REVIEW

Anticancer, Chemopreventive and Radioprotective Potential of Black Plum (*Eugenia Jambolana* Lam.)

Manjeshwar Shrinath Baliga

Abstract

Despite good understanding of the molecular basis of the disease and advances in treatment, globally cancer is still a major cause of death. Estimates are that it will surpass cardiovascular disease as the leading cause of death, with higher incidences in the developing countries that have minimal resources. Chemotherapy and radiotherapy, the two most commonly used treatment modalities, are associated with untoward side effects. This has necessitated the search for alternatives that are effective, non toxic and easily affordable for patients and traditional medicinal plants are an ideal source. *Eugenia jambolana* Lam., commonly known as black plum or 'jamun' is an important medicinal plant in various traditional systems of medicine. It is effective in the treatment of diabetes mellitus, inflammation, ulcers and diarrhea and preclinical studies have also shown it to possess antineoplastic, chemopreventive and radioprotective properties. Here, for the first time, the effects of jamun in treatment and prevention of cancer, and the mechanisms responsible for these effects are appraised. Additionally the drawbacks in existing knowledge are also stressed to emphasize the possible avenues that need to be investigated, so that maximum effects on both prevention and cure can be attained.

Keywords: *Eugenia jambolana* - *Syzygium cumini* - Jamun - anticancer - radioprotective - chemopreventive

Asian Pacific J Cancer Prev, **12**, 3-15

Introduction

Recent reports suggest that globally, in the year 2008, 12.7 million new cancer cases and 7.6 million cancer deaths occurred (Ferlay et al., 2010). More worryingly, predictions are that by the year 2020, the global incidence of the cancer will increase by threefold, with a disproportionate rise in cases from the developing world countries that have limited resources to tackle the problem (Are et al., 2010). The conventional treatment modalities used in treating cancer, the surgery, radiotherapy, hormone therapy and chemotherapy remain prohibitively expensive to the large number of population in the developing countries. With an expected rise in cancer incidence, the mortality and associated morbidity will be enormous due to the compromised financial condition of the patients (Are et al., 2010; Ferlay et al., 2010).

Since the dawn of civilization, herbal drugs have been used in the ancient civilizations and their use in the treatment of cancer is on a rise especially in the developing and underdeveloped countries primarily due to its easy affordability, non toxic nature, easy acceptabilit, less toxic or no toxic effects and easy availability (Arora, 2010). Plants have been the main ingredients of various medications of the traditional Indian system of medicine, the Ayurveda and one such plant of immense importance is *Eugenia jambolana* Lam (Syn. *Syzygium cumini* Skeels or *Syzygium jambolana* Dc or *Eugenia cuminii* Druce). (Figure 1), colloquially known as Java plum, Portuguese plum, Malabar plum, black plum, Indian blackberry, jaman, jambu, jambul and jambool (Warrier et al., 1996).

Distribution and Characteristics

Jamun is an evergreen tree belonging to the family

Figure 1. Appearance of Jamun Fruits

*Research and Development, Father Muller Medical College, Mangalore, Karnataka, India *For correspondence : msbaliga@gmail.com*

Table 1. Phytochemicals Present in the Jamun Plant

Plant part	Chemicals present
Stem bark	Friedelin, friedelan-3-α-ol, betulinic acid, β-sitosterol, kaempferol, β-sitosterol-D-glucoside, gallic acid, ellagic acid, gallotannin and ellagitannin and myricetine (Rastogi and Mehrotra, 1990; Sagrawat et al., 2006).
Leaves	β-sitosterol, betulinic acid, mycaminose, crategolic (maslinic) acid, n-hepatcosane, n-nonacosane, n-hentriacontane, noctacosanol, n-triacontanol, n-dotricontanol, quercetin, myricetin, myricitrin and the flavonol glycosides myricetin 3-O-(4"-acetyl)-α-L-rhamnopyranosides (Rastogi and Mehrotra, 1990; Sagrawat et al., 2006).
Flowers	Oleanolic acid, ellagic acids, isoquercetin, quercetin, kampferol and myricetin (Sagrawat et al., 2006).
Fruit pulp	Anthocyanins, delphinidin, petunidin, malvidin-diglucosides (Li et al., 2009a; Sagrawat et al., 2006; Veigas et al., 2007).
Seeds	Jambosine, gallic acid, ellagic acid, corilagin, 3, 6-hexahydroxy diphenoylglucose, 1-galloylglucose, 3-galloylglucose, quercetin, β-sitoterol, 4,6-hexahydroxydiphenoylglucose, (Rastogi and Mehrotra, 1990; Sagrawat et al., 2006).
Essential oils	α-terpeneol, myrtenol, eucarvone, muurolol, α-myrtenal, 1, 8-cineole, geranyl acetone, α-cadinol and pinocarvone (Shafi et al., 2002).

Myrtaceae originally native to the Indian subcontinent. Today these trees are found growing throughout the Asian subcontinent, Eastern Africa, South America, Madagascar and have also naturalized to Florida and Hawaii in the United States of America (Warrier et al., 1996; Li et al., 2009a). The tree fruits once in a year and the berries are sweetish sour to taste. The ripe fruits are used for health drinks, making preserves, squashes, jellies and wine (Warrier et al., 1996). In association to its dietary use, all parts of the tree and, importantly the seeds are used to treat a range of ailments, the most important being diabetes mellitus (Sagrawat et al., 2006). Preclinical studies have shown that the various extracts of Jamun possess a range of pharmacological actions, such as antibacterial, antifungal, antiviral, anti-ulcerogenic, cardioprotective, anti-allergic, hepatoprotective and anti-diarrheal effects, thereby supporting its myriad traditional uses (Sagrawat et al., 2006).

Studies in the past one decade have also shown that Jamun possess antineoplastic (Barh and Viswanathan, 2008; Li et al., 2009a), radioprotective (Jagetia and Baliga, 2002; 2003; Jagetia et al., 2005; 2008) and chemopreventive effects (Parmar et al., 2010) all of which are useful in the prevention and treatment of cancer. The reasons for the myriad pharmacological effects are due to the presence of diverse phytochemicals like flavonoids, anthocyanins, terpenes (Sagrawat et al., 2006) and are enlisted in Table 1. The current review addresses these aspects with emphasis on the possible mechanisms responsible for the observed effects in the prevention and treatment of cancer.

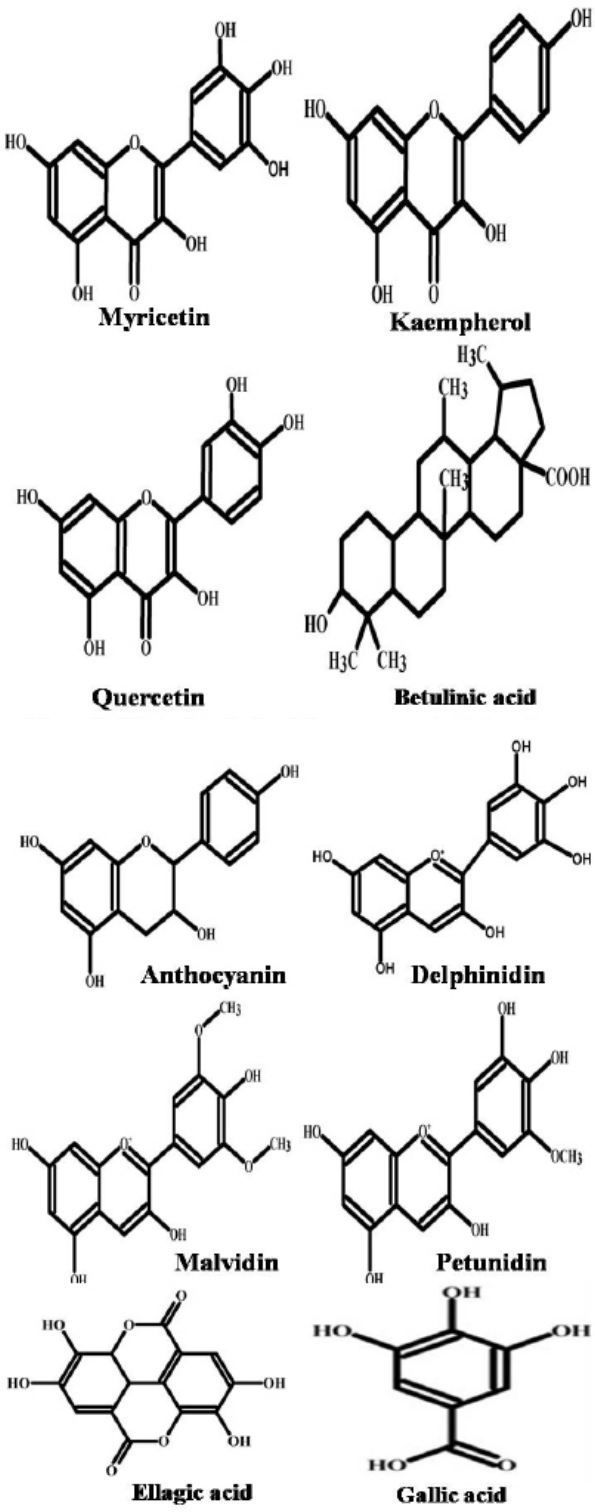

Figure 2. Structures of Phytochemicals in Jamun Reported to be of Use in the Prevention and Treatment of Cancer

Antineoplastic Effects of Jamun

Chemotherapy has been an important modality in cancer treatment for more than five decades and is an obligatory treatment modality when metastasis has ensued. Depending on the clinical stage and the patient compliance, chemotherapy is used either alone or in combination with radiation and surgery (DeVita et al., 2004). Studies suggest that of all the antineoplastic drugs being used nearly 47% of the drugs are from natural sources (Arora, 2010).

