Review on Discovery and Development of Novel Phytochemicals which can be used in Functional Foods

YEN-CHUN KOH and MIN-HSIUNG PAN*

Institute of Food Sciences and Technology, National Taiwan University, Taipei 10617, Taiwan.

Abstract

Phytochemicals intake has become a novel trend of prevention of diseases or medication due to their marvelous health benefits discovered for decades. The incidence of different diseases are elevated rapidly and phytochemicals have been found to be a promising intervention as chemoprevention strategy or to be involved in therapeutic compounds in either single therapy or combined therapy with developed drugs to reduce dosage or usage, with low cost and side effect consideration. The preventive and therapeutic effects of phytochemicals may include antioxidant, anti-inflammatory, anti-tumor, anti-obesity and metabolic syndromes, organs- and neuro-protection, gut micro biota modification and circadian rhythm realignment. Undeniable, the underlying mechanisms and major targets in these preventive or medical actions may be various and much more different from each other due to specific structure and functional groups. Therefore, research on the phytochemicals is imperative to clarify the role, suitability, limitation, and the biological availability. In this review, the researchers briefly summarize some recent studies focused on the potential ameliorative effects of selected dietary bioactive compound on different diseases, in order to provide the primary summary of these novel compounds to be involved in the human life style and eating habits.

Introduction

Phytochemicals, commonly known as non-nutritive plant-based chemicals are ubiquitous in different plant organs or algae, and they are recently being involved in preventive and/or therapeutic action of different diseases due to their cost effectiveness, safety, abundance and bioactive potentials[1]. Some of the advantages could overcome several distressing problems including costs and side effects, rather than using synthetic therapeutics[2]. Most phytochemicals possess anti-inflammation capacity due to their antioxidant and free radical scavenging ability and these capabilities have become the basis to reduce chronic disease incidence, such as cancer,

metabolic diseases, anti-viral infection and neuro-degeneration, and bring some health benefits like retarding aging and hormones regulatory effect[3]. Due to static elevation of morbidity and mortality in different cancer cases for decades, positive impacts of phytochemicals in cancer improvements have been broadly pointed out in cancerous cells apoptosis activation, cell proliferation and tumor angiogenesis inhibitions, suppressive effect on cell migration and invasion, induction of tumor suppressing genes, procarcinogen bioactivity repression, detoxification and detoxification, and DNA damage prevention[4]. Some of the major functions of phytochemicals are introduced as following; briefly explain the basic mechanisms and several amelioration strategies in dietary compound involvements.

Anti-Oxidation

Oxidation is essential for energy generation in many organisms as long as the balance between oxygen free radicals production and elimination is maintained. Several diseases in elevating number of evidences have been reported as consequence of oxidative stress imposed by uncontrolled reactive oxygen species (ROS) including diabetes, and cardiovascular disease as resultant from aging degeneration[5]. ROS generation is found to be up-regulated by NADPH oxidase and bioactive redox phytochemical could eventually normalize the imbalance[3]. Most phytochemicals exhibited in a general two-stage anti-oxidation mechanism to trap the radical and form a non-radical materials[6]. Evaluation of phytochemical anti-oxidative capacity is normally conducted as in in vitro experiments, including total antioxidant content as compared to known compound, reducing power, free radical scavenging ability and metal chelating ability. However, phytochemicals are expected to transform after digestion, so called first pass effect, and therefore, in vivo anti-oxidation effect is more concerned. Nonetheless, in vivo anti-oxidation capability evaluation is still limited and so far, serum or tissue superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) concentrations have become the basic target for determination[7].

Anti-Inflammation

As a primary response to infection or injury caused by irritation or wounding, inflammation is critical for both innate and adaptive immunity[8]. Stimuli such as LPS can trigger inflammation process by M1 macrophage activation, which leads to secretion of pro-inflammatory cytokines, normally including interleukin-1β (IL-1β), interleukin-6 (IL-6) and Tumor Necrosis Factor α (TNF-α), and these cytokines are responsible to diseases like immunological disorder, organ dysfunction caused by tissue injury and various kinds of cancer[9]. Although M2 macrophages play an anti-inflammatory role in human body, cytokines produced by M2 macrophages would increase migration and invasion ability of cancer cells in later stage[10]. Inhibition of pro-inflammatory cytokines has found to be therapeutically important and considered as the major strategy in most diseases improvement. On the other hand, some studies focused on inhibiting inflammatory signaling pathways rather than production of inflammatory cytokines. For instance, Mitogen-Activated Protein Kinase (MAPK) pathway activated by inflammatory cytokines or stimuli like LPS, stress signals and others, and messengers in MAPK pathway may be involved in cell apoptosis, differentiation, cytokine production and autophagy[10].

Anti-Cancer

Besides of anti-inflammatory and anti-oxidative effect as above mentioned that highly related to tumorigenesis, there are several strategies to be used in cancer chemoprevention, including apoptosis, cell cycle arrest, autophagy, epigenetic modification and phase 2 enzyme induction.

Apoptosis

Being an important role in cell growth, proliferation and regulating plenty of protein expression, mammalian target of rapamycin (mTOR) has become one of the major target in cancer therapeutic actions because PI3K/Akt/mTOR pathway is found to overexpress in most cancer types, and subsequently lead to reduction in apoptosis and induce cancer cell survival[11]. Furthermore, as downstream targeting proteins for cancer therapy, caspases including caspase-3, -9, and -8, and anti-apoptotic protein like Bcl2 and Bcl-x are also highly concerned[12].

Autophagy

Autophagy is described as a double-edged sword in clinical point of view for cancer therapy. Protective effect of autophagy can promote cancer cells

survival by providing nutrients to damaged cells while the cytotoxic effect of autophagy has become an interesting and promising anti-cancer strategy. Similar to apoptosis, inhibition of PI3K/Akt/mTOR pathway is one of the major targets for autophagy activation. Furthermore, activation of AMPK could induce AMPK dependent autophagy and up-regulation of p21 and p53, which is also a favorable result of autophagy[13].

Phase 2 Enzymes

The main function of phase 2 enzymes is normally recognized as detoxification of phase 1 enzymes bio transformed carcinogen, through several reactions that include acetylation, glucoronidation, sulfation and glutathione conjugation[14]. Phase 1 enzymes introduce reactive or polar groups like −NH2, -COOH, and −OH onto the potential carcinogens, such as BaP and TCDD, followed by conjugation with hydrophilic molecules[15]. Phase 2 enzymes that carry out these reactions consist of superoxide dismutase (SOD), reduced glutathione (GSH). GSH peroxidase (GPx). GSH-transferase (GST) NAD(P)H quinone oxidoreductase 1 (NQO1) and more[14]. Due to their positive impacts on cancer prevention, transcriptional expression of phase 2 enzymes has caught the sight of researchers in recent years.

Epigenetic Modification

Compared to genetic changes, epigenetic modifications, including DNA methylation, histone modification and microRNA, are theoretically reversible and the gene expression regulated are not relevant to changes in DNA sequences.

DNA Methylation

Covalent methylation on cytosine base of 5'CpG3' dinucleotide, normally appear at promoter region, is known as the major DNA modification that can be found in mammalians. It is believed that DNA methylation can be transmitted to next generation as a gene regulatory epigenetic mark, and the presence of DNA methyltransferases is found to be critical in the case[16]. Basically, when DNA methyltransferase adds methyl group to the C-5 position of cytosine bases of CpG region that overlaps with promoters, downstream gene will be silenced[17]. In fact, several environmental factors or toxicants, or physical activities like smoking and lipid levels have been found to alter DNA methylation status[18]. On the top of that, the multiple impacts of phytochemicals on expression and activity of DNA methyltransferase and regulatory effect on level of methylation have been extensively studied if they are contributing in cancer prevention, and also histone modification, as introduced as following[19].

Histone Modification

Histone modifications can be simply classified by the outcomes whether they resulted in activation or repression of gene expression because until now, some functions of modifications are still not clearly elucidated depending on different situations[20]. Identified post-translational histone modifications consists of acetylation or methylation of lysines and arginines, phosphorylation of serines and threonines, ubiquitynation and sumoylation occurred on lysines, and ribosylation[21]. Acetylation and methylation of lysines have been widely discussed and comparably understood in some studies. First of all, histone acetyl transferases (HATs) can reduce chromatin condensation by transferring an acetyl group from acetyl-CoA to lysine at amino-terminal tail, subsequently neutralize positive charge of histone and lead to gene expression while histone deacetylases (HDACs) has an opposite effect on histone that causes gene repression effect[21]. On the other hand, Histone methylation can either activate or silence gene expression after transferring a methyl group from S-adenosylmethionine (SAM), an enzymatic donor, to the H3 and H4 tails of lysine and arginine[21]. The mechanism of histone modification helps to control gene expression, and cell and tissue differentiation which are normally out of control in progression of cancer[22].

MicroRNA (miRNA)

There is a class of single stranded, noncoding regulatory RNA molecule, normally consists 18-25 nucleotides, expressed endogenously and can result in degradation of mRNA or inhibiting translation by binding to 3'-untranslated region of mRNA[23]. As recorded until June, 2014, there are up to 28645 identified entries in miR Base[24]. Each miRNA are potent to target more than one gene, and therefore, studies on miRNA focusing on oncogenes suppression, so called oncomiRs, have raised recent years via multiple pathways as mentioned above, including cell proliferation,

apoptosis, metastasis, autophagy, angiogenesis and others that may result in anti-tumor effect. Therefore, down-regulation or dysfunction of miRNA can be crucial in cancer progression that may lead to oncogenes overexpression[25]. Because of that, some researchers have started putting efforts in exploring more functions of miRNA, at the same time identifying new miRNA, and investigating the way to regulate expression of miRNA. In latest review, miRNA expression has been pointed out that can be regulated by transcription factors, methylation, maturating-enzymes activity and stability[26].

Anti-Obesity and Metabolic Diseases Improvement

Excess fat accumulation is one of the leading causes for obesity or overweight and is majorly due to imbalanced energy intake and expenditure and it has shown its negative effect on acceleration and increment in risk of metabolic problems including cardiovascular diseases, type 2 diabetes, hypertension, dyslipidemia, insulin resistance and other diseases that related to chronic inflammation[27]. There are multiple strategies to alleviate adverse effect of obesity via treatment of phytochemicals, including regulation the cell cycle and differentiation of adipocytes, inhibition of adipogenesis and induction of lipolysis, activation of brown adipose tissue to stimulate energy expenditure, transformation of white adipose tissue into beige adipose tissue, and focusing on inflammation suppression to reduce secretion of adipokines[27-29]. On the other hand, epigenetic changes, like histone methylation can be targeted to down-regulate genes related to adipogenesis. Therefore, some phytochemicals are highlighted due to their multi-targeting effect on health improvement[30].

Besides of the amelioration in above mentioned diseases or problems, novel function of phytochemicals in some minor or latest studies, including neuroprotection and brain function, circadian rhythm and gut micro biota, are also briefly introduced in this review.

Phytochemicals

There are some important groups of phytochemicals include phenolic compounds that can be subdivided into phenolic acids, flavonoids and lignans, alkaloids, terpenes, organosulfides and glycosinolates,

and each of them presents specific or shares some common effects on health improvement[31]. Although phytochemical is sometimes as similated with nutraceuticals, functional food and phytopharmaceuticals in some marketing strategies, phytochemicals, in definition, are totally different from the others[4]. There are some limitations of phytochemicals; for example, one of the shortcomings of phytochemicals is having higher minimum inhibitory concentration (MIC) than drugs, and therefore, compared to monotherapy, some studies are focusing on effect of phytochemicals as in mixture to provide plethora of bioactivity against disease or combined with antibiotics to reduce drug usage and dosage[2]. On the other hand, some phytochemicals like carotenoids and tocopherols have already been widely discussed and their benefits are mostly reported. Therefore, here in this review, researchers are going to introduce some novel phytochemicals, including stilbenes, flavonoids and their derivatives, together with their newly defined functions in latest studies. The studies mentioned in this review are mostly advanced research which have been done from year 2016 to 2018, with some exceptions that published in year 2012 to 2015, due to their expertized view in particular field that could not be neglected.

Stilbene

Stilbene is produced by some plant species, which also known as secondary metabolism derivative that provides antimicrobial effect, UV light damage protection and defense responses[32]. Among stilbene-derived compounds, its hydroxylated derivatives, so-called stilbenoids have rendered compelling impacts on health issues.

