Biochemistry & Pharmacology: Open Access

OPEN ACCESS Freely available online

Review Article

# Pharmacological Intervention of Phytochemical Therapy for Inflammatory and Chronic Diseases

**Quratulain Malik*, Husna Ifthikhar**

*Independent Researcher, Pakistan Administrative Services, Pakistan*

## ABSTRACT

Plant isolated phytochemicals have been used since ancient times as both primary and supplemental treatment for various ailments as well as to support normal physiological functions. Phytochemical based pharmacological interventions recently received a great attention for the treatment and prevention of inflammatory and chronic diseases including cancer, diabetes, cardiovascular, hepatic and neurological diseases. Anti-inflammatory effects of phytochemicals are mediated by the modulatory actions on multifaceted cell signalling pathways including inflammatory transcription factors, cytokines, redox status, protein kinases, and enzymes that generally promote inflammation. Imbalance redox status has been reported to be associated with the pathogenesis of chronic disease. Phytochemicals have the ability to correct oxidative stress by modulating redox status and cure various chronic diseases. Based on *in-vitro*, *in-vivo* and human data, this study summarizes the recent knowledge regarding the potential effect of various phytochemicals via cellular transduction pathways and provides an in depth assessment of therapeutic value in the treatment and prevention of various chronic inflammatory diseases.

**Keywords:** Phytochemicals; Anti-inflammatory effects; Chronic inflammatory diseases; Carotene; Carotenoids; Antioxidant

## INTRODUCTION

Inflammation is the body's defensive response to injury and infection; it is a complex process involving many cell types, as well as different components of blood. The inflammatory process works quickly to destroy and eliminate foreign and damaged cells and to isolate the infected or injured tissues from the rest of the body. Inflammatory disorders arise when inflammation becomes uncontrolled, and causes destruction of healthy tissue. Many such disorders occur when the immune system mistakenly triggers inflammation in the absence of infection, such as inflammation of the joints in rheumatoid arthritis. Others result from a response to tissue injury or trauma but affect the entire body. Whereas, chronic disease is a long-lasting condition that can be controlled but not cured [1]. Chronic diseases are persistent or otherwise long-lasting in its effects or a disease that comes with time and affects the population worldwide [2].

Phytochemicals refers to a wide variety of compounds made by plants, but is mainly used to describe those compounds that may affect human health. Phytochemicals are found in plant-based foods such as fruits, vegetables, beans, and grains. Scientists have identified thousands of phytochemicals, although only a small fraction has been studied closely [3]. Some of the better-known phytochemicals include beta carotene and other carotenoids, ascorbic acid (vitamin C), folic acid, and vitamin E. Some phytochemicals have either antioxidant or hormone-like actions. There is some evidence that a diet rich in fruits, vegetables, and whole grains reduces the risk of certain types of cancer and other diseases. Researchers are looking for specific compounds in these foods that may account for these healthful effects in humans. Phytochemicals are promoted for the prevention and treatment of many health conditions, including cancer, heart disease, diabetes, and high blood pressure [4,5]. There is some evidence that certain phytochemicals may help prevent the formation of potential carcinogens (substances that cause cancer), block the action of carcinogens on their target organs or tissue, or act on cells to suppress cancer development. Many experts suggest that people can reduce their risk of cancer significantly by eating more fruits, vegetables, and other foods from plants that contain Phytochemicals.

## LITERATURE REVIEW

In recent times, Phytochemicals are used in as a pharmacological intervention to cure long- lasting diseases. Phytochemical supplements are the talk of the town but available scientific

**Correspondence to:** Quratulain Malik, Independent Researcher, Pakistan Administrative Services, Pakistan, Tel: 03315262393; E-mail: quratfaiz@outlook.com

**Received:** May 04, 2020, **Accepted:** August 21, 2020, **Published:** August 28, 2020

**Citation:** Malik Q, Ifthikhar H (2020) Pharmacological Intervention of Phytochemical Therapy for Inflammatory and Chronic Diseases. Biochem Pharmacol (Los Angel). 9:272. doi: 10.35248/2167-0501.20.9.272

evidence does not support claims that taking phytochemical supplements is as good for long-term health as consuming the fruits, vegetables, beans, and grains from which they are taken [6-15]. Recently, researches have been done by using glycoprotein to mediate multidrug resistance. Experimentation has been done to work out the role of quercetin as an alternative for obesity treatment. Phytochemical screening and broad targeting of angiogenesis is also been done [15-21]. Anticancer potential of medicinal plants and their phytochemicals have also been studies to make a change in the world and to decrease the mortality rate.

Phytochemicals are promoted for the prevention and treatment of many health conditions, including cancer, heart disease, diabetes, and high blood pressure. There is some evidence that certain phytochemicals may help prevent the formation of potential carcinogens (substances that cause cancer), block the action of carcinogens on their target organs or tissue, or act on cells to suppress cancer development. Many experts suggest that people can reduce their risk of cancer significantly by eating more fruits, vegetables, and other foods from plants that contain phytochemicals [22-25].

### Mechanism underlying the biological activity of phytochemicals

Chemopreventive compounds are able to prevent or slow down carcinogenesis [26]. Furthermore, free radicals induce DNA damage, which may cause cancer, while antioxidants are free-radical scavengers and have been reported to slow down and prevent DNA damage that facilitates the development of cancer. Citrus fruits have been shown to influence multiple molecular targets and exhibit pleiotropic effects. Citrus facilitates antioxidant activity by reacting with free radicals, thus resulting in the protection of cellular damage [27].

