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Article *in* Current Medicinal Chemistry · October 2015

DOI: 10.2174/0929867322301510191038l0

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3462 *Current Medicinal Chemistry,* 2015, *22,* 3462-3471

The Role of Hesperidin in Cell Signal Transduction Pathway for the Prevention or Treatment of Cancer

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Abstract: During past two decades, plant-derived bioactive compounds have been reported as novel therapeutic agents for prevention and/or mitigation of different human diseases such as cancer, inflammation, cardiovascular and neurodegenerative diseases. Hesperidin is known as one of the most common and bioactive constituents of *Citrus* (C) species which possesses multiple health-promotion effects. A plethora of scientific literature reported that hesperidin possesses *in-vitro* and *in-vivo* anticancer activities. In addition, there are numerous scientific evidences regarding the molecular mechanisms of anticancer activities of hesperidin and its aglycone, hesperetin. However, in this case, the number of comprehensive reviews on molecular mechanisms underlying the anticancer effects of hesperidin is sparse. Therefore, in this work we present a critical review of the available literature regarding the molecular mechanisms of the anticancer effects of hesperidin and its aglycone, hesperetin.

Keywords: Aglycone, anticancer, citrus, flavonoid, hesperetin, hesperidin.

1. INTRODUCTION

Signal transduction is the process of conversion of external signals produced by outside stimuli, including some hormones, growth factors, neurotransmitters, inflammatory cytokines and chemokines, to a biochemical response leading to a cellular response [1]. As a result of these responses, changes in cellular metabolism, expression of different genes, cell division as well as cell death may occur. It has been reported that in most diseases, these signaling dysfunctions have occurred. Cancer is a complex process, comprised of different stages such as initiation, promotion, and progression. Among them, the promotion stage has advantages over the others in therapeutics intervention because during this stage the single initiated cancerous cell proliferated and became resistant. Therefore, comprehending the molecular mechanisms of promotion and progression is critical for the discovery and development of chemopreventive compounds with high efficacy [2].

During past two decades, much attention has been paid to the discovery of novel therapeutic agents from nature [3-7]. Because of the availability, efficacy, and safety of herbal compounds, recent research has been focused on the beneficial effects of plant-derived bioactive compounds [8-14]. Among them, flavonoids are known as one of the most common groups of bioactive phytochemicals that possess multiple pharmacological actions such as antioxidant, anticancer, anti-inflammatory, etc [15-18].

Hesperidin is known as one of the most common flavonone glycosides, which is found in different *Citrus* (C) species. It has been reported that hesperidin possesses different pharmacological effects such as antioxidant, anti-inflammatory, and anticancer effects [19]. A growing body of evidence has shown potent antican-

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0929-8673/15 $58.00+.00

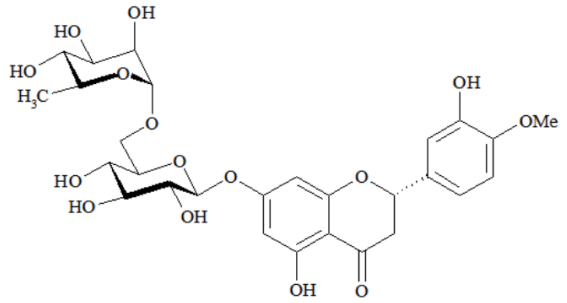
cer effects of both hesperidin and its aglycone form [20, 21]. Furthermore, it can be hypothesized that anti-inflammatory and anti-oxidant effects of hesperidin and its aglycone play crucial roles in the anticancer effects of these compounds [22]. In the chemical structure of hesperidin, the presence of hydroxyl moieties is responsible for these pharmacological effects.

Chemically, hesperidin consists of an aglycone (the form lacking the sugar moieties), hesperetin, and the sugar rutinoside: hesperetin-7-rutinoside. Hesperidin is the main flavonoid in *C* fruits, and can be found in large concentrations in *C* rinds. Until now, it has been isolated from rinds of different C species such as *C. aurantium* L., *C. sinensis* L., and *C. unshiu* Marcov. [23].

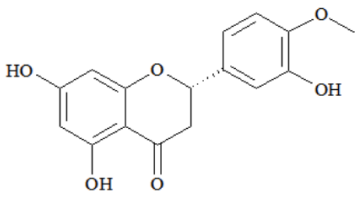
Hesperidin is absorbed from the intestine intact as a glycoside. Its aglycone hesperetin appears in the plasma 3 h after ingestion and reaching a peak concentration between 5 and 7 h. It has also been reported that glucuronides and sulfoglucuronides are known as circulating forms of hesperetin [24]. In the present review, we have focused on anticancer effects of hesperidin in addition to its chemistry and natural sources.

2. CHEMISTRY OF HESPERIDIN

Hesperidin is the glycoside form of hesperetin (methyl eriodictyol) (Fig. **1**), which is bonded to rutinose [25, 26]. It has been reported that the glycoside moiety in the chemical skeleton of hesperetin is a disaccharide generated from rhamnose and glucose and widely found as rutinose and/or neohesperidose [26].



Hesperidin



Hesperetin

Fig. (1). Chemical structures of hesperetin and hesperidin.

It is well known that rutinose (6-*O*-(α-L-rhamnopyranosyl)-D-glucopyranose and/or 6-*O*-(α-L-rhamnosyl)-D-glucose) is widely found in nature [26-28]. Another isomeric form, neohesperidose (2-*O*-α-L-rhamnopyranosyl-D-glucopyranose), has been identified in different C species as hesperetin 7-*O*-neohesperidoside [29, 30]. It is well known that the presence and structures of the glycoside moieties are responsible for C bitterness [26]. It has also been reported that the presence of rutinosides and neohesperidosides is responsible for tastelessness and bitterness of C species [26]. A plethora of evidence has shown that herperidin is most frequently identified as the rutinoside form, which is non-bitter [26, 31, 32]. However, the neohesperidoside form of herperidin has been identified in grapefruit [26, 32, 33]. The aglycone form of herperidin (hesperetin, (*S*)-2,3-dihydro-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one) is a bioflavonoid with a heterocyclic structure [25, 26, 34]. It has been reported that the presence and number of hydroxyl moieties in both the aromatic and heterocyclic rings of bioflavonoids are responsible for their pharmacological effects [26]. For example, it has been reported that the presence and number of hydroxyl moieties in the structure of hesperetin closely correlates with its antioxidant activity [26].

3. NATURAL SOURCES

A number of sources have shown that hesperetin has been identified in different parts of C such as the epicarp, mesocarp, and endocarp [26, 35]. Hesperetin has also found in the C juice and seeds [36]. A growing body of literature has shown that herperidin is found predominantly in the rinds of *C. aurantium*, *C. sinensis*, and *C. unshiu* in large scale amounts [37-40]. It has been found that the total amount of hesperetin in albedo, membranes and pith of C is higher than juice vesicles and seeds. Peppermint is another important and common source of hesperidin [41].

