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REVIEW

Diet-derived small molecules (nutraceuticals) inhibit cellular proliferation by interfering with key oncogenic pathways: an overview of experimental evidence in cancer chemoprevention

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Abstract

Discouraging statistics of cancer disease has projected an increase in the global cancer burden from 19.3 to 28.4 million incidences annually within the next two decades. Currently, there has been a revival of interest in nutraceuticals with evidence of pharmacological properties against human diseases including cancer. Diet is an integral part of lifestyle, and it has been proposed that an estimated one-third of human cancers can be prevented through appropriate lifestyle modification including dietary habits; hence, it is considered significant to explore the pharmacological benefits of these agents, which are easily accessible and have higher safety index. Accordingly, an impressive embodiment of evidence supports the concept that the dietary factors are critical modulators to prevent, retard, block, or reverse carcinogenesis. Such an action reflects the ability of these molecules to interfere with multitude of pathways to subdue and neutralize several oncogenic factors and thereby keep a restraint on neoplastic transformations. This review provides a series of experimental evidence based on the current literature to highlight the translational potential of nutraceuticals for the prevention of the disease through consumption of enriched diets and its efficacious management by means of novel interventions. Specifically, this review provides the current understanding of the chemopreventive pharmacology of nutraceuticals such as cucurbitacins, morin, fisetin, curcumin, luteolin and garcinol toward their potential as anticancer agents.

Keywords Cancer · Nutraceuticals · Signaling pathways · Apoptosis · Chemoprevention

Introduction

Cancer registries world over since decades provide a dismal statistics that report an accelerated rate of cancer incidence, and the latest one from IARC has already projected an increase in the global cancer burden from the current 19.3–28.4 million incidences annually within the next two decades (Sung et al. 2021). Breast and lung cancers remain the most frequently diagnosed cancers and the leading causes of cancer death in women and men, respectively, though anti-tobacco campaigns and screening strategies had a positive impact on the overall rate of incidence. There is factual evidence to suggest that cancer incidence and related mortality have traditionally varied between geographical regions, predominantly associated with higher economic strata, as developed nations contributed to higher rates. However, as an apparent challenge there is a notable shift of cancer burden to less developed nations, which currently account for about 57% of cases and 65% of cancer deaths

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worldwide (Lindsey et al. 2016). It is believed that advanced age is indeed a non-modifiable risk factor for many diseases including cancer; however, lifestyle that increases the cancer risk has major implication in the perspective of modifiable factors, which are preventable. Experts in the cancer prevention epidemiology have estimated that two-third of human cancers could be prevented through appropriate lifestyle modification including dietary habits, which can influence the undesired transition from a healthy to a diseased state (Khan et al. 2010). Since last few decades, there have been numerous studies appearing in the literature that have indicated a vital inverse association between fruit/vegetable intake and cancer risk and incidence (IARC 2003; Abuajah et al. 2015), suggesting that consumption of diet rich in fruits and vegetables offers a significant protection against cancer. Dietary patterns enriched with specific phyto-ingredients have thus been identified and have shown to be protective against a number of cancer types including those of lung, breast, esophagus, oral cavity, larynx, pancreas, liver, stomach, colorectal, bladder, prostate, cervix, ovarian and endometrium (Anand et al. 2008c, a, b; Ullah et al. 2016).

Cancer is a micro-evolutionary phenomenon, which has a multifactorial dimension associated with a dynamic, long-term and multistage process that involves many complex factors in its initiation, promotion and progression. The fundamental properties associated with the limitless replicative potential of cancer cells are insensitivity to anti-growth signal and evasion of apoptosis (Hanahan and Weinberg 2000; Ullah et al. 2014). Studies have shown that multiple oncogenic factors contributing to the normal cells to acquire pro-oncogenic potential are subject to the influence of diet-derived agents known as nutraceuticals (Vainio and Weiderpress 2006). These include intracellular and extracellular mechanisms that have the ability to interfere with different stages of carcinogenesis (Mukhtar 2012). Such chemopreventive benefits of nutraceuticals extend to a host of extracellular, intracellular and nuclear contrivance in order to alter oncogenic factors related to xenobiotic metabolism, antioxidant defense, gene expression, cell cycle, tumor microenvironment, apoptosis or autophagy, invasiveness and metastasis (Fig. 1) (Ullah et al. 2014; Ullah 2015). Further, it is considered that cancer cells, which are characterized by multiple erroneous cell signaling, have the ability to counter the current anticancer therapies with drugs that are engaged in the modulation of a single target. Presumably, dietary agents unlike drugs may have the advantage of concomitantly influencing various pathways that underlie diseases like cancer (Ullah and Khan 2008). Moreover, several of these molecules have been tested in clinical trials, and some of them have shown promise in combination therapy when administered along with standard chemotherapeutic agents (Bishayee and Sethi 2016). Marino et al. (2020) have recently reviewed 750 clinical trials on polyphenolic compounds or related extracts registered in the last 20 years, which provide an insight into certain unexplored aspects and further endorse innovative and novel research designs for future intervention studies. Furthermore, Cháirez-Ramírez et al. (2021) have presented compiled data on clinical trials of polyphenols with "high potential of cancer health benefits." It is also known that of all the 175 small molecules approved for cancer therapy from 1940 to 2014, 49% (85) were natural products or their derivatives, an observation that is also true for most of the other diseases (Newman and Cragg 2016). Accordingly, there are four major groups of plant-derived anticancer drugs in clinics, and these include vinca alkaloids (e.g., anticancer drugs vinblastine and vincristine), epipodophyllotoxin derivatives (e.g., anticancer drugs etoposide and teniposide), taxanes (e.g., anticancer drug paclitaxel) and camptothecin derivatives (e.g., anticancer drugs topotecan and irinotecan) (Cragg and Newman 2004).

The use of natural molecules as drugs has been described in the earliest records of human civilization from Mesopotamia in 2600 B.C., and countries like India and China still engage an active system of alternative medicine derived from natural sources (Koehn and Carter 2005). Observations and studies on natural product pharmacology have offered, throughout the ancient and modern times, an enormous and inexhaustible potential in disease prevention. The subject of this review offers to seek an update of the current knowledge for a plausible futuristic role of diet-derived small molecules (nutraceuticals) in cancer chemoprevention paradigm, based on some interesting and convincing experimental evidence in the literature.

