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Therapeutic Potential of Polyphenols in Parkinson's Disease

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1. Introduction

Increased human life expectancy has resulted in larger geriatric population throughout the world. Consequently, there is increased prevalence of age-associated neurodegenerative diseases including Parkinson's disease (PD) with serious impact on healthcare. This has intensified the scientific research on the pathology and therapy of the central nervous system (CNS). Although modern approach in biomedical research has made major breakthroughs in understanding the pathological basis of PD, the knowledge about therapy is limited. Consequently, PD does not have a permanent cure.

During recent years, there have been several options for PD therapy including both pharmacological and neurosurgical approaches. These strategies are primarily aimed at improving the motor symptoms without any major side effects ultimately improving the quality of the life of the patient. Drugs such as L-dihydroxyphenyl alanine (levodopa or L-DOPA) replenish the lost dopamine in the brain in early PD and provide symptomatic relief. Apart from L-dopa therapy, other drugs including dopamine receptor agonists, MAO-B inhibitors and anti-cholinergic drugs have been utilized in the pharmacotherapy of PD (Almeida & Hyson, 2008). But, each class of drugs is limited by potential side effects and motor complications with chronic treatment. Further, most PD medications do not effectively tackle tremor, postural instability and cognitive deficits. Moreover, most of these drugs are not completely effective against degeneration of the remaining dopaminergic neurons (Almeida & Hyson, 2008). Due to these serious lacunae, there is a tremendous momentum to develop newer treatments involving disease modifying, restorative, possibly curative drugs with lesser side effects. Most importantly, these drugs should protect the dying neurons thus preventing further neuronal loss. In this direction there have been novel strategies of PD pharmacotherapy applicable either as independent therapies or as a supplement with the existing therapies. These have been tested in experimental models and although many of these molecules show promise, their toxicology, bioavailability and clinical efficacy in human subjects needs to be examined thoroughly before application to PD.

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Neurodegeneration in PD involves multiple pathways such as oxidative stress, mitochondrial damage, protein aggregation, neuroinflammation etc. Modern medicine utilizes a well-defined chemical molecule(s) for pharmacotherapy which might not be effective against different disease pathways. Hence, the challenge is to come up with novel molecules that could simultaneously target multiple disease pathways without significant side-effects, be non-toxic at higher concentrations and have the ability to cross the blood-brain barrier indicating a paradigm shift from monotherapy to multi-therapy based on various targets. Towards this, natural phytochemicals which possess medicinal properties are being exploited (Kumar, 2006) which has increased the interest in the use of herbal products (Tsao, 2010). Consequently, there is increasing support for combination of modern drugs with medicine to evolve better therapies. It is interesting to note that although phytochemicals normally function as toxins and protect the plant source against damage due to pests and harmful organisms, at the lower concentrations consumed by humans, these compounds activate adaptive cellular stress responses *in vivo* ("hormetic mechanisms") thereby providing cytoprotection against exogenous toxins. Such hormetic mechanisms relevant to neuronal survival and improved brain function ultimately elevate the levels of antioxidant enzymes, protein chaperones and neurotrophic factors (Mattson et al., 2007). Polyphenols from various plant sources form a major group of phytochemicals with potential therapeutic and curative properties.

2. Polyphenols: Structure and biological properties

Polyphenols are the most widely distributed natural compounds in the plant kingdom. They are the secondary metabolites which were originally synthesized to protect the plants against microbial attack, pests and ultraviolet radiation. Polyphenols are present in fruits, vegetables, oils etc. and provide plants with brilliant colours and fragrance. Polyphenols might possess many biologically significant functions with implications for human degenerative diseases (Han et al., 2007).

2.1 Chemistry of Polyphenols

Polyphenols in general have a phenolic structure with several hydroxyl groups. Natural polyphenols vary from simple molecules (viz., phenolic acids) to complex polymeric forms (viz., condensed tannins) (Tsao, 2010). Flavonoids are the largest group of polyphenols and have been studied extensively. Currently more than 8000 phenolic structures are known and among them over 4000 flavonoids have been identified (Bravo, 1998, Cheynier, 2005, Harborne & Williams, 2000).They are classified based on the number of phenolic rings and the structural elements that link these rings (Butterfield et al., 2002, Ramassamy, 2006) (Figures 1 and 2) as follows:

a. **Phenolic acids:** These are non-flavonoid polyphenols that constitute less than 1/3 of the phenolic content in our diet and are represented mainly by benzoic acids and cinnamic acid derivatives.

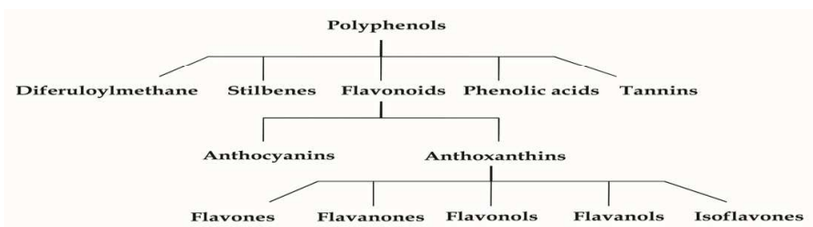

Fig. 1. Classification of polyphenols.

