



**Journal of  
Medicinal Plant Research**

**Volume 10 Number 46, 16 December, 2016**

**ISSN 1996-0875**



*Academic  
Journals*

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**ARTICLES**

**Polyphenols derived from four indigenous Indian fruits for cancer chemoprevention and chemotherapy**

**838**

Sutapa Biswas Majee, Vansh Khattry, Vaibhav Agarwal and Gopa Roy Biswas

Review

## Polyphenols derived from four indigenous Indian fruits for cancer chemoprevention and chemotherapy

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Received 30 October, 2016; Accepted 15 December, 2016

Cancer is one of the major causes of death worldwide, including developing and underdeveloped nations. Mortality and morbidity data suggest that incidences are higher than those of the cardiovascular diseases. High cost and occurrence of numerous side and adverse effects associated with conventional anticancer regimes has necessitated shifting the focus towards the practice of traditional alternative and complementary medicine. Emerging evidence on the beneficial link of dietary components with lower cancer occurrence has been instrumental in determining the course of cancer-related studies. Consumption of fruits rich in polyphenols has proven to inhibit the process of carcinogenesis and tumor growth, with positive outcomes in terms of survival and quality of life of the patient and thus should be encouraged to combat cancer. The objective of the present review is to highlight the underlying mechanisms of apoptosis induced by the different polyphenolic constituents in four Indian fruits, namely litchi, Indian gooseberry, Indian blackberry and *Ziziphus jujube*. However, it must be kept in mind that benefits of consuming fruits rich in polyphenols should not be over-judged through food fortification or supplementation with these active principles. Conclusive evidence of the beneficial effects is yet to come through future studies in humans since most of the data have been obtained from *in vitro* studies.

**Key words:** Polyphenols, flavonoids, anthocyanins, tannins, antioxidant, apoptosis, chemopreventive, chemotherapeutic.

### INTRODUCTION

Several factors have been associated with increased incidences of different types of cancers. They can be categorized as lifestyle behaviors, socio-cultural habits like tobacco smoking and alcohol consumption, intake of unbalanced high-fat, low-fiber diet, foods of low nutritional value, processed and preserved food and meat, presence of aflatoxins in food items, absence of fruits and

leafy vegetables in regular diets, exposure to various levels of environmental pollution, transition metals (Cd, Hg, Pb, Fe and As), certain drugs (cyclosporine, tacrolimus, gentamycin and bleomycin), industrial solvents, cooking (smoked meat, used oil and fat), radiation and xenobiotics. The ultimate consequence of exposure to such high risk factors is "build-up" of free

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radicals in the system due to decomposition and metabolism and over-exploitation of the body's natural anti-oxidant defense mechanisms. Imbalance between free radical production and the defense mechanism leads to development of oxidative stress associated with damage to cell membranes, breakdown of endogenous substances like lipids, proteins, lipoproteins, nucleic acids and finally injury to the tissues. Damaged tissues in turn show increased activity of radical generating enzymes like xanthine oxidase, lipogenase, cyclooxygenase, activation of phagocytes, disruption of the electron transport chains of oxidative phosphorylation, producing excess reactive oxygen species (ROS). ROS contribute to initiation and progression of carcinogenesis by enhancing their metastatic potential. They induce genomic damage, genetic instability, promote cell mobility, induce inflammation/repair and angiogenesis in the tumor microenvironment (Booker and Zuckermann, 2015; Arrabal et al., 2013; Lobo et al., 2010; Pham-Huy et al., 2008; Key et al., 2004; Borek, 2004). Intake of vegetables and fruits has been recommended as a preferable approach in the nutrition and health policies of the governments of the West to mitigate the risks of obesity and different chronic diseases like type 2 diabetes mellitus, hypertension, coronary heart disease (CHD), stroke, chronic inflammatory bowel disease (IBD), rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), asthma, osteoporosis, eye diseases and dementia (Boeing et al., 2012). Patients especially in developing countries have restricted access to conventional anticancer treatment approaches because of huge financial expenditure involved. Moreover, they are associated with considerable damage to the normal tissues. It has been reported in a previous study by Cancer Council of Australia that >10% of cancers including those of lungs, bowel, breast and prostate, can be accounted for due to diets low in fruit and vegetable (Position Statement, 2010). Maintaining a healthy lifestyle and intake of antioxidant-rich diet lowers the risk of cancers and protects the normal cells against untoward adverse effects of anticancer drugs. Inclusion of whole fruit-phytochemical-rich supplements in the diets can delay the onset of cancer by strengthening the army of anti-oxidant enzymes, protecting against the action of carcinogenic stimuli of various types on the target tissues, improving DNA damage repair mechanisms, thereby reducing oxidative damage to DNA and also can arrest progression of cancer and metastasis as in the case of prostate cancer, lung cancer, cancers of the digestive tract, such as cancer of the mouth, pharynx, larynx, oesophagus, stomach and colorectum (Thomas et al., 2015; Vance et al., 2013; Position Statement, 2010; Nutrition and Colon Cancer). Therefore, dietary consumption of fruits can be regarded as a chemopreventive approach which facilitates reversal, suppression or prevention of premalignancy before it develops into an all-invasive and pervasive cancer. Not

only that, daily intake of fruits can also add to the therapeutic benefits and improve safety quotient of conventional antineoplastic drugs and thus can be considered as chemotherapeutics also (Zhao et al., 2015; Chunglok et al., 2014; Srivastava et al., 2014; Sumalatha, 2013).