Stilbenoid

Stilbenoids share a C_6-C_2-C_6 structure, and it can be classified into two sub-types, aglycones and glycosides. Stilbenoid alycones consist of resveratrol, pterostilbene and piceatannol, while piceid and astrigin, derivatives of resveratrol and piceatannol are classified as stilbenoid glucosides[33].

Chemopreventive Effects of Stilbenoid

Resveratrol is a polyphenol that can be commonly found in grapes, peanut and wines. Due to its efficacious anti-oxidative and anti-inflammatory capability, it has been further evaluated on its effects

in different protective or ameliorative actions in health issues. For instance, it was able to protect spinal cord from injury by suppressive effect in iNOS/p38 MAPK pathway activation in rat model, exhibit neuroprotection effect in hNSC after inflammation and oxidative stress being induced by amyloid-β and aging-related deficits using SH-SY5Y neuroblastoma and middle-aged and old mice, by activating AMPK-dependent signaling pathways and promoting ERK ½ pathway, respectively[33-35]. In addition, resveratrol also demonstrated therapeutic effect of Alzheimer's disease by facilitating mesenchymal stem cell transplantation, subsequently enhancing neurogenesis and SIRT1 signaling[36]. Intervention of resveratrol exhibited conspicuous effect in chemo preventive action, including promising caspase-3 activity increment in hepatocellular carcinoma cell line, and inhibiting invasion of human gastric cancer cells (SGC7901) induced by IL-6, and suppressing human breast cancer cells migration, invasion and stemness by its inhibitory effect in Sox2, Akt and STAT3 expression and activation[37-39]. Research on the effect of resveratrol is still elevating, showing its important role in several diseases amelioration and potential to be focused in future.

Being a natural analogue of resveratrol, piceatannol shares some similar effects with resveratrol in health improvement potential, such as lowering postprandial hyperglycemia and inhibiting α-glucosidase activity in intestine, reducing adrenal androgens production by CYP17A1 inhibition in adrenocortical cells and signaling of androgen receptor in normal and cancerous prostate cells[40,41]. Furthermore, both resveratrol and piceatannol had exhibited similar inhibitory effect in hydrogen peroxide accumulation and modulation in activity of monoamine oxidase, although piceatannol performed a stronger lipolysis stimulation while resveratrol presented stronger anti-lipolytic action in adipose tissue[42]. To be mentioned that, biosynthesis of resveratrol and piceatannol was found to be enhanced by mechanical stress in some plant products[43]. Nonetheless, of cause there are differences between the analogues, for example, resveratrol has shown potential benefits in antiarrhythmic properties in acquired long-QT-syndrome but piceatannol didn't[44]. Based on that, research on piceatannol has also increased within these few years. Piceatannol has been reported to stimulate neurite outgrowth, maintain

neuronal cells function and promote cell survival against oxidative stress-inducement[45]. Additionally, piceatannol showed a better ability than resveratrol and oxyresveratrol, to reduce the negative impact of Amyloid-β without causing cell death but activating α-secretase and MMP-9[46]. Piceatannol was also found to be protective against photo-oxidative damage induced by vitamin-A dimer accumulation in ARPE-19 cells via Nrf2/NQO1 signaling pathway activation, which indicated its effect in age-related retinal degenerative diseases improvement[47]. Gut micro biota has recently become a slight-catching topic among raising health issues and piceatannol has promised itself as adipogenic proteins- and gut micro biota-modulating compound, in turns of being an anti-obesity effect enhancer in mice model[48].

Pterostilbene can be naturally found in blueberries and similar to other hydroxylated stilbene derivatives, it has exhibited anti-tumor and anti-inflammatory activities in several studies. It was suggested as a promising compound to improve AGEs-induced oxidative stress and inflammatory effect via regulation in RAGE/MAPK/NF-κB pathway[49]. Moreover, pterostilbene was capable to attenuate inflammatory effect and endoplasmic reticulum stress (ERS) induced by TNF-α by down-regulating ERS-related protein (p-eIF2α, GRP78 and p-IRE1) and inflammatory cytokines (IL-8, MCP-1, ICAM1 and MMP9) expression[50]. On top of that, pterostilbene administration has stabilized its role as therapeutic agent of diabetic dyslipidemia by normalizing Nrf2-mediated mechanism in streptozotocin-induced diabetic mice model[51]. It could also ameliorate insulin sensitivity and oxidative stress in fructose-induced diabetic rats, promote energy metabolism and prevent white adipose tissue accumulation in obese rats, and repress atherosclerosis inflammation induced by high fat diet in TLR-5 deficient mice through NF-κB signaling modulation[52-54]. In obesity or overweight preventive action, pterostilbene up-regulated HO-1 expression by acting as C/EBP homologous protein 10 (CHOP10) regulator and suppressing initiation stage of mitotic clonal expansion during 3T3-L1 cell differentiation[55]. Alleviation effects in liver damage occurred after being treated with pterostilbene in sepsis-induced liver-injured mice model with activation of SIRT1 signaling and reduction in serum inflammatory cytokine level including TNF-α and IL-6[56]. Additionally, pterostilbene had

possessed positive impact in anti-cancer effect in hepatocellular carcinoma by promoting PTEN acetylation and apoptosis and/or ER stress and autophagy activation, alleviating skin cancer in B[a]P skin cancer model, and suppressing colon cancer by activating GRP78-eIF2α-ATF3 and apoptosis cascade[57-61]. Neuroprotective effect of pterostilbene has been pointed out against oxidative stress injury induced by glutamate or high glucose in neuronal cell by activating NQO1 and Nrf2/HO-1 signaling pathways, respectively[62,63]. Similar result was obtained which indicating that pterostilbene may be efficacious in hypoxic/ischemic-associate brain injury in newborns as it seemed to be capable to ameliorate brain damage in neonatal rat via HO-1 mediation[64]. Finally, due to its compelling effect in reversing hypoxia-induced damage and anti-inflammatory ability, intervention of pterostilbene has surpassed adverse effect of hypoxia-re-oxygenation injury and myocardial ischemia/reperfusion injury by enhancing SIRT1 function restoration and suppressive oxidative/nitrative stress, respectively[65,66].

On the other hand, there are only comparably fewer research have been done on hydroxylated stilbenoids, such as 3'-hydroxypterostilbene, which as known as a metabolites of pterostilbene that can also be naturally found in some herbs. It has presented its efficacy in anti-cancer effect in human colon xenograft tumors by modulation of PI3K/Akt/mTOR signaling pathway and down-regulating protein expression of COX-2, MMP-9, VEGF and cyclin-D, consequently lead to occurrence of apoptosis[67]. Other effects including anti-adipogenic, neuroprotection and anti-cancer capability via modulation of HDAC and SIRT1 activity were reported previously, indicating the potential contribution of hydroxylated pterostilbene and other stilbenoid derivatives in health improvement[68].

Flavonoid
Flavonoid, a subgroup of polyphenol, can be structurally classified into seven groups based on the differences on aglycone C ring, including anthoxanthin (flavones and flavonols), flavanones, flavanols, flavanonols, isoflavanols, and anthocyanidins. The structure variation of flavonoid is provided by the modifications of functional groups by hydroxylation, methylation, or glycosylation on a basic skeleton of 15-C. Flavonoids have been reported in several epidemiological studies, having beneficial effects in amelioration of chronic diseases and health improvement[69].

Anthoxanthin
Chemopreventive Effects of Flavones
Among the flavones, apigenin, tangeretin and nobiletin have shown their capabilities in anti-inflammatory action and tumor suppression.

Tangeretin (5, 6, 7, 8, 4'-pentamethoxyflavone) and nobiletin (5, 6, 7, 8, 3', 4'-hexamethoxyflavone), two of polymethoxyalted flavones (PMFs), are naturally found to be abundant in citrus fruits such as sweet orange peels, especially in immature fruits and a variety of remarkable advantages have been reported, for instance anti-inflammatory, neuroprotection, anti-tumor and anti-metastatic effects[69,70]. Interestingly, nobiletin and tangeretin exert efficacious preventive/suppressive capability in xenobiotic-or chemically-induced carcinogenesis by regulating tumor promotion via xenobiotics/drug-metabolizing enzyme (XMEs) system activation[15]. Hydroxylated polymethoxyflavones (HPMFs), including 5-demethylnobiletin and its acetyl derivative, 5-acetyloxy-6, 7, 8, 3', 4'-pentamethoxyflavone are considered as novel phytochemicals that seldom being discussed in their bioactive functions. However, the modification on the natural phytochemicals can dramatically elevate their bioavailability and bioactive efficiency, and results in more pronounced reduction in lipid accumulation by altering transcriptional factors via AMPK pathway and lipogenesis enzymes[71]. Nobiletin is suggested as a rising star in novel bioactive compound research due to a broad range of multiple hydroxylated metabolites yield that may be predominant in health benefits[72].

Apigenin is well-known with its bioactivity in several herbs including parsley, peppermint and vegetable like celery. It has exhibited potential to promote TRAIL-apoptosis by suppressing Akt/mTOR signaling pathway with ROS generation and autophagy activation in liver cancer cell lines, and colorectal cancer cell migration and metastasis suppression by NEDD9 down-regulation[73,74]. Besides of cancer therapeutic effect, it has also demonstrated its protective role against ROS-mitochondria inducement and caspase-dependent apoptotic pathway activated by mycotoxin-derived toxicity in human embryonic kidney cell[75]. On the other hand,

efficacy of apigenin in dopamine content as well as life span increment and reduction in oxidative stress was reported in Parkinson's disease transgenic *Drosophila* model[76]. Moreover, hydroxylated metabolites of apigenin such as 3-phenylpropionic acid and 3-(3, 4-dihydroxyphenyl) propionic acid by microbiota may be considered as compelling novel phytochemicals to be further discussed in future studies[72].

Chemopreventive Effects of Flavonols
Among up to 15 type of flavonols that commonly being discussed, quercetin and kaempferol are very representative due to their anti-inflammatory effects to treat unwanted immune response by blockade of NF-κB activation and their abundancy in vegetables and fruits such as onion, broccoli and berries[77]. Most importantly, there was no adverse effect examined in toxicity at high concentration up to 3000 mg/kg in clinical studies[78]. Recent research in producing flavonoid fermentatively by yeast metabolis enginnering has sucessfully developed yeast strains that produced quercetin and kaempferol with enormous extracellular concentration, via tyrosine and pohenylalanine supplying routes[79].

Kaempferol can be produced by hydroxylation on naringenin, the flavanone mentioned above, followed by introducing double bond by flavonol synthase[80]. Intervention of kaempferol in $Fe-Cl_3$-induced carotid arterial thrombus model and acute thromboembolism models induced by collagen/eninerphrine and thrombin has revealed its potent effect against fibrin clot formation and suppressive activity of pro-coagulant protease and platelet activation in cardiovascular disease[78]. As the only lipid-soluble antioxidant synthesized endogenously, Coenzyme Q is normally supplemented in diet with Q10 in therapies in deficient patients, even the difficulty in absorption is already known. Fortunately, kaempferol, along with isotope technique, has recently been identified with its action as biosynthetic ring precursor, participating in enzyme Q biosynthesis[81]. Positive results in bone loss inhibition have been rendered with kaempferol intake in ovariectomy-induced osteopenia and osteopenic condition induced by glucocorticoid in rat models[82,83]. On the other hand, astragalin, which known as kaempferol with glucosyl unit at C-3 position that can also be naturally found in tea and berries, itself possesses anti-inflammatory capacity

as kaempferol by down-regulating LPS-induced inflammatory response, majorly in NF-κB signaling pathway repression in mouse and human cells models and murine model[84-87]. Novel galactosylation of astragalins by β-galactosidase can hopefully overcome the shortcoming of poor solubility of astragalin for more industrial application potent[88].