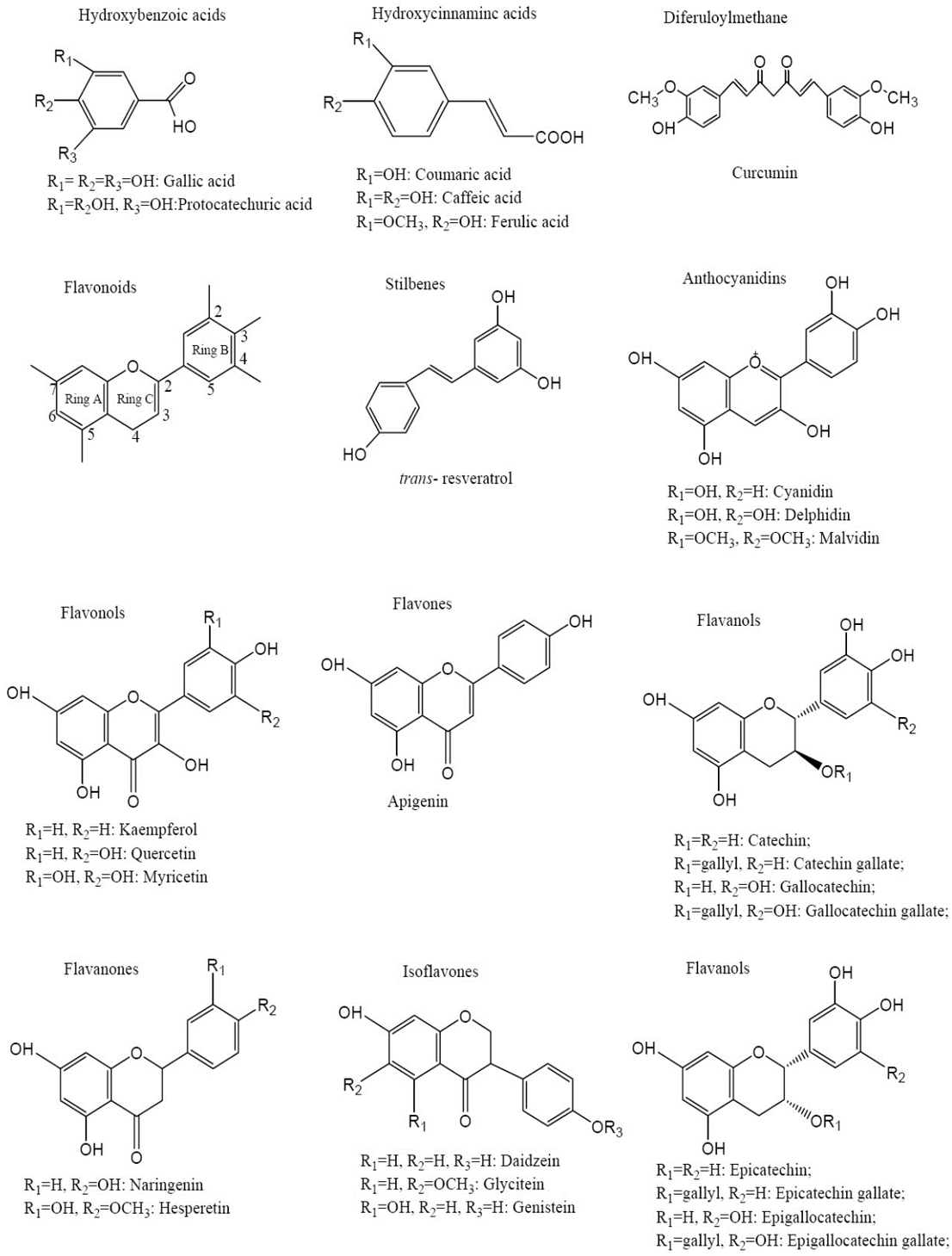

Fig. 2. Chemical structures of common polyphenols.

b. **Flavonoids:** These represent approximately 2/3 of the polyphenolic content in our diet. They have the C6-C3-C6 strucural backbone, of which two are phenolic rings named Ring A and Ring B, and one chromane ring (Tsao 2010). Flavonoids are further classified based on the oxidation state of the chromane ring into Anthocyanins and anthoxanthins. Anthoxanthins are further classified into Flavones, Flavonols, Flavonones, Isoflavones, Flavanols (D'Archivio et al., 2007).
c. **Stilbenes:** Stilbenes are characterized by the presence of 1,2-diphenylethylene nucleus with hydroxyl groups substituted on the aromatic rings (Han et al., 2007). The best known compound among Stilbenes is trans-resveratrol.
d. **Tannins:** Tannins are water soluble polyphenols and are classified into condensed and hydrolysable tannins.
e. **Diferuloylmethanes:** Diferuloylmethanes are characterized by two aromatic rings substituted with hydroxyls, and linked by aliphatic chain containing carbonyl groups. Curcumin is one of the best known polyphenol among diferuloylmethanes.

Most polyphenols are chemically modified by acetylation, hydroxylation, methoxylation. These modifications could significantly influence the physicochemical properties and *in vivo* absorption/degradation of the polyphenols. For e.g., acetylated flavonoids (epicatechin, epigallocatechin) are absorbed without deconjugation and hydrolysis (Rice-Evans & Miller 1996, Scalbert & Williamson 2000). Similarly, polyphenols with most antioxidant potential possess 3- 6 hydroxyl groups. However, hydroxylation in the C3 position significantly inhibits the antioxidant activity and chelation of metals (Huguet et al., 1990, van Acker et al., 1996). Most polyphenols also exist as glycosides with the addition of sugar and acylated sugars at different positions of the polyphenolic structure (one to three moieties per polyphenol) (Tsao, 2010). The attached sugar could be either glucose or rhamnose and each glycosylation influences the physicochemical properties and intestinal absorption of the polyphenol (Rice-Evans & Miller, 1996, Scalbert & Williamson, 2000). Accordingly, if polyphenols are glycosylated with glucose/galactose, they will be absorbed through the small intestine by specific carriers (Scalbert & Williamson, 2000). Those containing rhamnose cannot be absorbed through the small intestine and are degraded by rhamnosidases produced by the colonic microflora. Further, glycosylation of polyphenols might decrease their antioxidant properties (Fukumoto & Mazza, 2000).