Compounds isolated from citrus are potential antioxidants owing to their phenolic and flavonoid content [28,29]. Among these flavonoids, hesperidin is the most dominant flavonoid, which has significant antioxidant activity [30]. Hesperidin, nobiletin, and tangeretin have been investigated for their *in-vitro* antioxidant activity [31]. *In-vivo* studies showed that the ethanolic extract of *C. reticulata* at the concentration of 500 mg/kg suppresses c-Myc expression and reduces the number of cells expressing N-Ras in rats with DMBA-induced hepatic carcinogenesis [32,33]. Nobiletin, another flavonoid obtained from the peel of *C. reticulata*, inhibits DMBA-induced carcinogenesis in the skin of mice [34]. Additionally, the biological effects of nobiletin and tangeretin from *C. reticulata* have been extensively investigated [35]. These flavonoids do not bind with c-Src, but stabilize imatinib-c-Src binding as compared to that of ATP-c-Src [32,36]. Molecular docking of nobiletin and tangeretin with CYP1A2 indicated that the binding of tangeretin to CYP1A2 is stronger than that of α-naphtoflavon, whereas nobiletin fails to bind [36]. However, further investigations are needed to elucidate the mechanism of action of certain flavonoids, which will provide novel insights in this field.

*Citrus aurantifolia* is a prominent member of the citrus family, which inhibits DMBA-induced mammary carcinogenesis in female Sprague Dawley rats by inducing apoptosis and inhibiting cellular proliferation [37,38]. *C. aurantifolia* peels contain several flavonoids such as naringin, hesperidin, naringenin, hesperitin, rutin, nobiletin, and tangeretin [39]. Daily oral administration of hesperetin (20 mg/kg BW) for 15 weeks inhibits carcinogenesis in rats with 1,2 dimethylhydrazine-induced colon cancer [40]. Nobiletins have shown cytotoxic effects by modulating the cell cycle in TMK-1, MKN-45, MKN-74, and KATOIII human gastric carcinoma cells [41]. These compounds have also been shown to block cell cycle transition from G1 phase of the cell cycle and induce cell death in cancer cells [42,43]. Tangeretin has been reported to arrest G1 phase by increasing the expression of CDK inhibitors p27 and p21 in COLO 205 human colon carcinoma cells [44]. Tangeretin also inhibits estradiol-stimulated T47D cells [45]. On the other hand, the compound induces apoptosis in MCF-7 cell by facilitating cell-cycle arrest at G1 phase [42]. Hesperetin has been shown to facilitate anticancer activity in MCF-7 cells through down-regulation of CDK2, CDK4, and Cyclin D and by increasing the expression of p21 and p27, which induces cell death [39]. Naringenin also inhibits the proliferation of MDA-MB-435 cells and demonstrated antiestrogenic activity on ERα cells [46,47]. Additionally, naringin, a glycoside form of naringenin, inhibits the replication of bladder cancer cells and induces G1 arrest by inducing the over-expression of tumor suppressor proteins [48]. Naringin also blocks the cell survival by inhibiting the activation of PI3K pathway [37].

Apoptosis or programmed cell death is characterized by cell shrinkage, membrane blebbing, chromatin condensation, formation of apoptotic bodies, and DNA fragmentation [49]. Apoptosis can occur through two main pathways, the extrinsic and intrinsic pathways. The extrinsic pathway involves the activation of death receptors by activation of caspases, whereas the intrinsic pathway occurs through mitochondrial activation [49]. Tangeretin has the ability to trigger apoptosis and p53 over-expression in COLO 205 human colon cancer cells, more potently than do apigenin, kaempferol, myricetin, quercetin, luteolin, nobiletin, and rutin [44]. Tangeretin also induces apoptosis in HL-60 human promyelocytic leukemia cells [50]. Nobiletin, another flavonoid obtained from *C. reticulata* coverings, induces cytotoxicity and apoptosis in TMK-1, MKN-45, MKN-74, and KATO-III human gastric carcinoma cells [41]. Both *in-vitro* and *in-vivo* studies have well documented the antiproliferative effect of *C. reticulata* peel extracts in rat mammary and liver carcinogenesis models. The ethanolic extract containing several flavonoids potentially induces apoptosis in liver cells, but not in mammary cells, although the tumor suppressor protein p53 is over-expressed in both tissues [51].

Hesperetin shows cytotoxic effects, at concentrations of 40 and 80 μM, through caspase 3 activation in HL-60 cells and is more cytotoxic than hesperidin. The rutinoside group present at C-7 of hesperidin attenuates the apoptotic cell death in HL-60 cells [52]. Naringenin induces apoptosis of KATOIII and MKN-7 gastric cancer cells and HepG2, Hep3B, and Huh7 liver cancer cells through the p53-independent pathway and via the intrinsic pathway by the up-regulation of Bax and down-regulation of Bcl2, caspase 3 activation, and PARP cleavage in THP-1 leukemia cells [46,53]. On the other hand, antiangiogenic effect of the ethanolic extract of *C. reticulata* peel in the chorioallantoic membrane (CAM) was shown to be induced by bFGF, which inhibits the formation of new blood vessels and reduces the number of macrophages [53,54]. Despite limited data in the literature, the reported studies indicate that these phytochemicals have the potential to emerge as therapeutic as well as prophylactic agents for various diseases.

