

## REVIEW

# The Promise of Dried Fruits in Cancer Chemoprevention

Joydeb Kumar Kundu, Kyung-Soo Chun\*

### Abstract

Chemoprevention is an attempt to use nontoxic natural and synthetic substances or their mixtures to intervene the relatively early stages of carcinogenesis, before invasive characteristics are manifested. The consumption of fruits is well known to reduce the risk of human cancers. Although most fruits are available only on a seasonal basis, recent advances in food processing technologies have made it possible to extend the shelf life of fruits and fruit-products. Fruits can be preserved by applying different drying processes to reduce the moisture content. Different varieties of dried fruits are now sold in supermarkets, thereby making them readily accessible to consumers. Since oxidative stress and chronic inflammation play important roles in cancer development, dried fruits with antioxidative and anti-inflammatory properties hold promise for cancer chemoprevention. The antioxidant, anti-inflammatory and chemopreventive activities of dried fruits are largely attributed to their polyphenols and vitamins. Dried fruits contain adequate amounts of bioactive principles, such as anthocyanins, acetogenins, catechins, coumarins, phenolic acids, terpenes, xanthenes, and others. Since numerous health beneficial phytochemicals in fruits are conserved even after processing, regular intake of dried fruits can help prevent cancer. This review addresses the chemopreventive potential of representative dried fruits and their active constituents.

**Keywords:** Chemoprevention - cancer - dried fruits - antioxidants - anti-inflammatory phytochemicals

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### Introduction

Over the past several decades, extensive efforts have been made to find a cure for cancer. However, the number of new cancer cases, which has been recorded as about 3 million in the year 2000, is expected to be 7.1 million by the year 2020 (Mackay et al., 2006; Park et al., 2008). The increasing cancer incidence and mortality, and the lack of effective treatment have spurred extensive research on chemoprevention. The term "Chemoprevention" refers to the use of non-toxic compounds from natural or synthetic sources to inhibit, retard or reverse carcinogenesis (Sporn, 1976). It is generally accepted that the consumption of fruits may reduce the risk of human cancers (La Vecchia et al., 2001). Multiple lines of evidence suggest that fruits, such as berries, figs, persimmon, pomegranate, avocado, mango, kiwi, etc. possess cancer chemopreventive activities. However, the regular consumption of these fruits is limited by their availability in a particular seasonal basis. Recent advances in food processing technologies have made it possible to extend the shelf life of many fresh fruits by applying different drying processes to reduce the moisture content. While the natural sun-drying is commonly employed for drying of many fruits, mechanical devices, such as dryers and microwaves are also used nowadays. Another technique for fruit preservation is freeze drying process, which is used for extending the shelf life of foods by preventing the microbial growth and retarding

lipid oxidation to preserve thermolabile components, such as carotenoids, vitamins, and phenolics in dried fruits (Ratti, 2001; Marques et al., 2007). The choice of an effective drying method is dependent on the types of fruits. A wide variety of dried fruits are now readily available in local markets indicating their popularity among different communities (Jesionkowska et al., 2008). Because of the presence of numerous antioxidant and anti-inflammatory phytochemicals, dried fruits can be excellent natural resource for preventing cancer.

### Chemopreventive Potential of Dried Fruits

Dried fruits with anti-inflammatory and antioxidative properties can be good candidate for cancer chemopreventive agent because oxidative stress and chronic inflammation play important roles in cancer development (Kundu and Surh, 2008). The anti-inflammatory, antioxidant, and chemopreventive activities of dried fruits are largely attributed to their polyphenols and vitamins (Donovan et al., 1998; Karakaya et al., 2001). Drying of fruits by sun-exposure or using dryers with high temperature often causes loss of bioactive phytochemicals. For example, carotenoids in fresh grapes can be lost in raisins, which are the dried form of grapes. Some types of thermolabile vitamins can be degraded during drying of fruits at high temperature. While the fruit processing may cause decomposition of some volatile compounds, it

is possible that new volatile compounds are synthesized during the drying process (Stacewicz et al., 2001). Despite the processing-oriented loss certain active ingredients, dried fruits retains considerable amount of bioactive phytochemicals, such as anthocyanins, acetogenins, catechins, coumarins, phenolic acids, terpenes, xanthenes, and others. Since numerous beneficial phytochemicals are conserved even after processing of fruits, daily intake of dried fruits can help prevent cancer. Table 1 summarizes *in vivo* chemopreventive effects of representative dried fruits and their active constituents. Chemical structures of dried fruit constituents with well-defined role in cancer chemoprevention are presented in Figure 1.