2.2 Biological functions of polyphenols

Polyphenols might ameliorate neurodegeneration mainly via (i) intrinsic antioxidant properties and/or by (ii) modulation of cell signalling pathways that control cell survival, death and differentiation (Chen et al., 2000, Molina et al., 2003, Shen et al., 2007, Spencer, 2007).

2.2.1 Antioxidant properties

It has been suggested that consumption of foods or beverages which are rich in polyphenols can increase the antioxidant levels *in vivo* (Frankel et al., 1993). Polyphenols can protect against cellular oxidative stress by directly scavenging free radicals and by chelation of divalent metal ions. The phenolic hydroxyl groups are potent nucleophiles that neutralize free radicals and form aroxyl radicals and this is central to the antioxidant properties of polyphenols. The antioxidant potential is enhanced by the vicinal hydroxyl groups depending on their number and orientation relative to the electron withdrawing groups

such as COOH, CH_2COOH, or $(CH)_2CO_2CH$ (Rice-Evans et al., 1996). The radical scavenging activity of polyphenols is measured by Trolox (a water soluble α-tocopherol analog)-equivalent antioxidant capacity (TEAC) assay and expressed as the millimolar concentration of Trolox (TEAC=1) equivalent to the activity of a 1 mM solution of the given compound (Rice-Evans et al. 1996). Most of the common polyphenols have higher TEAC value compared to the endogenous antioxidant glutathione (GSH), whose TEAC is 1.0.
Since free divalent metal ions such as iron generate free radicals by fenton reaction, chelation of free iron by polyphenols protects neurons from oxidative stress (Li et al., 2010) with implications for PD and Alzheimer's disease (AD) (Sahu & Gray 1997, Sugihara et al., 1999). Flavonoids protect against oxidative damage either by forming complexes with iron or copper or by direct detoxification due to inherent structural characteristics that enhance the antioxidant potential (Bors et al., 1990).

2.2.2 Modulation of cell signalling pathways

Beyond antioxidant activities, polyphenols such as curcumin, resveratrol, quercetin and other flavonoids modulate cellular signalling pathways, that could affect the gene expression and interfere with cell death mechanisms (Williams et al., 2004). Polyphenols exert modulatory effects on neurons by selectively interacting with protein kinase and lipid kinase signalling cascades such as phosphatidylinositol 3-kinase (PI3 kinase or PI3K)/akt, tyrosine kinase, protein kinase C (PKC) and Mitogen activated protein kinase (MAPK) pathways (Agullo et al., 1997, Gamet-Payrastre et al., 1999, Matter et al., 1992, Schroeter et al., 2002, Spencer et al., 2003, Vlahos et al., 1994). Inhibitory or stimulatory actions at these pathways immensely affect the cellular functions by altering the phosphorylation states of target molecules and/or by modulating gene expression (Spencer, 2007). Many Polyphenols bind to ATP binding sites of proteins (Conseil et al., 1998) like PKC (Gamet-Payrastre et al. 1999, Kantengwa & Polla, 1991), protein kinase A (PKA) (Revuelta et al., 1997), calcium plasma membrane ATPase, mitochondrial ATPase and topoisomerase (Boege et al., 1996). For example, the stilbene resveratrol and the citrus flavones, naringenin and hesperetin have been shown to inhibit the activity of a number of protein kinases (Spencer 2007). Flavonoids and their metabolites can selectively interact within MAPK signalling pathways (Kobuchi et al., 1999, Kong et al., 2000).

a. **Extracellular signal-regulated kinase (ERK) pathway:** Some flavonoids are found to have inhibitory effect on the ERK pathway and some others activate this pathway. Flavonoids have close structural homology to specific inhibitors of ERK pathway, such as PD98059 (2'–amino-3'-methoxyflavone), which is a selective non-competitive inhibitor of the mitogen activated kinase, MEK 1 (Alessi et al., 1995). Flavonoids and their metabolites may also act on this pathway in a similar manner. Certain flavonoids such as Quercetin and its O-methylated metabolites are shown to induce neuronal apoptosis by inhibition of ERK pathway (Spencer 2003). The MEK inhibitor PD98059 has been shown to effectively block inducible nitric oxide synthase (iNOS) expression and generation of nitric oxide (NO•) (Bhat et al., 1998), suggesting that flavonoids may also be capable of exerting anti-inflammatory actions via inhibitory actions on MEK1 within the ERK signalling pathway. Studies have indicated that flavanols (Huang et al., 2005, Li et al., 2004), flavones (Chen et al., 2004, Kim et al., 2001, Lee et al., 2003, Shen et al., 2002, Woo et al., 2006), and flavonols (Chen et al., 2005) are all capable of inhibiting the release of NO• by activated microglia via the down-regulation of iNOS gene

expression. Epicatechin (EC), and one of its metabolites, 3'-O–methyl-(–)- epicatechin (mEC), have been shown to stimulate phosphorylation of ERK1/2 and the downstream transcription factor cAMP response element binding protein (CREB) at physiological concentrations (Schroeter et al., 2007). Some polyphenols may act on the ERK pathway via acting through steroid-like receptors in neurons to modulate ERK and CREB-mediated gene expression. For example, resveratrol rapidly activates ERK signalling through alpha and beta estrogen receptors (Klinge et al., 2005).