## THERAPEUTIC ROLE OF PHYTOCHEMICALS

### Anti-inflammatory effects of phytochemicals

Inflammation is a part of complex biological responses of vascular tissues to injurious stimuli for protecting the organism

and initiating the healing process. It is normally epitomized by enhanced permeability of endothelial tissue and influx of blood leukocytes into the interstitium, causing edema. Each step in the inflammation cascade is influenced by a variety of biological mediators [15,23]. Anti-inflammatory agents display therapeutic characteristics by inhibiting the synthesis or actions of these mediators. Inflammation, a normal response towards the tissue injury, becomes uncontrollable in chronic disorders, which then require therapeutic administration of anti-inflammatory compounds to control the inflammatory response [15,23]. Various natural products obtained from plant sources have been successfully used as therapeutic agents for controlling inflammatory responses. Among these, flavonoids obtained from citrus and other plant sources have been traditionally known for their anti-inflammatory activities [15]. The application of bioflavonoids in a general anti-inflammatory and antiaging therapy for humans remained a debatable issue for a long time. Loss of function due to metabolic processing and low bioavailability are the two major reasons that diminish the efficiency of dietary supplementation with plant flavonoids [55]. However, clinical trials and *in-vivo* research have provided strong evidence that are highly supportive of the use of flavonoids. Their availability at lower cost than a number of anti-inflammatory drugs and lack of side effects have popularized their use. A number of citrus flavonoids including hesperidene and diosmin have been recognized for their anti-inflammatory properties.

A number of enzymes such as phosphodiesterase, phospholipase, lipoxygenase (LOX), protein kinase C, and cyclooxygenase (COX) regulate the influence of biological mediators that are responsible for the activation of endothelial cells and specialized cells concerned with inflammation [23]. Flavonoids inhibit the inflammatory responses and thus inhibit the enzymes associated with the inflammatory process. It is worth mentioning that citrus flavonoids were found to be capable of inhibiting the kinases and phosphodiesterases necessary for cellular signal transduction and activation. Furthermore, these flavonoids also influence the activation of a number of cells concerned with the immune response, including T and B lymphocytes [15]. Herein, we have summarized few reports on the anti-inflammatory effects of various citrus flavonoids.

COX and LOX are inflammatory mediators, which release arachidonic acid, the initial event in the general inflammatory response. Furthermore, chemotactic compounds are created by the neutrophils containing lipoxygenase from arachidonic acid. Several studies have revealed that certain selected phenolic compounds produced effective inhibitory effects on both cyclooxygenase and 5-lipoxygenase pathways [56,57]. This inhibition consequently reduces the release of arachidonic acid [58]. However, the exact mechanism through which the flavonoids inhibit these enzymes is not clearly understood. The activities of both COX-2 and lipoxygenase are also inhibited by other members of the flavonoids. Among these, quercetin, in particular, decreased the formation of the inflammatory metabolites through its enzyme inhibiting activities [8,59].

Another promising anti-inflammatory activity of the flavonoids is related to their capability to restrain the biosynthesis of eicosanoid [5,60]. Certain eicosanoids, like prostaglandins, are associated with several immunologic responses [61] and are the end products of the cyclooxygenase and lipoxygenase pathways. Integral membrane proteins such as tyrosine 3-monooxygenase kinase are associated with a multiplicity of tasks, such as enzyme catalysis, transport across membranes, transduction of signals from receptors of hormones and growth factors, and energy transfer in ATP synthesis. To facilitate a controlled cell growth and proliferation, the inhibition of these proteins is essential. Flavonoids can hinder both cytosolic and membrane tyrosine kinase [5]. Tyrosine kinase substrates seem to play key roles in the signal transduction pathway that regulates cellular proliferation. Few studies have reported that anti-inflammatory properties of diosmin and hesperidin are due to their inhibition of the synthesis and biological activities of different proinflammatory mediators, mainly arachidonic acid derivatives, prostaglandins E2 and F2, and thromboxane A2 [15]. It has been reported that citrus flavonoids such as apigenin and diosmetin are effective in attenuating LPS-induced nitric oxide (NO) and tumor necrosis factor α (TNF-α) release at concentrations in the low micromolar range and proposed their use in the treatment of septic shock [62]. The effect of apigenin and diosmetin on AGE-induced NO production and TNF-R release in microglia have been studied previously. Furthermore, the inhibition of iNOS and COX-2 expression in LPS-activated RAW264.7, with a half-maximal inhibitory concentration (IC50) of 15 μM, has been observed [63,64]. Additionally, *in-vitro* studies have demonstrated that the inhibitory effects of flavonoid on the critical reactions are catalyzed by phospholipase A2, COX, and LOX [15].

A comparative study reported the difference between the activity of 29 commercially existing polyphenol-containing plant extracts and pure compounds employed to prevent LPS-induced up-regulation of NO production. The overall results revealed that all the extracts inhibited BSA-AGE–induced NO production, whereas TNF-R was only reduced by apigenin, diosmetin, and silymarin, but not by the other compounds [62]. Based on their activity and toxicity, it was concluded that apigenin and diosmetin are outstanding candidates for clinical trials provided their bioavailability is optimized by their mode of delivery to facilitate lower concentrations in the target tissue. This therapeutic rule could be applied for various inflammatory conditions involving AGEs, particularly those related to diabetes and renal failure.

