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MINOR FRUITS IN THE MANAGEMENT OF DISEASES INCLUDING CANCER: A COMPREHENSIVE REVIEW

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ABSTRACT

Fruits have played a key role in world health. Population rises, inadequate supply of drugs, prohibitive cost of treatment, side effects of several allopathic drugs and development of resistance to currently used drugs for infectious diseases, have led to increased emphasis on the use of fruit material as a source of medicine for a wide variety of ailments. Fruit medicine refers to the application, approach, knowledge and belief in incorporating plant-based properties in remedies, singularly or in combination, for the purpose of treating or preventing disease as well as to maintain the well-being of an individual. Cancer is becoming a big load on families and economies. Cancer is one of the most dreaded diseases of the 20th century and spreading further with increasing incidence in 21st century. Cancer, next to heart diseases, is the second leading cause of deaths in the United States of America and many other nations in the world. India ranks third among Nations in terms of highest number of cancer cases, India as a single country contributes 7.8% of global cancer burden and over 13 lakhs people suffer from cancer every year. According to the latest World Cancer Report from the World Health Organisation (WHO), more women in India are being newly diagnosed with cancer annually. The spreading of cancer is increasing over the world and the percentage of deaths caused by this fatal disease is rising especially in the developing countries. Scientists and researchers are giving more attention to the herbal medicine to provide treatment for the disease in order to get rid of serious side effects caused by chemical therapy. Therefore, cancer research has become a major area of scientific research supporting the foundations of modern biology to a great extent and efforts are still being made for the search of effective naturally occurring anticarcinogens that would prevent, slow or reverse cancer development. Fruits have real significance and fruits have been a prime source of highly effective conventional drugs for the treatment of many forms of cancer. The present chapter deals with minor fruits in the management of diseases including cancer.

***Keywords*:** Minor fruits, cancer, diseases, herbal medicine, anticarcinogens.

Introduction

There is strong, consistent evidence that high intake of fruits protects against various cancers especially cancers of respiratory and digestive tracts. These protective effects of high fruit consumption are attributed to the active micronutrients (vitamins and minerals) and non-nutritive components (phytochemicals) that exhibit a potential for modulating human metabolism in a manner favorable for the prevention of cancer. In other words, we can say that fruits consumed in our daily diet could be a solution to this deadly disease by providing chemoprotective and chemotherapeutic remedy. Regular consumption of fruits is associated with reduced risk of cancers and additive/ synergistic effects of phytochemicals in fruits are responsible for their potent antioxidant / anticancer activities.

A comprehensive review was conducted to assess the safety and efficacy of some minor fruits used by patients in an attempt to prevent various diseases

including cancer. A seminal description of the minor fruits that have been selected is given in the following pages. The information within braces in order is: Family, English name, Hindi name. This system has been followed throughout while describing the minor fruits.

***Aegle marmelos* [Rutaceae, Wood apple, Sirphal / Bael]**

Aegle marmelos L. Corr. has enormous traditional values against various diseases as fruit, leaves, stem, roots of the plant are used as ethno medicine against various human ailments (Badam *et al*., 2002; Gupta and Tondon, 2004). Fruit part of bael possess high nutritional value and its pulp reported for the availability of steroids, terpenoids, flavonoids, phenolic compounds, lignin, fat/oil, inulin, proteins, carbohydrates, alkaloids, cardiac glycosides and flavonoids (Rajan *et al.,* 2011). Methanol and aqueous extracts of bael fruit pulp were screened for antioxidant activity by DPPH radical scavenging method, reducing power assay, nitric oxide scavenging assay, superoxide radical scavenging assay, ABTS radical scavenging assay and H_2O_2 radical scavenging assay. Results demonstrated that both the extracts exhibited good antioxidant activity (Rajan *et al.,* 2011). Antioxidant activity / free radical scavenging activity of the ripe and unripe fruit of *Aegle marmelos* was compared and it was found that the enzymatic antioxidants increased in ripe fruit when compared to unripe fruit extract (except glutathione peroxidase). The percentage of free radical inhibition was also high in unripe fruit than that of the ripe fruit (Sharmila and Devi, 2011). Extracts of bael were evaluated for anticancer potential using brine shrimp lethality assay, sea urchin eggs assay and MTT assay using tumor cell lines and the extracts exhibited toxicity on all used assays (Latica and Costa, 2005). The anticancer effect of hydroalcoholic extract of bael was reported in the animal model of Ehrlich ascites carcinoma (Gagetia *et al.,* 2005).