However, a close correlation between level of hesperetin and stage of fruit maturity has been reported [26, 42]. In addition, seed germination has positive effects on the level of hesperetin, which is due to the effects of light exposure that stimulates hesperetin production [26, 42, 43].

In addition to C species, hesperetin has also been found in several species from the families Fabaceae, Betulaceae, Lamiaceae and Papilionaceae [26, 44-46]. Hesperetin has also been found in *Acanthopanax setchuenensis* (Araliaceae), *Zanthoxylum avicennae* and *Zanthoxylum cuspidatum* (Rutaceae) [47-49]. Fur-

thermore, hesperetin has been identified as neohesperidin form in *Cynara* (Asteraceae) species [26, 50].

4. ANTICANCER EFFECTS OF HESPERIDIN: CELL SIGNAL TRANSDUCTION PATHWAY

4.1. Janus Kinase-signal Transducers and Activators of Transcription (JAK-STAT) Pathway

The Janus kinase/signal transducer and activator of transcription, JAK/STAT, is known as one of the most important signaling pathways for different cytokines and growth factors. This pathway affects many cellular functions such as metastasis, proliferation, growth, and immune response [51]. Up until now, 4 mammalian JAKs (JAK1, 2, 3 and Tyk2) and 7 mammalian STATs (STAT1, 2, 3, 4, 5a, 5b and 6) have been recognized. Of the seven STAT family members, STAT1 and STAT3 have been involved in cancer progression but have opposite effects. STAT1 has been reported to enhance anti-proliferative and pro-apoptotic responses in cancerous tissues while STAT3 can significantly enhance proliferation [52]. Constitutive activation of STAT is promoted by immoderate stimulation through cytokines and/or growth factors.

Through the activation of various tyrosine kinases, STATs can undergo phosphorylation, dimerization, and nuclear localization, and these proteins can bind with specific Deoxyribonucleic acid (DNA) elements to activate transcription of targeted genes [53]. It has also been reported there is a close correlation between JAK/STAT activation and an increase in the invasion and metastasis of different types of cancer. Among the target gene of STATs, cyclins D1/D2, Myc, B-cell lymphoma-extra-large (Bcl-xL), and Myeloid cell leukemia 1 (Mcl-1) are known to play crucial roles in cancer metastasis through activation of cell cycle and apoptosis [54]. These cellular events play important roles in regulation of hematopoiesis, immune development, tumor biology and other processes [55]. Many studies have demonstrated that the JAK/STAT pathway is involved in various cancers such as prostate, breast, pancreatic, and colon [56-59]. In addition, there is evidence that various chemopreventive agents are potent inhibitors of the JAK-STAT signaling pathway and cancer metastasis [60].

Furthermore, it has been reported that JAK/STAT signaling can be activated by interleukin 6 (IL6), which leads to an increase in the migration and invasion under in-vitro conditions and metastasis under in-vivo conditions [62]. Li *et al.* reported that 7,3′-dimethoxyhesperetin repressed the serum levels of IL-6 as well as IL-6 mRNA expression in the synovium of rats with adjuvant arthritis. They found that 7,3′-dimethoxyhesperetin significantly decreased mRNA expression of JAK2 and STAT3 as well as protein expression of p-JAK2 and p-STAT3 in the synovium of rats [61].

Another study showed that 5,7,3′-triacetylhesperetin (TAHP) (66, 132 mg/kg) down-regulated the serum level of IL-6 and also decreased the level of IL-6 in the synovial tissues of adjuvant arthritis rats. In addition, it was shown that administration of 5,7,3′-triacetylhesperetin reduced expression of mRNA of STAT3 and JAK2, as well as the ratio of p-JAK2/JAK2 protein and p-STAT3/STAT3 protein in the synovial tissues of rats [62].

The inhibition of STAT3 phosphorylation has led to a reduction of STAT3 expression targets such as cyclin D1, survivin, and Bcl-xL, which are responsible for the survival of cancerous and cancer stem cells (CSCs). In addition, oxidized low-density lipoprotein (LDL) caused the activation of JAK2, STAT1, and STAT3 via oxidative stress in the cells. It has been reported that hesperetin significantly reduced the oxidized LDL-induced 2′,7′-dichlorofluorecein staining, which is due to the inhibitory effects of hesperetin against oxidized LDL-triggered reactive oxygen species and apoptosis. Choi *et al.* indicated that hesperetin decreased p38MAPK phosphorylation and its downstream c-myc and signal STAT1, which was caused by oxidized LDL. Furthermore, hesperetin suppressed oxidized LDL-activated JAK2/STAT3-dependent signaling pathways [63] (Fig. **2**).

4.2. The PI 3-Kinase/Akt and mTOR Pathways

The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) pathway control various biological processes and play an important role in different aspects of cell growth and survival in physiological as well as in pathological conditions [64].

It has been reported that activation of several growth factor receptor protein tyrosine kinases results in autophosphorylation on tyrosine residues. Thereafter, PI3K is recruited to the membrane and due to its activation, second messenger phosphatidylinositol-3,4,5-triphosphate (PI3,4,5-P3) from the substrate phosphatidylinositol-4,4-bisphosphate (PI-4,5-P2) is produced. Subsequently phosphatidylinositol 3-phosphate (PIP3) recruits 3-phosphoinositide dependent protein kinase-1 (PDK1) and Akt/protein kinase B (PKB), signaling proteins with pleckstrin homology (PH) domains, to the membrane [60].

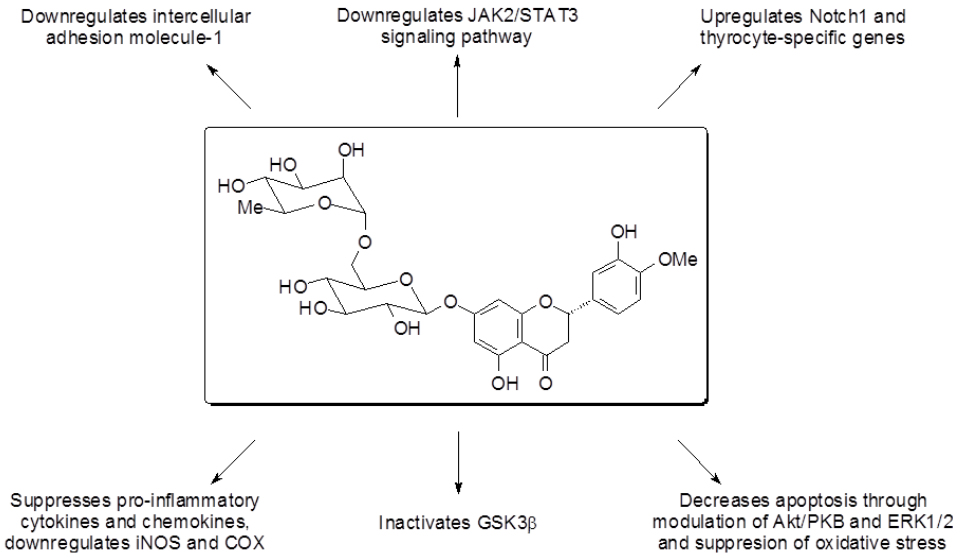


Fig. (2). Molecular mechanisms underlying anticancer effects of hesperidin.

