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Cancer chemopreventive pharmacology of phytochemicals derived from plants of dietary and non-dietary origin: implication for alternative and complementary approaches

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Abstract The poor survival statistics of the fatal cancer diseases highlight the need for multiple alternative treatment options. An impressive embodiment of evidence shows that naturally occurring herbal products contain a wide variety of phytochemicals that are regarded as effective cancer protective agents, possessing the ability to retard, block or reverse carcinogenesis. These include dietary agents often termed as nutraceuticals and also the components of non-dietary plants. Many studies in different cell lines, animal models and human epidemiological trials suggest a protective role of a large number of medicinal molecules of herbal origin against different types of cancers. The standard chemotherapeutic regime against cancer faces an unequivocal challenge due to the severity of the side-effects and the post therapeutic management of the disease. Cancer control may therefore benefit from the anti-cancer potential of alternative therapies that may include herbal treatment which nonetheless has been an effective curative strategy reported for a number of diseases since ancient times. In congruence of the above idea, it has been observed that in recent years the demand to utilize alternative approaches to the treatment of cancer is escalating. Additionally, the emergence of resistance to cancer chemotherapy has forced researchers to turn to natural products of herbal and marine origin. Currently, in the armamentarium of anti-cancer pharmaceuticals there are effective plant-derived drugs such as paclitaxel (a complex taxane diterpene isolated from the bark of *Taxus brevifolia*) which acts as microtubule disruptor. Further there are plant-based dietary agents such as sulphoraphane (an isothiocyanate derived from cruciferous vegetables) and non-dietary agents such as pomiferin (an isoflavonoid from *Maclura pomifera*) which strongly mimic chemotherapeutic drugs such as vorinostat (suberoylanilidehydroxamic acid) possessing histone diacetylase inhibition activity. In this review we provide a comprehensive outline of the translational potential of plant-based herbal medicine for complementing the current treatment modalities as an adjuvant or alternative therapy for cancer patients.

Keywords Phytochemicals · Chemoprevention · Alternative and complementary therapy

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Introduction

According to the report of the American Cancer Society, Cancer Statistics 2014, more than 1.66 million new cases of cancer will be diagnosed and an alarming number of around 585,720 mortalities from cancer will occur in USA alone, in the year 2014 (Siegel et al. 2014). Cancer is responsible for approximately 13 % of deaths worldwide (WHO 2011) and remains a growing health problem around the world particularly with the steady rise in life expectancy. Cancer development is a dynamic, long-term and multistage process that involves many complex factors in its initiation, promotion, and progression. During this process, accumulation of genetic and epigenetic alterations leads to the progressive transformation of a normal cell into a localized tumor mass which later metastasize to near and distant tissues and organs. Cancer cells acquire immunity against physiologically imposed restrictions to growth and division by their ability to posses: (1) self-sufficiency in growth signals, (2) insensitivity to anti-growth signals, (3) evasion of programmed cell death (apoptosis), (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion and metastasis (Hanahan and Weinberg 2000). Thus it is understood that cancer as characterized by the dysregulation of multiple cell signaling pathways, has the ability to evade current anticancer therapies involved in the modulation of single target. However, the data obtained from the anti-cancer pharmacological profiling of large number of plant-derived dietary and non-dietary agents have re-christen the potential value of herbal medicine as they exhibit pleiotropic action mechanism simultaneously influencing multiple pathways.

Approximately 60–80 % of the world's population still relies on traditional medicines for the treatment of common illnesses (WHO 2002; Patwardhan et al. 2005) and such a statistic also supports the potential of herbal constituents as an evidence-based complementary therapy for chronic disorders including cancer. It is estimated that Chinese, Indian, Arabian and other traditional systems of medicines make extensive use of about 5,000 plants and that more than 3,000 different plant species have been used to treat cancer worldwide (Mooi et al. 2012). China has demonstrated the best use of traditional medicine in providing the health care by pharmacologically validating and improving many traditional herbal medicines and eventually integrating them in formal health care system for common illnesses as well as fatal disorders such as cancer (Zhou et al. 2008). In a recent publication, a newly established database "NPACT: Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target database" reported 1,574 compounds from plant sources possessing anticancer properties against various cancer types, validated through evidence from in vitro and in vivo studies (Fig. 1) (Mangal et al. 2013). Chemoprevention using plant-derived dietary and non-dietary factors is an effective approach to extend the latency period of carcinogenesis in humans which will mean a better quality life before death by some other cause (Sporn and Suh 2002). In this regard such factors interfering with tumor development are of potential clinical value as they possess elevated margin of safety and desired range of efficacy. In one such study examining the efficacy of the pharmacological molecules of herbal origin, triterpenes such as 3-*O*-caffeoyloleanolic acid, betulinic acid, euscaphic acid and ursolic acid were isolated from the stem bark extract of *Physocarpus intermedius* as active principles responsible for the cytotoxicity against a panel of human tumor cell lines, i.e., A549 (non-small cell lung), SK-OV-3 (ovary), SK-MEL-2 (melanoma) and HCT-15 (colon), in vitro. The study reported the anticancer activity of these triterpenes against the A549 lung cancer cells in the increasing order of potency (represented as ED50); ursolic acid (4.2 mg/ml), euscaphic acid (3.7 mg/ml), betulinic acid (2.0 mg/ml) and 3-*O*-caffeoyloleanolic acid (1.6 mg/ml). The ED_{50} for all these agents were significantly lower compared to the standard anti-cancer drug cisplatin (11.4 mg/ml) and thus were shown to be more effective (Kim et al. 2000).

Increasing interest in natural product pharmacology has led to the identification of phytochemicals which could interfere with key cellular signaling pathways (Fig. 2) with significant alterations observed in cancer cells (Lee et al. 2013). Protein Kinase C (PKC) plays essential roles in multiple cellular signal transduction pathways and in cancer cells, PKC has been known to play its vital role in tumor development and maintenance of malignant phenotype and thus has been identified as one of the prime anti-cancer targets (Griner and Kazanietz 2007). In a recent study, Mooi et al. (2012) have demonstrated the ability of maslinic acid, a natural tri-terpene to suppress the expression of PKC βI, δ, and ζ in human B-lymphoblastoid cells in a

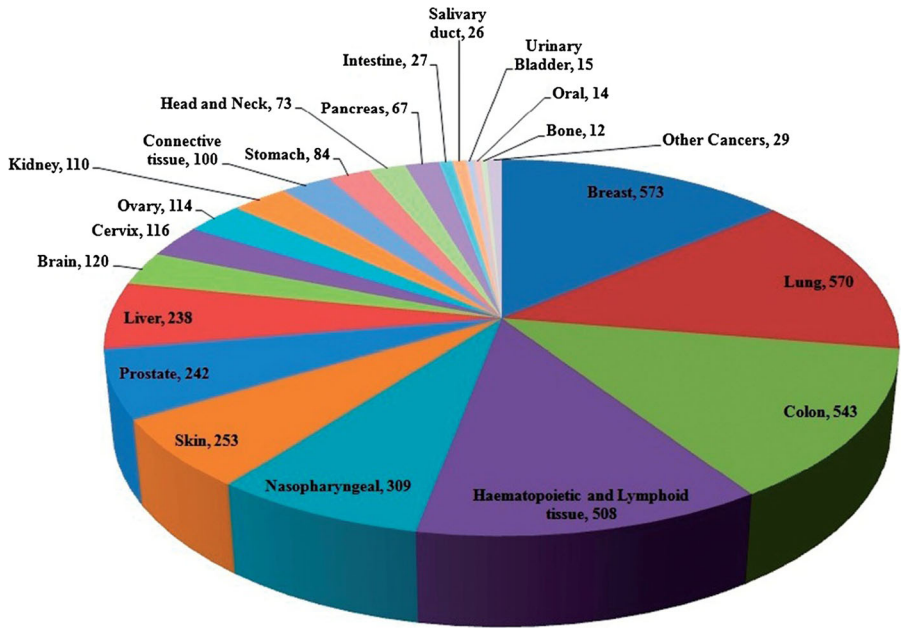

Fig. 1 Cancer-wise distribution of the plant-derived natural compounds in NPACT database. Reproduced from the original source (Mangal et al. 2013) with permission of Oxford publishing Ltd