## Antiproliferative activities

In addition to being nontoxic to human and animal cells, a number of citrus flavonoids have demonstrated inhibitory effect on many carcinogenic cells lines. The antiproliferative effects of citrus flavonoids such as tangeretin, nobiletin, quercetin, and taxifolin have been observed in HTB43 squamous cell carcinoma. Antiproliferative activity of quercetin (10 μM) has been demonstrated against meningioma, colon cancer, and Caco-2 and HT-29 cells. Similarly, other important citrus flavonoids (diosmin) have demonstrated antiproliferative activity in Caco-2 and HT-29 colon cancer cell lines with IC50 of 203 μM. Certain citrus flavones have the ability to restrain the proliferation of MDA-MB-435 and MCF-7 human breast cancer cells. A comprehensive study revealed the antiproliferative activities of 27 citrus flavonoids against several tumor and normal cell lines. Among these, seven flavonoids were found active against the tumor cell lines, including gastric TGBC11TKB cancer cells and lung carcinoma A549; however, they did not substantially affect the proliferation of normal cell lines. It is noteworthy that the IC50 for the inhibition of cell proliferation by active flavonoids found in most of the studies was in the low micromolar range.

The most important finding in all these reports was the antiproliferative effects of flavonoids against carcinogenic cells, and the fact that the flavonoids were completely nontoxic to the normal cells. These results highlight the relationship between flavonoid structure and their antiproliferative activity. In this regard, some studies have used flavonoids of citrus origin against melanoma lines (B16F10 and SKMEL-1 cells), and reported that the occurrence of C2-C3 double bond on the C ring in conjugation with 4-oxo functional group was critical for the antiproliferative activity. Further studies indicated that the presence of three or more hydroxyl moieties in any of the rings of the flavonoid skeleton significantly increases the antiproliferative activity as observed in B16F10 cell cultures [20].

Importantly, the cytotoxicity of almost all polyphenols was either moderate or negligent, except from baicalein and myricetin. These findings are in accordance with other related reports that investigated the cytotoxicity of various flavonoids in HT-29 and Caco-2 colon cancer cell lines [30]. Although lower cytotoxicity of four polymethoxyflavones was reported against normal cells, they demonstrated appreciable antiproliferative effects in LLC-MK2 and C6 tumor cell lines. The investigation of the efficiency of phenolic compounds in the inhibition of cell growth indicated that tangeretin was the most effective flavonoid in B16F10 cells.

## Anticarcinogenic effects of phytochemicals

A number of methods including suppression, blockage, and transformation are currently in practice to control cancer. Suppressing agents stop the initiation, progression, and development of cancers and flavonoids have the potential to act in all these three ways [15]. Flavonoids can act in variety of manner in response to various developmental stages of tumor. These may protect DNA against oxidative damage, inactivate the carcinogens, inhibit the expression of mutagenic genes and enzymes involved in activating procarcinogenic materials, and activate the systems responsible for xenobiotic detoxification [18]. The enzyme inhibition and antiproliferative activities of citrus flavonoids have been extensively investigated in the last decade. A number of studies have investigated and established the structural-functional relationship between flavonoids and their antioxidant, enzyme-inhibition, or antiproliferative activities [65]. Important structural features that may define the flavonoid activity are structure oxidation stage (flavanone, flavone), nature, number, and position of the attached substituent groups in both the A and B ring of the flavonoid structure, and the presence of glycosylation.

## Anti-invasive effects

After tumor initiation, the next major step in cancers is the metastasis, where the cancer cells cross the borders of the primary site and develop new tumors in distant organs. Most of the cancer deaths are caused by metastasis that leads to uncontrollable cancer. Because it has been a matter of serious concern, considerable research is carried out to investigate the mechanisms by which cancers progresses to the metastatic stage. The invasion of neighboring tissues by cancer cells involves several steps, including matrix metalloproteinase (MMP) secretion, migration, invasion, and adhesion. A number of natural products including citrus flavonoids have shown effects in the control or inhibition of metastasis. Here, the anti-invasive role of some flavonoids is discussed.

Secretion of MMPs in numerous cancerous lines has been down-regulated by polymethoxylated flavones (tangeretin and nobiletin), in both *in-vitro* and *in-vivo* models. Another study demonstrated that quercetin inhibits the expression of MMP-2 and MMP-9 in PC-3 prostate cancer cells. Similarly, apigenin exhibits inhibitory effects on the *in-vitro* motility and invasiveness of MO4 mouse cells into embryonic chick heart fragments. Furthermore, luteolin produce strong antimigration and invasion effects in hepatoma HepG2 cells. The application of a number of citrus flavonoids in an experimental *in-vivo* model of pulmonary metastasis indicated significant antimetastatic effects in the melanoma B16F10 cell lines [58]. It has been reported that diosmin reduced vein dispensability at the microcirculation level, thus reinforcing capillary resistance and consequently inhibiting the invasion of tumor cells. This anti-invasion effect is likely facilitated by the ability to restrain the release of inflammation mediators, such as prostaglandins (PGE2) or block the key enzymes in their biosynthesis, thereby modulating the adhesion of leukocytes and preventing endothelial damage.

## Effect of phytochemicals in cardiovascular diseases

Increased level of reactive oxygen species (ROS) has been found to induce various physiological disorders. Among these health problems, cardiovascular diseases are linked to excessive generation of ROS that cause oxidative stress. Elevated levels of vascular superoxide anion production have been found in animal models of hyperlipidemia, hypertension and diabetes. Furthermore, clinical studies have established that hypercholesterolemia and diabetes in humans are also related to increased vascular superoxide anion production. The reported data strongly suggest that augmented oxidative stress influences the pathogenesis of cardiovascular disease.

