Introduction
INTRODUCTION

Cancer prevention: Role of dietary constituents

With more than 12 million new cases each year, cancer is, at present, one of the most devastating diseases worldwide. Despite the development of various therapies, cancer remains the second leading cause of death, accounting for nearly one in every four deaths in the United States of America and in many other nations of the world. The American Cancer Society in its recent annual report, "Cancer Statistics, 2012", estimates approximately 1.64 million new cancer cases to be diagnosed and nearly 577,000 mortalities from cancer projected to occur in USA alone in the year 2012 (Siegel et al., 2012). Despite being one of the major causes of death across the world, cancer has been shown to be a largely preventable disease, highly susceptible to modulation by dietary factors. Dietary patterns, foods, nutrients and other dietary constituents are closely associated with the risk for several types of cancer, and in this regard, it has been estimated that 35% of all cancers can be prevented through appropriate dietary modifications (Doll and Peto, 1981; Manson, 2003).

Carcinogenesis in humans is a multistage process involving a series of events and generally occurs over an extended period. During this process, accumulation of genetic and epigenetic alterations leads to the progressive transformation of a normal cell into a malignant cell. Cancer cells acquire several abilities that most healthy cells do not possess: they become resistant to growth inhibition, proliferate without dependence on growth factors, replicate without limit, evade apoptosis, and invade, metastasize, and support angiogenesis (Hanahan and Weinberg, 2000). It is currently accepted that diet can affect the overall process of carcinogenesis in different ways. Its constituents may contain cancer causing substances but can also contain
several cancer preventive agents. These dietary agents can retard or prevent the process of carcinogenesis by multiple mechanisms, namely i) enhanced detoxification of the carcinogenic intermediates through induction of Phase II drug metabolizing enzymes ii) reduced carcinogen activation due to suppression of cytochrome P450- dependent monooxidases, iii) perturbations in cell cycle progression, iv) selective promotion of apoptosis in cancerous or precancerous cells and v) inhibition of angiogenesis and metastasis formation (Stan et al., 2008). Since apoptosis provides a physiologic mechanism for eliminating abnormal cells, dietary factors affecting apoptosis can lead to important effects on carcinogenesis. Conceivably, activation of apoptosis in pre-cancerous cells offers a prevention mechanism of cancer by dietary factors.

Epidemiological studies have consistently shown that diet plays a crucial role in the protection against several chronic diseases (Willett, 1994; Temple, 2000). Consumption of fruits and vegetables as well as grains, has been strongly associated with reduced risk of cancer, cardiovascular diseases, diabetes, Alzheimer’s disease, cataract and age related functional decline (Willett, 1994; Willett, 1995; Temple, 2000). The biologically active chemicals present in fruits, vegetables and grains are termed as phytochemicals, many of which provide desirable health benefits beyond nutrition to reduce the risk of a number of chronic diseases (Liu, 2003). It is believed that phytochemicals have the ability to modify the disease process thus relating the food stuffs, beyond their basic nutritional benefits, to disease prevention (Roger et al., 1993; Thomasset et al., 2007). Such foods have also been termed as ‘functional foods’. Thus convincing evidence suggests that a change in dietary behaviour such as increasing the consumption of fruits and vegetables is a practical strategy for significantly reducing the incidence of chronic diseases.
Of particular relevance is the consistent cancer protective effect reported for individuals consuming high quantities of fruits and vegetables compared to those with low intakes (Block et al., 1992; Pavia et al., 2006). In fact, multiple epidemiological and animal studies have shown that consumption of foods rich in fruits and vegetables decreased the incidence of cancers, suggesting that certain dietary constituents may thus be effective in preventing the disease (Steinmetz et al., 1996; Reddy et al., 2003; Benetou et al., 2008; Freedman et al., 2008). Similarly, a wealth of information is available, implicating dietary agents in cancers of the skin (Khan et al., 2008), prostate (Syed et al., 2008; Haseen et al., 2009), breast (Bougnoux et al., 2010) and lung (Cranganu and Camporeale, 2009; Goralczyk, 2009).

There are two major diet related prevention strategies that have been involved in combating cancer, i.e. cancer chemoprevention and dietary prevention, with an appreciable overlap existing between them. Generally, cancer chemoprevention is recognized as the pharmacological intervention with synthetic or naturally occurring non-toxic chemicals to prevent, inhibit or reverse carcinogenesis or prevent development of invasive cancer (Boone et al., 1997; Mayne and Lippman, 1997). On the other hand dietary prevention is recognized as the changes in food consumption pattern necessary to reduce the risk of cancer development (Goodman, 1997).

**Cancer chemoprevention and dietary polyphenols**

Fruits and vegetables contain a wide variety of phytochemicals that are regarded as effective protective agents. One such prominent class of phytochemicals, plant derived foods and beverages are rich in, are dietary polyphenols that have received much attention over the last two decades for their health benefits, including cancer chemopreventive effects. Polyphenols are plant secondary metabolites that serve as a component of plant defense
mechanisms against predation by microorganisms, insects and herbivores. They are widely distributed plant derived dietary constituents and have been implicated as the active components in a number of herbal and traditional medicines (Wollenweber, 1988). Polyphenols are known to possess a wide range of pharmacological properties including cardioprotective, neuroprotective, anti-inflammatory and anticancer properties (Szewczuk et al., 2004; Dai et al., 2006; Thomasset et al., 2007; Ullah and Khan, 2008).

Plant derived polyphenolic compounds are important constituents of human diet which include resveratrol from red grapes and red wines, epigallocatechin-3-gallate from green tea, curcumin from spice turmeric, apigenin from parsley, quercetin from onion and isoflavone genistein from soybean. Figure 1 illustrates some of the popular dietary polyphenols that have been known to possess chemopreventive potential and their dietary sources.