Phytochemicals, belonging to the polyphenolics have been isolated in large percentages from the edible fruits grown in different geographical regions. They have been isolated in varying proportions from the edible as well as non-edible parts of the fruit. More than 8000 compounds have been isolated and characterized. However, depending on the cultivars, the percentage content of different polyphenolic constituents may vary (Chunglok et al., 2014). Pharmacognostically speaking, polyphenols belong to a class of compounds known as plant secondary metabolites. They play a crucial role in providing protection and defense to the plant species against pests and pathogens (Kabera et al., 2014). Moreover, they have demonstrated a plethora of pharmacological activities and considerable contribution to human health by warding off numerous diseases. They have been studied extensively owing to their ability to act as antioxidants or scavengers of reactive oxygen species (ROS) which has been correlated directly with its beneficial effect on cancer prevention and treatment (Lin et al., 2012; Afify et al., 2011; Lea et al., 2008). They have displayed anticancer effects by targeting different cellular functions and multiple signaling pathways. They are reported to induce expression of genes encoding antioxidant and detoxification enzymes. Most of them have also reported antiproliferative effect on tumor cells and increased sensitivity of cancer cells towards conventional chemotherapeutic agents and radiotherapy. This will ultimately lower the dose, minimize toxicity, will have a positive impact on the ever-increasing economic burden of the society and will finally translate into benefits on human health (Ismail et al., 2016; Afrin et al., 2016).

Polyphenols are polyhydroxylated aromatic phytochemicals and are present as esters with glucose and other carbohydrates (glycosides) or as free aglycones. Depending on the basis of chemical structure, they can be subdivided into 10 different classes. Plant polyphenolics consist primarily of flavonoids (anthocyanidins and anthocyanins, flavonols, flavanols, etc.) and non-flavonoids (tannins, simple phenols, phenolic acids etc.). Tannins present in fruits have been classified as condensed or non-hydrolysable tannins (proanthocyanidins) and hydrolysable tannins (ellagitannins and gallotannins) (Ismail et al., 2016; Lima et al., 2014).

There has been a paradigm shift in the mindset of common people and medical practitioners towards cancer management. Since last few decades, more emphasis is being put on preventive approaches to cut down on the cost of conventional therapeutic modalities like drugs, surgery and radiotherapy. There are instances

and reports of relapse of different cancers, like colon cancers and development of resistance against conventional anticancer agents. The aim of the present review is to elucidate the anticancer effects, molecular mechanisms of different polyphenolic components present in four indigenous Indian fruits, which are easily affordable, available and acceptable to most of the Indian taste. Literature surrounding the chemopreventive and chemotherapeutic effects of consumption of *Litchi chinensis* (litchi), *Phyllanthus emblica* (Indian gooseberry), *Syzygium cumini* (Indian blackberry) and *Ziziphus jujube* is explored here in order to summarize the existing evidences and to determine the future scope of research to integrate these fruit-derived bioactive principles into effective methods for cancer treatment.

### DESCRIPTION OF FRUITS AND SPECTRUM OF PHARMACOLOGICAL ACTIVITIES

Litchi or lychee (*L. chinensis* Sonn; Family: Sapindaceae) is an evergreen tree grown in tropical and subtropical climates of India, China and other countries of South Asia. It is very popular because of its translucent sweet, delicious and juicy pulp. The pulp is of high nutritional value, being rich in vitamin C and several other minerals like copper, potassium and phosphorus. The outer pericarp of the fruit constitutes about 15% of the total weight of the fresh fruit, is pinkish-red in color and has a slightly rough texture. The globose, inedible seeds of the fruit are glossy and deep brown in color. Different parts of the fresh or dried litchi fruit, their extracts or their dried powder forms have been used in Indian herbal medicine and traditional Chinese medicine (Agroforestry database, 2009). Pharmacognostic study and phytochemical screening of different fruit parts has revealed them to be a treasure box of several biologically active molecules. They are reported to possess anti-inflammatory, anti-allergic, anti-flatulent, anti-diabetic, anti-hyperlipidemic, anti-platelet, anti-pyretic, anti-obesity, cardio-protective, anti-viral and anti-cancer effects (Kilari and Putta, 2016; Ibrahim and Mohamed, 2015; Islam et al., 2013; Patel et al, 2012; Zhao et al., 2007). They have been traditionally used to treat gastralgia, neuralgia, cough, hernia-like conditions, blood stasis in women and testicular swelling (Hsu et al., 2012). Litchi seed extract was found to inhibit degradation of collagen, elastin and hyaluronic acid, increase production of collagen in normal human fibroblasts and thus can be effectively used to maintain the tension and moisture of the skin, preventing wrinkles. Inhibition of tyrosinase can be used to use the seed extract in skin whitening (Litchi seed extract ver 6.0, 2012).