concentration-dependent manner. It needs a mention that herbal-based phytochemicals of non-dietary origin such as those described above serve as leads for anticancer drugs and their exposure is intended for therapeutic regimen. However an added advantage to natural product armamentarium is that it has hundreds of photochemical from the dietary sources such as fruits, vegetables and spices. These diet-derived agents have also been shown to possess effective anti-cancer properties and thus play a strong role in not only the therapeutic regimen but also in prophylactic regimen to prevent the risk of cancer incidence. It has been estimated that more than two-third of human cancers could be prevented through appropriate lifestyle modification including dietary habits as the chances of developing cancer are significantly affected by the choice of our lifestyle (Khan et al. 2010). In this regard a transition has been observed in the recent decade which may be called as "herbal renaissance" showing people being attracted towards ethnic cuisines (derived from vegetable, fruits and spices) based on perceived health benefits (Christine and Milner 2011). It has been reported that about 75 % of U.S. households use dietary approaches to reduce their risk of diseases including cancer (Christine and Milner 2011; Sloan 2005) a philosophy widely accepted and practiced in countries like India and China for centuries. Dietary nutraceuticals have attracted much attention in cancer chemoprevention primarily due to the four distinct advantages associated with these agents; their diverse structure, pleiotropic action mechanism, significantly lower toxicity and selective killing of cancer cells (by certain dietary agents). Many of such dietary sources have been shown to be strongly associated with chemopreventive and therapeutic properties against cancer (Ahmad et al. 2013a, b, c, 2014). These include Pomegranate (ellagic acid and delphinidin as principal bioactive components) (Adhami et al. 2009), Soy (isoflavones such as genistein and daidzein) (Adlercreutz 2002), black berries and red grapes (stilbenes such as resveratrol) (Jang et al. 1997), Crucifers (isothiocyanate such as sulforaphone) (Qazi et al. 2010), citrus fruits (ascorbic acid) (Ullah et al. 2012), spices turmeric and black seeds (curcumin and thymoquinone respectively) (Chauhan 2002; Banerjee et al. 2009). In the underlying sections we focus on providing an evidence based overview of the translational potential of dietary and non-dietary plant-derived agents (Fig. 3) with substantial evidence from epidemiological, pre-clinical and clinical studies for complementary management of cancer disease.

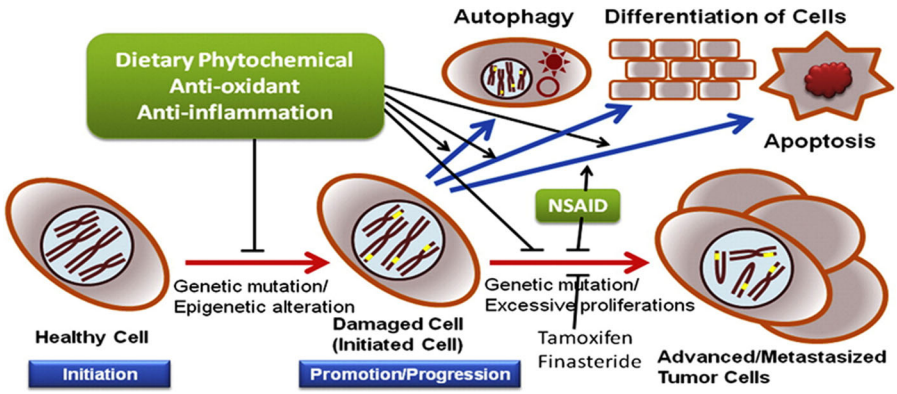

Fig. 2 Cancer chemoprevention strategy using dietary phytochemicals: Applying dietary phytochemicals at the early stage of carcinogenesis may block further development of carcinogenesis. Treatment with dietary phytochemicals and/or relatively non-toxic therapeutic drugs on cancer cells may induce positive results, including autophagy, cell cycle arrest, apoptosis, and differentiation, and may block tumor development. Reproduced from the original source (Lee et al. 2013) with permission of Elsevier Inc. Ltd

Evidence of cancer chemopreventive properties of plant-derived agents

Terpenoids

Terpenoids composed of isoprenoid units constitute one of the largest groups of natural products accounting for more than 40,000 individual compounds (Thoppil and Bishayee 2011). Studies on the development of anti-cancer drugs derived from non-dietary natural products have led to the identification of a variety of terpenoids that inhibit cancer cell proliferation and are considered strong candidate for anti-cancer chemopreventive regimen (Huang et al. 2012). Currently, several phase I/II clinical trials have been initiated to evaluate the chemopreventive as well as the anticancer efficacy of a number of tri-terpenoids (Liby et al. 2007; Fulda 2009).

Epidemiological and experimental studies suggest that mono-, di- and tri-terpenoids may be helpful in the prevention and therapy of several cancers, including mammary, skin, lung, forestomach, colon, pancreatic and prostate carcinomas (Kris-Etherton et al. 2002; Gould 1997; Reddy et al. 1997; Vigushin et al. 1998; Crowell 1999; Burke et al. 2002; Carvalho and Fonseca 2006; Barile et al. 2008; Corea et al. 2009). Numerous preclinical efficacy studies have provided extensive evidence that both naturally occurring and synthetic derivatives of triterpenoids possess chemopreventive and therapeutic effects against colon, breast, prostate and skin cancer (Liby et al. 2007; Chaturvedi et al. 2008; Rabi and Gupta 2008; Mullauer et al. 2010; Bishayee et al. 2011; Patlolla and Rao 2012; Lanzotti et al. 2012; Zolfaghari et al. 2013).

Chinese traditional medicine system has included terpenoids isolated from the species of *Rhizoma Curcumae* as approved anti-cancer therapeutics for use in Chinese medicine (The State Pharmacopoeia Commission of P.R. China, 2005). Pharmacological studies on terpenoids isolated from *Rhizoma Curcumae*, including β-elemene, δ-elemene, furanodiene, furanodienone, curcumol, and germacrone, have shown these to be related to the retardation of cell cycle arrest, induction of apoptosis, and inhibition of metastasis or tissue invasion (Lu et al. 2012). Elemene has already been approved by China's State Food and Drug Administration as an anti-cancer adjuvant drug and has been prescribed as a part of some cancer treatment regimens in China. As reviewed elegantly by Lu et al. (2012) β-elemene exhibits broad-spectrum anti-cancer activity against many types of cancer cells, including leukemia, brain, breast, prostate, ovarian, cervical, colon, laryngeal, and lung carcinoma cells. Moreover, it was reported that β-elemene exhibits low toxicity to normal cells (Li et al. 2005a, b, c; Wang et al. 2005). Furanodiene, a sesquiterpene exhibits growth inhibitory properties towards HeLa, Hep-2, HL-60, PC-3, SGC-7901, MCF-7, MDA-MB-231, and HT-1080 cancer cell lines (Zhong et al. 2012; Sun et al. 2009) as well against in vivo growth of tumors in