## Berries

Commonly consumed berry fruits include strawberry (*Fragaria x ananassa*, D.), black raspberry (*Rubus occidentalis* L.), blueberry (*Vaccinium corymbosum*, L.), blackberry (*Rubus fruticosus*, L.), cranberry (*Vaccinium macrocarpon*, A.), red raspberry (*Rubus idaeus*, L.), white currant (*Ribes rubrum*, L.), black currant (*Ribes nigrum*, L.) and bilberry (*Vaccinium myrtillus*, L.). Berries contain various phytochemicals with antioxidant, anti-inflammatory and anticancer activities. The major berry phenolics were anthocyanins, ellagitannins, flavonols, flavanols, proanthocyanidins, and phenolic acids (Seeram et al., 2006).

### Strawberry

Strawberry is among the most widely consumed berries, either in fresh or processed forms. Dietary administration of freeze-dried strawberry (5 or 10%) suppressed *N-nitrosomethylbenzylamine* (NMBA)-induced esophageal carcinogenesis in F344 rats (Stoner et al., 1999). A series of isothiocyanates, such as phenylpropylisothiocyanate, phenylethylisothiocyanate and benzylisothiocyanate present in freeze-dried strawberry extract also inhibited NMBA-induced rat esophageal carcinogenesis by suppressing NMBA-DNA adduct formation through the inhibition of cytochrome p450 (CYP) enzymes, which are responsible for metabolic activation of NMBA (Stoner et al., 1999). Organic extract of freeze-dried strawberry (Sweet Charlie cultivar) diminished the mutagenesis caused by a direct acting mutagen methyl methanesulfonate or the metabolically activated carcinogen benzo(a)pyrene, suggesting the anticancer potential of dried strawberry extract (Hope Smith et al., 2004). A recent study demonstrated that topical application of lyophilized strawberry extract attenuated 7,12-dimethylbenz(a)anthracene (DMBA)-induced oral carcinogenesis in hamster cheek pouch (Casto et al., 2013).

### Blueberry

In terms of U.S. fruit consumption, blueberries rank only second to strawberries in popularity of berries. Blueberries are not only popular, but also repeatedly ranked in the U.S. diet as having one of the highest antioxidant capacities among all fruits, vegetables, and seasonings. Oral administration of blueberry extract

decreased hemangioendotheliomas tumor growth in nude mice subcutaneously inoculated with transformed murine endothelial cells and enhanced the survival of tumor bearing mice (Gordillo et al., 2009). Dietary administration of blueberry powder reduced the multiplicity and volume of 17 $\beta$ -estradiol-induced mammary tumors in female ACI rats (Aiyer et al., 2008). Administration of whole blueberry powder in diet (10%) for 8 weeks significantly reduced the tumor volume in female nude mice implanted with human breast cancer MDA-MB231 cells and blocked the liver metastasis of these cells. The anti-metastatic effect of dietary blueberry powder was resulted from reduced activity of matrix metalloproteinase (MMP)-9 and secretion of urokinase plasminogen activator (uPA) (Adams et al., 2010).