b. **c-Jun-N-terminal kinase (JNK):** There are a number of potential sites where flavonoids may interact in the JNK pathway. EC and mEC have been shown to protect neurons against oxidative damage via a mechanism involving the suppression of JNK, and downstream partners, c-jun and pro-caspase-3 (Schroeter et al., 2001). The flavone, baicalein, significantly inhibits 6-hydroxydopamine (6-OHDA) induced JNK activation and neuronal cell death and quercetin suppresses JNK activity and apoptosis induced by hydrogen peroxide (Ishikawa & Kitamura 2000), 4-hydroxy-2-nonenal (4HNE) (Uchida et al., 1999) and tumour necrosis factor-alpha (TNF-α) (Kobuchi et al. 1999). Flavonoids may inhibit the activation of JNK pathway upstream by decreasing oxidative stress and maintaining calcium homeostasis (Davis 1999). They may also inhibit JNK activation by modulation of the apoptosis signal-regulating kinase 1 (ASK1) phosphorylation state, and its association with 14-3-3 protein, which is essential for suppression of cellular apoptosis (Zhang, L. et al., 1999). Investigations have indicated that flavonoids might have anti-apoptotic property by blocking oxidative stress induced activation of caspase-3 in neurons (Schroeter et al. 2001, Schroeter et al., 2000). Flavonoid o-quinones, formed from the intracellular oxidation of flavonoids also inhibit JNK and other MAPKs via the nucleophilic addition to the cysteine residues of these proteins (Spencer et al., 2004).

c. **PI3 kinase pathway:** Flavonoids can modulate signalling through the serine/threonine kinase, Akt/PKB, one of the main downstream effectors of PI3K in neuronal survival (Coffer et al., 1998). Experimental studies suggest that flavonoids inhibit PI3K via direct interactions with its ATP binding site. Indeed, one of the most selective PI3K inhibitors available, LY294002, was modelled based on the structure of quercetin (Matter et al. 1992).

In the current review, we have discussed the properties and therapeutic potential in PD of three important polyphenols: cucumin, resveratrol and tea polyphenols.

3. Curcumin

Curcumin, the yellow curry spice from the rhizome of turmeric is a polyphenolic compound with several beneficiary properties. Chemically characterized to be diferuloylmethane ($C_{21}H_{20}O_6$) or 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl), curcumin exists as a group of compounds called curcuminoids.

3.1 Absorption

Although curcumin has several beneficial properties *in vivo*, a major limiting factor is its poor bioavailability. Its poor bioavailability is due to insolubility in aqueous media, poor absorption, rapid metabolism and fast systemic elimination. Following oral administration of curcumin (1.0 g / kg) in mice, 0.13 μg / ml was detected in the plasma after 15 min and peaked at 0.22 μg / ml at 1 hr. Plasma concentration of curcumin however declined to 5 ng /

ml at 6 h. Following intraperitoneal administration of curcumin (0.1 g/kg), only 2.25 μg / ml appeared in the plasma in the first 15 min. Upto 99% of curcumin and 85% of tetrahydrocurcumin was conjugated with glucuronide thus limiting their bioavailability. It has also been suggested that oral administration of curcumin results in very low absorption into the blood. At 1 h time point, the intestine, spleen, liver and kidney had 177.04, 26.06, 26.90, and 7.51 μg/g curcumin respectively, while the brain had as less as 0.41 μg / g. Mass spectrometry analysis suggested that curcumin was first biotransformed to dihydrocurcumin and then tetrahydrocurcumin which were subsequently converted to monoglucuronide conjugates (Pan et al., 1999). In a more recent study, curcumin was administered orally to rats at 500 mg / kg and the peak curcumin concentration of ~36 mg / whole tissue, in the intestine was reached at 1 h time point, while in the blood, liver and kidney, peak concentrations were reached at 6 h (Suresh & Srinivasan 2010). In a pilot human trial on cancer patients, the concentration of curcumin in the liver following oral administration (450 – 3600 mg/ day for 1 week prior to surgery) was measured. The results indicated that only trace levels of curcumin and its metabolites were present in the liver and in circulation and the order of magnitude was too less to exert pharmacological effects (Garcea et al., 2004). As a result of this constraint, research is now directed towards enhancing the bioavailability of curcumin. Animal and human studies suggest that administration of curcumin along with piperine / turmeric oil enhances its bioavailability (Bishnoi et al., 2010, Suresh & Srinivasan 2010). Administration of curcumin along with piperine enables curcumin to stay for longer in the tissues. When administered with piperine, curcumin was detected in the brain at 24, 48 and 96 h and at 48 h the levels of curcumin in the brain exceeded that found in the kidney (5.87 μg vs 1.16 μg) (Suresh & Srinivasan 2010). More recently, curcumin nanoparticles which are entirely water soluble have been suggested to enhance its bioavailability (Ray et al., 2011). Curcumin complexation with phosphatidyl choline (PC) and liposomal curcumin PC complex enhanced its bioavailability in terms of better absorption and improved pharmacokinetics (Gupta & Dixit 2011a, b).

