

## **Curcumin, resveratrol and flavonoids as anti-inflammatory, cyto-and DNA protective dietary compounds**

Kavita Bisht<sup>1</sup>, Karl-Heinz Wagner<sup>2</sup>, Andrew C. Bulmer<sup>1\*</sup>

<sup>1</sup>Heart Foundation Research Centre, Faculty of Health, Griffith University, Australia

<sup>2</sup>Department of Nutritional Science, Emerging Field Oxidative Stress and DNA Damage, University of Vienna, Austria.

\*Corresponding author: Andrew C. Bulmer

Heart Foundation Research Centre

Faculty of Health, Griffith University

Parklands Drive

4222, Southport, Australia.

Ph: +61(0) 7 55528215

Fax: +61(0)7 55528908

e-mail: [a.bulmer@griffith.edu.au](mailto:a.bulmer@griffith.edu.au)

## **Abstract**

Numerous dietary compounds, ubiquitous in fruits, vegetables and spices have been isolated and evaluated during recent years for their therapeutic potential. These compounds include flavonoid and non-flavonoid polyphenols, which describe beneficial effects against a variety of ailments. The notion that these plant products have health promoting effects emerged because their intake was related to a reduced incidence of cancer, cardiovascular, neurological, respiratory, and age-related diseases. Exposure of the body to a stressful environment challenges cell survival and increases the risk of chronic disease developing. The polyphenols afford protection against various stress-induced toxicities through modulating intercellular cascades which inhibit inflammatory molecule synthesis, the formation of free radicals, nuclear damage and induce antioxidant enzyme expression. These responses have the potential to increase life expectancy. The present review article focuses on curcumin, resveratrol, and flavonoids and seeks to summarize their anti-inflammatory, cytoprotective and DNA protective properties.

**Key words: nutrition, polyphenols, chronic illness, anti-inflammatory, haem oxygenase, cytoprotective, DNA protection**

## **1. Introduction**

Organisms are continually exposed to various stresses derived from natural and chemical sources. These cellular stresses disturb cellular and systems homeostasis and can, if disturbed chronically, contribute to the onset of cardiovascular, neurodegenerative, respiratory diseases in addition to cancer and stroke. The social and economic costs of these diseases are devastating, affecting the lives of millions of persons world-wide, each year (Bengmark et al., 2009). Cytotoxins mechanisms of action include the activation of inflammatory pathways, release of reactive oxygen species (ROS), formation of DNA-adducts, and inhibition of cytoprotective proteins. An understanding of the toxicological mechanisms and identification of dietary substances that can protect from cytotoxicity will continue to reduce the burden of disease in future. Reducing the burden of disease could be achieved by providing the general population with easily accessible and relatively inexpensive foods with health benefits.

In recent years, the use of natural plant products has attracted increased attention among clinicians and the public for the prevention/treatment of various chronic diseases. Consumption of natural products reduces the risk of developing pathological conditions, including cancer, nervous system disorders, cardiovascular, genetic, and inflammatory diseases (Jurenka, 2009; Newman and Cragg, 2007). Plants contain numerous bioactive molecules that can improve the body's resistance to cellular stress and prevent the cytotoxicity of various agents. Among them, polyphenols such as curcumin, resveratrol (non-flavonoids), and flavonoids have received much attention for their ability to reduce cellular stress-induced injury (Mattson et al., 2007). These polyphenols inhibit toxin-mediated stress responses via their anti-inflammatory and antioxidant

properties in addition to inducing the expression of cytoprotective proteins (Aggarwal and Sung, 2009; Di Carlo et al., 1999; Shakibaei et al., 2009).

In this review, we present an overview of the anti-inflammatory, cyto-protective, and DNA-protective properties of curcumin, resveratrol, and flavonoids.

## **2 Curcumin**

Curcumin (diferuloylmethane; Fig. 1) is a bright yellow compound found in turmeric, which is derived from the rhizomes of the plant *Curcuma longa* Linn, a perennial herb of the Zingiberaceae family (Ammon and Wahl, 1991). Curcumin is comprised of curcumin I (94%), curcumin II (6%), and curcumin III (0.3%). Curcumin is a lipophilic polyphenol that is insoluble in water (Ruby et al., 1995). Table 1 summarises the most important findings presented in this section.

### **2.1 Anti-inflammatory properties**

Curcumin mitigates inflammatory responses by inhibiting cyclooxygenase-2 (COX-2), lipoxygenase, nuclear factor (NF)-kappa B, inducible nitric oxide synthase, and nitrite oxide (NO) production in lipopolysaccharide-, IFN- $\gamma$ -, or TNF- $\alpha$ -activated macrophages and NK cells (Bhaumik et al., 2000; Brouet and Ohshima, 1995; Surh et al., 2001). NF-kappa B is sequestered by inhibitor KappaB (*I*kB) $\alpha$  intercellularly (Karin, 1999). Curcumin inhibits the NF-kappa B activation in a TNF- $\alpha$ , phorbol 12-myristate 13-acetate (PMA)-, or H<sub>2</sub>O<sub>2</sub>-stimulated human myelomonoblastic cell line (ML-1a) by preventing the phosphorylation and degradation of *I*kB $\alpha$  (Singh and Aggarwal, 1995). PMA is an activator of protein kinase C (PKC), which is a regulator of cell proliferation and survival. In addition to PMA, TNF- $\alpha$  and LPS also activate

PKC, which subsequently activates NF-kappa B (Holden et al., 2008). Thus, curcumin may attenuate NF-kappaB activation by inhibiting PKC (Singh and Aggarwal, 1995). The anti-inflammatory effects of curcumin are partly mediated via inhibition of the transcription factor NF-kappa B and activator protein (AP)-1. Together, AP-1 and NF-kappaB act synergistically and may promote tumor progression. Treatment of glioma cells with 25  $\mu$ M curcumin decreases AP-1 and NF-kappa B binding (Dhandapani et al., 2007). Curcumin also suppresses the activation of AP-1 in TNF- $\alpha$  activated bovine aortic endothelial cells (BAECs) (Bierhaus et al., 1997; Xu et al., 1997). The release of pro-inflammatory cytokines from activated immune cells plays an important role in the inflammatory response. Curcumin exerts inhibitory effects on the expression of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, and IFN- $\gamma$ - by LPS- or PMA-stimulated splenic lymphocytes, monocytes, macrophages, and dendritic cells (Abe et al., 1999; Gao et al., 2004; Kim et al., 2005). Cell adhesion molecules are important for adhesion of T cells to antigen presenting and endothelial cells and play a prominent role in inflammation. Pre-treatment with curcumin blocked the adhesion of monocytes to endothelial cells and down-regulated expression of intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and endothelial leukocyte adhesion molecule (ELAM)-1 by interfering with NF-kappa B activation in TNF-stimulated human umbilical vein endothelial cells (HUVEC)(Kumar et al., 1998).

## **2.2 Cyto-protective effects**

Curcumin and its analogues ameliorate cytotoxicity induced by various kinds of toxins. Curcumin is generally cytoprotective, however, can also be cytotoxic in paracetamol treated rat hepatocytes. Low concentrations of curcumin reduce paracetamol-mediated lipid peroxidation,

without affecting lactate dehydrogenase (LDH; a marker of cell membrane rupture) leakage and glutathione depletion (GSH). On the contrary, at 100 times higher concentration curcumin increased LDH leakage and promoted glutathione depletion, however, still protected the cells from lipid peroxidation (Donatus et al., 1990). Thus, despite protecting from lipid peroxidation, curcumin may promote paracetamol mediated cytotoxicity by elevating the LDH-leakage and reducing GSH levels. Curcumins cyto-protective effects may be attributed to its potent antioxidant activity. However, curcumin is conjugated to GSH, thereby reducing the intercellular GSH pool, which may increase LDH-leakage by reducing the concentration of this important thiol containing compound (Donatus et al., 1990).

Curcumin also attenuates inflammatory responses in acute or chronic inflammatory disease conditions. In rats suffering from carrageenan-induced oedema, curcumin treatment significantly reduced inflammation (Rao et al., 1982; Srivastava and Srimal, 1985). Curcumin also inhibited the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and arachidonic acid (AA)-induced inflammation in mouse skin epidermis (ear oedema; Huang et al., 1991). Curcumin administration to rats prior to arthritis induction mitigated joint inflammation (Funk et al., 2006). In another study, a curcumin dosage of 1200 mg daily to patients suffering from rheumatoid arthritis reduced inflammatory symptoms (Deodhar et al., 1980). Curcumin also inhibits cerulean- and ethanol-induced pancreatitis (Gukovsky et al., 2003). Daily doses of curcumin (550 mg twice/day) to patients with inflammatory bowel diseases also ameliorated the patients inflammatory symptoms (Holt et al., 2005). Administration of curcumin (375 mg) daily for 12 weeks to patients with anterior uveitis showed complete symptomatic recovery. Improvements were observed in visual acuity and aqueous flare and were accompanied by a decrease in keratic precipitates (Lal et al., 1999).

In shiga toxin (Stx) 1 or 2 treated human proximal tubule cells (HK-2), curcumin attenuated the detrimental effects of Stx 1 and 2, increasing cell viability, reducing the necrotic cell population, lowering DNA fragmentation and elevating the expression of molecular chaperone HSP 70 (Sood et al., 2001). In another study, co-administration of curcumin with H<sub>2</sub>O<sub>2</sub> significantly reduced the H<sub>2</sub>O<sub>2</sub>-induced oxidative stress in neuroblastoma-glioma hybrid cell line (NG108-15). However, pre-treatment with curcumin before H<sub>2</sub>O<sub>2</sub> challenge did not protect NG108-15 cells from oxidative damage (Mahakunakorn et al., 2003).

1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>)-induced cytotoxicity and apoptosis in rat pheochromocytoma (PC12) cells were suppressed by curcumin. Curcumin enhanced the level of Bcl-2, alleviated the loss of mitochondrial membrane potential, blocked the release of reactive oxygen species and the expression of iNOS in MPP<sup>+</sup>-stimulated PC12 cells (Chen et al., 2006a). Pre-incubation with curcumin at 50-200 nM significantly reduced ethanol-mediated oxidative stress in HT22 hippocampal cells through inhibition of mitogen-activated protein kinase (MAPK) pathways and activation of MAPK phosphatases (MKPs)-1. Incubation of HT22 cells with curcumin led the dose dependent phosphorylation of MKP-1 which in turn inactivated MAPK pathways (Pae et al., 2009). MAPKs play an important role in cell proliferation, differentiation, stress responses, apoptosis and immune defense. A number of proteins are known to deactivate MAPKs, including tyrosine, serine/threonine and dual specificity phosphatases (Wang and Liu, 2007). In mammalian cells, the dual-specificity phosphatases, which are known as MKPs, are the primary phosphatases responsible for dephosphorylation/deactivation of MAPKs. MKP-1 is one of the MAPK-specific dual-specificity phosphatases and has been extensively studied (Boutros et al., 2008; Wang and Liu, 2007). MKP-1 dephosphorylates both phosphotyrosine and phosphothreonine residues of MAPKs and is regarded as an important

feedback control mechanism (Wang and Liu, 2007). Therefore, up-regulation of MKP-1 in HT22 cells by curcumin during ethanol stimulation may have a cyto-protective, anti-apoptotic effect (Pae et al., 2009).

Haem oxygenase (HO)-1 is an antioxidant phase 2 enzyme that degrades haem to carbon monoxide, iron and biliverdin. Curcumin induces HO-1 expression and activity. HO-1 has been suggested to be an important therapeutic target in various disease models (Ryter et al., 2006; Soares and Bach, 2009). Curcumin at 5-25  $\mu\text{M}$  significantly enhanced the expression of HO-1 protein in rat astrocytes and neurons through activation of the transcription factor nuclear factor-E2-related factor (Nrf2). In addition, pre-incubation with curcumin protected the neurons from glucose oxidase-mediated cell death (Scapagnini et al., 2006). Curcumin and its constituents induced HO-1 expression in MIN6 cells, a mouse  $\beta$  pancreatic cell line. The induction of HO-1 by curcumin is influenced by transcription factor Nrf2 and phosphatidylinositol 3-kinase (PI3-kinase)/Akt-mediated signaling. Curcumin also augmented the mRNA levels of two important phase 2 enzymes: GCLM and NQO1, which are involved in the synthesis of glutathione and detoxification of quinones respectively (Pugazhenti et al., 2007).