Many studies in different cell lines, animal models and human epidemiological trials suggest a protective role of dietary polyphenols against different types of cancers (Watson, et al., 2000; Wenzel et al., 2000; Yang et al., 2001). Clinical trials have correlated polyphenolic intake with prevention of particular cancers, showing a decreased risk for different types of cancers (Knekt et al., 1997; Key et al., 1999; Arts et al., 2002; Su and Arab, 2002) or a diminished recurrence of cancer (Nakachi et al., 1998; Le Marchand et al., 2000) after the consumption of polyphenols or certain foods or drinks, such as tea and red wine, rich in these phenolic compounds. The most direct evidence of beneficial effects by a particular food rich in polyphenols, or individual compounds, have come from animal models and in vitro experiments. In fact, cell culture studies constitute a valuable tool for identifying the molecular targets modulated by dietary polyphenolic compounds in cancer cells.
Figure 1: Some chemopreventive polyphenolic compounds and their sources
The wide array of chemopreventive phytochemicals present in fruits and vegetables can be of two types, namely cancer blocking and cancer suppressing agents. The former prevent carcinogens from initiation of carcinogenesis by several mechanisms such as (a) enhancing carcinogen detoxification, (b) modifying carcinogen uptake and metabolism, (c) scavenging free radicals and (d) enhancing DNA repair. Cancer suppressing agents, on the other hand, inhibit cancer promotion and progression after the formation of preneoplastic cells by interfering with (a) cell cycle regulation, (b) signal transduction, (c) transcriptional regulation and (d) apoptosis (Greenwald, 2002; Surh, 2003). Many potential chemopreventive polyphenols may interrupt or reverse the carcinogenesis process by acting on intracellular signalling network molecules involved in the initiation and/or promotion, but also these compounds may arrest or reverse the progression stage of cancer (Manson, 2003; Surh, 2003). The anticarcinogenic activity of these plant derived dietary polyphenolic compounds may be attributed to a combination of their cytoprotective effect on normal cells (cancer blocking effect) and their cytotoxic effect on preneoplastic and/or neoplastic cells (cancer suppressing action).

An ideal chemopreventive agent should be selective for damaged or transformed cells, display a significant bioavailability in the target region and have more than one mechanism of action. Moreover, it should be highly effective, easy to administer, and inexpensive. Dietary polyphenols, in this regard, are particularly attractive because of human long standing exposure to them and their relative lack of toxicity. In fact, numerous polyphenolic compounds have been shown to display antiproliferative and cytotoxic effects towards several tumor cells, showing cancer cell specific toxicity in comparison to normal cells (Lepley et al., 1996; Agullo et al., 1997; Skaper et al., 1997; Sergediene et al., 1999). Dietary polyphenols are mainly consumed through fruits, vegetables and beverages such as juice, wine, tea and coffee,
apart from cereals and olive derivatives (Hollman & Katan, 1999; Visioli & Galli, 2002). Their average daily intake has been reported to be around 1g (Scalbert and Williamson, 2000; Scalbert et al., 2005), which is much higher than intake of all other classes of dietary antioxidants. For instance, it is approximately 10 times higher than vitamin C intake and 100 times the intakes of vitamin E and carotenoids (Scalbert and Williamson, 2000). However, an important drawback with polyphenols being effective chemopreventive agents is their low bioavailability after ingestion (Manach et al., 2005; Scalbert et al., 2005). Nonetheless, polyphenols as chemopreventive agents found in human diet are considered a very promising group of compounds, on account of their safety, low-toxicity, and general acceptance.

**Chemical structure and basic classification of polyphenolic compounds**

Polyphenols are one of the most numerous and widely distributed groups of compounds in the plant kingdom. More than 8000 compounds having a polyphenol structure, i.e. several hydroxyl groups on aromatic rings, have been identified in higher plants, of which several hundred are found in edible plants. Polyphenolic compounds are frequently found attached to sugars (glycosides), thus tending to be water-soluble. Occasionally, polyphenols also occur in plants as aglycones.

Most of these heterogeneous compounds may be broadly classified into four different general classes based on the number of phenol rings that they contain and of the structural elements that bind these rings to one another. Distinctions are, therefore, made between the phenolic acids, flavonoids, stilbenes, and lignans (Figure 2). Two subclasses of phenolic acids can be distinguished: derivatives of benzoic acid and derivatives of cinnamic acid (Figure 2). Hydroxybenzoic acids are, furthermore, components of complex
Introduction

Phenolic Acids

Hydroxybenzoic acids

\[ \text{R}_1=\text{R}_2=\text{OH}, \text{R}_3=\text{H}: \text{Protocatechuic acid} \]
\[ \text{R}_1=\text{R}_2=\text{R}_3=\text{OH}: \text{Gallic acid} \]

Hydroxycinnamic acids

\[ \text{R}_1=\text{OH}: \text{Coumaric acid} \]
\[ \text{R}_1=\text{R}_2=\text{OH}: \text{Caffeic acid} \]
\[ \text{R}_1=\text{OCH}_3, \text{R}_2=\text{OH}: \text{Ferulic acid} \]

Stilbenes

Lignans

Flavonoids

Figure 2: General chemical structures of major classes of polyphenols

structures such as hydrolyzable tannins (gallotannins in mangoes and ellagitannins in red fruit such as strawberries, raspberries, and blackberries) (Clifford & Scalbert, 2000). Because these hydroxybenzoic acids are found in only a few plants eaten by humans, they have not been extensively studied and are not considered to be of great nutritional interest. The hydroxycinnamic acids are more common than the hydroxybenzoic acids and consist chiefly of p-coumaric, caffeic, ferulic, and sinapic acids.

Flavonoids, phenolic acids, stilbenes and lignans are the most abundantly occurring polyphenols in plants, of which flavonoids and phenolic acids account for 60 and 30%, respectively, of dietary polyphenols. More than 5000 different flavonoids have been identified and classified according to their
molecular structure (Ross and Kasum, 2002). Flavonoids, therefore, are the major dietary polyphenols which are derived from a wide variety of plant sources. They share a common basic structure, consisting of a heterocyclic skeleton of flavan (2-phenylbenzopyrane). The structure is represented by 2 aromatic rings (A and B) that are joined together by a linear three-carbon chain that forms an oxygenated heterocycle (ring C). The constituent polyphenolic units are derived from the secondary plant metabolism of the shikimate pathway (Dewick, 1995). Flavonoids may themselves be divided into 6 subclasses as a function of the type of heterocycle involved. The six major subclasses of flavonoids include the flavones (e.g. apigenin, luteolin), flavonols (e.g. quercetin, myricetin), flavanones (e.g. naringenin, hesperidin), catechins or flavanols (e.g. epicatechin, epigallocatechin-3-gallate), anthocyanidins (e.g. delphinidin, malvidin), and isoflavones (e.g. genistein, daidzein). Table I gives a classification of flavonoid subclasses along with their important members that are known to possess pharmacological properties.

Flavonoids are often hydroxylated at positions 3, 5, 7, 2′, 3′, 4′, 5′. In addition to this diversity, polyphenols may be associated with various carbohydrates and organic acids and with one another. Usually in the plant system, these flavonoids exist in conjugated forms, the most common being the glycosides. When glycosides are formed, the glycosidic linkage is normally located at position 3 or 7 and the carbohydrate moiety can be L-rhamnose, D-glucose, gluco-rhamnose, galactose or arabinose (Middleson, 1984).