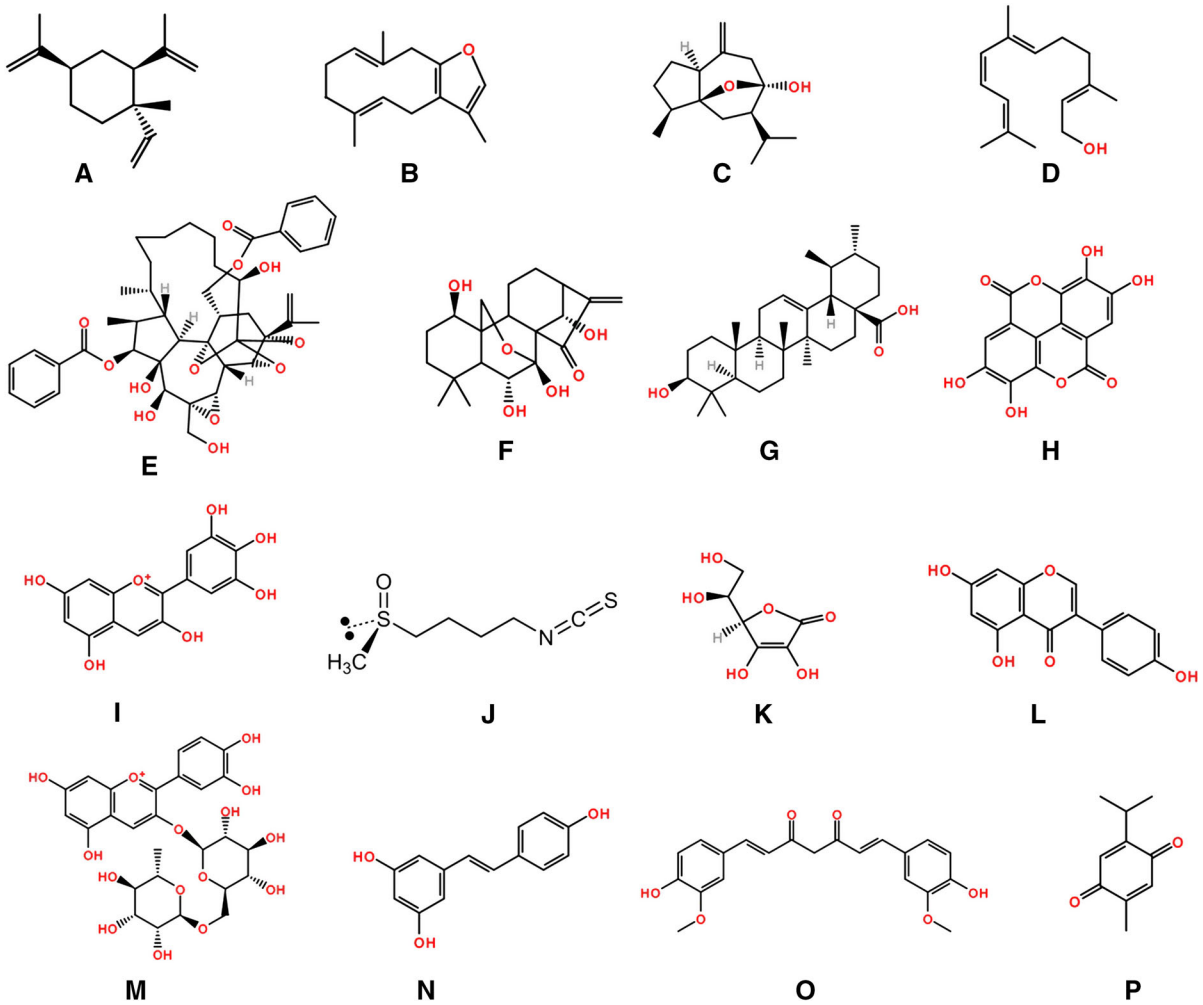

Fig. 3 Chemical structures of certain plant derived chemopreventive agents as described: **a** β-elemene; **b** Furanodiene; **c** Curcumol; **d** Farnesol; **e** Gnidimacrin; **f** Oridonin; **g** Urosolic acid; **h** Ellagic acid; **i** Delphinidin; **j** Sulphoraphane; **k** Ascorbic acid; **l** Genistein; **m** Cyanidin-3-*O*-rutinoside; **n** Resveratrol; **o** Curcumin; **p** Thymoquinone

mice (Zheng et al. 2008). Curcumol, another sesquiterpenoid inhibits the proliferation of MCF- 7, MM-231, HeLa, and OV-UL- 2 cancer cells and has been shown to have negligible effects on normal breast cells (Xu et al. 2005). A dose of 50 mg/ml of curcumol significantly inhibits the total RNA synthesis in MCF-7, MM-231 and HeLa cells (Xu et al. 2005). Curcumol has been reported to cause concentration-dependent cell death in human lung adenocarcinoma ASTC-a-1 cells and to induce G2/M phase arrest (Zhang et al. 2011). The sesquiterpene farnesol inhibited the incidence and mean number of visible hepatocyte nodules, as well as the size of total, persistent and remodeling GSTp-positive preneoplastic lesions (Ong et al. 2006). Gnidimacrin, a daphnane-type diterpenoid, was reported to inhibit the growth of protein kinase C βII gene-transfected human hepatoma HLE cells through G2 phase arrest (Yoshida et al. 2009). In another study oridonin, a diterpenoid isolated from *Rabdosia rubescences*, promoted cytotoxic activities against HepG2 cells through an increase in the apoptotic cell death and reactive oxygen species (ROS) generation (Huang et al. 2008).

Traditional Chinese medicinal herbs, such as *Hedyotic diffusa* and *Radix actinidiae*, are commonly used in colorectal cancer treatment in China. Ursolic acid, a pentacyclic triterpene acid is an active compound present in these herbs. Studies showed that

ursolic acid had strong inhibitory effects against a number of cancer cell lines (Subbaramaiah et al. 2000; Shishodia et al. 2003). Ursolic acid inhibits proliferation and induces apoptosis of HT-29 human colon cancer cells by inhibiting the EGFR/MAPK pathway (Shan et al. 2009). It also inhibited the growth of HT-29 cells in dose- and time-dependent manners. The median inhibition concentration (IC_{50}) values for 24, 48, and 72 h treatment were 26, 20, and 18 μmol/l, respectively leading to the apoptotic rates up to 40.5 % for the highest dose. In a recent study using transgenic adenocarcinoma of mouse prostate (TRAMP) mice, the effect of diet enriched with 1 % w/w ursolic acid was investigated to evaluate the stage specific chemopreventive activity against prostate cancer (Shanmugam et al. 2012). It was reported that TRAMP mice fed with UA diet for 8 weeks delayed formation of prostate intraepithelial neoplasia (PIN). Other group in which mice were fed with urosolic acid diet for 6 weeks inhibited progression of PIN to adenocarcinoma as determined by hematoxylin and eosin staining. Further, TRAMP mice fed with tri-terpinoid diet for 12 weeks demonstrated markedly reduced tumor growth without any significant effects on total body weight and prolonged overall survival. Another study explored the effect of ursolic acid on the growth of gastric cancer cell line BGC-803 and hepatocellular cancer cell H22 xenograft (Wang et al. 2011). It was demonstrated that the agent inhibited growth of BGC-803 cells in vitro in a dose-dependent and time-dependent manner and also lead to inhibit the progression of tumor cells which were found to be arrested at G0/G1 stage. The apoptotic rate was significantly increased in tumor cells treated with urosolic acid both in vitro and in vivo. The treatment leads to DNA fragmentation in BGC-803 and enhanced expression of activated caspase-3, -8, and -9 and down regulated expression of Bcl-2 in BGC-803 cells. Moreover, the expression of caspase-3 and -8 was also elevated in tumor cells from xenograft treated with tri-terpenoid agent. Interestingly, ^{18}F-FLT PET-CT imaging confirmed the effectiveness of the chemopreventive terpenoid against tumor growth. Further, ursolic acid inhibited the proliferation of different colon cancer cell lines which correlated with inhibition of constitutive NF-κB activation and down-regulation of cell survival (Bcl-xL, Bcl-2, cFLIP, and survivin), proliferative (cyclin D1), and metastatic (MMP-9, VEGF, and ICAM-1) proteins. The observations were extrapolated in animal model as when examined in an orthotopic nude mouse model, ursolic acid significantly inhibited tumor volume, ascites formation, and distant organ metastasis (Prasad et al. 2012). The study further reported that urosolic acid enhance the therapeutic effects of capecitabine (chemosensitization) through the suppression of multiple biomarkers linked to inflammation, proliferation, invasion, angiogenesis, and metastasis. Moreover, urosolic acid also significantly potentiated the apoptotic effects of thalidomide and bortezomib in multiple myeloma cells, thus showing its translational value as adjuvant therapy (Pathak et al. 2007). Taxanes, the remarkable cytotoxic di-terpenes derived from natural products (Fauzee et al. 2012) act as mitotic inhibitors with strong anticancer properties reported from numerous experimental and clinical trials for breast, ovarian, lung, prostate, pancreas, gastric and head and neck cancer (Tannock et al. 2004; Khan et al. 2003; Roth and Ajani 2003; Nabell and Spencer 2003). As reviewed by Fauzee et al. (2012), the taxanes mainly include paclitaxel (Taxol) and docetaxel (Taxotere) as well as taxanes homologs, which are derived from natural sources. The popular taxol is derived originally from *Taxus Brevifolia* (bark of Pacific yew/Western yew conifers) (Wani et al. 1971) while docetaxel is an esterified derivative of 10-deacetylbaccatin-III (10-DAB) extracted from *Taxus Baccata* (needles of European yew tree) (Bissery et al. 1991). In 2005, FDA approved Abraxane®, a nanoparticle paclitaxel (nab-paclitaxel) from Abraxis Bioscience in breast metastasis and the findings were followed in June 2010, when clinical outcome in NSCLC (non-small cell lung cancer) again proved its efficacy in clinical trials (Fauzee et al. 2012; Pazdur 2005; Gen news highlights 2010).