Table 2. Phytochemicals in Jamun with Reported Antineoplastic Activities

Agent	Antineoplastic activity and the mechanisms operating
Oleanolic acid	1). Causes a dose and a time dependent cell kill of the human colon carcinoma cell line HCT15. Inhibits proliferation and arrested the cells in G0/G1 phase (Li et al., 2002). 2). Induces apoptosis in human leukemia cells HL60 through caspase activation (Zhang et al., 2007). 3). Selectively inhibits growth of ras oncogene-transformed R6 cells (Wu et al., 2009). 4). Induces apoptosis in human liver cancer HepG2, Hep3B, Huh7 and HA22T cell lines (Yan et al., 2010). 5). Inhibits growth of ascitic tumors in mice (Hsu et al., 1997).
Quercetin	1). Causes dose-dependent cell kill, chromatin condensation in the colon cancer cells (Caco-2 and HT-29) (Kuo, 1996). 2). Potentiates inhibitory effect of a non-toxic dose of cisplatin, inhibits lung colonization of B16-BL6 colonies and in a dose-dependent manner (Caltagirone et al., 2000). 3). Inhibits the growth of the highly aggressive PC-3 prostate cancer cell line and the moderately aggressive DU-145 prostate cancer cell line, but ineffective on the poorly aggressive LNCaP prostate cancer cell line or the normal fibroblast cell line BG-9 (Nair et al., 2004). 4). Inhibits expression of specific oncogenes and genes controlling G1, S, G2 and M phases of the cell cycle. It also up-regulated the expression of several tumor suppressor genes (Nair et al., 2004). 5). Down regulates gelatinases A and B (matrixmetalloproteinases 2 and 9) in the human prostate cancer cells (PC-3) in vitro (Vijayababu et al., 2006).
Kaempferol	1). Inhibits proliferation and induces cell death in human glioma cells through caspase-dependent mechanisms involving down-regulation of XIAP and survivin regulating by ERK and Akt (Jeong et al., 2009). 2). Mediates p53-dependent growth inhibition and induces apoptosis in human HCT116 colon cancer cell line by affecting Bcl-2 family proteins, PUMA and inducing ATM and H2AX phosphorylation (Li et al., 2009b). 3). Induces apoptosis in various oral cancer cell lines (SCC-1483, SCC-25 and SCC-QLL1) through the caspase-3-dependent pathway (Kang et al., 2010). 4). Induces apoptosis via endoplasmic reticulum stress and mitochondria-dependent pathway in human osteosarcoma U-2 OS cells (Huang et al., 2010).
Myricetin	1). Induce apoptosis in HT-29 (Kuntz et al., 1990), Caco-2 cells (Kuntz et al., 1990), MCF7 (Rodgers and Grant, 1998), Jurkat T cells (Chen et al., 2005), OE33 (Zhang et al., 2008) and HepG-2 (Zhang et al., 2010). 2). Inhibits proliferation, causes G2/M and S phase arrest and induces mitochondria-mediated apoptosis by activation of caspase 3, 9 of HepG-2 (Zhang et al., 2010). 3). Possess cytotoxic effects against the OE33 (human oesophageal adenocarcinoma cell line), causes G2/M cell cycle arrest by up-regulation of GADD45beta and 14-3-3sigma and down-regulation of cyclin B1; and p53-independent mitochondrial-mediated apoptosis through up-regulation of PIG3 and cleavage of caspase-9 and 3 (Zhang et al., 2008). 4). Possess moderate proteasome inhibitory effects and induce apoptosis in the human leukemia cells Jurkat T cells (Chen et al., 2005).
Gallic acid	1). Induces apoptosis in human prostate LNCaP cells (Reddivari et al., 2010). 2). Induces cytotoxic effects on DU145 prostate cancer cells, through generation of reactive oxygen species and mitochondria-mediated apoptosis (Chen et al., 2009). 3). Blocks the growth of DU145 cells at G2/M phases by activating Chk1 and Chk2 and inhibiting Cdc25C and Cdc2 activities (Chen et al., 2009). 4). Inactivates phosphorylation of cdc25A/cdc25C-cdc2 via ATM-Chk2 activation, leading to cell cycle arrest, and induces apoptosis in human prostate carcinoma DU145 cells (Agarwal et al., 2006). 5). Possess anti-proliferative, pro-apoptotic and anti-tumorigenic effects against human prostate cells DU145 and 22Rv1 in vitro and in nude mice (Kaur et al., 2009). 6). Synergizes with doxorubicin to suppress the growth of DU145 cells (Chen et al., 2009). 7). Induces apoptosis through both caspase-dependent and -independent pathways in the in A375.S2 human melanoma cells (Lo et al., 2010). 8). Possesses in vitro anticancer effects against the human prostate cancer cells (Raina et al., 2008).
Betulinic acid	1). Is effective against a variety of cancer types but relatively safe to the normal cells and tissue at equal concentrations (Rabi et al., 2008). 2). Induces potent effect on growth inhibition, G2/M cell cycle arrest and triggers apoptosis in the human gastric adenocarcinoma AGS cells in vitro, possibly by the down-regulation of Hiwi and its downstream target Cyclin B1 expression (Yang et al., 2010). 3). Causes a dose dependent cytotoxic effect on the rhabdomyosarcoma cell line RMS by inducing apoptosis through the intrinsic mitochondrial pathway. It also decreased GLI1, GLI2, PTCH1, and IGF2 expression as well as hedgehog-response in vitro. It also caused retarded the growth of RMS-13 xenografts by causing apoptosis and down-regulating GLI1 expression without affecting the microvascular density, cell proliferation, and myogenic differentiation unaffected (Eichenmüller et al., 2010). 4). Induces apoptosis through the mitochondrial pathway and inducing cytochrome c release directly via PT Pore. The process is momentarily inhibited by the anti-apoptotic members of the Bcl-2 family, and is observed to be independent of Bax and Bak (Mullauer et al., 2009). 5. Induces cancer cell death by apoptosis through the mitochondrial pathway and also sensitizes the anticancer effects of 5-fluorouracil (SNU-C5/5FU-R), irinotecan (SNU-C5/IRT-R) and oxaliplatin (SNU-C5/OXT-R) in chemoresistant colon cancer cell lines derived from the colon adenocarcinoma cell line (SNU-C5/WT) (Jung et al., 2007). 6. Effective against the androgen-refractory human prostate carcinoma PC-3 cells and this it achieves by inhibiting DNA binding, reduced nuclear levels of the NF-kappaB/p65, decreased IKK activity and phosphorylation of IkappaBalpha at serine 32/36 followed by its degradation (Rabi et al., 2008). 7). Inhibits the proliferation of Jurkat cells by regulating the cell cycle and arresting the cells at G0/G1 phase by down-regulating the expression of cyclin D3. It also induces apoptosis through the bcl-xl (Chen et al., 2008).
1, 8-Cineole	1). Induces apoptosis in human leukemia Molt 4B and HL-60 cells, but not in human stomach cancer KATO III cells (Moteki et al., 2002).

Table 2 (continued). Phytochemicals in Jamun with Reported Antineoplastic Activities

Agent	Antineoplastic activity and the mechanisms operating
β-Sitosterol	1). Inhibits growth of HT-29 human colon cancer cells by activating the sphingomyelin cycle (Awad et al., 1998). 2). Activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells (von Holtz et al., 1998). 3). Stimulates apoptosis in MDA-MB-231 human breast cancer cells in vitro and inhibits growth and metastasis of MDA-MB-231 in SCID mice (Awad et al., 1996; 2000a,b,c; 2001a,b; 2003). 4). Inhibits growth and metastasis of human prostate cancer PC-3 cells, in vitro and in SCID mice (Awad et al., 2001b). 5). Induces apoptosis by stimulating Bax and activation of caspases in the HT116 human colon cancer cells (Choi et al., 2003). 6). Induces apoptosis in MCA-102 murine fibrosarcoma cells by activation of ERK and the downregulation of Akt (Moon et al., 2007; 2008). 7). Inhibits cell growth and induces apoptosis in SGC-7901 human stomach cancer cells in vitro (Zhao et al., 2009). 8). Induces significant dose-dependent growth inhibition, suppressed expression of beta-catenin and PCNA antigens in human colon cancer cells COLO 320 cells in vitro. Feeding beta-sitosterol also caused a dose dependent reduction in the number of aberrant crypt and crypt multiplicity in DMH-initiated rats with no toxic effects (Baskar et al., 2010).
Delphinidin	1). Inhibits proliferation of human cancer cell lines MCF-7 (breast), SF-268 (central nervous system, CNS), HCT-116 (colon), and NCI-H460 (lung) (Seeram et al., 2003). 2). Induce cell cycle perturbations and apoptosis in human cell lines (Lazzè et al., 2004). 3). Inhibits the growth and induced apoptosis in HL60 cells (Katsube et al., 2003). Inhibited the growth of HCT116 cells (Katsube et al., 2003). 4). Preferentially inhibited the growth of the human vulva carcinoma cell line A431 by affecting the epidermal growth-factor receptor (EGFR), the tyrosine kinase activity and inhibited the activation of the GAL4-Elk-1 (Meiers et al., 2001). 5). Potent inducer of intracellular hydrogen peroxide and causes apoptosis in a time- and dose-dependent manner. Stimulates JNK pathway activation including JNK phosphorylation and c-jun gene expression, and activates caspase-3 and causes DNA fragmentation in HL-60 cells (Hou et al., 2003). 6). Reduces cell growth, is potent EGFR- or PDE-inhibitor and the cAMP hydrolysis (Marko et al., 2004). 7). Inhibits cell proliferation of human cancer cell lines, AGS (stomach), HCT-116 (colon), MCF-7 (breast), NCI H460 (lung), and SF-268 (Zhang et al., 2005). 8). Possess strong growth inhibitory effects against human hepatoma HepG(2), but were less effective against Hep3B, induced apoptotic cell death by up-regulation of Bax and down-regulation of Bcl-2 protein (Yeh et al., 2005). 9). Induces apoptosis in HT-29 cells (Srivastava et al., 2007). 10). Inhibits HGF-mediated membrane translocation of PKCalpha, decreases phosphorylation of STAT3. Repress HGF-activated NFkB transcription, phosphorylation of IKKalpha/beta and IkappaBalpha, and activation and nuclear translocation of NFkappaB/p65 (Syed et al., 2008a). 11). Suppress the phosphorylation of the epidermal growth factor receptor (EGFR) in human colon carcinoma cell line (HT29), human vulva carcinoma cell line A431 (Fridrich et al., 2008). 12). Treatment to AU-565 cells, a EGFR in the positive breast cancer cells inhibited the phosphorylation of EGFR, activation of PI3K, phosphorylation of AKT and MAPK, inhibited EGF-induced autophosphorylation of EGFR, AKT and MAPK, activation of PI3K and cell invasion (Afaq et al., 2008). 13). Treatment of in human colon cancer HCT116 cells with delphinidin decrease cell viability; induces apoptosis; cleaves PARP; activates caspases-3, -8, and -9; increase Bax with a concomitant decrease in Bcl-2 protein; causes G2/M cell cycle arrest; inhibited IKKalpha, phosphorylation and degradation of IkappaBalpha, phosphorylation of NF-kappaB/p65 at Ser(536), nuclear translocation of NF-kappaB/p65, NF-kappaB/p65 DNA binding activity, and transcriptional activation of NF-kappaB (Yun et al., 2009). 14). Treatment to human PCa LNCaP, C4-2, 22Rnu1, and PC3 cells resulted in a dose-dependent inhibition of cell growth without having any substantial effect on normal human prostate epithelial cells. It caused a dose-dependent induction of apoptosis and arrest of cells in G2-M phase, decrease in phosphorylation of IkappaB kinase gamma, phosphorylation of nuclear factor-kappaB (NF-kappaB) inhibitory protein IkappaBalpha, phosphorylation of NF-kappaB/p65 at Ser(536) and NF-kappaB/p50 at Ser(529), NF-kappaB/p65 nuclear translocation, and NF-kappaB DNA binding activity. It also inhibited the tumor growth in athymic nude mice implanted with PC3 cells by causing decrease in the expression of NF-kappaB/p65, Bcl2, Ki67, and PCNA (Hafeez et al., 2008). 15). Attenuates neoplastic transformation in JB6 Cl41 mouse epidermal cells by blocking Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling (Kang et al., 2008). 16). Possess antiproliferative, anti-invasive and apoptotic effects in human hepatoma Hep3B cells. It also caused concentration dependent increase in the sub-G1 fraction, mitochondrial dysfunction and reduction in antiapoptotic proteins (Bcl-2, xIAP, cIAP-1, and cIAP-2) (Shin et al., 2009). 17). Selectively causes cytotoxic effects on the LoVo and LoVo/ADR, human colorectal cancer cell lines; while the non cancerous cells Caco-2 were unaffected (Cvorovic et al., 2010). 18). Inhibits receptor tyrosine kinases of the ErbB and VEGFR family (Teller et al., 2009).
Petunidin	1). Induces apoptosis in HT-29 cells (Srivastava et al., 2007). 2). Inhibits the human breast cancer (MCF-7) cell growth (Zhang et al., 2005).
Malvidin	1). Inhibits growth and induced apoptosis in HL60 cells (Katsube et al., 2003). 2). Induces cell cycle perturbations and apoptosis in human cell lines (Lazzè et al., 2004). 3). Reduces cell growth, is potent EGFR- or PDE-inhibitors and effectively inhibited the cAMP hydrolysis (Marko et al., 2004). 4). Malvidin inhibited AGS (stomach), HCT-116 (colon), MCF-7 (breast), NCI and H460 (lung) (Zhang et al., 2005). 5). Exhibits strong growth inhibitory effects against human hepatoma HepG(2), but were less effective against Hep3B (Yeh et al., 2005). 6). Induces apoptosis in HT-29 cells (Srivastava et al., 2007). 7). Effective on metastatic colorectal cancer cell lines LoVo and LoVo/ADR (Cvorovic et al., 2010). 8). Possess antiproliferative, anti-invasive and apoptotic effects in human hepatoma Hep3B cells. It also caused concentration dependent increase in the sub-G1 fraction, mitochondrial dysfunction and reduction in antiapoptotic proteins (Bcl-2, xIAP, cIAP-1, and cIAP-2) (Shin et al., 2009). 9). Possess good COX-1 and -2 inhibitory activities (Seeram et al., 2003).