### Raspberry

There are three main varieties of raspberries: black,

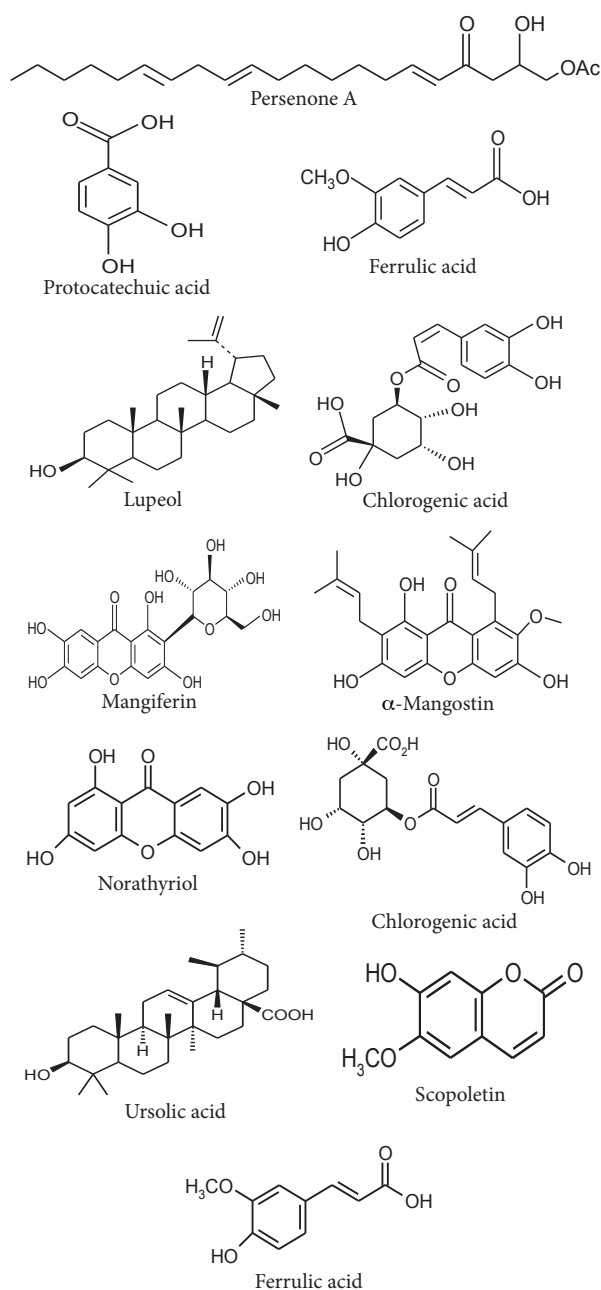


Figure 1. Chemical Structures

**Table 1. Cancer Chemoprevention with Dried Fruits and Their Active Ingredients**

Treatment	Major findings & Experimental model
<b>Berry fruits</b>	
Freeze-dried strawberry	Suppression of NMBA-induced esophageal cancer in F344 rats (Stoner et al., 1999) Inhibition of DMBA-induced oral cancer in hamster cheek pouch (Casto et al., 2013)
Blueberry extract	Decrease of the incidence and size of hemangioendotheliomas and increase of survival in nude mice (Gordillo et al., 2009)
Blueberry powder	Reduction of the multiplicity and volume of 17 $\beta$ -estradiol-induced mammary tumors in female ACI rats (Aiyer et al., 2008) Decrease of the tumor volume in female nude mice implanted with MDA-MB231 cells and reduction of the liver metastasis of the cells (Adams et al., 2011; Adams et al., 2010)
Freeze-dried black raspberry	Reduction of the multiplicity of NMBA-induced esophageal tumors (Kresty et al., 2001) Suppression of AOM-induced ACF formation in F344 rats (Harris et al., 2001) Attenuation of DSS-induced colitis in C57BL/6 mice (Montrose et al., 2011) Blocking of UVB-induced tumor promotion in mouse skin (Duncan et al., 2009)
Freeze-dried bilberry	Inhibition of intestinal adenomas formation in APC <sup>min+</sup> mice (Misikangas et al., 2007)
Bilberry fruit preparation (Mitroselect)	Decreased adenoma formation in APC <sup>min+</sup> mice (Cooke et al., 2006)
Freeze-dried white currant	Attenuation of intestinal adenomas formation in APC <sup>min+</sup> mice (Rajakangas et al., 2008)
Black currant skin extract	Inhibition of DEN-induced hepatic preneoplastic foci in rat liver (Bishayee et al., 2011)
<b>Mango</b>	
Mangiferin	Inhibited B(a)P-induced lung carcinogenesis in Swiss albino mice (Rajendran et al., 2008) Reduction of the incidence and multiplicity of colon tumor formation in AOM-treated F344 rats (Yoshimi et al., 2001)
Norathyriol	Suppression of UVB-induced mouse skin papillomagenesis (Li et al., 2012)
Lupeol	Inhibition of TPA-induced mouse skin tumorigenesis (Saleem et al., 2004)
<b>Prunes</b>	
Chlorogenic acid	Inhibition of TPA-induced papillomagenesis in mouse skin (Huang et al., 1988) Protection of MNU-induced glandular stomach carcinogenesis in rats (Shimizu et al., 1999)
<b>Persimmon</b>	
Liposomal encapsulated diospyrin	Reduction of Ehrlich ascites tumor growth in Swiss mice (Hazra et al., 2005)
Ursolic acid	Attenuation of human prostate cancer cells xenograft growth in nude mice (Shanmugam et al., 2011b) Suppression of prostate cancer metastatic progression in TRAMP model (Shanmugam et al., 2011a)
<b>Avocado</b>	
Personeone A	Attenuation of TPA-induced H <sub>2</sub> O <sub>2</sub> production in mouse skin (Kim et al., 2000b)
Scopoletin	Reduction of the size of skin papillomas induced by DMBA plus croton oil
<b>Mangosteen</b>	
$\alpha$ -Mangostin	Inhibition of lymph node metastasis in mice inoculated with metastatic BJMC3879luc2 cells (Shibata et al., 2011) Reduction of 22Rv1 prostate cancer cells growth in athymic nude mouse (Johnson et al., 2012)
Ferulic acid	Inhibition of DMBA-induced rat mammary tumor formation (Baskaran et al., 2010) Inhibition of DMBA-induced hamster buccal pouch carcinomas formation (Balakrishnan et al., 2008) Inhibition of DMBA plus TPA-induced mouse skin papilloma (Alias et al., 2009) Attenuation of 4NQO-induced rat tongue carcinogenesis (Tanaka et al., 1993) Attenuation of AOM-induced ACF formation in rat colon (Kawabata et al., 2000)
Protocatechuic acid	Decrease of tongue squamous cell carcinomas formation in rats (Suzuki et al., 2003) Suppression of DMBA-induced hamster cheek pouch carcinogenesis (Ohnishi et al., 1997) Suppression of BOP-induced hamster pancreatic carcinogenesis (Nakamura et al., 2000)
<b>Fig fruit</b>	
Fig latex	Suppress the growth of spontaneous mammary tumors in mice (Ullman et al., 1952)
<b>Pomegranate</b>	
Pomegranate juice	Suppression of tumor growth in the prostate tissues (Adhami et al., 2012) Decrease of the number of ACF and dysplastic ACF and proliferative cells percentage (Banerjee et al., 2013)
Pomegranate extract	Suppression of B(a)P and NTCU-induced lung carcinogenesis in AOM-treated rats (Khan et al., 2007) Inhibition of DMBA plus TPA-induced skin tumor promotion in CD-1 mouse (Afaq et al., 2005)