Quercetin has recently gained its ground in wound healing in exogenous application, and thence, it may also provide benefit in endogenous wound closure and regeneration, maybe in colon ulcer, due to its conspicuous role in angiogenesis and epithelial cells and fibroblasts proliferation[89]. Compelling hepaprotective effects of quercetin have also been illustrated in ConA-induced acute hepatitis, type 1 diabetic liver damage in mice models and cell injury in HepG2 cell via erythropoietin, a cytoprotective protein, transcription regulation[90-92]. In cancer prevention and therapeutic action, quercetin showed its inhibitory capacity in cell proliferation, and induced impairment in cell migration and invasion in glioblastoma U251 cells via metallopeptidases MMP9 and MMP2 downregulation, and stop metastasis of A431-III by reducing RPS19 transactivation activity and blockage in Akt/mTOR/c-Myc signaling pathway[93,94]. In other applications, quercetin demonstrated its advantages to be used as packing material to indicate ageing time, fungal activity resistance and unsurprisingly, high antioxidant activities[95]. Furthermore in veterinary science, quercetin is capable to lower somatic cells count in dairy cows with mastitis after 8-day therapy and the importance of this result is just more than important in dairy production field[96].

Flavanones
Chemopreventive Effects of Flavanones
There are nearly up to 14 flavonones identified and among them, hesperetin, a major flavanoid in sweet oranges and lemons, has exhibited its anti-inflammatory, liver protective in LPS-induced RAW264.7 macrophage and CCl_4-induced liver injury, therapeutic implication for osteosarcoma by cytotoxic inducement in U2OS cells, and neuroprotective effect on recognition/memory impairment by reducing oxidative stress in Alzheimer's disease rat model[70,97,98]. Moreover, antihyperglycemic effect and renoprotective activity of hesperetin in streptozotocin-induced diabetic rats and cisplatin-

induced nepthrotoxicity, also strengthened its potential as a promising bioactive compound[99,100]. One of the novel application of hesperetin combined with chitosan conjugation and encapsulation in nanoparticle has highly increase the efficacy of hesperetin in colon cacer cell growth inhibition up to 6 times better than its original counterpart[101].

Besides of hesperetin, another flavanone, naringenin has also shown its beneficial potential in liver antioxidant status and fatty acid profile improvement in both young adult and aged rat models by stimulating AOE system[102]. Similar to hesperetin and most phytochemicals, oral bioavialability of naringenin is mostly concerned, followed by stability and solubility, and the limitations can also be surpassed by nanosuspension and surfactant stabilization[103]. On the other hand, methylation of hydroxyl groups has been suggested to improve metabolic stability and membrane transportion ability to facilitate bioavailability and absorption. For instance, methylated naringenin, including naringenin 7-O-methyl ether and 4', 7-dimethyl ether have promising anti-seizure effect in acute mouse model[104]. Since naringenin, which is abundant in citrus peels, has demonstrated its pain-killing effect in neuropathic and inflammatory pain models, lately synthetic phytochemicals with methylation or hydroxylation may also exhibit analgesic effects by recruiting neutrophil or inhibiting oxidative stress[105].

Flavanols
Chemopreventive Effects of Flavanols
Flavanol, which also referred to flavan-3-ols, is a group of flavan derivatives that shares 2-phenyl-3,4-dihydro-2H-chromen-3-ol skeleton that retains a ketone group compared to flavonols. Catechin and its epimer epicatechin, as well as their derivatives, epigallocatechin (EGC) and gallocatechin (EC) with an additional phenolic hydroxyl group, and catechin gallate especially epigallocatechin gallate (EGCG), the ester of epigallocatechin and gallic acid, are all recognized as the most common counterpart of catechin that abundant in tea[106].

Not in surprise, EGCG has been efficacious in chemoproventive action and exhibited therapeutic properties including cardiovascular, hepatic, metabolic, inflammatory, hyperuricemic and diabetic diseases in elevating numbers of research [106-110]. Latest study has elucidated the relationship of EGCG associates with circadian clock to ameliorate metabolic syndrome, explained the involvement and potential of diet mediating peripheral circadian genes[111]. Not neglectable, fortification of EGCG has also thrived and been applied widely in food industry in recent research. In bread processing, EGCG seemed to be feasible to decrease acrylamide formation during baking although the understanding of the mechanism should be further investigated[112]. Interestingly, combined effect of EGCG with fluoride has shown to provide dental protective effect by reducing erosive damages like loss of tooth structure and hardness that induced by softdrink[113]. Treatment of EGCG solution with ultrasonic promises quality of pre-cooked shrimp by inhibiting melanosis development[114]. ECGC has also demostrated microbial effect on pathogenic bacteria by inhibitory activity of S. Typhimurium type III protein to reduce bacterial invasion and biofilm formation by L.monocytogenes to decrease its antimicrobial resistance[115,116]. Back to the human health improvement issues, assessment of EGCG on effective anti-virus effect has been reported recently. Capability of EGCG was noted to be able to inhibit the entry of Zika virus by more than 90% with 100 μM concentration in Vero E6 cells[117]. EGCG was suggested to be used as natural disinfectant to be incorporated on food surface due to its antiviral activity against hepatitis A virus and murine norovirus[118]. As a supportive information, oxidized EGCG has contributed in Alzheimer's disease and Parkinson's disease therapeutic strategies by inhibiting amyloid formation and peracetylated EGCG showed its efficacy in skin carcinogenesis by repressing PKD1-dependent signaling pathway[119,120].

Isoflavones
Chemopreventive Effects of Isoflavones
One of the highlights on daidzein and genistein is basically due to their structures similar to natural and synthetic estrogen that provides themselves capability to bind on estrogen receptor ERα and ERβ (121). Therefore, there are increasing research on treatments of genistein and daidzein in female animals like adult hippocampal neurogenesis enhancement by daidzein as estrogen substituent and uterine homeostasis affection of daidzein and genistein in ovary-intact rats, indicates the potential

efficacy of isoflavones in menopausal discomforts alleviation[121,122]. Thus, a randomized control trial in premenopausal women has been conducted and resultant in novel effects of these phytoestrogenic isoflavones to be strongly associated with serum calcium and chloride level and cardiovascular diseases morbidity reduction[122].

Like other phytochemicals, daidzein and its derivaties with sulfonic acid esterification have demonstates anti-inflammatory ability, as well as in repression of severe acute pancreatitis, a pancreas inflammatory process by inhibitory effect in trypsin, and suppressive effect in IL-6 and activation of MEK/ERK and PI3K/Akt pathway in MG-63 osteoblast cells as a prediction for bone loss treatment in postmenopausal females[121,123-125]. As abovemention, metabolism of phytochemicals can highly increase the bioactivity than its original counterpart, and these metabolites are normally produced by gut microbiota. For instance, peri- and post-menopausal women with obesity were reported lacking of gut microbial community that is capable to metabolize daidzein to O-desmethylangolensin that associated to bone density[125]. Surprisingly, some lactic acid bacteria and common gut bacteria *bididobacterium* strain can transform daidzein and genistein into other bioactive forms, like dihydrodaidzein and dihydrogenistein[121]. These results have provided crucial evidences of important relationship between gut microbiota, bioactive compounds and phytochemical bioavailability. Other daidzein metabolites, including 6, 7, 4'-trihydroxyisoflavone was found to be possible in learning and memory improvement via p-CREB/BDNF signaling pathway while 7, 8, 4'-trihydroxyisoflavone may be able to exhibit anti-atherosclerotic effect by inhibiting monocyte endothelial cell adhesion[126,127]. Therefore, it is believed that hydroxylated daidzein may show its potential in future studies.

Genistein has gained its potential role in brain science by exerting anti-depressant-like effect via serotonergic system coupled with 5-HT1A receptor, ameliorating anxiety-like condition by enhancing serotonergic transmission, which includes serotonin and (p)-CaMKII and CREB phosporylation upregulation in amygdala in post-traumatic stress disorder, and attenuating hippocampal brain-derived neurotrophic factor (BDNF) overexpression that

induced by seizure[128-130]. Other neuroprotective effect of genistein in neuro-inflammatory modulation in diebetic mice with cognitive decline mice and sensorimotor gating improvement to ameliorate Huntington's disease have been demonstrated in recent studies as well[131,132]. As mentioned before, due to the estrogen-like in structure, genistein has potential gonadoprotective effect like inhibiting small follicles recruitment via anti-inflammatory mechanisms to prevent cyclophosphamide-induced toxicity in ovary[133]. Furthermore, genistein, as partial substituent of estrogen, has sucessfully improved dry eye condition by upregulating estrogen receptor-β, ER-β and MUC5AC expression and suppress IL-1β level in ovariectomized rats, even estrogen is majorly produced in ovary[134]. Lastly, possible chemopreventive effect of genistein has been administrated in prevention of thyroid cancer in Hashimoto thyroiditis patients and inhibitory action in endometrial cell proliferation by regulating expression of ERα and ERβ expression by different genistein concentrations[135,136].

Anthocyanidins And Anthocynins
Chemopreventive Effects Of Anthocyanidins And AnthocyNINS

Anthocyanidins are commonly known as pigment compounds found in different fruits and vegetables. Among identified anthocyanidins, cyanidin and delphinidin that gives magenta and blue/purple colors, respectively, are more popular than others. Furthermore, anthocyanidins are also commonly found in the forms of anthocyanins, known as anthocyanidin glycosides, and acylated anthocyanins, with better stability[137]. Even though there is positive charge at oxygen atom of the C-ring, it is considered as one of the flavonoids[138].

Several anthocyanidins and anthocyanins demonstrated their cytoprotective, anti-oxidative and inflammatory abilities[139-142]. Supportively, cyanidin had been administrated in protective effect against protein glycation and oxidative DNA damage induced by glucose and methylglyoxal (MGO) via its MG-trapping ability and free radical scavenging capability[143]. Besides, cyanidin also exhibited preventive effect on neurodegenerative diseases by reducing oxidative stress and apoptosis caused by Aβ1-40 peptide in SHSY5Y cells, and decreasing ER stress induced by Aβ25-35 in SK-N-SH, in turns

in a preventive action in Alzheimer's disease[142,144]. Moreover, inhibitory action of cyanidin-3-O-glucoside in ROS/COX-2 pathway in UVB-induced HaCaT cells indicated its therapeutic effect for skin disorder[145]. Metabolic syndrome is one of the major concerns recent years and cyanidin-3-O-glucoside, an anthocynin, has exhibited its capability in the amelioration. Treatment of cyanidin-3-O-glucoside in reversing the effects of palmitate-induced insulin resistance by reducing IRS-1 serine phosphorylation and upregulating in tyrosine phosphorylation, and promoting triglyceride excretion into bile, subsequently avoiding hepatic TG accumulation[146,147]. Positive impacts have been shown in metabolic diseases improvement after cyanidin-3-O-glucoside treatment. In obesity amelioration, resultant of intracellular cAMP level upregulation to induce formation of beige adipocytes from preadipocytes, and mitochondrial biogenesis and brown adipose tissue adipogenesis activation have sucessfully delineated and ensured the role of cyanidin-3-O-glucoside in anti-obesity treatment[146,148,149]. Due to the antioxidant properties, cyanidin-3-O-glucoside also presented preventive action in cardiovascular complications by caspase cascade and BAX inhibitory action in diabetic rats[150].

On the other hand, cyanidin-3-rutinoside is another raising star among anthocyanins that possesses efficacy in health improvement. Not only enhancement in inherent vasorelaxant actions, it can also provide preventive action in methylglyocal-induced vascular dysfunction in rat model[151]. Furthermore, oxidative hemolysis induced by insulin fibrils can be attenuated in human erthrocytes as amyloid fibril formation has been reported to be inhibited after treatment[152]. Lastly, cyanidin-3-rutinoside may serve as promising phytochemical to improve insulin resistance by regulating PI3K/Akt pathway to increase glucose uptake[153].