***Carissa carandas* [Apocynaceae, Cranberry, Karonda]**

Karonda is a large dichotomously branched evergreen shrub with short stem and strong thorns in pairs (Wiart, 2006). Karonda plant grows well under tropical and sub-tropical climatic condition (Karale, 2002). *Carissa carandas* Linn. is widely used throughout India in the treatment of scabies, intestinal worms, pruritus and its fruit have been studied for its analgesic, anti-inflammatory (Sharma *et al.,* 2007) and lipase (Mala and Dahot, 1995) activity. The karonda fruit is an astringent, antiscorbutic and as a remedy for biliousness and useful for cure of anaemia. The root extracts of *Carissa carandas* are known to have anti-inflammatory and antipyretic properties (Bhaskar and Balakrishnan, 2009). Chloroform extracts of *Carissa carandas* leaves also exhibited cytotoxicity on human ovarian carcinoma cells and n-hexane extracts of the unripe fruits is cytotoxic towards the lung cancer cell line (Sulaiman *et al.,* 2008). The root extracts of this plant are known to have anticonvulsant activity in experimental mice (Hegde *et al.,* 2009). Extracts of karonda were investigated on human ovarian carcinoma, Caov-3 and lung cancer cells. Chloroform extract from leaves showed good anticancer activity against Caov-3 while the n-hexane extract of the unripe fruit showed remarkable activity against the lung cancer cell line (Pino *et al.,* 2004; Pal *et al.,* 1975; Singh and Rastogi, 1972; Reisch *et al.,* 1990).

***Emblica officinalis* [Phyllanthaceae, Indian gooseberry, Amla]**

Emblica officinalis, originally native to India, is today found growing in Pakistan, Uzbekistan, Sri Lanka, South-East Asia, China and Malaysia. All parts of the plant are of use in treating various ailments, but the fruit, which is yellowish-green in color, globular in shape, fleshy and smooth, obtusely triangular six-celled nut, is of immense use in various folk and traditional systems of medicine (Warrier *et al.*, 1996; Zhang *et al.,* 2003; Khan, 2009). Amla is reported to possess hepatoprotective, cardioprotective, diuretic,

laxative, refrigerant, stomachic, restorative, alterative, antipyretic, anti-inflammatory properties, prevents peptic ulcer and is a digestive medicine. It is used for a variety of ailments such as anemia, hyperacidity, diarrhea, eye inflammation, leucorrhea, jaundice, nerve debility, liver complaints, cough, and anomalies of urine (Pandey, 2002). The aqueous extract of amla, inhibited the growth of A549 (lung), HepG2 (liver), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovarian) and SW620 (colorectal) cells *in vitro*. The extract also induced apoptosis in HeLa, A549, MDA-MB-231 and SK-OV3 cells (Ngamkitidechakul *et al.,* 2010). An amla extract possesses antiproliferative activity in MCF7 and MDA-MB-231 breast cancer cell lines and also induces an increase in ERam RNA in these cells (Lambertini *et al.,* 2004). The extract was devoid of cytotoxic effects on the normal Chinese hamster ovary cell line, suggesting it to be selectively cytotoxic to only neoplastic cells (Sumantran *et al.,* 2007).

Chemopreventive potential of amla against skin carcinogenesis and liver cancer has also been established (Sancheti *et al.,* 2005; Sultana *et al.,* 2008). The amla phytochemical, kaempferol, inhibited the expression of stromelysin 1(MMP-3) in the MDA-MB-231 breast cancer cell line (Phromnoi *et al.,* 2009). The polyphenol gallic acid is also reported to possess inhibitory effects on gastric adenocarcinoma cell migration, decreased expression of MMP-2/9 *in vitro* (Ho *et al.,* 2010) and metastasis of P815mastocytoma cells to the liver of DBA/2 mice (Ohno *et al.,* 2001). The flavanol, quercetin, decreased the expression of gelatinases A and B (MMP-2 and MMP-9) in the human metastatic prostate PC-3 cells (Vijayababu *et al.,* 2006) and inhibited the lung metastasis of murine colon 26-L5 carcinoma cells (Ogasawara *et al.,* 2007).

