoproteins[LDL]. After the treatment with α-tocopherol, it was found that down regulation of expression of CD36 occurred. Many AOs have been shown to affect the expression of genes and thereby increase the capacity of cells to withstand injurious insults.

New perspectives in oxidative Stress

Cells activate transcription factor Nrf2 which is present in the cytoplasm. Nrf2 acts as a detoxifier of ROS. In the situation of oxidative stress, Nrf2 induces transcription of antioxidant genes in the nucleus[20]. ROS plays a dual role in the process of carcinogenesis. High ROS levels initiate apoptosis in tumor cells and increases genetic damage by promoting tumor cell proliferation [24]. At low concentrations ROS regulate signaling mechanism and transform cells.

Oxidative stress biomarkers

It is shown by Jeffery Blumberg that the use of biomarkers play an important role in the regulation and control of oxidative stress related events [20]. Biomarkers can be an indicator of dietary AO in the body and pro-oxidant exposures. Oxidative stress and DNA damage arise due to exposure to carcinogens along with mutagenic and cytotoxic reactions. Oxidative stress biomarkers have the potential to inform the outcome and design measures of clinical trials as well as in establishing the stages of risk for diseases. Applying suitable biomarkers, should shorten the time to demonstrate the effect of an agent on health promotion and disease prevention.

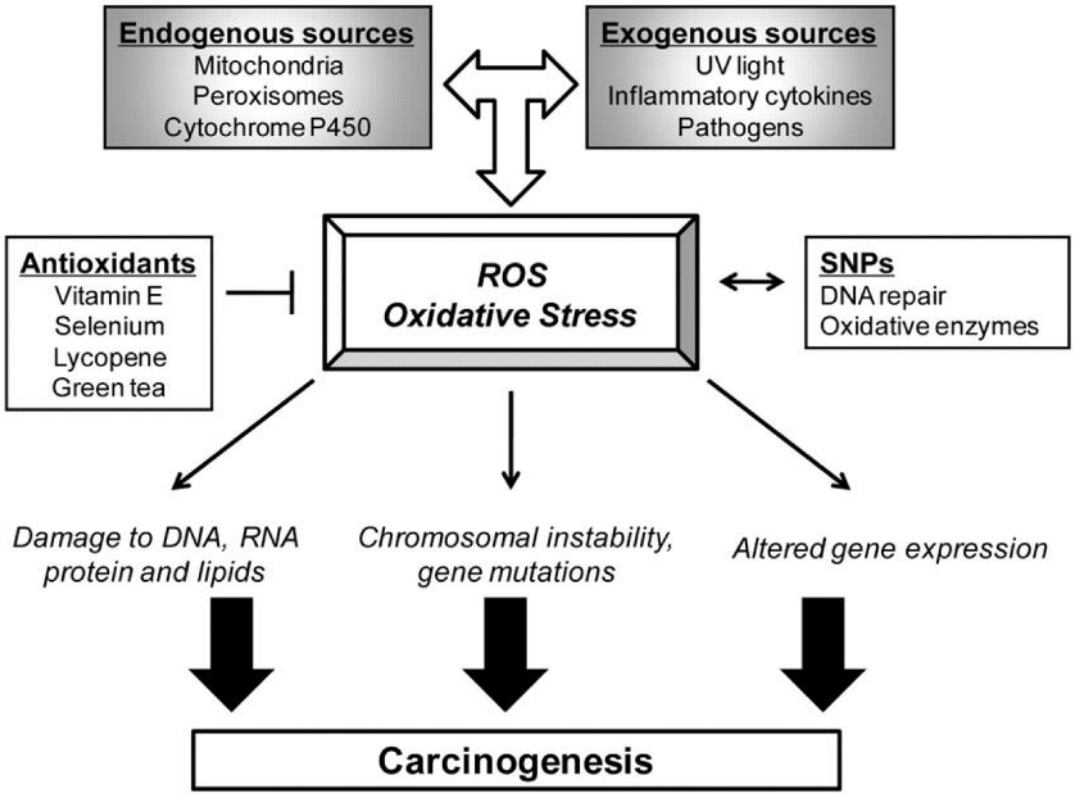


Fig.1 Role of ROS in the development of cancer

New directions of antioxidant action

In a recent report by Meyskens it has been shown that AOs behaving as pro-oxidants. Some experimental studies have shown that beta-carotene at high concentrations, acts as a pro-oxidant. [20] It has also been recently shown by the results of ATBC [α-tocopherol and β-carotene] study of cancer prevention that β-carotene causes lung cancer among the addicted smokers.[2,15] According to another data, treatment of randomly assigned heavy smokers was done with β carotene ,retinol and their combination.

There was a remarkable increase in the cases of heart diseases in the persons treated with β-carotene as compared to those who were supplied with the combination. The basic mechanism showing β-carotene as a pro-oxidant is due to the fact that it produces free radicals in the presence of oxygen and at very high doses.

Antioxidant , Polyphenol and Chemoprevention

There are various AO defense mechanisms like nonenzymatic systems and free radical scavenging systems including flavonoid compounds, water soluble compounds ,carotenoids and plasma proteins.[24].AO capacity is designated as, the generation of free radicals and the inhibition of its action by an added AO..AO either produces the total inhibition of free radical action, detected as a lag phase or a partial inhibition with no lag phase is detected.