golden and red. Raspberries may have been named after a 16th-century French wine called 'raspis'. Raspberries were once called hindberries. Oral administration of lyophilized black raspberry (10%) markedly suppressed NMBA-induced esophageal tumors development (Kresty et al., 2001) and azoxymethane (AOM)-induced aberrant crypt foci (ACF) formation in F344 rats (Harris et al., 2001). Administration of freeze-dried black raspberry extract (5 or 10%) in diet for 7-14 days reduced dextran sulphate sodium (DSS)-induced colitis, a dextran that often leads to the development of colon cancer, in C57BL/6 mice (Montrose et al., 2011). Moreover, topical application of standardized black raspberry extract (500  $\mu$ g) significantly reduced ultraviolet B (UVB) radiation-

induced skin carcinogenesis in female SKH-1 hairless mice (Duncan et al., 2009).

#### *Bilberry*

Bilberry, a low-growing shrub, is often called European blueberry because it grows abundantly in the mountainous areas of Europe. Historically, bilberry is best known as a specific remedy for the eyes. In World War II, British Royal Air Force noticed that their night vision was sharper when they consumed bilberry. This bioactivity of bilberry attracted researchers to study its health beneficial effects. Subsequent studies revealed that the anthocyanin-rich bilberry extract was a potent inhibitor of oxidative stress, inflammation and tumorigenesis

(Cooke et al., 2006; Piberger et al., 2011). Mice fed with dried bilberry or its anthocyanin fractions were protected against acute or chronic DSS-induced colitis (Piberger et al., 2011). Dietary freeze-dried bilberry significantly inhibited intestinal adenomas formation in APC<sup>min+</sup> mice via decrease of  $\beta$ -catenin and cyclin D1 expressions (Misikangas et al., 2007). Mirtoselect (0.3%), an anthocyanin mixture from bilberry, administered in the diet significantly decreased intestinal adenoma numbers compared to controls in APC<sup>min+</sup> mice. Cyanidin-3-glucoside, a major constituent of this bilberry mixture, also showed significant inhibitory effect on intestinal adenoma formation in this mouse model (Cooke et al., 2006). A recent study reported that feeding animals with bilberry extract could suppress premalignant liver lesions in N-diethylnitrosoamine (DENa)-initiated and piperonyl butoxide-promoted rats (Hara et al., 2014).

### Currant

There are two distinct fruits which are called currants: first, the dried zante grape; like a raisin, it is used in baked goods, and second, a fresh tiny berry related to the gooseberry. Currents are black, red, or white. The black ones are used for syrups and liqueurs; while the red and white berries are for eating out of hand. Freeze-dried white currant diet (10%) for 10 weeks attenuated the formation of intestinal adenomas via decrease of  $\beta$ -catenin and nuclear factor-kappa B (NF- $\kappa$ B) levels in APC<sup>min+</sup> mice (Rajakangas et al., 2008). Administration of an anthocyanin-rich black currant skin extract (100 or 500 mg/kg body weight) for 4 weeks inhibited DENa-induced hepatic preneoplastic foci in rat liver and decreased the expression of cyclooxygenase-2 (COX-2) and activation of nuclear factor-kappaB (NF- $\kappa$ B) in rat liver (Bishayee et al., 2011). Further study revealed that black currant skin extract upregulated the gene expression of a number of hepatic antioxidant and carcinogen detoxifying enzymes, such as NAD(P)H:quinone oxidoreductase (NQO), glutathione S-transferase (GST), and uridine diphosphate-glucuronosyltransferase via activation of redox-sensitive transcription factor nuclear factor erythroid-related factor-2 (Nrf2) (Thoppil et al., 2012). Since fortification of cellular antioxidant and detoxification pathways protects against DNA damage and mutagenesis, these findings suggest the cancer chemopreventive potential of dried black currant.