Pomegranate (*Punica granatum*)

Pomegranates have been used extensively in folk medicine in many cultures. The fruit of the tree *Punica granatum*, grown mainly in the Mediterranean region, has a vast ethno-medical history highlighting many medicinal properties (Longtin 2003). Recent studies have shown the ability of pomegranate extracts to inhibit the growth of breast, prostate, colon and lung cancer cells in culture and such anticancer effect were also observed in preclinical animal studies where oral administration of pomegranate extract lead to the

inhibition of the growth of lung, skin, colon and prostate tumors (Adhami et al. 2009). Pharmacological interference of all *Punica granatum* components against cancer which include inhibition of tumor cell proliferation, cell cycle arrest, retardation of invasion and angiogenesis suggest a wide range of clinical applications for the treatment and prevention of a variety of cancer types. In an earlier study which explored the anticancer activity of fermented juice, pericarp, and seed oil against human breast cancer cells in a comprehensive experimental design, it was observed that these components were able to block the endogenous estrogen biosynthesis by inhibiting key enzymes aromatase (60–80 %) and 17-beta-hydroxysteroid dehydrogenase (34–79 %) (Kim et al. 2002). The study reported the effect of pomegranate seed oil leading to 90 % inhibition of proliferation of MCF-7 (100 μg/ml), 75 % inhibition of invasion of MCF-7 across a Matrigel membrane (10 μg/ml) and 54 % apoptosis in MDA-MB-435 estrogen receptor negative metastatic human breast cancer cells (50 μg/ml).

Another study testing the components of pomegranate against prostate cancer also demonstrated strong activity inhibiting in vitro proliferation of LNCaP, PC-3, and DU 145 human cancer cell lines through mechanisms that included cell cycle arrest and apoptosis whereas normal prostate epithelial cells were significantly less affected. Furthermore, the study demonstrated potent inhibition of PC-3 xenograft growth in athymic mice (Albrecht et al. 2000). Mukhtar and coworkers reported an in vivo evidence for the clinical relevance of pomegranate fruit extract (PFE) against prostate cancer (Malik et al. 2005). Oral infusion of PFE to mice resulted in a significant inhibition in tumor growth as observed by prolongation of tumor appearance and consistent lower volume of tumor in mice that received PFE, with effects being dose-dependent. Interestingly an initial phase II clinical trial of pomegranate juice in patients with prostate cancer reported significant prolongation of prostate specific antigen doubling time strongly implicating its anti-cancer potential (Pantuck et al. 2006a, b). Pomegranate extracts have also been tested against chemically induced lung and colon cancer in animal models. Mice treated with PFE and exposed to B(a)P and NTCU had statistically significant lower lung tumor multiplicities than mice treated with carcinogens only (Khan et al. 2007). Similarly, administration of pomegranate seed oil in the diet significantly inhibited the incidence and multiplicity of colonic adenocarcinomas induced by azoxymethane in mice (Kohno et al. 2004).

Phytochemical analyses show that the fruit is a rich source of polyphenolic compounds including anthocyanins (such as delphinidin) and hydrolysable tannins (such as ellagic acid). Ellagic acid is the active ingredient responsible for over 50 % of the antioxidative activity of pomegranate juice (Pantuck et al. 2006a, b). Studies have reported the potential of ellagic acid in the induction of cell cycle arrest, apoptosis and anti-tumorigenic activity in models of prostate cancer and other cancer such as human bladder cancer and leukemia (Castonguay et al. 1997; Seeram et al. 2005; Li et al. 2005a, b). Ellagic acid modulate cellular signaling pathways by various mechanisms, including suppression of nuclear factor kappa, cyclooxygenase-2 and cyclin D1 levels, inducing p53 and p21 expression as well as lowering levels of vascular endothelial growth factor (VEGF) (Khanduja et al. 2006; Aggarwal and Shishodia 2006). Delphinidin, the major anthocynanidin present in pomegranate juice has also been shown to induce apoptosis in human pro-myelocytic leukemia (HL-60) cells and other cancer (Hou et al. 2003; Syed et al. 2007). In a recent report delphinidin was shown to exert cytotoxicity in metastatic and drug resistant (LoVo and LoVo/ADR) colon cancer cell lines (Cvorovic et al. 2010). Though individual constituents of pomegranate have shown significant anticancer activity, the synergistic action of the pomegranate constituents appears to be superior to that of single constituents and therefore whole fruit juice holds greater significance in dietary prevention of cancer.

Broccoli (*Brassica oleracea italic*)

The edible plants belonging to the family *Cruciferae* and genus *Brassica* such as broccoli are a rich source of glucoraphanin, a glucosinolate precursor of sulphoraphane (SFN), an isothiocyanate considered to be a potent anti-cancer agent (Clarke et al. 2008). Various epidemiologic studies have indicated that consumption of broccoli is associated with a lower risk of cancer incidence including breast, prostate, lung, stomach and colon cancers (Clarke et al. 2008; Ambrosone et al. 2004; Joseph et al. 2004; Poppel et al. 1999; Chung et al. 2000). As reviewed by

Donaldson (2004), a case–control study in China found that intake of cruciferous vegetables was inversely related to the risk of breast cancer; the quartile with the highest intake had only 50 % of the risk of the lowest intake group (Fowke et al. 2003). In the Nurses' Health Study a high intake of cruciferous vegetables (5 or more servings/week vs. less than two servings/week) was associated with a 33 % lower risk of non-Hodgkin's lymphoma (Zhang et al. 2000). Prostate cancer risk was also found to be reduced by cruciferous vegetable consumption in a population-based case control study carried out in western Washington state in which it was observed that three or more servings per week, compared to less than one serving of cruciferous vegetables per week resulted in a statistically significant 41 % decrease in prostate cancer risk (Cohen et al. 2000). A prospective study in Shanghai showed that men with detectable amounts of isothiocyanates in their urine had a 35 % decreased risk of lung cancer. Interestingly among men that had one or two genetic polymorphisms that caused them to eliminate these isothiocyanates slower, there was a 64 or 72 % decreased risk of lung cancer, respectively (London et al. 2000).The most consistent protective effects have been observed for higher levels–dietary intake, serum, plasma, or urinary metabolites of isothiocyanates and lung cancer/gastrointestinal cancer (Miller and Snyder 2012).

The chemopreventive effect of broccoli against cancer is attributed to the ability of SFN to inhibit phase 1 enzymes (catalyzing conversion of pro-carcinogens to carcinogens) and induce phase 2 enzymes (catalyzing detoxification and excretion of carcinogens from body) (Zhang et al. 1992).In addition a number of studies have implicated the anticancer effect of SFN through its inhibitory activity against histone deacetylase (HDACs) (Dashwood and Ho 2007). HDACs have many critical roles in regulation of gene expression, cell proliferation, cell migration, cell death, and angiogenesis. HDAC inhibitors (HDACi) can induce different phenotypes in various transformed cells, including growth arrest, apoptosis; reactive oxygen species facilitated cell death and mitotic cell death (Marks and Xu 2009). SFN has detrimental effects on cell cycle checkpoint controls and cell survival pathways leading to the induction of apoptosis in various cancer cells (Myzak et al. 2004). Furthermore, SFN was able to induce apoptosis via the intrinsic bcl-2 dependent mitochondrial pathway as well as by the extrinsic TRAIL-dependent pathway (Jin et al. 2007a, b; Matsui et al. 2006). Qazi et al. (2010) examined the therapeutic potential of SFN against Barrett esophageal adenocarcinoma (BEAC). The data showed that SFN induced both time- and dose-dependent decline in cell survival, cell cycle arrest, and apoptosis. The treatment with SFN also suppressed the expression of multidrug resistance protein, reduced drug efflux, and increased anticancer activity of other anti-proliferative agents including paclitaxel. In the same study a significant reduction in tumor volume was also observed by SFN in a subcutaneous tumor model of BEAC. Mechanistic studies revealed that anticancer activity could be attributed to the induction of caspase 8 and p21 and down-regulation of hsp90, a molecular chaperon required for activity of several proliferation-associated proteins. In another in vivo study PC-3 cell xenografts implanted subcutaneously into nude mice and examined for their growth characteristics after feeding SFN in the diet for 21 days demonstrated a significant retardation of tumor growth compared with animals given control diet (Myzak et al. 2007). In a long-term study aimed at exploring the correlation of SFN intake and the risk of colon cancer, Apc^{min} mice were administered $\sim$6 μmol SFN/day for 70 days, and this resulted in significant inhibition of spontaneous intestinal polyps, compared with controls fed AIN93 diet alone (Myzak et al. 2006). Anticancer activity of SFN has also been demonstrated in other in vivo cancer models such as those of human pancreatic cancer, murine osteosarcoma xenografts, skin tumors, and carcinogen-induced stomach tumor (Pham et al. 2004; Matsui et al. 2007; Dinkova-Kostova et al. 2006; Fahey et al. 2002).

