COMMENTARY

Citrus Fruits and their Bioactive Ingredients: Leading Four Horsemen from Front

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Abstract

Cancer is a multifaceted and genomically complex disease and rapidly accumulating high impact research is deepening our understanding related to the mechanisms underlying cancer development, progression and resistance to therapeutics. Increasingly it is being realized that genetic/epigenetic mutations, inactivation of tumor suppressor genes, overexpression of oncogenes, deregulation of intracellular signaling cascades and loss of apoptosis are some of the extensively studied aspects. Confluence of information suggested that rapidly developing resistance to therapeutics is adding another layer of complexity and overwhelmingly increasing preclinical studies are identifying different natural agents with efficacy and minimal off-target effects. We partition this multi-component review into citrus fruits and their bioactive ingredients mediating rebalancing of pro- and anti-apoptotic proteins to induce apoptosis in resistant cancer cells. We also discuss how oncogenic protein networks are targeted in cancer cells and how these findings may be verified in preclinical studies.

Keywords: Signaling - cancer - apoptosis - in-vivo 0 citrus fruits - bioactive ingredients

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Introduction

There has been a phenomenal progress in the field of apoptosis and increasingly it is being realized that cancer cells tactfully escape from apoptotic cell death. Apoptosis is generally triggered either by intrinsic or extrinsic mechanisms. The intrinsic apoptosis involves mitochondrial membrane permeablity that can be triggered by stress, cellular damage, UV light exposure etc. On the other hand extrinsic pathways are initiated by binding of ligands to trans-membrane receptors. Extrinsic apoptosis is being triggered by binding of TNF-alpha , FasL ligand and TRAIL (Tumor necrosis factor alpha-related apoptosis inducing ligand) to their respective receptor to form a trimeric complex that induces the formation of DISCs (Death inducing signaling complex) thus forming a signalosome consisting of proteins including FADD and procaspase-8. Caspase-8 further activates its downstream effector caspase-3. Intrinsic mechanism involves caspase-8 mediated proteolytically processed tBid induced increased permeability of mitochondrial membrane. There is an overwhelmingly increasing list of natural agents reported to efficiently induce apoptosis in cancer cells (Banjerdpongchai et al., 2014; Boonyarat et al 2014; Zhang et al., 2014).

In this review we summarize most recent advancements in our understanding of modulation of cellular activities and protein network by phytochemicals isolated from citrus fruits.

Apoptosis

Hesperetin, a flavonoid from citrus fruits, considerably activated caspase-8, caspase-9 and caspase-3 in cervical cancer cells. Moreover, receptor for Fas Ligand and its adaptor protein Fas-associated death domain-containing protein (FADD) were notably increased in treated cervical cancer cells (Alshatwi et al., 2013). Limonoids particularly, Obacunone glucoside (OG) and obacunone purified from Marsh White grapefruit seeds considerably inhibited SW480 cell proliferation. Higher cytosolic accumulation of cytochrome c indicated limonoids mediated activation of intrinsic pathway (Chidambara Murthy et al., 2011). Hesperetin, a flavanone glycoside has been noted to induce apoptosis in cancer cells primarily through activation of caspase-9, as pre-treatment with caspase-9 specific inhibitor (Z-LEHD-fmk) significantly abrogated induced Hesperetin apoptotic effect (Palit et al., 2014). 5-acetyl-6,7,8,4'-tetramethylnortangeretin, tangeretin derivative markedly functionalized intrinsic

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pathway in MCF-7 breast cancer cells (Wang et al., 2014).

Cell Cycle Arrest

It is becoming progressively more understandable that cell cycle is tactfully modulated by a intricate protein network consisting of cyclins and cyclin-dependent kinases (CDKs). Cyclin D1–CDK4 and cyclin D1–CDK6 complexes are activated in response to a mitogenic signal. Phosphorylation of Retinoblastoma proteins (Rb) by these complexes further results in release and activation of E2Fs. cyclin E–CDK2 complex mediated phosphorylation of Rb resulted in entry into S phase. There is a well orchestrated system activated via p53 mediated transcriptional upregulation of p21CIP (CDKN1A), which inhibited different cyclin–CDK complexes to induce cell cycle arrest.