*P. emblica* or *Emblica officinalis* (Family: Euphorbiaceae), commonly known as Indian gooseberry and colloquially known as 'amla' or 'amlaki' is consumed whole or as an extract or is a component of traditional

Indian remedy, *Triphala*. In ethnomedicine, it is respected for its high nutritional and medicinal values and is considered an excellent rejuvenating herb and promotes health and longevity (Sawant et al., 2010). The yellowish-green color fruits are smooth, globular and succulent. It has been used to treat pain and inflammation, fever, cancers, fungal and microbial infections. It is also reported to be anti-diabetic, antihyperlipidemic, antiatherosclerotic, antimutagenic, chemopreventive and hepatoprotective. Investigations have revealed that effects of diethylnitrosamine-induced liver cancer, 7,12-dimethylbenz(a)anthracene (DMBA)-induced skin cancer in rats and mice respectively were significantly lower on administration of the aqueous extract of the fruit (Singh et al., 2011; Madhuri et al., 2011). Numerous studies have reported it to be effective against cancers of breast, stomach, pancreas, uterus, skin and also ascites. It can act as antioxidant owing to its inhibitory effect on lipid peroxidation and free radical scavenging activity. Prophylactic use of the fruit extract reduced the genotoxicity and carcinogenicity of toxic elements and benzopyrene in mice (Zhao et al., 2015). Oxidative damage induced by chemicals such as chromium, lead acetate and other factors such as stress, UV rays and aging can be prevented and the fruit can protect and modulate the immune responses of the cells through restoration of production of IL-2 and IFN- $\gamma$ . It has been reported to lower the incidences of side effects observed with chemotherapy and radiation (Saha and Verma, 2015; Pereira and Mallya, 2015; Yang and Liu, 2014; Madhuri et al., 2011). Co-administration of the extract with drugs like cyclophosphamide, doxorubicin and cis-platinum demonstrated a synergistic effect on cytotoxicity towards the cancer cells. There is an evidence of cosmetic effect of the fruit extract as it has been shown to be a safe and effective skin lightener for normal as well as hyperpigmented skin (Chaudhuri et al., 2007).

The third indigenous Indian plant that warrants attention because of its traditional medicinal importance is *S. cumini* (Family: Myrtaceae), whose other well-known synonyms are *Syzygium jambolanum*, *Myrtus cumini*, *Eugenia jambolana*. Common names of the plant are Indian blackberry, black plum, jamun, Malabar plum, jambolan, etc. Its ability to ameliorate multiple disease symptoms and ailments is well-documented in traditional systems of Indian medicine. The different plant parts have been found to be effective in the enrichment of blood, strengthening of teeth and gums, treatment of cough, diabetes, dysentery, indigestion, stomachache, inflammation, blisters in the mouth, pimples and ringworm infections. Development of skin carcinogenesis induced by chemicals and UV-rays could be remarkably suppressed. It also exhibits radioprotective effect (Swami et al., 2012; Muniappan and Panduragan, 2012; Ayyanar and Subhas babu, 2012).

The fruit of *Z. jujube* (Family: Rhamnaceae) is an edible fruit where the ripe fruit is red to purplish-black in color.



The surface of the fruit is not smooth and it resembles a small date (Hoshyar et al., 2015; Gao et al., 2013; Taechakulwanijya et al., 2013). The fruit is delicious and also possesses numerous health benefits like anti-inflammatory, anti-obesity, hepato- and gastrointestinal protective, and anticancer properties (Tahergorabi et al., 2015).