The three major properties of SFN which enhances its clinical plausibility and translational value are: (1) It has been reported that the SFN has good bioavailability as it can reach high intracellular and plasma concentrations. Moreover, detectable levels of SFN were recorded for breast tissues after single oral administration (Myzak et al. 2004; Cornblatt et al. 2007), (2) In human subjects, a single ingestion of 68 g of broccoli sprouts inhibited HDAC activity in circulating peripheral blood mononuclear cells 3–6 h after consumption, with a concomitant induction of histone H3 and H4 acetylation. These study provided the first translational evidence for HDAC inhibition by a natural diet "broccoli sprouts", and support for an

anti-cancer pharmacological action at intake levels readily achievable in humans (Myzak et al. 2007; Dashwood and Ho 2008) and (3) Normal cells are relatively resistant to HDACi induced cell death, a characteristic of an ideal anti-cancer drug (Marks and Xu 2009). Broccoli sprouts which have the highest concentration of sulforaphane precursor than the mature edible broccoli has thus emerged as the rich source of dietary HDACi with evidence of translational potential in cancer chemoprevention.

Citrus fruits and ascorbic acid

Several of the epidemiological studies have shown that citrus fruit consumption is protective in a variety of human cancers (Milner 1994). Citrus fruits (Rutaceae), including oranges, lemons, limes and grape fruits are a principal source of important nutraceuticals such as ascorbic acid and bioactive components such as carotenoids and flavonoids, which are suggested to be responsible for their chemopreventive effects against number of diseases including cancer. Ascorbic acid (AA), the popular anti-oxidant in citrus fruits has a long historical perspective regarding its efficacy in cancer therapy (Ullah et al. 2012). Unlike most other chemotherapeutic drugs, higher doses of intravenous/oral administration of AA are well tolerated and clinically safe in cancer patients (Levine et al. 1999). Although partially discredited in the past due to few null clinical outcomes (Creagen et al. 1979; Moertal et al. 1985), relatively recent studies (Padayatty et al. 2004) related to the bioavailability of pharmacologically active doses of ascorbic acid in physiological system has enhanced its clinical plausibility.

In 1954, McCormick, a Canadian physician, proposed that cancer is a collagen disease implicated to an AA deficiency (McCormick 1954). His observations that the generalized stromal changes of scurvy are identical with the local stromal changes observed in the immediate vicinity of invading neoplastic cells provided the first evidence to link cancer with AA (McCormick 1959). It was believed that the nutrient known to be capable of preventing such generalized changes in scurvy presumably shall have similar effects in cancer. Several mechanisms have been proposed for the anticancer activity of ascorbic acid which include antioxidant as well as pro-oxidant properties, stimulation of the immune system, altering carcinogen metabolism, enhancement of collagen synthesis necessary for tumor encapsulation and interference with cancer cell signaling (Ullah et al. 2012).

Epidemiological studies provide strong evidence of a protective effect of AA for cancers such as of esophagus, lung, pancreas, stomach, colorectal, breast and cervix (Block 1991; Kathleen 1998). An inverse relationship between plasma levels of AA and cancer mortality has been reported in literature (Khaw et al. 2001). One of the most consistent epidemiological findings on AA has been an association with high intake of AA or AA rich foods and reduced risk of stomach cancer (Schorah et al. 1991; Sobala et al. 1991; Drake et al. 1996). A study analyzing the existing epidemiological data in literature showed that 9 of 10 case control studies and 10 of 11 non-controlled studies yielded a significant inverse relationship between AA intake and stomach cancer risk (Cohen and Bhagavan 1995). Further epidemiological evidence of a dietary link to pancreatic cancer reported consistent inverse relationships between AA and the incidence of pancreatic cancer (Howe and Burch 1996). Another study examining the relationship of dietary and supplemental factors with esophageal cancer reported that the high index of AA intake was associated with decreased risks of esophageal cancer (Mettlin et al. 1981). A systematic study of AA blood levels in patients with lung cancer and an evaluation of their modifications when the patients were orally treated with daily high doses of ascorbic acid (5 g/day) have shown hypo-vitaminosis C sub-clinic conditions (to lower level of physiologic range) and administration of periodic hematic dosages of AA have shown a rapid increase of its blood concentration (over 1,500 μg, the higher level of normal range). The study proposed that such high hematic levels of AA remain generally constant for some time and appear beneficial in increasing the defense reactions of the cancer patient (Greco et al. 1982).

Earlier studies by Cameron and Pauling reported clinical benefits and improved survival using both oral and intravenously administered AA in the treatment of terminal cancer (Cameron and Pauling 1978; Morishige and Murata 1979). Later, in two double blind, placebo-controlled trials, investigators at the Mayo clinic (Rochester, MN) found that a high-dose oral administration of AA had no effect on cancer survival (Creagen et al. 1979; Moertal et al. 1985). These trials were considered definitive possibly because the

difference in the in vivo levels of AA achieved between the oral and intravenous administration was not adequately appreciated. Plasma levels of ascorbic acid are tightly controlled and are around 50 μM (Omaya et al. 1986). However, Padayatty et al. (2004) have shown that intravenous administration of ascorbic acid bypasses such tight control and results in concentrations as much as 70-folds higher than those achieved by maximum oral consumption. Thus concentrations of ascorbic acid achieved through oral administration might have preventive role for cancer risk but the therapeutic intervention may require high pharmacological doses achievable only via intravenous administration. Levine and coworkers have demonstrated that pharmacologic AA concentrations achievable through intravenous administration were cytotoxic to many types of cancer cells in vitro and significantly impeded tumor progression in vivo without toxicity to normal tissues (Chen et al. 2011). A recent study tested 10 cancer cell lines with AA and the results showed that pharmacologic ascorbic acid induced cytotoxicity in all tested cancer cells, with IC50 <4 mM, a concentration easily achievable in humans. Treatment in mouse pancreatic cancer xenografts showed that intra-peritoneal ascorbic acid at 4 g/kg daily reduced tumor volume by 42 % (Biswas et al. 1997).

Among the highly sought for alternative medical treatments AA is one of the most popular drug used by non-mainstream physicians orally for many decades as a therapeutic agent to treat diverse conditions including infections, autoimmune diseases and cancer. A partial validation of the possible role of AA in prevention or regression of cancer as a lead drug or adjuvant to standard chemotherapeutic regimen has emerged with the feasibility of high bioavailable levels achieved through pharmacologically active doses. A recent Phase I clinical trial reported by Monti et al. (2012) provided an initial safety evaluation of AA added to gemcitabine and erlotinib in patients with stage IV pancreatic cancer. In the nine patients who completed the study, AA concentrations as high as 30 mM were reached safely and with minimal associated adverse events that could be attributed to AA. Moreover, the observation that ascorbic acid acts as a pro-drug targeting the cancer cells while sparing the normal ones (Chen et al. 2011), provides the molecule one of the desired characteristic of an ideal anti-cancer drug.

Soy and isoflavones

Since the last two decades a large number of evidence based on epidemiological, pre-clinical and clinical data have emerged leading to the popularity of soy and its components such as isoflavones for their anticancer potential (Messina 2003). In 1998, the Chemoprevention Branch of the NCI judged genistein, the main isoflavone in soybeans, to be a key chemopreventive agent (Messina 2003; Ahmad et al. 2013b). Further, the International Prostate Health Council, a European group of experts; have opined that isoflavones prevent the progression of the latent form of prostate cancer to the more advanced stages of this disease (Grif 2000). The American Cancer Society includes dietary consumption of fruits and vegetables derived foods including soy foods as one of the recommendations for reducing cancer risk (ACS guidelines, accessed 2013). The significance of soy as a diet was experimentally observed in a study that investigated the effects of the soybean isoflavone genistein and a commercially-available isoflavone-containing soy extract on the growth of F3II mouse mammary adenocarcinoma (Hewitt and Singletary 2003). Female Balb/c mice injected (s.c.) with F3II cells and fed diets supplemented with 0.6 % soy extract (containing genistein at 750 ppm) exhibited a significant 90 % reduction in tumor weight compared to controls, whereas female mice fed diets supplemented with 750 ppm genistein alone exhibited a significant 40 % reduction in tumor weight compared to controls. It was suggested that the genistein fed to mice as part of the soy extract resulted in a greater magnitude of inhibition of mouse mammary adenocarcinoma tumor growth, compared to tumor growth of animals fed an equivalent amount of genistein alone. Similarly, the effect of a soy-derived isoflavone mixture (designated as SI-I, containing 71 % daidzein, 14.3 % genistein and 14.7 %glycitein) on HeLa cells and its mechanism were investigated. SI-I in concentration range 5–80 μg/ml significantly reduced the survival rate of HeLa cells showing typical apoptotic morphological changes, including nuclear fragmentation, cytoplasm shrinkage and decrease of cell volume (Xiao et al. 2011). Thus it was suggested that SI-I might be a potential chemotherapeutic agent candidate against human cervical cancer from a natural product.