Full activation of Akt also requires phosphorylation at a second site by a distinct protein kinase (mTORC2), which is also stimulated by growth factors. It has been reported that once activated, Akt phosphorylates some of the target proteins such as proteins that are known as direct regulators of cell survival transcription factors, as well as other protein kinases [65].

Akt/PKB and its substrates such as Bad, GSK-3, pro-caspase9, IkB kinase (IKK), forkhead transcription factors and Yes-associated protein (YAP) have anti-apoptotic role [66]. mTOR is a serine/threonine protein kinase, and its activity is due to two different complexes, mTORC1 and mTORC2, which regulate metastasis cascades including cell growth, proliferation, motility, survival, and cell invasion and migration. In addition, the canonical pathway of mTOR activation depends on mitogen-driven signaling by the PI3K/Akt pathway, although alternative non-Akt-dependent activation by the Ras/MEK/ERK pathway has also been identified.

Taken together, activation of this pathway leads to increased protein synthesis. These include several that have been implicated in the pathogenesis of various tumors, e.g., cyclin D1, which allow progression of cells through the cell cycle, and hypoxia-inducible factor (HIF), which drive the expression of pro-angiogenic growth factors such as vascular endothelial growth factor (VEGF) [64]. Several phytochemicals have been identified that suppress the activation of Akt/PI3K/mTOR pathway. Saiprasad *et al.* indicated that hesperidin caused apoptosis and also triggers autophagic factors via suppression of Aurora-A-mediated PI3K/Akt/mTOR and glycogen synthase kinase 3 beta (GSK-3β) signaling cascades in experimental colon carcinogenesis. Their finding showed that Akt and PI3K phosphorylation and activation increased in azoxymethane (AOM) induced animals. Phosphatase and tensin homolog (PTEN), a tumor suppressor, negatively regulates the PI3K and Akt activation suppressing tumorigenesis. Hesperidin treatment restored the decreased PTEN activity seen in AOM-induced animals and this may likely be a reason for hesperidin's inhibitory role against PI3K/Akt signaling cascade.

Meanwhile, hesperidin significantly reduced mTOR expressions associated with an increase in autophagic proteins Beclin-1 and microtubule-associated protein 1A/1B-light chain 3-phosphatidylethanolamine conjugate (LC3-II). GSK-3β is another downstream effector of the PI3K/Akt pathway [53]. Moreover, GSK-3β initiates the degradation and inactivation of several oncogenic transcription factors (c-myc and c-jun) and proto-oncoproteins (β-catenin) via phosphorylation. These results have demonstrated that hesperidin administration significantly inhibits phosphorylation of GSK-3β, leading to the reduction of oncogenic β-catenin, c-myc and c-jun. Indeed, this study revealed that hesperidin was able to actively inhibit the PI3K/Akt/GSK-3β and mTOR signaling cascades [67].

In nervous tissues, hesperetin (100 nmol/L) and its metabolite 5-nitro-hesperetin efficiently prevent apoptosis via Akt/PKB activation/phosphorylation and also via an activation of extracellular signal-regulated kinase 1/2 (ERK1/2) [68] (Fig. **2**).

4.3. Notch Pathway

The Notch pathway plays an important role in the cell fate determination, proliferation, differentiation and survival at different stages including development, neurogenesis and homeostasis. It has also been involved in cell–cell communications. Direct interaction of Notch family receptors (Notch 1–4) with ligands (JAG1, JAG2, Dll-1, Dll-3, and Dll-4), which are expressed on adjacent to cells, leads to initiation of Notch pathways. It has also been reported that gamma-secretase stimulates the Notch intracellular domain releasing from the membrane. Thereafter, the Notch intracellular domain translocates into the cell nucleus and interacts with DNA-binding transcription factors and in this way leads to Notch target genes. Impairment of this signaling pathway is linked to several diseases including cancer. The aberrant regulation of Notch signaling contributes to tumor development [69]. Notch genes possess oncogenic and also tumor suppression activities in different malignancies for example, inducing keratinocyte growth arrest in the skin [70]. It has also been reported that Notch inhibitors or inducers can serve as growth inhibitors. Notch1 signaling activity is downregulated in many cancers such as thyroid cancer, pancreatic cancer, liver cancer, brain tumor, etc.

Previous studies have suggested that Notch signaling is reduced in neuroendocrine tumors, including carcinoids, and it has been shown that increased signaling of this pathway reduces carcinoid cell proliferation as well as neuroendocrine tumor marker expression among the tumors [71]. Zarebczan and colleagues demonstrated that hesperetin causes expression of Notch1 among the carcinoid cells (BON), with subsequent suppression of cell proliferation and hormone generation. Indeed, hesperetin reduced the expression of neuroendocrine tumor markers such as ASCL1 and CgA [72]. In anaplastic thyroid cancer (ATC), Notch1 acts as tumor suppressor. Therefore restoration of functional Notch1 signaling is a therapeutic approach in ATC. Recently, Patel *et al.* showed that administration of hesperetin induces expression of Notch1 and its downstream effectors hairy and enhancer of split 1 (Hes1), and Hes1 related with YRPW motif was observed in hesperetin-treated ATC cells. Hesperetin exhibited antiproliferative effect on ATC cell proliferation. Inhibition of cell growth was mainly due to apoptosis as demonstrated by an increase in the ratio of cleaved poly ADP ribose polymerase (PARP) and cleaved caspase-3 as well as diminished survivin. Moreover, these workers found that hesperetin administration upregulates thyrocyte-specific genes including thyroid transcription factor 1 (TTF1), TTF2, paired box gene 8, thyroid stimulating hormone receptor, and sodium/iodide symporter [73] (Fig. **2**).

4.4. MAPK-ERK Pathway

Mitogen-activated protein (MAP) kinases are known to be regulators of a wide range of cellular processes including cell growth and differentiation, gene expression, mitosis, cell motility, metabolism, survival as well as apoptosis by phosphorylation of target protein substrates. The classic MAP kinases are classified into three sub-families including extracellular signal-regulated kinases (ERK; ERK1 and ERK2), c-Jun N-terminal kinases (JNK; JNK1, JNK2, and JNK3), as well as p38 mitogen-activated protein kinase (p38-MAP kinases) (a, b, d, and g) [74, 75].