## PHYTOCHEMICAL CONSTITUENTS

### Litchi

The tannin constituents of litchi seeds include litchitannin A1, litchitannin A2, aesculitannin A, epicatechin-(2βOf7,4βf8)-epiafzelechin-(4Rf8)-epicatechin, proanthocyanidin A1, proanthocyanidin A2, proanthocyanidin A6, epicatechin-(7,8-bc)-4β-(4-hydroxyphenyl)-dihydro-2(3H)-pyranone, and epicatechin. Flavonoid glycosides that have also been identified in the litchi seed include litchioside D (-)-pinocembrin 7-O-neohesperidoside, (-)-pinocembrin 7-O-rutinoside, taxifolin 4-O-β-D-glucopyranoside, kaempferol 7-O-neohesperidoside, tamarixetin 3-O-rutinoside and phlorizin. A cyclopropyl containing fatty acid glucoside has also been obtained from the seed (Sui et al., 2016; Lv et al., 2015; Lin et al., 2013). Litchi pulp has been found to be rich in polysaccharides showing antioxidant activity (Huang et al., 2014). Litchi pericarp accounts for 15% of total weight of whole fresh fruit (Li et al., 2012). Polyphenolic compounds with ortho-diphenolic structure are abundant in litchi pericarp. Flavonoids and anthocyanins, like procyanidin B2, B4, epicatechin, cyanidin-3-retinoside, cyanidin-3-glucoside, quercetin-3-retinoside and quercetin-3-glucoside constitute significant percentage of bioactive principles of litchi pericarp (Queiroz et al., 2015; Lin et al., 2013; Wang et al., 2006). Phenolic constituents of litchi pup may exist in free or bound form and their composition depends greatly on selection of proper extraction solvent mixture. It has been reported that the aqueous acetone solvent mixture could effectively extract highest percentage of phenolic, flavonoid and tannin compounds (Su et al., 2014). Different new δ-tocotrienols, macrolitchocotrienol A and meroditerpene chromane, cyclolitchocotrienol A have been detected in the leaves of *L. chinensis* (Lin et al., 2015). There have been reports on phenolic profiles and antioxidant activity of nine commercially available varieties of litchi (Li et al., 2012).

### Indian gooseberry

Diterpenoid molecules like gibberellins, triterpenes, sterols, flavonoids and polyphenols have been isolated from the fruit. Tannins are present in high concentration in the fruit and its extract and include different compounds such as ellagic acid, ellagitannins, corilagin,

isocorilagin, pyrogallol, chebulagic acid, chebulanin, gallic acid, emblicanin, phyllantidin, phyllembin, furosin, geraniin and mallotusininsin. Other hydrolysable tannins that have been isolated include mucic acid gallate, mucic acid lactone gallate, monogalloylglucose, digalloylglucose, putranjivain A, galloyl-HHDP-glucose, elaeocarpusin. Flavonoid constituent, quercetin is also present (Li et al., 2015; Yang and Liu, 2014; Mahata et al., 2013). The fruit is also rich in essential trace elements, vitamin C and several amino acids (Zhu et al., 2013).

### Indian blackberry

Indian plum has been found to be a reservoir of a large number of bioactive principles with potential therapeutic benefits. The principal constituent is anthocyanin and various other chemicals are also present such as glucoside, ellagic acid, gallic acid, oleanolic acid, isoquercetin, kaempferol and myrecetin. Anthocyanins that have been extracted include delphinidin-3-gentiobioside, malvidin-3-lamaribioside, petunidin-3-gentiobioside, cyanidin diglycoside, petunidin, peonidin and malvidin. The anthocyanins contribute to the purple color of the fruit and sourness of the fruit is attributed to the gallic acid. Fruits also contain citric acid, mallic acid, amino acids (alanine, asparagine, tyrosine, glutamine and cysteine). The seeds contain hexahydroxydiphenic (HDDP) acid-derived hydrolysable tannins, terpenes like α-terpineol, eugenol, betulinic acid, flavonoids, sugars (raffinose, glucose and fructose), mineral salts of sodium, potassium, calcium, phosphorus, iron, zinc water-soluble vitamins (ascorbic acid, thiamine, niacin) and proteins. Alkaloid, jambosine and glycoside jambolin or antimellin are also found in the seeds. Although, no anthocyanins could be isolated from the seed, higher percentages of ellagic acid/ellagitannins and total polyphenolics could be detected as compared to that in pulp powder (Charepalli et al., 2016; Chagas et al., 2015; Muniappan and Panduragan, 2012; Ramya et al., 2012; Aqil et al., 2012).

### Ziziphus

Bioactive compounds namely, triterpenic acids, flavonoids, phenolic acids, α-tocopherol, β-carotene; polysaccharides have been isolated from the fruit. A variant of the plant, *Z. jujuba Mill var. Spinosa* has been found to possess eight different flavonoids: swertish (1), puerarin (2), 6<sup>'''</sup>-feruloylspinosin (3), apigenin-6-C-β-d-glucopyranoside (4), spinosin (5), 6<sup>'''</sup>-feruloylisospinosin (6), isospinosin (7), and isovitexin-2<sup>'''</sup>-O-β-d-glucopyranoside (8). The compounds 1, 3 and 5 exist as rotamers (Cheng et al., 2000). Dried jujube fruit has been found to contain ten different triterpenic acids like ceanothenic, alipholic, zizyberanal, zizyberanolic, epiceanothic, ceanothenic, betulinic (BA), oleanolic (OA),