Commonly used drugs like vincristine, vinblastine, taxol, docetaxal, teniposide, etoposide and campatothecin are all derived from plants (DeVita et al., 2004). Unfortunately, these compounds possess severe side effects by affecting the normal cells, thereby necessitating search for novel non toxic agents.

With regard to Jamun many compounds exert beneficial influence (see Figure 1 and Table 2). *In vitro* studies by Barh and Viswanathan, (2008) have shown that whole Jamun extract possess cytotoxic effects on the cultured human cervical cancer cells, the HeLa (HPV-18 positive) and SiHa (HPV-16 positive). The extract caused a concentration dependent cell death with the effect being more pronounced in the HeLa than SiHa cells (Barh and Viswanathan, 2008). Additionally, both crude as well as the methanolic extracts of the pulp caused a time dependent increase in apoptosis when cultured with 80% concentration of the extracts. The crude extract was observed to be better than the methanolic extract in both the cell lines (Barh and Viswanathan, 2008).

In a study that has wide clinical implications, recent studies by Li et al., (2009a) have shown that the standardized Jamun fruit extract possess antiproliferative and pro-apoptotic effects in the estrogen dependent/ aromatase positive (MCF-7aro), and estrogen independent (MDA-MB-231) breast cancer cells. The extract was highly effective against MCF-7aro and the IC50 was observed to be 27 μg/ml to that of 40 μg/ml in MDA-MB-231. Most importantly, at equivalent concentrations the extract was relatively non toxic as it did not induce cell death and apoptosis in the normal/nontumorigenic (MCF-10A) breast cell line (IC50 > 100 μg/ml). Together these results clearly indicate that at supra dietary levels the fruit pulp extract possesses selective antineoplastic effects against breast cancer (Li et al., 2009a).

Chemopreventive Effects

Chemoprevention, a science that has emerged during the three last decade, presents an alternative approach to reducing mortality from cancer. It aims at blocking, reversing, or delaying carcinogenesis before the development of invasive disease by targeting key molecular derangements using pharmacological or nutritional agents

Table 3. Phytochemicals of Jamun with Reported Chemopreventive Effects

Agent	Chemopreventive effects and the mechanisms operating
Oleanolic acid	1). Inhibits tumor promotion in mouse skin (Tokuda et al., 1986). 2). Inhibits azoxymethane (AOM)-induced colonic aberrant crypt foci and multi-crypt aberrant crypt/foci in a dose dependent manner (Janakiram et al., 2008). 3). Suppress preneoplastic lesions induced by 1, 2-dimethylhydrazine in rat colon (Furtado et al., 2008).
Ellagic acid	1). Inhibitor of benzo[a]pyrene-induced pulmonary adenoma and 7,12-dimethyl benz[a]anthracene-induced skin tumorigenesis in Swiss mice (Lesca, 1983). 2). Topical application (Mukhtar et al., 1984a) as well as oral feeding of ellagic acid (Mukhtar et al., 1986) rendered protection against 3-methylcholanthrene -induced skin tumorigenesis in mice and decreased tumor incidence, number of tumors, tumors per mouse and tumors per tumor bearing animal (Mukhtar et al., 1984a, 1986). 3). Topical application of ellagic acid and oral before a tumor-initiating by B[a]P 7,8-diol-9,10-epoxide-2 and promotion with 12-O-tetradecanoylphorbol-13-acetate inhibited the number of skin tumors per mouse (Chang et al., 1985). 4). Ellagic acid applied topically to female CF-1 mice 20 min before each 12-O-tetradecanoylphorbol-13-acetate (TPA) treatment inhibit the inductions of epidermal ornithine decarboxylase activity, hydroperoxide production and DNA synthesis, and also inhibit the promotion of skin papillomas and carcinomas in the two-step initiation-promotion protocol (Gali et al., 1992). 5). Topical application of ellagic acid simultaneously with phorbol-12-myristate-13-acetate (PMA) or mezerein resulted in significant protection against 7, 12-dimethyl-benz[a]anthracene-induced skin tumors in mice (Kaul et al., 1998). 6). The levels of aryl hydrocarbon hydroxylase (AHH) activity in skin and liver and the extent of 3H-BP-binding to skin, liver and lung DNA were decreased (Mukhtar et al., 1984a). 7). Is a potent inhibitor of benzo[a]pyrene metabolism and its subsequent glucuronidation, sulfation and covalent binding to DNA in cultured BALB/C mouse keratinocytes (Mukhtar et al., 1984b). 8). Inhibited the epidermal microsomal aryl hydrocarbon hydroxylase (AHH) activity and of benzo[a]pyrene (BP)-binding to both calf thymus DNA in vitro and to epidermal DNA in vivo (Del et al., 1983).
Gallic acid	1). Inhibits the TPA-induced inductions of epidermal ornithine decarboxylase activity, hydroperoxide production and DNA synthesis, and also inhibit the promotion of skin papillomas and carcinomas in the two-step initiation-promotion protocol (Gali et al., 1992). 2). Administering (0.3% to 1%) for twenty consecutive weeks from four weeks of age to the male TRAMP mice (a transgenic mice develops prostate tumor) caused a decrease tumors with decreasing the proliferative index with a concomitant increase in the apoptotic cells which were due to decrease in the expression of Cdc2, Cdk2, Cdk4, Cdk6, cyclin B1 and E (Raina et al., 2008).
Quercetin	1). Possesses chemopreventive effects against 4-nitroquinoline 1-oxide-induced and its administration during both initiation or post-initiation phases caused a significant reduction in the frequency of tongue carcinoma in rats. It reduced the polyamine levels and the proliferation (Makita et al., 1996). 2). Prevents N-nitrosodiethylamine-induced lung tumorigenesis in mice (Khanduja et al., 1999). 3). Prevents 20-methyl cholanthrene-induced cervical neoplasia in virgin Swiss albino mice by increasing the antioxidant enzymes, decreasing DNA damage and he lipid peroxidation (De et al., 2000; 2004). 4). Decreases DMBA-induced DNA damage (Sengupta et al., 2001). 5). In a bioengineered human gingival epithelial tissue, quercetin was observed to inhibit BaP-DNA binding, a precursor for mutagenesis and carcinogenesis (Walle et al., 2006). 6). Quercetin supplementation prevents benzo(a)pyrene-induced carcinogenesis by modulating the antioxidants and decreasing lipid peroxidation, aryl hydrocarbon hydroxylase, gamma glutamyl transpeptidase, 5'-nucleotidase, lactate dehydrogenase and adenosine deaminase (Kamaraj et al., 2007).