Phytochemicals such as hesperidin suppressed ROS-induced inflammations that are involved in most diseases including cancer. Moon and Kim demonstrated the anti-inflammatory effects of HES in HaCaT cells. Their result indicated that HES inhibited the hydrogen-peroxide-induced interleukin-8 and tumor necrosis factor-α generation and also p38 phosphorylation as well as activation of COX-2. [76]. In addition, ERK activation has been reported in response to oxidative damage and served as an important factor in the cell survival. Peroxynitrite is also known as an important contributor in the initiation and progression of different diseases such as cancer, cardiovascular and neurodegenerative diseases. Hesperetin exposure to fibroblasts is shown to upregulate ERK1/2 phosphorylation and to modify peroxynitrite-mediated reduction in ERK1/2 phosphorylation [77]. A study by Pollard *et al.* has shown that modulation of fibroblast signaling, as well as scavenging of intracellular peroxynitrite, plays important role in the promising effects of hesperetin on fibroblasts [77].

In addition, treatment with hesperetin modified the kidney nuclear factor-kappa B (NF-κB)-mediated gene expression through regulation of ERK, Jun N-terminal kinase (JNK) and p38 in rats [78]. Rainey *et al.* concluded that hesperetin significantly increased the level of ERK1/2 phosphorylation when used at concentrations of 100–300 nM, although, at this concentration, hesperetin did not increase CREB phosphorylation. Treatment with hesperetin (300 nM concentration) reduced staurosporine-caused cell death among primary neurons [79]. Indeed, it was shown that hesperetin and 5-nitrohesperetin, when used at the concentration of 100 nM/L, were effective in preventing neuronal apoptosis via two mechanisms: activation/phosphorylation of both ERK1/2 and Akt/PKB [68, 80] (Fig. **2**).

4.5. Wingless and INT-1 (Wnt) Pathway

Members of the Wnt family are secreted growth factors that bind to a complex of receptors of the Frizzled families (canonical pathway). These proteins also activate non-canonical pathways by stimulating cytoskeletal reorganization and regulating planar cell polarity. Stabilization of β-catenin occurs due to Frizzled signaling, which acts as a transcriptional activator in the Wnt pathway [81].

Wnt/β-catenin pathway was reported to regulate the process of cell proliferation, migration, apoptosis, differentiation, epithelial–mesenchymal interactions, as well as stem cell self- renewal. It has also been reported that β-catenin is phosphorylated through GSK-3 β in complex with the proteins axin and APC in the absence of Wnt signaling. β-Catenin phosphorylation leads to its ubiquitination and degradation. Due to Wnt binding, Disheveled phosphorylation occurs (a cytoplasmic protein that interacts with Frizzled), which then increases phosphorylation of LRP. This process provides binding sites for axin, leading to association of axin with the receptor, followed by disruption of the connection complex of axin, casein kinase-1 and GSK-3β with β-catenin. Disruption of the axin complex averts β-catenin degradation [65].

Many studies indicated that Wnt/β-catenin activation is implicated in most human cancers including gastric, leukemia, endometrial, thyroid, melanoma, ovarian, breast, colon, liver, lung and head and neck. Wnt signaling increases accumulation of β-catenin within the cell nucleus, leading to the consequent transcriptional activation of some target genes such as c-myc, cyclin D, c-jun, gastrin, CD44, surviving, VEGF, endothelin-1, interleukinβ-8, nanog and snail [60].

Melanogenesis is known to be a complex process that regulates skin pigmentation to protect against photodamage. Huang and colleagues evaluated hesperetin activities on melanin synthesis among murine B16-F10 melanoma cells. Their results showed that hesperetin increased mitogen-activated protein kinases activation, cAMP-responsive element binding protein phosphorylation and glycogen synthase kinase-3β, and led to induced β-catenin accumulation. GSK3β was inactivated by hesperetin through phosphorylation of the Serine 9 site of this protein kinase. Thus, β-catenin degradation is reduced by hesperetin. The Wnt/β-catenin pathway plays an important role in melanocyte differentiation [82].

Another study conducted by Kim *et al.* indicated that hesperetin diminished suppression actions of high glucose during the differentiation of osteoblasts in periodontal ligament stem cells. They also found that hesperetin up-regulated the expression of total β-catenin in a dose-dependent manner and that hesperetin also caused nuclear translocation of β-catenin. In support of this they showed that suppression of Akt and/or β-catenin decreased the ameliorative activity of hesperetin against high glucose-suppressed osteogenic differentiation [83] (Fig. **2**).

4.6. NF-κB and Cyclooxygenase (COX)-2 Pathways

The NF-κB family includes different transcription factors such as RELA (p65), c-BEL, RELB, NF-κB1 (p50/p105), as well as NF-κB2 (p52/p100) which plays key roles in the immune system and in inflammation as well as in regulation of proliferation and survival. A variety of stimuli, including reactive oxygen species, inflammatory agents, cytokines, carcinogenic materials, tumor inducers, bacterial and viral infections, γ-radiation, UV light, and X-rays, can activate members of this transcription factor family [84].

It has also been reported that tumor necrosis factor (TNF), interleukins, chemokines, COX-2, 5-lipoxygenase (LOX), as well as matrix metallopeptidase (MMP)-9 are restored via NF-kB. In unstimulated cells, NF-κB proteins are connected to inhibitory IκB proteins, which preserve NF-κB in an inactive form in the cytosol. TNF and Toll-like receptor activation leads to recruitment of adaptor proteins that activate the inhibitor of NF-κB (IκB) kinase, which phosphorylates IκB. Following phosphorylation, IκB is targeted by the proteasome for ubiquitination and degradation. Released NF-κB translocates to the cell nucleus and results in expression of its target genes including cyclin D1, Bcl-2, Bcl-xL, MMP, as well as VEGF [60, 65].

COX is a prostaglandin H synthase, which is responsible for the production of prostanoids from arachidonic acid (AA). Three isoforms of COX, COX-1, COX-2, and COX-3, have been recognized. COX-1 mainly exists in most tissues; COX-2, however, is primarily present at sites of inflammation. Among these isoforms, COX-2 expression is normalized by mitogens, tumor cytokines, as well as growth factors. COX-2 expression, regulated by NF-kB, mediates tumorigenesis [85]. It has been reported that COX-2 expression in human tumors can be triggered by different growth factors, cytokines, oncogenes, as well as other factors [86]. The anti-inflammatory effects of hesperidin are accomplished through various mechanisms including:

1. Down-regulation of intercellular adhesion molecule-1 expression which plays a crucial role in the inhibi-

tion of monocyte adhesion to endothelial cells [87, 88].

2. Suppression of expression of different pro-inflammatory cytokines and chemokines [89-91].
3. Increased production of nitric oxide and consequent improvement in endothelial function [87].
4. Inhibition of Janus kinase (JNK), a group of proteins activated by various types of environmental stress and cytokines, and consequent decreased production of metalloproteinases [92].