Cucurbitacins

Cucurbitacins are structurally diverse tetracyclic triterpenes reported predominantly in the plants of *Cucurbitaceae* family (Chen et al. 2005a, b). These have been classified into several types according to their substituents, with hundreds of derivatives appearing from the modification of basic cucurbitane skeleton [19-(10 → 9β)-abeo-10α-lanost-5-ene]. Among these, cucurbitacins B, D, E, I, IIa and Q have been reported to possess notable properties against cancer (Cai et al. 2015). These phytochemicals (Table 1) which are responsible for much of the bitter taste of cucurbits have shown relatively significant cytotoxic effects toward a number of human cancer cell lines such as those derived from lung, breast, prostate, colon, liver, pancreatic and cervical cancer (Lee et al. 2010). Several mechanistic studies have highlighted inviolable evidence of cucurbitacin-induced action against cancer cells through growth inhibition, cell cycle arrest, inhibition of cell migration, disruption of microtubule assembly and

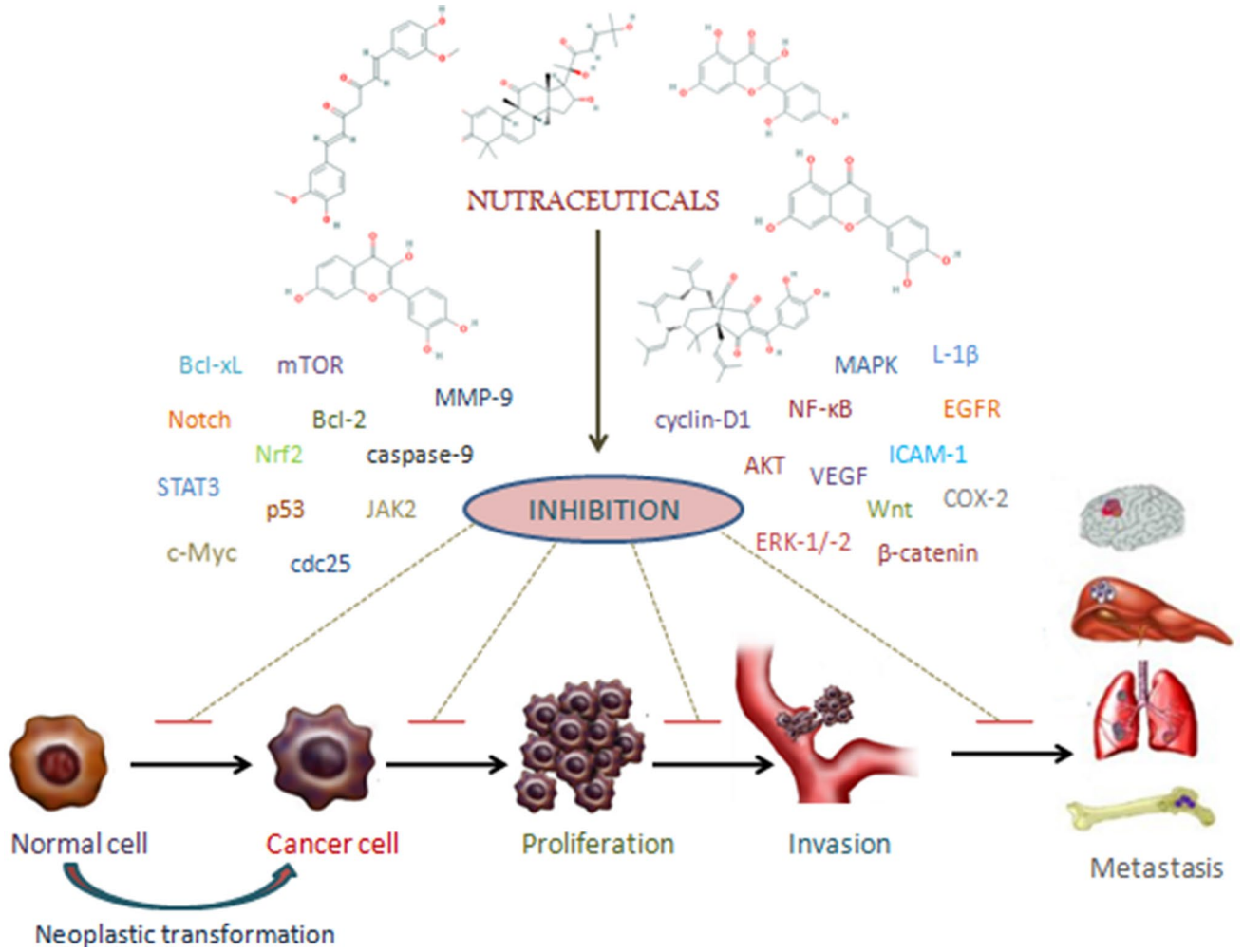
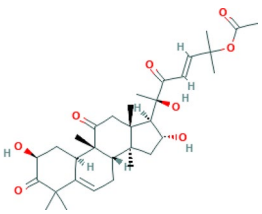
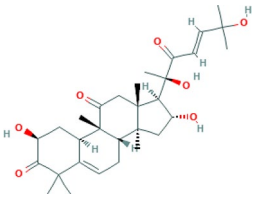
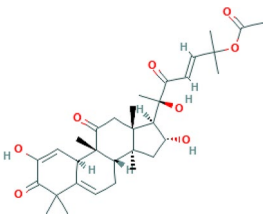
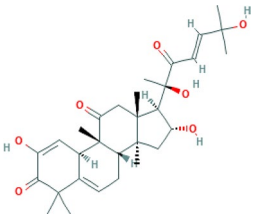
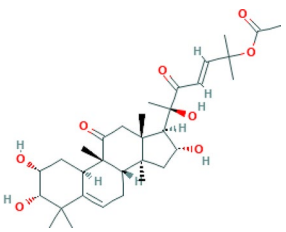