Table 3 (continued). Phytochemicals of Jamun with Reported Chemopreventive Effects

Agent	Chemopreventive effects and the mechanisms operating
Myricetin	1). Inhibits epidermal growth factor (EGF)-activated cell transformation of JB6 cells by modulating DNA-binding and transcriptional activity of STAT3 (Kumamoto et al., 2009a, b), and mitogen-activated protein kinase kinase (MEK) (Lee et al., 2007a) and inhibitor of of neoplastic cell transformation and MEK1 (Lee et al., 2007b). 2). Prevents TPA-induced transformation, PKC activation, and c-jun expression in mouse fibroblast cells (Lee and Lin, 1997). 3). Suppresses UVB-induced skin cancer by targeting Fyn in JB6 cells (Jung et al., 2008). Inhibits Akt survival signaling and induces Bad-mediated apoptosis in immortalized human keratinocytes (HaCaT cells) (Kim et al., 2010). 4). Inhibits matrix metalloproteinase 2 protein expression and enzyme activity in colorectal carcinoma cells (Ko et al., 2005) and also down-regulates phorbol ester-induced cyclooxygenase-2 expression in mouse epidermal cells by blocking activation of nuclear factor kappa B (Lee et al., 2007b). 5). Inhibits polycyclic aromatic hydrocarbon-DNA adduct formation in epidermis and lungs of SENCAR mice (Das et al., 1987).
Kaempferol	1). Possess inhibitory effects on phosphatidylinositol 3-kinase and inhibits the neoplastic transformation (Lee et al., 2010).
Betulinic acid	1). Topical application of betulinic acid inhibited the TPA-induced inflammation and decreased the levels of ornithine decarboxylase (Yasukawa et al., 1991). 2). Markedly inhibited the 7, 12-dimethylbenz[a]anthracene and TPA promoted skin tumor formation in mice (Yasukawa et al., 1991).
β- sitosterol	1). Topical application of β-sitosterol inhibited the TPA-induced inflammation (Yasukawa et al., 1991). 2). Induces dose-dependent growth inhibition, induces apoptosis, suppresses the expression of β-catenin and PCNA antigens in human colon cancer cells (COLO 320 DM cells) (Baskar et al., 2010). 3). β-sitosterol supplementation reduced the number of aberrant crypt and crypt multiplicity in DMH-initiated rats in a dose-dependent manner with no toxic effects (Baskar et al., 2010).
Delphinidin	1). Suppresses 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cell transformation and activator protein-1 transactivation in the JB6 cells by blocking the phosphorylation of protein kinases in the extracellular signal-regulated protein kinase (ERK) and the c-Jun N-terminal kinase (JNK) signaling pathways (Hou et al., 2004). 2). Possess chemopreventive effects against prostate carcinogenesis in both in vitro and vivo study models (Syed et al., 2008b). 3). Suppresses ultraviolet B-induced cyclooxygenases-2 expression through inhibition of MAPKK4 and PI-3 kinase (Kwon et al., 2009).

(Aggarwal et al., 2009). Chemopreventive interventions may be applied at any time during carcinogenesis, from the initial molecular defect through the accumulated molecular, cellular and histopathologic aberrations that characterize disease progression before an invasive and potentially metastatic stage (Aggarwal et al., 2009).

Recently, Parmar et al., (2010) have reported that jamun possess cancer chemopreventive properties in the DMBA-induced croton oil promoted two stage skin carcinogenesis in Swiss albino mice. Feeding of 125 mg/ kg/ b. wt. / animal /day of the extract either during the peri-initiation (i.e. 7 days before and 7 days after the application of DMBA) or post-initiation (i.e. from the day of start of croton oil treatment and continued till the end of the experiment) phases reduced the cumulative numbers of papillomas, the tumor incidence and increased the average latency period when compared with the control group (carcinogen alone) (Parmar et al., 2010). Very recently Goyal et al., (2010) have also observed that administration of the jamun extract (25 mg/kg b.wt/ day) was effectivein preventing benzo-a-pyrene-induced forestomach carcinogenesis. Jamun reduced the tumor incidence, tumor burden and cumulative number of gastric carcinomas.

The authors postulate that the free radical scavenging and the antioxidant effects are responsible for the observed effects. Additionally, Jamun extract has been shown to be selectively cytotoxic to the human neoplastic breast cancer cells (Li et al., 2009a) and it is logical to suggest that the constituents of Jamun may have inhibited the process of carcinogenesis by selectively killing the mutated, preneoplastic and neoplastic cells resulting from the carcinogen treatment. Reports also suggest that gallic acid, ellagic acid, flavonoids and anthocyanins (Figure 2) present in Jamun are reported to prevent experimental carcinogenesis in various organs (Table 3) and may have contributed to the anti-carcinogenesis.

Additionally, recent observations also suggest that ellagitannin, a constituent of Jamun and its colonic metabolite, urolithin A inhibit Wnt signaling crucial in the process of colon carcinogenesis (Sharma et al., 2010). Urolithin A reduces proliferation of colon cancer cells, induces cell cycle arrest and modulates MAPK signaling in vitro (Larrosa et al., 2006 a,b; 2009; Gonzalez-Sarrias et al., 2009; 2010), while animal studies have shown it to reduces the inflammatory markers (iNOS, COX-2, PGE synthase and PGE2) in the colonic mucosa of rat with colitis (Larrosa et al., 2006 a,b), mechanisms vital in preventing / retarding the process of carcinogenesis.

Radioprotective Effects

The effect of ionizing radiation is impartial and both neoplastic as well as the normal cells are affected during treatment for cancer. The affect felt by the normal cells are irreparable damage, leading to the untoward effects forcing the physicians to discontinue or reduce the treatment dose. In such situations, an agent that can render a therapeutic differential between the cancer and normal cell will be highly beneficial (Hosseinimehr, 2007). Therapeutic differential may be achieved with chemical compounds that may selectively protect the normal cells from the deleterious effects of radiation termed as radioprotectors (Hosseinimehr, 2007).

Table 4. Phytochemicals of Jamun with Reported Radioprotective Activities

Phytochemical	Radioprotective effects and the mechanisms operating
Gallic acid	1). Inhibits radiation-induced damage to DNA and lipid peroxidation in both in vitro and in vivo conditions (Gandhi and Nair, 2005).
Ellagic acid	1). Protects yeast cells from γ-radiation-induced damage by reducing DNA damage (Nemavarkar et al., 2004). 2). Inhibits γ-radiation induced lipid peroxidation in a concentration-dependent manner in vitro (Priyadarsini et al., 2002). 3). Enhances the cytotoxic effects of radiation in neoplastic cells (Ehrlich ascites carcinoma and Hela) by inducing free radicals, reducing antioxidant enzymes and altering the mitochondrial potential, but protects the normal cells (splenic lymphocytes) of tumor-bearing mice against the radiation damage (Bhosle et al., 2005).
Quercetin	1). Protected yeast cells from γ-radiation damage by reducing DNA damage (Nemavarkar et al., 2004). 2. Effective in protecting against γ-radiation-induced DNA damage to the human peripheral blood lymphocytes in vitro (Devipriya et al., 2008; Benković et al., 2008a) and plasmid DNA (Devipriya et al., 2008). The protective mechanisms were mediated by the antioxidant and inhibition of lipid peroxides (Devipriya et al., 2008). 3). Intraperitoneal administration of quercetin 100 mg kg/kg for 3 consecutive days before and/or after irradiation prevented radiation-induced DNA damage in WBC of mice. Pronounced effects were when querecetin was administered before radiation (Benkovic et al., 2008b, 2009).
Oleanolic acid	1). Inhibits the growth of ascitic tumors and enhances the recovery of hematopoietic system in irradiated mice (Hsu et al., 1997).

Since the observations of Patt et al., (1949) that the natural amino acid cysteine protected mice against radiation-induced sickness and mortality, many compounds with varied pharmacological properties have been synthesized and evaluated for their radioprotective effects. However to date no compound is observed to be optimal as most, including the FDA approved radioprotector WR-2721 (amifostine) are observed to possess inherent toxicity at their optimal protective concentrations (Hosseinimehr, 2007). This has necessitated search for effective and cheaper alternatives to the already existing options (Hosseinimehr, 2007).

Studies have shown that the intraperitoneal administration of the hydroalcoholic extract of the Jamun seed and the dichloromethane extract of Jamun leaf possess radioprotective effects (Jagetia and Baliga, 2004; Jagetia et al., 2005). Pretreatment with hydroalcoholic extract of jamun seeds (5 to 160 mg/kg body weight) for five consecutive days before exposure to supralethal dose of radiation (10 Gy) protected mice against the radiation-induced sickness and mortality. The best effect was observed at 80 mg/kg but only when administered through the intraperitoneal route as 50% of the animals survived when compare to 22% in the oral route and none in the radiation alone cohorts. Administering 80 mg/kg of the seed extract before exposure to 6 to 11 Gy of radiation caused a significant increase in the animal survival when compared with the concurrent radiation alone cohorts and also resulted in a dose reduction factor of 1.24 (Jagetia et al., 2005).

The intraperitoneal administration of the organic extract (dichloromethane-methane) of leaves (5, 10, 20, 30, 40, 50, 60 and 80 mg/kg b. wt.) for five days before irradiation was also observed to be effective in preventing the radiation-induced sickness and mortality in mice. The optimal effects were observed for 30 mg/kg b. wt. cohorts as the number of survivors after 30 days post-irradiation was the highest (41.66 %) in this group when compared with the other doses (Jagetia and Baliga, 2003). Histopathological investigations showed that Jamun leaf treatment before radiation elevated the villus height, the number of crypts and reduced the goblet and dead cells when compared with the concurrent irradiation control. The recovery and regeneration was faster in Jamun pretreated animals than the irradiation alone (Jagetia et al., 2008). Jamun extracts also provides protection to the DNA against the radiation-induced DNA damage (explained later) (Jagetia and Baliga, 2002). The phytochemicals ellagic acid, gallic acid, quercetin and oleanolic acid (Figure 2) present in Jamun also possess radioprotective effects (addressed in Table 4).

Mechanistic Aspects of Radioprotective and Chemopreventive Effects

Production of the free radicals, the reactive oxygen and nitrogen species the superoxide anion radical (O_2•), hydroxyl radical (OH•), hydrogen peroxide (H_2O_2), nitric oxide (NO) and peroxynitrite (ONOO) are the most important as they can cause damage to cell structures, including lipids and membranes, proteins, and DNA, thereby playing a major role in the process of mutagenesis, inflammation and carcinogenesis as well as radiation ill effects (Hall, 2000; Devasagayam et al., 2004). Accordingly, their control is vital for the prevention of both carcinogenesis and radiation damage. Studies have shown that Jamun possess all these properties and this may have contributed towards the observed chemoprevention and radioprotection and are addressed in the following sections.

Antioxidant Effects

Multiple studies in the recent past have shown that the Jamun fruit, seed, leaves and bark possess antioxidant and free radical scavenging effects. Benherlal and Arumughan (2007), evaluated the antioxidant effects of the ethanolic extract of the fruit pulp, kernel and seed coat in various *in vitro* assays (DPPH•, OH•, $O_2^{\bullet-}$ and lipid peroxidation) with gallic acid, quercetin and trolox as reference molecules. In the DPPH scavenging assay and lipid peroxidation assays the kernel extract was better than the seed coat and pulp extract, but less than the reference molecules. However in the superoxide radical scavenging activity the kernel extract was six times more effective than trolox and three

times than catechin. In hydroxyl radical scavenging assay, the kernel extract was comparable to the effect of catechin (Benherlal and Arumughan, 2007).

The hydroethanolic extract of the seed (Raquibul-Hasan et al., 2009), methanolic extracts of stem (Kshirsagar and Upadhyay, 2009), anthocyanin-rich fruit peel extract (Veigas et al., 2007) and the methanolic extract of the leaves (Kshirsagar and Upadhyay, 2009; Nahar et al., 2009) are observed to be free radical scavengers in the DPPH$^{\bullet}$ scavenging assay. The hydrolysable and condensed tannins in the fruit are also reported to possess antioxidant activity in the DPPH radical scavenging and FRAP assays (Zhang and Lin, 2009). The organic extract of the leaf (methanoldichloromethane extract) as well as the hydroethanolic extract of the seed is reported to be a scavenger of nitric oxide in vitro (Jagetia et al., 2004).