Moon and Kim have demonstrated the anti-inflammatory activity of hesperidin in HaCaT cells. Their results indicated that hesperidin inhibits interleukin-8 and tumor necrosis factor-α generation and also its mRNA expression, phosphorylation of p38 and COX-2 activation caused by hydrogen peroxide. They suggested that hesperidin suppressed NF-κB activation, the phosphorylation of IkBα and the p38 mitogen-activated protein kinase, and also COX-2 activation [76]. In another study, Kim and coworkers reported that hesperetin plays an important role in modulation of aging. They found that hesperetin inhibited the activation of NF-κB and also related gene expressions. Indeed, another interesting point of this study was that hesperidin inhibited NF-κB via different signal transduction pathways including NIK/IKK, ERK, p38, as well as JNK [78].

Previous studies have indicated that in colon malignancies, immunoreactivity of NF-κB abruptly increased. Additionally, it has been demonstrated that NF-κB expression in AOM-induced colonic tissues is significantly increased. Saiprasad and coworkers reported that hesperidin treatments significantly down-regulated the NF-κB-dependent inflammatory responses including inducible nitric oxide synthase (iNOS) and COX-2 activation. Hesperidin supplementation inhibited NF-κB expression at both the initiation and the post-initiation phases. Since increased NF-κB expression activates downstream inflammatory molecules such as iNOS and COX-2, hesperidin significantly reduced these inflammatory markers [93]. Chronic inflammation is considered a risk factor for colorectal cancer. Hesperetin supplementation showed a suppression of expression of COX-2 mRNA and induction of apoptosis [94] (Fig. **2**).

CONCLUSION

Hesperidin is one of the most common bioactive constituents of *C* species which possesses multiple health-promotion effects. This review has presented that hesperidin and its aglycone, hesperetin, have suppressed the growth of various cancer cells, both *in vitro* and *in vivo* conditions, through different cellular pathways. Hesperidin primarily targets the NF-kB pathway and also activates different apoptotic and pro-apoptotic pathways in different types of cancerous cells. However, our search in the http://clinicaltrials.gov/ with keywords “hesperidin” and “hesperetin” in March 8, 2014 demonstrated that there are only 8 clinical trials regarding the impacts of hesperidin and its aglycone, hesperetin. In this regard, it is difficult to make a clear decision about its most effective doses for future clinical trials with respect to its anticancer activity. Finally, we conclude that hesperidin and its aglycone act as anticancer compounds by suppressing carcinogenesis through pleiotropic mechanisms.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Bode, A.M.; Dong, Z. Signal transduction pathways in cancer development and as targets for cancer prevention. *Prog. Nucleic Acid Res.,* **2005**, *79*, 237-276.

[2] Levitzki, A.; Klein, S. Signal transduction therapy of cancer. *Mol. Aspects Med.,* **2010**, *31*, 287–329.

[3] Nabavi, S.F.; Nabavi, S.M.; Ebrahimzadeh, M.A.; Eslami, B.; Jafari, N. *In vitro* antioxidant and antihemolytic activities of hydroalcoholic extracts of *Allium scabriscapum* Boiss. & Ky. aerial parts and bulbs. *Int. J. Food Prop.,* **2013**, *16*(4), 713-722.

[4] Nabavi, S.F.; Nabavi, S.M.; Moghaddam, A.H.; Naqinezhad, A.; Bigdellou, R.; Mohammadzadeh, S. Protective effects of Allium paradoxum against gentamicin-induced nephrotoxicity in mice. *Food Funct.,* **2012**, *3*(1), 28-29.

[5] Nabavi, S.F.; Nabavi, S.M.; Ebrahimzadeh, M.A.; Jafari, N.; Yazdanpanah, S. Biological activities of freshwater algae, *Spirogyra singularis* Nordstedt. *J. Aquat. Food Prod. Technol.,* **2013**, *22*(1), 58-65.

[6] Hill, A.J.; Williams, C.M.; Whalley, B.J.; Stephens, G.J. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol. Ther.,* **2012**, *133*(1), 79-97.

[7] Koehn, F.E.; Carter, G.T. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.,* **2005**, *4*(3), 206-220.

[8] Nabavi, S.F.; Nabavi, S.M.; Habtemariam, S.; Moghaddam, A.H.; Sureda, A.; Jafari, M.; Latifi, A.M. Hepatoprotective effect of gallic acid isolated from *Peltiphyllum peltatum* against sodium fluoride-induced oxidative stress. *Ind. Crops Prod.,* **2013**, *44*, 50-55.

[9] Nabavi, S.F.; Daglia, M.; Moghaddam, A.H.; Habtemariam, S.; Nabavi, S.M. Curcumin and liver disease: from chemistry to medicine. *Compr. Rev. Food Science Food Safe.,* **2014**, *13*(1), 62-77.

[10] Curti, V.; Capelli, E.; Boschi, F.; Nabavi, S.F.; Bongiorno, A.I.; Habtemariam, S.; Nabavi, S.M.; Daglia, M. Modulation of human miR-17–3p expression by methyl 3-O-methyl

gallate as explanation of its *in vivo* protective activities. *Mol. Nutr. Food Res.,* **2014**, *58*(9), 1776-1784.

[11] Nabavi, S.M.; Marchese, A.; Izadi, M.; Curti, V.; Daglia, M.; Nabavi, S.F. Plants belonging to the genus Thymus as antibacterial agents: From farm to pharmacy. *Food Chem.,* **2015**, *173*, 339-347.

[12] Nabavi, S.F.; Nabavi, S.M.; N Setzer, W.; Nabavi, S.A.; Nabavi, S.A.; Ebrahimzadeh, M.A. Antioxidant and anti-hemolytic activity of lipid-soluble bioactive substances in avocado fruits. *Fruits,* **2013**, *68*(03), 185-193.

[13] Pistollato, F.; Giampieri, F.; Battino, M. The use of plant-derived bioactive compounds to target cancer stem cells and modulate tumor microenvironment. *Food Chem. Toxicol.,* **2015**, *75*, 58-70.

[14] Licciardi, P.V.; Underwood, J.R. Plant-derived medicines: a novel class of immunological adjuvants. *Int. Immunopharmacol.,* **2011**, *11*(3), 390-398.

[15] Nabavi, S.M.; Nabavi, S.F.; Eslami, S.; Moghaddam, A.H. *In vivo* protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. *Food Chem.,* **2012**, *132*(2), 931-935.

[16] Nabavi, S.F.; Russo, G.L.; Daglia, M.; Nabavi, S.M. Role of quercetin as an alternative for obesity treatment: You are what you eat! *Food Chem.,* **2015**, *179*, 305-310.