Fig. 1 Schematic presentation of the inhibition of the multistage process of carcinogenesis by nutraceuticals through modulation of oncogenic factors

induction of apoptosis (Liu et al. 2008; Silva et al. 2016; Wang et al. 2017a, b). The molecular mechanisms implicated in these actions include selective inhibition of the JAK/STAT and MAPK pathways, PARP cleavage, expression of active caspase-3, decreased pSTAT3 and JAK3 levels, as well as downregulation of various downstream STAT3 targets such as Mcl-1, Bcl-2, Bcl-xL and cyclin D3 (Ríos et al. 2012). These proteins are elementally involved in programmed cell death and the cytostatic arrest, pathways which are essentially regulating cancer cell proliferation and survival. In a cellular model of lung cancer in *vitro*, both natural (DDCB/CB) and semi-synthetic (ACB/DBCB) derivatives of cucurbitacin B were found to potentially suppress human NSCLC cell growth by interfering with PI3 kinase and MAPK pathways, leading to apoptotic cell death, inhibition of cellular migration and loss of invasive potential (Silva et al. 2016). The authors, based on the observation, proposed that the results were comparable to those obtained with the anticancer drug paclitaxel (PTX), which was used as a positive control. In another study that used an approach of co-treatment, a concurrent administration of a semi-synthetic derivative of cucurbitacin B (2-deoxy-2-amine-cucurbitacin E-DACE) along with PTX showed an interesting synergistic phenomenon in a human NSCLC xenograft model. It was demonstrated that the combined treatment (1 mg/kg DACE + PTX 10 mg/kg) leads to an effective reduction in the relative tumor volume and marked reduction in tumor growth and proliferation, in contrast to the single treatments (Marostica et al. 2017). As reported in the study, there was an evident loss of tumor burden in vivo indicating the potential chemotherapeutic relevance of cucurbitacin. Such synergistic effects have also been reported for a combination of doxorubicin (DOX) and cucurbitacin I that produced a significant increase in cytotoxicity against M5076 ovarian sarcoma cell in vitro. It also resulted in a significant decrease in

Table 1 Chemical structures of certain curcubitacins with known anticancer cytotoxic effects

Compound	Chemical structure
Cucurbitacin B	
Cucurbitacin D	
Cucurbitacin E	
Cucurbitacin I	
Cucurbitacin Q	

tumor size and weight, following an increase in DOX concentration in the tumor of M5076 ovarian sarcoma bearing mice in vivo (Sadzuka et al. 2012). In human hepatoma (BEL7402/5-Fu cells in vitro and BEL7402 tumor-bearing mice in vivo), cucurbitacin B and curcumin in combination showed synergistic anticancer activity and this was also accompanied with the reversal in multidrug resistance (Sun et al. 2015). Moreover, a consequential inhibition was also observed for cervical cancer cell-derived orthotopic xenograft tumors, following an intratumoral administration of Cucurbitacin D (1 mg/kg body weight) in athymic nude mice (Sikander et al. 2016). Cucurbitacin D was also reported inhibiting the viability and growth of cervical cancer cells (CaSki and SiHa) in vitro in a dose-dependent manner, which was associated with the induction of apoptosis, cell cycle arrest (G1/S phase), inhibition of E6, cyclin D1, CDK4, pRb and enhanced expression of p21 and p27 proteins. The study further showed the ability of cucurbitacin D to inhibit phosphorylation of STAT3 as well as its downstream target genes c-Myc and MMP9, along with an enhanced expression of tumor suppressor microRNAs (miR-145, miRNA-143, and miRNA 34a) (Sikander et al. 2016). Likewise, in breast cancer cells (MCF 7, MDA-MB-231, SKBR3), cucurbitacin D-induced cytotoxic action was related to the interference in Stat3 and Akt signaling pathways leading to the suppression of their active forms (phosphorylated) and that of NF-κB (Ku et al. 2016). Similar mechanism has been reported for cucurbitacin E-induced decrease in the viability of pancreatic cancer cells, by suppression of Stat3 phosphorylation and upregulation of tumor suppressorp53 (Chen et al. 2005a, b). As mentioned in the literature, the suppression of the oncogene STAT 3 (signal transducer and activator of transcription 3) has an established role in tumor inhibition. In conformity with this, it was observed that cucurbitacin Q induces apoptosis in human and murine tumors derived from cells that contain constitutively activated STAT3 (i.e., A549, MDA-MB-435 and v-Src/NIH 3T3) effectively as compared to others that do not show STAT3-mediated oncogenic signaling (i.e., H-Ras, MDA-MB-453 and NIH 3T3 cells) (Sun et al.2005). On the contrary, cucurbitacin IIa has been reported to exhibit anticancer potential by stabilizing actin aggregation and inducing inhibition of survivin; and both of these actions were independent of STAT3 phosphorylation (Boykin et al. 2011). The structural diversity of these molecules is believed to be responsible for varied action mechanisms against cancer cells. However, irrespective of the kind of mechanism involved, it is understood that these molecules are natural anticancer agents with therapeutic potential that might be rated at par with the current cancer drugs and possess advantages that can circumvent the associated limitations of conventional therapy. As a promising adjuvant, cucurbitacin B showed a positive synergistic effect that enhanced the apoptotic action of anticancer drug arsenic trioxide against lymphoma Ramos cells, whereas there was no toxicity observed in normal lymphocyte (Ding et al. 2017). Recently, cucurbitacins-inspired estrone analogs have been synthesized as inhibitors of EGFR-MAPK pathways and hybrid drug candidates for cancer therapy (Mahnashi et al. 2019; Abou-Salim et al. 2019). Interestingly, *Cucurbitaceae* family has hundreds of plant species which offer a huge variety of cucurbitaceous fruits and vegetables that are rich in cucurbitacins and their consumption is believed to provide sustainable chemopreventive benefits (Jing et al. 2020).

