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Proof-of-concept about the role of dietary agents in the inhibition and prevention of carcinogenesis and metastasis: Focus on animal model studies

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ABSTRACT: The field of nutrigenomics has gained considerable limelight and interdisciplinary researchers have started to realize its significance as a goldmine for the discovery of pathways that are important as dietary targets. Emerging evidence has provided wealth of exciting proof-of-concept studies highlighting an important role in the elucidation of oncogenic signaling cascades that can be pharmacologically targeted by dietary agents, whole extracts and isolated compounds for the inhibition/prevention of carcinogenesis and metastasis. In this review, we have critically analyzed some of the mechanistic animal models studies which have rationally propelled the field in a frontward direction. We also provide an overview of the fruits-mediated anti-metastatic effects in metastasis models that highlight how nutrigenomics may be combined with pharmacological therapies for synergistic effects, potentially ushering a path towards precision nutrition for cancer.

KEYWORDS: Cancer; Nutrigenomics; Metastasis; Cell signaling; Apoptosis.

1. INTRODUCTION

Cancer cells differ from normal cells in their remarkable capacity to proliferate and survive by rewiring of the deregulated pathways. Deregulated transduction cascades are frequently overexpressed in highly active and metastatically competent cancer cells [1-3]. Cellular and clinical studies have unraveled wide ranging mechanisms which underlie uncontrolled proliferation of cancer cells, acquired drug resistance, tumor cell plasticity, loss of apoptosis, invasion and colonization of metastatic cancer cells to the distant organs [4,5]. However, acquired resistance, off-target effects and drug-induced toxicities are some of the major issues associated with the clinical drugs. Landmark developments in the era of molecular biology have dissected the signaling pathways and protein networks which regulate the cancer progression and metastasis. Thus, basic and clinical researchers have witnessed significant enrichment in the existing knowledge about transcriptional, post-transcriptional, translational and post-translational aspects which centrally drive multiple stages of the cancer onset and progression [6,7]. Regulation of different oncogenic pathways and protein networks by natural products and dietary agents has increased exponentially after noteworthy discoveries in the functional genomics [8-12].

High-fat diet has a central role in metastasis. Tumor-conditioned media (TCM) induced an experimental pre-metastatic niche in the lungs and fueled pulmonary metastasis. It was shown that injection of 4T07 cancer cells in mice pre-treated with 4T1 tumor-derived TCM resulted in a 6.8-fold increase in metastatic invasion and colonization of cancer cells. There was an increase in the concentration of palmitate in the lungs during the formation of pre-metastatic niches. Alveolar type II (AT2) cells increased the lipid release in response to tumor-conditioned media. AT2 cells isolated from mice undergoing spontaneous pre-metastatic niche formation by dissemination of 4T1 primary breast tumors displayed a significant overexpression of the lipid production and pulmonary surfactant release genes. It was found that high fat diet induced an increase in the percentage of AT2 cells. Carnitine palmitoyltransferase 1a (CPT1a) promoted metastasis [13, 14].

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High-fat diet enhances liver metastasis in mice intrasplenically injected with prostate cancer cells [15, 16]. Progression of lung cancer has also been reported to be enhanced in mice fed with high-fat diet [17, 18]. High-fat diet enhances circulating extracellular vesicles in diet-induced obesity mouse models. These vesicles are loaded with ECM (extracellular matrix protein-1) and deliver ECM1 to the breast cancer cells. High-fat diet not only increased ECM1 within extracellular vesicles but also in the breast cancer tissues derived from E0771 cancer cells in tumor-bearing mice. Importantly, diet-induced obese mouse models had larger tumors and enhanced lung metastasis. Similar results were observed in the 4T1-bearing BALB/c mouse model, where high-fat diet increased ECM1 in the circulating extracellular vesicles and in the tumor tissues [19]. 60% high-fat diet led to the development of more pulmonary nodules as compared to the mice fed 10% fat diet as evidenced by significant increase in lung weight and metastatic nodule counts [20]. Overall, there is a rapid increase in published evidence related to central role of high-fat diet in cancer progression [21, 22].

In this mini-review, we have made efforts to critically and mechanistically analyze how fruits played role in the prevention/inhibition of different cancers.