Moreover, several epidemiological studies have indicated that populations with high intake of soy have

lower incidence of breast, prostate, and colon cancer (Adlercreutz 1995; Adlercreutz et al. 1995; Park and Sur 2004). The most compelling evidence for chemoprevention comes from studies of Asian populations that consume traditional diets rich in plant foods, particularly soy products. Compared to western countries, the incidence and mortality from breast and prostate cancer have historically been lower in Asian countries. Although genetic and other environmental factors may also contribute to these observed differences, dietary habits have been thought to account in part for the reduced cancer incidence. A cross-national study involving 50 countries identified soy products as functional foods with substantial protective effects against prostate cancer (Herbert et al. 1998). It has been reported that Asian women consuming relatively large amounts of soy-derived foods have a low incidence of breast cancer (Adlercreutz et al. 1991; Lee et al. 1991). Asian women usually have higher urinary and plasma levels of phytoestrogens such as genistein than women in western populations (Adlercreutz 2002). Furthermore, documented evidence of increased breast cancer risk among Asian immigrants to the United States and second generation descendants has been attributed in part to their intake of increasingly western style diets (Ziegler et al. 1993; Wu and Chan 2007). Moreover urinary levels of soy-derived isoflavones including genistein were found to be lower in breast cancer patients compared with case-controls (Ingram et al. 1997; Zheng et al. 1999). Generally, soybean isoflavones consist of two chemopreventive agents, genistein (5,7,4-trihydroxyisoflavone) and daidzein (7,4-dihydroxyisoflavone), are likely predominant in the cancer prevention activity of soybeans (Li et al. 2005a, b). Purified genistein and daidzein alone or in combination with chemotherapy, radiation therapy, and/or immune-therapies have been proved to inhibit the growth of various cancer cells in vitro and in vivo by inducing apoptosis and arrest of cell cycle progression (Chang et al. 2009; Khan et al. 2009; Wang et al. 2008). Isoflavones are phytoestrogens which interact with ERs and generally function as weak estrogens in rodent and cell culture models. These estrogen-like effects have raised concern regarding soy/isoflavone consumption, particularly in the case of postmenopausal women at high risk for breast cancer. Currently there is little evidence to suggest that any potential weak estrogenic effects of dietary isoflavones have a clinically relevant impact on breast tissue in healthy women and limited data suggest this is also the case for breast cancer survivors (Messin and Wood 2008). In this regard more clinical evidence is required to obtain a clear dietary protocol for soy and breast *c*ancer which will support a more judicious recommendation.

Extensive investigations have been performed to determine the molecular mechanisms underlying genistein's anti-neoplastic activity, with results indicating that this molecule can inhibit several proteins involved with primary tumor growth and apoptosis, including the cyclin class of cell cycle regulators and the Akt family of proteins. At lower concentrations that are similar to those achieved through dietary consumption, genistein can inhibit the pro-metastatic processes of cancer cell detachment, migration, and invasion through a variety of mechanisms, including the transforming growth factor (TGF)-β signaling pathway. Several in vitro findings have been corroborated in both in vivo animal studies and in early-phase human clinical trials, demonstrating that genistein can both inhibit human cancer metastasis and also modulate markers of metastatic potential in humans, respectively (Pavese et al. 2010; Banerjee et al. 2008). Isoflavone genistein has also been shown to expand the therapeutic window of the standard anticancer therapies thereby sensitizing the cancer cells towards these treatments. The cytotoxic effect of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is limited in some carcinoma cancer cells. However, it was found that treatment with TRAIL in combination with nontoxic concentrations of genistein sensitized TRAIL-resistant human hepatocellular carcinoma Hep3B cells and AGS gastric adenocarcinoma cells to TRAIL-mediated apoptosis (Jin et al. 2009, 2007a, b). Further, it was demonstrated that in several studies that soy isoflavones, which are safe dietary agents, act as potent radio-sensitizers in prostate cancer (PCa) both in vitro and in vivo (Raffoul et al. 2006, 2007; Gupta et al. 2009). It was shown that the viability of PC-3 and LNCaP prostate cancer cells decreased with increasing concentrations and exposure time of genistein and daidzein. Genistein increased G_2/M phase cells in PC-3 cells while decreased S phase cells in LNCaP cells in a dose-dependent manner and the apoptosis percentage of LNCaP cells was elevated significantly by daidzein (Cao et al. 2006).Wang et al. reported the genistein and daidzein induced inhibition of human colon tumor

(HCT) cells and on the cell growth, cell cycle progression, and differentiation of murine K1735M2 and human WM451 cells. It was found that genistein could inhibit the cell growth of two metastatic melanoma cell lines, murine Kl735M2 and human WM45l in a dose-dependent manner (Wang et al. 2002).

In humans, plasma or serum levels of genistein from soy food ingestion range from less than 1 μM to about 5 μM (Wiseman et al. 2004). Studies by King et al. (2006) demonstrated the effects of genistein on breast tumor cell growth in culture and observed apparent enhanced growth of breast cancer cells BT-474, MCF-7 and MDA-MB-468 with the MTS assay after a 72 h treatment with a low dietary relevant genistein (3.125 μM) dose. However, this short-term enhancement of growth was not sustained over the long-term, as shown in 7-day growth curve assays with re-supplementation of the genistein at 48 h intervals which showed cumulative dose dependent inhibition of MCF-7 and MDA-MB-468 cell growth of 30–50 % over the 7 days. Similarly, cell growth inhibition was shown by the low genistein dose of 5 μM over a 72 h growth curve in TRAMP-C2 mouse prostate model cells (Touny and Banerjee 2006). Thus as a chemopreventive strategy a sustained intake of Isoflavones in the form of soy foods may maintain the required physiologically relevant intracellular concentrations that are cytotoxic to neoplastic cells.

Freeze-dried berries and red grapes

Stoner and coworkers have made some interesting studies developing a food-based approach to the prevention of esophageal and colon cancer utilizing freeze-dried berries and berry extracts (Stoner et al. 2007). Dietary freeze-dried berries were shown to inhibit chemically induced cancer of the rodent esophagus by 30–60 % and of the colon by up to 80 %. The berries were found to be effective at both the initiation and promotion/progression stages of tumor development through modulation of genes involved with proliferation, apoptosis, inflammation and angiogenesis. Studies show that the anticancer effects of berry bio-active extracts and its constituent agents are partially mediated through their abilities to counteract, reduce, and also repair damage resulting from oxidative stress and inflammation which are strong intracellular insults known to be associated with cancer risk (Seeram 2008). In addition, berry constituents regulate carcinogen and xenobiotic metabolizing enzymes, various transcription and growth factors, inflammatory cytokines, and subcellular signaling pathways of cancer cell proliferation, apoptosis, and tumor angiogenesis (Seeram 2008; Wang and Stoner 2008). Moreover, clinical trials for a toxicity study indicated that freeze-dried black raspberries are well tolerated in humans when administered orally for 7 days at a dose of 45 g/day (Stoner et al. 2005). A study evaluated the preventative effects of the berry extract on human oral cancer cell lines and found inhibition of cell proliferation, VEGF production, nitric oxide synthase activity, apoptosis, and terminal cell differentiation (Rodrigo et al. 2006).

Extracts of red raspberries and other varieties of berries have been demonstrated to be effective inhibitors of the growth of human cervical cancer (HeLa) cells (Ross et al. 2007) and HT-29 colon cancer cells (Wu et al. 2007) in vitro. A freeze-dried black raspberries (BRB) diet was shown to prevent colon cancer development in F344 rats induced by the chemical carcinogen, azoxymethane (AOM) (Harris et al. 2001). Tumor multiplicity was reduced significantly by 42, 45 and 71 % in the 2.5, 5 and 10 % BRB + AOM groups, respectively, when compared to animals treated with AOM alone. Similarly in a model of esophageal tumors induced by chemical carcinogen *N*-nitrosomethylbenzylamine (NMBA), the tumor multiplicity was reduced significantly by 40–50 % when rats were administered freeze-dried BRBs (Kresty et al. 2001). The most active components of berry extracts included the anthocyanins: cyanidin-3-*O*-glucoside, cyanidin-3-*O*-rutinoside and cyanidin 3-*O*-(2G-xylosylrutinoside) and ellagitannins (Ross et al. 2007; Hecht et al. 2006) which are believed to have pleiotropic action mechanism against cancer where they interfere with cell survival pathways and angiogenesis and stimulate cell death (Huang et al. 2006).