**Table 1.** Principal bioactive polyphenolic constituents of four selected indigenous Indian fruits.

Fruit	Flavonoids (anthocyanidins and anthocyanins, flavonols, flavanols)	Non-flavonoids tannins
Litchi or lychee ( <i>Litchi chinensis</i> )	Litchioside D (-)-pinocembrin 7-O-neohesperidoside, (-)-pinocembrin 7-O-rutinoside, taxifolin 40-O-β-D-lucopyranoside, kaempferol 7-O-neohesperidoside, tamarixetin 3-O-rutinoside, and phlorizin epicatechin-(7,8-bc)-4β-(4-hydroxyphenyl)-dihydro- 2(3H)-pyranone, and epicatechin cyanidin-3-retinoside, cyanidin-3-glucoside, quercetin-3-retinoside and quercetin-3-glucoside	Litchitannin A1, litchitannin A2, aesculitannin A, proanthocyanidin A1, proanthocyanidin A2, proanthocyanidin A6
Indian gooseberry ( <i>Phyllanthus emblica</i> or <i>Emblica officinalis</i> )	Quercetin	Ellagic acid, ellagitannins, corilagin, isocorilagin, pyrogallol, chebulagic acid, chebulanin, gallic acid, emblicanin, phyllantidin, phyllembin, furosin, geraniin and mallotusininsin
Indian blackberry <i>Syzygium cumini</i> or <i>Eugenia jambolana</i>	Delphinidin-3-gentiobioside, malvidin-3-lamaribioside, petunidin-3-gentiobioside, cyanidin diglycoside, petunidin, peonidin, malvidin isoquercetin, kaempferol, myrecetin	Ellagic acid, gallic acid
<i>Ziziphus jujube</i>	Swertish, puerarin, 6 <sup>'''</sup> -feruloylspinosin, apigenin-6-C-β-d-glucopyranoside, spinosin, 6 <sup>'''</sup> -feruloylisospinosin, isospinosin, isovitexin-2 <sup>''</sup> -O-β-d-glucopyranoside	

ursonic and zizyberanolic acids, and two triterpenes, that is, zizyberanolic acid and ursolic acid (UA) (Tahergorabi et al., 2015). Different amino acids, proteins, essential unsaturated fatty acids such as, oleic, linoleic (omega-6), palmitic and palmitoleic acids have also been detected in the dried pulp. Sugars that are abundant include glucose, sucrose and rhamnose. Moreover, it is a rich source of vitamin C, thiamine, riboflavin, niacin, vitamin B6 and also minerals like sodium, potassium, magnesium, zinc and phosphorus.

A summary of the phytochemical constituents of the four fruits chosen in the current review has been presented in a tabular form (Table 1).

## MECHANISMS OF ANTI-CANCER ACTIVITY

### Litchi

Ethanollic extracts of litchi seed have been reported to induce apoptosis and arrest cell growth in G2/M phase in colorectal cancer cell lines, SW480 and Colo320DM, in dose-dependent manner. *In-vitro* and *vivo* growth of S180 sarcoma and Ehrlich Ascites carcinoma (EAC), HepG 2 human liver cancer has been inhibited by the seed extract. Bcl-2/Bax ratio in S180 sarcoma and colorectal cancer cells was altered. Levels of cyclin D1, A and B1 were also lower. The water extract suppressed the CNE-2Z cell proliferation in cases of nasopharynx cancer. Telomerase activity in liver cancer cells is reduced by administration of the aqueous extract. The

seeds have also been found to exert cytotoxic effects on breast cancer cell line, MCF-7, human neuroblastoma SH-SY5Y cells, cervical cancer and lung cancer. Apoptosis occurs as a result of inhibition of expression of the signaling molecule, NF-Kβ followed by decreased expression of p65 unit and finally reduction in the levels of antiapoptotic members of Bcl-2 family. The caspase cascade is activated and expression of Fas protein is stimulated (Zhang and Zhang, 2015). Production and secretion of cytokines, epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), platelet derived growth factor (PDGF) and tumor necrosis factor-α (TNF-α) and inflammatory factors, IL-1, TNF-α, IFN-γ is facilitated by litchi seed extract (Lin et al., 2013; Hsu et al., 2012).

High molecular weight compounds are present in the fresh pulp of the fruit whereas lower weight compounds occur in the dried pulp. Higher cytotoxicity was observed with the dried pulp with additional anti-inflammatory activity. Dried pulp induced strong stimulation and proliferation of B lymphocytes. It is also responsible for inhibition of ConA-induced proliferation of splenocytes when there is a competition with ConA for the specific receptor (Huang et al., 2014).