### **2.3 DNA-protective properties**

Curcumin at low doses (up to 5  $\mu\text{g}/\text{mL}$ ) is anti-genotoxic but at high doses (more than 8  $\mu\text{g}/\text{mL}$ ) can cause genotoxicity (Antunes et al., 1999; Cao et al., 2007; Mendonca et al., 2009). Curcumin (10  $\mu\text{g}/\text{mL}$ ) induced mutagenic changes and potentiated doxorubicin and gamma radiation-mediated chromosomal aberrations in Chinese hamster ovary cells (Antunes et al., 1999; Araujo et al., 1999). Curcumin alone at 8 and 16  $\mu\text{g}/\text{mL}$  enhanced micronucleus (MN) formation and at doses higher than 8  $\mu\text{g}/\text{mL}$  and increased the frequency of chromosomal

aberrations in human hepatoma G2 (HepG2) cells. On the contrary, pre-treatment of curcumin at a low dose (2 µg/mL) significantly decreased the cyclophosphamide (CPA)-induced MN formation in HepG2 cells (Cao et al., 2007). Pre-treatment of curcumin at low concentrations (1-5 µg/mL) alleviated the increased frequency of MN induced by cisplatin (cDDP) in PC12 cells but at high dose (10 µg/mL, alone) it significantly augmented the MN frequency. At doses greater than 16 µg/mL, curcumin caused a reduction in cell viability (Mendonca et al., 2009). Ingestion of a curcumin containing diet ameliorated DNA damage in a transgenic mouse model of Alzheimer's disease (AD) showing a 10 fold reduction in buccal MN frequency. Furthermore, these AD mice had a 2 fold increase in buccal cell and brain telomere length compared to AD control group (Thomas et al., 2009).

### **3 Resveratrol**

Resveratrol (3, 4', 5-trihydroxystilbene, Fig. 1) is a white powder with yellow cast and a polyphenolic phytoalexin found in grapes, red wine, mulberries, pines, peanuts, and other plant derived products (Burns et al., 2002; Delmas et al., 2006; Ibern-Gomez et al., 2000). Resveratrol has two phenolic rings linked by a styrene double bond and it exists in two isoforms, *trans* and *cis*. The *trans*-isomer is more stable than *cis*-isomer (Shakibaei et al., 2009). Table 2 summarises findings of the most important investigations presented in this section.

#### **3.1 Anti-inflammatory effects**

Resveratrol is a potent inhibitor of inflammatory molecules. The anti-inflammatory properties of resveratrol are associated with inhibition of NF-kappa B in LPS-, TNF- $\alpha$ -, or PMA-mediated macrophages, dendritic, myeloid (U-937), Jurkat, and epithelial (HeLa) cells (Gao et al., 2001;

Manna et al., 2000). Resveratrol inhibits NF-kappa B activation by inhibiting I $\kappa$ B kinase (Holmes-McNary and Baldwin, 2000). Resveratrol also inhibits the expression of iNOS and COX-2 in cytokine (TNF- $\alpha$ , IL-1 $\beta$ , or IFN- $\gamma$ )-stimulated human primary airway epithelial cells (Donnelly et al., 2004) and blocks COX-2 transcription in PMA-stimulated human mammary epithelial cells (Subbaramaiah et al., 1998). Resveratrol significantly suppresses the secretion of TNF- $\alpha$  and nitric oxide in LPS-stimulated rat cortical microglia and N9 microglial cells (Bi et al., 2005) and also inhibits the production of TNF- $\alpha$ , IL-1, IL-6, IL-12 and IFN- $\gamma$  by splenic lymphocytes and macrophages (Gao et al., 2001; Kowalski et al., 2005). Resveratrol also exhibits strong anti-inflammatory activity in *in vivo* C5 anaphylatoxin (C5a)-mediated inflammation (Issuree et al., 2009). Pre-incubation with resveratrol (10-40  $\mu$ M) abrogated the release of inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and MIP-1 $\alpha$ ) from C5a-stimulated human and mouse neutrophils. Further, resveratrol treatment inhibited C5a-induced oxidative burst (superoxide anion production), release of  $\beta$ -glucuronide (responsible for neutrophil degranulation) and ERK-phosphorylation (Issuree et al., 2009). Additionally, resveratrol inhibits C5a-stimulated neutrophil migration/recruitment, and production of inflammatory cytokines in a mouse model of C5a-induced acute peritonitis (Issuree et al., 2009).

Resveratrol shows inhibitory effects on the expression of cell adhesion molecules. Resveratrol attenuated the IL-6 induced expression of ICAM-1 in endothelial cells (ECs; Wung et al., 2005) and also inhibited *Porphyromonas gingivalis* LPS-induced endothelial dysfunction in human microvascular endothelial cells (HMECs; Park et al., 2009). Furthermore, it blocked the expression of adhesion molecules, ICAM-1 and VCAM-1 on HMECs by inhibiting NF-kappa B activation (Park et al., 2009).

### 3.2 Cyto-protective effects

A growing body of research show that resveratrol exerts potent cyto-protective activity. Resveratrol incubation protected cultured hippocampal neurons from NO induced neurotoxicity (Bastianetto et al., 2000). The addition of resveratrol (15-40  $\mu$ M) to rat hippocampal cells abolished  $\beta$ -amyloid-induced toxicity through activation of protein kinase C (Han et al., 2004). In mid-brain slice cultures, concurrent treatment of resveratrol with neurotoxins such as 1-MPP<sup>+</sup>, sodium azide, thrombin, and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) significantly protected dopaminergic neurons from these neurotoxins. In addition, resveratrol inhibited the MPP<sup>+</sup>-induced glutathione depletion and suppressed the MNNG-induced release of acetylated P<sup>53</sup> levels (Okawara et al., 2007).

Incubation of rat aortic smooth muscle cells (ASMCs) with resveratrol at 25, 50, and 100  $\mu$ M for 24, 48, and 72 h significantly increased cellular antioxidants and phase II enzymes including superoxide dismutase (SOD), catalase, GSH, glutathione reductase (GR), glutathione peroxidase (GPx), glutathione S-transferase (GST), and NAD(P)H:quinone oxidoreductase-1 (NQO1) in a concentration and/or time-dependent fashion (Li et al., 2006). Resveratrol also elevated the mRNA levels of catalase, GSTA1, and NQO1. Moreover, pre-treatment with resveratrol protected against xanthine oxidase (XO)/xanthine induced cytotoxicity, increasing cell viability and reducing the intracellular accumulation of reactive oxygen species (Li et al., 2006). Resveratrol treatment also prevents apoptosis in embryonic rat cardiomyocytes exposed to ischemia. The anti-apoptotic effect of resveratrol in cardiomyocytes is mediated by the sirtuin 1-forkhead transcription factor 1 (SIRT1-FOXO1) pathway. The exposure of cardiomyocytes to resveratrol (20  $\mu$ M) under ischemic conditions elevated the expression of SIRT1 but reduced the

expression of FOXO1 (Chen et al., 2009). SIRT1 is responsible for cell defense and survival in response to oxidative stress (Brunet et al., 2004; Motta et al., 2004). FOXOs mediate the transcription of genes involved in the oxidative stress response, DNA-repair, cell cycle arrest, and apoptosis (Birkenkamp and Coffey, 2003; Van Der Heide et al., 2004). SIRT1 differentially affects FOXOs functions, stimulating FOXOs effects on cell cycle arrest and expression of DNA-repair genes but inhibiting FOXOs effects on apoptosis in the presence of stress stimuli. Therefore, decreased FOXO1 expression by resveratrol under ischemic conditions is mediated by activation of SIRT1 (Chen et al., 2009), leading to cyto-protection.

Epidemiological studies show that consumption of a resveratrol rich diet is related to a reduction in the risk of cardiovascular diseases in segments of the French population. This is despite of their regional consumption of high fat and high cholesterol diets and smoking habits and is referred to as the phenomenon of the French paradox (Gordon, 1996; Renaud and de Lorgeril, 1992). Resveratrol is effective against *in vivo* and *in vitro* cigarette smoke-induced vascular oxidative stress and inflammation and prevents smoking-induced expression of reactive oxygen species and inflammatory markers such as ICAM-1, iNOS, TNF- $\alpha$ , IL-1  $\beta$ , IL-6, NF-kappa B in rat arteries and cultured coronary arterial endothelial cells (CAECs; Csiszar et al., 2008). These protective effects of resveratrol are mediated through the activation of SIRT1. In addition, resveratrol significantly protected endothelial cells against cigarette smoke extract-induced DNA damage (Csiszar et al., 2008). Resveratrol (40  $\mu$ M) also protects HepG2 cells from triglyceride accumulation induced by a high fat diet (palmitate) by enhancing the expression of SIRT1 and FOXO1 and reducing sterol regulatory element binding protein1 (SREBP1) expression (Wang et al., 2009). Pre-treatment of resveratrol rescued the rat endothelial cells and arteries against TNF- $\alpha$ , ox-LDL, and H<sub>2</sub>O<sub>2</sub>-induced apoptotic cell death via inhibition of caspase-3/7 activity and

elevation of antioxidant enzymes (catalase and GPx). Resveratrol also has been shown to attenuate UV-induced DNA damage (Ungvari et al., 2007). Dietary administration of resveratrol (1 mg/kg/day) to rats prior to or with dextran sulphate sodium (DSS; induces intestinal inflammation, diarrhea and bloody stools) for 20 days ameliorated DSS-induced symptoms such as colon shortening, degradation of colon wall structure and changes in haematological parameters (lower levels of red blood corpuscles (RBCs), haemoglobin (Hb), haematocrit (HCT)). Additionally, DSS-stimulated an increase in COX-2, NO, prostaglandins, and prostaglandin E synthase protein (PTGES) levels in the colonic mucosa, which was reduced by resveratrol treatment (Larrosa et al., 2009).

Oral administration of resveratrol to streptozotocin (STZ) treated rats led to significant decrease in blood glucose level and improved myocardial function. Resveratrol exerted angiogenic actions by enhancing the expression of HO-1, thioredoxin (Trx-1), vascular endothelial growth factor (VEGF), and endothelial nitric oxide synthase (eNOS). Additionally, resveratrol protects cardiomyocytes from ischemia/reperfusion injury through an increase in MnSOD activity (Thirunavukkarasu et al., 2007). Resveratrol also induces the expression of HO-1 in a concentration-dependent manner. Treatment of human ASMCS with low concentrations ( $\leq 10$  mM) of resveratrol increased HO-1 expression and promoter activity whereas higher concentrations ( $\geq 20$  mM) of resveratrol showed the reverse. Resveratrol appears to regulate HO-1 induction through the NF-kappa B pathway. At low concentrations (1-10 mM) resveratrol enhanced the NF-kappa B binding activity, however, concentrations greater than 20 mM blocked the NF-kappa B binding activity (Juan et al., 2005).

### 3.3 DNA-protective effects

Concurrent treatment of resveratrol with 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) or estradiol exposed MCF-10 F cells inhibited the estrogen metabolism and DNA-adduct formation. TCDD-induced expression of CYP1B1 was decreased in the presence of resveratrol (Lu et al., 2008). Benzo( $\alpha$ )pyrene induced sperm DNA damage and cell death which were prevented by concomitant treatment with resveratrol. Resveratrol inhibited the B $\alpha$ P-diol-epoxide (BPDE) adduct formation in sperm DNA and apoptotic and necrotic cell death (Revel et al., 2001). In another study, daily oral administration of resveratrol (8 mg/kg) with 1, 2-dimethylhydrazine (DMH) for 30 weeks protected rat leukocytes from DMH-induced DNA damage and oxidative stress, decreasing comet attributes and up-regulating the level of antioxidant enzymes (catalase, SOD, GR, GPx, and GST (Sengottuvelan et al., 2009). Formation of ROS may contribute to DNA damage, which is typified by the release of base oxidation products. 8-oxo-7,8-dihydro-2'-deoxyguanosine (oxo8dG) is one of the base oxidation products, resulting from C-8 hydroxylation of guanine residues. The ratio of oxo8dG to an undamaged nucleoside, deoxyguanosine, is a biomarker for oxidative DNA damage (Floyd, 1990). Resveratrol protected from potassium bromate (KBrO<sub>3</sub>; renal carcinogen that promotes free radical formation) induced DNA damage by decreasing the level of kidney oxo8dG (Cadenas and Barja, 1999). Resveratrol also inhibited advanced glycation end-product (AGEs; promotes free radical formation)-induced oxidative DNA damage, decreasing the level of vascular smooth muscle cell (VSMC) oxo8dG in stroke-prone rats (Mizutani et al., 2000). However, combined treatment of resveratrol with UVA

exposure promoted the formation of oxo8dG, DNA strand breaks and cell death in HaCa T human keratinocytes (Seve et al., 2005).

## **4 Flavonoids**

Flavonoids are ubiquitous polyphenolic compounds comprised of several classes including flavonols, flavanones, flavanols, isoflavones and flavans (Manach et al., 2004). Many flavonoids possess anti-inflammatory, anti-viral, antioxidant and anti-carcinogenic properties (Di Carlo et al., 1999; Middleton et al., 2000; Riboli and Norat, 2003). Table 3 summarises findings of the most important investigations discussed in this section.