### Mango

Mango (*Mangifera indica* L.) is one of the most popular of all tropical fruits and abundantly grown in Thailand, Taiwan, India and the Philippines during summer. Mango fruit contains high amount of flavanol-O-glycosides, xanthone-C-glycosides (Berardini et al., 2005b), and carotenoids (Chen et al., 2004), and dried mango peel is a good source of pectin and polyphenols (Berardini et al., 2005a). A major chemopreventive phytochemical present in mango fruit is mangiferin (1,3,6,7-tetrahydroxyxanthone-C2-beta-D-glucoside), which is a C-glycosylxanthone.

Administration of mangiferin (100 mg/kg body

weight) in diet for 18 weeks inhibited B(a)P-induced lung carcinogenesis in Swiss albino mice. According to this study, mangiferin induced the activities of several antioxidant and detoxification enzymes in lung and liver of tumor bearing mice (Rajendran et al., 2008). Dietary administration of mangiferin (0.1%) for 4 weeks reduced the incidence and the multiplicity of colon tumor formation in AOM-treated male F344 rats (Yoshimi et al., 2001). There is no evidence of adverse side effects of mangiferin so far (Telang et al., 2013). Therefore, mangiferin could be a promising candidate for cancer chemopreventive agent. Norathyriol (1,3,6,7-tetrahydroxy-9H-xanthone-9-one) is an aglycone of a xanthone C-glycoside mangiferin. Topical application of norathyriol (0.5 or 1 mg) significantly suppressed UVB-induced formation of skin papillomas by blocking the activation of NF- $\kappa$ B and activator protein-1 (AP-1) in SKH-1 hairless mice (Li et al., 2012). Topical treatment with lupeol (1 or 2 mg), a triterpene constituent present in mango pulp extract, attenuated 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse skin carcinogenesis by decreasing the expression of ornithine decarboxylase (ODC), COX-2 and inducible nitric oxide synthase (iNOS) through inactivation of NF- $\kappa$ B and Akt in CD-1 mice (Saleem et al., 2004).

### Prunes

Prunes are dried plums, fruits of *Prunus domestica*, L., which belongs to the Rosaceae family that originated in the Caucasus region of Western Asia. It was reported that the antioxidant capacity of prunes extracts was the highest among dried fruits (Pellegrini et al., 2006; Wu et al., 2004). Although carotenoids in fresh plums undergo degradation during processing into prunes, adequate amount of lutein,  $\beta$ -carotene and  $\alpha$ -carotene were detected in prunes (Stacewicz et al., 2001). The antioxidative and chemopreventive activity of carotenoids, such as  $\beta$ -carotene and lutein have been well investigated (Gunasekera et al., 2007; Huang et al., 2007; Sindhu et al., 2010). Dried prunes also contains  $\beta$ -carboline alkaloids (Tsuchiya et al., 1995) and phenolic compounds, such as chlorogenic acid, neochlorogenic acid, hydroxycinnamates (Donovan et al., 1998), and oligomeric proanthocyanidins (Kimura et al., 2008). Topical application of chlorogenic acid (10  $\mu$ mol) suppressed TPA-induced papilloma formation in CD-1 mouse skin (Huang et al., 1988). Dietary administration of chlorogenic acid (250 or 500 ppm) for 22 weeks suppressed N-methyl-N-nitrosourea (MNU)-induced glandular stomach carcinogenesis in male F344 rats (Shimizu et al., 1999). One of the risk factors for colorectal cancer is the generation of secondary bile acids from primary bile acids by large intestinal microflora (Reddy et al., 1988). Administration of dried plum diet (9.5%) for 10 days significantly lowered fecal concentrations of lithocholic acid and hyodeoxycholic acid in rats (Yang and Gallaher, 2005). In a pilot human study comprising 41 men, intake of prunes decreased the fecal content of secondary bile acids lithocholic acid (Tinker et al., 1991). These data suggest that prunes may have protective effect against colorectal carcinogenesis.

## Persimmon

Persimmon (*Diospyros kaki* T.) fruits, widely grown in North-Eastern part of Asia, are consumed either fresh or in dried form. Sun-dried persimmon, known as “kot-kham”, is a very popular snack in Korea. Methanol extract of dried persimmon fruit hold almost equal antioxidant and free radical scavenging property as that of fresh fruits (Jung et al., 2005). Epigallocatechin-3-gallate (EGCG) is the major polyphenolic compound present in persimmon fruit. A large body of experimental findings have documented the cancer chemopreventive activity of EGCG (Park and Surh, 2004). Diospyrin, a bis-naphthoquinoid, has been isolated from persimmon fruits. Intraperitoneal (i.p.) transplantations of liposomal encapsulated diospyrin (1 mg/kg body weight) in male Swiss mice reduced the growth of Ehrlich ascites tumor as well as prolonged the survival of tumor-bearing mice (Hazra et al., 2005). Other major chemopreventive phytochemicals present in persimmon fruit are triterpenoids, such as oleanolic acid and ursolic acid (Zhou et al., 2010). Treatment with ursolic acid (i.p. 200 mg/kg body weight) for 6 weeks suppressed the growth of human prostate cancer cells (DU-145) xenograft in athymic Balb/c nude mice with decreased activation of NF- $\kappa$ B and signal transducer and activator of transcription-3 (STAT3) signaling pathways (Shanmugam et al., 2011b). Moreover, administration of ursolic acid (1%) in diet for 12 weeks suppressed metastatic progression of prostate cancer by blocking the activation of NF- $\kappa$ B and inhibiting the expression of chemokine receptor CXCR4 in a transgenic adenocarcinoma of mouse prostate (TRAMP) model (Shanmugam et al., 2011a).