Morin

Morin is a nutraceutical found in the fig and other plants belonging to family *Moraceae*, and many of such plants are used as components of herbal medicine. Morin is related as an isomer to quercetin, another nutraceutical constituent from grapes, berries and red wine, which has been a focus of much attention as a lead compound for anticancer targets both *in vitro* and *in vivo* (Khan et al. 2016). The compound has shown antiproliferative effect against various cancer types including those of liver, breast, colon, oral and bladder cancer (Brown et al. 2003; Kumar et al. 2009; Jin et al. 2014; Hyun et al. 2015; Shin et al. 2017). The anticancer effect of morin has also been demonstrated against several human leukemic cell lines such as U937 cells which were shown to undergo caspase-dependent apoptosis in a dose-defined manner. The apoptotic activity coincided with a substantial loss of mitochondrial membrane potential along with cytochrome c release, downregulation of Bcl-2 and up-regulation of BAX proteins (Park et al. 2015). In case of cervical cancer cells (HeLa), morin-induced apoptosis was reported to be regulated via multiple cell death mechanism, including both intrinsic and extrinsic pathways. The fundamental mechanisms implicated for the observed cytotoxicity were found to be associated with the phytochemical-induced concomitant alterations in an array of cellular signaling molecules that included higher expression of Bax, Bad, cytochrome c, Apaf-1, caspases-9, DR3, DR5, FasL, FADD, caspases-10, PARP, PI3K, AKT, mTOR, P70S6K and Smac genes; increased level of intracellular ROS; and lower level of Bcl-2, Bcl-xL, AMPK, cIAP-1, cIAP-2, PKCε and NF-κB (Zhang et al. 2018a, b). Additionally, in the context of an in vivo effect, it was reported that morin supplementation for 15 weeks resulted in a significant reduction in the colonic pre-neoplastic lesions in rats challenged with the colon-specific experimental procarcinogen DMH (1,2-dimethylhydrazine) (Kumar et al. 2010). This protective effect of morin against such carcinogenic assault has been further linked to the downregulated NF-Kb activity and its downstream inflammatory mediators like TNF-α, IL-6, COX-2 and prostaglandin E2 (Sharmaa et al. 2018). As reported earlier, constitutive NF-κB activation and associated cross talks with a number of oncogenic signals have been inculpated in various stages of carcinogenesis (Aggarwal and Sung 2011), and thus, agents interfering with this pathway seem to provide significant protection against neoplastic transformations. A similar in vivo study showed morin supplementation effectively targeting metabolic activity of cancer cells via β-catenin/c-myc signaling and interfering with glycolysis and glutaminolysis to abate colon cancer in rats treated with the pro-carcinogen DMH (Sharmaa et al. 2018). The expression of glucose and glutamine transporters and the crucial enzymes of glycolytic pathway exhibited susceptible alterations. Moreover, the neoplastic markers such as mucin-depleted foci, beta-catenin-accumulated crypts and markers of cell proliferation including proliferating cell nuclear antigen, argyrophilic nucleolar antigen, c-myc, c-jun and c-fos were consistently found to be highly influenced by morin to attenuate the neoplastic changes. Several other experimental models of carcinogenesis have displayed the chemopreventive potential of morin, such as containing the diethylnitrosamine-induced hepatocellular carcinoma (Sivaramakrishnan and Devaraj 2010), evincing anti-carcinogenic and anti-inflammatory effects in DMBA-induced mammary carcinogenesis (Nandhakumar et al. 2012). Morin also caused significant inhibition of TNF-induced cancer cell adhesion to HUVECs by impeding ICAM-1 and VCAM-1 expression, and its treatment suppressed endothelial–mesenchymal transition via N-cadherin, thereby featuring its anti-metastatic attributes in vivo (Lee et al. 2016). Morin also regulated EMT signaling in ovarian cancer cells, thereby decreasing the cell adhesion properties required for effective metastasis (Novak et al. 2020). Additionally, in TOV-21G (cisplatin-sensitive) and SK-OV-3 (cisplatin-resistant) ovarian cancer cells, morin was reported to reduce the cell viability and induce apoptosis which were found to be associated with a decrease in the expression of galectin-3, and also enhanced the cisplatin-induced cytotoxicity in combination (Bieg et al. 2018). Moreover, as a potential candidate for an adjuvant therapy, it was reported that morin treatment can reduce the toxicity induced by a chemotherapeutic agent 5-FU by ameliorating oxidative stress in vivo (Nandhakumar et al. 2013). Activation of Nrf2-ARE signaling by morin was also able to protect the cells against streptozotocin-induced oxidative stress-mediated DNA damage as it is well known that Nrf-2 as master regulator of redox homoeostasis plays a significant role in cancer initiation and progression (Vanithaa et al. 2017). Studies have shown that morin has least or no toxicity against normal cells even at relatively higher concentrations compared to cancer cells as investigated in both in vitro and in vivo experimental models (Mottaghi and Abbaszadeh 2021). These recent studies investigating the anticancer potential of morin have highlighted novel mechanistic approaches by which morin exerts its anticancer effects and generates much interest toward its chemopreventive pharmacology. As a notable mention, fig which is rich in morin is an essential ingredient of medicinal formulations which are part of traditional medicines worldwide.

Fisetin

Fisetin (3,7,3,4-tetrahydroxyflavone) is a naturally occurring flavonoid, commonly found in various acacia trees and shrubs belonging to *Fabaceae* family, and is also widely distributed in fruits and vegetables such as strawberry, grape, apple, persimmon, cucumber and onion (Arai et al. 2000; Manach et al. 2004). Fisetin, which is regarded as a nutraceutical with abundant anti-oxidative properties, has in recent years attracted much attention for its therapeutically beneficial effects against a number of human diseases including cancer. It is known that dysregulation of cell cycle checkpoints and over-expression of cell cycle growth-promoting factors (such as cyclin D1 and cyclin E) are associated with carcinogenesis and its multiple stages (Bendris et al. 2015). Fisetin has been reported to alter cell cycle mechanisms, thereby causing cytostatic arrest in a number of cancer cell type including colon cancer (G1-S arrest) (Lu et al. 2005), lung cancer (cyclin D1 downregulation) (Sung et al. 2007), bladder cancer (G0/G1 arrest) (Li et al. 2011), epidermoid carcinoma (inhibition of CDK proteins) (Pal et al. 2013), endometrial cancer (inhibition of CDK proteins) (Wang et al. 2015a, b), prostate cancer (G1–S arrest) (Haddad et al. 2010), breast cancer (G1 phase arrest) (Smith et al. 2016a, b), leukemia (Adan and Baran. 2015) and melanoma (Syed et al. 2014) (inhibition of CDK proteins). Fisetin possesses the ability to block multiple signaling pathways such as the PI3 kinase, protein kinase B, mammalian target of rapamycin (mTOR), MAPK, NF-κB, Wnt and EGFR signaling, which play a central role in various cellular processes contributing to the neoplastic transformation and progression (Kashyap et al. 2018; Suh et al. 2009). Further, it has been reported that in colon cancer cells (HCT-116) fisetin also exhibited an increased level of cleaved caspase-8, Fas/Fas ligand, death receptor 5/TRAIL and p53 levels, which favored apoptotic cell death through both the mechanisms, including activation of mitochondrial and death receptor-dependent pathways (Lim and Park 2009). Caspase cascade-driven activation with lower Bcl 2 and increased BAX protein levels, along with ROS generation, have also been reported in fisetin-induced cell death inhuman non-small cell lung cancer cell line—NCI-H460 (Kang et al. 2015). In a distinctive action, triple negative breast cancer cells (TNBC), which are non-responsive to therapies even with targeted agents, were found to be sensitive to fisetin which displayed significant cytotoxic effects on TNB cells (MDA-MB-231 and MDA-MB-468) (Smith et al. 2016a, b). The study further demonstrated that the cytotoxic effects of anticancer drugs (cisplatin, 5-fluorouracil and cyclophosphamide) on TNBC cells were enhanced when co-administered with fisetin, reflecting its clinical significance for an adjuvant therapy. Another recent study reported that fisetin, at physiologically achievable concentrations, acts synergistically with clinical doses of PTX to produce growth inhibitory and pro-apoptotic effects on A549 human non-small cell lung cancer cells and retards its metastatic potential (Wisniewska et al. 2018). It was proposed that the co-treatment of fisetin and PTX significantly reduced cancer cell migration and invasion, which was partially manifested through a notable rearrangement of actin and vimentin cytoskeleton and the modulation of metastasis-related genes. Interestingly, several such studies have observed enhanced efficacy of cancer therapeutic drugs when used in combination with fisetin. This also includes the effect of fisetin on the activities of sorafenib (a multi-kinase inhibitor of MAPK) on melanoma where combination of both agents was shown to downregulate MAPK and PI3K/AKT signaling, resulting in an enhanced apoptosis of BRAF-mutated melanoma cells (A375 and SK-MEL-28). An extrapolation of the similar protocol to an in vivo study has observed abrogation of tumor growth in athymic xenograft mouse model (Pal et al. 2015). A recent study has reported that fisetin can enter nucleolus and influence rRNA biogenesis and RNA Pol I activity by modulating MAPK/ERK in breast cancer cells and effectively causes a decrease in lung colonization of breast cancer cells (60% reduction) (Kammerud et al. 2021). In a recent study, it was demonstrated that fisetin and polymeric micelles (encapsulating fisetin) had cytotoxic effects against cancer cells but normal cells which included human vascular smooth muscle cells, human bronchial epithelial cells and human ovarian surface epithelial cells were refractory to such cytotoxic effects of fisetin (Xiao et al. 2018). Fisetin, as mentioned, has the ability to modulate several cancer-related pathways and thus could be exploited against cancer disease. The clinical effectiveness of fisetin can also be further enhanced by utilizing synergistic drug treatments. However, since the compound is present in fair concentrations in several fruits and vegetables, its consumption as part of routine diet might be significant in prevention of neoplastic transition.