3.2 Antioxidant properties of curcumin

The antioxidant activity of curcumin has been attributed to the various functional groups of curcumin. Jovanovic et al. suggest that the central methylenic group rather than the phenolic group is the H-atom donor, while others attribute its radical scavenging property to the phenolic group (Barclay et al., 2000, Priyadarsini et al., 2003) and the methoxy group further enhances this activity (Priyadarsini et al. 2003). The interactions between curcumin and biological relevant free radicals have been thoroughly investigated. Iwunze and McEwan demonstrated by biophysical techniques that curcumin directly detoxified the reactive nitrogen species peroxynitrite (PN) (Iwunze & McEwan 2004). Our group demonstrated that curcumin can protect neuronal mitochondria against PN induced nitration and nitrosylation of brain mitochondrial proteins (Mythri et al., 2007). It was also shown that curcumin protected against PN induced protein nitration and inhibition of enzyme activity of mitochondrial complex I with implications for PD (Mythri et al. 2007). Recently, we demonstrated that curcumin protects against PN mediated loss of mitochondrial membrane potential and mitochondrial integrity and curcumin derivatives offered improved protection compared to curcumin (Mythri et al. 2011). Mishra et al demonstrated that at low superoxide concentrations, curcumin effectively caused superoxide dismutation without itself undergoing any chemical change, but at higher

concentrations of superoxide, curcumin inhibited superoxide activity by reacting with it (Mishra et al., 2004). The enol structure with the intramolecular hydrogen bond of curcumin strongly enhances the free radical scavenging activity (Ohara 2005, Toniolo et al., 2002). *In vivo*, the antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). Curcumin has been shown to serve as a Michael acceptor, reacting with GSH and thioredoxin (Adams et al., 2005). Curcumin has been found to be at least ten times more active as an antioxidant than even vitamin E (Khopde et al., 2000). The phenolic and the methoxy group on the phenyl ring and the 1,3-diketone system seem to be important structural features of curcumin that can contribute to these effects. The antioxidant activity of curcumin increases when the phenolic group has a methoxy group at the ortho position (Motterlini et al., 2000).

3.3 Intracellular targets

The important molecular targets of curcumin include growth factors, growth factor receptors, transcription factors, transcription factor receptors, cytokines, enzymes and genes which regulate apoptosis. Curcumin activates the NF-E2-related factor 2/ Antioxidant Response Element (Nrf2/ARE) pathway which in turn induces synthesis of phase II antioxidant (Jeyapaul & Jaiswal, 2000, Wild et al., 1999), glutathione-S-transferase (GST) (Chanas et al., 2002, Ye et al., 2007), NADH quinone oxidoreductase 1 (NQO1) (Ye et al., 2007) and hemeoxygenase-1 (HO-1). Curcumin suppresses activation of the pro-survival transcription factor, nuclear factor kappa B (NFκB) by inhibition of IκB kinase (Jobin et al., 1999, Plummer et al., 1999). Suppression of NFκB leads to down regulation of cell cycle regulatory protein cyclin D1, cyclooxygenase 2 (COX2) and matrix metalloproteinase 9 (MMP-9) (Shishodia et al., 2005). Curcumin further, suppresses interleukin 6 (IL-6) mediated signal transducers and activators of transcription (STAT-3) phosphorylation and its subsequent nuclear translocation (Bharti et al., 2003). Curcumin, it has been reported, activates the peroxisome proliferator activated receptor γ (PPAR γ) and hence mediates expression of cyclin D1 and epidermal growth factor receptor (EGFR) (Chen & Xu, 2005). Curcumin down regulates the transcription factor, AP-1, by direct interaction with its DNA binding motif, (Bierhaus et al., 1997, Huang, T. S. et al., 1991) and also inhibits interleukin 1 alpha (IL-1α) and TNF-induced AP-1 activation (Xu, Y. X. et al., 1997). Moreover, curcumin targets the JNK pathway preventing JNK 1/2 and c Jun phosphorylation and caspase 3 activation (Yu et al., 2010). Curcumin probably interferes with the signalling molecules at the same level or proximally upstream of MAPKKK level, hence indirectly affects the JNK pathway (Chen, Y. R. & Tan 1998). Furthermore, curcumin induces anti apoptotic genes such as Bcl-2 and inhibits iNOS resulting in reduction of ROS, abrogates oxidative stress mediated cytochrome c release or caspase 3 activation, significantly increases levels of anti apoptotic proteins Bcl-2 and Bcl-xL and decreases levels of pro-apoptotic proteins Bax and Bad (Chen, J. et al., 2006, Chen, Y. R. & Tan 1998). Curcumin treatment causes a 3-7 fold increase in the modifier subunit of the GSH synthesizing enzyme, gamma-glutamyl cysteine ligase (γ-GCL), in both the neurons and astrocytes (Dale & Russell 1956, Lavoie, S. et al., 2009) and enhances GSH levels (Jagatha et al., 2008) probably by enhancing astrocytic efflux of GSH (Stridh et al., 2010). In addition, curcumin regulates iron metabolism by activation of iron regulatory protein and repression of ferretin, suggesting a role as an iron chelator (Jiao et al., 2006, Jiao et al., 2009).