### **4.1 Anti-inflammatory effects**

Apigenin (4', 5, 7-trihydroxyflavone) is found in parsley and celery and possessed strong anti-inflammatory effects. Apigenin down-regulated the expression of IL-1 $\beta$  and TNF- $\alpha$  in LPS-stimulated mouse macrophages and human monocytes (Kowalski et al., 2005; Nicholas et al., 2007). Moreover, pre-treatment with apigenin before LPS exposure significantly mitigated serum TNF levels and protected mice from LPS-induced toxicity. Apigenin also blocked the secretion of IL-8 in LPS-stimulated cells (Nicholas et al., 2007). Apigenin has been reported as the most potent inhibitor of COX-2 and iNOS expression in LPS-stimulated mouse macrophages (Liang et al., 1999) and suppresses inflammatory responses through inactivation of NF-kappa B (Liang et al., 1999; Nicholas et al., 2007). It also attenuates neutrophil and lymphocyte adhesion to endothelial cells and adhesion of monocytes to HUVECs, by regulating the expression of ICAM and VCAM (Gerritsen et al., 1995; Lee et al., 2007).

Genistein (4', 5, 7-Trihydroxyisoflavone; Fig 1) is found in soy bean and related products. Genistein suppressed LPS-induced TNF- $\alpha$  and IL-6 production in mouse macrophages (Calixto et al., 2004) and blocked the secretion of TNF- $\alpha$  and IL-1 $\beta$  in phytohemagglutinin-stimulated macrophages (Kesharwani and Sodhi, 2007). LPS-induced expression of COX-2 and iNOS by mouse macrophages was down-regulated by genistein treatment (Liang et al., 1999).

Other flavonoids such as luteolin, kaempferol, and quercetin (see Fig. 1) also have demonstrated anti-inflammatory potential. Luteolin (3', 4', 5, 7-tetrahydroxyflavone) isolated from *Lonicera japonica* inhibited the LPS induced release of TNF- $\alpha$ , IL-6, and NO by macrophages (Park et al., 2005; Xagorari et al., 2001). Luteolin, at 5-25  $\mu$ M, significantly decreased the LPS-induced secretion of INF- $\gamma$ , IL-6, COX-2, and iNOS in alveolar macrophage and peripheral macrophage RAW 264.7 cell lines. This anti-inflammatory action was accompanied by the suppression of NF-kappa B, I $\kappa$ B degradation, and AP-1 in LPS-activated macrophages (Chen et al., 2007). Luteolin inhibits carrageenan-induced paw oedema in rats receiving luteolin orally. Moreover, luteolin at 10 and 50 mg/kg significantly blocked COX-2 expression (Ziyan et al., 2007). Luteolin suppressed PMA-induced oedema in mice and also reduced the LPS-induced expression of ICAM-1 (Calixto et al., 2004).

Kaempferol (3', 4', 5, 7-tetrahydroxyflavone) and quercetin (3, 3', 4', 5, 7-pentahydroxyflavone) are flavonols, commonly found in broccoli, tea, onions, apples, and leafy green vegetables. Kaempferol at 5, 10, and 20  $\mu$ M inhibited the TNF- $\alpha$  -induced production of IL-6 in mouse osteoblasts in a dose-dependent manner (Pang et al., 2006). Kaempferol and quercetin have been reported to reduce the activity of iNOS and COX-2 by suppressing the signalling of STAT-1, NF-kappa B and AP-1 in LPS- or cytokine-stimulated macrophages and HUVECs (Crespo et al.,

2008; Hamalainen et al., 2007). Strong inhibitory effects on adhesion molecules (VCAM, ICAM-1, and E-selectin) expression were observed in kaempferol treated human endothelial cells (Crespo et al., 2008). Quercetin attenuated the expression of pro-inflammatory cytokines in PMA and calcium ionophore (PMACI)-stimulated mast cells and suppressed the TNF- $\alpha$  induced recruitment of NF-kappa B to pro-inflammatory gene promoters in murine epithelial intestinal cells (Park et al., 2008; Ruiz et al., 2007). Quercetin reduced the PMA- or TNF- $\alpha$ -mediated expression of ICAM-1 in human endothelial cells (Kobuchi et al., 1999). Kaempferol and quercetin also inhibit LPS-induced nitrite oxide and NF-kappa B production in mice (Liang et al., 1999).

#### **4.2 Cyto-protective effects**

Flavonoids enhance survival against cytotoxic compound exposure. Pre-incubation of cardiomyocytes with flavonoids abolished doxorubicin-induced oxidative stress (Psotova et al., 2004). Pre-treatment with genistein afforded a marked protection against IL-1 $\beta$  and IFN- $\gamma$ -mediated cytotoxicity in rat insulinoma cells (RINm5F) and rat pancreatic islets. Genistein inhibits cytokine-induced cell death, NO production, iNOS expression, and NF-kappa B through the suppression of extracellular signal-regulated kinase (ERK)-1/2 phosphorylation. Genistein also blocked the cytokine-induced phosphorylation of STAT proteins (Kim et al., 2007). Epidemiological research suggests that consumption of soy containing foods may reduce the risk of breast cancer (Messina et al., 1994). Experimental studies have found that the soy isoflavone genistein is in part responsible for cancer prevention because of its strong affinity for oestrogen receptors (ERs; Messina et al., 1994). Genistein competes with oestrogens in binding estrogens receptors (ERs) and regulates oestrogen-regulated gene expression (Markiewicz et al., 1993).

Genistein also acts synergistically with tamoxifen (TAM) (chemotherapeutic for oestrogen receptor positive (ER<sup>+</sup>) breast cancer; (Fisher et al., 1996)) in treating breast cancer. Genistein alone or with TAM inhibited the growth of ER<sup>+</sup>/HER2 (human epidermal growth factor receptor2)-overexpressing BT-474 human breast cancer cells. The HER2 gene is associated with TAM resistance (Mai et al., 2007). Genistein (3.125, 6.25, 12.5, and 25 µM) treatment increased the cell population in the G1 phase. The combination of genistein and TAM showed even greater G1 arrest. DNA ladder (characteristic of apoptosis) formation was observed in BT-474 cells following genistein or the genistein and TAM combination. The inhibition apoptotic protein, also named survivin, was down-regulated by the combined treatment of genistein and TAM in both its mRNA and protein expression. Therefore, supplementation of genistein with TAM may improve the efficacy of TAM on prevention and/or treatment of ER<sup>+</sup> and HER2-overexpressing breast malignancies (Mai et al., 2007). Apart from being an estrogen receptor agonist, genistein also inhibits tyrosine kinase activity via interaction with its ATP-binding site (Akiyama et al., 1987). That tyrosine kinase activity is greater in smooth muscle than in skeletal or cardiac muscle suggests that tyrosine kinases regulate smooth muscle contraction, cellular growth, proliferation, and secretory activities (Di Salvo et al., 1997). Injection of ovariectomized spontaneously hypertensive rats (SHR; estrogen deficient) with a low-dose (2.5 mg/kg) of genistein for two days reduced renal artery contraction and aortic tyrosine phosphorylation (Nevala et al., 2002). However, daily administration of the same dose for two weeks showed no effect. Further, both treatment regimes attenuated angiotensin II and noradrenaline-induced smooth muscle contraction in rats (Nevala et al., 2002). Angiotensin II stimulation activates tyrosine kinases such as focal adhesion kinases, janus kinases, the receptor kinases, epidermal growth factor and platelet derived-growth factor. Therefore, angiotensin II-regulated tyrosine

kinases seem to be required for angiotensin II-mediated vasoconstriction (Berk, 1999). The noradrenaline-induced contractions activate tyrosine kinases in rat aortic (Abebe and Agrawal, 1995) and pulmonary artery smooth muscle (Savineau et al., 1996) *in vitro*. Thus, inhibition of angiotensin II and noradrenaline by the low-dose genistein treatment for two days may be due to inhibition of tyrosine kinases by genistein (Nevala et al., 2002). Genistein at a higher concentration ( $> 1 \mu\text{M}$ ) binds to and transactivates peroxisome proliferator-activated receptor (PPAR)- gamma (transcriptional factor for adipogenesis; (Dang et al., 2003). Incubation with genestein shows biphasic effects on osteogenesis and adipogenesis in KS483 and mouse bone marrow cells. Genestein at  $0.1\text{-}10 \mu\text{M}$  stimulates alkaline phosphate (ALP) activity, nodule formation, and catalase deposition (characteristics of osteogenesis), while at concentrations of  $>25 \mu\text{M}$  showed the reverse. Incubation with genestein ( $0.1\text{-}1 \mu\text{M}$ ) decreased the number of adipocytes, while a concentration  $>10 \mu\text{M}$  stimulated adipogenesis (Dang et al., 2003). It is suggested that at lower concentration, genistein has ER-dependent effects on osteogenesis and adipogenesis but at higher concentrations, genistein has an anti-estrogenic effect due to activation of PPAR-gamma (Dang et al., 2003).

Flavonoids such as (-)-epigallocatechin gallate and quercetin protect human umbilical vein endothelial cells (HUVEC) from  $\text{Cu}^{2+}$ -oxidized LDL and  $\text{H}_2\text{O}_2$ -induced cytotoxicity. These flavonoids attenuated oxidative stress-induced apoptosis, nuclear condensation and fragmentation, expression of Bax-2 and caspase-3 cleavage but restored the expression of Bcl-2 protein in endothelial cells (Choi et al., 2003; Jeong et al., 2005). Supplementation of quercetin to peritoneal dialysis fluid treated mesothelial cells blocked the LDH release and restored the cell viability (Riesenhuber et al., 2007). Pre-treatment with quercetin protected the rat pancreas in response to STZ administration. The STZ-mediated increase in NO level, malondialdehyde

(MDA), and decrease in antioxidant enzyme activity were prevented by daily treatment with quercetin (15 mg/kg/day) for 4 weeks (Coskun et al., 2005).

Flavonoids may act as pro-oxidants at increased concentrations. Quercetin at concentrations  $\geq 100 \mu\text{M}$  cause cytotoxicity in rat aortic smooth muscle cells, producing reactive oxygen species, inducing apoptosis, increasing the phosphorylation of the p38 and JNK pathway, and enhancing the binding activity of NF-kappa B (Shih et al., 2004).

Flavonoid mediated cytoprotection is purportedly due to the induction of HO-1. Kaempferol and quercetin inhibit LPS-mediated inflammatory signals in RAW 264.7 cells by inducing HO-1 expression. The cytoprotective effects of flavonoids were inhibited by pre-treatment of the cells with tin protoporphyrin, a HO inhibitor. Additionally, the flavonoid treated cells showed an increase in bilirubin production (Lin et al., 2003). Bilirubin, which is derived from biliverdin, is the end product of haem catabolism. Bilirubin is a potent antioxidant present in human extracellular fluid and may reduce the risk of cardiovascular disease (CVD) by delaying the copper induced oxidation of lipids (Bulmer et al., 2008). That flavonoids increase bilirubin production may suggest that their mechanism of protection is mediated via bilirubins antioxidant capacity. Kaempferol treatment provided protection to PC12 cells against low serum or serum deprivation-induced cell death. Pre-treatment of kaempferol abrogated  $\text{H}_2\text{O}_2$ -mediated oxidative stress by expressing an elevated level of HO-1 protein. The ERK pathway was activated in these kaempferol treated PC 12 cells (Hong et al., 2009). Quercetin abolished the  $\text{H}_2\text{O}_2$ -induced apoptotic changes, elevation in intracellular peroxide levels, phosphorylation of ERK, and expression of  $\text{P}^{53}$  proteins in rat glioma C6 cells. In addition, quercetin supplementation also afforded a significant protection against chemical anoxia-induced cytotoxicity in C6 cells. The

cyto-protective effects of quercetin against H<sub>2</sub>O<sub>2</sub> and chemical anoxia involve the induction of HO-1 (Chen et al., 2006b) with increased bilirubin production likely protecting against H<sub>2</sub>O<sub>2</sub> mediated radical production (Bulmer et al., 2008; Bulmer et al., 2007). Concomitant exposure of quercetin with LPS or IFN- $\gamma$  inhibited the expression of NO, iNOS, NF-kappa B, I $\kappa$ B $\alpha$ , AP-1, and STAT-1 in BV-2 microglia by inducing the HO-1 protein (Chen et al., 2005).

Apigenin exerted inhibitory effects on HO-1 protein activation. The administration of apigenin to mouse embryonic fibroblasts prevented the haemin-mediated HO-1 induction and activity and also decreased the basal level of HO-1 protein expression (Abate et al., 2005). Incubation of luteolin protected auditory cells from cisplatin-induced cell damage and abrogated cisplatin-induced cell death, elevated the expression of HO-1, and activated the ERK pathway (Choi et al., 2008).