Measurements of tissue levels of AOs like vit.C, vit.E, polyphenols, flavonoids influence the AO status. Measures of AO capacity have proved to be an important tool in the assessment of antioxidant status .Many techniques have been developed to assess AO status by utilizing different free radical sources [21,23].Ideally an assay should measure both hydrophilic and lipophilic AO .The ORAC assay determines the AO activity against peroxyl radicals [ROO.].It measures AO including vit.C, α-tocopherol, β-carotene and flavonoids. The assay measures the total number of AOs present in the sample.

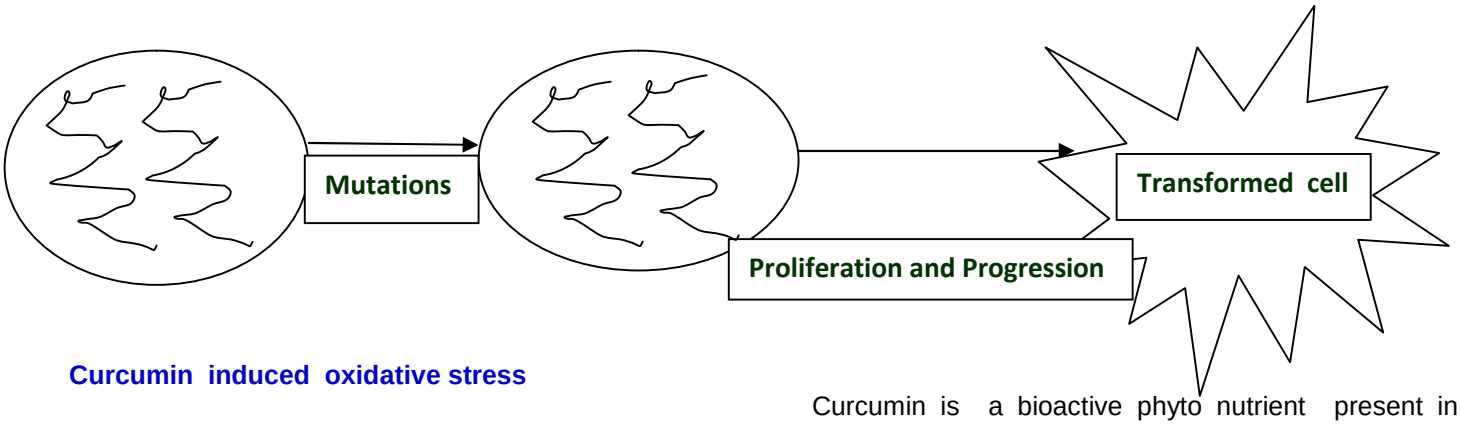
The process of antioxidant action is divided into two stages:

1. Radical trapping

$$S^{\cdot} + AH \longrightarrow SH + A^{\cdot}$$

2. Radical termination stage

$$A^{\cdot} \longrightarrow \text{non radical material}$$



Curcumin induced oxidative stress

Balz Frai reviewed the levels on antioxidant damage defense and were categorized into small molecule and proteinaceous molecules[20].The AO proteins comprise of proteins having non -enzymatic defense system like ferritin ,albumin preventing metal ions from producing free radicals in the solution. In extacellular fluids AO enzymes like SOD, peroxidases, catalases are present in very small amounts. In plasma water soluble AOs such as ascorbate , urate and bilurubin are present in high concentrations. Relating to the formation of consumption of endogenous AOs and that of lipid hydro-peroxide was measured as a marker of oxidative damage. Vit. C acts as a first line of defense where no lipid per-oxidation occurs during this time.[18]

Curcumin is a bioactive phyto nutrient present in turmeric which displays strong antioxidant properties.[8] It is soluble in lipid and has the property of chain breaking.It has two sites of free radical - o-methoxy-phenolic moity PR^1 and methylenic moity CR^1. From the biochemical studies of curcumin, it is concluded that methoxy-phenolic -OH group is important for AO activity.[19]. A copper complex of curcumin is found to show SOD activity with free radical scavenging ability.[12,18,22]

National Cancer Institute has carried out an extensive study on the mechanism of curcumin as a chemopreventive drug.[12,18]

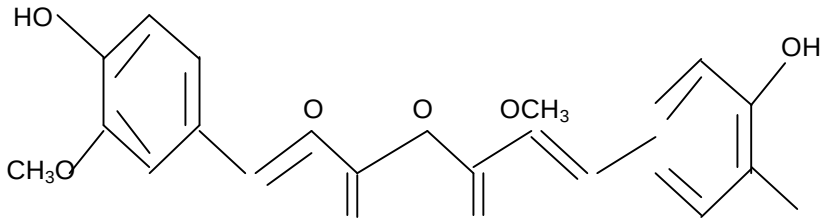


Fig.1. Chemical structure of curcumin (1, 7 –bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione[12]

Conclusion

The paper describes external stress induced oxidative reactions inside a cell .The ROS produced by oxidative process damages vital cellular molecules transforming the cell to disease state. Both endogenous and exogenous antioxidants neutralize the generated ROS. Mechanisms of chemical reactions involved in cancer induction have been described. Molecular mechanism of AOs in prevention and treatment of cancer have been delineated. The growing newer mechanisms of action of AOs have been explained including activation and expression of genes in the mechanism of induction and treatment of cancer. Moreover, It has been re-emphasized that antioxidants were involved in the process of apoptotic cell death.

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