Curcumin has been used as an antioxidant, antiseptic, anti-inflammatory, antibacterial and antitumor agent and has been used against various disorders such as arthritis,

cardiovascular diseases, lung fibrosis, gall stone formation, cardiotoxicity, diabetes, wound healing, AD and many more (Aggarwal 2006, Sharma et al., 2006). Recent studies have also shown curcumin to be protective against cancer (Duvoix et al., 2005), diabetes (Cheng et al., 2009, Peeyush et al., 2009) and for the reduction of blood cholesterol (Alwi et al., 2008, Ejaz et al., 2009, Jang et al., 2008). Curcumin protects against ischemia induced elevation in malondialdehyde (MDA) and lactate dehydrogenase (LDH) release in animal models (Dikshit et al., 1995). Faster restoration of muscle architecture upon curcumin treatment in injury models is probably mediated via NFκB activation (Thaloor et al., 1999).

3.4 Effects of curcumin in models of PD

More recently, curcumin has found its role as a therapeutic agent in models of neurological disorders such as stroke and AD (Lim et al., 2001, Thiyagarajan & Sharma 2004, Yang et al., 2005). Lim et al. have shown that dietary curcumin reduces amyloid pathology, oxidative stress and pro-inflammatory markers in transgenic mice, in addition curcumin reduces the levels of GFAP, a marker of astrocytic proliferation (Lim et al. 2001). Further, curcumin not only prevented formation of abeta aggregates but could also disintegrate preformed aggregates by directly binding to plaques (Yang et al. 2005). Curcumin can cross the blood brain barrier and is found to be least toxic in human subjects at high doses (Lao et al., 2006, Qureshi et al., 1992, Shankar et al., 1980, Shoba et al., 1998). It can detoxify ROS, prevent protein aggregation and induce neurogenesis *in vivo* (Kim, S. J. et al., 2008, Priyadarsini et al. 2003, Xu, Y. et al., 2007).

Since PD is a neurological condition involving oxidative and nitrosative stress pathways, curcumin can serve as a potential therapeutic molecule for PD. Although thiol reducing agents such as GSH have been evaluated for their anti-PD activity, their efficiency is limited due to poor ability to cross the blood brain barrier (Bharath et al., 2002). Curcumin on the other hand can cross the blood brain barrier and can be administered at higher doses without the risk of toxicity. Curcumin treatment protects substantia nigra (SN) neurons, improves striatal dopamine levels and chelates Fe^{2+}, following administration of 6-hydroxy dopamine (6-OHDA) in rats (Zbarsky et al., 2005). Curcumin treatment abrogates dopamine induced striatal neuron cell death (Luo et al., 1999). Curcumin treatment could further increase the density of dopaminergic neurons in the SN (Vajragupta et al., 2003). In all these studies, protection was afforded only by pretreatment with curcumin prior to administration of the toxin. A recent study in our laboratory indicated that chronic dietary consumption of turmeric caused an increase in the tyrosine hydroxylase (TH) positive neurons in the SN (Mythri et al. 2011). This is consistent with earlier reports suggesting that curcumin contributes to neurogenesis (Kim, S. J. et al. 2008, Xu, Y. et al. 2007). Similarly, our laboratory also demonstrated that curcumin derivatives with improved bioavailability offers better defense against 1-methyl-4-phenylpyridinium (MPP^+) in dopaminergic neurons (Mythri et al. 2011).

Curcumin treatment attenuates 3-nitropropionic acid mediated oxidative stress *in vivo* (Kumar, A. et al., 2007). PN is a highly labile reactive nitrogen species which inflicts severe cellular damage by nitrosative protein modifications. However, PN mediated nitrosative stress and mitochondrial dysfunction were attenuated by pretreatment with curcumin *in vitro* (Mythri et al. 2011). Curcumin mediated protection from PN toxicity is probably due to its direct interaction with and inactivation of PN *in vitro* (Iwunze & McEwan 2004, Mythri et al. 2007) or indirectly by enhancing GSH levels *in vivo* ((Jagatha et al. 2008, Mythri et al.

2007). Curcumin down regulates iNOS which is probably mediated by the cJun/AP-1 pathway (Brouet & Ohshima 1995, Chan et al., 1998, Chen, J. et al. 2006). It has been suggested that curcumin binding to the AP-1 binding site on the promoter region of iNOS, results in its inactivation (Brouet & Ohshima 1995). Pan et al. have further reported that curcumin reduces iNOS mRNA levels and blocks induction of NFκB (Pan, M. H. et al., 2000). Rajeswari and colleagues have reported an increase in striatal dopamine and dihydroxy phenyl acetic acid (DOPAC) levels following curcumin injection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-injected mice (Rajeswari & Sabesan 2008). In addition curcumin restores mitochondrial membrane potential, causes elevation in Cu-Zn SOD and modulates NFκB nuclear translocation (Wang, J. et al., 2009a) by inhibition of IL6 and TNFα (Wang, S. L. et al., 2009b). Curcumin treatment inhibits AP-1 pathway by prevention of c-Jun phosphorylation (Luo et al. 1999) in addition to inhibition of JNK phosphorylation (Sawada et al., 2002, Yu et al. 2010) and caspase 3 activation (Yu et al. 2010). It has been reported that curcumin induces anti apoptotic genes such as Bcl-2 and inhibits iNOS resulting in reduction of ROS, abrogates oxidative stress mediated cytochrome c release or caspase 3 activation, significantly increases levels of anti apoptotic proteins Bcl-2 and Bcl-xL and decreases levels of pro-apoptotic proteins Bax and Bad (Chen, J. et al. 2006, Chen, Y. R. & Tan 1998). Curcumin induced cytoprotection was probably mediated by the Bcl-2 – mitochondria – reactive oxygen species (ROS) – iNOS pathway.