### **4.3 DNA-protective properties**

Administration of quercetin at 3, 6, 12, 24, and 48  $\mu$ M to human peripheral blood lymphocytes (PBMCs) dose-dependently alleviated DNA damage in response to gamma radiation. Gamma radiation-elicited DNA strand breaks, MN frequencies, comet attributes, and the levels of thiobarbituric acid reactive substances (TBARS) were suppressed by pre-treatment with quercetin. Additionally, quercetin treatment prior to radiation exposure elevated the levels of antioxidant enzymes such as GSH, SOD, CAT, and GPx (Devipriya et al., 2008). Quercetin and quercetin-rich juice treatment prior to H<sub>2</sub>O<sub>2</sub> and B $\alpha$ P challenge protected the human lymphocytes both in *in vivo* and *in vitro* by abolishing oxidative DNA damage and the formation of BPDE-

DNA adducts (Wilms et al., 2005). Grape seed extract diets containing gallic acid, catechins, epicatechin and proanthocyanidins also protect AD mice from DNA damage by reducing the MN frequency (10 fold) and increasing the buccal cell telomere length (2 fold; Thomas et al., 2009).

Flavonoids may also contribute to DNA damage. Incubation with kaempferol (100  $\mu$ M) for 90 min decreased ROS levels in HL-60 cells, however, increased the number of DNA strand breaks. Kaempferol did not increase the level of oxidized DNA purines, therefore, kaempferol-induced DNA damage could be mediated by highly localised changes in ROS generation that do not lead to a general increase in oxidative stress. Hydroxyl radical formation ( $\text{HO}^\circ$ ) close to DNA molecules may initiate strand breakage (Bestwick et al., 2005). Kaempferol elevates  $\text{HO}^\circ$  generation in the presence of ferric-EDTA chelate. When citrate and ascorbate were used and iron chelates, kaempferol had little or no effect on  $\text{HO}^\circ$  formation. Therefore, kaempferol shows adverse effects on DNA integrity despite reducing ROS levels (Bestwick et al., 2005). Kaempferol (10-100  $\mu$ M) promoted DNA damage and lipid peroxidation in a concentration-dependent manner in rat liver nuclei, which was stimulated by the presence of ferric (Fe(III)) and Cu(II) ions (Sahu and Gray, 1994). Both quercetin and luteolin can induce DNA cleavage and form DNA ladders. Quercetin induces DNA damage, enhancing the formation of 8-hydroxydeoxyguanosine (8-OHdG), an indicator of oxidative DNA damage in HL-60 cells. On the contrary, luteolin reduced topoisomerase II (topo II) activity of nuclear extract and cleaved DNA by forming a luteolin-topo II-DNA ternary complex (Yamashita and Kawanishi, 2000).

## 5 Bioavailability

Although polyphenols are important constituents in the human diet they show poor bioavailability. Once absorbed by the intestine, polyphenols are distributed into the body's tissues and metabolized/excreted by the liver. Only a few studies have reported data on polyphenol concentration in human tissues. Most polyphenols are rapidly metabolised (sulphation, methylation, and glucuronidation) and excreted by the liver, therefore, tissue concentrations remain low. Metabolites of polyphenols are excreted into the urine and bile (Manach et al., 2004).

The absorption, metabolism, and tissue distribution of curcumin has been studied in *in vivo* studies. Approximately 60 and 75% of curcumin was excreted in the faeces of rats receiving curcumin orally (400 mg, 1 g/kg respectively). Only traces of curcumin were found in portal blood ( $< 5 \mu\text{g/mL}$ ) and in the liver and kidney ( $<20 \mu\text{g/tissue}$ ; Ravindranath and Chandrasekhara, 1980; Wahlstrom and Blennow, 1978). Curcumin and its metabolites (curcumin glucuronide or curcumin sulphate) showed variation in their distribution into the plasma and colonic mucosa depending their mode of administration. Following i.g. administration of curcumin (500 mg/kg), the plasma levels of curcumin were ~3 to 5 times higher in rats than in those that received curcumin (2 % in diet for 3 h) orally (Sharma et al., 2001). Furthermore, LC-MS/MS analysis of rat plasma revealed a low maximum plasma concentration ( $C_{\text{max}}$ ;  $0.06 \pm 0.01 \mu\text{g/ml}$ ) after oral administration (500 mg/kg) compared to i.v. administration of curcumin (10 mg/kg;  $0.36 \pm 0.05 \mu\text{g/ml}$ ). Blood samples were collected at 10-50 min and 1-3 h after dosing. Curcumin was metabolised rapidly after oral administration with a half-life  $28.1 \pm 5.6$  and  $44.5 \pm$

7.5 min for p.o. and i.v. administration respectively and showed 1% oral bioavailability (Yang et al., 2007).

Estimations of curcumin bioavailability in humans are rare. In one study, oral administration of curcumin at 4, 6, and 8 g/day in 25 patients with precancerous lesions yielded plasma curcumin concentrations of 0.19, 0.20, and 0.60  $\mu\text{g/mL}$ , respectively. No metabolites of curcumin were detected in the study (Cheng et al., 2001). Another study was conducted in six patients with advanced colorectal cancer. The ingestion of curcumin at 3.6 g daily for up to three months yielded glucuronides and sulphates of curcumin and desmethoxycurcumin in plasma. Curcumin and its conjugates were also detected in urine samples of all six patients. The urinary levels varied between 0.1 and 1.3  $\mu\text{M}$  (curcumin), 19 and 45 nM (curcumin sulphate), 210 and 510 nM (curcumin glucuronide; Sharma et al., 2004). The bioavailability of curcumin has also been studied in 12 healthy human volunteers who were given curcumin orally in a single dose of 10 or 12 g. The maximum concentrations of curcumin glucuronide and curcumin sulphate at the 10 g dose were  $2.04 \pm 0.31 \mu\text{g/L}$  and  $1.06 \pm 0.40 \mu\text{g/L}$  respectively, and at 12 g/L were  $1.40 \pm 0.74 \mu\text{g/L}$  and  $0.87 \pm 0.44 \mu\text{g/L}$ , respectively (Vareed et al., 2008).

The absorption and metabolism of resveratrol have been shown in *in vitro* studies utilising an isolated rat small intestine perfusion model. Forty-six percent of resveratrol was excreted by the small intestine, 21% was absorbed into the vascular compartment and 2 % appeared in the intestinal tissue (Andlauer et al., 2000). In another study, the absorption and metabolism of resveratrol across the jejunum and ileum were measured. Very little resveratrol was absorbed intact (0.3 nmol/cm jejunum). The major compound detected on the serosal side of jejunal enterocytes was the glucuronide conjugate of resveratrol (96 % of the amount absorbed),

indicating the ready metabolism of this compound (Kuhnle et al., 2000). The *in vitro* metabolism and stability of resveratrol was studied after incubation of resveratrol (0.1 mM) with human hepatocytes for 4 h. LC-UV-MS/MS showed three resveratrol glucuronide peaks, resveratrol-4-glucuronide, resveratrol-3-glucuronide, and cis-resveratrol-4-glucuronides (Yu et al., 2002).

The bioavailability of resveratrol has also been studied in *in vivo* rodent and human models also. Resveratrol is rapidly absorbed and reaches its highest concentration in the liver and kidney after 60 min in rats that were administered 4 mL of red wine (corresponding to 86 µg/kg resveratrol) (Bertelli et al., 1996). After receiving resveratrol (20 mg/kg, i.p.), rat hepatocytes produced resveratrol glucuronide and resveratrol sulphate as two major metabolites of resveratrol. These two metabolites were also detected in the urine. Similar metabolite peaks were found in mouse serum samples, when resveratrol was administered at two different doses of 20 and 60 mg/kg i.p. or i.g. (Yu et al., 2002).

The absorption of resveratrol in humans was first conducted in 12 healthy human males who were given 25 mg/70 kg resveratrol, orally. The highest concentration of resveratrol was achieved in serum after 30 min and 17% was excreted in the urine after 24 h (Goldberg et al., 2003). In another study, oral administration of 25 mg of <sup>14</sup>C labelled resveratrol (110 µmol) to human subjects showed that resveratrol is rapidly absorbed in plasma with peak plasma levels of resveratrol 491 ± 90 ng/mL. Both sulphate and glucuronide conjugates of resveratrol were detected in urine and plasma, however, only traces of unchanged resveratrol were detected in plasma (Walle et al., 2004).

The absorption and metabolism of quercetin is well understood among the flavonoids. Administration of a quercetin containing diet (50 or 500 mg/kg) to rats for 11 weeks resulted in a

wide distribution of quercetin metabolites in the body tissues. A quercetin diet (500 mg/kg) administered to pigs for three days revealed quercetins in tissues including the liver and kidneys (de Boer et al., 2005). Plasma quercetin concentrations were first observed in 27 healthy human volunteers who consumed four quercetin capsules (each containing 250 mg quercetin, 50 mg rutin, and 250 mg other bioflavonoids) daily for 28 days. At day 0 (pre-supplementation), quercetin was essentially undetectable ( $0.10 \pm 0.09 \mu\text{M}$ ). The plasma quercetin concentrations then increased from  $0.10 \pm 0.09 \mu\text{M}$  to  $1.5 \pm 0.3 \mu\text{M}$  after 28 days (Conquer et al., 1998). In another study, three doses of quercetin (8, 20, and 50 mg) were administered orally to 16 human subjects. Quercetin was detected in plasma as the glucuronide, sulphate and as the unconjugated form. The volunteers also showed a dose dependent increase in the  $C_{\text{max}}$  value (0.14, 0.22, 0.29  $\mu\text{M}$ ; Erlund et al., 2000). Isoflavones show higher plasma concentrations after oral administration. The isoflavone genistein induced a higher plasma concentration ( $341 \pm 74 \text{ ng/mL}$ ) than daidzein (isoflavone;  $194 \pm 30.6 \text{ ng/mL}$ ) in women who were administered a single bolus dose (50 mg) of each isoflavone (Setchell et al., 2001).

The health effects of polyphenols depend on their dietary intake and bioavailability, which show great variation. Dietary consumption of turmeric up to 150 mg/day shows no adverse effects in humans. The intake of curcumin up to 350 mg/kg body weight for 3 months was not harmful in rats, dogs or monkeys (Sharma et al., 2005). Half-life values for curcumin administration are 28 and 44 min for p.o. and i.v. administration, respectively (Yang et al., 2007). Resveratrol at concentrations and doses ranging from  $\sim 32 \text{ nM} - 100 \mu\text{M}$  and  $\sim 100 \text{ ng} - 1,500 \text{ mg/kg}$  body weight have been widely used in *in vitro* and in *in vivo* studies and show very short half life (8-14 min; Baur and Sinclair, 2006). The elimination of quercetin and isoflavones are slow with half-lives in the order of 11 to 28h and 4-8h, respectively (Manach et al., 2004). The distribution

of polyphenols into body tissues varies depending on their mode of administration. The oral bioavailability of polyphenols ranges from 2-20% (Hu, 2007).

## **6 Conclusion**

The present review discusses the anti-inflammatory, cyto-and DNA protective effects of dietary polyphenols, including curcumin, resveratrol, and flavonoids. Curcumin (turmeric), resveratrol (wines and berries), and flavonoids (fruits and vegetables) induce potent anti-inflammatory effects, protecting cells and DNA from stress-mediated injury.

Curcumin shows a myriad of anti-inflammatory activities in *in vitro* studies in response to various stressors. Curcumin's anti-inflammatory effects are attributed to its inhibition of cell adhesion molecule, NF-kappa B and AP-1 expression. *In vitro* studies show that curcumin protects from oxidative stress by preventing the release of free radicals. Curcumin also elevates the expression of MKP-1, which inhibits MAPKs activation during stress conditions. *In vivo*, the administration of curcumin attenuates inflammation in various clinical trials (Jurenka, 2009). Curcumin is a potent activator of HO-1 mRNA and protein expression via the Nrf2 transcription factor. Curcumin also enhances the expression of phase II enzymes and exerts a biphasic effect on DNA damage, protecting DNA at low doses (1-5 µg/ml) but promoting it at higher doses (>8 µg/ml).

Resveratrol also possesses anti-inflammatory activities both in *in vitro* and in *in vivo* studies, inhibiting the release of inflammatory cytokines, activation of transcription factors NF-kappa B, cell adhesion molecules and ERK-phosphorylation. *In vitro* incubation with resveratrol affords protection against NO, neurotoxin, xanthine oxidase and ischemic stress. Resveratrol induces

cyto-protective effects by activating the SIRT1 (responsible for cell defense and cell survival during oxidative stress) transcription factor and elevating the levels of phase II enzymes. *In vivo* administration of resveratrol protects from DSS-induced colitis and streptozotocin-induced cardiac dysfunction in rats. Pre-treatment with resveratrol protects rats from cigarette smoke-induced oxidative stress and inflammation. Resveratrol shows a dose-dependent effect on HO-1 activation, inhibiting expression at low concentrations (1-10 mM) but elevating it at high concentrations >20 mM. Resveratrol reduces DNA damage from TCDD, benzo( $\alpha$ )pyrene, DMH, KBrO<sub>3</sub>, and AGEs decreasing DNA-adduct formation, levels of oxo8dG, comet attributes and necrotic cell death. However, resveratrol can promote DNA damage in the presence of UVA radiation, increasing the formation of oxo8dG.