Other Novel Phytochemicals
Chemopreventive Effects of Curcumin
Curcumin is the major phenolic component in *Curcuma longa,* and it has been suggested that the pharmacological properties of *C. longa* is majorly dictated by the level and the composition of curcuminoids. Low bioavailability, permeability, and poor absorption of curcumin in animal model and human body have slowly become a raising issue to be addressed to sufficiently perform its compelling advantages[154]. Plenty of studies of curcumin focused on elucidating the bioactivity and its benefits, certainly resulted in marvel success, have been done while research on curcumin and its derivative is still continued to explore its infinite and multitasking potential. Similar to other phytochemicals, curcumin possesses anti-inflammatory and anti-oxidation capability. For instance, cardiac dysfunction induced by mechanisal trauma could be ameliorated by enervating impacts from ROS production[155]. On the other hand, curcumin-derived analogs have recently been developed to act as MD2 inhibitor to provide anti-inflammatory activity to compete with LPS as myeloid differentiation protein 2 (MD2), known as a TLR4 co-receptor, which may be crucial because TLR4 contributes as a pathogenic factor in acute and chronic inflammation[156]. Furthermore, anti-tumor properties of curcumin has been examined and resulted in positive impact in pancreatic cancer treatment by inhibiting NEDD4 that may consequence in tumogenesis, cancer cell growth, migration and invasion[157]. Besides, proapoptotic effect was enhanced in U266 cell by activating p53-p21 axis and inhibiting expression of NF-κB with curcumin intervention[158]. Additonally, curcumin has exhibited several liver protective effects in multi-pathway. First of all, curcumin was able to regulate cholesterol metabolism by activating AMPK/LXRα signaling pathway and reducing migrating capability of human macrophage THP-1[159]. Moreover, curcumin may be beneficial to high fat diet intake by decrement of inflammatory mediators (IL-6, TNFα and NK-κB) gene expression in liver[160]. In aflatoxin B1-induced liver injury model, preventive effect of curcumin in hepatotoxicity reduction with phase-II enzyme increment was performed via activation of Nrf2 pathway, resultant in GSH expression[161]. On the other hand, ameliorative effect of curcumin was exhibited in cadmium-induced nephrotoxicity by inhibiting oxidative stress and cell apoptosis, and neorological disorders by decresing AchE activity that highly related to various insults like oxidative stress[162,163]. Notably, curcumin has also exhibited multiple functions in the neuroprotective and inhibitory effects on osteoporosis, including alleviation of traumatic brain damage by Nrf2 signaling modulation in microglia/macrophages, and inducement of osteoblast differentiation by mild ER-stress and inhibitionof osteoclastogenesis [164,165].

Lastly, curcumin demonstrated anti-viral activity against influenza virus, and anti-bacteria effect on foodborne and spoilage bacteria, indicating its multi-potential effects to be applied in foods[166,167].

Chemopreventive Effects of Forskolin

Forskolin, a diterpene derived from Coleus forskohii, known as a direct activator of adenylate cyclase enzyme to raise intracellular cAMP levels from ATP. Based on its capability on cAMP modulation, it may be a crucial key in cancer prevention or therapy via either PKA-dependent and/or PKA independent pathways. For instance, it has exhibited its supportive effect in improving the sensitivity of triple negative breast cancer cells to doxorubicin, a potent chemotherapeutic agent, by down-regulating ERK expression via cAMP/PKA mechanism, expectedly[168]. Doxorubicin is used in tumor medication, but its therapeutic limitation is concerned. Chronic cardiotoxicity induced by doxorubicin, which may lead to heart failure, was identified as due to asymmetric-dimethylarginine (ADMA) accumulation, and fortunately, forskolin was able to mitigate ADMA accumulation without inhibit the efficacy of doxorubicin, but reducing methyltransferase activity in monocytoid cells[169]. Although forskolin was unable to alleviate toxicity induced by doxorubicin, it did illustrate anti-ototoxicity induced by cisplatin in HEI-OC1 cell line and mouse cochlear tissue explant models by its inhibitory effect on mitochondrial apoptotic pathway and ROS generation, to surpass the side effect of tumor medication[170]. Additionally, forskolin has also been found to be efficacious in metabolic related diseases amelioration. Serum cholesterol level induced by high fat diet could lead to amyloid-β production and accumulation, which may consequently lead to neurocognitive disorder and cognitive decline, and forskolin has exbihited protective and preventive effects due to its hypolipidemic effect to prevent amyloid-β peptides accumulation in brain, enervating adverse effect in dementia and combating memory impairment[171]. Interesting, forskolin had been pointed out to induce circadian gene expression in mammalian rat-1 fibroblasts early in year 2000 although the issues related to circadian clock and circadian rhythm raise only in this few years[172]. It is believed that forskolin may gain more attention due to its madulatory effect in metabolic syndromes, circadian rhythms and cancer therapeutic actions.

Chemopreventive Effects of Garcinol

Except from forskolin, garcinol is another medicinal component discovered in plants in India. It is tranditionally used for treatment of gastric aliments and skin irritation but some recent studies have revealed that, its therapeutic effects in anti-oxidation, anti-inflammation and anti cancer in both in vitro or animal models[173]. Its significant effects on cancer inhibitory action has been widely reported for several years. For example, there are therapeutic effect in human non-small cell lung carcinomas supression via inhibition of Wnt/β-catenin/STAT3 signaling pathway and ameliorative efficacy in skin inflammation and tumorigenesis induced by 12-O-tetradecanoylphorbol 13-acetate in mice model[174,175]. It was reported that, C8 side chain and 13, 14 dihydroxyl group of garcinol can be considered as key functional groups that the chemopreventive efficacy on DMBA-induced oral squamous cell carcinoma and SCC15 could be enervated after changing these functional groups into methyl group[176,177]. Furthermore, garcinol has also exerted potent neuroinflammatory effect agianst nueropathic pain in LPS-induced microglia by inhibiting acetylation of NF-κB/p65, subsequently stopping activation of NF- κB[178]. Protective effect of garcinol was also exhibited in liver diseases. Garcinol has shown remarkable suppresive effect in decreasing intrinsic and extrinsic caspase cascade to evade hepatic apoptosis induced by LPS/D-galactosamine[179].

Conclusion

Phytochemicals have exhibited sufficient evidences to conclude their importance in health benefits improvement, and the intervention of phytochemicals may no longer be a novel insight in coming days. New phytochemicals are explored, no matter in natural or artificial/synthetic ways, and their efficacious effects are demonstrated almost synchronously. It is virtually certaired that phytochemicals can thrive in the prevention and medication field. Therefore, for their plethora of potentials, continueing the studies on phytochemicals are
imperative.

Conflicts of interest
There are no conflicts to declare

References

1. Bacanlı, M.; Aydın, S.; Basaran, A. A.; Basaran, N., Are all phytochemicals useful in the preventing of DNA damage? *Food and Chemical Toxicology*. 2017;*109*:210-217.

2. Barbieri, R.; Coppo, E.; Marchese, A.; Daglia, M.; Sobarzo-Sánchez, E.; Nabavi, S. F.; Nabavi, S. M., Phytochemicals for human disease: An update on plant-derived compounds antibacterial activity. *Microbiological Research*.2017;*196*:44-68.

3. Cilla, A.; Alegría, A.; Attanzio, A.; Garcia-Llatas, G.; Tesoriere, L.; Livrea, M. A., Dietary phytochemicals in the protection against oxysterol-induced damage. *Chemistry and Physics of Lipids*. 2017;*207*:192-205.

4. Kapinova, A.; Stefanicka, P.; Kubatka, P.; Zubor, P.; Uramova, S.; Kello, M.; Mojzis, J.; Blahutova, D.; Qaradakhi, T.; Zulli, A.; Caprnda, M.; Danko, J.; Lasabova, Z.; Busselberg, D.; Kruzliak, P., Are plant-based functional foods better choice against cancer than single phytochemicals? A critical review of current breast cancer research. *Biomedicine & Pharmacotherapy*. 2017;*96:*1465-1477.

5. Zhang, L.-S.; Wang, X.; Dong, L.-L., Antioxidation and antiglycation of polysaccharides from Misgurnus anguillicaudatus. *Food chemistry*. 2011;*124*:183-187.

6. Masuda, T.; Akiyama, J.; Fujimoto, A.; Yamauchi, S.; Maekawa, T.; Sone, Y., Antioxidation reaction mechanism studies of phenolic lignans, identification of antioxidation products of secoisolariciresinol from lipid oxidation. *Food chemistry*. 2010;*123*:442-450.

7. Zheng, X. J.; Xiao, H.; Zeng, Z.; Sun, Z. W.; Lei, C.; Dong, J. Z.; Wang, Y., Composition and serum antioxidation of the main flavonoids from fermented vine tea (Ampelopsis grossedentata). *Journal of Functional Foods*. 2014;*9*:290-294.

8. Lawrence, T.; Fong, C., The resolution of inflammation: Anti-inflammatory roles for NF-κB. *The International Journal of Biochemistry & Cell Biology*. 2010;*42*:519-523.

9. Liu, M.; Li, S.; Wang, X.; Zhu, Y.; Zhang, J.; Liu, H.; Jia, L., Characterization, anti-oxidation and anti-inflammation of polysaccharides by Hypsizygus marmoreus against LPS-induced toxicity on lung. *International journal of biological macromolecules*. 2018;*111*:121-128.

10. Zhang, C.; Qian, D.; Zhao, H.; Lv, N.; Yu, P.; Sun, Z., MiR17 improves insulin sensitivity through inhibiting expression of ASK1 and anti-inflammation of macrophages. *Biomedicine & Pharmacotherapy*. 2018;*100*:448-454.

11. Dogan, F.; Biray Avci, C., Correlation between telomerase and mTOR pathway in cancer stem cells. *Gene*. 2018;*641*:235-239.

12. Fulda, S., Therapeutic opportunities based on caspase modulation. Seminars in Cell & Developmental Biology. 2017.

13. Russo, M.; Russo, G. L., Autophagy inducers in cancer. *Biochemical Pharmacology*. 2018.

14. Kwak, M.-K.; Egner, P. A.; Dolan, P. M.; Ramos-Gomez, M.; Groopman, J. D.; Itoh, K.; Yamamoto, M.; Kensler, T. W., Role of phase 2 enzyme induction in chemoprotection by dithiolethiones. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2001;*480-481*:305-315.

15. Wu, J.-C.; Lai, C.-S.; Tsai, M.-L.; Ho, C.-T.; Wang, Y.-J.; Pan, M.-H., Chemopreventive effect of natural dietary compounds on xenobiotic-induced toxicity. *Journal of Food and Drug Analysis*. 2017;*25:*176-186.

16. Duan, L.; Hu, J.; Xiong, X.; Liu, Y.; Wang, J., The role of DNA methylation in coronary artery disease. *Gene*. 2018;*646*, 91-97.

17. Ginder, G. D.; Williams, D. C., Readers of DNA methylation, the MBD family as potential therapeutic targets. *Pharmacology*

& *Therapeutics.* 2018;***184***:98-111.

18. Wahl, A.; Kasela, S.; Carnero-Montoro, E.; van Iterson, M.; Štambuk, J.; Sharma, S.; van den Akker, E.; Klaric, L.; Benedetti, E.; Razdorov, G.; Trbojevic-Akmacic, I.; Vuckovic, F.; Ugrina, I.; Beekman, M.; Deelen, J.; van Heemst, D.; Heijmans, B. T.; Consortium, B. I. O. S.; Wuhrer, M.; Plomp, R.; Keser, T.; Šimurina, M.; Pavic, T.; Gudelj, I.; Krištic, J.; Grallert, H.; Kunze, S.; Peters, A.; Bell, J. T.; Spector, T. D.; Milani, L.; Slagboom, P. E.; Lauc, G.; Gieger, C., IgG glycosylation and DNA methylation are interconnected with smoking. *Biochimica et Biophysica Acta (BBA) – General Subjects.* 2018;***1862***:637-648.

19. Wu, J.-C.; Lai, C.-S.; Lee, P.-S.; Ho, C.-T.; Liou, W.-S.; Wang, Y.-J.; Pan, M.-H., Anti-cancer efficacy of dietary polyphenols is mediated through epigenetic modifications. *Current Opinion in Food Science.* 2016;***8***:1-7.

20. Wu, Q.; Guan, J.; Zhou, S., Histone modification patterns in highly differentiation cells. *Neurocomputing.* 2016;***206***:42-49.

21. Chrun, E. S.; Modolo, F.; Daniel, F. I., Histone modifications: A review about the presence of this epigenetic phenomenon in carcinogenesis. *Pathology – Research and Practice.* 2017;***213***:1329-1339.

22. Carson, W. F.; Kunkel, S. L., Chapter Seven – Regulation of Cellular Immune Responses in Sepsis by Histone Modifications. In *Advances in Protein Chemistry and Structural Biology, Donev, R., Ed. Academic Press.* 2017;***106***:191-225.

23. Luo, Z.; Cui, R.; Tili, E.; Croce, C., Friend or Foe: MicroRNAs in the p53 network. *Cancer Letters.* 2018;***419***:96-102.

24. Phiwpan, K.; Zhou, X., MicroRNAs in regulatory T cells. *Cancer Letters*. 2018;***423***:80-85.

25. Karbasforooshan, H.; Roohbakhsh, A.; Karimi, G., SIRT1 and microRNAs: The role in breast, lung and prostate cancers. *Experimental Cell Research.* 2018.