Curcumin

Curcumin is a chemopreventive phytochemical which is regarded as the most biologically active constituent of the spice turmeric (*Curcuma longa* L.) and has a recorded evidence of health benefits in traditional medicine (Heath et al. 2004). Chemopreventive properties of curcumin against cancer have been a subject of considerable research in the last two decades, and reports archived in the literature provide an impressive evidence of its potent anticancer properties, influencing multiple cellular targets (Kunnumakkara et al. 2008).

An inverse rate of colorectal and other cancer types has been demonstrated in epidemiological studies in Asian countries where curcumin is part of ethnic cuisines in the form of dietary spice turmeric (Chauhan 2002). Curcumin has been observed to display therapeutic potential against a range of cancers including leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers and sarcoma (Anand et al. 2008c, a, b). Neutralizing the pro-survival signals via inhibition of transcription factors NF-κB, activating protein-1 (AP-1) and c-JUN, and downregulation of proto-oncogenes Erg1 and c-MYC have a major role in curcumin-induced apoptosis in cancer cells (Han et al., 1999). Additionally, there are alternative pro-apoptotic mechanisms which include oxidative stress, p53 induction and upregulation of pro-apoptotic proteins (BAX) while downregulating anti-apoptotic genes (Bcl-2 and Bcl-XL) (Tsvetkov et al. 2005). In an experimental model of lung cancer cells (A549 and H1299), curcumin was shown to decrease the expression of certain cancer stem cell markers such as CD133, CD44, ALDHA1, Nanog and Oct4, by blocking Wnt/beta catenin and Sonic Hedgehog pathways, which are known to have critical importance in cancer growth and metastasis (Zhu et al. 2017). It was also shown that in colon cancer, curcumin was able to sensitize oxaliplatin-resistant tumor cells by decreasing the expression of CXCL1 and CXCL8 effectors leading to NFkB inhibition (Ruiz et al. 2016). A combination of curcumin with anticancer drug celecoxib also demonstrated that the co-administration synergistically inhibited cell proliferation and induced apoptosis by downregulating COX-2 expression in a variety of colon cancer cells (HT29, IEC-18-Kras, Caco-2 and SW-480) (Lev-Ari et al. 2005). Evidence in the literature is indicative of the fact that much of the positive clinical results of curcumin administration are currently restricted to patients with colorectal cancer as sufficient curcumin concentrations are available in the colonic mucosa, unlike the limited bioavailability observed in other tissues (Adiwidjaja et al. 2017). In an animal model of *N*-nitrosodimethylamine (hepatocarcinogen)-induced experimental carcinogenesis, curcumin treatment was found to exhibit 81% reduction in the multiplicity and a 62% reduction in the incidence of hepatocarcinoma compared with the non-treated group (Chuang et al. 2000). In its activity against prostate cancer, curcumin has been observed to impede NICD (active product of Notch-1 receptor) binding to DNA, that induces apoptosis of prostate cancer cells (Yang et al. 2017). Another study which evaluated the effects of curcumin on prostate cancer (DU-145) cell invasion, in both in vitro and in vivo models, demonstrated a marked reduction in tumor volume associated with lower MMP-2 and MMP-9 (matrix metalloproteinase) activity in the tumor-bearing site. Moreover, the metastatic nodules in the in vivo experiment were concurrently found to be significantly fewer in the curcumin-treated group than untreated group (Hong et al. 2006). The pleiotropic effects of curcumin have also been reported in the inhibition of melanoma growth and progression, by blocking the cell cycle in the G2/M phase, activating apoptosis upon inhibition of NF-κB and by scavenging endogenous nitric oxide which resulted in the inhibition of inducible nitric oxide synthase (Zheng et al. 2004). The administration of curcumin has been earlier shown to decrease the number of lung tumor nodules and retard lung metastasis of melanoma in animals (Menon et al. 1995). A pilot Phase II clinical study, assessing the efficacy of the co-administration of docetaxel and curcumin in patients who were introduced to chemotherapy and exhibit metastatic castration-resistant prostate cancer, supported curcumin supplementation as a complementary treatment for prostate cancer, with considerable response and tolerance (Mahammedi et al. 2016). Moreover, curcumin in human studies has also been reported to exert beneficial effects in patients with pancreatic cancer and exhibited the potential to slow down the disease progression in patients with monoclonal gammopathy and smoldering multiple myeloma (Dhillon et al. 2008; Golombick et al. 2012). These chemopreventive effects have been evident in in vitro assays and in vivo *models*; and as such, some have also been corroborated in patient trials either through the isolated use of curcumin or in combination therapy with conventional anticancer drugs. Furthermore, novel derivatives of curcumin have shown enhanced bioavailability and efficacy as compared to naturally occurring parent compound (Vyas et al. 2013; Di Martino et al. 2017). In a recent study, three curcumin analogs, C509, C521 and C524, were reported to possess superior, 40 times more potent cytotoxic activity compared to the natural dihydroxy-dimethoxycurcumin in human pancreatic cancer cells (Szebeni et al. 2017). The results suggested that curcumin and its derivatives initiate an activated unfolded protein response (UPR)-mediated cascade resulting in mitochondrial depolarization, ER stress, caspase activation, DNA damage and subsequent cell death. Interestingly, a recent clinical trial has found that curcumin when administered intravenously in combination with anticancer drug for solid tumors paclitaxel was superior to the paclitaxel–placebo with respect to objective response rate and physical performance in patients with advanced metastatic breast cancer after 12 weeks of treatment; and the intravenous administration of curcumin was safe (Saghatelyan et al. 2020). Curcumin which is also referred as golden spice is one of the most studied nutraceuticals in cancer prevention, and much of its pharmacological importance is derived from the vast literature associated with traditional system of medicine worldwide. Moreover, with the advent of novel approaches that can increase the systemic and tissue bioavailability, it is expected that the efficacy of this nutraceutical would be further enhanced for human health.