Flavonoids are a family of compounds including flavonols, flavanones, flavanols, isoflavones, and flavans. The present review focuses primarily on apigenin, genistein, luteolin, kaempferol and quercetin, all of which strongly inhibit inflammatory responses. Genistein possess strong cyto-protective activity, inhibiting cytokine-mediated toxicity, breast cancer and promoting chemotherapeutic efficacy. Genistein's mechanisms of action include inhibition of tyrosine kinases, activation of PPAR-gamma and binding of oestrogen receptors. Kaempferol, quercetin, and luteolin also afford protection against oxidative stress by inducing the expression of HO-1, however, apigenin inhibits HO-1 induction. Quercetin ameliorates DNA damage resulting from gamma radiation, reducing DNA strand breaks, MN formation, comet attributes, and levels of reactive oxygen species. Quercetin administration, both in *in vivo* and *in vitro*, prevents H<sub>2</sub>O<sub>2</sub>, and benzo( $\alpha$ )pyrene-induced DNA damage. Flavonoids can also induce DNA damage. For example, in the presence of transition metals, kaempferol promotes DNA damage and lipid

peroxidation. Quercetin and luteolin have also been shown to induce DNA cleavage and ladder formation in HL-60 cells.

A vast number of *in vitro* and laboratory animal studies and some *in vivo* studies show polyphenols induce cytoprotective responses/mechanisms against various environmental toxins and could prevent disease. Therefore, natural product based therapy could be a promising preventative/treatment for chronic diseases. However, currently, more evidence is required so that the aforementioned plant extracts can be used as cytoprotective agents in human population studies. Additionally, polyphenols exert dual effects with low doses protecting cells but inducing toxicity at high doses. Moreover, there is not sufficient data concerning the bioavailability of polyphenols in humans. Further research with the aim of determining the effects of polyphenols on stress-mediated responses should include human trials and the elucidation of their cytoprotective mechanism of action responsible for their pharmacological efficacy.

### **Conflict of interest**

The authors declare no conflict of interest

## References

- Abate, A., Yang, G., Wong, R. J., Schroder, H., Stevenson, D. K., Dennery, P. A. 2005. Apigenin decreases hemin-mediated heme oxygenase-1 induction. *Free Radic Biol Med* 39, 711-718.
- Abe, Y., Hashimoto, S., Horie, T. 1999. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol Res* 39, 41-47.
- Abebe, W., Agrawal, D. K. 1995. Role of tyrosine kinases in norepinephrine-induced contraction of vascular smooth muscle. *J Cardiovasc Pharmacol* 26, 153-159.
- Aggarwal, B. B., Sung, B. 2009. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci* 30, 85-94.
- Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M., Fukami, Y. 1987. Genistein, a specific inhibitor of tyrosine-specific protein kinases. *J Biol Chem* 262, 5592-5595.
- Ammon, H. P., Wahl, M. A. 1991. Pharmacology of *Curcuma longa*. *Planta Med* 57, 1-7.
- Andlauer, W., Kolb, J., Siebert, K., Furst, P. 2000. Assessment of resveratrol bioavailability in the perfused small intestine of the rat. *Drugs Exp Clin Res* 26, 47-55.
- Antunes, L. M., Araujo, M. C., Dias, F. L., Takahashi, C. S. 1999. Modulatory effects of curcumin on the chromosomal damage induced by doxorubicin in Chinese hamster ovary cells. *Teratog Carcinog Mutagen* 19, 1-8.
- Araujo, M. C., Dias, F. L., Takahashi, C. S. 1999. Potentiation by turmeric and curcumin of gamma-radiation-induced chromosome aberrations in Chinese hamster ovary cells. *Teratog Carcinog Mutagen* 19, 9-18.
- Bastianetto, S., Zheng, W. H., Quirion, R. 2000. Neuroprotective abilities of resveratrol and other red wine constituents against nitric oxide-related toxicity in cultured hippocampal neurons. *Br J Pharmacol* 131, 711-720.
- Baur, J. A., Sinclair, D. A. 2006. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov* 5, 493-506.
- Bengmark, S., Mesa, M. D., Gil, A. 2009. Plant-derived health: the effects of turmeric and curcuminoids. *Nutr Hosp* 24, 273-281.
- Berk, B. C. 1999. Angiotensin II signal transduction in vascular smooth muscle: pathways activated by specific tyrosine kinases. *J Am Soc Nephrol* 10 Suppl 11, S62-68.
- Bertelli, A. A., Giovannini, L., Stradi, R., Urien, S., Tillement, J. P., Bertelli, A. 1996. Kinetics of trans- and cis-resveratrol (3,4',5-trihydroxystilbene) after red wine oral administration in rats. *Int J Clin Pharmacol Res* 16, 77-81.
- Bestwick, C. S., Milne, L., Pirie, L., Duthie, S. J. 2005. The effect of short-term kaempferol exposure on reactive oxygen levels and integrity of human (HL-60) leukaemic cells. *Biochim Biophys Acta* 1740, 340-349.
- Bhaumik, S., Jyothi, M. D., Khar, A. 2000. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS Lett* 483, 78-82.
- Bi, X. L., Yang, J. Y., Dong, Y. X., Wang, J. M., Cui, Y. H., Ikeshima, T., Zhao, Y. Q., Wu, C. F. 2005. Resveratrol inhibits nitric oxide and TNF-alpha production by lipopolysaccharide-activated microglia. *Int Immunopharmacol* 5, 185-193.

- Bierhaus, A., Zhang, Y., Quehenberger, P., Luther, T., Haase, M., Muller, M., Mackman, N., Ziegler, R., Nawroth, P. P. 1997. The dietary pigment curcumin reduces endothelial tissue factor gene expression by inhibiting binding of AP-1 to the DNA and activation of NF-kappa B. *Thromb Haemost* 77, 772-782.
- Birkenkamp, K. U., Coffey, P. J. 2003. Regulation of cell survival and proliferation by the FOXO (Forkhead box, class O) subfamily of Forkhead transcription factors. *Biochem Soc Trans* 31, 292-297.
- Boutros, T., Chevet, E., Metrakos, P. 2008. Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer. *Pharmacol Rev* 60, 261-310.
- Brouet, I., Ohshima, H. 1995. Curcumin, an anti-tumour promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. *Biochem Biophys Res Commun* 206, 533-540.
- Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., Tran, H., Ross, S. E., Mostoslavsky, R., Cohen, H. Y., Hu, L. S., Cheng, H. L., Jedrychowski, M. P., Gygi, S. P., Sinclair, D. A., Alt, F. W., Greenberg, M. E. 2004. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science* 303, 2011-2015.
- Bulmer, A. C., Blanchfield, J. T., Toth, I., Fassett, R. G., Coombes, J. S. 2008. Improved resistance to serum oxidation in Gilbert's syndrome: a mechanism for cardiovascular protection. *Atherosclerosis* 199, 390-396.
- Bulmer, A. C., Ried, K., Coombes, J. S., Blanchfield, J. T., Toth, I., Wagner, K. H. 2007. The anti-mutagenic and antioxidant effects of bile pigments in the Ames Salmonella test. *Mutat Res* 629, 122-132.
- Burns, J., Yokota, T., Ashihara, H., Lean, M. E., Crozier, A. 2002. Plant foods and herbal sources of resveratrol. *J Agric Food Chem* 50, 3337-3340.
- Cadenas, S., Barja, G. 1999. Resveratrol, melatonin, vitamin E, and PBN protect against renal oxidative DNA damage induced by the kidney carcinogen KBrO<sub>3</sub>. *Free Radic Biol Med* 26, 1531-1537.
- Calixto, J. B., Campos, M. M., Otuki, M. F., Santos, A. R. 2004. Anti-inflammatory compounds of plant origin. Part II. modulation of pro-inflammatory cytokines, chemokines and adhesion molecules. *Planta Med* 70, 93-103.
- Cao, J., Jiang, L. P., Liu, Y., Yang, G., Yao, X. F., Zhong, L. F. 2007. Curcumin-induced genotoxicity and antigenotoxicity in HepG2 cells. *Toxicol* 49, 1219-1222.
- Chen, C. J., Yu, W., Fu, Y. C., Wang, X., Li, J. L., Wang, W. 2009. Resveratrol protects cardiomyocytes from hypoxia-induced apoptosis through the SIRT1-FoxO1 pathway. *Biochem Biophys Res Commun* 378, 389-393.
- Chen, C. Y., Peng, W. H., Tsai, K. D., Hsu, S. L. 2007. Luteolin suppresses inflammation-associated gene expression by blocking NF-kappaB and AP-1 activation pathway in mouse alveolar macrophages. *Life Sci* 81, 1602-1614.
- Chen, J., Tang, X. Q., Zhi, J. L., Cui, Y., Yu, H. M., Tang, E. H., Sun, S. N., Feng, J. Q., Chen, P. X. 2006a. Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2-mitochondria-ROS-iNOS pathway. *Apoptosis* 11, 943-953.
- Chen, J. C., Ho, F. M., Pei-Dawn Lee, C., Chen, C. P., Jeng, K. C., Hsu, H. B., Lee, S. T., Wen Tung, W., Lin, W. W. 2005. Inhibition of iNOS gene expression by quercetin is mediated

- by the inhibition of IkappaB kinase, nuclear factor-kappa B and STAT1, and depends on heme oxygenase-1 induction in mouse BV-2 microglia. *Eur J Pharmacol* 521, 9-20.
- Chen, T. J., Jeng, J. Y., Lin, C. W., Wu, C. Y., Chen, Y. C. 2006b. Quercetin inhibition of ROS-dependent and -independent apoptosis in rat glioma C6 cells. *Toxicology* 223, 113-126.
- Cheng, A. L., Hsu, C. H., Lin, J. K., Hsu, M. M., Ho, Y. F., Shen, T. S., Ko, J. Y., Lin, J. T., Lin, B. R., Ming-Shiang, W., Yu, H. S., Jee, S. H., Chen, G. S., Chen, T. M., Chen, C. A., Lai, M. K., Pu, Y. S., Pan, M. H., Wang, Y. J., Tsai, C. C., Hsieh, C. Y. 2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res* 21, 2895-2900.
- Choi, B. M., Lim, D. W., Lee, J. A., Gao, S. S., Kwon, D. Y., Kim, B. R. 2008. Luteolin suppresses cisplatin-induced apoptosis in auditory cells: possible mediation through induction of heme oxygenase-1 expression. *J Med Food* 11, 230-236.
- Choi, Y. J., Kang, J. S., Park, J. H., Lee, Y. J., Choi, J. S., Kang, Y. H. 2003. Polyphenolic flavonoids differ in their antiapoptotic efficacy in hydrogen peroxide-treated human vascular endothelial cells. *J Nutr* 133, 985-991.
- Conquer, J. A., Maiani, G., Azzini, E., Raguzzini, A., Holub, B. J. 1998. Supplementation with quercetin markedly increases plasma quercetin concentration without effect on selected risk factors for heart disease in healthy subjects. *J Nutr* 128, 593-597.
- Coskun, O., Kanter, M., Korkmaz, A., Oter, S. 2005. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and beta-cell damage in rat pancreas. *Pharmacol Res* 51, 117-123.
- Crespo, I., Garcia-Mediavilla, M. V., Gutierrez, B., Sanchez-Campos, S., Tunon, M. J., Gonzalez-Gallego, J. 2008. A comparison of the effects of kaempferol and quercetin on cytokine-induced pro-inflammatory status of cultured human endothelial cells. *Br J Nutr* 100, 968-976.
- Csiszar, A., Labinsky, N., Podlutzky, A., Kaminski, P. M., Wolin, M. S., Zhang, C., Mukhopadhyay, P., Pacher, P., Hu, F., de Cabo, R., Ballabh, P., Ungvari, Z. 2008. Vasoprotective effects of resveratrol and SIRT1: attenuation of cigarette smoke-induced oxidative stress and proinflammatory phenotypic alterations. *Am J Physiol Heart Circ Physiol* 294, H2721-2735.
- Dang, Z. C., Audinot, V., Papapoulos, S. E., Boutin, J. A., Lowik, C. W. 2003. Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. *J Biol Chem* 278, 962-967.
- de Boer, V. C., Dihal, A. A., van der Woude, H., Arts, I. C., Wolfram, S., Alink, G. M., Rietjens, I. M., Keijer, J., Hollman, P. C. 2005. Tissue distribution of quercetin in rats and pigs. *J Nutr* 135, 1718-1725.
- Delmas, D., Lancon, A., Colin, D., Jannin, B., Latruffe, N. 2006. Resveratrol as a chemopreventive agent: a promising molecule for fighting cancer. *Curr Drug Targets* 7, 423-442.
- Deodhar, S. D., Sethi, R., Srimal, R. C. 1980. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res* 71, 632-634.
- Devipriya, N., Sudheer, A. R., Srinivasan, M., Menon, V. P. 2008. Quercetin ameliorates gamma radiation-induced DNA damage and biochemical changes in human peripheral blood lymphocytes. *Mutat Res* 654, 1-7.