5-Geranyloxy-7-methoxycoumarin, isolated from hexane extract of *Citrus aurantifolia* induced cell cycle arrest at G0/G1 phase in colon cancer (SW480) cells (Patil et al., 2013). Cell cycle arrest was induced in A549 lung cancer cells upon treatment with flavonoids isolated from Korean Citrus aurantium L (Park et al., 2012).

Ethanolic extract of *Citrus aurantifolia* lime peels (CPE) has recently been reported to enhance sensitivity of MCF-7 cells to doxorubicin. Dose dependently, CPE exerted cell cycle arrest as evidenced by cell accumulation at G1 phase at 6 μg/mL and cell accumulation at G2/M phase at 15 μg/mL (Adina et al., 2014).

Akt

Obacunone and obacunone glucoside (OG) dose dependently induced downregulation of Akt in LNCaP cells (Murthy et al., 2015). Akt activity was also inhibited in TSGH-8301 bladder cancer cells upon treatment with Naringenin (Liao et al., 2014).

NFKB

Naringin, a bioflavonoid notably reduced expression of p-NF-κB p65 in cervical cancer cells (Zeng et al., 2014).

ASK1/JNK pathway

JNK was functionally active in Hesperetin treated cells and JNK inhibitor SP600125 remarkably reduced Hesperetin mediated effects. On a similar note, ASK1 was also observed to be active upon treatment and ASK silenced cells did not show expected results upon treatment with Hesperetin. Mechanistically it was shown that apoptosis was triggered via ROS accumulation and ASK1/JNK pathway activation in hesperetin treated MCF-7 cells (Palit et al., 2014).

ERK1/2 Pathway

MAPK superfamilies are serine/threonine protein kinases reported to modulate multifaceted biological activities by transducing the signals to downstream effectors. MAPK pathway was noted to be inhibited in colon cancer HT-29 cells treated with Bergamot juice extract (Visalli et al., 2014).

Nobiletin, a polymethoxyflavonoid considerably inhibited phosphorylated ERK1/2 levels in nasopharyngeal carcinoma NPC-BM and HONE-1 cells (Chien et al., 2015). Nobiletin suppressed proliferation of C6 glioma cells by inhibiting Ras activity. Phosphorylated levels of both MEK and ERK were reduced after treatment. Another important link explored in the study was Ca2+-sensitive PKC exerted inhibitory effects on ERK induced signalling in Nobiletin treated cells (Aoki et al., 2013). Phosphorylated levels of p38 MAPK were also reduced in 5-Geranyloxy-7-methoxycoumarin treated colon cancer (SW480) cells (Patil et al., 2013).

MMP

MMP2 expression was also noted to be reduced in Nobiletin treated nasopharyngeal carcinoma NPC-BM and HONE-1 cells (Chien et al., 2015). Metastasis was inhibited in chemically induced cancer model via inhibition of MMP2 and MMP9 by Tangeretin (Arivazhagan and Sorimuthu Pillai, 2014). Migratory potential of TSGH-8301 bladder cancer cells was reduced upon Naringenin mediated targeting of MMP2 (Liao et al., 2014).

VCAM-1

Vascular cell adhesion molecule-1 (VCAM-1) of the immunoglobulin superfamily is noted to be involved in cancer progression. Both migratory and invasive potentials of chondrosarcoma cells were reduced upon treatment with naringin. Mechanistically it was shown that naringin induced expression of miR-126 that negatively regulated VCAM-1 (Tan et al., 2014). It has recently been convincingly revealed that Flavonoids from Citrus unshiu Marc considerably inhibited VCAM-1 expression in breast cancer MDA-MB-231 cells (Jin et al., 2013).