Antioxidants inhibit ROS generation and attenuate their oxidative effects. Flavonoids possess antioxidative properties, and, therefore, have been recognized to have a greater influence in the vascular system. Oxygen radicals can oxidize LDL, which injures the endothelial wall and thus facilitates the atherosclerotic changes. Several clinical studies have reported that flavonoid intakes can provide protection against coronary heart disease [1]. It has been stated that flavonoids regularly consumed in foods might reduce the risk of death from coronary heart disease in elderly men. It is speculated that flavonoids reduce the risk of coronary heart disease by (1) their effect on capillary fragility, (2) decreasing the platelet aggregation, and (3) preventing LDLs from oxidizing.

**Effect of phytochemical in obesity and diabetes:** In the last two decades, a huge amount of research has been published on curcumin, which revealed that it modulates many regulatory proteins, including those of transcription factors, enzymes, cytokines, and growth factors. Studies have shown that curcumin inhibits a number of signaling pathways and molecular targets involved in inflammation and obesity-related metabolic diseases [36]. Curcumin can inhibit the IKK signaling complex that is responsible for the phosphorylation of IkB, thereby blocking improper activation of NF-kB induced by various inflammatory agents [37]. Anti-obesity effects of curcumin are also linked with the inhibition of inflammatory and angiogenic biomarkers such as COX-2 and vascular endothelial growth factor (VEGF). Curcumin downregulates the expression of various pro-inflammatory cytokines including TNF-a, VEGF, interleukins 1, 2, 6, 8, 12 (IL-1, IL-2, IL-6, IL-8, IL-12) by inactivation of the NF-kB. Studies

have shown that curcumin treatment reduced the tumor-induced overexpression of COX-2 and serum VEGF in HepG2 groups significantly (p\0.001), indicating that curcumin has potential role in angiogenesis [38]. In addition, curcumin has been shown to down-regulate the expression of various NF-kB-regulated proinflammatory adipocytokines including chemokines (such as monocyte chemotactic protein 1, 4 (MCP-1, MCP-4), and eotaxin) [39]. Curcumin was reported as excellent inhibitors of b-catenin/TCF-LEF and hence reduced the b-catenin/TCF signaling, which is closely linked to obesity. This effect is mediated through the inhibition of the GSK-3b, which is responsible for the b-catenin phosphorylation [40]. Recent studies have shown that curcumin-induced suppression of adipogenic differentiation in 3T3-L1 cells is accompanied by activation of Wnt/b-catenin signaling. During differentiation, curcumin restored nuclear translocation of the integral Wnt signalling component beta-catenin in a dose-dependent manner. In parallel, curcumin reduced differentiation-stimulated expression of CK1a, GSK-3b, and Axin, components of the destruction complex targeting b-catenin [41]. Several studies have also demonstrated the antioxidant role of curcumin in obesity. Transcription factors such as AP-1 are activated in response to stress, growth factors, and inflammatory cytokines. Curcumin can inhibit the stress-stimulated activation of AP-1 and has been shown to ameliorate oxidative stress–induced renal injury in mice [42]. Curcumin in the dose of 10 lM prevented the protein glycosylation and lipid peroxidation caused by high glucose levels in erythrocyte cell model. Curcumin inhibited oxygen free radical production caused by high glucose concentrations in a cell-free system and increased glucose utilization in erythrocytes [43]. Numerous studies have indicated that curcumin reduces serum cholesterol concentrations by increasing the expression of hepatic low-density lipoprotein (LDL) receptors, blocks the oxidation of LDL, increased bile acid secretion and metabolic excretion of cholesterol, represses the expression of genes involved in cholesterol biosynthesis, and protects against liver injury and fibrogenesis in animal models [36]. The hypocholesterolemic effect of curcumin was correlated with increase in LDLreceptor mRNA, whereas mRNAs of the genes encoding the sterol biosynthetic enzymes HMG CoA reductase and farnesyl diphosphate synthase were only slightly increased in human hepatoma cell line (HepG2). Although curcumin strongly inhibited alkaline phosphatase activity, an activation of a retinoic acid response element reporter employing alkaline phosphatase secretion was observed [44]. Moreover, curcumin has been identified as a potent inducer of hem oxygenase-1 (HO-1), a redox-sensitive inducible protein via regulation of nuclear factor E2-related factor 2 (Nrf2) and the antioxidant-responsive element (ARE), which provides protection against various forms of stress. Curcumin stimulates HO-1 gene activity through inactivation of the Nrf2–Keap1 complex, leading to increased Nrf2 binding to the resident HO-1 and AREs [45]. The early growth response (Egr-1) gene is a transcription factor that modulates the activity of plasminogen activator inhibitor type-1 that has been associated with insulin resistance and obesity. Curcumin inhibits the expression of the plasminogen activator inhibitor type-1 by reducing the activity of Egr-1 in obesity-related diseases [46]. Several studies have shown that curcumin blocks the leptin signaling by reducing the phosphorylation levels of the leptin receptor (Ob-R) and increases the induction of adiponectin, which improves obesity-associated inflammation [47,48]. These finding support the existence of direct and indirect molecular mechanisms by which curcumin inhibits several inflammatory pathways that are responsible for obesity and obesity-related metabolic diseases.