- Dhandapani, K. M., Mahesh, V. B., Brann, D. W. 2007. Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NFkappaB transcription factors. *J Neurochem* 102, 522-538.
- Di Carlo, G., Mascolo, N., Izzo, A. A., Capasso, F. 1999. Flavonoids: old and new aspects of a class of natural therapeutic drugs. *Life Sci* 65, 337-353.
- Di Salvo, J., Nelson, S. R., Kaplan, N. 1997. Protein tyrosine phosphorylation in smooth muscle: a potential coupling mechanism between receptor activation and intracellular calcium. *Proc Soc Exp Biol Med* 214, 285-301.
- Donatus, I. A., Sardjoko, Vermeulen, N. P. 1990. Cytotoxic and cytoprotective activities of curcumin. Effects on paracetamol-induced cytotoxicity, lipid peroxidation and glutathione depletion in rat hepatocytes. *Biochem Pharmacol* 39, 1869-1875.
- Donnelly, L. E., Newton, R., Kennedy, G. E., Fenwick, P. S., Leung, R. H., Ito, K., Russell, R. E., Barnes, P. J. 2004. Anti-inflammatory effects of resveratrol in lung epithelial cells: molecular mechanisms. *Am J Physiol Lung Cell Mol Physiol* 287, L774-783.
- Erlund, I., Kosonen, T., Alfthan, G., Maenpaa, J., Perttunen, K., Kenraali, J., Parantainen, J., Aro, A. 2000. Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers. *Eur J Clin Pharmacol* 56, 545-553.
- Fisher, B., Dignam, J., Bryant, J., DeCillis, A., Wickerham, D. L., Wolmark, N., Costantino, J., Redmond, C., Fisher, E. R., Bowman, D. M., Deschenes, L., Dimitrov, N. V., Margolese, R. G., Robidoux, A., Shibata, H., Terz, J., Paterson, A. H., Feldman, M. I., Farrar, W., Evans, J., Lickley, H. L. 1996. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 88, 1529-1542.
- Floyd, R. A. 1990. The role of 8-hydroxyguanine in carcinogenesis. *Carcinogenesis* 11, 1447-1450.
- Funk, J. L., Oyarzo, J. N., Frye, J. B., Chen, G., Lantz, R. C., Jolad, S. D., Solyom, A. M., Timmermann, B. N. 2006. Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis. *J Nat Prod* 69, 351-355.
- Gao, X., Kuo, J., Jiang, H., Deeb, D., Liu, Y., Divine, G., Chapman, R. A., Dulchavsky, S. A., Gautam, S. C. 2004. Immunomodulatory activity of curcumin: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production in vitro. *Biochem Pharmacol* 68, 51-61.
- Gao, X., Xu, Y. X., Janakiraman, N., Chapman, R. A., Gautam, S. C. 2001. Immunomodulatory activity of resveratrol: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production. *Biochem Pharmacol* 62, 1299-1308.
- Gerritsen, M. E., Carley, W. W., Ranges, G. E., Shen, C. P., Phan, S. A., Ligon, G. F., Perry, C. A. 1995. Flavonoids inhibit cytokine-induced endothelial cell adhesion protein gene expression. *Am J Pathol* 147, 278-292.
- Goldberg, D. M., Yan, J., Soleas, G. J. 2003. Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clin Biochem* 36, 79-87.
- Gordon, M. 1996. Dietary antioxidants in disease prevention. *Nat Prod Rep* 13, 265-273.
- Gukovsky, I., Reyes, C. N., Vaquero, E. C., Gukovskaya, A. S., Pandol, S. J. 2003. Curcumin ameliorates ethanol and nonethanol experimental pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 284, G85-95.

- Hamalainen, M., Nieminen, R., Vuorela, P., Heinonen, M., Moilanen, E. 2007. Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappaB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappaB activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators Inflamm* 2007, 45673.
- Han, Y. S., Zheng, W. H., Bastianetto, S., Chabot, J. G., Quirion, R. 2004. Neuroprotective effects of resveratrol against beta-amyloid-induced neurotoxicity in rat hippocampal neurons: involvement of protein kinase C. *Br J Pharmacol* 141, 997-1005.
- Holden, N. S., Squires, P. E., Kaur, M., Bland, R., Jones, C. E., Newton, R. 2008. Phorbol ester-stimulated NF-kappaB-dependent transcription: roles for isoforms of novel protein kinase C. *Cell Signal* 20, 1338-1348.
- Holmes-McNary, M., Baldwin, A. S., Jr. 2000. Chemopreventive properties of trans-resveratrol are associated with inhibition of activation of the IkappaB kinase. *Cancer Res* 60, 3477-3483.
- Holt, P. R., Katz, S., Kirshoff, R. 2005. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci* 50, 2191-2193.
- Hong, J. T., Yen, J. H., Wang, L., Lo, Y. H., Chen, Z. T., Wu, M. J. 2009. Regulation of heme oxygenase-1 expression and MAPK pathways in response to kaempferol and rhamnocitrin in PC12 cells. *Toxicol Appl Pharmacol* 237, 59-68.
- Hu, M. 2007. Commentary: bioavailability of flavonoids and polyphenols: call to arms. *Mol Pharm* 4, 803-806.
- Huang, M. T., Lysz, T., Ferraro, T., Abidi, T. F., Laskin, J. D., Conney, A. H. 1991. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res* 51, 813-819.
- Ibern-Gomez, M., Roig-Perez, S., Lamuela-Raventos, R. M., de la Torre-Boronat, M. C. 2000. Resveratrol and piceid levels in natural and blended peanut butters. *J Agric Food Chem* 48, 6352-6354.
- Issuree, P. D., Pushparaj, P. N., Pervaiz, S., Melendez, A. J. 2009. Resveratrol attenuates C5a-induced inflammatory responses in vitro and in vivo by inhibiting phospholipase D and sphingosine kinase activities. *FASEB J* 23, 2412-2424.
- Jeong, Y. J., Choi, Y. J., Kwon, H. M., Kang, S. W., Park, H. S., Lee, M., Kang, Y. H. 2005. Differential inhibition of oxidized LDL-induced apoptosis in human endothelial cells treated with different flavonoids. *Br J Nutr* 93, 581-591.
- Juan, S. H., Cheng, T. H., Lin, H. C., Chu, Y. L., Lee, W. S. 2005. Mechanism of concentration-dependent induction of heme oxygenase-1 by resveratrol in human aortic smooth muscle cells. *Biochem Pharmacol* 69, 41-48.
- Jurenka, J. S. 2009. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. *Altern Med Rev* 14, 141-153.
- Karin, M. 1999. How NF-kappaB is activated: the role of the IkappaB kinase (IKK) complex. *Oncogene* 18, 6867-6874.
- Keshewani, V., Sodhi, A. 2007. Involvement of tyrosine kinases and MAP kinases in the production of TNF-alpha and IL-1beta by macrophages in vitro on treatment with phytohemagglutinin. *J Interferon Cytokine Res* 27, 497-505.

- Kim, E. K., Kwon, K. B., Song, M. Y., Seo, S. W., Park, S. J., Ka, S. O., Na, L., Kim, K. A., Ryu, D. G., So, H. S., Park, R., Park, J. W., Park, B. H. 2007. Genistein protects pancreatic beta cells against cytokine-mediated toxicity. *Mol Cell Endocrinol* 278, 18-28.
- Kim, G. Y., Kim, K. H., Lee, S. H., Yoon, M. S., Lee, H. J., Moon, D. O., Lee, C. M., Ahn, S. C., Park, Y. C., Park, Y. M. 2005. Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. *J Immunol* 174, 8116-8124.
- Kobuchi, H., Roy, S., Sen, C. K., Nguyen, H. G., Packer, L. 1999. Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway. *Am J Physiol* 277, C403-411.
- Kowalski, J., Samojedny, A., Paul, M., Pietsz, G., Wilczok, T. 2005. Effect of apigenin, kaempferol and resveratrol on the expression of interleukin-1beta and tumor necrosis factor-alpha genes in J774.2 macrophages. *Pharmacol Rep* 57, 390-394.
- Kuhnle, G., Spencer, J. P., Chowrimootoo, G., Schroeter, H., Debnam, E. S., Srail, S. K., Rice-Evans, C., Hahn, U. 2000. Resveratrol is absorbed in the small intestine as resveratrol glucuronide. *Biochem Biophys Res Commun* 272, 212-217.
- Kumar, A., Dhawan, S., Hardegen, N. J., Aggarwal, B. B. 1998. Curcumin (Diferuloylmethane) inhibition of tumor necrosis factor (TNF)-mediated adhesion of monocytes to endothelial cells by suppression of cell surface expression of adhesion molecules and of nuclear factor-kappaB activation. *Biochem Pharmacol* 55, 775-783.
- Lal, B., Kapoor, A. K., Asthana, O. P., Agrawal, P. K., Prasad, R., Kumar, P., Srimal, R. C. 1999. Efficacy of curcumin in the management of chronic anterior uveitis. *Phytother Res* 13, 318-322.
- Larrosa, M., Yanez-Gascon, M. J., Selma, M. V., Gonzalez-Sarrias, A., Toti, S., Ceron, J. J., Tomas-Barberan, F., Dolara, P., Espin, J. C. 2009. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J Agric Food Chem* 57, 2211-2220.
- Lee, J. H., Zhou, H. Y., Cho, S. Y., Kim, Y. S., Lee, Y. S., Jeong, C. S. 2007. Anti-inflammatory mechanisms of apigenin: inhibition of cyclooxygenase-2 expression, adhesion of monocytes to human umbilical vein endothelial cells, and expression of cellular adhesion molecules. *Arch Pharm Res* 30, 1318-1327.
- Li, Y., Cao, Z., Zhu, H. 2006. Upregulation of endogenous antioxidants and phase 2 enzymes by the red wine polyphenol, resveratrol in cultured aortic smooth muscle cells leads to cytoprotection against oxidative and electrophilic stress. *Pharmacol Res* 53, 6-15.
- Liang, Y. C., Huang, Y. T., Tsai, S. H., Lin-Shiau, S. Y., Chen, C. F., Lin, J. K. 1999. Suppression of inducible cyclooxygenase and inducible nitric oxide synthase by apigenin and related flavonoids in mouse macrophages. *Carcinogenesis* 20, 1945-1952.
- Lin, H. Y., Juan, S. H., Shen, S. C., Hsu, F. L., Chen, Y. C. 2003. Inhibition of lipopolysaccharide-induced nitric oxide production by flavonoids in RAW264.7 macrophages involves heme oxygenase-1. *Biochem Pharmacol* 66, 1821-1832.
- Lu, F., Zahid, M., Wang, C., Saeed, M., Cavalieri, E. L., Rogan, E. G. 2008. Resveratrol prevents estrogen-DNA adduct formation and neoplastic transformation in MCF-10F cells. *Cancer Prev Res (Phila Pa)* 1, 135-145.