Oxidative damage of lipids results in the formation of aldehydes such as 4HNE and MDA, which can integrate into lipid membranes resulting in disruption of membrane integrity, energy crisis and eventually cell death. Increased levels of 4HNE adducts have been reported in PD brains (Yoritaka et al., 1996). Lipid peroxidation mediated mitochondrial damage and apoptosis were abrogated by curcumin treatment and this was probably by checking cytochrome c release and caspase and PARP activation (Zhu et al., 2004). Curcumin was further able to protect from 4HNE mediated alterations in mitochondrial respiratory function and redox metabolism, cytochrome c release, DNA fragmentation and PARP activation in PC12 cells suggesting a protective function against lipid peroxidation mediated damage (Raza et al., 2008).

Interestingly, not only is curcumin an antioxidant molecule but can also increase the levels of GSH, an endogenous antioxidant molecule, probably by enhancing astrocytic efflux of GSH (Stridh et al. 2010). Results from our laboratory and others have shown that curcumin enhances GSH levels *in vitro* and *in vivo* (Jagatha et al. 2008, Rajeswari 2006), in addition to enhancing the antioxidant enzyme activities of SOD and catalase in the striatum and mid brain of MPTP injected mice (Rajeswari 2006). In addition curcumin treatment results in a 3-7 fold increase in the modifier subunit of the GSH synthesizing enzyme, γ-GCL, in both the neurons and astrocytes (Dickinson et al., 2003, LaVoie, M. J. et al., 2005). Curcumin mediated increase in the transcription of GCL genes is probably via regulation of the binding of transcription factors to the 12-tetradecanoate 13-acetate (TPA)-responsive elements (TRE) and electrophilic response element (EpRE) elements (Dickinson et al. 2003). It further activates the Nrf2/ARE pathway which in turn induces synthesis of phase II antioxidant enzymes such as GCL (Jeyapaul & Jaiswal 2000, Wild et al. 1999), GST (Chanas et al. 2002, Ye et al. 2007), NQO1 (Ye et al. 2007) and HO-1. We have used diester derivatives of curcumin (di-piperoyl, di-valinoyl and di-glutamoyl) with a resultant enhanced protection against GSH depletion mediated oxidative stress and toxin induced cell death in a dopaminergic neuronal cell line (Harish et al., 2010, Mythri et al. 2011). Particularly the di-glutamoyl derivative showed maximum protection due to its deesterification following

absorption thus providing glutamate as a precursor for GSH synthesis. Thus one could use such pro drugs with improved uptake and better radical scavenging properties to combat oxidative and nitrosative stress in various neurodegenerative disorders such as PD.

Curcumin further inhibits aggregation of α-synuclein *in vitro* (Pandey et al., 2008, Wang, M. S. et al., 2010) and aggregation of A53T mutant α-synuclein in SH-SY5Y cells in a dose dependent manner. Curcumin, thus enhances α-synuclein solubility rendering them non-toxic (Pandey et al. 2008). It also exhibits neuro-restorative properties as shown by its ability to disintegrate preformed α-synuclein fibrils (Ono & Yamada 2006). Curcumin pre-treatment resulted in a reduction in aggregation of synphilin-1, a component of Lewy neuritis seen during PD, as a function of rotenone induced nitrosative stress, in SH-SY5Y dopaminergic cells suggesting its efficacy in ameliorating nitrosative stress induced damage (Pal et al. 2011).

Curcumin has been suggested to regulate proteins involved in iron metabolism. Increased brain iron content is a major risk factor for PD pathogenesis. It has been reported that the SN of PD brains has increased iron content (Sofic et al., 1988). Not only is iron responsible for the production of ·OH radical, but also promotes dopamine autooxidation in the SN neurons resulting in the release of H_2O_2 (Ben-Shachar et al., 1995). It has been reported that curcumin induces activation of iron regulatory protein and repression of ferretin and a reduction in levels of hepcidin, suggesting a role as an iron chelator (Jiao et al. 2006, Jiao et al. 2009).

Epidemiological studies have suggested that consumption of curcumin by the Asian Indians is probably the reason for the low incidence of AD / PD in India when compared to the Caucasians (Ganguli et al., 2000). A study exploring the effect of race and age on the prevalence of PD reported that there are approximately 40% less melanized nigral neurons in Indian brains when compared to Caucasian brains (Muthane et al., 1998). Furthermore, there was no change in the number of nigral neurons with advancing age in the Asian Indian population (Alladi et al., 2009). Hence the lower prevalence of PD in India despite lower numbers of nigral neurons suggests protective mechanism probably related to the dietary habits. Chronic consumption of spices such as turmeric provide antioxidant defense against various conditions such as diabetes and cancer (Sinha et al., 2003, Srinivasan 2005). We have recently demonstrated that chronic dietary consumption of turmeric ameliorated the MPTP induced neurotoxicity in mice (Mythri et al. 2011). Although curcumin is the most active ingredient of turmeric, it could be more effective in its natural milieu. Also the biological properties of natural extracts would probably be mediated by their various constituents rather than a single compound. Therefore it would be interesting to study the pharmacokinetics and pharmacodynamics of curcumin or the other biologically active components of turmeric in order to completely understand its mechanism of action.