## Effect of phytochemical in neuroprotection

Sulforaphane is an isothiocyanate present in high amounts in broccoli, brussels sprouts and other cruciferous vegetables. Several studies have reported neuroprotective effects of sulforaphane in animal models of both acute and chronic neurodegenerative conditions. In a rodent model of stroke, sulforaphane administration reduced the amount of brain damage, brain edema and protected retinal pigment epithet [44]. Sulforaphane has been reported to protect cultured neurons against oxidative stress and dopaminergic neurons against mitochondrial toxins [45].

## Hypericin and pseudohypericin

Naphthodianthrones such as hypericin and pseudohypericin are predominant components of Hypericum perforatum. There is strong evidence that hypericin and pseudohypericin contribute to the antidepressant action. Inhibition of monoamine oxidase is one mechanism by which some antidepressants operate to increase levels of neurotransmitters such as serotonin, norepinephrine, or dopamine [46]. This chemical appears to block synaptic re-uptake of serotonin, dopamine, and norepinephrine [47]. Blocking neurotransmitter re-uptake elevates their synaptic concentration. This represents another mechanism by which synthetic antidepressants may operate [47].

## Curcumin

Several beneficial effects of curcumin for the nervous system (at least 10 known neuroprotective actions) have been reported. In an animal model of stroke, curcumin treatment protected neurons against ischemic cell death and ameliorated behavioral deficits [48]. Indeed, accumulating cell culture and animal model data show that dietary curcumin is a strong candidate for use in the prevention or treatment of major disabling age-related neurodegenerative diseases like Alzheimer's, Parkinson's, and stroke. Moreover, curcumin has been shown to reverse chronic stress-induced impairment of hippocampal neurogenesis and increase expression of brain-derived neurotrophic factor (BDNF) in an animal model of depression [48].

## Resveratrol

Resveratrol, a phytophenol present in high amounts in red grapes exhibits antioxidant activity. However, more recent findings shown that resveratrol enters the CNS rapidly following peripheral administration, and can protect neurons in the brain and spinal cord against ischemic injury. Administration of resveratrol to rats reduced ischemic damage to the brain in a model of stroke, and also protected spinal cord neurons against ischemic injury [49]. Resveratrol can protect cultured neurons against nitric oxide-mediated oxidative stress-induced death. Similarly, resveratrol protected dopaminergic neurons in midbrain slice cultures against metabolic and oxidative insults, a model relevant to Parkinson's disease [49]. Resveratrol protected cells against the toxicity of mutant huntingtin in worm and cell culture models [50]. In models relevant to Alzheimer's disease, resveratrol protected neuronal cells from being killed by amyloid β-peptide and promoted the clearance of amyloid β-peptide from cultured cells [51].

### Allium and allicin

Organosulfur compounds, such as the allium and allicin are present in high amounts in garlic and onions, and have been shown to be neuroprotective. In addition to their antioxidant activities, allyl-containing sulfides might activate stress-response pathways, resulting in the upregulation of neuroprotective proteins such as mitochondrial uncoupling proteins [52]. Moreover, allicin activates transient receptor potential (TRP) ion channels in the plasma membrane of neurons. Numerous other phytochemicals also activate TRP channels in neurons, including isothiocyanates, garlic alliums and cannabinoids, resulting in adaptive cellular stress responses [52-65].

## DISCUSSION AND CONCLUSION

Anti-inflammatory effects of phytochemicals are mediated by the modulatory actions on multifaceted cell signalling pathways including inflammatory transcription factors, cytokines, redox status, protein kinases, and enzymes that generally promote inflammation. Imbalance redox status has been reported to be associated with the pathogenesis of chronic disease. Phytochemicals have the ability to correct oxidative stress by modulating redox status and cure various chronic diseases. Based on *in-vitro*, *in-vivo* and human data, this study summarizes the recent knowledge regarding the potential effect of various phytochemicals via cellular transduction pathways and provides an in depth assessment of therapeutic value in the treatment and prevention of various chronic inflammatory diseases.