2. FRUITS

2.1. Citrus Fruits

Citrus fruits are increasingly being recognized to have a central role in exerting health-promoting effects. Furthermore, citrus fruits have been shown to inhibit/prevent cancer progression [23, 24]. In this section, we have critically analyzed how the extracts and pharmacologically active chemicals from citrus fruits inhibit carcinogenesis and metastasis.

DOT1L (disruptor of telomeric silencing 1-like) is a methyltransferase that catalyzes mono-, di-, and tri-methylation of H3K79 [25]. DOT1L works synchronously with c-Myc and p300 acetyltransferase for epigenetic activation of epithelial-to-mesenchymal transition (EMT) regulators in progression of gastric cancer. DOT1L increased the levels of H3K79me2 and stimulated the expression of N-cadherin, Fibronectin, Twist, MMP-2 and MMP-9. Stability of DOTL1 is necessary for the metastasis of gastric cancer cells. CBP (CREB-binding protein), a histone acetyltransferase regulates the acetylation of DOT1L thus preventing its binding with E3 ubiquitin ligase and consequent degradation through the ubiquitination [26]. Hesperetin, a citrus flavanone is isolated from citrus fruits. Hesperetin enhances ubiquitination and proteasomal degradation of DOT1L through inhibition of CBP activity (Figure 1). There was a profound reduction in the number of pulmonary metastatic nodules in mice injected with DOT1L-knockdown MKN45 cancer cells [27]. Nobiletin, a flavonoid derived from citrus peel has also been shown to highly effective against different cancers. Nobiletin suppressed invasive and migratory abilities of breast cancer cells by inactivation of ERK/STAT and JNK/c-JUN signaling. Nobiletin markedly reduced the hepatic metastatic lesions in mice injected with breast cancer cells into the spleens of a liver metastasis model (Figure 1) [28].

Peel of Citrus unshiu Marcow Fruits is also rich in different anticancer biomolecules. Ethanolic extracts induced an increase in the levels of pro-apoptotic Bax and concomitantly downregulated anti-apoptotic BCL-2 in B16F10 melanoma cells. Ethanolic extracts decreased the levels of MMP-2 and MMP-9 in B16F10 cells. However, Ethanolic extracts dose-dependently increased TIMPs (Tissue Inhibitor of Metalloproteinases). There was a remarkable reduction in the number of metastatic tumor nodules in mice orally administered with ethanolic extracts (Figure 1). Similarly, brown-spotted tumor cells were increased by B16F10 cells inoculation, whereas ethanolic extracts caused significant reduction. Additionally, ethanolic extracts suppressed lung inflammation in mice. Overexpression of TNFα in lung metastatic tissues was found in mice injected with B16F10 melanoma cells. However, ethanolic extracts significantly downregulated the levels of TNFα [29]. These findings clearly indicated that ethanolic extracts of Citrus unshiu efficiently reduced tumor progression, pulmonary metastasis and inflammation.

2.2 Grapes

Grape seed proanthocyanidins have the ability to reduce the metastatic spread of breast cancers. 4T1 breast tumor cells metastasize from primary tumor sites to the distantly located organs within 2 weeks in animal models. Grape seed proanthocyanidins inhibited metastatic dissemination of 4T1 cancer cells from the primary tumor sites to the lungs as evidenced by reducing the size and number of the metastatic tumor nodules on the surface of lungs [30].