CXC Chemokine Receptor-4 (CXCR4)

CXC chemokine receptor-4 (CXCR4), is a receptor for the CXCL12/stromal cell-derived factor-1α (SDF-1α), frequently overexpressed in different cancers. Constitutive expression of HER2 and CXCR4 was notably reduced in MDA-MB-231 cells treated with supercritical extracts of phalsak peel (SEPS). Mechanistically it was revealed that SEPS inhibited NFLB induced transcriptional activation of CXCR4 (Kim et al., 2014). Similarly, nobiletin, a citrus bioflavonoid also inhibited NFKB mediated upregulation of CXCR4 (Baek et al., 2012).

JAK-STAT Pathway

Interestingly, constitutive activity of STAT3 was considerably inhibited in multiple myeloma cells treated with Bergamottin (BGM), a natural furanocoumarin. Detailed mechanistic insights indicated that tyrosine phosphatase SHP-1 was upregulated in multiple myeloma cells treated with BGM. Expectedly, BGM was unable to

exert inhibitory effects on STAT3 in SHP-1 silenced cells (Kim et al., 2014). Chloroform fraction of Dangyuja leaves (DCF) was noted to effectively inhibit STAT3 activity in prostate carcinoma DU145 cells. STAT3 inhibition consequently inhibited transcriptional upregulation of STAT3 target genes particularly, bcl-2 and bcl-xl (Chiang et al., 2012).

Wnt Signaling Pathway

The Wnt/β-catenin pathway is an evolutionarily conserved signaling transduction mechanism between adjacent cells that plays a critical role in embryonic development, tumorigenesis and self-renewal of stem cells. There is increasing evidence that a variety of biologically active compounds of citrus fruits such as hesperidin, naringin, and auraptene, are implicated in the regulation of the Wnt/β-catenin signaling pathway, and therefore involved in tumorigenicity and development.

Accumulating evidence for the preventive role of citrus fruits in the early phase of colon carcinogenesis came from colorectal pre-neoplastic lesions studies using mice models. It was reported that treatment of dietary Auraptene (AUR), an antioxidant agent isolated from citrus fruit, significantly reduces the number of β-catenin accumulated crypts (BCAC) meanwhile AUR suppresses cell proliferation and increases apoptosis in C57BL/KsJ-db/db (db/db) mice(Hayashi et al., 2007). Similar function was found in another citrus fruits extract, the citrus unshiu segment membranes (CUSMs), a waste after squeezing juice, could decrease the frequency and histological evolution of BCACs by inhibiting cellular proliferation(Suzuki et al., 2007). It stands to reason thatBCAC requires some of the constituents in citrus fruits. A more important fact has been disclosed that it appears some citrus flavonoids could be novel chemotherapeutic agents which should lead to a better outcome of colorectal cancer. It has been observed that hydroxylated poly methoxy flavones (PMFs) down-regulates the activation of β-catenin signaling pathways partially issue in suppressing of proliferation and angiogenesis,in enhancing apoptosis in a chemical-induced colon cancer animal model(Lai et al., 2011). Given that citrus fruits have been shown to interferewith Wnt/β-catenin signaling in the process of colonic tumorigenesis, it is imperative that a detailed study of the molecular mechanisms driving β-catenin is obtained in order to improve more in-depth knowledge. It has been pointed out that 5HHMF, one of the flavonoid compounds from citrus peels, stimulates the cellular levels of E-cadherin and decreases nuclear levels of β-catenin through restrain nuclear translocalization function of β-catenin protein as well as transactivation mediated by β-catenin/LEF-1 binding in colon cancer cells, which is responsible for inhibitory functionof 5HHMF in growth of colon cancer cells (Qiu et al., 2011). It stands to reason that the potential application of dietary citrus fruits administration to exert promising preventive and anticancer activities for colorectal cancer.