- Mahakunakorn, P., Tohda, M., Murakami, Y., Matsumoto, K., Watanabe, H., Vajaragupta, O. 2003. Cytoprotective and cytotoxic effects of curcumin: dual action on H<sub>2</sub>O<sub>2</sub>-induced oxidative cell damage in NG108-15 cells. *Biol Pharm Bull* 26, 725-728.
- Mai, Z., Blackburn, G. L., Zhou, J. R. 2007. Genistein sensitizes inhibitory effect of tamoxifen on the growth of estrogen receptor-positive and HER2-overexpressing human breast cancer cells. *Mol Carcinog* 46, 534-542.
- Manach, C., Scalbert, A., Morand, C., Remesy, C., Jimenez, L. 2004. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 79, 727-747.
- Manna, S. K., Mukhopadhyay, A., Aggarwal, B. B. 2000. Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation. *J Immunol* 164, 6509-6519.
- Markiewicz, L., Garey, J., Adlercreutz, H., Gurbide, E. 1993. In vitro bioassays of non-steroidal phytoestrogens. *J Steroid Biochem Mol Biol* 45, 399-405.
- Mattson, M. P., Son, T. G., Camandola, S. 2007. Viewpoint: mechanisms of action and therapeutic potential of neurohormetic phytochemicals. *Dose Response* 5, 174-186.
- Mendonca, L. M., Dos Santos, G. C., Antonucci, G. A., Dos Santos, A. C., Bianchi Mde, L., Antunes, L. M. 2009. Evaluation of the cytotoxicity and genotoxicity of curcumin in PC12 cells. *Mutat Res* 675, 29-34.
- Messina, M. J., Persky, V., Setchell, K. D., Barnes, S. 1994. Soy intake and cancer risk: a review of the in vitro and in vivo data. *Nutr Cancer* 21, 113-131.
- Middleton, E., Jr., Kandaswami, C., Theoharides, T. C. 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev* 52, 673-751.
- Mizutani, K., Ikeda, K., Nishikata, T., Yamori, Y. 2000. Phytoestrogens attenuate oxidative DNA damage in vascular smooth muscle cells from stroke-prone spontaneously hypertensive rats. *J Hypertens* 18, 1833-1840.
- Motta, M. C., Divecha, N., Lemieux, M., Kamel, C., Chen, D., Gu, W., Bultsma, Y., McBurney, M., Guarente, L. 2004. Mammalian SIRT1 represses forkhead transcription factors. *Cell* 116, 551-563.
- Nevala, R., Lassila, M., Finckenberg, P., Paukku, K., Korpela, R., Vapaatalo, H. 2002. Genistein treatment reduces arterial contractions by inhibiting tyrosine kinases in ovariectomized hypertensive rats. *Eur J Pharmacol* 452, 87-96.
- Newman, D. J., Cragg, G. M. 2007. Natural products as sources of new drugs over the last 25 years. *J Nat Prod* 70, 461-477.
- Nicholas, C., Batra, S., Vargo, M. A., Voss, O. H., Gavrillin, M. A., Wewers, M. D., Guttridge, D. C., Grotewold, E., Doseff, A. I. 2007. Apigenin blocks lipopolysaccharide-induced lethality in vivo and proinflammatory cytokines expression by inactivating NF-kappaB through the suppression of p65 phosphorylation. *J Immunol* 179, 7121-7127.
- Okawara, M., Katsuki, H., Kurimoto, E., Shibata, H., Kume, T., Akaike, A. 2007. Resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults. *Biochem Pharmacol* 73, 550-560.
- Pae, H. O., Jeong, S. O., Zheng, M., Ha, H. Y., Lee, K. M., Kim, E. C., Kim, D. H., Hwang, S. Y., Chung, H. T. 2009. Curcumin attenuates ethanol-induced toxicity in HT22

- hippocampal cells by activating mitogen-activated protein kinase phosphatase-1. *Neurosci Lett* 453, 186-189.
- Pang, J. L., Ricupero, D. A., Huang, S., Fatma, N., Singh, D. P., Romero, J. R., Chattopadhyay, N. 2006. Differential activity of kaempferol and quercetin in attenuating tumor necrosis factor receptor family signaling in bone cells. *Biochem Pharmacol* 71, 818-826.
- Park, E., Kum, S., Wang, C., Park, S. Y., Kim, B. S., Schuller-Levis, G. 2005. Anti-inflammatory activity of herbal medicines: inhibition of nitric oxide production and tumor necrosis factor-alpha secretion in an activated macrophage-like cell line. *Am J Chin Med* 33, 415-424.
- Park, H. H., Lee, S., Son, H. Y., Park, S. B., Kim, M. S., Choi, E. J., Singh, T. S., Ha, J. H., Lee, M. G., Kim, J. E., Hyun, M. C., Kwon, T. K., Kim, Y. H., Kim, S. H. 2008. Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. *Arch Pharm Res* 31, 1303-1311.
- Park, H. J., Jeong, S. K., Kim, S. R., Bae, S. K., Kim, W. S., Jin, S. D., Koo, T. H., Jang, H. O., Yun, I., Kim, K. W., Bae, M. K. 2009. Resveratrol inhibits *Porphyromonas gingivalis* lipopolysaccharide-induced endothelial adhesion molecule expression by suppressing NF-kappaB activation. *Arch Pharm Res* 32, 583-591.
- Psotova, J., Chlopickova, S., Miketova, P., Hrbac, J., Simanek, V. 2004. Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part III. Apigenin, baicalein, kaempferol, luteolin and quercetin. *Phytother Res* 18, 516-521.
- Pugazhenti, S., Akhoy, L., Selvaraj, G., Wang, M., Alam, J. 2007. Regulation of heme oxygenase-1 expression by demethoxy curcuminoids through Nrf2 by a PI3-kinase/Akt-mediated pathway in mouse beta-cells. *Am J Physiol Endocrinol Metab* 293, E645-655.
- Rao, T. S., Basu, N., Siddiqui, H. H. 1982. Anti-inflammatory activity of curcumin analogues. *Indian J Med Res* 75, 574-578.
- Ravindranath, V., Chandrasekhara, N. 1980. Absorption and tissue distribution of curcumin in rats. *Toxicology* 16, 259-265.
- Renaud, S., de Lorgeril, M. 1992. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 339, 1523-1526.
- Revel, A., Raanani, H., Younglai, E., Xu, J., Han, R., Savouret, J. F., Casper, R. F. 2001. Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects sperm from DNA damage and apoptosis caused by benzo(a)pyrene. *Reprod Toxicol* 15, 479-486.
- Riboli, E., Norat, T. 2003. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 78, 559S-569S.
- Riesenhuber, A., Kasper, D. C., Vargha, R., Endemann, M., Aufricht, C. 2007. Quercetin protects human mesothelial cells against exposure to peritoneal dialysis fluid. *Pediatr Nephrol* 22, 1205-1208.
- Ruby, A. J., Kuttan, G., Babu, K. D., Rajasekharan, K. N., Kuttan, R. 1995. Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett* 94, 79-83.
- Ruiz, P. A., Braune, A., Holzlwimmer, G., Quintanilla-Fend, L., Haller, D. 2007. Quercetin inhibits TNF-induced NF-kappaB transcription factor recruitment to proinflammatory gene promoters in murine intestinal epithelial cells. *J Nutr* 137, 1208-1215.
- Ryter, S. W., Alam, J., Choi, A. M. 2006. Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. *Physiol Rev* 86, 583-650.

- Sahu, S. C., Gray, G. C. 1994. Kaempferol-induced nuclear DNA damage and lipid peroxidation. *Cancer Lett* 85, 159-164.
- Savineau, J. P., Gonzalez De La Fuente, P., Marthan, R. 1996. Effect of modulators of tyrosine kinase activity on agonist-induced contraction in the rat pulmonary vascular smooth muscle. *Pulm Pharmacol* 9, 189-195.
- Scapagnini, G., Colombrita, C., Amadio, M., D'Agata, V., Arcelli, E., Sapienza, M., Quattrone, A., Calabrese, V. 2006. Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxid Redox Signal* 8, 395-403.
- Sengottuvelan, M., Deeptha, K., Nalini, N. 2009. Resveratrol ameliorates DNA damage, prooxidant and antioxidant imbalance in 1,2-dimethylhydrazine induced rat colon carcinogenesis. *Chem Biol Interact* 181, 193-201.
- Setchell, K. D., Brown, N. M., Desai, P., Zimmer-Nechemias, L., Wolfe, B. E., Brashear, W. T., Kirschner, A. S., Cassidy, A., Heubi, J. E. 2001. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J Nutr* 131, 1362S-1375S.
- Seve, M., Chimienti, F., Devergnas, S., Aouffen, M., Douki, T., Chantegrel, J., Cadet, J., Favier, A. 2005. Resveratrol enhances UVA-induced DNA damage in HaCaT human keratinocytes. *Med Chem* 1, 629-633.
- Shakibaei, M., Harikumar, K. B., Aggarwal, B. B. 2009. Resveratrol addiction: to die or not to die. *Mol Nutr Food Res* 53, 115-128.
- Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., Shafayat, A., Hewitt, H. R., Marczylo, T. H., Morgan, B., Hemingway, D., Plummer, S. M., Pirmohamed, M., Gescher, A. J., Steward, W. P. 2004. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res* 10, 6847-6854.
- Sharma, R. A., Gescher, A. J., Steward, W. P. 2005. Curcumin: the story so far. *Eur J Cancer* 41, 1955-1968.
- Sharma, R. A., Ireson, C. R., Verschoyle, R. D., Hill, K. A., Williams, M. L., Leuratti, C., Manson, M. M., Marnett, L. J., Steward, W. P., Gescher, A. 2001. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. *Clin Cancer Res* 7, 1452-1458.
- Shih, C. M., Lin, H., Liang, Y. C., Lee, W. S., Bi, W. F., Juan, S. H. 2004. Concentration-dependent differential effects of quercetin on rat aortic smooth muscle cells. *Eur J Pharmacol* 496, 41-48.
- Singh, S., Aggarwal, B. B. 1995. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane) [corrected]. *J Biol Chem* 270, 24995-25000.
- Soares, M. P., Bach, F. H. 2009. Heme oxygenase-1: from biology to therapeutic potential. *Trends Mol Med* 15, 50-58.
- Sood, A., Mathew, R., Trachtman, H. 2001. Cytoprotective effect of curcumin in human proximal tubule epithelial cells exposed to shiga toxin. *Biochem Biophys Res Commun* 283, 36-41.
- Srivastava, R., Srimal, R. C. 1985. Modification of certain inflammation-induced biochemical changes by curcumin. *Indian J Med Res* 81, 215-223.
- Subbaramaiah, K., Chung, W. J., Michaluart, P., Telang, N., Tanabe, T., Inoue, H., Jang, M., Pezzuto, J. M., Dannenberg, A. J. 1998. Resveratrol inhibits cyclooxygenase-2

- transcription and activity in phorbol ester-treated human mammary epithelial cells. *J Biol Chem* 273, 21875-21882.
- Surh, Y. J., Chun, K. S., Cha, H. H., Han, S. S., Keum, Y. S., Park, K. K., Lee, S. S. 2001. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. *Mutat Res* 480-481, 243-268.
- Thirunavukkarasu, M., Penumathsa, S. V., Koneru, S., Juhasz, B., Zhan, L., Otani, H., Bagchi, D., Das, D. K., Maulik, N. 2007. Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: Role of nitric oxide, thioredoxin, and heme oxygenase. *Free Radic Biol Med* 43, 720-729.
- Thomas, P., Wang, Y. J., Zhong, J. H., Kosaraju, S., O'Callaghan, N. J., Zhou, X. F., Fenech, M. 2009. Grape seed polyphenols and curcumin reduce genomic instability events in a transgenic mouse model for Alzheimer's disease. *Mutat Res* 661, 25-34.
- Ungvari, Z., Orosz, Z., Rivera, A., Labinsky, N., Xiangmin, Z., Olson, S., Podlutzky, A., Csiszar, A. 2007. Resveratrol increases vascular oxidative stress resistance. *Am J Physiol Heart Circ Physiol* 292, H2417-2424.
- Van Der Heide, L. P., Hoekman, M. F., Smidt, M. P. 2004. The ins and outs of FoxO shuttling: mechanisms of FoxO translocation and transcriptional regulation. *Biochem J* 380, 297-309.
- Vareed, S. K., Kakarala, M., Ruffin, M. T., Crowell, J. A., Normolle, D. P., Djuric, Z., Brenner, D. E. 2008. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. *Cancer Epidemiol Biomarkers Prev* 17, 1411-1417.
- Wahlstrom, B., Blennow, G. 1978. A study on the fate of curcumin in the rat. *Acta Pharmacol Toxicol (Copenh)* 43, 86-92.
- Walle, T., Hsieh, F., DeLegge, M. H., Oatis, J. E., Jr., Walle, U. K. 2004. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos* 32, 1377-1382.
- Wang, G. L., Fu, Y. C., Xu, W. C., Feng, Y. Q., Fang, S. R., Zhou, X. H. 2009. Resveratrol inhibits the expression of SREBP1 in cell model of steatosis via Sirt1-FOXO1 signaling pathway. *Biochem Biophys Res Commun* 380, 644-649.
- Wang, X., Liu, Y. 2007. Regulation of innate immune response by MAP kinase phosphatase-1. *Cell Signal* 19, 1372-1382.
- Wilms, L. C., Hollman, P. C., Boots, A. W., Kleinjans, J. C. 2005. Protection by quercetin and quercetin-rich fruit juice against induction of oxidative DNA damage and formation of BPDE-DNA adducts in human lymphocytes. *Mutat Res* 582, 155-162.
- Wung, B. S., Hsu, M. C., Wu, C. C., Hsieh, C. W. 2005. Resveratrol suppresses IL-6-induced ICAM-1 gene expression in endothelial cells: effects on the inhibition of STAT3 phosphorylation. *Life Sci* 78, 389-397.
- Xagorari, A., Papapetropoulos, A., Mauromatis, A., Economou, M., Fotsis, T., Roussos, C. 2001. Luteolin inhibits an endotoxin-stimulated phosphorylation cascade and proinflammatory cytokine production in macrophages. *J Pharmacol Exp Ther* 296, 181-187.
- Xu, Y. X., Pindolia, K. R., Janakiraman, N., Chapman, R. A., Gautam, S. C. 1997. Curcumin inhibits IL1 alpha and TNF-alpha induction of AP-1 and NF-kB DNA-binding activity in bone marrow stromal cells. *Hematopathol Mol Hematol* 11, 49-62.