The crude ethanollic pericarp extract (PE) has demonstrated strong dose- and time-dependent anticancer activity on human breast cancers. Various mechanisms have been postulated for DNA damage and induction of apoptotic effects of the extract in the tumors. Up-regulation of the genes (CYP1A1 and ADPRTL1) and down-regulation of the genes (BIRC3, ADAM9 and

HMMR) exhibit an effect on cell cycle regulation and hence, cell proliferation. Signal transduction and transcription processes are also affected (Wang et al., 2006). The anticancer activity has been attributed to the three flavonoid constituents: epicatechin, proanthocyanidin B2 and proanthocyanidin B4, although there was a difference in the degree of cytotoxicity to the cancer cells, which was lower than that of paclitaxel in all the cases. The ethyl acetate fraction demonstrated immunomodulatory effect on mouse splenocytes *in vitro* (Zhao et al., 2007). Microbial transformation of litchi pericarp extract by *Aspergillus awamori* GIM 3.4 results in modification of percentage content of bioactive principles and hence, the extent of biological activity. Presence of flavonoid-degrading enzymes in the microorganism led to decrease in flavonoid content and increase in 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity and elevated antioxidant activity from the extract in the fermentation broth. DNA protection was attributed to the occurrence of catechin and quercetin in the fermented aqueous extract of the fruit pericarp (Lin et al., 2012).

### Indian gooseberry

Anticancer activity can be partly attributed to the antioxidant action mediated through the numerous polyphenolic constituents of the fruit. Detailed study has been carried out to elucidate the mechanism of anticancer effect of the amla extract on cervical cancer cells. It down-regulates the expression of AP-1 protein component and other proteins controlled by AP-1 in redox transcriptional apparatus as well as induce complete and partial abrogation of constituent members of the DNA-binding proteins such as c-Jun, JunB, JunD and c-Fos. All these effects controlling the signaling pathway for AP-1 expression led to dose-dependent suppression of HPV 16 and HPV 18 transcription resulting in inhibition of viral oncogene expression. The AP-1 inhibitory activity of the fruit was found to be species-specific. Regulation of upstream signaling events through inhibition of ERK1/2 and JNK was also observed (Mahata et al., 2013). NF- $\kappa$ B inhibition is mediated primarily through chebulagic acid, ellagic acid, corilagin and gallic acid and ultimately leads to apoptosis of the cancer cells. Investigations on the cytotoxic effects of corilagin on ovarian cancer cell lines SKOV3ip, Hey and HO-8910PM revealed induction of cell cycle arrest at G2/M phase and thus, programmed cell death via attack on the TGF- $\beta$ /AKT/ERK/Smad signaling pathways (Yildirim and Kutlu, 2015). On the other hand, quercetin induces apoptosis by inhibiting growth factor signaling pathways such as EGFR and hence modulating the relay process of oncogenic growth signals (Zhao et al., 2015). The extract has been found to be effective against a battery of cancer cell lines such as A549, HepG2, HeLa,

MDA-MB-231, SK-OV3 and SW620. HeLa cell proliferation was inhibited by arresting the cells in G2/M phase. Moreover, karyomorphism of the cells was also affected followed by triggering of apoptotic pathway. Levels of three molecular markers of apoptotic pathway, Fas, FasL and cleaved caspase-8 were also found to be elevated in the extract-treated HeLa cells (Zhu et al., 2013).

### Indian blackberry

The aqueous seed extract has been found to reduce the chromosomal damage induced by 7,12-dimethylbenz[a]anthracene (DMBA) to mice. Administration of methanolic extract lowered the formation of hepatic malondialdehyde, less formation of micronuclei and lower cytotoxicity towards bone marrow cells. In both cases, lipid peroxidation was strongly inhibited which was also evident from higher levels of antioxidant enzymes like glutathione-S-transferase, superoxide dismutase and catalase. These phenomena collectively are responsible for antioxidant activity of the fruit (Chagas et al., 2015). In another study, it was revealed that kaempferol 7-O-methylether and sitosterol, present in the ethanolic fruit extract were responsible for the free-radical scavenging activity and hence, anticancer activity (Afify et al., 2011). Gallic acid inhibited the expression of Cdc2, Cdk2, Cdk4, Cdk6, cyclin B1 and E, thereby triggering apoptosis in cancer cells. Kaempferol and betulinic acid have been reported to inhibit the enzymes, phosphatidylinositol 3-kinase and ornithine decarboxylase, respectively. Anthocyanins present in the blackberry are able to arrest the growth of cancer cells selectively. Presence of ellagic acid/ellagitannin along with anthocyanins potentiated the chemoprotective and chemopreventive effects of jamun fruit extract. Anti-proliferative effect of the hydrolysed jamun pulp and seed extract was more against human lung cancer A 549 cells than the unhydrolysed extract (Aqil et al., 2012). Recurrence and metastasis of non-small cell lung cancer has been suppressed synergistically by administration of less-than-optimum concentrations of blackberry equimolar anthocyanidins with little or no effects on normal cells. The observed effects have been greater than in the case of individual anthocyanidins. The mixture exhibited regulation on oncogenic Notch and WNT pathways and their numerous downstream targets followed by cleavage of Bcl-2 and PARP and inhibition of TNF $\alpha$ -induced activation of NF- $\kappa$ B, leading to apoptosis (Kausar et al., 2012). Delphinidin inhibited the phosphorylation of protein kinases in ERK/JNK signaling pathways leading to suppression of AP-1 transactivation. In case of UV-irradiated cancer, cyclooxygenase-2 expression was suppressed through inhibition of MAPKK4 and PI-3 kinase (Swami et al., 2012). The extract could effectively act against early stage HCT-116