Similar to the berries, grapes and grape-based products have also shown cancer chemopreventive potential and are also known to improve overall human health. Aggarwal and co-workers have proposed a number of experimental evidence for the chemopreventive efficacy of grape seed extract (GSE) against skin, colorectal, prostate, and breast cancers. These included anticancer activity of the extract against human lung cancer A427, A549, and H1299

cells, human gastric adenocarcinoma CRL-1739 cells, oral squamous cell carcinoma CAL27 and SCC25 cells, Jurkat, U937, and HL-60 (Kaur et al. 2009). Studies on anti-tumor-promoting effect of GSE polyphenolic fraction (GSP) in a 2-stage SENCAR mouse skin carcinogenesis model showed that topical application of GSP resulted in a highly significant inhibition of 12-Otetradecanoylphorbol-13-acetate-caused skin tumor promotion, as evidenced by a significant reduction in tumor incidence, tumor multiplicity, and tumor volume (Zhao et al. 1999). Anticancer activity of GSE was also reported against LoVo and HT-29 human colorectal carcinoma cell lines and tumor xenografts in athymic nude mice (Kaur et al. 2006). Further extract was also found to be potent against cancerous colon tissues of humans via inhibition in DNA turnover enzymes, thus demonstrating its translational significance (Durak et al. 2005). Further, Agarwal et al. (2002) examined the effect of GSE against the DU145 cell line, which represents advanced metastatic hormone refractory human prostate cancer and the data showed GSE to be effective in inducing apoptotic death of cancer cells. Thus study was extrapolated by in vivo evidence reporting an overall growth inhibitory effect against DU145 xenografts in nude mice via anti-proliferative and anti-angiogenic effects and interference with IGF-1 signaling (Singh et al. 2004).

Skin from fresh grapes contains about 50–100 μg of resveratrol (a bioactive stilbene) per gram wet weight, which contributes to a relatively high concentration of resveratrol in red wine and grape juice (Cal et al. 2003). Resveratrol was first described as a component in the root of *Polygonum cuspidatum*, a weed whose extract is well known in Asian medicine for its anti-inflammatory properties (Ulrich et al. 2005). Resveratrol has been shown to cause growth inhibition and induce apoptosis in several cancer cells in vitro, including prostate, breast, skin, liver, pancreatic, lung and leukemic cancer cells (Shih et al. 2004; Li et al. 2006; Aziz et al. 2005; Kuo et al. 2002; Kotha et al. 2006; Kim et al. 2003; Cecchinato et al. 2007). Further, the anti-cancer effects of resveratrol in vivo tumor models have also been demonstrated (Aziz et al. 2003; Aggarwal et al. 2004). Resveratrol affects all three defined stages of carcinogenesis (initiation, promotion, and progression) by modulating signal transduction pathways that control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis. A study on metastatic cells demonstrated that resveratrol has a potent anti-proliferative and pro-apoptotic effect on MDA-MB-231, a highly invasive and metastatic cell line from human breast cancer known to be resistant to several anti-cancer drugs (Francesca et al. 2003). The resveratrol-induced biological effect was dose dependent and correlated with an increase of endogenous ceramide, a lipid mediator which regulates cellular targets involved in proliferation and apoptosis. In human multiple myeloma cells, resveratrol suppresses constitutively active NF-kappaB through the inhibition of IkBα kinase and thus down-regulates a number of pro-proliferation and anti-apoptotic gene products such as Akt, cyclin D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TRAF2; thereby suppressing cell proliferation (Ulrich et al. 2006). The evidence in support of berries, red grapes and their bioactive fractions/constituents such as anthocyanidins and resveratrol are suggestive of their prophylactic value against cancer risk and adjuvant therapeutic intervention.

Curcumin and thymoquinone (spice constituents)

Curcumin is regarded as the most biologically active constituent of the spice turmeric (*Curcuma longa* L.) and it comprises 2–8 % of most turmeric preparations (Heath et al. 2004). Curcumin has been shown to possess wide range of pharmacological activities including anti-inflammatory, anti-oxidant, anti-cancer and other potentially chemotherapeutic properties such as inducing early wound healing (Menon and Sudheer 2007; Brouet and Ohshima 1995; Joe et al. 2004; Sidhu et al. 1998). Chemopreventive properties of curcumin against cancer have been extensively investigated and well documented reports in literature provide an impressive evidence of its efficacy in multi-targeted therapy (Kunnumakkara et al. 2008). Epidemiological studies have suggested the role of curcumin for the lower rate of colorectal and other cancer types in Asian countries where curcumin is consumed in the form of dietary spice turmeric (Chauhan 2002). The anti-carcinogenic effects of curcumin and its underlying mechanisms have been examined in several animal tumour model, including skin, colon, lung, duodenal, stomach, oesophageal, and oral carcinogenesis (Surh and Chun 2007).

Curcumin has been shown to interfere with xenobiotic metabolism and inhibit chemical carcinogenesis

in experimental animal models (Huang et al. 1992). In these studies curcumin was shown to inhibit the tumor initiation by benzo[a]pyrene (BaP) and 7, 12-dimethylbenz[a]anthracene (DMBA) in mouse epidermis (Huang et al. 1992; Conney et al. 1991). Administration of 0.5–2.0 % curcumin in the diet decreased BaP-induced forestomach tumors per mouse by 51–53 % when administered during the initiation period and 47–67 % when administered during the post-initiation period (Huang et al. 1994; Singh et al. 1998). In human subjects a combination treatment with curcumin 480 mg and quercetin 20 mg orally 3 times a day was studied in five familial adenomatous polyposis (FAP) white patients with previous colectomy for a period of 6–9 months. Over a time period of 3–6 months there was a significant decrease in the number as well as the average size of the polyps. The mean decrease in polyp number from baseline was 60.4 % and the average size from baseline was found to be reduced to 50.9 % with one patient reporting complete regression (Cruz-Correa et al. 2006). Inflammation plays a critical role in the pathogenesis of several diseases ranging from carcinogenesis to autoimmune disorders. Curcumin exerts potent anti-inflammatory activity by inhibiting enzymes, such as COX-2, LOX, and inducible nitric oxide synthase (iNOS), which generate reactive oxygen species. Aberrant up-regulation of COX-2 and iNOS has been associated with the pathophysiology of certain types of human cancer as well as inflammatory diseases. Curcumin has been demonstrated to inhibit both activity and induced expression of COX-2 has been demonstrated in various cell lines and animal models (Surh 1999). NF-κB is a ubiquitously present eukaryotic transcription factor that regulates expression of genes involved in controlling cellular proliferation, inflammatory responses, and cell adhesion and cell transformation (Chen et al. 1995). The data from experimental studies have demonstrated that curcumin inhibits the activation of NF-κB in different cancer cell lines (Singh and Aggarwal 1995). Moreover, curcumin also significantly decreased breast cancer metastasis to the lung and suppressed NF-κB, COX-2 and MMP9 expression in a human breast cancer xenograft model (Aggarwal et al. 2005).