[17] Nabavi, S.F.; Nabavi, S.M.; Mirzaei, M.; Moghaddam, A.H. Protective effect of quercetin against sodium fluoride induced oxidative stress in rat's heart. *Food Funct.,* **2012**, *3*(4), 437-441.

[18] Orhan, I.; Daglia, M.; Nabavi, S.; Loizzo, M.; Sobarzo-Sánchez, E.; Nabavi, S. Flavonoids and dementia: an update. *Curr. Med. Chem.,* **2014**, *22*(8), 1004-1015

[19] Garg, A.; Garg, S.; Zaneveld, L.J.D.; Singla, A.K. Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytother. Res.,* **2001**, *15*, 655–669.

[20] Yumnam, S.; Park, H.S.; Kim, M.K.; Nagappan, A.; Hong, G.E.; Lee, H.J.; Lee, W.S.; Kim, E.H.; Cho, J.H.; Shin, S.C.; Kim, G.S. Hesperidin induces paraptosis like cell death in hepatoblatoma, HepG2 cells: involvement of ERK1/2 MAPK. *PLoS One* **2014**, *9*(6), e101321.

[21] Ghorbani, A.; Nazari, M.; Jeddi-Tehrani, M.; Zand, H. The citrus flavonoid hesperidin induces p53 and inhibits NF-κB activation in order to trigger apoptosis in NALM-6 cells: involvement of PPARγ-dependent mechanism. *Eur. J. Nutr.*, **2012**, *51*(1), 39-46.

[22] Roohbakhsh, A.; Parhiz, H.; Soltani, F.; Rezaee, R.; Iranshahi, M. Molecular mechanisms behind the biological effects of hesperidin and hesperetin for the prevention of cancer and cardiovascular diseases. *Life Sci.*, **2015**, *124*, 64-74.

[23] Wilmsen, P.K.; Spada, D.S.; Salvador, M. Antioxidant activity of the flavonoid hesperidin in chemical and biological systems. *J. Agric. Food Chem.,* **2005**, *53*, 4757-4761.

[24] Manach, C.; Morand, C.; Gil-Izquierdo, A.; Bouteloup-Demange, C.; Rémésy, C. Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. *Eur. J. Clin. Nutr.,* **2003**, *57*(2), 235-242.

[25] Li, C.; Schluesener, H. Health-promoting effects of the citrus flavanone hesperidin. *Crit. Rev. Food Sci. Nutr.,* **2014**, DOI:10.1080/10408398.2014.906382

[26] Garg, A.; Garg, S.; Zaneveld, L.; Singla, A. Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytother. Res.,* **2001**, *15*(8), 655-669.

[27] Konishi, F.; Esaki, S.; Kamiya, S. Synthesis and taste of flavanone and dihydrochalcone glycosides containing 3-o-α-l-rhamnopyranosyl-d-glucopyranose or 4-o-α-l-rhamnopyranosyl-d-glucopyranose in the sugar moiety. *Agric. Biol. Chem.,* **1983**, *47*(2), 265-274.

[28] Shimoda, K.; Hamada, H.; Hamada, H. Glycosylation of hesperetin by plant cell cultures. *Phytochemistry,* **2008**, *69*(5), 1135-1140.

[29] Bilbao, M.d.L.M.; Andrés-Lacueva, C.; Jáuregui, O.; Lamuela-Raventos, R.M. Determination of flavonoids in a Citrus fruit extract by LC–DAD and LC–MS. *Food Chem.,* **2007**, *101*(4), 1742-1747.

[30] Gattuso, G.; Barreca, D.; Gargiulli, C.; Leuzzi, U.; Caristi, C. Flavonoid composition of citrus juices. *Molecules,* **2007**, *12*(8), 1641-1673.

[31] Manach, C.; Morand, C.; Gil-Izquierdo, A.; Bouteloup-Demange, C.; Remesy, C. Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. *Eur. J. Clin. Nutr.,* **2003**, *57*(2), 235-242.

[32] Ooghe, W.C.; Ooghe, S.J.; Detavernier, C.l.M.; Huyghebaert, A. Characterization of orange juice (*Citrus sinensis*) by flavanone glycosides. *J. Agric. Food Chem.,* **1994**, *42*(10), 2183-2190.

[33] Gavish, H.; Lewinsohn, E.; Vardi, A.; Fluhr, R. Production of flavanone-neohesperidosides in Citrus embryos. *Plant Cell Rep.,* **1989**, *8*(7), 391-394.

[34] Grohmann, K.; Manthey, J.A.; Cameron, R.G. Acid-catalyzed hydrolysis of hesperidin at elevated temperatures. *Carbohydr. Res.,* **2000**, *328*(2), 141-146.

[35] Joseph, G.H. Chemistry of citrus fruits. *J. Chem. Educ.,* **1957**, *34*(10), 513.

[36] Kanaze, F.I.; Gabrieli, C.; Kokkalou, E.; Georgarakis, M.; Niopas, I. Simultaneous reversed-phase high-performance liquid chromatographic method for the determination of diosmin, hesperidin and naringin in different citrus fruit juices and pharmaceutical formulations. *J. Pharm. Biomed. Anal.,* **2003**, *33*(2), 243-249.

[37] Rouseff, R.L.; Martin, S.F.; Youtsey, C.O. Quantitative survey of narirutin, naringin, hesperidin, and neohesperidin in citrus. *J. Agric. Food Chem.,* **1987**, *35*(6), 1027-1030.

[38] Castillo, J.; Benavente, O.; José, A. Naringin and neohesperidin levels during development of leaves, flower buds, and fruits of *Citrus aurantium*. *Plant Physiol.,* **1992**, *99*(1), 67-73.

[39] Barthe, G.A.; Jourdan, P.S.; McIntosh, C.A.; Mansell, R.L. Radioimmunoassay for the quantitative determination of hesperidin and analysis of its distribution in *Citrus sinensis*. *Phytochemistry,* **1988**, *27*(1), 249-254.

[40] Inoue, T.; Tsubaki, S.; Ogawa, K.; Onishi, K.; Azuma, J.I. Isolation of hesperidin from peels of thinned Citrus unshiu fruits by microwave-assisted extraction. *Food Chem.,* **2010**, *123*(2), 542-547.

[41] Areias, F.M.; Valentao, P.; Andrade, P.B.; Ferreres, F.; Seabra, R M. Phenolic fingerprint of peppermint leaves. *Food Chem.*, **2001**, *73*(3), 307-311.

[42] Yoo, K.M.; Lee, K.W.; Park, J.B.; Lee, H.J.; Hwang, I.K. Variation in major antioxidants and total antioxidant activity of Yuzu (*Citrus junos* Sieb ex Tanaka) during maturation and between cultivars. *J. Agric. Food Chem.,* **2004**, *52*(19), 5907-5913.