Luteolin

Luteolin is a flavone present in fruits and vegetables, including broccoli, onion leaves, carrots, peppers, cabbages and apple skins; and high luteolin content has also been reported in parsley, thyme, peppermint, basil, celery and artichoke (Aziz et al. 2018). Luteolin has been reported as one of the most potent inhibitors of cell growth, with an effective cytotoxic action against a variety of cancer cells including breast cancer (MCF-7), neuroblastoma (SHEP and WAC2), human lung carcinoma (A 549), human T-cell leukemia (CCRF-HSB-2), human gastric cancer (TGBC11TKB), human squamous cell cancer (A43), human colon cancer (HT-29) and prostate cancer (PC-3); and the active concentrations have been related to an effective IC_{50}, which was less than 100 µM (Seelinger et al. 2008). Similar chemopreventive effect of luteolin was reported in a 1,2-dimethyl hydrazine (DMH)-induced colon carcinogenesis model. On luteolin administration, both the colon cancer incidence and number of tumors/animal were reported to be significantly reduced along with certain protein markers prominently involved in the initiation and post-initiation stages of colon carcinogenesis, in a dose-dependent manner (Manju and Nalini 2007). Prostate cancer Du145-III cells are considered highly invasive; the treatment of these cells with luteolin resulted in an array of anti-oncogenic events such as suppression of metastatic potential, anchorage-independent spheroid formation and expression of certain cancer stem cell markers (including Nanog, Sox2, CD44 and ABCG2) (Tsai et al. 2016). A study reported high miR-301 expression to be associated with a significantly shorter overall survival in patients with prostate cancer (Han et al. 2016). In the same study, luteolin was shown to inhibit androgen-sensitive and androgen-independent PCa cell lines' growth and induced apoptosis, through a mechanism that also involved miR-301suppression. For gastric cancer, another microRNA subtype (miR-34a) expression has been found to be downregulated and its subdued expression was associated with a significantly shorter overall survival and disease-free state. The miR-34a over-expression could inhibit gastric cancer cells and induce G1 phase arrest via p53/p21 and MAPK /ERK pathways and as reported in one of the studies luteolin decreased the viability of these cells in a dose-dependent manner through marked upregulation of miR-34a (Zhou et al. 2018). Another study previously observed that luteolin exhibited selective killing of STAT3 over-activated gastric cancer cells that show poor prognosis due to drug resistance. The treatment of luteolin in such cells significantly inhibited STAT3 phosphorylation and reduced the expression of STAT3 targeting gene Mcl-1, Survivin and Bcl-xl (Song et al. 2017). It is well known that activated STAT3 in cancer cells is linked with a poor prognosis, drug resistance and shorter survival period in patients as observed in clinical investigations (Gritsko 2006). Studies on metastatic malignancies have shown that ribosomal protein S19 (RPS19) regulates the epithelial–mesenchymal transition (EMT) markers and influence the metastatic abilities of cancer cells as a downstream target of c-Myc activation (Hunecke et al. 2012). Luteolin has been shown to inhibit the metastasis of A431-III cancer cells through inhibition of Src/Cortatin, Akt/mammalian target of rapamycin (mTOR)/c-Myc–RSP12 signaling, thereby blocking the EMT process (Chen et al. 2008; Lin et al. 2011). Furthermore, in another study the anticancer and anti-metastatic activity of luteolin and its oxidovanadium IV complex (VOlut) were investigated and metastasis of colon cancer cells CT26 from the spleen to the liver of mouse was monitored. The presence of the metastatic nodules when the mice were treated with luteolin alone, VOlut, oxidovanadium IV cation and PBS (control group) was also observed. Interestingly, there was no evidence of metastatic nodules in the liver of VOlut-treated mice (100% loss of metastatic potential). Moreover, luteolin alone treatment also resulted in the reduction in colon cancer liver metastasis by 24% (Naso et al. 2016). These observations have a consequential impact on our understanding of multiple processes, which are influenced by luteolin in a diseased state like cancer. Reports on the anticancer studies of luteolin have provided evidence indicating no associated systemic toxicity in the in vivo experimental models (Fang et al. 2007). As mentioned earlier, luteolin has an effective and potent manifestation against cancer cells at lower concentrations, and therefore, it could provide encouraging pharmacological benefits at systemic/tissue concentrations achievable through consumption of luteolin-enriched diet.