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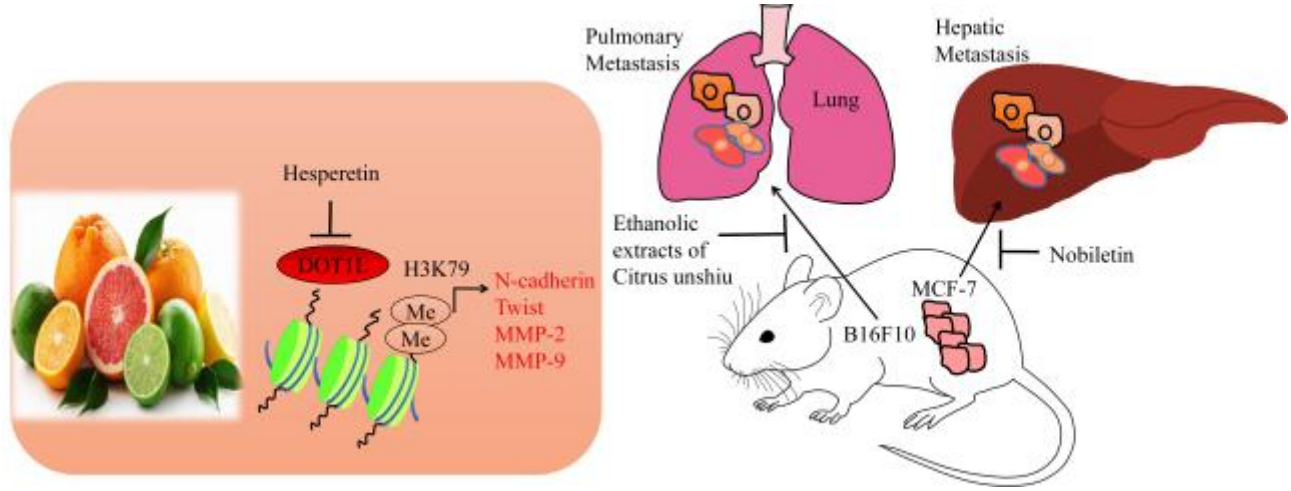

Figure 1. Hesperetin enhances ubiquitination and proteasomal degradation of DOT1L. DOT1L stimulates the expression of N-cadherin, twist, MMP-2 and MMP-9. Ethanolic extracts of Citrus unshiu inhibited metastatic dissemination of B16F10 to the lungs. Nobiletin inhibits the metastatic spread of breast cancer cells to the liver.

MDA-MB-435 cells were injected orthotopically into the mammary fat pad of female nude mice for the establishment of primary tumors. Moreover, MDA-MB-435 cell line has the ability to preferentially metastasize to the bones. Grape polyphenols although did not effectively block metastases of cancer cells to the lungs but efficiently reduced metastatic lesions in bones and liver [31]. Grape polyphenols (resveratrol, catechin and quercetin) did not inhibit metastatically competent cancer cells from being released to the vascular system or lymphatics from the primary tumors. Grape polyphenols also did not block the entry of cells into the lungs. Instead, consequent metastatic dissemination and invasion of the cancer cells to the bones and liver were potently suppressed by Grape polyphenols. These findings indicated that Grape polyphenols prevented the establishment of further metastases either by blocking the exit from the lung vasculatures or at the entry points of localized transduction pathways within the microenvironments of liver and bones [31].

2.3 Berries

Malvidin-3-galactoside, an anthocyanin isolated from blueberry, suppressed the onset and progression of hepatocellular carcinoma. PTEN (Phosphatase and Tensin homolog deleted on chromosome 10) is a tumor suppressor and negatively regulates the activation of AKT. Malvidin-3-galactoside increased the levels of PTEN and exerted repressive effects on phosphorylated levels of AKT. Malvidin-3-galactoside potently reduced the tumor growth in mice injected with HepG2 cells [32].

Myricetin isolated from different berries has been found to be effective against cancer. Myricetin suppressed the levels of MMP-2 and MMP-9 in breast cancer brain metastasis cell lines (MDA-Mb-231Br). ST6GALNAC5 increased the brain extravasation ability of MDA-MB-231Br cells. Myricetin also considerably reduced the levels of ST6GALNAC5. Intraperitoneally administered myricetin has been shown to suppress the metastatic lesions on the surface of the lungs in mice injected with 4T1-breast cancer cells [33].

c-MET is a receptor tyrosine kinase and promotes cancer progression. HGF (hepatocyte growth factor) activates intracellular signaling via c-MET. HGF/c-MET activates AKT and ERK activation in colon cancer cells. Ellagitannin-rich cloudberry inhibits HGF/c-MET axis and inactivates AKT and ERK-mediated signaling. The Apc^{Min} mouse is a highly acclaimed model of intestinal neoplasia. Ellagitannin-rich cloudberry effectively reduced intestinal tumors [34].