***Grewia asiatica* [Tilaceae, Indian Sherbet Berry, Phalsa]**

Grewia asiatica is used in ayurvedic management of menopause and included in the class of drugs that have an overall anti-aging effect in the body. Phalsa fruit contains pelargonidin 3,5-diglucoside, naringenin-7-*O*-β-D-glucoside, quercetin, quercetin 3-*O*-β-D-glucoside, tannins, catechins, cyanidin-3-glucoside (Chattopadhyay and Pakrashi, 1975) and claimed to be beneficial for heart, blood / liver disorders, anorexia, indigestion, thirst, toxemia, stomatitis, hiccough, asthma, spermatorrhoea, fevers and diarrhea. Fruits are also used for treating throat, tuberculosis and sexual debility troubles (Sharma and Sisodia, 2009; Pallavi *et al*., 2011; Mishra *et al.,* 2012). Nutritionally essential amino acids such as threonine and methionine are present in pulp and seeds respectively, whereas phosphoserine, serine and taurine are the dominant amino acids in juice (Hasnain and Ali, 1988). Fruits of *G. asiatica* are reported for their antitumor and cytotoxic activity (Kakoti *et al*., 2011). Some *Grewia* species have free radical scavenging activities which may be responsible for therapeutic action against tissue damage (Kshirsagar *et al.,* 2009). *Grewia*'s extracts are also supposed to be helpful in curing hepatitis and used as herbal antidiabetic (Tripathi *et al*., 2011).

***Morinda citrifolia* [Rubiaceae, Indian Mulberry, Shehtoot]**

Mulberry is traditionally used in Chinese medicines as a pharmaceutical for antifever, diuretics, liver protection, eyesight improvement, blood pressure reduction and cardiovascular disease prevention. Dietary mulberry has been reported to have not only antioxidative, antitumor and antidiabetic effects, but also cardiovascular, hepato and neuro-protective properties (Andallu *et al.,* 2001; Huang *et al.,* 2008; El-Beshbishy *et al.,* 2006; Kimura *et al.,* 2007; Isabelle *et al.,* 2008; Wang *et al.,* 2000). Six cancer cell lines; AGS, MCF7, SW742, SKLC6, A375 and PLC/PRF/5 exposed to nine novel candidate herbal extracts and cytotoxic drug were performed. The IC_{50} related to candidate herbal extracts were calculated in a range from 22.2 to 99.9 µg/ml, the minimum IC_{50} related to *M. alba* extract and maximum IC_{50} related to C. limon

extract (bulk extract) on AGS, indicating the better chemopreventive efficacy of mulberry (Sardari *et al.,* 2009). Mulberry anthocyanins, cyanidin 3-rutinoside and cyanidin 3-glucoside, exhibited an inhibitory effect on the migration and invasion of a human lung cancer cell line by regulating the activation of c-Jun and NF-κB (Chen *et al.,* 2006). Mulberry fruit extracts result in human glioma cell death *in vitro* through the reactive oxygen species (ROS)-dependent mitochondrial pathway and glioma tumor growth *in vivo* via reduction of tumor cell proliferation and the induction of apoptosis (Jeong *et al.,* 2010). By targeting p38/p53 and the c-jun pathways, mulberry anthocyanins (MACs) suppressed gastric cancer cell survival and tumorigenesis and induced apoptotic death *in vitro* and *in vivo* (Huang *et al.,* 2011).

***Olea europaea* [Oleaceae, Olive, Jaitun]**

Olive is native to tropical and warm temperate regions of the world. The tree well known for its fruit is commercially essential in the Mediterranean region as a most important source of olive oil. The health benefits of olive oil are mainly ascribed to the existence of high content of monounsaturated fatty acid (MUFAs) and functional bio-actives including tocopherols, carotenoids, phospholipids, phenolics with numerous biological activities (Covas *et al.,* 2006; Ribarova *et al.*, 2003). Olive fruit extracts inhibit proliferation and induce apoptosis in HT-29 human colon cancer cells (Juan *et al.,* 2006). Olive fruits and olive oil are helpful in cancer prevention (Owen *et al.,* 2004). Potential anticancer effects of olive oil on colorectal carcinogenesis models *in vitro* (Gill *et al.,* 2005) and on human adenocarcinoma caco-2 cells (Mateos *et al.,* 2013) has also reported. Recent epidemiological evidence and animal studies suggest olive and its by-products show anticancer activity. Antioxidants are present in olive/olive oil and consumption of antioxidants is believed to reduce the risk of mutagenesis and carcinogenesis (Waterman and Lockwood, 2007; Visioli *et al.,* 2004). Olive oil intake has been shown to induce significant levels of apoptosis in various cancer cells including breast, prostate and colon. These anti-cancer properties are thought to be mediated by phenolic compounds present in olive (Han *et al.,* 2009).