Ruan et al., (2008) subjected the methanolic extract of leaf to various fractions (viz water, ethyl acetate, chloroform and *n*-hexane) and studied their free radical scavenging effects in the DPPH and FRAP assays. It was observed that in the DPPH assay the efficacy was as follows ethyl acetate fraction ≈ methanolic extract > chloroform fraction ≈ water fraction > *n*-hexane. In the FRAP assays similar observations were observed and except for the hexane fraction, all other fractions showed high ferric reducing power at high concentrations (Ruan et al., 2008).

The fruit skin of Jamun possess antioxidant effects as confirmed by results from the hydroxyl radical-scavenging assay, superoxide radical-scavenging assay, DPPH radical-scavenging assay and lipid peroxidation (Banerjee et al., 2005). The anthocyanin-rich fruit peel extract is also observed to be an effective reducing agent (Veigas et al., 2007). Recently, Bajpai et al., (2005), have also observed that the hydromethanolic extract of the Jamun seed was effective in scavenging (90.6%) free radicals as evaluated in the auto-oxidation of β-carotene and linoleic acid assay and was due to the presence of high total phenolic content in the extract (Bajpai et al., 2005).

Inhibition of Lipid Peroxidation

Studies by Veigas et al., (2007) have shown that the anthocyanin rich pulp extract inhibited the iron (FeSO4)-induced lipid peroxidation in the various organs (rat brain, liver, liver mitochondria, testes and human erythrocyte ghost cells) *in vitro*. The observations suggest that the extract was an efficient preventor of lipid peroxidation in all organs but the degree of protection was variable. At the lowest concentration of 5 ppm the anti-lipid peroxidative effects were high in the rat brain (68.3%) followed by rat liver (83%), mitochondria (86%) testes (72%), and the erythrocyte ghost cells (48%) (Veigas et al., 2007). The extract was also observed to decrease the levels of CCl4-induced LPx in the primary rat hepatocytes *in vitro* (Veigas et al., 2008). Animal studies have also shown that administering Jamun decreased the levels of lipid peroxides in the stomachs of animals subjected to ulcerogenic treatments (Chaturvedi et al., 2007, 2009a,b), in the brain, liver, kidneys and serums of diabetic animals (Prince et al., 1998; Ravi et al., 2004; Chaturvedi et al., 2009a,b). A similar mechanism may be operating towards prevention of carcinogenesis and radiation-induced ill effects and needs to be validated.

Prevention of DNA Damage

The process of carcinogenesis is extended and involves a complex series of events. Exposure to genotoxic chemicals causes mutations and icancer (Jagetia and Baliga, 2002). Studies with the human peripheral blood lymphocytes have shown that the extract prevented radiation-induced DNA damage as evaluated by the micronuclei assay (Jagetia and Baliga, 2002). Pretreatment of lymphocytes with various concentrations of Jamun (0.0, 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 μg/ml) resulted in a significant decline in the radiation-induced (3 Gy) DNA damage. The optimal effect was observed at 12.5 μg/ml drug concentration; where the micronuclei frequency was approximately fourfold lower than that of the non-drug treated irradiated cultures (Jagetia and Baliga, 2002).

Studies have also shown that the aqueous and ethanolic extracts of Jamun seed reduced the hydroxyl radical-induced strand breaks in pBR322 DNA in vitro and that the aqueous extract was also effective in decreasing the urethane and DMBA-induced chromosomal aberration in mice (Arun et al., 2010). Together these observations clearly indicate the usefulness of Jamun in preventing mutagenesis and initiation of carcinogenesis.

The individual phytochemicals of Jamun like anthocyanins (Lazzé et al., 2003), carvacrol (Horvathova et al., 2007), linalool (Mitić-Culafić et al., 2009), myrcene (Mitić-Culafić et al., 2009), myricetin (Aherne and O'Brien, 1999; Duthie and Dobson, 1999), quercetin (Aherne and O'Brien, 1999; Delgado et al., 2009), myricetin (Duthie and Dobson, 1999) and kaempferol (Duthie and Dobson, 1999) have all been observed to prevent DNA damage against the various oxidants in different systems of study. The flavonoid myricetin is also reported to enhance the repair of iron-induced DNA oxidation in primary rat hepatocyte cultures and may have contributed to the observed protection by enhancing efficient repair process (Abalea et al., 1999). The presence of these compounds may have been responsible for the prevention of DNA damage and mutagenesis.

Anti-inflammatory Effects

Preclinical studies have shown that the chloroform fraction of the seed inhibited the carrageenin, kaolin and other mediator-induced edema in rats (Chaudhuri et al., 1990). The extract inhibited exudation of protein, leakage of dye in peritoneal inflammation and migration of leucocytes. The extract also caused inhibition of granuloma formation, experimental arthritis and turpentine-induced joint edema (Chaudhuri et al., 1990). Ethyl acetate and methanol extracts of seed have also been observed to possess anti-inflammatory activity in the carrageenan-induced paw edema in Wister rats (Kumar et al., 2008).

The ethanolic extract of the tree bark possess anti-inflammatory effects in animal models of study. Administering the extract (100, 300 and 1000 mg/kg, p. o.) caused a significant decrease in the inflammatory reactions induced by the inflammogens carrageenin, kaolin-carrageenin, and formaldehyde-induced paw edema and

the cotton pellet granuloma in rats (Muruganandan et al., 2001). Studies with individual autacoids have also shown that the bark extract was effective in inhibiting the histamine, 5-HT and PGE2-induced rat paw edema (Muruganandan et al., 2002). Unlike standard anti-inflammatory agents the NSAIDs, the extract did not induce any gastric lesion in both, acute and chronic ulcerogenic tests in rats suggesting it to be safe and potentially useful (Muruganandan et al., 2001).

Conclusions

Studies in the recent past indicate the potential of Jamun in cancer treatment and prevention. However, gaps in the studies conducted are apparent which need to be bridged in order to exploit the full medicinal potential of Jamun. With regard to the antineoplastic activities studies suggest that Jamun is selective in its action in breast cancer cells. However studies should also be conducted with human tumor cells of other histological origins to observe for its diversity and also in tumor bearing animals of different histological and metastatic potentiality to appraise for its efficacy in vivo.

With regard to chemoprevention and radiation protection all published observations have been with experimental animals and help to validate the applicability on the human system. However detailed studies to understand the radioprotective effects should be performed preferably with oral route of administration with emphasis to understand its selective radioprotective effects in tumor bearing animals. The effect of Jamun and its phytochemicals should also be investigated for its chemopreventive effects in other models of carcinogens, that includes chemical, radiation and viral carcinogenesis models. M echanistic studies responsible for the chemopreventive and radioprotective effects are also lacking and need to be studied in detail.

From phytochemical perspective, there is considerable variation in the composition among various samples of Jamun. A quality control should be established for the authenticity of the plant and the presence of active phytochemicals in the required levels. In this regard the availability of authentic metabolite standards for quantification of the phytochemicals will make the scientific observations more reliable and reproducible. Studies should also be on understanding which of the phytochemicals are responsible for the observed beneficially effects and if effective, their mechanism of action.

Due to its abundance, low cost and safety in consumption, Jamun remains a species with tremendous potential and countless possibilities for further investigation. As human beings have been consuming Jamun since time immemorial, the major advantage of this over the synthetic drugs lies in its easy acceptability, safe when regularly consumed and easy affordability. Preliminary observations suggest that Jamun has the potential to develop as a non-toxic antineoplastic, chemopreventive and radioprotective agent only when the lacunae in the existing knowledge are bridged. The outcomes of such studies may be useful for the clinical application of Jamun in humans and may open up a new therapeutic avenue.

Acknowledgments

The author is grateful to Rev. Fr. Patrick Rodrigus (Director), Rev. Fr. Denis D'Sa (Administrator), Dr. Sanjeev Rai (Chief of Medical Services) and Dr. Jai Prakash Alva, (Dean) of Father Muller Medical College for their unstinted support. Thanks are also due to Mr Harshith P Bhat for drawing the chemical structures. This study was not supported by any private or public funding body. The author further declares no conflict of interest.

References

Abalea V, Cillard J, Dubos MP, et al (1999). Repair of iron-induced DNA oxidation by the flavonoid myricetin in primary rat hepatocyte cultures. *Free Radic Biol Med*, **26**, 1457-66.

Afaq F, Zaman N, Khan N, et al (2008). Inhibition of epidermal growth factor receptor signaling pathway by delphinidin, an anthocyanidin in pigmented fruits and vegetables. *Int J Cancer*, **123**, 1508-15.

Agarwal C, Tyagi A, Agarwal R (2006). Gallic acid causes inactivating phosphorylation of cdc25A/cdc25C-cdc2 via ATM-Chk2 activation, leading to cell cycle arrest, and induces apoptosis in human prostate carcinoma DU145 cells. *Mol Cancer Ther*, **5**, 3294-302.

Aggarwal BB, Van Kuiken ME, Iyer LH, et al (2009). Molecular targets of nutraceuticals derived from dietary spices: potential role in suppression of inflammation and tumorigenesis. *Exp Biol Med*, **234**, 825-49.

Aherne SA and O'Brien NM (1999). Protection by the flavonoids myricetin, quercetin, and rutin against hydrogen peroxide-induced DNA damage in Caco-2 and Hep G2 cells. *Nutr Cancer*, **34**, 160-6.

Are C, Colburn L, Rajaram S, et al (2010). Disparities in cancer care between the United States of America and India and opportunities for surgeons to lead. *J Surg Oncol*, **102**, 100-5.

Arun R, Prakash MV, Abraham SK, et al (2010). Role of Syzygium cumini seed extract in the chemoprevention of in vivo genomic damage and oxidative stress. J Ethnopharmacol,

Awad AB, Chen YC, Fink CS, et al (1996). beta-Sitosterol inhibits HT-29 human colon cancer cell growth and alters membrane lipids. *Anticancer Res*, **16**, 2797-804.

Awad AB, Downie A, Fink CS, et al (2000c). Dietary phytosterol inhibits the growth and metastasis of MDA-MB-231 human breast cancer cells grown in SCID mice. *Anticancer Res*, **20**, 821-4.

Awad AB, Downie AC, Fink CS (2000a). Inhibition of growth and stimulation of apoptosis by beta-sitosterol treatment of MDA-MB-231 human breast cancer cells in culture. *Int J Mol Med*, **5**, 541-5.

Awad AB, Fink CS, Williams H, et al (2001a). In vitro and in vivo (SCID mice) effects of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells. *Eur J Cancer Prev*, **10**, 507-13.