Garcinol

Garcinol is a polyisoprenylated benzophenone derivative extracted from the dried rind of the fruit of *Garcinia indica* tree, belonging to family *Clusiaceae*. The fruit is commonly known as kokum or mangosteen, which has medicinal significance in the traditional literature (Padhye et al. 2009; Ahmad et al. 2012a, b). Anticancer action of garcinol has been reported against the breast cancer (ER-positive MCF-7 cells and the TNBC MDA-MB-231 cells), prostate cancer (AR-positive LNCaP, AR-positive but androgen non-responsive C4-2B cells and AR-negative PC3 cells), pancreatic cancer (BxPC-3 cells), colon cancer (HT-29, HCT-116, ICE-6 cells), lung cancer (A-549 cells), cervical cancer (HeLa cells), hepatocellular carcinoma and Burkitt lymphoma (Ito et al. 2003; Hokaiwado et al. 2004;

Hong et al. 2007; Arif et al. 2009; Koeberle et al. 2009; Ahmad et al. 2012a, b). Similar to the activities of other cancer chemopreventive nutraceuticals, garcinol possesses the ability to interfere with pro-oncogenic factors in multiple cell signaling pathways associated with neoplastic transformation. Garcinol was shown to have a strong antitumor activity through inhibition of autophagy and induction of apoptosis in human prostate cancer cells PC-3 mediated by the activation of p-mTOR and p-PI3 kinase/AKT signaling (Wang et al. 2015a, b). The results obtained in the study in a xenograft mouse model were in line with the in vitro anticancer activity as the tumor size was reduced by more than 80% after the administration of garcinol doses. Studies have proposed that most tumors contain a small subset of cells, known as cancer stem cells (CSCs), and this subpopulation of cells are believed to induce, maintain and enhance tumor growth and support invasiveness and metastasis, which is responsible for the failure in chemotherapeutic response and support subsequent relapse (Chen et al. 2012). In a study against NSCLC, A549 cells were observed to undergo extensive apoptotic cell death by garcinol treatment, and as such the cells demonstrated preferential expression of aldehyde dehydrogenase 1 family member A1 (ALDH1A1), a cancer stem-like cell biomarker, that was downregulated by garcinol (Wang et al. 2017a, b). The mechanism also involved garcinol-induced stimulation of DNA damage-inducible transcript 3 (DDIT3), followed with an altered interaction of DDIT3-CCAAT–enhancer-binding proteins beta (C/EBPβ), thereby interfering with the binding of C/EBPβ to the endogenous ALDH1A1 promoter. Moreover, similar inhibition of ALDH1A1 was also reported when garcinol was administered in a xenograft mice model (Wang et al. 2017a, b). Studies have also reported ALDH1A1 expression to be significantly associated with the incidence of lung cancer and with various stages of differentiation in lung cancer and breast cancer, suggesting that its inhibition might be a promising approach in chemopreventive strategies (Zhou et al. 2015). In a recent study, garcinol significantly altered the ability of the H441 and A549 NSCLC cells to form spheres and sensitively inhibited the viability of lung cancer stem cells and differentiated lung cancer cells in a dose-dependent manner (Huanga et al. 2018). The treatment with garcinol also impaired the phosphorylation of LRP6, a co-receptor of Wnt and STAT3signaling cascade, and further downregulated β-catenin, Dvl2, Axin2 and cyclin D1 expressions in NSCLC-generated spheres. These results when further verified in vivo using H441 mouse xenograft model demonstrated that the administration of garcinol significantly inhibited the tumor growth. As described previously, noncoding RNA sequences such as miRNAs modulate cellular mechanisms through posttranscriptional regulation, by either degrading or suppressing the expression of messenger RNAs (mRNAs) which code for critical proteins involved in cancer development and progression (Parasramka et al. 2012). It was shown that garcinol synergizes with gemcitabine to inhibit cell proliferation and induce apoptosis in pancreatic cancer PaCa cells with significant modulation of key cancer regulators including PARP, VEGF, MMPs, ILs, caspases and NF-κB. In addition, these two agents in combination modulated a number of microRNAs (miR-21, miR-196a, miR-495, miR-605, miR-638, and miR-453) linked to various oncogenic signaling pathways (Parasramka et al. 2013). The effects of garcinol in combination with cisplatin in head and neck squamous cell carcinoma (HNSCC) also indicated its chemosensitizing effects by negatively modulating the activation of NF-κB and various proliferative and inflammatory biomarkers both in vitro and in vivo (Li et al. 2015). In the xenograft mouse model, it was observed that garcinol or cisplatin alone reduced tumor volume by 50%, but the co-administration of the two agents enhanced the effect to a significantly greater extent, along with the suppression of proliferative biomarkers (Ki-67 and CD31). Further analyses of tumor tissues showed that garcinol also downregulated the expression of critical oncogenic molecules involved in proliferation (cyclin D1, COX-2), survival (Bcl-xL, survivin), angiogenesis (VEGF) and invasion (MMP-9, ICAM-1), and such effects were further enhanced with cisplatin cotreatment. As stated, the effect of garcinol against the cancer stem cells and proliferative markers provides evidence that these nutraceuticals have the ability to nip the cancer in bud before an abnormal differentiation toward neoplastic disease occurs. The stem cells are also an integral element of normal tissue and are found in various organs where these cells are engaged in significant roles in cell renewal and tissue repair. Higher concentrations of garcinol (40%) have been shown to be well tolerated in rodent models (Majeed et al. 2018). Thus, nutraceuticals such as garcinol under routine dietary course might have beneficial preventive outcomes by blocking the undesired cellular events that lead toward abnormal differentiation.

Conclusions for future biology

It has been known throughout the human civilization that there is a methodical relationship between diet and human diseases, which in recent decades has been evinced owing to the enduring influence of dietary components on cellular mechanisms. Hippocrates advocating the utilization of food as medicine was one of the earliest (460–377 B.C) recognition of the above relationship, which, nonetheless, reflected the importance of dietary ingredients for their therapeutic and preventive bioactive components due to their elevated margin of safety and desired range of efficacy. The term nutraceutical has been a recent addition to the literature, to bring into focus certain components of dietary origin