## Avocado

Avocado (*Persea americana* M.) fruits, also known as Alligator Pear, are widely consumed throughout the world. Avocado fruit is known to contain more than 25 chemopreventive phytochemicals including alkanols or aliphatic acetogenins (e.g., persin, persinone A and B), flavonoids (e.g., catechin, epicatechin, luteolin, apigenin, quercetin), carotenoids (e.g., zeaxanthin, lutein,  $\beta$ -carotene), terpenoid glycosides and coumarins (Lu et al., 2005; Ding et al., 2007). Both persinone A and B showed the inhibitory effects on lipopolysaccharide (LPS) plus interferon- $\gamma$  (IFN $\gamma$ )-induced generation of superoxide and nitric oxide (NO) in murine macrophage RAW 264.7 cells, and inhibited superoxide generation in TPA-treated human promyelocytic leukemia HL-60 cells (Kim et al., 2000a). Topical treatment with persinone A (810 nmol) attenuated TPA-induced H<sub>2</sub>O<sub>2</sub> production in female ICR mouse skin (Kim et al., 2000b). Scopoletin (7-hydroxy, 6-methoxy-coumarin) is a bioactive compound present in avocado fruit. Mice fed with scopoletin (50 or 100 mg/kg body weight) for 24 weeks decreased the size of skin papillomas induced by DMBA plus croton oil (Bhattacharyya et al., 2010).

## Mangosteen

Mangosteen (*Garcinia mangostana* L.) fruit, also

known as ‘queen of fruits’, is widely grown in tropical countries. The fruit contains dark purple or reddish pericarp (peel and rind) with white, soft and juicy edible pulp (arils). Mangosteen fruit contains more than 50 xanthone derivatives, which have been isolated from pericarp and pulp of mangosteen fruit (Mahabusarakam et al., 2006). Examples include  $\alpha$ -,  $\beta$ - or  $\gamma$ -mangostin, gartanin, garcinone, mangostenone, euxanthone, cudraxanthone, calabaxanthone, and demthethylcalabaxanthone (Pedraza et al., 2008). Freeze-dried mangosteen fruit peel, rind and aril parts also contain high content of phenolic acids, such as hydroxybenzoic acid derivatives (e.g., p-hydroxybenzoic acid, protocatechuic acid, vanillic acid), hydroxycinnamic acid derivatives (e.g., p-coumaric acid, caffeic acid, ferrulic acid), and other phenolic acids (e.g., benzoic acid, cinnamic acid, p-hydroxyphenylacetic acid) (Zadernowski et al., 2009).

Many of these xanthones, anthocyanins and phenolic acids have been demonstrated to possess antioxidant and cancer chemopreventive properties (Jung et al., 2006; Shan et al., 2011). The xanthones showed antioxidant activity with  $\alpha$ -mangostin being the most active. Shibata et al. reported that treatment with  $\alpha$ -mangostin using mini-osmotic pump (20 mg/kg body weight) suppressed lymph node metastasis in Balb/c mice inoculated with BJMC3879luc2 mammary carcinoma cells and increased the survival of tumor bearing mice compared to control animals (Shibata et al., 2011). In athymic nude mice, administration of  $\alpha$ -mangostin (100 mg/kg body weight) by oral gavage significantly inhibited the growth of 22Rv1 prostate cancer cells (Johnson et al., 2012). Treatment with  $\gamma$ -mangostin attenuated LPS-induced expression of COX-2 in C6 rat glioma cells by blocking the activation of NF- $\kappa$ B (Nakatani et al., 2004). Besides xanthones, phenolic acids and anthocyanins present in mangosteen fruit possess cancer chemopreventive activity. Dietary administration of either caffeic acid or ferrulic acid suppressed B(a)P-induced forestomach tumor formation in female ICR/Ha mice (Wattenberg et al., 1980). Oral administration of ferrulic acid (40 mg/kg body weight) by gavage significantly attenuated DMBA-induced rat mammary tumor formation (Baskaran et al., 2010), mouse skin papilloma (Alias et al., 2009) and hamster buccal pouch carcinomas (Balakrishnan et al., 2008). Administration of ferrulic acid (500 ppm) in diet for 7 weeks significantly reduced the incidences of rat tongue neoplasms induced by 4-nitroquinoline-1-oxide (4NQO) (Tanaka et al., 1993) and AOM-induced ACF formation in rat colon (Kawabata et al., 2000). Treatment with protocatechuic acid, another chemopreventive phenolic acid present in mangosteen fruit, attenuated the liver metastasis of implanted B16/F10 melanoma cells by blocking the activity of MMP-2 and NF- $\kappa$ B in C57/BL6 mice (Lin et al., 2011). Feeding with protocatechuic acid (2000 ppm) significantly decreased the development of tongue squamous cell carcinomas in male F344 rats (Suzuki et al., 2003). Administration of protocatechuic acid (2000 ppm) in diet for 17 weeks also suppressed DMBA-induced hamster cheek pouch carcinogenesis (Ohnishi et al., 1997) and *N*-nitroso-bis(2-oxopropyl)amine (BOP)-induced hamster pancreatic carcinogenesis (Nakamura et al., 2000). These studies