A polyphenolic fraction extracted from olive oil was investigated on proliferation, the cell cycle distribution profile, apoptosis and differentiation of the promyelocytic leukemia cells (HL60). A phenolic extract showed antiproliferative effect in a time and concentration-dependent manner in HL60 cells. Cell growth was blocked at a concentration of 13.5 mg/l and the treatment with it induced apoptosis and differentiation. These beneficial health effects of olive and olive oil attributed to the presence of hydroxytyrosol and oleuropein (Fabiani *et al.,* 2006). In another study, the differentiation inducing ability of hydroxytyrosol was found on HL60 with a maximum effect (22% of cells) at 100 mmol/L after exposure for 72 h. Among the proteins involved in the regulation of the cell cycle, hydroxytyrosol reduced the level of cyclin-dependent kinase (CDK) 6 and increased that of cyclin D3 whereas the expression of p21WAF1/Cip1 and p27Kip1 was increased at both protein and mRNA, p15 was not altered by hydroxytyrosol (Fabiani *et al.,* 2008). The high content of squalene in olive oil could supply a chemo-protective effect to skin and may also provide defense against many other forms of cancer (Newmark, 1997 and Smith, 2000).

***Punica granatum* [Punicaceae, Pomegranate, Anaar]**

Punica granatum is a native of Iran and is considered as one of the oldest known edible fruits that is mentioned in the Koran, the Bible, the Jewish Torah and the Babylonian Talmud as 'Food of Gods' that is symbolic of plentyness, fertility and prosperity (Madihassan, 1984; Aviram *et al*., 2000; Seeram *et al.,* 2006). Anaar is featured virtually in all major religions and has been used for centuries as a folk medicine for the management and treatment of diverse ailments (Schubert *et al*., 1999). Pomegranate fruit is a rich source of two types of polyphenolic compounds: anthocyanins and hydrolyzable tannins, which account

for 92% of the antioxidant activity of the whole fruit (Gil *et al.,* 2000). Pomegranate fruit extracts/ constituents possesses immense biological activities such as anticarcinogenic (Whitley *et al.,* 2003; Afaq *et al.,* 2005), antibacterial (Akiyama *et al.,* 2001; Prashanth *et al.,* 2001; Duman *et al.,* 2009), antidiarrhoeal (Das *et al.,* 1999), antifungal (Dutta *et al.,* 1998), antiulcer (Gharzouli *et al.,* 1999) and free radical scavenging (Festa *et al.,* 2001). Fruit also contributes to the strengthening of immune system (Lee *et al.,* 2008), prevention of heart disease (Johanningsmeier & Harris, 2011) and liver fibrosis (Thresiamma & Kuttan, 1996).

Pomegranate fruit extracts rich in ellagitannins proved their efficacy as anticancer agents especially against breast and colon cancer (Lansky and Newman, 2007; Adams *et al.,* 2010; Kasimsetty *et al.,* 2010; Sharma *et al.,* 2010). Anticancer and antioxidant activities of standardized whole fruit, pulp and peel extract of Egyptian pomegranate has also been reported (Motaal and Shaker, 2011). Pomegranate, consumed as whole fruit, juice or any form of derivates, possess anti-proliferative, pro-apoptotic and/or anti-angiogenic effects superior to those observed with their isolated active compounds, suggesting therapeutic strategies that may depart from preference for pure single agents. There are several publications on the anticarcinogenic effects of pomegranate (Ahmed *et al.,* 2005; Jeune *et al.,* 2005; Jurenka, 2008; Faria and Calhau, 2010; Miguel *et al.,* 2010). *In vitro* studies stated that several pomegranate products inhibit prostate cancer cell growth, induce apoptosis of several prostate cancer cell lines, suppress invasive potential of PC-3 cells and decrease proliferation of DU-145 prostate cancer cells (Lansky *et al.,* 2005; Pantuck *et al.,* 2006).