## REFERENCES

1. Hugli T, Samad F. Torrey Pines Institute for Molecular studies: The Center for Managing Chronic Disease, University of Michigan, 2011.
2. Craig WJ. Health-promoting properties of common herbs. Am J Clin Nutr. 1999;70:491S-499S.
3. Gruenwald J. PDR for herbal medicines. (3rd edn). Montvale, NJ: Thomson PDR; USA, 2004.
4. Kushi LH, Doyle C, McCullough M, Rock CL, Wahnefried WD, Bandera EV, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2012;62(1):30-67.
5. Linus Pauling Institute. Micronutrient Information Center: Phytochemicals. 2012.
6. Setchell KD, Cassidy A. Dietary isoflavones: Biological effects and relevance to human health. J Nutr. 1999;129(3):758S-767S.
7. Wang YH, Chao PD, Hsiu SL, Wen KC, Hou YC. Lethal quercetin-digoxin interaction in pigs. Life Sci. 2004;74(10):1191-1197.
8. Hertog MG, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease. Lancet. 1993;342(8878):1007-1011.
9. Keys A. 1995. Mediterranean diet and public health: Personal reflections. American J Clin Nutri. 1995;61(6):1321-1323.
10. Rahman K. Studies on free radicals, antioxidants, and co-factors. Clin Interv Aging. 2007;2(2): 219-236.
11. Shehzad A, Khan S, Lee YS. Curcumin molecular targets in obesity and obesity-related cancers. Future Oncol. 2012;8(2):179-190.
12. Es-Safi EN, Ghidouche NE, Ducrot P. Flavonoids: Hemisynthesis, reactivity, characterization and free radical scavenging activity. Molecules. 2007;12(9)2228-2258.
13. Nijveldt RJ, Nood E, Hoorn DEC, Boelens PG, Norren K, Leeuwen PA. Flavonoids: A review of probable mechanisms of action and potential applications. Am J Clin Nutr. 2001;74(4):418-425.
14. Guardia T, Rotelli AE, Juarez AO, Pelzer LE. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin, and hesperidin on adjuvant arthritis inrat. Farmaco. 2001;56(9):683-687.
15. Gentile C, Allegra M, Angileri F, Pintaudi AM, Livrea MA, Tesoriere L. Polymeric proanthocyanidins from Sicilian pistachio (Pistacia vera L.) nut extract inhibit lipopolysaccharide-induced inflammatory response in RAW 264.7 cells. Eur J Nutr. 201251(3):353-363.
16. Tinahones FJ, Rubio MA, Sánchez LG, Ruiz C, Gordillo E, Cabrerizo F. Green tea reduces LDL oxidability and improves vascular function. J Am Coll Nutr. 2008;27(2):209-213.
17. Manach C, Scalbert A, Morand C. Polyphenols: Food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727-747.
18. Kaufman P, Duke BJ, Brielmann HA, Boik J, Hoyt JE. A comparative survey of leguminous plants as sources of the isoflavones, genistein and daidzein: Implications for human nutrition and health. J Altern Complement Med. 1997;3(1):7-12.
19. Zand RS, Jenkins DJ, Diamandis EP. Steroid hormone activity of flavonoids and related compounds. Breast Can Res Treat. 2000;62:35-49.
20. Maeda H, Hosokawa M, Sashima T, Funayama K, Miyashita K. Fucoxanthin from edible seaweed, Undaria pinnatifida, shows antiobesity effect through UCP1 expression in white adipose tissues. Biochem Biophys Res Commun. 2005;332(2):392-397.
21. Maeda H, Hosokawa M, Sashima T, Miyashita K. Dietary combination of fucoxanthin and fish oil attenuates the weight gain of white adipose tissue and decrease blood glucose in obese/diabetic KK-Ay mice. J Agric Food Chem. 2007;55(19):7701-7706.
22. Chang HP, Chen YH. Differential effects of organosulfur compounds from garlic oil on nitric oxide and prostaglandin E2 in stimulated macrophages. Nutr. 2005;21(4):530-536.
23. Pelletier JM, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in articular tissues. Semin Arthritis Rheum. 2003;33(3):155-167.
24. Sharangi AB. Medicinal and therapeutic potentialities of tea (Camellia sinensis L.)-A review. Food Res Int. 2009;42(5-6):529-535.
25. Chan EWC, Soh EY, Tie PP, Law YP. Antioxidant and antibacterial properties of green, black, and herbal teas of Camellia sinensis. Pharmacognosy Res. 2011;3(4):266-272.
26. Wang Y, Ho CT. Polyphenolic chemistry of tea and coffee: A century of progress. J Agrc Food Chem. 2009;57(18):8109-8114.
27. Pan MH, Lai CS, Wang H, Lo CY, Ho CT, Li S. Black tea in chemoprevention of cancer and other human diseases. Food Sci Hum Well. 2013;2(1):12-21.
28. Mukhtar H, Ahmad, N. Tea polyphenols: prevention of cancer and optimizing health. Am J Clin Nutr. 2000;71(6 Suppl): 1698S-1702S.
29. Nomura M, Ma W, Chen N, Bode AM, Dong Z. Inhibition of 12-O-tetradecanoylphorbol-13-acetate-induced NF-kappaB activation by tea polyphenols, (–)-epigallocatechin gallate and theaflavins. Carcinogenesis. 2000;21(10):1885-1890.
30. Arent SM, Senso M, Golem DL. The effects of theaflavi enriched black tea extract on muscle soreness, oxidative stress, inflammation, and endocrine responses to acute anaerobic interval training: a randomized, double-blind, crossover study. J Int Soc Sports Nutr. 2010;7:11.

31. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270-278.

32. Ma X, Li Y, Gao FQ, Ye ZG, Lu XJ, Wang HP, et al. Inhibition of superoxide anion-mediated impairment of endothelium by treatment with luteolin and apigenin in rat mesenteric artery. Life Sci. 2008;83(3-4):110-117.

33. Mahadevan S, Park Y. Multifaceted Therapeutic Benefits of Ginkgo biloba L.:Chemistry, Efficacy, Safety, and Uses. J Food Sci. 2008;73(1):R14-R19.

34. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr. 2005;81(1 Suppl):243S-255S.

35. Suzuki J, Isobe M, Morishita R, Nagai R. Tea polyphenols regulate key mediators on inflammatory cardiovascular diseases. Mediators Inflamm. 2009;2009:494928.

36. Faridi Z, Njike V, Dutta Y, Ali AS, Katz DL. Acute dark chocolate and cocoa ingestion and endothelial function: A randomized controlled crossover trial. Am J Clin Nutr. 2008;88(1):58-63.

37. Fimognari C, Lenzi M, Hrelia P. Chemoprevention of Cancer by Isothiocyanates and Anthocyanins: Mechanisms of Action and Structure-Activity Relationship. Curr Med Chem. 2008;15(5):440-447.

38. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54(11):4069-4075.

39. Burdulis D, Ivanauskas L, Dirse V, Kazlauskas S, Razukas A. Study of diversity of anthocyanin composition in bilberry (*Vaccinium myrtillus* L.) fruits. Medicina (Kaunas). 2007;43(12):971-977.

40. Pan MH, Ho CT. Chemopreventive effects of natural dietary compounds on cancer development. Chem Soc Rev. 2008;37(11):2558-2574.

41. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006;71(10):1397-1421.

42. Nobili S, Lippi D, Witort E, Donnini M, Bausi L, Mini E, et al. Natural compounds for cancer treatment and prevention. Pharmacol Res. 2009;59(6):365-378.

43. Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. Nat Rev Cancer. 2007;7(2):139-147.

44. Youssef DT, Yamaki RK, Kelly M. Salmahyrtisol A, a novel cytotoxic sesterterpene from the Red Sea sponge Hyrtios erecta. J Nat Prod. 2002;65(1):2-6.

45. Artali R, Beretta G, Morazzoni P, Bombardelli E, Meneghetti F. Green tea catechins in chemoprevention of cancer: A molecular docking investigation into their interaction with glutathione S-transferase (GST P1-1). J Enzyme Inhib Med Chem. 2009;24(1):287-295.

46. Higginson J. Etiological factors in gastrointestinal cancer in man. J Natl Cancer Inst. 1966;37:527-545.

47. Chen D, Milacic V, Chen MS, Wan SB, Lam WH, Huo C, et al. Tea polyphenols, their biological effects and potential molecular targets. Histol Histopathol. 2008;23:487-496.

48. Baker JA, Boakye K, McCann SE, Beehler G, Rodabaugh KJ, Villella JA, et al. Consumption of black tea or coffee and risk of ovarian cancer. Int J Gynecol Can. 2003;17(1):50-54.

49. Dora I, Arab L, Martinchik A, Sdvizhkov A, Urbanovich L, Weisgerber U. Black tea consumption and risk of rectal cancer in Moscow population. Ann Epidemiol. 2003;13(6):405-411.

50. Tang N, Wu Y, Zhou B, Wang B, Yu R. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer. 2009;65(3):274-283.

51. Goldbohm RA, Hertog MG, Brants HA, Poppel G, Brandt PA. Consumption of black tea and cancer risk: a prospective cohort study. J Natl Cancer Inst. 1996;88(2):93-100.

52. Nakachi K, Suemasu K, Suga K, Takeo T, Imai K, Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. Japanese J Cancer Res. 1998;89(3):254-261.

53. Banerjee S, Manna S, Saha P, Panda CK, Das S. Black tea polyphenols suppress cell proliferation and induce apoptosis during benzo (a) pyrene-induced lung carcinogenesis. European J Cancer Preven. 2005;14(3):215-221.

54. Qanungo S, Das M, Haldar S, Basu A. Epigallocatechin-3-gallate induces mitochondrial membrane depolarization and caspase-dependent apoptosis in pancreatic cancer cells. Carcinogenesis. 2005;26(5):958-967.

55. Khan N, Mukhtar H. Tea polyphenols for health promotion. Life Sci. 2007;81:519-533.

56. Pezzato E, Sartor L, Aica ID, Dittadi R, Gion M, Belluco C, et al. Prostate carcinoma and green tea: PSA-triggered basement membrane degradation and MMP-2 activation are inhibited by (–) epigallocatechin-3-gallate. Int J Cancer. 2004;112(5):787-792.

57. Chung FL, Schwartz J, Herzog CR, Yang YM. Tea and cancer prevention: studies in animals and humans. J Nutr. 2003;133(10):3268S-3274S.

58. Berthold IG, Sachinidis A. Molecular mechanisms explaining the preventive effects of catechins on the development of proliferative diseases. Curr Pharmaceut Design. 2004;10(11):1261-1271.

59. Roy P, Nigam N, George J, Srivastava S, Shukla Y. Induction of apoptosis by tea polyphenols mediated through mitochondrial cell death pathway in mouse skintumors. Cancer Biol Ther. 2008;8(13):1281-1287.

60. Li W, Wu JX, Tu YY. Synergistic effects of tea polyphenols and ascorbic acid on human lung adenocarcinoma SPC-A-1 cells. J Zhejiang Univ Sci B. 2010;11:458-464.

61. Bahorun T, Ramma AL, Gunness TK, Sookar D, Bhoyroo S, Jugessur R, et al. Black tea reduces uric acid and C-reactive protein levels in humans susceptible to cardio vascular diseases. Toxicology. 2010;278(1):68-74.

62. Bahorun T, Ramma AL, Bhujun VSN, Gunness TK, Googoolye K, Auger C, et al. The effect of black tea on risk factors of cardiovascular disease in a normal population. Prev Med. 2012;54(Suppl 1):98-102.

63. Powolny AA, Singh SV. Multitargeted prevention and therapy of cancer by diallyl trisulfide and related Allium vegetable-derived organosulfur compounds. Cancer Lett. 2008;269:305-314.

64. Raghu R, Lu KH, Sheen LY. Recent research progress on garlic as a potential anticarcinogenic agent against major digestive cancers. J Trad Complement Med. 2012;2(3):192-201.

65. Gebhardt R, Beck H. Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. Lipids. 1996;31(12):1269-1276.