[43] Lu, Y.; Zhang, C.; Bucheli, P.; Wei, D. Citrus flavonoids in fruit and traditional Chinese medicinal food ingredients in China. *Plant Foods Hum. Nutr.,* **2006**, *61*(2), 55-63.

[44] Bhalla, N.; Dakwale, R. Chemotaxonomy of Indigofera Linn. *J. Indian Bot. Soc,* **1978**, *57*, 180-185.

[45] Pawłowska, L. Flavonoids in the leaves of polish species of the genus Betula L. L The flavonoids of B. pendula Roth. and B. obscura Kot. leaves. *Acta Soc. Bot. Pol.,* **1980**, *49*(3), 281-296.

[46] Kokkalou, E.; Kapetanidis, I. Flavonoids of the aerial parts of *Acinos suaveolens*. *Pharm. Acta Helv.,* **1988**, *636*, 170-173.

[47] Negi, J.; Bisht, V.; Bhandari, A.; Singh, P.; Sundriyal, R. Chemical constituents and biological activities of the genus Zanthoxylum: a review. *Afr. J. Pure Appl. Chem.,* **2011**, *5*(12), 412-416.

[48] Arthur, H.; Hui, W.; Ma, C. An examination of the rutaceae of Hong Kong. Part I. Flavonoid glycosides from Zanthoxylum species and the occurrence of optically active hesperetin. *J. Chem. Soc.,* **1956**, 632-635.

[49] Zhao, W.; Qin, G.; Xu, R.; Li, X.; Liu, J.; Wang, Y.; Feng, M. Constituents from the roots of *Acanthopanax setchuenensis*. *Fitoterapia,* **1999**, *70*(5), 529-531.

[50] Orlovskaya, T.; Luneva, I.; Chelombit'ko, V. Chemical composition of Cynara scolymus leaves. *Chem. Nat. Comp.,* **2007**, *43*(2), 239-240.

[51] Rawlings, J.S.; Rosler, K.M.; Harrison, D.A. The JAK/STAT signaling pathway. *J. Cell Sci.,* **2004**, *117*, 1281-1283.

[52] Teng, Y.; Ross, J.L.; Cowell, J.K. The involvement of JAK-STAT3 in cell motility, invasion, and metastasis. *JAKSTAT,* **2014**, *1*(3), 1-17.

[53] Batra, P.; Sharma, A.K. Anti-cancer potential of flavonoids: recent trends and future perspectives. *3 Biotech* **2013**, *3*, 439-459.

[54] Ozawa, Y.; Williams, A.H.; Estes, M.L.; Matsushita, N.; Boschelli, F.; Jove, R. Src family kinases promote AML cell survival through activation of signal transducers and activators of transcription (STAT). *Leuk. Res.,* **2008**, *32*(6), 893–903.

[55] Aaronson, D.S.; Horvath, C.M. A road map for those who don't know JAK-STAT. *Science* **2002**, *296*(5573), 1653–1655.

[56] Kwon, E.M.; Holt, S.K.; Fu, R.; Kolb, S.; Williams, G.; Stanford, J.L. Androgen metabolism and JAK/STAT pathway genes and prostate cancer risk. *Cancer Epidemiol.,* **2012**, *36*(4), 347-353.

[57] Uluer, E.T.; Aydemir, I.; Inan, S.; Ozbilgin, K.; Vatansever, H.S. Effects of 5-fluorouracil and gemcitabine on a breast cancer cell line (MCF-7) via the JAK/STAT pathway. *Acta Histochem.,* **2012**, *114*(7), 641–646.

[58] Masamune, A.; Satoh, M.; Kikuta, K.; Suzuki, N.; Shimosegawa, T. Activation of JAK-STAT pathway is required for platelet-derived growth factor-induced proliferation of pancreatic stellatecells. *World J. Gastroenterol.,* **2005**, *11*(22), 3385–3391.

[59] Slattery, M.L.; Lundgreen, A.; Kadlubar, S.A.; Bondurant, K.L.; Wolff, R.K. JAK/STAT/SOCS-signaling pathway and colon and rectal cancer. *Mol. Carcinogen.,* **2011**, *52*(2), 155-166.

[60] Singh, B.N.; Singh, H.B.; Singh, A.; Naqvi, A.H.; Singh, B.R. Dietary phytochemicals alter epigenetic events and signaling pathways for inhibition of metastasis cascade. *Cancer Metastasis Rev.,* **2014**, *33*, 41-85.

[61] Li, R.; Cai, L.; Ren, D.Y.; Xie, X.F.; Hu, C.M.; Li, J. Therapeutic effect of 7, 3′-dimethoxy hesperetin on adjuvant arthritis in rats through inhibiting JAK2-STAT3 signal pathway. *Int. Immunopharmacol.,* **2012**, *14*, 157-163.

[62] Ren, D.Y.; Xu, T.; Li, R.; Huang, C.; Huang, Y.; Li, R.Q.; Li, H.Y.; Li, J. 5,7,3'-Triacetyl hesperetin suppresses adjuvant-induced arthritis in rats through modulating JAK2/STAT3 pathway. *Am. J. Chin. Med.,* **2013**, *41*(3), 601-614.

[63] Choi, J.S.; Choi, Y.J.; Shin, S.Y.; Li, J.; Kang, S.W.; Bae, J.Y.; Kim, D.S.; Ji, G.E.; Kang, J.S.; Kang, Y.H. Dietary flavonoids differentially reduce oxidized LDL-Induced apoptosis in human endothelial cells: role of MAPK- and JAK/STAT-signaling. *J. Nutr.,* **2008**, *138*(6), 983-990.

[64] Porta, C.; Paglino, C.; Mosca, A. Targeting PI3K/Akt/mTOR signaling in cancer. *Front. Oncol.,* **2014**, *14*(4), 1-11.

[65] Cooper, G.M.; Hausman, R.E., 5th ed; *The Cell,* ASM Press: Washington, **2009**.

[66] Sale, E.M.; Sale, G.J. Protein kinase B: signalling roles and therapeutic targeting. *Cell. Mol. Life Sci.,* **2008**, *65*, 113-127.

[67] Saiprasad, G.; Chitra, P.; Manikandan, R.; Sudhandiran, G. Hesperidin induces apoptosis and triggers autophagic markers through inhibition of Aurora-A mediated phosphoinositide-3-kinase/Akt/mammalian target of rapamycin and glycogen synthase kinase-3 beta signalling cascades in experimental colon carcinogenesis. *Eur. J. Cancer,* **2014**, *50*, 2489-2507.

[68] Vauzour, D.; Vafeiadou, K.; Rice-Evans, C.; Williams, R.J.; Spencer, J.P. Activation of pro-survival Akt and ERK1/2 signalling pathways underlie the anti-apoptotic effects of flavanones in cortical neurons. *J. Neurochem.,* **2007**, *103*, 1355-1367.