Awad AB, Gan Y, Fink CS (2000b). Effect of beta-sitosterol, a plant sterol, on growth, protein phosphatase 2A, and phospholipase D in LNCaP cells. *Nutr Cancer*, **36**, 74-8.

Awad AB, Roy R, Fink CS (2003). Beta-sitosterol, a plant sterol, induces apoptosis and activates key caspases in MDA-MB-231 human breast cancer cells. *Oncol Rep*, **10**, 497-500.

Awad AB, von Holtz RL, Cone JP, et al (1998). beta-Sitosterol inhibits growth of HT-29 human colon cancer cells by activating the sphingomyelin cycle. *Anticancer Res*, **18**, 471-3.

Awad AB, Williams H, Fink CS (2001b). Phytosterols reduce in vitro metastatic ability of MDA-MB-231 human breast cancer cells. *Nutr Cancer*, **40**, 157-64.

Bajpai M, Pande, A, Tewari, SK, et al (2005). Phenolic compounds and antioxidant activity of some food and medicinal plants. *Int J Food Sci Nutrition*, **56**, 287-91.

Banerjee A, Dasgupta N, De BB (2005). In vivo study of Antioxidant activity of S. cumini fruit. *Food chemistry*, **90**, 727-33.

Barh D, Viswanathan G (2008). *Syzygium cumini* inhibits growth and induces apoptosis in cervical cancer cell lines: A primary study. *Ecancermedicalscience*, **2**, 83.

Baskar AA, Ignacimuthu S, Paulraj GM, et al (2010). Chemopreventive potential of beta-Sitosterol in experimental colon cancer model - an In vitro and In vivo study. *BMC Complement Altern Med*, **10**, 24.

Benherlal PS, Arumughan C (2007). Chemical composition and in vitro antioxidant studies on *Syzygium cumini* fruit. *J Sci Food Agric*, **87**, 2560-9.

Benkovic V, Knezevic AH, Dikic D, et al (2008b). Radioprotective effects of propolis and quercetin in gamma-irradiated mice evaluated by the alkaline comet assay. *Phytomedicine*, **15**, 851-8.

Benković V, Knezević AH, Dikić D, et al (2009). Radioprotective effects of quercetin and ethanolic extract of propolis in gamma-irradiated mice. *Arh Hig Rada Toksikol*, **60**, 129-38.

Benković V, Kopjar N, Horvat Knezevic A, et al (2008a). Evaluation of radioprotective effects of propolis and quercetin on human white blood cells in vitro. *Biol Pharm Bull*, **31**, 1778-85.

Bhosle SM, Huilgol NG, Mishra KP (2005). Enhancement of radiation-induced oxidative stress and cytotoxicity in tumor cells by ellagic acid. *Clin Chim Acta*, **359**, 89-100.

Caltagirone S, Rossi C, Poggi A, et al (2000). Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. *Int J Cancer*, **87**, 595-600.

Chang RL, Huang MT, Wood AW, et al (1985). Effect of ellagic acid and hydroxylated flavonoids on the tumorigenicity of benzo[a]pyrene and (+/-)-7 beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene on mouse skin and in the newborn mouse. *Carcinogenesis*, **6**, 1127-33.

Chaturvedi A, Bhawani G, Agarwal PK, et al (2009b). Antidiabetic and antiulcer effects of extract of *Eugenia jambolana* seed in mild diabetic rats: study on gastric mucosal offensive acid-pepsin secretion. *Indian J Physiol Pharmacol*, **53**, 137-46.

Chaturvedi A, Bhawani G, Agarwal PK, et al (2009a). Ulcer healing properties of ethanolic extract of Eugenia jambolana seed in diabetic rats: study on gastric mucosal defensive factors. *Indian J Physiol Pharmacol*, **53**, 16-24.

Chaturvedi A, Kumar MM, Bhawani G, et al (2007). Effect of ethanolic extract of *Eugenia jambolana* seeds on gastric ulceration and secretion in rats. *Indian J Physiol Pharmacol*, **51**, 131-40.

Chaudhuri N, Pal AK, Gomes S, et al (1990). Anti-inflammatory and related action of *Syzygium cumini* seed extract. *Phytotherapy Res*, **4**, 5-10.

Chen D, Daniel KG, Chen MS, et al (2005). Dietary flavonoids as proteasome inhibitors and apoptosis inducers in human leukemia cells. *Biochem Pharmacol*, **69**, 1421-32.

Chen HM, Wu YC, Chia YC, et al (2009). Gallic acid, a major component of Toona sinensis leaf extracts, contains a ROS-mediated anti-cancer activity in human prostate cancer cells. *Cancer Lett*, **286**, 161-71.

Chen Z, Wu QL, Chen Y, et al (2008). Effect of betulinic acid on proliferation and apoptosis in Jurkat cells and its mechanism. *Zhonghua Zhong Liu Za Zhi*, **30**, 588-92 (in Chinese).

Choi YH, Kong KR, Kim YA, et al (2003). Induction of Bax and activation of caspases during beta-sitosterol-mediated apoptosis in human colon cancer cells. *Int J Oncol*, **23**, 1657-62.

Cvorovic J, Tramer F, Granzotto M, et al (2010). Oxidative stress-based cytotoxicity of delphinidin and cyanidin in colon cancer cells. *Arch Biochem Biophys*, **501**, 151-7.

Das M, Khan WA, Asokan P, et al (1987). Inhibition of polycyclic aromatic hydrocarbon-DNA adduct formation in epidermis and lungs of SENCAR mice by naturally occurring plant phenols. *Cancer Res*, **47**, 767-73.

De S, Chakraborty J, Chakraborty RN, et al (2000). Chemopreventive activity of quercetin during carcinogenesis in cervix uteri in mice. *Phytother Res*, **14**, 347-51.

De S, Chakraborty RN, Ghosh S, et al (2004). Comparative evaluation of cancer chemopreventive efficacy of alpha-tocopherol and quercetin in a murine model. *J Exp Clin Cancer Res*, **23**, 251-8.

Del Tito BJ Jr, Mukhtar H, Bickers DR (1983). Inhibition of epidermal metabolism and DNA-binding of benzo[a]pyrene by ellagic acid. *Biochem Biophys Res Commun*, **114**, 388-94.

Delgado ME, Haza AI, García A, et al (2009). Myricetin, quercetin, (+)-catechin and (-)-epicatechin protect against N-nitrosamines-induced DNA damage in human hepatoma cells. *Toxicol In Vitro*, **23**, 1292-7.

Devasagayam TP, Tilak JC, Boloor KK, et al (2004). Free radicals and antioxidants in human health: current status and future prospects. *J Assoc Phys India*, **52**, 794-804.

Devipriya N, Sudheer AR, Srinivasan M, et al (2008). Quercetin ameliorates gamma radiation-induced DNA damage and biochemical changes in human peripheral blood lymphocytes. *Mutat Res*, **654**, 1-7.

DeVita VT, Lawrence TS, Hellman, Rosenberg's SA (2004). Cancer: Principles & Practice of Oncology, Eighth Edition, USA

Duthie SJ, Dobson VL (1999). Dietary flavonoids protect human colonocyte DNA from oxidative attack in vitro. *Eur J Nutr*, **38**, 28-34.

Eichenmüller M, Hemmerlein B, von Schweinitz D, et al (2010). Betulinic acid induces apoptosis and inhibits hedgehog signalling in rhabdomyosarcoma. *Br J Cancer*, **103**, 43-51.

Ferlay J, Shin HR, Bray F, et al (2010). EEstimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*.

Fridrich D, Teller N, Esselen M, et al (2008). Comparison of delphinidin, quercetin and (-)-epigallocatechin-3-gallate as inhibitors of the EGFR and the ErbB2 receptor phosphorylation. *Mol Nutr Food Res*, **52**, 815-22.

Furtado RA, Rodrigues EP, Araújo FR, et al (2008). Ursolic acid and oleanolic acid suppress preneoplastic lesions induced by 1,2-dimethylhydrazine in rat colon. *Toxicol Pathol*, **36**, 576-80.

Gali HU, Perchellet EM, Klish DS, et al (1992). Antitumor-promoting activities of hydrolyzable tannins in mouse skin. *Carcinogenesis*, **13**, 715-8.

Gandhi NM and Nair CK (2005). Protection of DNA and membrane from gamma radiation induced damage by gallic acid. *Mol Cell Biochem*, **278**, 111-7.

González-Sarrías A, Larrosa M, Tomás-Barberán FA, et al (2010). NF-kappaB-dependent anti-inflammatory activity of urolithins, gut microbiota ellagic acid-derived metabolites, in human colonic fibroblasts. *Br J Nutr*, **26**, 1-10.

Gonzalez-Sarrias A, Espin JC, Tomas-Barberan FA, et al (2009)

Comparative transcriptional analysis reveals key cell cycle and MAPK signaling genes involved in the S-G2/M-phase arrest of Caco-2 cells exposed to ellagic acid and its colonic derivatives, urolithins. *Mol Nutr Food Res*, **53**, 686-98.

Goyal PK, Verma P, Sharma P, et al (2010). Evaluation of anti-cancer and anti-oxidative potential of *Syzygium cumini* against benzo[a]pyrene (BaP) induced gastric carcinogenesis in mice. *Asian Pac J Cancer Prev*, **11**, 753-8.

Hafeez BB, Siddiqui IA, Asim M, et al (2008). A dietary anthocyanidin delphinidin induces apoptosis of human prostate cancer PC3 cells in vitro and in vivo: involvement of nuclear factor-kappaB signaling. *Cancer Res*, **68**, 8564-72.

Hall EJ (2000). Radiobiology for the Radiologist. 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, USA.

Horvathova E, Turcaniova V, Slamenova D (2007). Comparative study of DNA-damaging and DNA-protective effects of selected components of essential plant oils in human leukemic cells K562. *Neoplasma*, **54**, 478-83.

Hosseinimehr SJ (2007). Trends in the development of radioprotective agents. *Drug Discov Today*, **12**, 794-805.

Hou DX, Kai K, Li JJ, et al (2004). Anthocyanidins inhibit activator protein 1 activity and cell transformation: structure-activity relationship and molecular mechanisms. *Carcinogenesis*, **25**, 29-36.

Hou DX, Ose T, Lin S, et al (2003). Anthocyanidins induce apoptosis in human promyelocytic leukemia cells: structure-activity relationship and mechanisms involved. *Int J Oncol*, **23**, 705-12.

Hsu HY, Yang JJ, Lin CC (1997). Effects of oleanolic acid and ursolic acid on inhibiting tumor growth and enhancing the recovery of hematopoietic system postirradiation in mice. *Cancer Lett*, **111**, 7-13.