**Biosynthesis of plant polyphenols**

Plant polyphenols execute a vast array of important functions in plants (Croteu et al., 2000). For example, stilbenes and coumarins serve to defend pathogen attacks, flavonoids act as UV irradiation protectants while isoflavone
Table I: General chemical structure of different subclasses of flavonoids with their important constituent members

<table>
<thead>
<tr>
<th>Subclass</th>
<th>General Chemical structure</th>
<th>Representative compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavones</td>
<td><img src="image" alt="Flavone Structure" /></td>
<td>Apigenin, Luteolin, Chrysin</td>
</tr>
<tr>
<td>Flavonols</td>
<td><img src="image" alt="Flavonol Structure" /></td>
<td>Quercetin, Kaempferol,</td>
</tr>
<tr>
<td>Flavanones</td>
<td><img src="image" alt="Flavanone Structure" /></td>
<td>Hesperidin, Naringenin</td>
</tr>
<tr>
<td>Flavanols</td>
<td><img src="image" alt="Flavanol Structure" /></td>
<td>Catechins, Epicatechins, Epigallocatechin-3-gallate (EGCG)</td>
</tr>
<tr>
<td>Isoflavones</td>
<td><img src="image" alt="Isoflavone Structure" /></td>
<td>Genistein, Daidzein</td>
</tr>
<tr>
<td>Anthocyanidins</td>
<td><img src="image" alt="Anthocyanidin Structure" /></td>
<td>Delphinidin, Malvidin</td>
</tr>
</tbody>
</table>
and anthocyanins serve as flower pigments. The majority of polyphenolic compounds produced by plants are synthesized by a highly branched phenylpropanoid pathway (Figure 3). The initial compound is cinnamic acid, which arises from phenylalanine by the action of PAL (Phenyl-ammonia lyase). Several simple polyphenols with the basic C6-C3 skeleton of phenylalanine are produced from cinnamate via a series of hydroxylation, methylation and dehydration reactions; these include p-coumaric acid, caffeic acid, ferulic acid, siapic acids and other simple coumarins (Dixon and Paiva, 1995). In addition, compounds such as styrenes, benzoic acid and derivatives, acetophenones and gingerols arise from hydroxycinnamic acid by chain shortening and lengthening without ring formation.

The precursor molecules 4-coumaroyl-CoA and malonyl CoA give rise to tetraketide. Tetraketide may get converted into resveratrol by the enzyme Stilbene synthase (STS). Chalcone synthase (CHS) is the first step in the branch of the pathway that produces the flavonoids. CHS acts on tetraketide to form tetrahydroxychalcone. Tetrahydroxychalcone provides the basic structural skeleton for biosynthesis of all classes of flavonoids, including flavonones, isoflavones, flavones, flavonols, anthocyanins and flavanols. Chalcone Isomerase (CHI) acts upon tetrahydroxychalcone and converts it into the flavanone, naringenin. Naringenin by different reactions gives rise to isoflavone genistein, flavones apigenin and luteolin, and flavonols such as kaempferol, quercetin etc. Also, naringenin in a series of reactions leads to the formation of leucoanthocyanidins. Anthocyanidin synthase converts leucoanthocyanidins to anthocyanidins which finally lead to the formation of epigallocatechins by anthocyanidin reductase.
Figure 3: The phenylpropanoid pathway by which plants synthesize a wide range of polyphenols

PAL, phenylalanine ammonia lyase; CA4H, cinnamate 4-hydroxylase; 4CL, 4 coumarate:CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; IFS, isoflavone synthase; FN3H, flavanone 3-hydroxylase; FS, flavone synthase; F3’H, flavone 3’-hydroxylase; FLS, flavonol synthase; FL3’H, flavonol 3’-hydroxylase; FL5’H, flavonol 5’-hydroxylase; STS, stilbene synthase; ANR, anthocyanidin reductase.
Sources of plant derived dietary polyphenolic compounds

A large body of literature exists regarding the polyphenolic content of various plant-derived human foods. Common polyphenols belonging to different subgroups and the various food sources from which they are usually obtained are enlisted in Table II. Flavonols are the most ubiquitous flavonoids in foods, and the main representatives are quercetin and kaempferol. They are generally present at relatively low concentrations of 15-30 mg/kg fresh wt. The richest sources are onions (up to 1.2 g/kg fresh wt), curly kale, leeks, broccoli, and blueberries. Red wine and tea also contain up to 45 mg flavonols/L. These compounds are present in glycosylated forms. The associated sugar moiety is very often glucose or rhamnose, but other sugars may also be involved (eg, galactose, arabinose, xylose, glucuronic acid). Fruit often contains between 5 and 10 different flavonol glycosides (Macheix et al., 1990). Flavones are much less common than flavonols in fruit and vegetables. Flavones consist chiefly of glycosides of luteolin and apigenin. The important edible sources of flavones are parsley and celery. Cereals such as millet and wheat contain glycosides of flavones (Sartelet et al., 1996).

In human foods, flavanones are found in tomatoes and certain aromatic plants such as mint, but they are present in high concentrations only in citrus fruit. The main aglycones are naringenin in grapefruit, hesperetin in oranges, and eriodictyol in lemons. Flavanones are generally glycosylated by a disaccharide at position 7. Isoflavones are found almost exclusively in leguminous plants. Soya and its processed products are the main source of isoflavones in the human diet. They contain 3 main molecules: genistein, daidzein, and glycitein, generally in a concentration ratio of 1:1:0.2. These isoflavones are found in four forms: aglycone, 7-O-glucoside, 6-O-acetyl-7-O-glucoside, and 6-O-malonyl-7-O-glucoside (Coward et al., 1998). The isoflavone content of soya and its manufactured products varies greatly as a function of geographic zone,
### Table II: Main groups, representative compounds and dietary sources of common polyphenols

<table>
<thead>
<tr>
<th>Polyphenol subgroup</th>
<th>Representative polyphenols in diet</th>
<th>Common food sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonols</td>
<td>Quercetin, Kaempferol, Myricetin, Rutin</td>
<td>Onions, apples, broccoli, tea, red wine, berries, tomato, leek</td>
</tr>
<tr>
<td>Flavones</td>
<td>Apigenin, Luteolin, Chrysin</td>
<td>Parsley, celery, thyme, oregano, capsicum peppers</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Genistein, Daidzein, Biochanin A</td>
<td>Soybeans, soy foods, legumes</td>
</tr>
<tr>
<td>Flavanols</td>
<td><strong>Monomers</strong>&lt;br&gt;Catechin, Epicatechin, EGCG&lt;br&gt;<strong>Polymers</strong>&lt;br&gt;Proanthocyanidins</td>
<td>Tea (particularly green tea), Apples, pears, raspberries, chocolate, beans, apricot</td>
</tr>
<tr>
<td>Flavanones</td>
<td>Naringenin, Hesperitin, Eriodictyol</td>
<td>Orange, grapefruit, lemon</td>
</tr>
<tr>
<td>Anthocyanidins</td>
<td>Cyanidin, Malvidin, Delphinidin</td>
<td>Cherry, Strawberry, red wine, blue berry, black currant, rhubarb</td>
</tr>
<tr>
<td>Stilbenes</td>
<td>Resveratrol</td>
<td>Grapes, red wine, peanuts, berries</td>
</tr>
</tbody>
</table>
growing conditions, and processing. Soybeans contain between 580 and 3800 mg isoflavones/kg fresh wt. and soymilk contains between 30 and 175 mg/L (Reinli and Block, 1996; Cassidy et al., 2000).