human colon cancer cells and also triggered apoptosis and prevented self-renewal of colon cancer stem cells. Release of mitochondrial protein cytochrome c leads to activation of caspase cascade with elevated levels of caspase-3 and caspase-7, resulting in DNA fragmentation and culminating in apoptotic cell death. Urolithin A, a metabolite of ellagitannin was also responsible partly for protective effect against colon carcinoma (Charepalli et al., 2016). However, there was no indication of apoptosis in untransformed breast cancer cell line, MCF-10A, although the markers of apoptosis could be detected in MCF-7 and estrogen-dependent MCF-7aro as well as estrogen receptor-negative MDA-MB-231 cell lines, when studied *in vitro*. Over-expression of aromatase was more effectively suppressed in MCF-7aro cells (Li et al., 2009).

### Ziziphus

Betulinic acid, oleanolic acid and ursolic acid have demonstrated cytotoxic effects. Among these three triterpenic acids, UA and OA are structurally similar, differing only in the position of the methyl group in the E loop. They were effective in inducing apoptosis in lung adenocarcinoma, human colon carcinoma cell line HC T-15, HL-60 leukemia cells, B16F10 melanoma cells, MCF-7 breast cancer cells, and DU-145 prostate cancer cells. UA exerts anticancer activity in lung cancer cells through inhibition of catalytic activity of Vaccinia-related kinase -1 (VRK-1). Cell survival is thus affected. It also blocks VRK-1 induced 53BP1 foci formation and is responsible for improved efficacy during co-administration with DNA-damaging anticancer drugs (Kim et al., 2015). Since, UA is a multi-tasking agent, it can induce death of different cancer cell lines via different mechanisms. Inhibition of growth and proliferation, modulation of JNK, Akt and mTOR signaling pathways, induction of apoptosis through intrinsic and extrinsic death pathways, suppression of FoxM1 protein expression have been postulated as mechanisms for anticancer effect of UA on breast cancer cells. Melanoma is inhibited through regulation of mitochondrial intrinsic pathway, activation of p53 and caspase-3 expression, suppression of NF- $\kappa$ B mediated activation of Bcl-2 and promotion of differentiation by suppression of endogenous reverse transcriptase. Apoptosis is induced in prostate cancer cells via Beclin-1 and Akt/mTOR pathway. Downregulation of CXCR4 is also observed (Wozniak et al., 2015; Shanmugam et al., 2013). Selective cytotoxic effect has been shown by pentacyclic triterpene, BA on xenograft mouse models of human melanoma and neuroectodermal tumors (neuroblastoma, glioblastoma and medulloblastoma) with minimal effects on non-tumorigenic cells. Thus, BA is better than common anticancer drugs like camptothecin, taxol, vincristine, vinblastine, etoposide and elipticine (Patocka, 2003). BA

can exert cytotoxic effect via both apoptotic and non-apoptotic pathways. It can induce loss in mitochondrial membrane potential without affecting the caspase inhibitor. Alternatively, it can also activate NF- $\kappa$ B in some cancer cell lines. Overexpression of the enzyme aminopeptidase N in different cancers can be inhibited by BA which can regulate angiogenesis (Tahergorabi et al., 2015; Csuk, 2014). A recent study has demonstrated the role of bioactive components in Ziziphus in arresting the growth and proliferation of different breast cancer cell lines by boosting the activities of anti-oxidant enzymes and inducing apoptosis (Bonofiglio et al., 2016). Treatment of breast cancer induced by N-Methyl-N-Nitrosourea (NMU) in rats with jujube extract showed good results with alteration in levels of serum LDH, ALP, total protein and albumin (Hoshayar et al., 2015). Free radical scavenging capability of jujube methanolic extract was attributed to the presence of phenolic compounds and polysaccharides. The methanolic extract consisting of triterpenoids and polysaccharides also exhibited *in vitro* inhibitory effect on proliferation of breast cancer cells, human liver and skin cancer cells (Liu et al., 2016). Mechanism other than apoptosis was responsible for cell death in case of HeLa and Hep2 cell lines. BA has been reported to exhibit synergistic effect with vincristine in an *in vivo* model of metastatic melanoma in mice. Aqueous extract of jujube containing deproteinised polysaccharide arrested the growth of melanoma cells in the G2/M phases in dose- and time-dependent manner. Elevation in the activities of caspase-3 and caspase-9 were observed and apoptotic bodies were formed (Tahergorabi et al., 2015).