Some studies also indicate that the citrus flavonoids are essential regulators for Wnt/β-catenin signaling in tumorigenesis and progression of breast carcinoma. Though there is no particular proof of the specific chemical element which represents the attractive attributes, there is no doubt that the similar phenomenon from different citrus fruits extracts have been reported in different cancer types. It has been proved that tangeretin could strengthen intercellular adhesion and suppress invasion in human breast carcinoma cell line (MCF-7/6)by promoting the function of the E-cadherin/catenin complex *in vitro*, previously (Brack et al., 2002).On the other hand, a discouraging finding from same study is that this substance abolishes the therapeutic effectiveness of tamoxifen by immunosuppression *in vivo*. A different notion has been issued that the suppressing of β-catenin activity and the anticancer effect of naringin was demonstrated in triple negative breast cancer (TNBC) cells as well as in a TNBC xenograft mice model (Li et al., 2013). In addition, AUR exposure in post-initiation period suppresses the occurrence of hepatocellular carcinomas (HCCs) with β-catenin mutation,the molecular mechanism of the inhibitory effects, leads to effectively inhibition of chemical induced hepatocellular carcinogenesis in rats (Hara et al., 2005). Though it is generally recognized that the major flavonoids extracted from citrus fruits could exert inhibition effects on the growth potential of breast cancer cells through mediating β-catenin pathway, it should be made clear that there is no extensive investigation focusing on the effect of other citrus fruits extracts on cellular immune response by animal model. The first theory proposes that citrus fruits might be used as a potential supplement for the prevention and treatment of cancer, whereas the second theory proposes that the reducing of the anti-cancer cytotoxic competence in immunocompetent cells by some extracts is a more important disadvantage for this assumption.

However, other studies have revealed the opposing roles of citrus fruits extracts in Wnt-β-catenin signaling pathway. Hesperetin and naringenin are the most major flavonoids extracted from citrus fruits extracts(Huang et al., 2012). The intracellular accumulation of β-cateninhas been observed in both flavonoids in succession. Firstly, it had been reported that naringenin induces melanogenesis through promoting the intracellular accumulation of β-catenin as well as the phosphorylation of glycogen synthase kinase-3β (GSK3β)(Huang et al., 2011). Furthermore, another study from same group shows that hesperetin increases the lever of intracellular β-catenin by stimulatingthe activation of GSK3β, mitogen-activated protein kinases (MAPKs), andcAMP-responsive element binding (CREB) protein in melanoma cells(Huang et al., 2012).Consistent with these reports, a more recent study shows that hesperetin stimulates the Wnt/β-catenin pathwayand subsequently suppresses the inhibition of osteogenic differentiation mediated by high glucose in periodontal ligament stem cells (PDLSCs) (Kim et al., 2013).

As mentioned above, the pharmacological evidences are well provided for modulation of citrus fruits extracts in Wnt/β-catenin signaling. Since the diversity of the effects exerted, it is particularly significant in light of the fact that the detailed mechanisms of citrus fruits drivingWnt/β-catenin pathway seems to be highly context dependent.