Flavanols exist in both the monomer form (catechins) and the polymer form (proanthocyanidins). Catechins are found in many types of fruit (apricots, which contain 250 mg/kg fresh wt, are the richest source). They are also present in red wine (up to 300 mg/L), but green tea and chocolate are by far the richest sources. An infusion of green tea contains up to 200 mg catechins (Lakenbrink et al., 2000). Catechin and epicatechin are the main flavanols in fruit, whereas gallocatechin, epigallocatechin, and epigallocatechin gallate are found in certain seeds of leguminous plants, in grapes, and more importantly in tea (Arts et al., 2000a & b). In contrast to other classes of flavonoids, flavanols are not glycosylated in foods. Anthocyanidins are found in red wine, certain varieties of cereals, and certain leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), but they are most abundant in fruit. Cyanidin is the most common anthocyanidin in foods. Food contents are generally proportional to colour intensity and reach values up to 2-4 g/kg fresh wt. in blackcurrants or blackberries. These values increase as the fruit ripens. Anthocyanidins are found mainly in the skin, except for certain types of red fruit, in which they also occur in the flesh (cherries and strawberries).

Stilbenes are found in only low quantities in the human diet. One of these, resveratrol, which been extensively studied, is found in several edible natural products such as grapes, peanuts and berries (blue berries, cranberries, lingo berries etc) and wine. Fresh grape skins contain 50-100 mg resveratrol/g. Resveratrol is much more concentrated in red than in white wine. The average concentration of resveratrol in common varieties of red wine ranges from 2 to 40 µM (Gusman et al., 2001). Free resveratrol, however, occurs in low
quantities in wine (0.3-7 mg aglycones/L Vs 15 mg glycosides/L in red wine) (Bhat and Pezzuto, 2002; Vitrac et al., 2002).

Bioavailability of dietary polyphenols

It is important to realize that the polyphenols that are the most common in the human diet are not necessarily the most active within the body, either because they have a lower intrinsic activity or because they are poorly absorbed from the intestine, highly metabolized, or rapidly eliminated. In addition, the metabolites that are found in blood and target organs and that result from digestive or hepatic activity may differ from the native substances in terms of biological activity. Extensive knowledge of the bioavailability of polyphenols is thus essential if their health effects are to be completely understood.

Metabolism of polyphenols occurs via a common pathway (Scalbert and Williamson, 2000). The aglycones can be absorbed from the small intestine. However, most polyphenols are present in food in the form of esters, glycosides, or polymers that cannot be absorbed in their native form. These substances must be hydrolyzed by intestinal enzymes or by the colonic microflora before they can be absorbed. During the course of absorption, polyphenols are conjugated in the small intestine and later in the liver. This process mainly includes methylation, sulfation, and glucuronidation. This is a metabolic detoxication process common to many xenobiotics that restricts their potential toxic effects and facilitates their biliary and urinary elimination by increasing their hydrophilicity. The conjugation mechanisms are highly efficient, and aglycones are generally either absent in blood or present in low concentrations after consumption of nutritional doses. Polyphenols are able to penetrate tissues, particularly those in which they are metabolized. Polyphenols and their derivatives are eliminated mainly in urine and bile.
For any chemical moiety to exert a biological effect, it should be bioavailable i.e. it must be readily absorbed into the bloodstream and reach concentrations that have the potential to exert effects *in vivo*. Bioavailability is a key factor in the description of polyphenols and is an essential aspect for understanding the role they might play in addressing human disease. Most of the polyphenols are known to be readily absorbed (Scalbert and Williamson, 2000; Rowland et al., 2003) but are prone to be modified into other forms inside the body, one such common chemical modification being conjugation (Lambert et al., 2005). Table III summarises the major bioavailable forms of common dietary polyphenols.

Table III: Major dietary polyphenols and their bioavailable forms in plasma

<table>
<thead>
<tr>
<th>Polyphenols</th>
<th>Bioavailable forms in plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonols</td>
<td>Methyl, sulphate or glucuronic acid conjugates</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Sulphates or glucuronides conjugates; Also occur as glycosides and aglycones</td>
</tr>
<tr>
<td>Flavanols</td>
<td>Methyl, sulphate or glucuronic acid conjugates; EGCG occurs in the unconjugated form; Dimers</td>
</tr>
<tr>
<td>Anthocyanidins</td>
<td>Glucosides</td>
</tr>
<tr>
<td>Stilbenes</td>
<td>Glucuronides, Sulphate conjugates; Unconjugates are also present as product of fermentation</td>
</tr>
</tbody>
</table>

Curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol in rats and mice *in vivo* and in suspensions of human and rat hepatocytes (Ireson et al., 2001). Certain curcumin metabolites, such as tetrahydrocurcumin, possess anti-inflammatory (Mukhopadhyay et al., 1982) and antioxidant activities (Sugiyama et al, 1996)
Introduction

similar to those of their metabolic progenitor. Dietary resveratrol is rapidly absorbed and predominantly present in plasma as glucoronide and sulphate conjugates. When administered in food, such as wine or grape juice, resveratrol metabolism is significantly inhibited by other polyphenols due to competitive reactions with metabolizing phase II enzymes resulting in an increased concentration of the free form (Wenzel and Somoza, 2005). Isoflavones such as genistein are also known to undergo conjugation with glycosides and is metabolized in human intestine to dihydrogenistein and 6′-hydroxy-O-desmethylangolensin. Concentration of genistein has been shown to be higher in individuals consuming soy rich diet (Adlercreutz et al., 1993) and consequently genistein and its metabolites have been detected in plasma, breast aspirate and prostatic fluid (Mills et al., 1989). Similarly, other polyphenols are also known to be absorbed and metabolized into various end products which may or may not possess the biological effects of the parent compound.

