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

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 cumini 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...
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.

### Table 1. Phytochemicals Present in the Jamun Plant

<table>
<thead>
<tr>
<th>Plant part</th>
<th>Chemicals present</th>
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<tbody>
<tr>
<td>Stem bark</td>
<td>Friedelin, friedelan-3-α-ol, betulinic acid, β-sitosterol, kaempferol, β-sitosterol-D-glucoside, gallic acid, ellagic acid, gallocatexin and ellagitannin and myricetin (Rastogi and Mehrrota, 1990; Sagrawat et al., 2006).</td>
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<tr>
<td>Leaves</td>
<td>β-sitosterol, betulinic acid, mycaminose, crategolic (maslinic) acid, n-heptacosane, n-nonacosane, n-hentriacontane, n-octacosanol, n-triacontanol, n-dotriacontanol, quercetin, myricetin, myricitrin and the flavonol glycosides myricetin 3-O-(4”-acetyl)-α-L-rhamnopyranosides (Rastogi and Mehrrota, 1990; Sagrawat et al., 2006).</td>
</tr>
<tr>
<td>Flowers</td>
<td>Oleanolic acid, ellagic acids, isoquercetin, quercetin, kaempferol and myricetin (Sagrawat et al., 2006).</td>
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<tr>
<td>Fruit pulp</td>
<td>Anthocyanins, delphinidin, petunidin, malvidin-diglucosides (Li et al., 2009a; Sagrawat et al., 2006; Veigas et al., 2007).</td>
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<tr>
<td>Seeds</td>
<td>Jambosine, gallic acid, ellagic acid, corilagin, 3, 6-hexahydroxy diphenoylgucose, 1-galloylgucose, 3-galloylgucose, quercetin, β-sitoterol, 4,6-hexahydroxydiphenoylgucose, (Rastogi and Mehrrota, 1990; Sagrawat et al., 2006).</td>
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<tr>
<td>Essential oils</td>
<td>α-terpeneol, myrtenol, eucarvone, muurolol, α-myrenhol, 1, 8-cineole, geranly acetone, α-cadinol and pinocarvone (Shafi et al., 2002).</td>
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![Figure 2. Structures of Phytochemicals in Jamun Reported to be of Use in the Prevention and Treatment of Cancer](image)

### 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>
<thead>
<tr>
<th>Agent</th>
<th>Antineoplastic activity and the mechanisms operating</th>
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<tbody>
<tr>
<td>Oleanolic acid</td>
<td>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).</td>
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<tr>
<td>Quercetin</td>
<td>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 gelatinase A and B (matrixmetalloproteinases 2 and 9) in the human prostate cancer cells (PC-3) in vitro (Vijayababu et al., 2006).</td>
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<tr>
<td>Kaempferol</td>
<td>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 Bel-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).</td>
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<td>Myricetin</td>
<td>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 HepG2 (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 HepG2 (Zhang et al., 2010). 3). Causes 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).</td>
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<tr>
<td>Betulinic acid</td>
<td>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 Kiwi 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, PITCH1 and IGF2 expression as well as hedgehog-response in vitro. It also caused retarded the growth of RMS-L3 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 Bel-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/SFU-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 bel-2xl (Chen et al., 2008).</td>
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<tr>
<td>1,8-Cineole</td>
<td>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).</td>
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</table>
Table 2 (continued). Phytochemicals in Jamun with Reported Antineoplastic Activities

<table>
<thead>
<tr>
<th>Agent</th>
<th>Antineoplastic activity and the mechanisms operating</th>
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<tr>
<td>Delphinidin</td>
<td>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-Eik-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 (Zheng et al., 2005). 8. Possess strong growth inhibitory effects against human hepatoma HepG2(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 EGFR-induced autophosphorylation of EGFR, AKT and MAPK, activation of PI3K and cell invasion (Afq 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, 22Rm1, 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 in cells in G2-M phase, decrease in phosphorylation of IkappaB kinase gamma, phosphorylation of nuclear factor-kappaB (NF-kappaB) inhibitory protein protein 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).</td>
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<tr>
<td>Petunidin</td>
<td>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).</td>
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<tr>
<td>Malvidin</td>
<td>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 HepG2(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).</td>
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Commonly used drugs like vincristine, vinblastine, taxol, docetaxel, teniposide, etoposide and camptothecin 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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chemopreventive effects and the mechanisms operating</th>
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<tbody>
<tr>
<td>Oleanolic acid</td>
<td>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).</td>
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<tr>
<td>Ellagic acid</td>
<td>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-ben[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).</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>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).</td>
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<tr>
<td>Quercetin</td>
<td>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 cholanthere-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).</td>
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</table>
The process of carcinogenesis by selectively killing cancer cells (Li et al., 2009a) and it is logical to suggest that administration of the jamun extract (25 mg/kg b.wt/day) was effective in preventing benzo-a-pyrene-induced forestomach carcinogenesis. Jamun reduced the tumor latency period when compared with the control group (carcinogen alone) (Parmar et al., 2010). Very recently Goyal et al., (2010) have also observed the average latency period during carcinogenesis in various organs (Table 3) and may have contributed to the anti-carcinogenesis.

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 effective in 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 (Figure 2) 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).

The 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>
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<tr>
<th>Agent</th>
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<tr>
<td>Myricetin</td>
<td>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 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 metalloproteins 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).</td>
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<tr>
<td>Kaempferol</td>
<td>1). Possess inhibitory effects on phosphatidylinositol 3-kinase and inhibits the neoplastic transformation (Lee et al., 2010).</td>
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<tr>
<td>Betulinic acid</td>
<td>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).</td>
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<tr>
<td>β- sitosterol</td>
<td>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).</td>
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<tr>
<td>Delphinidin</td>
<td>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). 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 metalloproteins 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).</td>
</tr>
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(Agarwal 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).
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 fruit 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-methanol) 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 pretreated animals than the irradiation alone (Jagetia et al., 2008). The phytochemicals ellagic acid, gallic acid, quercetin and oleomorphic 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 (O₂•⁻), hydroxyl radical (OH•), hydrogen peroxide (H₂O₂), nitric oxide (NO) and peroxyxenitrite (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•, O₂•⁻ 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
In hydroxyl radical scavenging assay, the kernel extract was comparable to the effect of catechin (Benheral 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 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 (methanol/dichloromethane 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 (vitr 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 (Ahern and O’Brien, 1999; Duthie and Dobson, 1999), quercetin (Ahern 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. Mechanistic 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.

Premature 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.

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