26. Wierinckx, A.; Roche, M.; Legras-Lachuer, C.; Trouillas, J.; Raverot, G.; Lachuer, J., MicroRNAs in pituitary tumors. *Molecular and Cellular Endocrinology.* 2017;***456***:51-61.

27. Hu, X.; Tao, N.; Wang, X.; Xiao, J.; Wang, M., Marine-derived bioactive compounds with anti-obesity effect: A review. *Journal of Functional Foods.* 2016;***21***:372-387.

28. Scheele, C.; Nielsen, S., Metabolic regulation and the anti-obesity perspectives of human brown fat. *Redox Biology.* 2017;***12***:770-775.

29. Ohashi, K.; Shibata, R.; Murohara, T.; Ouchi, N., Role of anti-inflammatory adipokines in obesity-related diseases. *Trends in Endocrinology & Metabolism.* 2014;***25***:348-355.

30. Lai, C.-S.; Wu, J.-C.; Pan, M.-H., Molecular mechanism on functional food bioactives for anti-obesity. *Current Opinion in Food Science.* 2015;***2***:9-13.

31. Moosavi, M. A.; Haghi, A.; Rahmati, M.; Taniguchi, H.; Mocan, A.; Echeverría, J.; Gupta, V. K.; Tzvetkov, N. T.; Atanasov, A. G., Phytochemicals as potent modulators of autophagy for cancer therapy. *Cancer Letters.* 2018;***424***:46-69.

32. Chong, J.; Poutaraud, A.; Hugueney, P., Metabolism and roles of stilbenes in plants. *Plant Science.* 2009;***177***:143-155.

33. Fu, S.; Lv, R.; Wang, L.; Hou, H.; Liu, H.; Shao, S., Resveratrol, an antioxidant, protects spinal cord injury in rats by suppressing MAPK pathway. *Saudi Journal of Biological Sciences.* 2018;***25:2***59-266.

34. Chiang, M.-C.; Nicol, C. J.; Cheng, Y.-C., Resveratrol activation of AMPK-dependent pathways is neuroprotective in human neural stem cells against amyloid-beta-induced inflammation and oxidative stress. *Neurochemistry International.* 2018;***115***:1-10.

35. Allen, E. N.; Potdar, S.; Tapias, V.; Parmar, M.; Mizuno, C. S.; Rimando, A.; Cavanaugh, J. E., Resveratrol and pinostilbene confer neuroprotection against aging-related deficits through an ERK1/2-dependent mechanism. *The Journal of nutritional biochemistry.* 2018;***54***:77-86.

36. Wang, X.; Ma, S.; Yang, B.; Huang, T.; Meng, N.; Xu, L.; Xing, Q.; Zhang, Y.; Zhang, K.; Li, Q.; Zhang, T.; Wu, J.; Yang, G. L.; Guan, F.; Wang, J., Resveratrol promotes hUC-MSCs engraftment and neural repair in a mouse model of Alzheimer's disease. *Behavioural Brain Research.* 2018;***339***:297-304.

37. Suh, J.; Kim, D.-H.; Surh, Y.-J., Resveratrol suppresses migration, invasion and stemness

of human breast cancer cells by interfering with tumor-stromal cross-talk. *Archives of Biochemistry and Biophysics.* 2018;*643*:62-71.

38. Yang, T.; Zhang, J.; Zhou, J.; Zhu, M.; Wang, L.; Yan, L., Resveratrol inhibits Interleukin-6 induced invasion of human gastric cancer cells. *Biomedicine & Pharmacotherapy.* 2018;*99*:766-773.

39. Ismail, N.; Abdel–Mottaleb, Y.; Eissa Ahmed, A. A.; El-Maraghy, N. N., Novel combination of thymoquinone and resveratrol enhances anticancer effect on hepatocellular carcinoma cell line. *Future Journal of Pharmaceutical Sciences.*

40. Lundqvist, J.; Tringali, C.; Oskarsson, A., Resveratrol, piceatannol and analogs inhibit activation of both wild-type and T877A mutant androgen receptor. *The Journal of Steroid Biochemistry and Molecular Biology.* 2017;*174*:161-168.

41. Zhang, A. J.; Rimando, A. M.; Mizuno, C. S.; Mathews, S.T., α-Glucosidase inhibitory effect of resveratrol and piceatannol. *The Journal of nutritional biochemistry.* 2017;*47*:86-93.

42. Les, F.; Deleruyelle, S.; Cassagnes, L.-E.; Boutin, J. A.; Balogh, B.; Arbones-Mainar, J. M.; Biron, S.; Marceau, P.; Richard, D.; Nepveu, F.; Mauriège, P.; Carpéné, C., Piceatannol and resveratrol share inhibitory effects on hydrogen peroxide release, monoamine oxidase and lipogenic activities in adipose tissue, but differ in their antilipolytic properties. *Chemico-Biological Interactions.* 2016;*258*:115-125.

43. Billet, K.; Houillé, B.; Besseau, S.; Mélin, C.; Oudin, A.; Papon, N.; Courdavault, V.; Clastre, M.; Giglioli-Guivarc'h, N.; Lanoue, A., Mechanical stress rapidly induces E-resveratrol and E-piceatannol biosynthesis in grape canes stored as a freshly-pruned byproduct. *Food chemistry.* 2018;*240*:1022-1027.

44. Ellermann, C.; Wolfes, J.; Kochhäuser, S.; Dechering, D. G.; Reinke, F.; Wasmer, K.; Eckardt, L.; Frommeyer, G., Divergent antiarrhythmic effects of resveratrol and piceatannol in a whole-heart model of long QT syndrome. *International Journal of Cardiology.* 2017;*243*:233-238.

45. Gerszon, J.; Walczak, A.; Rodacka, A., Attenuation of H2O2-induced neuronal cell damage by piceatannol. *Journal of Functional Foods.* 2017;*35*:540-548.

46. Choi, B.; Kim, S.; Jang, B.-G.; Kim, M.-J., Piceatannol, a natural analogue of resveratrol, effectively reduces beta-amyloid levels via activation of alpha-secretase and matrix metalloproteinase-9. *Journal of Functional Foods.* 2016;*23:*124-134.

47. Lu, B.; Sun, T.; Li, W.; Sun, X.;Yao, X.; Sun, X., Piceatannol protects ARPE-19 cells against vitamin A dimer-mediated photo-oxidative damage through activation of Nrf2/NQO1 signalling. *Journal of Functional Foods.* 2016;*26*:739-749.

48. Pan, M.-H.; Tung, Y.-C.; Kalyanam, N.; Lin, Y.-H.; Ho, C.-T., P 053 – Piceatannol exerts anti-obesity effect through modulating adipogenic proteins and gut microbiota in C57BL/6 mice. *Free Radical Biology and Medicine.* 2017;*108*:S35.

49. Yu, W.; Hu, X.;Wang, M., Pterostilbene inhibited advanced glycation end products (AGEs)-induced oxidative stress and inflammation by regulation of RAGE/MAPK/NF-κB in RAW264.7 cells. *Journal of Functional Foods.* 2018;*40*:272-279.

50. Liu, J.; Fan, C.; Yu, L.; Yang, Y.; Jiang, S.; Ma, Z.; Hu, W.; Li, T.; Yang, Z.; Tian, T.; Duan, W.; Yu, S., Pterostilbene exerts an anti-inflammatory effect via regulating endoplasmic reticulum stress in endothelial cells. *Cytokine*. 2016;*77*:88-97.

51. Bhakkiyalakshmi, E.;Sireesh, D.;Sakthivadivel, M.; Sivasubramanian, S.; Gunasekaran, P.; Ramkumar, K. M., Anti-hyperlipidemic and anti-peroxidative role of pterostilbene via Nrf2 signaling in experimental diabetes. European *Journal of Pharmacology.* 2016;*777*:9-16.

52. Kosuru, R.; Singh, S., Pterostilbene ameliorates insulin sensitivity, glycemic control and oxidative stress in fructose-fed diabetic rats. *Life Sciences.* 2017;*182*:112-121.

53. Nagao, K.; Jinnouchi, T.; Kai, S.; Yanagita, T., Pterostilbene, a dimethylated analog of resveratrol, promotes energy metabolism in obese rats. *The Journal of nutritional biochemistry.* 2017;*43*:151-155.

54. Zhang, Y.; Zhang, Y., Pterostilbene, a novel natural plant conduct, inhibits high fat-induced atherosclerosis inflammation via NF-κB signaling pathway in Toll-like receptor 5 (TLR5) deficient mice. *Biomedicine & Pharmacotherapy.* 2016;*81*:345-355.

55. Seo, Y.-J.; Kim, K.-J.; Koh, E.-J.; Choi, J.; Lee, B.-Y., Anti-adipogenesis mechanism of pterostilbene through the activation of heme oxygenase-1 in 3T3-L1 cells. *Phytomedicine.* 2017;*33*:7-13.

56. Liu, X.; Yang, X.; Han, L.; Ye, F.; Liu, M.; Fan, W.; Zhang, K.; Kong, Y.; Zhang, J.; Shi, L.; Chen, Y.; Zhang, X.; Lin, S., Pterostilbene alleviates polymicrobial sepsis-induced liver injury: Possible role of SIRT1 signaling. *International Immunopharmacology.* 2017;*49*:50-59.

57. Qian, Y.-y.; Liu, Z.-s.; Yan, H.-j.; Yuan, Y.-f.; Levenson, A. S.; Li, K., Pterostilbene inhibits MTA1/HDAC1 complex leading to PTEN acetylation in hepatocellular carcinoma. *Biomedicine & Pharmacotherapy.* 2018;*101*:852-859.

58. Chiou, H. L.; Yu, C. L.; Hsieh, Y. H., 314 – Activation of ER stress and autophagy induced by pterostilbene via Akt/mTOR pathway in human hepatocellular carcinoma cells. *European Journal of Cancer.* 2016;*61*:S61.

59. Chen, R.-J.; Lee, Y.-H.; Yeh, Y.-L.; Wu, W.-S.; Ho, C.-T.; Li, C.-Y.; Wang, B., Jr.; Wang, Y.-J., Autophagy-inducing effect of pterostilbene: A prospective therapeutic/preventive option for skin diseases. *Journal of Food and Drug Analysis.* 2017;*25*:125-133.

60. Singh, P.; Arora, D.; Shukla, Y., Enhanced chemoprevention by the combined treatment of pterostilbene and lupeol in B[a]P-induced mouse skin tumorigenesis. *Food and Chemical Toxicology.* 2017;*99*:182-189.

61. Kim, K.-J.; Chei, S.; Choi, S.-Y.; Lee, O.-H.; Lee, B.-Y., Pterostilbene activates the GRP78–eIF2α–ATF3 cascade of ER stress and subsequently induces apoptosis in human colon cancer cells. *Journal of Functional Foods.* 2016;*26*:539-547.

62. Yang, Y.; Fan, C.; Wang, B.; Ma, Z.; Wang, D.; Gong, B.; Di, S.; Jiang, S.; Li, Y.; Li, T.; Yang, Z.; Luo, E., Pterostilbene attenuates high glucose-induced oxidative injury in hippocampal neuronal cells by activating

nuclear factor erythroid 2-related factor 2. Biochimica et Biophysica Acta (BBA) – *Molecular Basis of Disease.* 2017;*1863*:827-837.

63. Wang, B.; Liu, H.; Yue, L.; Li, X.; Zhao, L.; Yang, X.; Wang, X.; Yang, Y.; Qu, Y., Neuroprotective effects of pterostilbene against oxidative stress injury: Involvement of nuclear factor erythroid 2-related factor 2 pathway. *Brain Research.* 2016;*1643:*70-79.

64. Li, D.; Song, T.; Yang, L.; Wang, X.; Yang, C.; Jiang, Y., Neuroprotective actions of pterostilbene on hypoxic-ischemic brain damage in neonatal rats through upregulation of heme oxygenase-1. *International Journal of Developmental Neuroscience.* 2016;*54*:22-31.

65. Guo, Y.; Zhang, L.; Li, F.; Hu, C.-P.; Zhang, Z., Restoration of sirt1 function by pterostilbene attenuates hypoxia-reoxygenation injury in cardiomyocytes. *European Journal of Pharmacology.* 2016;*776*:26-33.