Therapeutic potentials of dietary polyphenols

A longstanding tenet of nutrition holds that people with diets rich in fruits and vegetables enjoy better health than those eating few such foods. Much of current research shows that free radicals are linked to various chronic diseases. As a result dietary antioxidants such as plant derived polyphenols hold promise in at least delaying the onset/progression of these diseases. An insight into the investigations, both in vitro and in vivo, reveals the properties of plant derived dietary polyphenols that can form the basis of their use in the prevention and cure of certain human disorders. A large number of pharmacological properties, including cardioprotective, neuroprotective and anticancer effects, are thought to be associated with their beneficial effects. For instance, resveratrol, a polyphenol found in grapes and red wine, is widely
recognized as a bioactive agent with potential benefits for human health (Figure 4).

Figure 4: Proposed targets for beneficial effects of dietary polyphenol resveratrol on human health (from Shukla Y and Singh R. Ann N Y Acad Sci 2011; 1215: 1-8).

Some of the important therapeutic properties of plant derived polyphenols with some strong evidence from the existing literature have been discussed below.

**Cardioprotective properties**

The “French Paradox” – the observation that mortality from coronary heart disease is relatively low in France despite relatively high levels of dietary
saturated fat, led to the idea that regular consumption of red wine (rich source of polyphenols) might provide additional protection from cardiovascular diseases (Criqui and Ringel, 1994). Regular, moderate consumption of red wine is linked to a reduced risk of coronary heart disease. Resveratrol, a red wine polyphenol has been linked to a number of potentially cardioprotective effects (Szewczuk et al., 2004). Anthocyanidins have also been found to have antioxidant potential (Falchi et al., 2006). Similarly, green tea consumption has also been associated with a lower risk of coronary artery disease in Japanese populations (Sano et al., 2004). Studies suggest that EGCG (a major polyphenol in green tea) can suppress active oxygen species and thereby prevent the development of cardiac hypertrophy (Li et al., 2006).

Endothelial dysfunction is involved in the initiation and progression of arteriosclerosis. Some polyphenols have been shown to relax endothelium-denuded arteries. There have been reports that extracts from grape and wine induce endothelium-dependent relaxation via enhanced and/or increased biological activity of nitric oxide (NO) which leads to the elevation of cGMP levels (Andriambeloson, 1997). Resveratrol has been found to promote vasodilation by enhancing the production of NO (Wallerath et al., 2002).

Recently, Lowenstein and co-workers have shown that EGCG has the potential to reduce aggregation of the inflammatory leukocytes that directly contribute to atherosclerosis (Yamakuchi et al., 2008]. Genistein, one of the major isoflavones in soy protein, binds to estrogen receptor β with much higher affinity than to ERα (Kuiper et al., 1998) and can elicit endothelium dependant vasorelaxation in vitro (Figtree et al., 2000) and in vivo (Walker et al., 2001). Other isoflavones such as dihydrodaidzeins have also been reported to enhance endothelial function (Shen et al., 2006). Flavonoids have also been found to be good hypochlorite scavenger in vitro and could have favourable effects in diseases such as atherosclerosis, in which hypochlorite is known to
Polyphenols such as dicvertin have been reported to produce a 12% decrease in LDL along with a 14% increase in HDL in coronary heart disease patients (Belaia et al, 2006). Lipid-lowering activity has also been reported in tea flavonoids (Li et al, 2006).

Chronic low levels of ROS are known to promote cardiovascular diseases (Barchowsky et al., 1996). Therefore, in the prevention of cardiovascular diseases, many of the observed effects of polyphenols, can be attributed to their recognized antioxidant and radical scavenging properties, which may delay the onset of atherogenesis by reducing chemically and enzymatically mediated peroxidative reaction (German and Walzem, 2000).

Neuroprotective properties

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, including the brain, spinal cord and peripheral nerves, which have different etiologies. The multifactorial etiology of these diseases suggests that interventions such as polyphenols having multiple targets could have therapeutic potential for them. Moreover, epidemiological studies indicate that dietary habits and antioxidants from diet can influence the incidence of neurodegenerative disorders such as Alzheimer and Parkinson's diseases (Morris et al., 2002). The nervous system is rich in fatty acids and iron. High levels of iron can lead to oxidative stress via the iron-catalyzed formation of ROS (Bauer and Bauer, 1999). In addition brain regions that are rich in catecholamines are vulnerable to free radical generation. One such region of the brain is the substantia nigra, where a connection between antioxidant depletion and tissue degeneration has been established (Perry et al., 2002).
There is substantial evidence that oxidative stress is a causative or at least an ancillary factor in the pathogenesis of many neurodegenerative diseases, including Alzheimer’s disease (AD), Parkinson’s disease (PD), Amyotrophic lateral sclerosis (ALS) (Ghadge et al., 1997), Huntington’s disease (HD) and Schizophrenia (Philips et al., 1993). Neuroprotective capacity is believed to be a characteristic property of plant derived polyphenolic compounds (Yazawa et al., 2006; Ritz et al., 2008). Polyphenols exhibit biological effects such as anti-inflammatory, antioxidant and metal chelating properties, which augment their role in neuroprotection. Reports also suggest that red wine that contains high levels of antioxidant polyphenols reduces the incidence of AD (Wang et al., 2006). Polyphenols such as EGCG, curcumin, extracts of blue berries and Scutellaria are also known to help in AD (Dai et al., 2006). In vitro studies show that green tea extract rich in catechins could protect neurons from the amyloid beta-induced damages in AD (Bastianetto et al., 2006). EGCG is also found to be of use in ALS (Xu et al., 2006) and PD (Ramassamy, 2006). Extract of Scutellaria stem and polyphenols such as curcumin and naringenin also exhibit neuroprotection in PD (Shang et al., 2006). Alzheimer’s disease is characterized by chronic inflammation and oxidative damages in the brain. Curcumin possess antioxidative and anti-inflammatory properties and has thus been shown to exert a protective effect against oxidative damages initiated by divalent metals or suppress inflammatory damage by preventing metal induction of NF-kB and also inhibits amyloid beta fibril formation (Kim et al., 2005). Dietary polyphenols have potential as protective agents against neuronal apoptosis, through selective actions within stress activated cellular responses including protein kinase signalling cascade (Schroeter et al., 2006). Several dietary supplements with blueberries extracts have been reported to reduce some neurological deficits in aged animal models (Joseph et al., 1999; Joseph et al., 2003).
Anticancer properties

The role of polyphenols as anticancer agents is complex and extensive research has indicated that their anticancer effects are exerted at multiple levels including inhibition of gene expression (Liu et al., 2008), inhibition of angiogenesis (Shankar et al., 2008), inhibition of metastasis (Shankar et al., 2008; Kushima et al., 2009) and suppression of cell proliferation (Gu et al., 2009). The anticancer properties of dietary polyphenolic compounds, including their subcategory flavonoids, have been widely documented by several studies (Bosetti et al., 2006; Cardenas et al., 2006; Walle et al., 2007). Epidemiologic studies have consistently shown an inverse relation between flavonoid consumption and risks for certain types of cancer (Mukhtar and Ahmad, 2000; Russo, 2007). Several studies have demonstrated that some naturally occurring flavonoids such as genistein (Jeune et al., 2005), apigenin (Lim et al., 2007) and luteolin (Way et al., 2005) possess significant suppressive effects on human cancers.