indicate that regular intake of dried mangosteen fruit would be beneficial for preventing cancer.

## Fig Fruits

Fig (*Ficus carica*, L.) fruit is widely used both as a food and as medicine in the Middle East. The fresh and dried fig have been reported as an important source of vitamins, minerals, carbohydrates, sugars, organic acids, phenolic compounds, high amounts of fiber and polyphenols (Slatnar et al., 2011). Figs are an excellent source of phenolic compounds, such as proanthocyanidins (Vinson et al., 2001). Different parts of *Ficus carica* were studied as herbal medicine. The latex released on picking the fruits is used to treat skin tumors and warts (Ghazanfar, 1994). Fig latex and its derivatives have been shown to suppress the growth of spontaneous mammary tumors in mice (Ullman et al., 1952). Moreover, higher concentration of organic acids and phenolic compounds, such as chlorogenic acid, catechin, epicatechin, kaemferol-3-*O*-glucoside and luteolin-8-*C*-glucosides were also detected in either sun-dried or oven-dried figs as compared to fresh figs (Slatnar et al., 2011). Thus, dried figs may be utilized for the prevention and therapy of cancer.

## Pomegranate

Pomegranate, *Punica granatum* L., is native to the area once known as Armenia, Persia and Iraq. They have been cultivated since ancient times, and spread to Asian countries. Pomegranate extract has been demonstrated to regulate intracellular redox status (Lansky et al., 2005). As compared to red wine or green tea, pomegranate extract has a three times greater antioxidant capacity (Gil et al., 2000). Pomegranate extracts contain ellagic acid, caffeic acid, luteolin and punicic acid, all of which have been reported to possess anticancer effects in preclinical models (Lansky et al., 2005). Ellagic acid is considered as the most active component of pomegranate extract, accounting for more than 50% of its antioxidant effects (Gil et al., 2000). Antioxidant activities of freeze-dried preparations of pomegranate and its three major anthocyanidins (delphinidin, cyanidin, and pelargonidin) were evaluated (Noda et al., 2002).

Oral pomegranate juice supplementation significantly suppressed prostate tumor growth by inhibition of Akt/mTOR pathways in TRAMP model (Adhami et al., 2012). Recently, Banerjee et al. reported that the number of ACF and dysplastic ACF was significantly decreased as well as the percentage of proliferative cells by pomegranate juice treatment in AOM-treated Sprague-Dawley rats (Banerjee et al., 2013). Since freeze-drying can retain the bioactive constituents present in fruit juice, dried pomegranate fruit juice extract would also have similar cancer chemopreventive effects. Thus, female A/J mice given pomegranate extract (0.2%) in drinking water for 1 week and exposed to B(a)P and N-nitroso-tris-chloroethylurea (NTCU) had statistically significant lower lung tumor multiplicities than mice treated with carcinogens alone (Khan et al., 2007). Moreover, the topical application of pomegranate extract inhibited TPA-induced skin tumor

promotion in DMBA-initiated CD-1 mice (Afaq et al., 2005).

