**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. Some of the advantages could overcome several distressing problems including costs and side effects, rather than using synthetic therapeutics. 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. 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. 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. ROS generation is found to be up-regulated by NADPH oxidase and bioactive redox phytochemical could eventually normalize the imbalance. Most phytochemicals exhibited in a general two-stage anti-oxidation mechanism to trap the radical and form a non-radical materials. 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-oxidative 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.

**Anti-Inflammation**

As a primary response to infection or injury caused by irritation or wounding, inflammation is critical for both innate and adaptive immunity. 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. 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. 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.

**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. 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.

**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.

**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. 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. 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. 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. 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. In fact, several environmental factors or toxicants, or physical activities like smoking and lipid levels have been found to alter DNA methylation status. 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.

**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. Identified post-translational histone modifications consists of acetylation or methylation of lysines and arginines, phosphorylation of serines and thereonines, ubiquitination and sumoylation occurred on lysines, and ribosylation. 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. 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. 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.

**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. As recorded until June, 2014, there are up to 28645 identified entries in miR Base. 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. 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, maturation-enzymes activity and stability.

**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. 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. 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. Among stilbene-derived compounds, its hydroxylated derivatives, so-called stilbenoids have rendered compelling impacts on health issues.

**Stilbenoid**
Stilbenoids share a C₆-C₂-C₆ structure, and it can be classified into two sub-types, aglycones and glycosides. Stilbenoid aglycones consist of resveratrol, pterostilbene and piceatannol, while piceid and astrigin, derivatives of resveratrol and piceatannol are classified as stilbenoid glucosides.

**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. In addition, resveratrol also demonstrated therapeutic effect of Alzheimer’s disease by facilitating mesenchymal stem cell transplantation, subsequently enhancing neurogenesis and SIRT1 signaling. Intervention of resveratrol exhibited conspicuous effect in chemo preventive action, including promoting 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. 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. 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. To be mentioned that, biosynthesis of resveratrol and piceatannol was found to be enhanced by mechanical stress in some plant products. 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. 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. 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. 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. 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.

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. Moreover, pterostilbene was capable to attenuate inflammatory effect and endoplasmic reticulum stress (ERS) induced by TNF-α by down-regulating ERS-related protein (p-ɛIF2α, GRP78 and p-IKE1) and inflammatory cytokines (IL-8, MCP-1, ICAM1 and MMP9) expression. 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. 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. 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. 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. 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. 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. 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. 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.

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. Other effects including anti- adipogenic, neuroprotection and anti-tumor 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.

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, flavanones, isoflavonoids, 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.

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. 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. 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. 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.

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. 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. 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. Moreover, hydroxylated metabolites of apigenin such as 3-phenypropionic acid and 3-(3, 4-dihydroxyphenyl) propionic acid by microbiota may be considered as compelling novel phytochemicals to be further discussed in future studies.

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 abundance in vegetables and fruits such as onion, broccoli and berries. Most importantly, there was no adverse effect examined in toxicity at high concentration up to 3000 mg/kg in clinical studies. Recent research in producing flavonoid fermentatively by yeast metabolis engineering has successfully developed yeast strains that produced quercetin and kaempferol with enormous extracellular concentration, via tyrosine and pheynylalanine supplying routes.

Kaempferol can be produced by hydroxylation on naringenin, the flavonone mentioned above, followed by introducing double bond by flavonol synthase. Intervention of kaempferol in Fe-Cl\textsubscript{3}-induced carotid arterial thrombus model and acute thromboembolism models induced by collagen/eninephrine and thrombin has revealed its potent effect against fibrin clot formation and suppressive activity of pro-coagulant protease and platelet activation in cardiovascular disease. 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. 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. 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. Novel galactosylation of astragals by β-galactosidase can hopefully overcome the shortcoming of poor solubility of astragalin for more industrial application potent.

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. 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. 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. 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. 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.

Flavanones
Chemopreventive Effects of Flavanones
There are nearly up to 14 flavanones 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\textsubscript{4}-induced liver injury, therapeutic implication for osteosarcoma by cytotoxic-induced cellular loss in U2OS cells, and neuroprotective effect on recognition/memory impairment by reducing oxidative stress in Alzheimer’s disease rat model. Moreover, antihyperglycemic effect and renoprotective activity of hesperetin in streptozotocin-induced diabetic rats and cisplatin-
induced nephrotoxicity, also strengthened its potential as a promising bioactive compound\textsuperscript{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 cancer cell growth inhibition up to 6 times better than its original counterpart\textsuperscript{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\textsuperscript{102}. Similar to hesperetin and most phytochemicals, oral bioavailability of naringenin is mostly concerned, followed by stability and solubility, and the limitations can also be surpassed by nanosuspension and surfactant stabilization\textsuperscript{103}. On the other hand, methylation of hydroxyl groups has been suggested to improve metabolic stability and membrane transportation 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\textsuperscript{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\textsuperscript{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\textsuperscript{106}.