Furthermore, numerous studies have reported antiproliferative effects mediated by polyphenolic compounds against both human and rodent ovarian, leukemic, intestinal, lung, breast, bladder and prostate cancer cells. For example, it has been shown that genistein could induce apoptosis in MDA-MB-231, MDA-MB-435, and MCF-7 breast cancer cells; PC3 and LNCaP prostate cancer cells; H460 and H322 non-small cell lung cancer cells; HN4 head and neck squamous carcinoma cells, and pancreatic cancer cells (Davis et al., 1998; Lian et al., 1998; Li et al., 1999; Alhasan et al., 2000; Banerjee et al., 2005, 2007). Moreover, Genistein is also reported to be inhibitory at concentrations similar to conventional anticancer drugs such as methotrexate and doxorubicin (Hirano et al., 1994). Moiseeva et al. (2007) reported that physiological concentrations of a dietary phytochemical such as genistein results in reduced growth and induction of apoptosis in cancer cells. Quercetin
and luteolin are shown to induce apoptosis in a wide range of tumor cells such as A431, MiaPaCa-2, Hep G2 and MCF 7 (Huang et al., 1999; Lee et al., 2002). Similarly, Shukla and Gupta (2004) have demonstrated apigenin-mediated growth inhibition and induction of apoptosis in DU145 prostate cancer cells. Genistein and quercetin, in addition, to their antiproliferative action, appear to alter the metastatic potential of rat breast adenocarcinoma cells, measured as a reduced ability to migrate within collagen matrix (Lu et al., 1996).

The citrus flavonoid tangeretin suppresses HL60 proliferation quite strongly, with an IC$_{50}$ of 0.17 $\mu$M (Hirano et al., 1995). Also it has been shown that gallocatechins, found in green tea and which include tannic acid, gallic acid, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG), can potentially induce apoptosis in various cancer cell lines (Ahmad et al., 1997). Curcumin, a natural phenolic compound found in spice turmeric, has been shown to have antiproliferative action against colon cancer, breast cancer and myeloid leukemia (Tsvetkov et al., 2005; Maheshwari et al., 2006). Resveratrol, the polyphenol found in berries and grapes, has been reported to possess anticancer properties (Aggarwal et al., 2004) and is able to inhibit the growth of prostate tumors by acting on the regulatory genes such as p53 (Narayanan, 2006). Androgen independent DU145 human prostate cancer cells manifest resistance to radiation-induced apoptotic death (Yacoub et al., 2001). Scarlatti et al (2007) have reported that pre-treatment with resveratrol significantly enhances radiation induced cell death in DU145 cells. Similarly, isoflavones have also been shown to sensitize cancer cells to radiotherapy (Hillman and Singh-Gupta, 2011).

Further, the capacity of certain dietary polyphenols to protect against both chemically induced or spontaneous formation of tumors in animals is well established. For instance, quercetin administered to rats in combination with dimethyl-benz-(a)-anthracene (DMBA) or N-nitrosomethylurea (NMU)
reduced the incidence and multiplicity of carcinogen induced mammary tumor by 30% and 50% respectively (Verma et al., 1988). Quercetin and luteolin (10 g/Kg diet) decreased fibrosarcoma incidence (52% and 60% respectively) and tumor size in male Swiss albino mice following treatment with the model chemical carcinogen 20-methylcholanthrene (Elangovan et al., 1994). Quercetin (20 g/Kg b.w) also increases the survival and reduces the tumor burden of mice transplanted intrasplenically with ML-3 hepatoma cells (Chi et al., 1997). The citrus flavonoid naringenin inhibits the in vivo development of DMBA induced mammary tumors in Sprague-Dawley rats (So et al., 1996). Jang et al. (1997) first reported that topical resveratrol applications prevented skin cancer development in mice treated with a carcinogen In further studies on mice and rats, resveratrol was found to be able to inhibit the carcinogenic activity of DMBA and Neuro-2a cells subcutaneously injected to induce breast cancer (Whitsett et al., 2006) and neuroblastoma (Chen et al., 2004a), respectively.

Several studies have described a protective effect of tea polyphenols against carcinogenesis. Rats fed on a diet containing 10 g green tea catechins/kg b.w have a considerably reduced mortality from mammary tumors following DMBA treatment compared with rats given carcinogen alone (Hirose et al., 1994). In a comprehensive study, Yang et al (1998) described the ability of both green and black tea infusions to inhibit N-nitrosodiethyl-amine-induced lung carcinogenesis in mice model. EGCG, the main tea polyphenolic, in a model of transgenic mice for skin cancer, has exhibited a preventive effect (Meeran et al., 2006). EGCG has also shown beneficial effects in lung cancer by decreasing the growth of the primary tumors and metastasis when mice were intraperitoneally injected with B16-F3m cells (Liu et al., 2001)

In addition to their potential as anticancer agents, an important role of plant polyphenols as natural modulators of cancer multidrug resistance (MDR) has
been documented (Ullah, 2008). Resistance of recurrent disease to cytotoxic drugs is the principal factor limiting long-term treatment success against cancer. Flavonoids have been found to inhibit breast cancer resistance protein (BCRP), an ABC transporter, which plays an important role in drug disposition leading to chemoresistance in breast cancer (Shuzhong et al., 2005). Isoflavones such as biochanin A, daidzein (Chung et al., 2005) and green tea polyphenol EGCG (Feng et al, 2005) have also been shown to exhibit anti MDR activities in various drug resistant cancer cell lines, such as doxorubicin resistant KB-A1 cells through the inhibition of P-glycoprotein transporters. Curcumin has been reported to induce apoptosis in chemoresistant ovarian cancer cell lines SKOV3 and ES-2 (Wahl et al., 2007).