## Raisins

Raisins contain higher amount of phenolics than fresh grapes (Wu et al., 2004; Parker et al., 2007). Major phenolic compounds of raisins are phenolic acids and flavonols. As compared to fresh and frozen grapes, sun-dried raisins showed better radical scavenging capacity (Parker et al., 2007). The increased concentration of phenolics in raisins may result from the lack of polyphenol oxidase in raisins, and modification of certain phenolic compounds during drying (Wu et al., 2004). However, drying process leads to the loss of vitamin A, C and K in raisins (Morgan et al., 1935) and procyanidins and flavonols are decomposed during processing of raisins (Karadeniz et al., 2000). However, the presence of adequate amount of isoflavones, such as diadzein and genistein (Reinli and Block, 1996) and chlorogenic acid (Zhao and Hall, 2008) in raisins suggest the cancer chemopreventive potential of these dried fruits. Daily intake of raisins attenuated excretion of prostaglandin (PG) metabolite 8-epi-PGF<sub>2</sub>α (Rankin et al., 2008) and 8-hydroxy-2-deoxyguanosine (Spiller et al., 2003) in urine, which are the markers of inflammation and oxidative DNA damage, respectively. Recently, Kountouri et al. reported that the methanol extracts of corinthian raisins suppressed cell proliferation with significant reduction in p65, COX-2, and interleukin (IL)-8 levels in human colon cancer HT29 cells (Kountouri et al., 2013). Based on its antioxidant and anti-inflammatory effects, the assessment of anticancer effects of raisins merits further investigation.

## Others

Several other dried fruits are commercially available and widely consumed throughout the world. These include grapefruit, apricot, longan, snake fruit, star fruit, etc. A limited number of studies have shown the cancer chemopreventive effects of these dried fruits. For example, grapefruit is a rich source of bioactive compounds, which may act as cancer chemopreventive agents (Miyata et al., 2002). The dried grapefruit is also a popular snack because of its pleasant chewy texture and sweetness. Grapefruits contain flavonoids, limonoids, vitamin C, folic acid, soluble fiber, carotenoids (e.g. lycopene and beta-carotene), and coumarin-related compounds (e.g. auraptene). Limonin and obacunone isolated from grapefruit have been shown to decrease the incidence of colonic adenocarcinomas induced by AOM in male F344 rats (Tanaka et al., 2001). Madrigal-Bujaidar et al. reported that oral administration of grapefruit juice (0.8, 4.1, and 8.2 μl/g) for seven weeks dose-dependently suppressed the number of CF-1 female mouse colon ACF induced by AOM. Moreover, administration of grapefruit juice significantly decreased the levels of protein and lipid oxidation in AOM-treated mice (Madrigal-Bujaidar et al., 2013). Thus, dried grape fruit juice extract would have chemopreventive potential due to its antioxidant capacity.

Apricot is an important foodstuff due to its minerals

and other nutrients. Sulphurized (sulfur-dried) apricot retains selenium, which is known to possess anticancer properties (Dennert et al., 2011), though to a lesser extent than the fresh fruit (Munzuroglu et al., 2003). Consumption of dried Japanese apricot suppressed *Helicobacter pylori*-induced chronic atrophic gastritis, a pathological condition often leads to gastric cancer (Enomoto et al., 2010). Moreover, dietary administration of sun-dried apricot powder (15 or 30%) protected ethanol-induced liver damage in rats by activating the cytoprotective enzymes such as superoxide dismutase, quinone reductase, GST and glutathione peroxidase, indicating its potential to prevent liver carcinogenesis (Yurt and Celik, 2011).

Longan, *Euphoria longana* L., is a major Thai fruit and is widely grown in Southern China, India, and Southeast Asia. Several studies demonstrated that a dried longan seed extract contained high levels of antioxidant polyphenolic compounds such as corilagin, gallic acid, and ellagic acid (Rangkadilok et al., 2005) and induced apoptosis (Chung et al., 2010) and inhibited invasion in colorectal cancer cells (Panyathep et al., 2013).

## Conclusions

Most fruits are generally consumed for their nutritional value. However, fruits as the reservoir of many plant secondary metabolites possess various health beneficial effects including anticancer effect. When the cancer chemoprevention is concerned, fruits can be the right choice. With the advances in food processing technology, a wide variety of dried fruits are now available in supermarkets throughout the year. Dried fruits can also be added to granola or hot cereals, salads, pilafs, meat dishes and much more, making them very popular snack today. A wide variety of dried fruits can be formulated as functional foods for the prevention of cancer. Recently, Gu and colleagues developed black raspberry-contained functional food products, such as confections and nectars, which retain large quantities of anthocyanins and ellagitannins (Gu et al. 2013). When given to prostate cancer patients, these raspberry-based functional foods have been well tolerated in terms of sensory tests and a clinical outcome of their anticancer activities is expected to be reported soon. Although dried fruits as a whole or as functional food products holds immense potential for reducing the risk of cancer, ascertaining the clinical effectiveness of these products and understanding their molecular mechanisms remain as the daunting task to accomplish. Moreover, dried fruits are often contaminated with various fungal toxins, such as aflatoxins, ochratoxin A, kojic acid, patulin or zearalenone (Trucksess and Scott, 2008). Thus, chemoprevention with dried fruits must be coupled with routine quality assessment of dried fruits.

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