66. Yu, Z.; Wang, S.; Zhang, X.; Li, Y.; Zhao, Q.; Liu, T., Pterostilbene protects against myocardial ischemia/reperfusion injury via suppressing oxidative/nitrative stress and inflammatory response. *International Immunopharmacology.* 2017;*43*:7-15.

67. Cheng, T.-C.; Lai, C.-S.; Chung, M.-C.; Kalyanam, N.; Majeed, M.; Ho, C.-T.; Ho, Y.-S.; Pan, M.-H., Potent Anti-Cancer Effect of 3′-Hydroxypterostilbene in Human Colon Xenograft Tumors. *PLOS ONE.* 2014;9:e111814.

68. Tsai, H.-Y.; Ho, C.-T.; Chen, Y.-K., Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene. *Journal of Food and Drug Analysis.* 2017;*25*:134-147.

69. Feng, S.-L.; Yuan, Z.-W.; Yao, X.-J.; Ma, W.-Z.; Liu, L.; Liu, Z.-Q.; Xie, Y., Tangeretin, a citrus pentamethoxyflavone, antagonizes ABCB1-mediated multidrug resistance by inhibiting its transport function. *Pharmacological Research.* 2016;*110*:193-204.

70. Coutinho, L.; Oliveira, H.; Pacheco, A. R.; Almeida, L.; Pimentel, F.; Santos, C.; Ferreira de Oliveira, J. M. P., Hesperetin-etoposide combinations induce cytotoxicity in U2OS cells: Implications on therapeutic

developments for osteosarcoma. *DNA Repair.* 2017;*50*:36-42.

71. Tung, Y.-C.; Li, S.; Huang, Q.; Hung, W.-L.; Ho, C.-T.; Wei, G.-J.; Pan, M.-H., 5-Demethylnobiletin and 5-Acetoxy-6,7,8,3′,4′-pentamethoxyflavone Suppress Lipid Accumulation by Activating the LKB1-AMPK Pathway in 3T3-L1 Preadipocytes and High Fat Diet-Fed C57BL/6 Mice. *Journal of agricultural and food chemistry.* 2016;*64*:3196-3205.

72. Chiou, Y.-S.; Wu, J.-C.; Huang, Q.; Shahidi, F.; Wang, Y.-J.; Ho, C.-T.; Pan, M.-H., Metabolic and colonic microbiota transformation may enhance the bioactivities of dietary polyphenols. *Journal of Functional Foods.* 2014;*7*:3-25.

73. Kang, C.-H.; Molagoda, I. M. N.; Choi, Y. H.; Park, C.; Moon, D.-O.; Kim, G.-Y., Apigenin promotes TRAIL-mediated apoptosis regardless of ROS generation. *Food and Chemical Toxicology.* 2018;*111*:623-630.

74. Dai, J.; Van Wie, P. G.; Fai, L. Y.; Kim, D.; Wang, L.; Poyil, P.; Luo, J.; Zhang, Z., Downregulation of NEDD9 by apigenin suppresses migration, invasion, and metastasis of colorectal cancer cells. *Toxicology and Applied Pharmacology.* 2016;*311*:106-112.

75. Zhong, Y.; Jin, C.; Gan, J.; Wang, X.; Shi, Z.; Xia, X.; Peng, X., Apigenin attenuates patulin-induced apoptosis in HEK293 cells by modulating ROS-mediated mitochondrial dysfunction and caspase signal pathway. *Toxicon.* 2017;*137*:106-113.

76. Siddique, Y. H.; Jyoti, S., Alteration in biochemical parameters in the brain of transgenic Drosophila melanogaster model of Parkinson's disease exposed to apigenin. *Integrative Medicine Research.* 2017;*6*:245-253.

77. García-Mediavilla, V.; Crespo, I.; Collado, P. S.; Esteller, A.; Sánchez-Campos, S.; Tuñón, M. J.; González-Gallego, J., The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. *European Journal of Pharmacology.* 2007;*557*:221-229.

78. Choi, J.-H.; Park, S.-E.; Kim, S.-J.; Kim, S., Kaempferol inhibits thrombosis and platelet activation. *Biochimie.* 2015;*115*:177-186.

79. Rodriguez, A.; Strucko, T.; Stahlhut, S. G.; Kristensen, M.; Svenssen, D. K.; Forster, J.; Nielsen, J.; Borodina, I., Metabolic engineering of yeast for fermentative production of flavonoids. *Bioresource Technology.* 2017;*245*:1645-1654.

80. Devi, K. P.; Malar, D. S.; Nabavi, S. F.; Sureda, A.; Xiao, J.; Nabavi, S. M.; Daglia, M., Kaempferol and inflammation: From chemistry to medicine. *Pharmacological Research.* 2015;*99*:1-10.

81. Fernández-del-Río, L.; Nag, A.; Gutiérrez Casado, E.; Ariza, J.; Awad, A. M.; Joseph, A. I.; Kwon, O.; Verdin, E.; de Cabo, R.; Schneider, C.; Torres, J. Z.; Burón, M. I.; Clarke, C. F.; Villalba, J. M., Kaempferol increases levels of coenzyme Q in kidney cells and serves as a biosynthetic ring precursor. *Free Radical Biology and Medicine.* 2017;*110*:176-187.

82. Adhikary, S.; Choudhary, D.; Ahmad, N.; Karvande, A.; Kumar, A.; Banala, V. T.; Mishra, P. R.; Trivedi, R., Dietary flavonoid kaempferol inhibits glucocorticoid induced bone loss by promoting osteoblast survival. *Nutrition.* 2018.

83. Nowak, B.; Matuszewska, A.; Nikodem, A.; Filipiak, J.; Landwójtowicz, M.; Sadanowicz, E.; Jedrzejuk, D.; Rzeszutko, M.; Zduniak, K.; Piasecki, T.; Kowalski, P.; Dziewiszek, W.; Merwid-Lad, A.; Trocha, M.; Sozanski, T.; Kwiatkowska, J.; Bolanowski, M.; Szelag, A., Oral administration of kaempferol inhibits bone loss in rat model of ovariectomy-induced osteopenia. *Pharmacological Reports.* 2017;*69*:1113-1119.

84. Soromou, L. W.; Chen, N.; Jiang, L.; Huo, M.; Wei, M.; Chu, X.; Millimouno, F. M.; Feng, H.; Sidime, Y.; Deng, X., Astragalin attenuates lipopolysaccharide-induced inflammatory responses by down-regulating NF-κB signaling pathway. *Biochemical and Biophysical Research Communications.* 2012;*419*:256-261.

85. Li, F.; Liang, D.; Yang, Z.; Wang, T.; Wang, W.; Song, X.; Guo, M.; Zhou, E.; Li, D.; Cao, Y.; Zhang, N., Astragalin suppresses inflammatory

responses via down-regulation of NF-κB signaling pathway in lipopolysaccharide-induced mastitis in a murine model. *International Immunopharmacology.* 2013;**17**:478-482.

86. Li, F.; Wang, W.; Cao, Y.; Liang, D.; Zhang, W.; Zhang, Z.; Jiang, H.; Guo, M.; Zhang, N., Inhibitory effects of astragalin on lipopolysaccharide-induced inflammatory response in mouse mammary epithelial cells. *Journal of Surgical Research.* 2014;**192**:573-581.

87. Ma, Z.; Piao, T.; Wang, Y.; Liu, J., Astragalin inhibits IL-1β-induced inflammatory mediators production in human osteoarthritis chondrocyte by inhibiting NF-κB and MAPK activation. *International Immunopharmacology.* 2015;**25**:83-87.

88. Han, S.; Hanh Nguyen, T. T.; Hur, J.; Kim, N. M.; Kim, S.-B.; Hwang, K.-H.; Moon, Y.-H.; Kang, C.; Chung, B.; Kim, Y.-M.; Kim, T. S.; Park, J.-S.; Kim, D., Synthesis and characterization of novel astragalin galactosides using β-galactosidase from Bacillus circulans. *Enzyme and Microbial Technology.* 2017;**103**:59-67.

89. Kant, V.; Jangir, B. L.; Nigam, A.; Kumar, V.; Sharma, S., Dose regulated cutaneous wound healing potential of quercetin in male rats. *Wound Medicine.* 2017;**19**:82-87.

90. Wu, L.; Wang, C.; Li, J.; Li, S.; Feng, J.; Liu, T.; Xu, S.; Wang, W.; Lu, X.; Chen, K.; Xia, Y.; Fan, X.; Guo, C., Hepatoprotective effect of quercetin via TRAF6/JNK pathway in acute hepatitis. *Biomedicine & Pharmacotherapy.* 2017;**96**:1137-1146.

91. Nishimura, K.; Matsumoto, R.; Yonezawa, Y.; Nakagawa, H., Effect of quercetin on cell protection via erythropoietin and cell injury of HepG2 cells. *Archives of Biochemistry and Biophysics.* 2017;**636**:11-16.

92. Maksymchuk, O.; Shysh, A.; Rosohatska, I.; Chashchyn, M., Quercetin prevents type 1 diabetic liver damage through inhibition of CYP2E1. *Pharmacological Reports.* 2017;**69**:1386-1392.

93. Chen, K.-C.; Hsu, W.-H.; Ho, J.-Y.; Lin, C.-W.; Chu, C.-Y.; Kandaswami, C. C.; Lee, M.-T.; Cheng, C.-H., Flavonoids Luteolin and Quercetin Inhibit RPS19 and contributes to

metastasis of cancer cells through c-Myc reduction. *Journal of Food and Drug Analysis.* 2018.

94. Liu, Y.; Tang, Z.-G.; Lin, Y.; Qu, X.-G.; Lv, W.; Wang, G.-B.; Li, C.-L., Effects of quercetin on proliferation and migration of human glioblastoma U251 cells. *Biomedicine & Pharmacotherapy.* 2017;**92**:33-38.

95. Masek, A.; Latos, M.; Piotrowska, M.; Zaborski, M., The potential of quercetin as an effective natural antioxidant and indicator for packaging materials. *Food Packaging and Shelf Life.* 2018;**16**:51-58.

96. Burmanczuk, A.; Hola, P.; Milczak, A.; Piech, T.; Kowalski, C.; Wojciechowska, B.; Grabowski, T., Quercetin decrease somatic cells count in mastitis of dairy cows. *Research in Veterinary Science.* 2018;**117**:255-259.

97. kheradmand, E.; Hajizadeh Moghaddam, A.; Zare, M., Neuroprotective effect of hesperetin and nano-hesperetin on recognition memory impairment and the elevated oxygen stress in rat model of Alzheimer's disease. *Biomedicine & Pharmacotherapy.* 2018;**97:**1096-1101.

98. Chen, X.; Ding, H.-W.; Li, H.-D.; Huang, H.-M.; Li, X.-F.; Yang, Y.; Zhang, Y.-L.; Pan, X.-Y.; Huang, C.; Meng, X.-M.; Li, J., Hesperetin derivative-14 alleviates inflammation by activating PPAR-γ in mice with CCl4-induced acute liver injury and LPS-treated RAW264.7 cells. *Toxicology Letters.* 2017;**274**:51-63.

99. Jayaraman, R.; Subramani, S.; Sheik Abdullah, S. H.; Udaiyar, M., Antihyperglycemic effect of hesperetin, a citrus flavonoid, extenuates hyperglycemia and exploring the potential role in antioxidant and antihyperlipidemic in streptozotocin-induced diabetic rats. *Biomedicine & Pharmacotherapy.* 2018;**97**:98-106.

100. Kumar, M.; Dahiya, V.; Kasala, E. R.; Bodduluru, L. N.; Lahkar, M., The renoprotective activity of hesperetin in cisplatin induced nephrotoxicity in rats: Molecular and biochemical evidence. *Biomedicine & Pharmacotherapy.* 2017;**89**:1207-1215.

101. Mary Lazer, L.; Sadhasivam, B.; Palaniyandi, K.; Muthuswamy, T.; Ramachandran, I.; Balakrishnan, A.; Pathak, S.; Narayan, S.; Ramalingam, S., Chitosan-based nano-formulation enhances the anticancer efficacy

of hesperetin. *International journal of biological macromolecules.* 2018;**107**:1988-1998.

102. Miler, M.; Živanovic, J.; Ajdžanovic, V.; Oreščanin-Dušic, Z.; Milenkovic, D.; Konic-Ristic, A.; Blagojevic, D.; Miloševic, V.; Šošic-Jurjevic, B., Citrus flavanones naringenin and hesperetin improve antioxidant status and membrane lipid compositions in the liver of old-aged Wistar rats. *Experimental Gerontology.* 2016;**84**:49-60.