Matrix metalloproteinases (MMPs) have been found to be associated with invasion and metastatic dissemination of cancer cells. Gomisin A, a lignan isolated from the fruits of *Schisandra chinensis* efficiently inhibited the activity of MMP-2 and MMP-9 in B16F10 and A375SM melanoma cells. Gomisin A markedly inhibited the pulmonary metastasis of melanoma cells in an animal model [35].

2.4 Tomatoes

α-Tomatine, a glycoalkaloid isolated from tomatoes has been found to be effective against colon cancer cells. α-Tomatine induced caspase-independent cell death of colon cancer cells. α-tomatine efficiently promoted the nuclear accumulation of AIF (apoptosis-inducing factor) and downregulation of survivin. More importantly, intraperitoneally administered α-tomatine inhibited tumor progression in BALB/c mice intracutaneously transplanted with CT-26 cancer cells [36].

α-Tomatine works synergistically with paclitaxel and inhibits the growth of PC-3 cells. Moreover, α-tomatine and paclitaxel combinatorially inhibit PI3K/AKT signaling in prostate cancer cells. Moreover, α-tomatine and paclitaxel remarkably suppressed BCL-2/ BCL-xL and concomitantly enhanced BAD levels in PC-3 cancer cells. Essentially, α-tomatine markedly improved the efficacy of paclitaxel and induced shrinkage of the tumors in mice xenografted with PC-3 cancer cells [37].

Lycopene enriched tomato extracts have been shown to reduce *N*-Nitrosodiethylamine induced hepatocellular carcinoma [38].

2.5 Mango

Mangiferin, a naturally occurring glucosylxanthone, isolated from *Mangifera indica* is an effective anticancer agent. Mangiferin enhanced cisplatin sensitivity in OVCAR8 cancer cells primarily through the inhibition of YAP. Cisplatin and mangiferin combinatorially induced regression of the tumor mass in BALB/c nude female mice inoculated with OVCAR8 cancer cells [39].

Mangiferin reduced the number of pulmonary metastatic tumor nodules upon intravenous puncture of colorectal cancer cells in the mouse tail veins (Figure 2). There was a dose-dependent reduction in the number of pulmonary surface metastatic nodules in mice injected with CT26 cancer cells [40].

Mangiferin inhibited the growth of tumors by stimulating the expression of PUMA, p53, phosphorylated-p53, cleaved caspase-3, cleaved PARP-1. Moreover, mangiferin exerted suppressive effects on anti-apoptotic proteins (survivin and BCL-xL). Mangiferin reduced the number of lung metastatic nodules in mice injected with B16BL6 melanoma cells into the footpad of mice. Orally administered mangiferin did not show detectable toxicities in treated mice [41].

PSM001, a homo-polysaccharide isolated from the seed kernel of Kottukonam variety of *Mangifera indica* has been found to be effective. Galactoxyloglucan (PST001) isolated from the seeds of *Tamarindus indica* is also an efficient cancer chemopreventive agent. Ehrlich ascites carcinoma (EAC) and Dalton's lymphoma ascites (DLA) were maintained in the peritoneal cavity of mice by intraperitoneally transplanted cells. PSM001 was reported to be active against EAC and DLA. PSM001 and PST001 reduced MMP-2 and MMP-9 levels in A375 cells. Overall, PSM001 and PST001-mediated inhibition of matrix metalloproteinases markedly reduced invasive potential of cancer cells. PSM001 and PST001 worked proficiently with vincristine and significantly reduced the number of pulmonary metastatic nodules in C57BL/6 mice injected with B16F10 melanoma cells (Figure 2) [42].

2.6 Coconut

Coconut water vinegar at a higher concentration (2 ml/kg body weight) significantly suppressed the tumor growth in mice xenografted with 4T1 breast cancer cells. Tumor-bearing mice treated with low concentration of Coconut water vinegar (0.08 mL/kg body) showed the metastasis of 4T1 cells in the liver but not in the lungs and spleen (single event). However, Coconut water vinegar at a higher concentration significantly inhibited metastasis in the liver, lungs and spleen. High concentration of coconut water vinegar significantly reduced the levels of VEGF and MMP9 in the tumor tissues of the mice xenografted with 4T1 breast cancer cells. Coconut water vinegar induced an increase in the subpopulations of cytolytic T lymphocyte ($CD3^+CD8^+$) and NK cells (NK1.1+) in the spleen of xenografted mice [43].