**Putative anticancer mechanisms of plant derived dietary polyphenols**

While the anticancer properties of several common dietary polyphenols like resveratrol, EGCG, genistein and quercetin have been well established, the underlying molecular mechanisms of their antiproliferative effects are not completely understood and clearly defined. Dietary polyphenols can affect the overall process of carcinogenesis by several mechanisms and their effects may depend on tissue or cell type and may differ at high and low doses. Polyphenols may interfere in several of the steps that lead to the development of malignant tumors, including protecting DNA from oxidative damage, inhibiting carcinogen activation, activating carcinogen detoxifying systems and modulating multiple key proteins involved in diverse signal transduction pathways such as regulation of cellular proliferation, differentiation, apoptosis, angiogenesis or metastasis (Galati et al., 2000; Ren et al., 2003; Surh, 2003; Ramos, 2007).

Several suggested mechanisms by which polyphenols exert anticancer effects are briefly discussed below.
Antioxidant action:

In addition to the natural defence mechanisms of the cell, dietary polyphenols can also act as antioxidants, preventing injury caused by free radicals and blocking the initiation step of cancer (Middleton et al., 2000; Watson et al., 2000; Alia et al., 2006). Polyphenolic compounds can prevent the DNA damage caused by free radicals or carcinogenic agents through different mechanisms, such as (i) direct radical scavenging (Sonee et al., 2004), (ii) chelating divalent cations involved in Fenton reaction (Nakagawa et al., 2004) and (iii) modulation of enzymes related to oxidative stress such as glutathione peroxidase (GPx), glutathione reductase (GR) and superoxide dismutase (SOD) (Alia et al., 2006). It is considered that many of the antiproliferative effects of polyphenols are attributable to their antioxidant properties (Mukhtar and Ahmad, 1999). Polyphenols like EGCG and genistein have been shown to act as powerful radical scavengers, protecting cells from oxidative stress induced toxicity (Murakami et al., 2002; Sonee et al., 2004).

Modulation of enzymes associated with carcinogen activation and detoxification:

One important mechanism by which flavonoids may exert their in vivo chemopreventive effects is through their inhibition of phase-I drug-metabolizing enzymes, such as cytochrome P450 (CYP), which metabolically activates procarcinogens to reactive intermediates that trigger carcinogenesis (Ren et al., 2003; Schwarz and Roots, 2003).

Another mechanism claimed to be responsible for the chemopreventive activity of polyphenolic compounds is the induction of phase-II metabolizing enzymes such as glutathione Stransferase (GST), NAD(P)H:quinone oxidoreductase (NQO), and UDP-glucuronyltransferase (UGT) (Galati et al.,
by which carcinogens are detoxified and therefore more readily eliminated from the body.

**Cell cycle arrest:**

In cancer, normal cell growth and behaviour is lost and alterations in the regulation of cell cycle have been described (Chen et al., 2004b; Thangapazham et al., 2007). Thus, any perturbation of cell cycle specific proteins by dietary polyphenols can potentially affect and block the continuous proliferation of tumorigenic cells. Studies have shown that polyphenols can inhibit different cells at different cell phases such as G1, S, S/G2, and G2 (Gusman et al., 2001). For instance, EGCG or green tea polyphenol treatments induced G1 phase cell cycle arrest through down-regulation of cyclin D, cyclin E, cyclins-dependent kinase (CDK)1, CDK2, CDK4 and proliferating cell nuclear antigen (PCNA) over time in breast and cervical cancer cells (Thangapazham et al., 2007). Similarly, resveratrol was also shown to induce apoptosis, preferentially in cells arrested in the G0/G1 phase (Surh et al., 1999). Therefore, cell cycle arrest can represent a chemopreventive mechanism by subsequent induction of apoptosis.

**Induction of apoptosis:**

Programmed cell death or apoptosis is a systems approach to get itself rid of defective cells in order to prevent the defect from invading the normal cells. However cancer cells have evolved mechanisms to evade inherent apoptotic signals of the individuals own immune system. Therefore, natural compounds capable of inducing apoptosis in cancer cells are considered potential chemopreventive agents. In this respect, many dietary chemopreventive polyphenols, including quercetin, EGCG, resveratrol, genistein, apigenin, chrysin, curcumin and ellagic acid, evoke their inhibitory effect on carcinogenesis through the induction of apoptosis (Manson et al., 2003; Surh,
Moreover, tumor cells are found to be more sensitive to the apoptotic action of dietary polyphenols than normal cells (Chen et al., 1998; Ahmad et al., 2000b; Park et al., 2005; Feng et al., 2007). For example, quercetin exerted the apoptotic effect in a selective manner by significantly inhibiting the growth of highly aggressive PC-3 and moderately aggressive DU-145 prostate cancer cell lines, while not affecting the poorly aggressive LNCaP prostate cancer cells and normal fibroblasts (Nair et al., 2004). Similarly, green tea polyphenols have been shown to induce a dose-dependent inhibition of cell growth, G0–G1-phase arrest of the cell cycle and induction of apoptosis in human osteosarcoma cells (MG-63 and Saos-2), but not in normal rat osteoblasts (Park et al., 2005).

The Bcl-2 family is the best characterized component of apoptotic signalling pathways and involves two functional groups including antiapoptotic proteins (Bcl-2 and Bcl- XL) and proapoptotic proteins (Bax, Bak and Bad). It is the fine balance of these two functional protein groups that provide the signal for cell survival or cell death which is transmitted to the downstream effector molecules such as intracellular caspases. Sarkar and co-workers have suggested that a downregulation of antiapoptotic Bcl-2 and up-regulation of proapoptotic Bax may be one of the molecular mechanisms by which polyphenol genistein induces apoptosis (Lian et al., 1998). They showed that the ratio of Bax to Bcl-2 was significantly increased after 24 h of treatment, corresponding with a significant increase in apoptotic cells after 48 h of genistein treatment.

In some studies, inhibition of the proteasome chymotrypsin-like activity has been reported to be associated with induction of apoptosis in tumor cells (Lopes et al., 1997). In one such study, apigenin was shown to inhibit proteasome activity and induce apoptosis in human breast cancer MDA-MB-231 cells (Chen et al., 2007). Moreover, in certain circumstances, polyphenol
induced apoptotic death has been shown to occur as a consequence of an inhibited telomerase activity (Yokoyama et al., 2004) and/or with the activation of both apoptotic pathways (extrinsic and intrinsic routes) (Hayakawa et al., 2001; Kawai et al., 2005). Polyphenols have also been suggested to induce apoptosis by inhibiting DNA topoisomerase-II, thereby preventing ligation of DNA double strand breaks (Lynch et al., 2003).