Nigella sativa (black seeds) has been used for medicinal purposes for centuries in various civilizations including Southeastern Asia, Egypt, Greece, Middle East and Africa. Thymoquinone is the bioactive constituent of the black seeds and experimental evidence suggest it to be the main compound responsible for the pharmacological effects of the seeds (Ghosheh et al. 1990). Thymoquinone is considered as a potent anti-oxidant (Badary et al. 2003), anti-carcinogenic and anti-mutagenic agent (Bourgou et al. 2008; Khader et al. 2010). Anticancer potential of black seeds and thymoquinone has been reported for a variety of cancers including lungs, breast, prostate, colon, pancreatic and hepatic cancer (Khan et al. 2011). Aqueous and alcohol extracts of *N. sativa* were found to be effective in vitro in inhibition of MCF-7 breast cancer cells (Farah and Begum 2003). Further, supplementation of diet with honey and *N. sativa* has a protective effect against MNU (methylnitrosourea)-induced oxidative stress, inflammatory response and carcinogenesis in lung, skin and colon tissue (Mabrouk et al. 2002). Interestingly, Thabrew et al. (2005) have reported an 88 % inhibitory effect on hepatic cancer cells (HepG2) after 24-h incubation with different concentrations (0–50 mg/ml) of the *N. sativa* extract. Moreover, Yi et al. (2008) found that thymoquinone, the bioactive constituent of *N. sativa* extract blocked angiogenesis in both in vitro and in vivo, preventing tumor angiogenesis in a xenograft human prostate cancer (PC3) model in mouse and also inhibited human prostate tumor growth at low doses. Thymoquinone has shown an ideal anticancer potential exhibiting high cancer specificity to the cytotoxic action towards prostate cancer, colon cancer, canine osteosarcoma, and skin cancer while showing low toxicity to normal cells (Kaseb et al. 2007; Gali-Muhtasib et al. 2004a, b; Shoieb et al. 2003; Gali-Muhtasib et al. 2004a, b). Several studies have revealed the cytotoxic and cytostatic mechanisms of thymoquinone for its reported anticancer action. Thymoquinone interferes with cell cycle progression and has been reported to induce G0/G1 arrest in colon cancer cells and mouse papilloma cells, G1/S phase arrest in prostate (Kaseb et al. 2007), and G2/M arrest in skin carcinoma cells (Gali-Muhtasib et al. 2004a, b; El-Mahdy et al. 2005; Roepke et al. 2007; Rooney and Ryan 2005). This cell cycle modulating activity was partly linked to the induced-expression of the cyclin-dependent kinase (CDK) inhibitors p16INK4, p21WAF1, and p27Kip1. Thymoquinone has also been shown to suppress tumor necrosis factor–induced NF-κB activation in a dose- and time-dependent manner. It also inhibited NF-κB activation induced by various carcinogens and inflammatory stimuli thus leading to the potentiating of apoptosis induced by

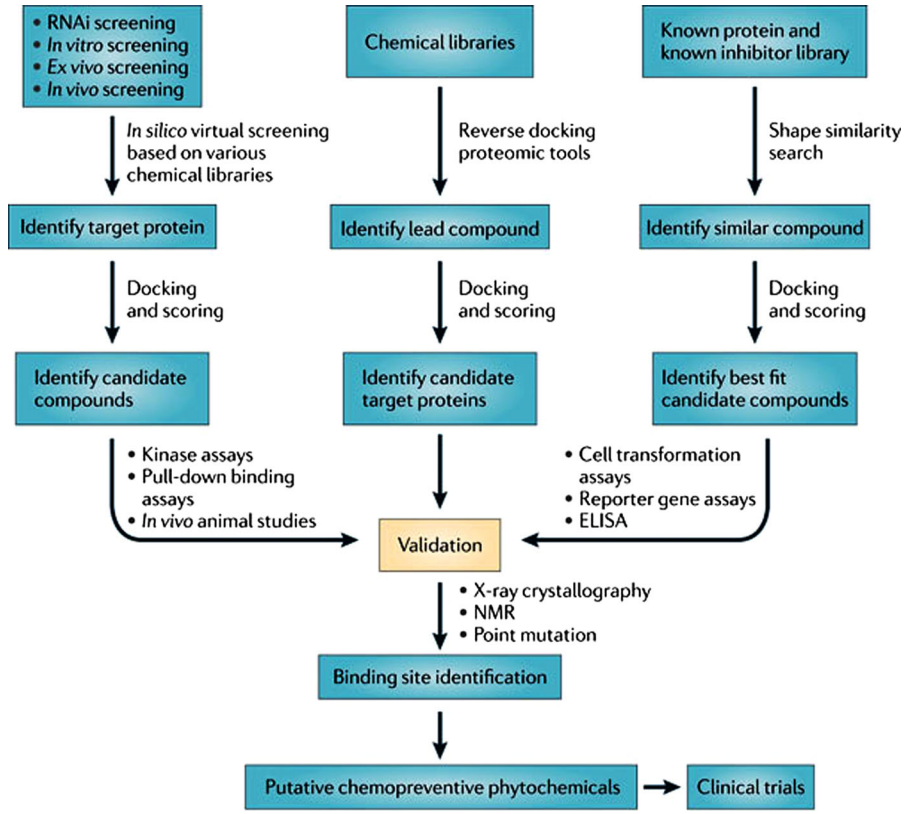

Fig. 4 Strategy for identifying preventive agents and molecular targets. Reproduced from the original source (Lee et al. 2011) with permission of Macmillan Publishers Ltd

tumor necrosis factor and chemotherapeutic agents (Sethi et al. 2008). The effect of thymoquinone on diethylnitrosamine (DENA), induced hepato-carcinogen in male wistar rats demonstrated thymoquinone supplementation completely reversed the biochemical and histopathological changes induced by DENA to the control values. Furthermore it also prevented the development of DENA-induced initiation of liver cancer by decreasing oxidative stress and preserving both the activity and mRNA expression of antioxidant enzymes (Sayed-Ahmed et al. 2010). These phytochemicals which are pre-dominant in Asian diet as constituents of spices are considered bioactive agents associated with the laboratory and epidemiological observations reporting lower risk of cancer incidence among these populations (Gullet et al. 2010).

Current challenges and future perspectives

A better understanding of the molecular basis for the ways in which these components affect the process of carcinogenesis would yield a therapeutic armamentarium capable of interfering in every stage of cancer development (Vallinas et al. 2013). However, in order to have consistent results in population based studies and clinical trials, the whole process of validation of these plant-derived agents needs to be streamlined (Fig. 4). This would have an advantage to relate the particular phytochemical agent with therapeutic relevance against the genetic/phenotypic defects in a certain stage of cancer through modulation of stage-specific molecular targets. Unlike the conventional drugs, these molecules have multiple targets and are thus of potential value in diseases like cancer where multiple pathways are altered. It also appears that cancer patients may respond differentially towards the chemopreventive effects of the nutraceuticals; some are more sensitive and responsive than others. Possibly genetics as well as pre-neoplasm lifestyle may be critical factors for the biased responses of the patients. In addition, due to the extensive metabolism of these plant-derived molecules, their bioavailability appears

to be an obvious obstacle in achieving the desired chemopreventive effect and warrants a substantial focus. A recent human intervention study demonstrated that resveratrol is well tolerated at daily oral doses of 0.5–1 g in colorectal cancer patients. Such oral doses produce and sustain resveratrol levels in tissues such as those of GI tract, sufficient to elicit chemopreventive effects (Patel et al. 2010). Novel approaches to enhance the bioavailability of this agent has shown promising potential. An interesting study demonstrated that piperine, an alkaloid derived from black pepper significantly improves the in vivo bioavailability of resveratrol (Johnson et al. 2011). Moreover, though generally regarded as safe these phytochemical compounds, should undergo the safety analysis of standard drug development protocols which would be essential to determine the pharmacokinetic/pharmacodynamics profiles of the compounds, as well as to confirm putative interactions with other molecules (Vallinas et al. 2013). The synergistic or additive preventive effects when the agents are combined could permit the administration of the lowest active dose of each agent and therefore lower the potential for adverse side effects. It is well established that a combination of various polyphenolic nutraceuticals is considerably more effective in cytotoxicity towards cancer cells than individual polyphenols alone (de Kok et al. 2008). In this regard the pharmacological synergism among dietary nutraceuticals which enhance their chemopreventive activity has strong potentials for developing cocktails of such agents for cancer patients. However, it has to be understood that no food/diet could be regarded as miraculous though their prophylactic and therapeutic effects against diseases like cancer are well established. Therefore the effects of nutraceuticals/diet on cancer risk should be concomitantly considered along with other lifestyle factors such as the importance of achieving and maintaining an ideal body weight, regular physical activity and avoiding a sedentary lifestyle and pro-carcinogenic habits such as smoking and tobacco consumption.

Conclusion

The large embodiment of evidence based on traditional practices and laboratory observations have made an impact on our current understanding to expand the horizon of anti-cancer drugs through rationalization of plant-derived pharmaceuticals as an evidence –based alternative treatment strategy against cancer. Moreover, as mentioned above for a number of plant-derived herbal agents, these have selective toxicity targeting the cancer cells while showing negligible damage to normal cells. Such properties supersede any current standard chemotherapeutic treatment modalities in the order of providing efficiency in both treatment and post-treatment management of cancer disease. As demonstrated from taxol to sulphoraphane, there exists an unprecedented potential in exploring the herbal diversity for anti-cancer drug candidates. Moreover, with the advent of evidence based practices, experimental support for plant-derived preparations and molecules has gained acceptance and validity, thus enhancing their translational effectiveness in clinics.

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