Table 2 A brief summary of the anticancer cell signaling by nutraceuticals

Nutraceuticals	Dietary sources	Cancer prevention	Signaling pathways	References
Cucurbitacins	Cucurbitaceous fruits and vegetables	Lung	P13 Kinase, MAPK	Silva et al. (2016)
		Breast/Osteosarcoma	Cytoskeleton	Wang et al. (2017a, b)
		Cervical	STAT3,Rb,p21,p27	Sikander et al. (2016)
		Breast	Akt, NF-kB	Ku et al. (2017)
		Liver	EGFR, MAPK	Mahnashi et al. (2019)
Morin	Fig, mulberry, almonds	Colon	Bcl-2, Fas receptor	Hyun et al. (2015)
		Bladder	MMP-9	Shin et al. (2017)
		Cervical	P21,p53,P13K,mTOR	Zhang et al.(2018a, b)
		Colon	β-catenin, c-myc	Sharmaa et al. (2017)
		Ovarian	EMT	Nowak et al. (2020)
Fisetin	Strawberry, apple, grapes, Onion	Endometrial	CDK, ATM-Chk1/2	Wang et al. (2015a, b)
		Breast	PTEN,Akt,GSK3β	Li et al. (2018)
		Pancreatic	ERK-MYC	Kim et al. (2018)
		Oral	Beclin-1	Park et al. (2019)
		Head & Neck	SESN2, mTOR, Mcl-1	Won et al. (2019)
Curcumin	Turmeric	Prostate	Notch-1	Yang et al. (2017)
		Lung	PI3K,Akt,mTOR	Liu et al. (2018)
		Colorectal	Nrf-2	Zhang et al. (2018a, b)
		Wilms' tumor Pancreatic	RECK	Jia et al. (2019)
			TIMP1/2,MMP2/9	Liu et al. (2020)
Luteolin	Broccoli, parsley, Thyme, pepper	Prostate	JNK, Nanog	Tsai et al. (2016)
		Gastric	MiR-34a, HK-1	Zhou et al. (2018)
		Liver	Trail, JNK	Uddin and Park(2019)
		Colon	ERK, FOXO3a	Potočnjak et al. (2020)
		Breast	Akt,mTOR	Wu et al. (2021)
Garcinol	Mangosteen	Oral	NF-kB	Aggarwal and Das (2016)
		Lung	DDIT3, C/EBPβ	Wang et al. (2017a, b)
		Cervical	T-cadherin	Zhao et al. (2018)
		Gastric	P13K/Akt	Zheng et al. (2020)
		Endometrial	JNK	Zhang et al. (2021)

that show associated health benefits. As mentioned, several epidemiological, laboratory, preclinical and clinical studies on carcinogenesis have indicated the pharmacological significance of nutraceuticals in cancer chemoprevention paradigm. Moreover, as a proponent of multi-targeted therapy, multiple action mechanisms have been reported for these diet-derived chemopreventive agents of herbal origin to prevent, retard, block or reverse carcinogenesis (Pandeya et al. 2017) (Table 2). Interestingly, unlike the conventional drugs, these molecules have multiple targets and are thus of potential value in diseases like cancer where multiple pro- and anti-oncogenic pathways are substantially altered. Such an approach for prevention of cancer also assumes significance in light of WHO (World Health Organization) observation that recognizes traditional medicine which is majorly based on phyto-ingredients and many of which are of dietary origin, as "an accessible, affordable and culturally acceptable form of health care trusted by large numbers of people" (WHO 2013). Interestingly, available data in the literature suggest that an appropriate dietary pattern and physical activities can prevent approximately one-third of all cancers (Anand et al. 2008c, a, b). It is believed that the dietary nutraceuticals have attracted much attention in cancer chemoprevention, primarily due to significantly lower toxicity by ensuring selective killing of cancer cells (by certain dietary agents). Moreover, as reported for various plant-derived nutraceuticals, these have selective cytotoxicity, targeting the cancer cells, whereas normal cells are refractory to such a cytotoxic action (Chang et al. 2014; Seydi et al. 2018). It is understood that such a pharmacological property has been a choice of prominence for any current standard chemotherapeutic regimen in order of providing efficacy in both the treatment and post-treatment management of cancer disease. Thus, the critical step in the approach for primary prevention of cancer disease must ensure to incorporate chemopreventive diets rich in nutraceuticals within the regular dietary routine. However, the limiting factor in the rationalization of these molecules in anticancer premises is high metabolic transformations and lower bioavailability, restricting the cells to achieve pharmacologically effective concentrations at the target site in a physiological state. Interestingly, several studies have focused on this issue and proposed novel approaches to circumvent it. The concept of "nanochemoprevention" was proposed to enhance the efficacy of dietary nutraceuticals in cancer chemoprevention (Siddiqui et al. 2010). It

has been demonstrated that low bioavailability and systemic toxicity can be addressed through the application of drug-loaded nanosized drug carriers, such as polymeric nanoparticles (NPs), liposomes, dendrimers and micelles (Aqil et al. 2013), which can deliver these phytochemicals at the target site in effective concentrations. Accordingly, curcumin encapsulated into monomethyl poly(ethylene glycol)–poly (ε-caprolactone)–poly(trimethylene carbonate) (MPEG-P(CL-co-TMC)) micelles has shown greater apoptosis induction and cellular uptake in colon cancer CT26 cells compared with free curcumin Yang et al. 2015). Curcumin micelles were also more effective in suppressing the tumor growth of subcutaneous CT26 colon in vivo, and the mechanisms included the inhibition of tumor proliferation and angiogenesis along with an accelerated rate of apoptosis of tumor cells. Several other studies have also reported enhanced efficiency of liposomal curcumin formulation for growth inhibitory and pro-apoptotic effects on cancer cells (Feng et al. 2017). Additionally, a novel garcinol-loaded PLGA-based nanoparticulated (GAR-NPs) drug delivery system using vitamin E TPGS as emulsifier has been recently reported (Gaonkar et al. 2017). The in vitro cytotoxicity experiments performed against different cancer cell lines demonstrated the comparatively high cytotoxic potentials of GAR-NPs than free GAR. Further, ^{99m}Tc-radiolabeled-GAR-NPs also exhibited substantially high cell binding, internalization and accumulation at the tumor site when administered to B16F10 melanoma tumor bearing mice. Though the variability in the in vivo effects and clinical trials observed for the chemopreventive action of these polyphenols are largely attributed to constraints associated with absorption, metabolic biotransformation and bioavailability, the least or no toxicity, easy accessibility and potential to interfere with multiple cancer cell signaling pathways have been the promising factors for exploring these small molecules for precise intervention in cancer chemoprevention. It is presumed that research on innovative approaches such as nano-carriers can circumvent the impediment associated with the lower bioavailability of these natural drugs, nutraceuticals. In addition, synergistic chemopreventive effects by the combined action of several of these nutraceuticals also hold a promising future consideration to circumvent bioavailability issues. Recently, we have also reviewed certain dietary molecules for their ability to influence the aberrant alterations in cell's epigenome and their significance in epigenetic therapy against cancer (Ullah et al. 2020). In light of the evidences discussed above and reported extensively in the literature, it may be stated convincingly that cancer prevention strategies may have a consequential benefit from the anticancer potential of dietary agents. Considering food as a part of culture, it is believed that since its inception, human civilizations have evolved with the sophisticated knowledge of diet-derived health benefits and have rather contributed enormously in associating food with their well-being. So can we make choices to change our future? Indeed, a determined approach to life style modifications including dietary habits can influence our state of health in a way that could prevent advancement to chronic illness.

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