- Yamashita, N., Kawanishi, S. 2000. Distinct mechanisms of DNA damage in apoptosis induced by quercetin and luteolin. *Free Radic Res* 33, 623-633.
- Yang, K. Y., Lin, L. C., Tseng, T. Y., Wang, S. C., Tsai, T. H. 2007. Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC-MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 853, 183-189.
- Yu, C., Shin, Y. G., Chow, A., Li, Y., Kosmeder, J. W., Lee, Y. S., Hirschelman, W. H., Pezzuto, J. M., Mehta, R. G., van Breemen, R. B. 2002. Human, rat, and mouse metabolism of resveratrol. *Pharm Res* 19, 1907-1914.
- Ziyan, L., Yongmei, Z., Nan, Z., Ning, T., Baolin, L. 2007. Evaluation of the anti-inflammatory activity of luteolin in experimental animal models. *Planta Med* 73, 221-226.

Table 1 Anti-inflammatory, cytoprotective, and DNA protective effects of curcumin

Mechanism	Dose/Concentration	Stimulation	Signalling pathways	References
Anti-inflammatory	10 $\mu$ M	LPS, IFN- $\gamma$	Inhibits NO and iNOS secretion from RAW264.7 macrophages	(Brouet and Ohshima, 1995)
	5-20 $\mu$ M	Rat histiocytoma (Ak-5)	Blocks the release of NO from peritoneal macrophages of AK-5 tumor bearing rats	(Bhaumik et al., 2000)
	2-60 $\mu$ M	TNF- $\alpha$ , PMA, H <sub>2</sub> O <sub>2</sub>	Inhibits NF-kappa B and I $\kappa$ B $\alpha$ in human myelomonoblastic cells	(Singh and Aggarwal, 1995)
	25, 50 $\mu$ M	None	Decreases NF-kappa B and AP-1 binding and expression in human glioma cells.	(Dhandapani et al., 2007)
	0.5-10 $\mu$ M	PMA, LPS,	Inhibits the release of Pro-inflammatory cytokines from human monocytes	(Abe et al., 1999)
	12.5-30 $\mu$ M	LPS, Con A,	Inhibits the expression of cytokines in murine lymphocytes and macrophages	(Gao et al., 2004)
	1-25 $\mu$ M	LPS	Down-regulates the cytokines expression from dendritic cells	(Kim et al., 2005)
	10-50 $\mu$ M	TNF- $\alpha$	Blocks expression of cell adhesion molecules	(Kumar et al., 1998)
Cytoprotective	20-80 mg/kg	Carrageen	Prevents oedema in rats	(Srivastava and Srimal, 1985)
	0.1-1.0 $\mu$ M	TPA	Inhibits epidermal inflammation in mouse	(Huang et al., 1991)
	3-100 $\mu$ M	AA	prevents epidermal inflammation in mouse	(Huang et al., 1991)
	1200 mg/day	Arthritis	Ameliorates inflammatory symptoms	(Deodhar et al., 1980)
	550 mg twice/day	IBD	Alleviates IBD-mediated inflammation	(Holt et al., 2005)
	375 mg/day	Anterior uveitis	Improves visual acuity and aqueous flare, reduces keratic precipitates	(Lal et al., 1999)
	200 mg/kg	Cerulean, ethanol	protects from pancreatitis	(Gukovsky et al., 2003)
	20 $\mu$ M	Shiga toxin	$\uparrow$ Cell survival, $\downarrow$ DNA damage, $\uparrow$ HSP70 in HK-2 cells	(Sood et al., 2001)
DNA-protective	12.5-100 $\mu$ M	H <sub>2</sub> O <sub>2</sub>	Inhibits oxidative stress in NG108-15 cells	(Mahakunakorn et al., 2003)
	50-200 nM	Ethanol	$\downarrow$ MAPK, $\uparrow$ MKP-1 in HT22 cells	(Pae et al., 2009)
	5-25 $\mu$ M	Glucose oxidase	Protects rat astrocytes and neurons by elevating HO-1 and Nrf2 expression	(Scapagnini et al., 2006)
	1-5 $\mu$ g/ml	CPA, cDDP	Alleviates MN formation, in HepG2 and PC12 cells telomere length	(Cao et al., 2007; Mendonca et al., 2009)
	0.07 % diet	AD	$\downarrow$ MN frequency, $\uparrow$ telomere length in mouse model of AD	(Thomas et al., 2009)

Abbreviations: AA, arachidonic acid; AD, alzheimer's disease; ConA, Concanavalin A; CPA, cyclophosphamide; cDDP, cisplatin; IBD, inflammatory bowel disease; IFN- $\gamma$ , interferon-gamma; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; LPS, lipopolysaccharide; PMA, phorbol 12-myristate 13-acetate; TNF- $\alpha$ , tumor necrosis factor alpha; TPA, 12-O-tetradecanoylphorbol-13-acetate.

Table 2

Anti-inflammatory, cytoprotective, and DNA protective effects of resveratrol

Mechanism	Doses/Concentrations	Stimulation	Signaling pathways	References
Anti-inflammatory	6.25-50 $\mu$ M	LPS	Inhibits NF-kappa B and cytokines expression in macrophages and splenocytes	(Gao et al., 2001)
	30 $\mu$ M	TNF, LPS	Down-regulates the expression of NF-kappa B and I $\kappa$ B kinase in human monocytes and macrophages	(Holmes-McNary and Baldwin, 2000)
	5 -25 $\mu$ M	TNF, PMA	Inhibits activation of NF-kappa B in Jurkat, Hela, and myeloid cells	(Manna et al., 2000)
	1,10, 100 $\mu$ M	Cytokines	Blocks the release of iNOS and COX-2 in human primary airway epithelial cells	(Donnelly et al., 2004)
	2.5, 10, 30 $\mu$ M	PMA	Prevents COX-2 transcription in human mammary epithelial cells	(Subbaramaiah et al., 1998)
	0.01-10 $\mu$ g/mL	LPS	Down-regulates the release of NO and TNF- $\alpha$ in microglial cells	(Bi et al., 2005)
	50 $\mu$ M	LPS	Inhibits secretion of cytokines from macrophages	(Kowalski et al., 2005)
	10, 20, 40 $\mu$ M	C5 anaphylatoxin	Reduces the expression of cytokines, oxidative burst, $\beta$ -glucuronide, ERK	(Issuree et al., 2009)
	1 or 10 $\mu$ M	P.gingivalis LPS	Suppresses cell adhesion molecules in HUMECS	(Park et al., 2009)
	100 $\mu$ M	IL-6	Down-regulates the expression of ICAM-1 in endothelial cells	(Wung et al., 2005)
Cytoprotective	5-40 $\mu$ M	$\beta$ -amyloid	Activates protein kinase C	(Han et al., 2004)
	10 30, 100 $\mu$ M	Neurotoxins	$\uparrow$ GSH, $\downarrow$ P <sup>53</sup> expression in neurons	(Okawara et al., 2007)
	25, 50, 100 $\mu$ M	XO/xanthine	$\uparrow$ phase II enzymes, $\downarrow$ ROS generation in ASMCs	(Li et al., 2006)
	20 $\mu$ M	Ischemia	$\uparrow$ SIRT1 $\downarrow$ FOXO1 in rat cardiomyocytes	(Chen et al., 2009)
	25 mg/kg/day	cigarette smoke	Blocks the release of cytokines and ROS from rat arteries and CAECs	(Csiszar et al., 2008)
	40 $\mu$ M	palmitate	Elevates the expression of SIRT1 and FOXO1	(Wang et al., 2009)
	1-100 $\mu$ M	TNF- $\alpha$ , ox-LDL, H <sub>2</sub> O <sub>2</sub>	Inhibits caspase-3/7 activity in rat endothelial cells and arteries	(Ungvari et al., 2007)
	1 mg/kg/day	DSS	Alleviates colon damage, blocks secretion of inflammatory molecules in rats	(Larrosa et al., 2009)
	2.5 mg/kg/day	STZ	Induces the expression of HO-1, Trx-1, VEGF, eNOS, and MnSOD in rats	(Thirunavukkarasu et al., 2007)
DNA protective	50 mg/kg/week	BaP	Prevents BPDE-DNA adduct formation and cell death in mouse	(Revel et al., 2001)
	16mg/kg/day	KBrO <sub>3</sub>	Decreases the level of oxo8dG in rat kidneys	(Cadenas and Barja, 1999)
	8 mg/kg/day	DMH	Inhibits comment attributes and elevates the level of anti-oxidant enzymes	(Sengottuvelan et al., 2009)

Abbreviations: BaP; benzo alpha pyrene; DMH, 1,2-dimethylhydrazine; DSS, dextran sulphate sodium; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; IL-6, interleukin-6; LPS, lipopolysaccharide; P.gingivalis LPS, Porphyromonas gingivalis lipopolysaccharide; KBrO<sub>3</sub>, potassium bromate; ox-LDL, oxidized low-density lipoprotein; PMA, phorbol 12-myristate 13-acetate; STZ, streptozotocin; TNF, tumor necrosis factor; XO-xanthine oxidase.

Table 3  
Anti-inflammatory, cytoprotective, and DNA protective effects of flavonoids

Mechanism	Dose/Concentration	Stimulation	Signaling pathways	References
Anti-inflammatory	30 $\mu$ M	LPS, PMA	Decreases the secretion of Inflammatory cytokines in mouse macrophages	(Kowalski et al., 2005)
	10 or 25 $\mu$ M	LPS	Attenuates the release of NF-kappa B and cytokines from human monocytes	(Nicholas et al., 2007)
	1-25 $\mu$ M	LPS	Suppresses the expression of iNOS, COX-2, NF-kappa B, I $\kappa$ B and inflammatory cytokines in mouse macrophages	(Chen et al., 2007; Liang et al., 1999)
	1-50 $\mu$ M	Cytokines	Abrogates the activation of iNOS, COX-2, NF-kappa B, AP-1, and cell adhesion molecules in HUVECs	(Crespo et al., 2008; Gerritsen et al., 1995)
	30 $\mu$ M	PMA, PMACI	Down-regulates the release of inflammatory cytokines from mast cells	(Park et al., 2008)
Cytoprotective	5-40 $\mu$ M	IL-1 $\beta$ , IFN- $\gamma$	Attenuates cell death, production of NO, iNOS, NF-kappa B, ERK-1/2, STAT protein in RINmF5 and rat islets	(Kim et al., 2007)
	3.125-25 $\mu$ M	Breast cancer	Induces apoptosis and arrest cell population at G1 phase in BT-474 cells	(Mai et al., 2007)
	50 $\mu$ M	H <sub>2</sub> O <sub>2</sub> , Cu <sup>2+</sup> -ox-LDL	Inhibits the expression of Bax-2 and caspase-3 but enhances Bcl-2 expression in HUVECs	(Choi et al., 2003; Jeong et al., 2005)
	200 $\mu$ M	Peritoneal dialysis fluid,	prevents LDH release from mesothelial cells	(Riesenhuber et al., 2007)
	15 mg/kg/day	STZ	Decreases NO and MDA in rat pancreas and erythrocytes	(Coskun et al., 2005)
	50, 100, 200 $\mu$ M	LPS	Induces HO-1 and bilirubin production in mouse macrophages, ERK, P <sup>53</sup>	(Lin et al., 2003)
	3, 10, 30 $\mu$ M	LPS, IFN- $\gamma$	Inhibits the activation of NO, iNOS, NF-kappa B, AP-1, and STAT-1 in BV-2 microglia	(Chen et al., 2005)
40 and 60 $\mu$ M	H <sub>2</sub> O <sub>2</sub> , low serum	Elevates HO-1 protein induction and abolishes ROS release in PC12 cells	(Hong et al., 2009)	
DNA protective	3-48 $\mu$ M	Gamma radiation	Attenuates DNA strand breaks, MN frequency, and levels of TBARS in PBMSc	(Devipriya et al., 2008)
	1, 10, 15, 100 $\mu$ M	H <sub>2</sub> O <sub>2</sub> , B $\alpha$ P	Ameliorate DNA damage and formation of BPDE-DNA adduct in human lymphocytes	(Wilms et al., 2005)
	2 % diet	AD	Reduces MN frequency and enhances buccal cell telomere length	(Thomas et al., 2009)

Abbreviations: AD, alzheimer's disease; B $\alpha$ P, benzo alpha pyrene; Cu<sup>2+</sup>-ox-LDL, copper oxidized low-density lipoprotein; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; IFN- $\gamma$ , interferon-gamma; IL-1 $\beta$ , interleukin-1 beta; LPS, lipopolysaccharide; PMA, phorbol 12-myristate 13-acetate; PMACI, PMA and calcium ionophore; STZ, streptozotocin