In vivo studies

Powdered Shiikuwasha extract or nobiletin from Citrus depressa is noted to be an effective anticancer agent. It was noted to work with effective synergy with paclitaxel in non-small-cell lung carcinoma cell lines A549 and H460. More importantly, tumor growth was remarkably reduced in nude mice xenografted with A549 cancer cells subcutaneously. Another important finding of the study indicated that cells percentage of cells undergoing apoptosis was decreased with increasing rates of nobiletin to paclitaxel and carboplatin (Uesato et al., 2014). Citrus bergamia (bergamot) juice efficiently reduced cell proliferation of neuroblastoma SK-N-SH and LAN-1 cells (Navarra et al., 2014). Although tumor weight was not reduced in xenografted mice however, markedly reduced pulmonary metastases and absence of systemic toxicity in treated group are some of the features which need detailed investigation. Grapefruit juice dose-dependently protected mice from colon aberrant crypts (AC) induced by intraperitoneally injected azoxymethane (Madrigal-Bujaidar et al., 2013). It has recently been convincingly revealed hat intestinal macrophages selectively uptake grapefruit-derived nanovesicles (GDNs) that consequently resulted in amelioration of dextran sulfate sodium (DSS)-induced mouse colitis. In accordance with this concept, GDN-based oral delivery system was developed and tested for efficacy in by incorporation of methotrexate (MTX), into GDNs. MTX incorporated GDNs were delivered to mice and noted to efficiently increase drug efficacy (Wang et al., 2014). Rapdly accumulating experimental evidence is also highlighting that citrus peels contain wide ranging natural agents which either individually or synergistically exert biological effects. Gold Lotion (GL), an extract of multiple varieties of citrus peels effectively exerted inhibitory effects on modulators of angiogenesis and metastasis. Tumor volumes were notably reduced in mice either orally administered or intraperitoneally injected with GL (Lai et al., 2013). pH-modified (MCP) and high temperature-modified (HTCP) citrus pectins were tested for efficacy and results revealed that HTCP considerably reduced tumor growth and enhanced survival time in tumor bearing mice (Hao et al., 2013). Dietary administered citrus flavonone hesperetin considerably reduced tumor growth in ovariectomized athymic mice transplanted with aromatase-overexpressing MCF-7 cells. Estrogen-responsive gene mRNA expression was noted to be downregulated and protein levels of CDK4, cyclin D1, and Bcl-x(L) were also reduced (Ye et al., 2012). Aromatase inhibitor induced bone loss is a major issue and a report has indicated bone loss inhibitory effects of a natural agent. Interestingly, hesperetin or letrozole markedly reduced tumor growth and plasma estrogen level but hesperetin reversed letrozole-induced bone loss thus minimizing the off target effect of letrozole (Li et al., 2013). Oral administration of naringenin considerably extended the life span of tumor resected mice and reduced metastatic tumor cells number in the lung. Proportion of IL-2 and IFN-γ expressing T cells increased significantly in naringenin treated mice (Qin et al., 2011). Naringin notably induced regression of tumor in mice xenografted with MDA-MB-231 cells. Both p21 upregulation and survivin downregulation were noted in Naringin treated xenografted mice (Li et al., 2013). Different metabolites identified from urine samples collected from mice fed with 5-demethylnobiletin were 5,3',4'-tridemethylnobiletin, 5,4'-didemethylnobiletin, and 5,3'-didemethylnobiletin. 5,3'-didemethylnobiletin was noted to be most effective against colon cancer cells among all metabolites tested for efficacy (Zheng et al., 2013).

Nobiletin significantly reduced tumor growth formation in mice xenografted with nasopharyngeal carcinoma cells (Chien et al., 2015). Orally administered Tangeretin, a citrus pentamethoxyflavone remarkably inhibited metastasis in chemically induced rat mammary carcinoma model (Arivazhagan and Sorimuthu Pillai, 2014).

Opposing roles of different natural agents

Ethylacetate extracts of citrus-press cakes (CCE) dose-dependently reduced melatonin content and melanogenesis in B16F10 melanoma cells (Kim et al., 2013). However, both tyrosinase activity and synthesis of melanin were notably increased in B16F10 exposed to naringenin. β-catenin accumulated intracellularly and phosphorylated from of glycogen synthase kinase-3β (GSK3β) also increased in naringenin treated cells. It was concluded that naringenin promoted melanogenesis through Wnt-β-catenin-mediated cascade (Huang et al., 2011).

Concluding Remarks

There are considerable advancements and breakthroughs both in our understanding of molecular basis of cancer and identification of agents to effectively modulate protein network to suppress cancer progression. Although citrus fruits and their bioactive ingredients have shown potential in efficiently inducing apoptosis in cancer cells and xenografted mice, many of the intracellular signaling cascades including Sonic Hedge Hog signaling, Notch signaling, TGF, VEGF and PDGF induced signaling with reported oncogenic activity are not yet investigated. Future studies must converge on detailed analysis and potential of bioactive ingredients isolated from citrus fruits in modulation of these cascades.

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