Not in surprise, EGCG has been efficacious in chemopreventive action and exhibited therapeutic properties including cardiovascular, hepatic, metabolic, inflammatory, hyperuricemic and diabetic diseases in elevating numbers of research\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{113}. Treatment of EGCG solution with ultrasonic promises quality of pre-cooked shrimp by inhibiting melanosis development\textsuperscript{114}. EGCG has also demonstrated 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 ER\textsubscript{α} and ER\textsubscript{β} (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\textsuperscript{121,122}. Thus, a randomized control trial in premenopausal women has been conducted and resulting in novel effects of these phytoestrogenic isoflavones to be strongly associated with serum calcium and chloride level and cardiovascular diseases morbidity reduction\textsuperscript{122}. Like other phytochemicals, daidzein and its derivatives with sulfonic acid esterification have demonstrated 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\textsuperscript{121,123-125}. As abovementioned, 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\textsuperscript{125}. Surprisingly, some lactic acid bacteria and common gut bacteria \textit{bididobacterium} strain can transform daidzein and genistein into other bioactive forms, like dihydrodaidzein and dihydrogenistein\textsuperscript{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\textsuperscript{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 phosphorylation upregulation in amygdala in post-traumatic stress disorder, and attenuating hippocampal brain-derived neurotrophic factor (BDNF) overexpression that induced by seizure\textsuperscript{128-130}. Other neuroprotective effect of genistein in neuro-inflammatory modulation in diabetec mice with cognitive decline mice and sensorimotor gating improvement to ameliorate Huntington’s disease have been demonstrated in recent studies as well\textsuperscript{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\textsuperscript{133}. Furthermore, genistein, as partial substituent of estrogen, has successfully improved dry eye condition by upregulating estrogen receptor-\(\beta\), ER-\(\beta\) and MUC5AC expression and suppress IL-1\(\beta\) level in ovariectomized rats, even estrogen is majorly produced in ovary\textsuperscript{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 ER\(\alpha\) and ER\(\beta\) expression by different genistein concentrations\textsuperscript{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\textsuperscript{137}. Even though there is positive charge at oxygen atom of the C-ring, it is considered as one of the flavonoids\textsuperscript{138}.

Several anthocyanidins and anthocynins demonstrated their cytoprotective, anti-oxidative and inflammatory abilities\textsuperscript{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\textsuperscript{143}. Besides, cyanidin also exhibited preventive effect on neurodegenerative diseases by reducing oxidative stress and apoptosis caused by A\(\beta\)1-40 peptide in SHSY5Y cells, and decreasing ER stress induced by A\(\beta\)25-35 in SK-N-SH, in turns...
in a preventive action in Alzheimer's disease.\textsuperscript{140,144} 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.\textsuperscript{146} Metabolic syndrome is one of the major concerns recent years and cyanidin-3-O-glucoside, an anthocyanin, 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.\textsuperscript{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 successfully delineated and ensured the role of cyanidin-3-O-glucoside in anti-obesity treatment.\textsuperscript{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.\textsuperscript{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 methylglycolal-induced vascular dysfunction in rat model.\textsuperscript{151} Furthermore, oxidative hemolysis induced by insulin fibrils can be attenuated in human erythrocytes as amyloid fibril formation has been reported to be inhibited after treatment.\textsuperscript{152} Lastly, cyanidin-3-rutinoside may serve as promising phytochemical to improve insulin resistance by regulating PI3K/Akt pathway to increase glucose uptake.\textsuperscript{153}

Other Novel Phytochemicals

Chemopreventive Effects of Curcumin

Curcumin is the major phenolic component in \textit{Curcuma longa}, and it has been suggested that the pharmacological properties of \textit{C. longa} is majorly dictated by the level and the composition of curcurcinoids. 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.\textsuperscript{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 mechanical trauma could be ameliorated by enervating impacts from ROS production.\textsuperscript{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.\textsuperscript{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.\textsuperscript{157} Besides, proapoptotic effect was enhanced in U266 cell by activating p53-p21 axis and inhibiting expression of NF-κB with curcumin intervention.\textsuperscript{158} Additionally, 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 in hepatotoxicity reduction with phase-II enzyme gene expression in liver.\textsuperscript{159} 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.\textsuperscript{160} 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 decreasing AchE activity that highly related to various insults like oxidative stress.\textsuperscript{152,163} 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 inhibition of osteoclastogenesis.\textsuperscript{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\textsuperscript{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\textsuperscript{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, but reducing methyltransferase activity in monocyteid cells\textsuperscript{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\textsuperscript{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-\(\beta\) production and accumulation, which may consequently lead to neurocognitive disorder and cognitive decline, and forskolin has exhibited protective and preventive effects due to its hypolipidemic effect to prevent amyloid-\(\beta\) peptides accumulation in brain, enervating adverse effect in dementia and combating memory impairment\textsuperscript{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\textsuperscript{172}. It is believed that forskolin may gain more attention due to its modulatory 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 traditionally used for treatment of gastric ailments 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\textsuperscript{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/\(\beta\)-catenin/STAT3 signaling pathway and ameliorative efficacy in skin inflammation and tumorigenesis induced by 12-O-tetradecanoylphorbol 13-acetate in mice model\textsuperscript{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\textsuperscript{176,177}. Furthermore, garcinol has also exerted potent neuroinflammatory effect against nueropathic pain in LPS-induced microglia by inhibiting acetylation of NF-\(\kappa\)B/p65, subsequently stopping activation of NF-\(\kappa\)B\textsuperscript{178}. Protective effect of garcinol was also exhibited in liver diseases. Garcinol has shown remarkable suppressive effect in decreasing intrinsic and extrinsic caspase cascade to evade hepatic apoptosis induced by LPS/D-galactosamine\textsuperscript{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 certained 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

Acknowledgments
This study was supported by the Ministry of Science and Technology [105-2320-B-002-031-MY3, 105-2628-B-002-003-MY3].

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