Modulation of cellular signalling pathways:

The cellular signalling pathways that regulate proliferation, survival and transformation of cells are indirectly involved in the regulation of apoptotic cell death. Components of these pathways include several kinases such as mitogen-activated protein kinases (MAPK) and protein kinase C (PKC) which contribute to the maintenance of cell homeostasis. Abnormal activation or silencing of these kinases or their downstream transcription factors can result in uncontrolled cell growth, leading to malignant transformation. Many dietary polyphenolic compounds can effectively suppress tumorigenic signalling in vitro. Some of the possible mechanisms by which polyphenols influence these signal transduction pathways are mentioned below.

(a) Suppression of NF-kB transcription factor activation and its nuclear translocation. (Ahmad et al. 1999; Davis et al., 1999; Alhasan et al., 2000; Manna et al., 2000).

(b) Suppression of AP-1 transcription factor activation (Yoshioka et al., 1995; Dong et al., 1997; Yu et al. 2001)

(c) Suppression of Protein Kinases, such as PKC (Protein kinase C), Akt/PKB (Protein Kinase B) and PTK (tyrosine kinases) (Markovits et al., 1989; Liu et al., 1993; Lin et al., 1997; Atten et al., 2001; Banerjee et al., 2007)

(d) Suppression of Mitogen Activated Protein Kinases (MAPK) (Kuo and Yang, 1995; Siddiqui et al., 2004)
Introduction

(e) Suppression of Growth-Factor Receptor (GFR)-mediated pathways
(Masuda et al., 2001; Masuda et al., 2002; Kaneuchi et al., 2003)

Anti-inflammatory action:

Epidemiological and clinical studies have reported an association between inflammation and cancer (Thun et al., 2004) and key signalling molecules like NF-kB and cyclooxygenase-2 (COX-2) are thought to be involved in this process (Lu et al., 2006). Inhibition of COX-2 and blocking the prostaglandin (PG) cascade may have an impact on neoplastic growth and its development by inhibiting proliferation, angiogenesis and metastasis. Flavone was shown to induce apoptosis in human colon carcinoma cells through changes in mRNA levels of COX-2 and NF-kB (Wenzel et al., 2000).

Anti-angiogenic action:

Angiogenesis, the process during which new blood vessels are formed from preexisting ones, can be classified as either physiological or pathological. Physiological angiogenesis provides a driving force for organ development and wound healing, while it is the pathological angiogenesis which occurs during tumor growth at primary and metastatic sites (Folkman, 2007). The signalling pathway governing tumor angiogenesis is exceedingly complex, involving various angiogenic mediators. The major signalling mediators include VEGF, platelet derived growth factor (PDGF), fibroblast growth factors (FGFs), epidermal growth factor, angiopoietins, endothelins, integrins, cadherins, and notch (Gordon et al., 2010). Many plant polyphenols have shown angiogenesis-modulating properties by targeting one or more of these mediators in the signalling pathway (Brakenhielm et al., 2001; Bagli et al., 2004; Fan et al., 2006)
Anti-metastatic action:

Tumor cell invasion and metastasis are interrelated processes involving cell growth, cell adhesion, cell migration, and proteolytic degradation of tissue barriers such as the extracellular matrix and basement membrane. Many proteolytic enzymes, including MMPs (chiefly MMP-2 and MMP-9) (Jiang et al., 2001; Sternlicht and Werb, 2001) and intercellular adhesion molecule (ICAM), participate in the degradation of these barriers (Kleiner and Stetler-Stevenson, 1993; Aimes and Quigley, 1995). Several polyphenolic compounds have been shown to inhibit tumor cell invasion and metastasis by targeting one or more molecules such as the MMPs and the CAMs (Hung et al., 2005; Yang et al., 2005; Piantelli et al., 2006; Zhen et al., 2006).

Prooxidant action:

It is generally understood that antioxidants counteract ROS production and inhibit the oxidative DNA damage and therefore reduce the risk of cancer. Notwithstanding these observations, growing experimental evidence suggests that polyphenolic antioxidants themselves mediate production of ROS (prooxidant action) which may be responsible for their ability to induce apoptosis of cancer cells (Hadi et al., 2007; Qian et al., 2009). Dietary polyphenols have been shown to exhibit both prooxidant and antioxidant activities. They act as prooxidants in systems containing redox-active metals, such as copper (Cu) and iron (Fe) that catalyze their redox cycling, leading to the formation of ROS and phenoxy radicals that can damage DNA, lipids, and other biological molecules (Ahmad et al., 1992; Li and Trush, 1994; Decker, 1997).

The anticancer properties of polyphenols are generally believed to reflect their ability to scavenge endogenous ROS. However, the prooxidant action of plant-derived polyphenolic compounds rather than their antioxidant action
may be an important mechanism for their anticancer and apoptosis-inducing properties (Michels et al. 2005), as ROS can mediate apoptotic DNA fragmentation (Hadi et al., 2000; Shen et al. 2004; Noda et al. 2007). The antioxidant properties of dietary polyphenolics may only partly explain their antitumor promotion effects, as ellagic acid is 10 times more potent an antioxidant than tannic acid. However, tannic acid was more effective than ellagic acid in inhibiting the promotion of skin tumor by 12-O-tetradecanoyl phorbol-13-acetate (Gali et al., 1992). It was suggested that the antioxidant effects of these polyphenols might be essential but not sufficient for their antitumor promotion. In any case ROS scavenging properties of plant polyphenols may account for their chemopreventive effects but not for any therapeutic action against cancer cells (Radin, 2003).

Further, it may be mentioned that the apoptotic DNA fragmentation properties of several anticancer drugs are considered to be mediated by ROS (Kaufmann, 1989; Turella et al. 2005; Kim et al. 2006). Certain properties of dietary polyphenolic compounds, such as binding and cleavage of DNA and the generation of ROS in the presence of transition metal ions (Rahman et al., 1990), are similar to those of known anticancer drugs. A putative mechanism for anticancer and apoptosis-inducing properties of plant derived dietary polyphenolic compounds, which involves mobilization of intracellular copper and consequent prooxidant action, has been proposed (Hadi et al., 2000). Compared with normal cells, preneoplastic cells and neoplastic cells have been shown to contain elevated levels of copper (Gupte and Mumper, 2008) and may be more sensitive to electron transfer with polyphenols to generate ROS. Therefore DNA damage induced by polyphenols in the presence of Cu(II) may be an important pathway through which preneoplastic cells and neoplastic cells can be killed while normal cells may survive (Figure 5).
Figure 5: Possible mechanism for anticancer effects of polyphenolic compounds (from Qian et al., J Med Chem 2009; 52(7): 1963-1974).