[69] Aithal, M.G.S.; Rajeswari, N. Role of Notch signalling pathway in cancer and its association with DNA methylation. *J. Genet.,* **2013**, *92*(3), 667-675.

[70] Takebe, N.; Nguyen, D.; Yang, S.X. Targeting Notch signaling pathway in cancer: Clinical development advances and challenges. *Pharmacol. Ther.,* **2014**, *141*, 140-149.

[71] Kunnimalaiyaan, M.; Chen, H. Tumor suppressor role of Notch-1 signaling in neuroendocrine tumors. *Oncologist* **2007**, *12*, 535-542.

[72] Zarebczan, B.; Pinchot, S.N.; Kunnimalaiyaan, M.; Chen, H. Hesperetin, a potential therapy for carcinoid cancer. *Am. J. Surg.,* **2011**, *201*, 329–333.

[73] Patel, P.N.; Yu, X.M.; Jaskula-Sztul, R.; Chen, H. Hesperetin activates the notch1 signaling cascade, causes apoptosis, and induces cellular differentiation in anaplastic thyroid cancer. *Ann. Surg. Oncol.,* **2014**, Suppl 4, S497-504.

[74] Lu, Z.; Xu, S. ERK1/2 MAP kinases in cell survival and apoptosis. *IUBMB Life,* **2006**, *58*(11), 621-631.

[75] Santarpia, L.; Lippman, S.L.; El-Naggar, A.K. Targeting the mitogen-activated protein kinase RAS-RAF signaling pathway in cancer therapy. *Expert Opin. Ther. Targets,* **2012**, *16*(1), 103-119.

[76] Moon, P.D.; Kim, H.M. Antiinflammatory Effects of traditional korean medicine, jinpi-tang and its active ingredient, hesperidin in hacat cells. *Phytother. Res,* **2012**, *26*, 657-662.

[77] Pollard, S.E.; Whiteman, M.; Spencer, J.P. Modulation of peroxynitrite-induced fibroblast injury by hesperetin: A role for intracellular scavenging and modulation of ERK signalling. *Biochem. Biophys. Res. Commun.,* **2006**, *347*, 916-923.

[78] Kim, J.Y.; Jung, K.J.; Choi, J.S.; Chung, H.Y. Modulation of the age-related nuclear factor-kappaB (NF-kappaB) pathway by hesperetin. *Aging Cell,* **2006**, *5*, 401-411.

[79] Rainey, S.S.; Schroetke, L.W.; Bahia, P.; Fahmi, A.; Skilton, R.; Spencer, J.P.; Rice-Evans, C.; Rattray, M.; Williams, R.J. Neuroprotective effects of hesperetin in mouse primary neurones are independent of CREB activation. *Neurosci. Lett.,* **2008**, *438*, 29-33.

[80] Nones, J.E.; Spohr, T.C.; Gomes, F.C. Hesperidin, a flavone glycoside, as mediator of neuronal survival. *Neurochem. Res.,* **2011**, *36*, 1776-1784.

[81] Nusse, R. Wnt Signaling. *Cold. Spring Harb. Perspect. Biol.,* **2012**, *4*, 1-3.

[82] Huang, Y.C.; Liu, K.C.; Chiou, Y.L. Melanogenesis of murine melanoma cells induced by hesperetin, a Citrus hydrolysate-derived flavonoid. *Food Chem. Toxicol.,* **2012**, *50*, 653-659.

[83] Kim, S.Y.; Lee, J.Y.; Park, Y.D.; Kang, K.L.; Lee, J.C.; Heo, J.S. Hesperetin alleviates the inhibitory effects of high glucose on the osteoblastic differentiation of periodontal ligament stem cells. *PLoS One,* **2013** *8*(6), e67504

[84] Surh, Y.J.; Chun, K.S.; Cha, H.H.; Han, S.S.; Keum, Y.S.; Park, K.K.; Lee, S.S. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-κB activation. *Mutat. Res.,* **2001**, *480-481*, 243-268.

[85] Coelho, R.C.; Hermsdorff, H.H.; Bressan, J. Anti-inflammatory properties of orange juice: possible favorable molecular and metabolic effects. *Plant Foods Hum. Nutr.,* **2013**, *68*(1), 1-10.

[86] Aggarwal, B.B.; Shishodia, S.; Sandur, S.K.; Pandey, M.K.; Sethi, G. Inflammation and cancer: How hot is the link? *Biochem. Pharmacol.,* **2006**, *72*, 1605-1621.

[87] Rizza, S.; Muniyappa, R.; Iantorno, M.; Kim, J.A.; Chen, H.; Pullikotil, P.; Senese, N.; Tesauro, M.; Lauro, D.; Cardillo, C.; Quon, M.J. Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. *J. Clin. Endocrinol. Metab.,* **2011**, *96*(5), 782-792.

[88] Kim, S.W.; Kim, C.E.; Kim, M.H. Flavonoids inhibit high glucose-induced up-regulation of ICAM-1 via the p38 MAPK pathway in human vein endothelial cells. *Biochem. Biophys. Res. Commun.,* **2011**, *415*, 602-607.

[89] Cha, J.Y.; Cho, Y.S.; Kim, I.; Anno, T.; Rahman, S.M.; Yanagita, T. Effect of hesperetin, a citrus flavonoid, on the liver triacylglycerol content and phosphatidate phosphohydrolase activity in orotic acid-fed rats. *Plant Foods Hum. Nutr.,* **2001**, *56*, 349–358

[90] Lee, R.Y.; Jung, J.H.; Kim, H.S. Hesperidin partially restores impaired immune and nutritional function in irradiated mice. *J. Med. Food,* **2011**, *14*, 475-482.

[91] Zanotti-Simoes-Dourado, G.K.; Abreu-Ribeiro, L.C.; Zeppone, C.; Borges-César, T. Orange juice and hesperidin promote differential innate immune response in macrophages ex vivo. *Int. J. Vitam. Nutr. Res.,* **2013**, *83*(3), 162-167.

[92] Choi, E.M.; Lee, Y.S. Effects of hesperetin on the production of inflammatory mediators in IL-1beta treated human synovial cells. *Cell. Immunol.,* **2010**, *264*, 1-3.

[93] Saiprasad, G.; Chitra, P.; Manikandan, R.; Sudhandiran, G. Hesperidin alleviates oxidative stress and downregulates the expressions of proliferative and inflammatory markers in azoxymethane-induced experimental colon carcinogenesis in mice. *Inflamm. Res,* **2013**, *62*, 425-440.

[94] Nalini, N.; Aranganathan, S.; Kabalimurthy, J. Chemopreventive efficacy of hesperetin (citrus flavonone) against 1,2-dimethylhydrazine-induced rat colon carcinogenesis. *Toxicol. Mech. Methods,* **2012**, *22*(5), 397-408.

Received: March 20, 2014 **Revised: April 16, 2014** **Accepted: April 20, 2014**