2.7 Pineapple

Bromelain is a collection of proteases isolated from pineapple. Bromelain and cisplatin combinatorially inhibited the tumor growth in mice inoculated with 4T1 breast cancer cells [44].

Bromelain was also found to be efficient against metastasis. Injection of B16F10 melanoma cells into BDF-1 mice resulted in the colonization of cancer cells to the lungs. Bromelain impaired metastasizing ability of melanoma cells to the surface of the lungs in mice [45]. Pineapple vinegar induced regression of the tumors in mice xenografted with 4T1 breast cancer cells. Pineapple vinegar increased the levels of $CD4^+/CD8^+$ and natural killer cell populations and concomitantly reduced the levels of macrophages in the mouse splenocytes significantly [46].

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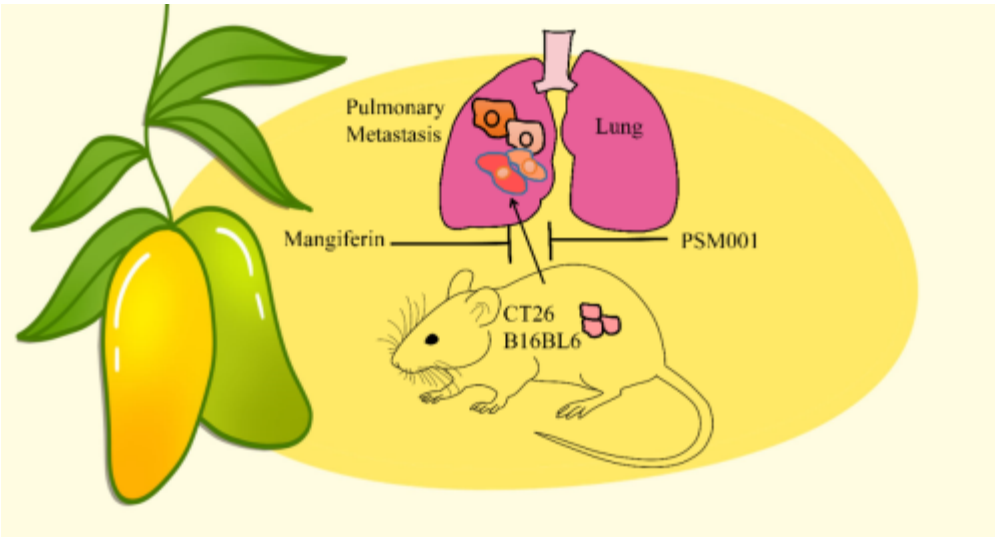

Figure 2. Mangiferin and PSM001 effectively impaired the metastasis of cancer cells to the lungs.

2.8 Apple

Pectic acid, a bioactive chemical isolated from apple effectively impaired the tumor growth in BALB/c female mice subcutaneously injected with 4T1 cancer cells [47]. Annurca apple polyphenol extracts reduced the number of polyps and eliminated high-grade dysplasia in ApcMin/+ mice [**48**].

Apple oligogalactan worked synergistically with chemotherapeutic drugs. Apple oligogalactan and celecoxib combinatorially protected ICR mice against chemical-induced colitis-associated colorectal cancer [49]. Apple oligogalactan and 5-fluorouracil combinatorially induced an increase in the levels of APAF-1 and Cytochrome c. Apple oligogalactan and 5-fluorouracil significantly reduced the xenograft tumor volume in mice inoculated with HT-29 cells [50].

2.9 Pomegranate

Pomegranate is a highly nutritional and delicious fruit. Tremendous amount of research works have highlighted mechanistic role of extracts and bioactive chemicals in prevention/inhibition of different cancers [51, 52]. Pomegranate extracts interfered with STAT3-mediated transcriptional upregulation of survivin. Survivin has been shown to inhibit apoptotic death in prostate cancer cells. Low concentrations of docetaxel induced an increase in survivin protein in prostate cancer cells. Whereas, pomegranate extracts effectively attenuated docetaxel-mediated increase in survivin. Collectively, these findings provided evidence that Pomegranate extracts antagonized docetaxel-induced survivin, activated apoptotic pathway and sensitized prostate cancer cells to docetaxel. Pomegranate extracts suppressed the levels of PSA (Prostate specific antigen) and impaired tumor growth in athymic nude mice bearing intratibial C4-2 xenografts. Pomegranate extracts in combination with docetaxel displayed improved architecture with reduced osteoblastic lesions and osteolytic destruction [53].