Huang WW, Chiu YJ, Fan MJ, et al (2010). Kaempferol induced apoptosis via endoplasmic reticulum stress and mitochondria-dependent pathway in human osteosarcoma U-2 OS cells. *Mol Nutr Food Res*, **54**, 1585-95.

Jagetia GC, Baliga MS (2003). Evaluation of the radioprotective effect of the leaf extract of *Syzygium cumini* (Jamun) in mice exposed to a lethal dose of gamma-irradiation. *Nahrung*, **47**, 181-5.

Jagetia GC, Baliga MS (2002). *Syzygium cumini* (Jamun) reduces the radiation-induced DNA damage in the cultured human peripheral blood lymphocytes: a preliminary study. *Toxicology Letters*, **132**, 19-25.

Jagetia GC, Baliga MS (2004). The evaluation of nitric oxide scavenging activity of certain Indian medicinal plants in vitro: a preliminary study. *J Med Food*, **7**, 343-8.

Jagetia GC, Baliga MS, Venkatesh P (2005). Influence of seed extract of *Syzygium cumini* (Jamun) on mice exposed to different doses of gamma-radiation. *J Radiat Res (Tokyo)*, **46**, 59-65.

Jagetia GC, Shetty PC, Vidyasagar MS (2008). Treatment of mice with leaf extract of jamun (*Syzygium cumini* linn. Skeels) protects against the radiation-induced damage in the intestinal mucosa of mice exposed to different doses of γ-radiation. *Pharmacologyonline*, **1**, 169-95.

Janakiram NB, Indranie C, Malisetty SV, et al (2008). Chemoprevention of colon carcinogenesis by oleanolic acid and its analog in male F344 rats and modulation of COX-2 and apoptosis in human colon HT-29 cancer cells. *Pharm Res*, **25**, 2151-7.

Jeong JC, Kim MS, Kim TH, et al (2009). Kaempferol induces cell death through ERK and Akt-dependent down-regulation of XIAP and survivin in human glioma cells. *Neurochem Res*, **34**, 991-1001.

Jung GR, Kim KJ, Choi CH, et al (2007). Effect of betulinic acid on anticancer drug-resistant colon cancer cells. *Basic Clin Pharmacol Toxicol*, **101**, 277-85.

Jung SK, Lee KW, Byun S, et al (2008). Myricetin suppresses UVB-induced skin cancer by targeting Fyn. *Cancer Res*, **68**, 6021-9.

Kamaraj S, Vinodhkumar R, Anandakumar P, et al., (2007). The effects of quercetin on antioxidant status and tumor markers in the lung and serum of mice treated with benzo(a)pyrene. *Biol Pharm Bull*, **30**, 2268-73.

Kang JW, Kim JH, Song K, et al (2010). Kaempferol and quercetin, components of *Ginkgo biloba* extract (EGb 761), induce caspase-3-dependent apoptosis in oral cavity cancer cells. *Phytother Res*, **suppl 1**, S77-82.

Kang NJ, Lee KW, Kwon JY, et al (2008). Delphinidin attenuates neoplastic transformation in JB6 Cl41 mouse epidermal cells by blocking Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase signaling. *Cancer Prev Res*, **1**, 522-31.

Katsube N, Iwashita K, Tsushida T, et al (2003). Induction of apoptosis in cancer cells by Bilberry (*Vaccinium myrtillus*) and the anthocyanins. *J Agric Food Chem*, **51**, 68-75.

Kaul A, Khanduja KL (1998). Polyphenols inhibit promotional phase of tumorigenesis: relevance of superoxide radicals. *Nutr Cancer*, **32**, 81-5.

Kaur M, Velmurugan B, Rajamanickam S, et al (2009). Gallic acid, an active constituent of grape seed extract, exhibits anti-proliferative, pro-apoptotic and anti-tumorigenic effects against prostate carcinoma xenograft growth in nude mice. *Pharm Res*, **26**, 2133-40.

Khanduja KL, Gandhi RK, Pathania V, et al (1999). Prevention of N-nitrosodiethylamine-induced lung tumorigenesis by ellagic acid and quercetin in mice. *Food Chem Toxicol*, **37**, 313-8.

Kim W, Yang HJ, Youn H, et al (2010). Myricetin inhibits Akt survival signaling and induces Bad-mediated apoptosis in a low dose ultraviolet (UV)-B-irradiated HaCaT human immortalized keratinocytes. *J Radiat Res*, **51**, 285-96.

Ko CH, Shen SC, Lee TJ, et al (2005). Myricetin inhibits matrix metalloproteinase 2 protein expression and enzyme activity in colorectal carcinoma cells. *Mol Cancer Ther*, **4**, 281-90.

Kshirsagar R, Upadhyay S (2009). Free radical scavenging activity screening of medicinal plants from Tripura, Northeast India. *Natural product Radiance*, **8**, 117-22.

Kumamoto T, Fujii M, Hou DX (2009a). Myricetin directly targets JAK1 to inhibit cell transformation. *Cancer Lett*, **275**, 17-26.

Kumamoto T, Fujii M, Hou DX (2009b). Akt is a direct target for myricetin to inhibit cell transformation. *Mol Cell Biochem*, **332**, 33-41.

Kumar A, Ilavarasan R, Jayachandran T, et al (2008). Anti-inflammatory activity of *Syzygium cumini* seed. *Afr J Biotechnol*, **7**, 941-3.

Kuntz S, Wenzel U, Daniel H (1999). Comparative analysis of the effects of flavonoids on proliferation, cytotoxicity, and apoptosis in human colon cancer cell lines. *Eur J Nutr*, **38**, 133-42

Kuo SM (1996). Antiproliferative potency of structurally distinct dietary flavonoids on human colon cancer cells. *Cancer Lett*, **110**, 41-8.

Kwon JY, Lee KW, Kim JE, et al (2009). Delphinidin suppresses ultraviolet B-induced cyclooxygenases-2 expression through inhibition of MAPKK4 and PI-3 kinase. *Carcinogenesis*, **30**, 1932-40.

Larrosa M, González-Sarrías A, García-Conesa MT, et al (2006a). Urolithins, ellagic acid-derived metabolites produced by human colonic microflora, exhibit estrogenic and antiestrogenic activities. *J Agric Food Chem*, **54**, 1611-20.

Larrosa M, Tomás-Barberán FA, Espín JC (2006b). The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma Caco-2 cells by using the mitochondrial pathway. *J Nutr Biochem*, **17**, 611-25.

Lazzé MC, Pizzala R, Savio M, et al (2003). Anthocyanins protect against DNA damage induced by tert-butyl-hydroperoxide in rat smooth muscle and hepatoma cells. *Mutat Res*, **535**, 103-15.

Lazzè MC, Savio M, Pizzala R, et al (2004). Anthocyanins induce cell cycle perturbations and apoptosis in different human cell lines. *Carcinogenesis*, **25**, 1427-33.

Lee KM, Kang NJ, Han JH, et al (2007a). Myricetin down-regulates phorbol ester-induced cyclooxygenase-2 expression in mouse epidermal cells by blocking activation of nuclear factor kappa B. *J Agric Food Chem*, **55**, 9678-84.

Lee KM, Lee DE, Seo SK, et al (2010). Phosphatidylinositol 3-kinase, a novel target molecule for the inhibitory effects of kaempferol on neoplastic cell transformation. Carcinogenesis. [Epub ahead of print]

Lee KW, Kang NJ, Rogozin EA, et al (2007b). Myricetin is a novel natural inhibitor of neoplastic cell transformation and MEK1. *Carcinogenesis*, **28**, 1918-27.

Lee SF and Lin JK (1997). Inhibitory effects of phytopolyphenols on TPA-induced transformation, PKC activation, and c-jun expression in mouse fibroblast cells. *Nutr Cancer*, **28**, 177-83.

Lesca P (1983). Protective effects of ellagic acid and other plant phenols on benzo[a]pyrene-induced neoplasia in mice. *Carcinogenesis*, **4**, 1651-3.

Li J, Guo WJ, Yang QY (2002). Effects of ursolic acid and oleanolic acid on human colon carcinoma cell line HCT15. *World J Gastroenterol*, **8**, 493-5.

Li W, Du B, Wang T, et al (2009b). Kaempferol induces apoptosis in human HCT116 colon cancer cells via the ataxia-telangiectasia mutated-p53 pathway with the involvement of p53 upregulated modulator of apoptosis. *Chem Biol Interact*, **177**, 121-7.

Li L, Adams LS, Chen S, et al (2009a). *Eugenia jambolana* Lam. berry extract inhibits growth and induces apoptosis of human breast cancer but not non-tumorigenic breast cells. *J Agric Food Chem*, **57**, 826-31.

Lo C, Lai TY, Yang JH, et al (2010). Gallic acid induces apoptosis in A375.S2 human melanoma cells through caspase-dependent and -independent pathways. *Int J Oncol*, **37**, 377-85.

Makita H, Tanaka T, Fujitsuka H, et al (1996). Chemoprevention of 4-nitroquinoline 1-oxide-induced rat oral carcinogenesis by the dietary flavonoids chalcone, 2-hydroxychalcone, and quercetin. *Cancer Res*, **56**, 4904-9.

Marko D, Puppel N, Tjaden Z, et al (2004). The substitution pattern of anthocyanidins affects different cellular signaling cascades regulating cell proliferation. *Mol Nutr Food Res*, **48**, 318-25.

Meiers S, Kemény M, Weyand U, et al (2001). The anthocyanidins cyanidin and delphinidin are potent inhibitors of the epidermal growth-factor receptor. *J Agric Food Chem*, **49**, 958-62.

Mitić-Culafić D, Zegura B, Nikolić B, et al (2009). Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide induced genotoxicity in bacteria and cultured human cells. *Food Chem Toxicol*, **47**, 260-6.

Moon DO, Kim MO, Choi YH, et al (2008). beta-Sitosterol induces G2/M arrest, endoreduplication, and apoptosis through the Bcl-2 and PI3K/Akt signaling pathways. *Cancer Lett*, **264**, 181-91.

Moon DO, Lee KJ, Choi YH, et al (2007). Beta-sitosterol-induced-apoptosis is mediated by the activation of ERK and the downregulation of Akt in MCA-102 murine fibrosarcoma cells. *Int Immunopharmacol*, **7**, 1044-53.

Moteki H, Hibasami H, Yamada Y, et al (2002). Specific induction of apoptosis by 1,8-cineole in two human leukemia cell lines, but not a in human stomach cancer cell line. *Oncol Rep*, **9**, 757-60.

Mukhtar H, Das M, Bickers DR (1986). Inhibition of 3-methylcholanthrene-induced skin tumorigenicity in BALB/c mice by chronic oral feeding of trace amounts of ellagic acid in drinking water. *Cancer Res*, **46**, 2262-5.