***Syzygium cumini* [Myrtaceae, Java Plum / Black Plum, Jamun]**

Syzygium cumini (L.) is a widely distributed forest tree in India and other tropical and subtropical regions of the world. The tree has a great economic importance since most of the parts like the bark, leaves, seed and fruits are used as an alternative medicine to treat various diseases. The fruit, seeds and even juice of the fruit play an important role in the treatment of diabetes. Jamun fruit is a very rich source of anthocyanin and has anti-cancer and anti-viral properties (Jain and Seshadri, 1975; Venkateswarlu, 1962). Jamun possess antineoplastic (Barh and Viswanathan, 2008), radioprotective (Jagetia and Baliga, 2002 & 2003; Jagetia *et al.,* 2005 & 2008) and chemo preventive 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 and terpenes (Sagrawat *et al.,* 2006). Jamun possess cancer chemo preventive properties in the DMBA-induced croton oil promoted two stage skin carcinogenesis in Swiss albino mice. Feeding of 125mg/ 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 (Parmar *et al.,* 2010). Jamun extract administration (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 (Goyal *et al.,* 2010). Jamun extract has been shown to be selectively cytotoxic to the human neoplastic breast cancer cells 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 (Li *et al.,* 2009).

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; Gonzalez-Sarriaset *et al.,* 2010).

***Ziziphus mauritiana* [Rhamnaceae, Indian plum, Ber]**

Ziziphus mauritiana is a fruit tree which grows in tropical and sub-tropical regions of the world. Different parts of this plant have been used in the traditional medicine for the treatment of different ailments such as asthma, allergies, depression and ulcers (Marwat *et al.,* 2009). Studies have also investigated the phenolics composition of the fruit and illustrated the scientific basis for the uses of different parts of this plant for the treatment of diabetes, ulcer and inflammation (Bhatia & Mishra, 2010; Cisse *et al.,* 2000; Gupta *et al.,* 2012; Memon *et al.,* 2012; Siddharth *et al.,* 2010). A study was conducted to investigate the chemical composition as well as biological (antioxidant, antimicrobial, antitumor and anticancer) attributes of different solvent extracts from the leaves of *Ziziphus mauritiana*. It was established that methanol extract exhibited higher DPPH free radical scavenging potential (IC_{50} = 0.11 mg/mL) and antimicrobial (antibacterial and antifungal) activity among others. Chloroform extract showed strongest antitumor (IC_{50} = 70.74µg/mL) and anticancer activity (IC_{50} values of 27.78 and 18.32 µg/mL against human cancer cell lines U937 and HCT-116, respectively) and significantly inhibited the viability of these cell lines (Ashraf *et al.,* 2015). The triterponic acid and betulinic acid extracted from *Z. jujuba* and *Z. mauritiana* showed selective toxicity against cultured human melanoma cells (Kim *et al.,* 1998). Recently, considerable *in vitro* evidence has demonstrated that betulinic acid is effective against small- and non-small-cell lung, ovarian, cervical and head / neck carcinomas (Pisha *et al.,* 1995). Published data suggest that betulinic acid induces apoptosis (Liu *et al.,* 2004) in sensitive cells in a p53-and CD95-independent fashion (Eiznhamer and Xu, 2004).

Conclusion

To conclude, diet rich in fruits has been shown to lower the risk of cancer incidence and other diseases and several phytochemicals that are present in fruits have been scientifically established to have properties that can prevent and treat several diseases including cancer. Minor fruits possess significant potential in disease management, including cancer, due to their rich nutrient content and bioactive compounds. These fruits are valuable sources of vitamins, minerals, phytochemicals and antioxidants that can support overall health and potentially reduce cancer risk. Their ability to combat oxidative stress further strengthens their role in disease prevention. The incorporation of these fruits into the diet can promote well-being, strengthen immunity and contribute to a healthier lifestyle. With growing interest in functional foods, there is a need to explore and promote the health benefits of these lesser-known fruits. Therefore, minor fruits deserve greater recognition for their medicinal value and should be integrated into public health strategies.

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