103. Singh, M.K.; Pooja, D.; Ravuri, H.G.; Gunukula, A.; Kulhari, H.; Sistla, R., Fabrication of surfactant-stabilized nanosuspension of naringenin to surpass its poor physiochemical properties and low oral bioavailability. *Phytomedicine.* 2018;**40**:48-54.

104. Copmans, D.; Orellana-Paucar, A. M.; Steurs, G.; Zhang, Y.; Ny, A.; Foubert, K.; Exarchou, V.; Siekierska, A.; Kim, Y.; De Borggraeve, W.; Dehaen, W.; Pieters, L.; de Witte, P. A. M., Methylated flavonoids as anti-seizure agents: Naringenin 4′,7-dimethyl ether attenuates epileptic seizures in zebrafish and mouse models. *Neurochemistry International.* 2018;**112**:124-133.

105. Pinho-Ribeiro, F. A.; Zarpelon, A. C.; Fattori, V.; Manchope, M. F.; Mizokami, S. S.; Casagrande, R.; Verri, W. A., Naringenin reduces inflammatory pain in mice. *Neuropharmacology.* 2016;**105**:508-519.

106. Zhong, Y.; Chiou, Y.-S.; Pan, M.-H.; Ho, C.-T.; Shahidi, F., Protective effects of epigallocatechin gallate (EGCG) derivatives on azoxymethane-induced colonic carcinogenesis in mice. *Journal of Functional Foods.* 2012;**4**:323-330.

107. Eng, Q. Y.; Thanikachalam, P. V.; Ramamurthy, S., Molecular understanding of Epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases. *Journal of Ethnopharmacology.* 2018;**210**:296-310.

108. Zhong, Y.; Chiou, Y.-S.; Pan, M.-H.; Shahidi, F., Anti-inflammatory activity of lipophilic epigallocatechin gallate (EGCG) derivatives in LPS-stimulated murine macrophages. *Food chemistry.* 2012;**134**:742-748.

109. Chiou, Y.-S.; Huang, Q.; Ho, C.-T.; Wang, Y.-J.; Pan, M.-H., Directly interact with Keap1 and LPS is involved in the anti-inflammatory

mechanisms of (-)-epicatechin-3-gallate in LPS-induced macrophages and endotoxemia. *Free Radical Biology and Medicine.* 2016;**94**:1-16.

110. Zhu, C.; Xu, Y.; Liu, Z.-H.; Wan, X.-C.; Li, D.-X.; Tai, L.-L., The anti-hyperuricemic effect of epigallocatechin-3-gallate (EGCG) on hyperuricemic mice. *Biomedicine & Pharmacotherapy.* 2018;**97**:168-173.

111. Mi, Y.; Qi, G.; Fan, R.; Ji, X.; Liu, Z.; Liu, X., EGCG ameliorates diet-induced metabolic syndrome associating with the circadian clock. Biochimica et Biophysica Acta (BBA) – *Molecular Basis of Disease.* 2017;**1863**:1575-1589.

112. Fu, Z.; Yoo, M. J. Y.; Zhou, W.; Zhang, L.; Chen, Y.; Lu, J., Effect of (–)-epigallocatechin gallate (EGCG) extracted from green tea in reducing the formation of acrylamide during the bread baking process. *Food chemistry.* 2018;**242**:162-168.

113. Wang, Y.-L.; Chang, H.-H.; Chiang, Y.-C.; Lu, Y.-C.; Lin, C.-P., Effects of fluoride and epigallocatechin gallate on soft-drink-induced dental erosion of enamel and root dentin. *Journal of the Formosan Medical Association.* 2018;**117**:276-282.

114. Sae-leaw, T.; Benjakul, S.; Vongkamjan, K., Retardation of melanosis and quality loss of pre-cooked Pacific white shrimp using epigallocatechin gallate with the aid of ultrasound. *Food Control.* 2018;**84**:75-82.

115. Du, W.; Zhou, M.; Liu, Z.; Chen, Y.; Li, R., Inhibition effects of low concentrations of epigallocatechin gallate on the biofilm formation and hemolytic activity of Listeria monocytogenes. *Food Control.* 2018;**85**:119-126.

116. Tsou, L. K.; Yount, J. S.; Hang, H. C., Epigallocatechin-3-gallate inhibits bacterial virulence and invasion of host cells. *Bioorganic & Medicinal Chemistry.* 2017;**25**:2883-2887.

117. Carneiro, B. M.; Batista, M. N.; Braga, A. C. S.; Nogueira, M. L.; Rahal, P., The green tea molecule EGCG inhibits Zika virus entry. *Virology.* 2016;**496**:215-218.

118. Falcó, I.; Randazzo, W.; Gómez-Mascaraque, L.; Aznar, R.; López-Rubio, A.; Sánchez, G., Effect of (–)-epigallocatechin gallate at different pH conditions on enteric viruses.

LWT – Food Science and Technology. 2017;*81*;250-257.

119. Chiou, Y.-S.; Ma, N. J.-L.; Sang, S.; Ho, C.-T.; Wang, Y.-J.; Pan, M.-H., Peracetylated (−)-Epigallocatechin-3-gallate (AcEGCG) Potently Suppresses Dextran Sulfate Sodium-Induced Colitis and Colon Tumorigenesis in Mice. *Journal of agricultural and food chemistry.* 2012;*60*:3441-3451.

120. An, T.-T.; Feng, S.; Zeng, C.-M., Oxidized epigallocatechin gallate inhibited lysozyme fibrillation more strongly than the native form. *Redox Biology.* 2017:*11*:315-321.

121. Sun, J.; Sun, W. J.; Li, Z. Y.; Li, L.; Wang, Y.; Zhao, Y.; Wang, C.; Yu, L. R.; Li, L. Z.; Zhang, Y. L., Daidzein increases OPG/RANKL ratio and suppresses IL-6 in MG-63 osteoblast cells. *International Immunopharmacology.* 2016;*40*:32-40.

122. Jaric, I.; Živanovic, J.; Miler, M.; Ajdžanovic, V.; Blagojevic, D.; Ristic, N.; Miloševc, V.; Nestorovic, N., Genistein and daidzein treatments differently affect uterine homeostasis in the ovary-intact middle-aged rats. *Toxicology and Applied Pharmacology.* 2018;*339*:73-84.

123. Zeng, H.-j.; Wang, Y.-p.; Yang, R.; You, J.; Qu, L.-b., Inhibitory effects of daidzein and genistein on trypsin: Insights from spectroscopic and molecular docking studies. *International journal of biological macromolecules.* 2016;*89*:336-343.

124. Jin, X.; Sun, J.; Yu, B.; Wang, Y.; Sun, W. J.; Yang, J.; Huang, S. H.; Xie, W. L., Daidzein stimulates osteogenesis facilitating proliferation, differentiation, and antiapoptosis in human osteoblast-like MG-63 cells via estrogen receptor–dependent MEK/ERK and PI3K/Akt activation. *Nutrition Research.* 2017;*42*:20-30.

125. Peng, Y.; Shi, Y.; Zhang, H.; Mine, Y.; Tsao, R., Anti-inflammatory and anti-oxidative activities of daidzein and its sulfonic acid ester derivatives. *Journal of Functional Foods.* 2017;*35*:635-640.

126. Ko, Y.-H.; Kim, S. Y.; Lee, S.-Y.; Jang, C.-G., 6,7,4′-Trihydroxyisoflavone, a major metabolite of daidzein, improves learning and memory via the cholinergic system and the p-CREB/BDNF signaling pathway in

mice. *European Journal of Pharmacology.* 2018;*826*:140-147.

127. Lee, C. C.; Dudonné, S.; Kim, J. H.; Kim, J. S.; Dubé, P.; Kim, J.-E.; Desjardins, Y.; Park, J. H. Y.; Lee, K. W.; Lee, C. Y., A major daidzin metabolite 7,8,4′-trihydroxyisoflavone found in the plasma of soybean extract-fed rats attenuates monocyte-endothelial cell adhesion. *Food chemistry.* 2018;*240*:607-614.

128. Hu, P.; Ma, L.; Wang, Y.-g.; Ye, F.; Wang, C.; Zhou, W.-H.; Zhao, X., Genistein, a dietary soy isoflavone, exerts antidepressant-like effects in mice: Involvement of serotonergic system. *Neurochemistry International.* 2017;*108*:426-435.

129. Wu, Z.-M.; Ni, G.-L.; Shao, A.-M.; Cui, R., Genistein alleviates anxiety-like behaviors in post-traumatic stress disorder model through enhancing serotonergic transmission in the amygdala. *Psychiatry Research.* 2017;*255*:287-291.

130. Khodamoradi, M.; Ghazvini, H.; Esmaeili-Mahani, S.; Shahveisi, K.; Farnia, V.; Zhaleh, H.; Abdoli, N.; Akbarnejad, Z.; Saadati, H.; Sheibani, V., Genistein attenuates seizure-induced hippocampal brain-derived neurotrophic factor overexpression in ovariectomized rats. *Journal of Chemical Neuroanatomy.* 2018;*89*:43-50.

131. Rajput, M. S.; Sarkar, P. D., Modulation of neuro-inflammatory condition, acetylcholinesterase and antioxidant levels by genistein attenuates diabetes associated cognitive decline in mice. *Chemico-Biological Interactions.* 2017;*268*:93-102.

132. Menze, E. T.; Esmat, A.; Tadros, M. G.; Abdel-Naim, A. B.; Khalifa, A. E., Genistein Improves 3-NPA-Induced Memory Impairment in Ovariectomized Rats: Impact of Its Antioxidant, Anti-Inflammatory and Acetylcholinesterase Modulatory Properties. *PLoS ONE.* 2015;10:e0117223.

133. Saleh, D. O.; Mansour, D. F., Ovario-protective effects of genistein against cyclophosphamide toxicity in rats: Role of anti-müllerian hormone and oestradiol. *European Journal of Pharmacology.* 2016;*789*:163-171.

134. Aldina, R.; Sujuti, H.; Permatasari, N.; Widodo, M. A., The effects of genistein on estrogen

receptor-β, IL-1β levels, and MUC5AC expression in ovariectomized rats with dry eye. *Clinical Nutrition Experimental.* 2017.

135. Liu, X.; Xue, X.; Wang, H.; Xu, X., Genistein modulates MMP-26 and estrogen receptor expression in endometrial cancer cells. *Journal of Traditional Chinese Medical Sciences.* 2016;3:242-247.

136. Zhang, K.; Wang, Y.; Ma, W.; Hu, Z.; Zhao, P., Genistein improves thyroid function in Hashimoto's thyroiditis patients through regulating Th1 cytokines. *Immunobiology.* 2017;*222*:183-187.

137. Gras, C. C.; Bause, K.; Leptihn, S.; Carle, R.; Schweiggert, R. M., Effect of chlorogenic acid on spectral properties and stability of acylated and non-acylated cyanidin-3-O-glycosides. *Food chemistry.* 2018;*240*:940-950.

138. Khoo, H. E.; Azlan, A.; Tang, S. T.; Lim, S. M., Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food & Nutrition Research.* 2017;*61*:1361779.

139. Serra, D.; Almeida, L. M.; Dinis, T. C. P., Anti-inflammatory protection afforded by cyanidin-3-glucoside and resveratrol in human intestinal cells via Nrf2 and PPAR-γ: Comparison with 5-aminosalicylic acid. *Chemico-Biological Interactions.* 2016;*260*:102-109.

140. Sivasinprasasn, S.; Pantan, R.; Thummayot, S.; Tocharus, J.; Suksamrarn, A.; Tocharus, C., Cyanidin-3-glucoside attenuates angiotensin II-induced oxidative stress and inflammation in vascular endothelial cells. *Chemico-Biological Interactions.* 2016;*260*:67-74.

141. Petroni, K.; Trinei, M.; Fornari, M.; Calvenzani, V.; Marinelli, A.; Micheli, L. A.; Pilu, R.; Matros, A.; Mock, H. P.; Tonelli, C.; Giorgio, M., Dietary cyanidin 3-glucoside from purple corn ameliorates doxorubicin-induced cardiotoxicity in mice. Nutrition, *Metabolism and Cardiovascular Diseases.* 2017;*27*:462-469.