A comprehensive analysis of the major mechanisms responsible for anticancer effects of the fruits or fruit parts or their extracts is provided in Table 2.

### FUTURE PERSPECTIVE

There exists significant differences in the phytochemical profile and their corresponding biological activities in different cultivars of the same plant collected from different geographical regions, in different stages of maturation and different conditions of harvesting and storage. Use of synthetic pesticides or adoption of principles of organic farming can produce remarkable changes in the content of polyphenol-based plant secondary metabolites (Li et al., 2009, 2015). Moreover, a single fruit extract usually contains numerous polyphenolic compounds, belonging to different classes and subclasses. Therefore, well-characterized and standardized methods for total profiling of individual constituents in the cultivated variety of the fruit and its extract are essential to be more beneficial in cancer prevention and therapy. Development of genetically modified higher-polyphenol producing plants and hybrid plants through breeding is a viable option to be

**Table 2.** Anti-carcinogenic effects of fruit/part/extract in *in vitro* models of cancer.

Sample type	Model cell lines or animals	Proposed mechanisms for anticancer effect
<b>Litchi</b>		
Ethanol extract of seed	SW480, Colo320DM, S180 sarcoma, EAC, HepG 2	Alteration in Bcl-2/Bax ratio Lower levels of cyclin D1, A and B1
Aqueous extract of seed	Liver cancer cells	Lowering in activity of telomerase Inhibition of expression NF-K $\beta$ Decreased expression of p65 unit
Seeds	MCF-7, human neuroblastoma SH-SY5Y cells, cervical cancer and lung cancer	Reduction in the levels of Bcl-2 proteins Activation of caspase cascade Stimulation of expression of Fas protein Induction of apoptosis
Pulp or extract		No concrete mechanism proposed
Ethanol extract of pericarp	Breast cancer cell line	Up-regulation of the genes (CYP1A1, ADPRTL1) Down-regulation of the genes (BIRC3, ADAM9, HMMR) Anti-proliferative
<b>Indian gooseberry</b>		
	Ovarian cancer cell lines :SKOv3ip, Hey and HO-8910PM Cervical cancer cells	Attack on the TGF- $\beta$ /AKT/ERK/Smad signaling pathways Inhibition of DNA-binding proteins such as c-Jun, JunB and JunD and c-Fos Down-regulation of AP-1 expression Inhibition of viral oncogene expression NF-K $\beta$ inhibition
<b>Indian blackberry</b>		
Aqueous seed extract	Human lung cancer A 549 Early stage HCT-116 human colon cancer cells	Free radical scavenging activity Regulation on oncogenic Notch and WNT pathways Cleavage of Bcl-2 and PARP Inhibition of TNF $\alpha$ -induced activation of NF-K $\beta$ Apoptosis Release of mitochondrial protein cytochrome c Activation of caspase cascade DNA fragmentation Apoptotic cell death
<b>Ziziphus</b>		
	Breast cancer cells Lung cancer cells	Inhibition of growth and proliferation, Modulation of JNK, Akt and mTOR signaling pathways, Induction of apoptosis through intrinsic and extrinsic death pathways, Inhibition of catalytic activity of Vaccinia-related kinase -1(VRK-1)

be investigated in future. The pharmacokinetic profile, dose requirement, toxicity studies and dosage form selection should be carried out on each of the active principles and also on its rational combination (Ismail et al., 2016). Synthesis of patentable, more effective, less toxic and more water-soluble derivatives of the principles present in the fruit or in an extract will open up new avenues. An important issue that warrants immediate attention is that most of the trials have been conducted *in vitro*. Thus, there is an urgent need for animal studies and finally human trials (Lima et al., 2014). It is

noteworthy to mention that although inclusion of fruits in the regular diet has proven beneficial, consumption of foods fortified with polyphenolic bioactive principles in large quantities, should not be encouraged (Halliwell, 2007).

## CONCLUSION

Different types of polyphenolic constituents in the four selected indigenous fruits of India have been shown to

possess antioxidant and anti-proliferative effect. They induce apoptosis via different mechanisms on different types of cancer cell lines with minimal effect on normal cells. Oxidative stress induced by exogenous harmful chemicals or stimuli can be effectively lowered by intake of fruits. Efficacy of standard chemotherapeutic drugs has been augmented by administration of the fruit extract and they have also demonstrated radio-protective effect. Easy availability and affordability of the above-mentioned widely grown fruits across different geographical regions of India can be suitably exploited to develop novel chemopreventive and chemotherapeutic agents from their extracts in the near future.

### Conflicts of Interests

The authors have not declared any conflict of interests.

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