Pomegranate peel extracts remarkably reduced invasive potential of prostate cancer cells via repression of MMP-2 and MMP9 [54]. Oral consumption of pomegranate fruit extracts effectively reduced lung tumor multiplicity and incidence induced by chemical carcinogens [55].

2.10 *Litchi chinensis*

Procyanidins isolated from the seeds of *Litchi chinensis* efficiently inhibit tumorigenesis and metastasis. Procyanidins generated anti-colon cancer T cell immunological responses primarily through gut microbiota and short-chain fatty acids. There was a significant reduction in the levels of CD3e+ T, CD8+ T, Granzyme B and butyric acid in mice treated with rifaximin (broad-spectrum antibiotic) and procyanidins. Therefore, procyanidins enhance gut microbiota and increase short-chain fatty acids. Procyanidins induced an increase in peripheral number of CD8+ cytotoxic T cells and increased the ratio of CD8+/CD4+ cells. Procyanidins repressed the metastasis rate by reducing the metastatic lesions and number of tumor nodules in mice injected with CT26 cancer cells [56].

2.11 *Cudrania tricuspidata*

6,8-Diprenylgenistein (6,8-DG), an isoflavonoid isolated from *Cudrania tricuspidata* was found to be efficient against oral cancer. Intraperitoneal injections of 6,8-DG inhibited lymph node metastasis in mice submucosally injected with VEGF-A overexpressing SCCVII cells into the tongue [57].

2.12 Indole-3-carbinol

Indole-3-carbinol (I3C) is a naturally occurring biomolecule present in cruciferous vegetables. Indole-3-carbinol exerted inhibitory effects on β-catenin, c-myc, and cyclin D1 in EC18 and TE1 cells. It also induced shrinkage of the tumors in BALB/c mice xenografted with EC18 cells [58]. Collectively, these findings indicated that Indole-3-carbinol inhibited Wnt/β-catenin signaling in esophageal squamous cell carcinoma cells.

2.13 Resveratrol

Recent advancements have led to considerable developments in developing a better comprehension of the mechanisms of invadosomes. WASP contains a binding region for CDC42. WASP also binds to ARP2/3 complex and activates it. WASP overexpression reversed the inhibitory effects of sulforaphane on invadopodia formation. Tyrosine phosphorylation of cortactin is essential to recruit and activate proteases associated with invadopodia formation. Enforced expression of phospho-cortactin levels in bladder cancer cells led to the reversal of the inhibitory effects of sulforaphane on invadopodia formation and cell invasion. Sulforaphane inhibits AKT1-mediated ATP production and impairs the formation of pseudopodia. Within ARP2/3 complex, ATP binds to ARP2 subunit. Sulforaphane suppressed the metastatic tumor growth by reducing the volume of pulmonary metastasis in mice injected with T24 cancer cells. Expression levels of ARP2 and cortactin were found to be significantly reduced in the metastatic lung tissues [59].

3. Concluding remarks

Exciting breakthroughs in the field of nutrigenomics have revolutionized the field of molecular biology. However, additional proof-of-concept studies dealing with the extraction of the active compounds from fruits and investigation of molecular regulatory mechanisms of the bioactive compounds in xenografted mice, zebrafish models are required to comprehensively characterize the efficacy of dietary agents and fruits in nutraceutical industries.

The ability to carry out in-vivo imaging, genetic and chemical screenings, and high-throughput transgenesis demonstrated novel opportunities for functional characterization of multi-dimensional aspects of nutrigenomics. Besides, increasingly sophisticated modeling of combinations of epigenetic and genetic alterations has shaped the zebrafish as a low-cost, functional cancer model to complement what can be achieved in other models, such as human cell culture systems and rodent models.

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