142. Meng, L.-s.; Li, B.; Li, D.-n.; Wang, Y.-h.; Lin, Y.; Meng, X.-j.; Sun, X.-y.; Liu, N., Cyanidin-3-O-glucoside attenuates amyloid-beta (1–40)-induced oxidative stress and apoptosis in SH-SY5Y cells through a Nrf2 mechanism. *Journal of Functional Foods.* 2017;*38*:474-485.

143. Suantawee, T.; Cheng, H.; Adisakwattana, S., Protective effect of cyanidin against glucose- and methylglyoxal-induced protein glycation and oxidative DNA damage. *International journal of biological macromolecules.* 2016;*93*:814-821.

144. Thummayot, S.; Tocharus, C.; Suksamrarn, A.; Tocharus, J., Neuroprotective effects of cyanidin against Aβ-induced oxidative and ER stress in SK-N-SH cells. *Neurochemistry International.* 2016;*101*:15-21.

145. He, Y.; Hu, Y.; Jiang, X.; Chen, T.; Ma, Y.; Wu, S.; Sun, J.; Jiao, R.; Li, X.; Deng, L.; Bai, W., Cyanidin-3-O-glucoside inhibits the UVB-induced ROS/COX-2 pathway in HaCaT cells. *Journal of Photochemistry and Photobiology B: Biology.* 2017;*177*:24-31.

146. Hashimoto, N.; Han, K.-H.; Fukushima, M., Intraduodenal infusion of cyanidin-3-glucoside transiently promotes triglyceride excretion into bile in rats. *Nutrition Research.* 2017;*38*:34-42.

147. Fratantonio, D.; Cimino, F.; Molonia, M. S.; Ferrari, D.; Saija, A.; Virgili, F.; Speciale, A., Cyanidin-3-O-glucoside ameliorates palmitate-induced insulin resistance by modulating IRS-1 phosphorylation and release of endothelial derived vasoactive factors. Biochimica et Biophysica Acta (BBA) – *Molecular and Cell Biology of Lipids.* 2017:*1862*:351-357.

148. Matsukawa, T.; Villareal, M. O.; Motojima, H.; Isoda, H., Increasing cAMP levels of preadipocytes by cyanidin-3-glucoside treatment induces the formation of beige phenotypes in 3T3-L1 adipocytes. *The Journal of nutritional biochemistry.* 2017;*40*:77-85.

149. You, Y.; Han, X.; Guo, J.; Guo, Y.; Yin, M.; Liu, G.; Huang, W.; Zhan, J., Cyanidin-3-glucoside attenuates high-fat and high-fructose diet-induced obesity by promoting the thermogenic capacity of brown adipose tissue. *Journal of Functional Foods.* 2018;*41*:62-71.

150. Li, W.; Chen, S.; Zhou, G.; Li, H.; Zhong, L.; Liu, S., Potential role of cyanidin 3-glucoside (C3G) in diabetic cardiomyopathy in diabetic rats: An in vivo approach. *Saudi Journal of Biological Sciences.* 2018;*25*:500-506.

151. Thilavech, T.; Abeywardena, M. Y.; Adams, M.; Dallimore, J.; Adisakwattana, S., Naturally

occurring anthocyanin cyanidin-3-rutinoside possesses inherent vasorelaxant actions and prevents methylglyoxal-induced vascular dysfunction in rat aorta and mesenteric arterial bed. *Biomedicine & Pharmacotherapy.* 2017;*95*:1251-1259.

152. Saithong, T.; Thilavech, T.; Adisakwattana, S., Cyanidin-3-rutinoside reduces insulin fibrillation and attenuates insulin fibrils-induced oxidative hemolysis of human erythrocytes. *International journal of biological macromolecules.* 2018.

153. Choi, K. H.; Lee, H. A.; Park, M. H.; Han, J.-S., Cyanidin-3-rutinoside increases glucose uptake by activating the PI3K/Akt pathway in 3T3-L1 adipocytes. *Environmental Toxicology and Pharmacology.* 2017;*54*:1-6.

154. Akolade, J. O.; Oloyede, H. O. B.; Onyenekwe, P. C., Encapsulation in chitosan-based polyelectrolyte complexes enhances antidiabetic activity of curcumin. *Journal of Functional Foods.* 2017;*35*:584-594.

155. Li, X.; Cao, T.; Ma, S.; Jing, Z.; Bi, Y.; Zhou, J.; Chen, C.; Yu, D.; Zhu, L.; Li, S., Curcumin ameliorates cardiac dysfunction induced by mechanical trauma. *European Journal of Pharmacology.* 2017;*814*:73-80.

156. Zhang, Y.; Liu, Z.; Wu, J.; Bai, B.; Chen, H.; Xiao, Z.; Chen, L.; Zhao, Y.; Lum, H.; Wang, Y.; Zhang, H.; Liang, G., New MD2 inhibitors derived from curcumin with improved anti-inflammatory activity. *European Journal of Medicinal Chemistry.* 2018;*148*:291-305.

157. Su, J.; Zhou, X.; Yin, X.; Wang, L.; Zhao, Z.; Hou, Y.; Zheng, N.; Xia, J.; Wang, Z., The effects of curcumin on proliferation, apoptosis, invasion, and NEDD4 expression in pancreatic cancer. *Biochemical Pharmacology.* 2017;*140*:28-40.

158. Allegra, A.; Speciale, A.; Molonia, M. S.; Guglielmo, L.; Musolino, C.; Ferlazzo, G.; Costa, G.; Saija, A.; Cimino, F., Curcumin ameliorates the in vitro efficacy of carfilzomib in human multiple myeloma U266 cells targeting p53 and NF-κB pathways. *Toxicology in Vitro.* 2018;*47*:186-194.

159. Sáenz, J.; Alba, G.; Reyes-Quiroz, M. E.; Geniz, I.; Jiménez, J.; Sobrino, F.; Santa-María, C., Curcumin enhances LXRα in an AMP-activated protein kinase-dependent manner in human macrophages. *The Journal of nutritional biochemistry.* 2018;*54*:48-56.

160. Mahmoud, A. A.; Abdelrahman, A.; Abd el Aziz, H. O., Protective effect of curcumin on the liver of high fat diet-fed rats. *Gene Reports.* 2018;*11*:18-22.

161. Wang, H.; Muhammad, I.; Li, W.; Sun, X.; Cheng, P.; Zhang, X., Sensitivity of Arbor Acres broilers and chemoprevention of aflatoxin B1-induced liver injury by curcumin, a natural potent inducer of phase-II enzymes and Nrf2. *Environmental Toxicology and Pharmacology* 2018;*59*:94-104.

162. Kim, K. S.; Lim, H.-J.; Lim, J. S.; Son, J. Y.; Lee, J.; Lee, B. M.; Chang, S.-C.; Kim, H. S., Curcumin ameliorates cadmium-induced nephrotoxicity in Sprague-Dawley rats. *Food and Chemical Toxicology.* 2018;*114*:34-40.

163. Akinyemi, A. J.; Oboh, G.; Fadaka, A. O.; Olatunji, B. P.; Akomolafe, S., Curcumin administration suppress acetylcholinesterase gene expression in cadmium treated rats. *Neuro Toxicology* 2017;*62*:75-79.

164. Hatefi, M.; Ahmadi, M. R. H.; Rahmani, A.; Dastjerdi, M. M.; Asadollahi, K., Effects of Curcumin on Bone Loss and Biochemical Markers of Bone Turnover in Patients with Spinal Cord Injury. *World Neurosurgery.* 2018.

165. Dong, W.; Yang, B.; Wang, L.; Li, B.; Guo, X.; Zhang, M.; Jiang, Z.; Fu, J.; Pi, J.; Guan, D.; Zhao, R., Curcumin plays neuroprotective roles against traumatic brain injury partly via Nrf2 signaling. *Toxicology and Applied Pharmacology.* 2018.

166. Asadpour, M.; Namazi, F.; Razavi, S. M.; Nazifi, S., Comparative efficacy of curcumin and paromomycin against Cryptosporidium parvum infection in a BALB/c model. *Veterinary Parasitology.* 2018;*250*:7-14.

167. Penha, C. B.; Bonin, E.; da Silva, A. F.; Hioka, N.; Zanqueta, É. B.; Nakamura, T. U.; de Abreu Filho, B. A.; Campanerut-Sá, P. A. Z.; Mikcha, J. M. G., Photodynamic inactivation of foodborne and food spoilage bacteria by curcumin. *LWT – Food Science and Technology.* 2017;*76*:198-202.

168. Illiano, M.; Sapio, L.; Salzillo, A.; Capasso, L.; Caiafa, I.; Chiosi, E.; Spina, A.; Naviglio, S., Forskolin improves sensitivity to doxorubicin

of triple negative breast cancer cells via Protein Kinase A-mediated ERK1/2 inhibition. *Biochemical Pharmacology*.

169. Ramachandran, S.; Loganathan, S.; Cheeran, V.; Charles, S.; Munuswamy-Ramanujan, G.; Ramasamy, M.; Raj, V.; Mala, K., Forskolin attenuates doxorubicin-induced accumulation of asymmetric dimethylarginine and s-adenosylhomocysteine via methyltransferase activity in leukemic monocytes. *Leukemia Research Reports.* 2018;*9*:28-35.

170. Guo, X.; Bai, X.; Li, L.; Li, J.; Wang, H., Forskolin protects against cisplatin-induced ototoxicity by inhibiting apoptosis and ROS production. *Biomedicine & Pharmacotherapy.* 2018;*99*:530-536.

171. Kaur, J.; Sodhi, R. K.; Madan, J.; Chahal, S. K.; Kumar, R., Forskolin convalesces memory in high fat diet-induced dementia in wistar rats—Plausible role of pregnane x receptors. *Pharmacological Reports.* 2018;*70*:161-171.

172. Yagita, K.; Okamura, H., Forskolin induces circadian gene expression of rPer1, rPer2 and dbp in mammalian rat-1 fibroblasts. *FEBS letters.* 2000;*465*:79-82.

173. Liu, C.; Ho, P. C.-L.; Wong, F. C.; Sethi, G.; Wang, L. Z.; Goh, B. C., Garcinol: Current status of its anti-oxidative, anti-inflammatory and anti-cancer effects. *Cancer Letters.* 2015;*362*:8-14.

174. Huang, W.-C.; Kuo, K.-T.; Adebayo, B. O.; Wang, C.-H.; Chen, Y.-J.; Jin, K.; Tsai, T.-H.;

Yeh, C.-T., Garcinol inhibits cancer stem cell-like phenotype via suppression of the Wnt/β-catenin/STAT3 axis signalling pathway in human non-small cell lung carcinomas. *The Journal of nutritional biochemistry.* 2018;*54*:140-150.

175. Hung, W.-L.; Liu, C.-M.; Lai, C.-S.; Ho, C.-T.; Pan, M.-H., Inhibitory effect of garcinol against 12-O-tetradecanoylphorbol 13-acetate-induced skin inflammation and tumorigenesis in mice. *Journal of Functional Foods.* 2015;*18*:432-444.

176. Zhou, X.-Y.; Cao, J.; Han, C.-M.; Li, S.-W.; Zhang, C.; Du, Y.-D.; Zhou, Q.-Q.; Zhang, X.-Y.; Chen, X., The C8 side chain is one of the key functional group of Garcinol for its anti-cancer effects. *Bioorganic Chemistry.* 2017;*71*:74-80.

177. Han, C.-M.; Zhou, X.-Y.; Cao, J.; Zhang, X.-Y.; Chen, X., 13,14-Dihydroxy groups are critical for the anti-cancer effects of garcinol. *Bioorganic Chemistry.* 2015;*60*:123-129.

178. Wang, Y.-w.; Zhang, X.; Chen, C.-l.; Liu, Q.-z.; Xu, J.-w.; Qian, Q.-q.; Li, W.-y.; Qian, Y.-n., Protective effects of Garcinol against neuropathic pain – Evidence from in vivo and in vitro studies. *Neuroscience Letters.* 2017;*647*:85-90.

179. Jing, Y.; Ai, Q.; Lin, L.; Dai, J.; Jia, M.; Zhou, D.; Che, Q.; Wan, J.; Jiang, R.; Zhang, L., Protective effects of garcinol in mice with lipopolysaccharide/D-galactosamine-induced apoptotic liver injury. *International Immunopharmacology.* 2014;*19*:373-380.