Mukhtar H, Das M, Del Tito BJ Jr, et al (1984a). Protection against 3-methylcholanthrene-induced skin tumorigenesis in Balb/C mice by ellagic acid. *Biochem Biophys Res Commun*, **119**, 751-7.

Mukhtar H, Del Tito BJ Jr, Marcelo CL, et al (1984b). Ellagic acid: a potent naturally occurring inhibitor of benzo[a]pyrene metabolism and its subsequent glucuronidation, sulfation and covalent binding to DNA in cultured BALB/C mouse keratinocytes. *Carcinogenesis*, **5**, 1565-71.

Mullauer FB, Kessler JH, Medema JP (2009). Betulinic acid induces cytochrome c release and apoptosis in a Bax/Bak-independent, permeability transition pore dependent fashion. *Apoptosis*, **14**, 191-202.

Muruganandan S, Srinivasan K, Chandra S, et al (2001). Anti-inflammatory activity of *Syzygium cumini* bark. *Fitoterapia*, **72**, 369-75.

Nahar L, Alam Ripa F, Rokonuzzaman, et al (2009). Investigation on antioxidant activities of six indigenous plants of bangladesh. *J Applied Sci Res*, **5**, 2285-8.

Nair HK, Rao KV, Aalinkeel R, et al (2004). Inhibition of prostate cancer cell colony formation by the flavonoid quercetin correlates with modulation of specific regulatory genes. *Clin Diagn Lab Immunol*, **11**, 63-9.

Nemavarkar P, Chourasia BK, Pasupathy K (2004). Evaluation of radioprotective action of compounds using *Saccharomyces cerevisiae*. *J Environ Pathol Toxicol Oncol*, **23**, 145-51.

Parmar J, Sharma P, Verma P, et al (2010). Chemopreventive action of *Syzygium cumini* on DMBA-induced skin papillomagenesis in mice. *Asian Pac J Cancer Prev*, **11**, 261-5.

Patt HM, Tyree EB, Straube RL, et al (1949). Cysteine protection against X irradiation. *Science*, **110**, 213-4.

Prince PS, Menon VP, Pari L (1998). Hypoglycemic activity of *Syzigium cumini* seeds: effect on lipid peroxidation in alloxan diabetic rats. *J Ethnopharmacol*, **61**, 1-7.

Priyadarsini KI, Khopde SM, Kumar SS, et al (2002). Free radical studies of ellagic acid, a natural phenolic antioxidant. *J Agric Food Chem*, **50**, 2200-6.

Rabi T, Shukla S, Gupta S (2008). Betulinic acid suppresses constitutive and TNFalpha-induced NF-kappaB activation and induces apoptosis in human prostate carcinoma PC-3 cells. *Mol Carcinog*, **47**, 964-73.

Raina K, Rajamanickam S, Deep G, et al (2008). Chemopreventive effects of oral gallic acid feeding on tumor growth and progression in TRAMP mice. *Mol Cancer Ther*, **7**, 1258-67.

Raquibul-Hasan SM, Hossain MM, Akter R, et al (2009). DPPH free radical scavenging activity of some Bangladeshi medicinal plants. *J Med Plants Res*, **3**, 875-9.

Rastogi RM, Mehrotra BN (1990). Compendium of Indian Medicinal Plants. Vol.1 (pp. 388-389). Central Drug Research Institute, Lucknow, India.

Ravi K, Ramachandran B, Subramanian S (2004). Protective effect of *Eugenia jambolana* seed kernel on tissue antioxidants in streptozotocin-induced diabetic rats. *Biol Pharm Bull*, **27**, 1212-7.

Reddivari L, Vanamala J, Safe SH, et al (2010). The bioactive

compounds alpha-chaconine and gallic acid in potato extracts decrease survival and induce apoptosis in LNCaP and PC3 prostate cancer cells. *Nutr Cancer*, **62**, 601-10.

Rodgers EH, Grant MH (1998). The effect of the flavonoids, quercetin, myricetin and epicatechin on the growth and enzyme activities of MCF7 human breast cancer cells. *Chem Biol Interact*, **116**, 213-28.

Ruan PZ, Zhang LL, Lin MY (2008). Evaluation of the antioxidant activity of Syzygium cumini leaves. *Molecules*, **13**, 2545-56.

Sagrawat H, Mann AS, Kharya MD (2006). Pharmacological potential of *Eugenia jambolana*: a review. *Pharmacognosy Magazine*, **2**, 96-105.

Seeram NP, Zhang Y, Nair MG (2003). Inhibition of proliferation of human cancer cells and cyclooxygenase enzymes by anthocyanidins and catechins. *Nutr Cancer*, **46**, 101-6.

Sengupta A, Ghosh S, Das S (2001). Modulation of DMBA induced genotoxicity in bone marrow by quercetin during skin carcinogenesis. *J Exp Clin Cancer Res*, **20**, 131-4.

Shafi PM, Rosamma MK, Jamil K, et al (2002). Antibacterial activity of *Syzygium cumini* and *Syzygium travancoricum* leaf essential oils. *Fitoterapia*, **73**, 414-6.

Sharma M, Li L, Celver J, et al (2010). Effects of fruit ellagitannin extracts, ellagic acid, and their colonic metabolite, urolithin A, on Wnt signaling. *J Agric Food Chem*, **58**, 3965-9.

Shin DY, Ryu CH, Lee WS, et al (2009). Induction of apoptosis and inhibition of invasion in human hepatoma cells by anthocyanins from meoru. *Ann N Y Acad Sci*, **1171**, 137-48.

Srivastava A, Akoh CC, Fischer J, et al (2007). Effect of anthocyanin fractions from selected cultivars of Georgia-grown blueberries on apoptosis and phase II enzymes. *J Agric Food Chem*, **55**, 3180-5.

Syed DN, Afaq F, Sarfaraz S, et al (2008a). *Delphinidin* inhibits cell proliferation and invasion via modulation of Met receptor phosphorylation. *Toxicol Appl Pharmacol*, **231**, 52-60.

Syed DN, Suh Y, Afaq F, et al (2008b). Dietary agents for chemoprevention of prostate cancer. *Cancer Lett*, **265**, 167-76.

Teller N, Thiele W, Boettler U, et al (2009). *Delphinidin* inhibits a broad spectrum of receptor tyrosine kinases of the ErbB and VEGFR family. *Mol Nutr Food Res*, **53**, 1075-83.

Tokuda H, Ohigashi H, Koshimizu K, et al (1986). Inhibitory effects of ursolic and oleanolic acid on skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate. *Cancer Lett*, **33**, 279-85.

Veigas JM, Narayan MS, Laxman PM, et al (2007). Chemical nature, stability and bioefficacies of anthocyanins from fruit peel of *Syzygium cumini* skeels. *Food Chemistry*, **105**, 619-27.

Veigas JM, Shrivasthava R, Neelwarne B (2008). Efficient amelioration of carbon tetrachloride induced toxicity in isolated rat hepatocytes by *Syzygium cumini* Skeels extract. *Toxicology In Vitro*, **22**, 1440-6.

Vijayababu MR, Arunkumar A, Kanagaraj P, et al (2006). Quercetin downregulates matrix metalloproteinases 2 and 9 proteins expression in prostate cancer cells (PC-3). *Mol Cell Biochem*, **287**, 109-16.

von Holtz RL, Fink CS, Awad AB (1998). beta-Sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells. *Nutr Cancer*, **32**, 8-12.

Walle T, Walle UK, Sedmera D, et al (2006). Benzo[A]pyrene-induced oral carcinogenesis and chemoprevention: studies in bioengineered human tissue. *Drug Metab Dispos*, **34**, 346-50.

Warrier PK, Nambiar VPK, Ramankutty C (1996). Orient Longman Ltd, Hyderabad, India. *Indian Med Plants*, **5**, 225-8.

Wu PK, Chi Shing Tai W, Liang ZT, et al (2009). Oleanolic acid isolated from Oldenlandia diffusa exhibits a unique growth inhibitory effect against ras-transformed fibroblasts. *Life Sci*, **85**, 113-21.

Yan SL, Huang CY, Wu ST, et al (2010). Oleanolic acid and ursolic acid induce apoptosis in four human liver cancer cell lines. *Toxicol In Vitro*, **24**, 842-8.

Yang LJ, Chen Y, Ma Q, et al (2010). Effect of betulinic acid on the regulation of Hiwi and cyclin B1 in human gastric adenocarcinoma AGS cells. *Acta Pharmacol Sin*, **31**, 66-72.

Yasukawa K, Takido M, Matsumoto T, et al (1991). Sterol and triterpene derivatives from plants inhibit the effects of a tumor promoter, and sitosterol and betulinic acid inhibit tumor formation in mouse skin two-stage carcinogenesis. *Oncology*, **48**, 72-6.

Yeh CT and Yen GC (2005). Induction of apoptosis by the Anthocyanidins through regulation of Bcl-2 gene and activation of c-Jun N-terminal kinase cascade in hepatoma cells. *J Agric Food Chem*, **53**, 1740-9.

Yun JM, Afaq F, Khan N, et al (2009). Delphinidin, an anthocyanidin in pigmented fruits and vegetables, induces apoptosis and cell cycle arrest in human colon cancer HCT116 cells. *Mol Carcinog*, **48**, 260-70.

Zhang P, Li H, Chen D, et al (2007). Oleanolic acid induces apoptosis in human leukemia cells through caspase activation and poly(ADP-ribose) polymerase cleavage. *Acta Biochim Biophys Sin* , **39**, 803-9.

Zhang Q, Zhao XH, Wang ZJ (2008). Flavones and flavonols exert cytotoxic effects on a human oesophageal adenocarcinoma cell line (OE33) by causing G2/M arrest and inducing apoptosis. *Food Chem Toxicol*, **46**, 2042-53.

Zhang X, Ling Y, Yu H, et al (2010). Studies on mechanism of myricetin-induced apoptosis in human hepatocellular carcinoma HepG-2 cells. *Zhongguo Zhong Yao Za Zhi*, **35**, 1046-50.

Zhang Y, Vareed SK, Nair MG (2005). Human tumor cell growth inhibition by nontoxic anthocyanidins, the pigments in fruits and vegetables. *Life Sci*, **76**, 1465-72.

Zhang LL, Lin YM (2009). Antioxidant tannins from *Syzygium cumini* fruit. *Afr J Biotechnol*, **8**, 2301-9.

Zhao Y, Chang SK, Qu G, et al (2009). Beta-sitosterol inhibits cell growth and induces apoptosis in SGC-7901 human stomach cancer cells. *J Agric Food Chem*, **57**, 5211-8.