4. Resveratrol

Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a phytoalexin and a stilbenoid derived is a naturally occurring polyphenol with strong antioxidant properties (Baur & Sinclair 2006, Fremont 2000). Resveratrol is a dietary polyphenol found in the skin of grapes, raspberries, mulberries, pistachios and peanuts under normal conditions and synthesized by other medicinal and edible plants under stress conditions (Rocha-Gonzalez et al., 2008, Saiko et al., 2008). It exists as cis- and trans- isomers which are either free or bound to glucose (Mattivi et al., 1995). The trans- form can undergo isomerisation to the cis- form when exposed to ultraviolet irradiation (Lamuela-Raventos et al., 1995). Experimental evidences *in*

vitro and *in vivo* have demonstrated the pharmacological potential of resveratrol in human diseases and aging with curative properties against neurodegenerative diseases (Rocha-Gonzalez et al. 2008).

4.1 Absorption of resveratrol

The oral absorption of resveratrol in humans is thought to occur mainly by transepithelial diffusion. However, a major portion of resveratrol administered orally is excreted via feces and urine (Wenzel & Somoza 2005). Following oral ingestion, trans-resveratrol is extensively metabolized in the enterocyte before it enters the blood and target organs. Since trans-resveratrol is photosensitive it is easily oxidized thus presenting unfavorable pharmacokinetics (Frozza et al., 2010). Extensive metabolism in the intestine and liver results in the bioavailability of resveratrol to be <1% and dose escalation and repeated dose administration does not significantly alter the bioavailability. Metabolic studies, both in plasma and in urine, have revealed that resveratrol is modified as glucuronides and sulfates. The sulfated and glucuronidated forms appeared within approximately 15 min of entering the bloodstream, and moderate consumption of red wine results in serum levels of resveratrol that barely reach the micromolar concentrations. In contrast, its metabolites, which may be the active principle, circulate in serum for up to 9 h (Saiko et al. 2008). However, reduced dihydroresveratrol conjugates, in addition to highly polar but unknown products, may account for ~ 50% of resveratrol following oral administration. Apart from the metabolism in the intestine and liver, colonic bacterial metabolism also contributes to resveratrol bioavailability (Walle 2011). Among these, extremely rapid sulfate conjugation by the intestine/liver appears to be the rate-limiting step in resveratrol's bioavailability. Although the systemic bioavailability of resveratrol is very low, accumulation of resveratrol in epithelial cells along the aerodigestive tract and potentially active resveratrol metabolites may still produce *in vivo* effects (North & Verdin 2004). Since low bioavailability of resveratrol is a major obstacle to biomedical applications, efforts are in progress to improve the absorption and slow down its metabolism (Biasutto et al., 2010). Oral and intravenous (i.v.) administration of resveratrol in human volunteers revealed that the absorption following oral administration of 25 mg oral dose was at least 70%, with peak plasma levels of resveratrol and metabolites at 491 ± 90 ng/ml (about 2 μM) and a plasma half-life of 9.2 ± 0.6 h. However, only trace amounts of unchanged resveratrol (<5 ng/ml) could be detected in plasma and most of the oral dose was recovered in urine.

4.2 Effects of resveratrol in models of PD

Similar to curcumin, the effectiveness of resveratrol is due to its ability to simultaneously target multiple pathways and proteins and thus may be effective in restoring homoestasis *in vivo*. The most important property relevant in abrogation of neuronal damage is its antioxidant potential. This has been extensively studied in different models and most of them refer to the systemic effects (Kovacic & Somanathan 2010). Experiments from our laboratory have showed that resveratrol prevented peroxynitrite mediated nitration of mitochondrial proteins and this was significantly higher compared to curcumin (Mythri et al. 2007). Apart from its antioxidant properties, resveratrol displays anti-cancer and anti-inflammatory properties. The anti-cancer properties arise due its ability to inhibit multiple target enzymes including kinases, cyclooxygenases, ribonucleotide reductase and DNA polymerases. Similarly, resveratrol protects the cardiovascular system against ischemic-

reperfusion injury, promotes vasorelaxation, protects the endothelium and displays anti-atherosclerotic properties and other functions thereby strongly supporting its role in cardioprotection. Resveratrol displays different properties depending on its concentration and also on the target cell and its physiology (Saiko et al. 2008). Resveratrol and its derivatives have shown promise in AD therapy and other neurodegenerative disorders (Albani et al., 2010) and more specifically on the inhibition of β-amyloid peptide aggregation (Richard et al., 2011).

Interestingly, resveratrol-mediated intracellular effects and protective mechanisms might be via its effects as an agonist of the sirtuins (also called SIRT or silent information regulator two-proteins), which belong to the histone deacetylase family (Pallas et al., 2008, Wang, F. et al., 2007, Zhuang et al., 2003). Sirtuins possess NAD^+ dependent deacetylase activity and mono-ribosyltransferase activity and are found in most organisms (North & Verdin 2004, Yamamoto et al., 2007). SIRT1 is a major modulator of metabolism and displays therapeutic properties (Finkel et al., 2009, Harikumar & Aggarwal 2008, Karuppagounder et al., 2009). It has been hypothesized that by activating SIRT1, resveratrol modulates the activity of numerous proteins, including peroxisome proliferator-activated receptor coactivator-1alpha (PGC-1 alpha), the FOXO family, Akt (protein kinase B) and NFκB (Pallas et al., 2009). The beneficial effects of resveratrol as an anti-aging compound are believed to be mediated via the activation of SIRT1 (Hung et al., 2010).

Resveratrol administration in adult mice protected the SN dopaminergic neurons and striatal dopamine against the neurotoxic effects of MPTP (Anderson et al., 2006, Blanchet et al., 2008). Resveratrol administration also significantly protected mice from MPTP-induced motor coordination impairment, hydroxyl radical overloading, and neuronal loss with implications for PD therapy (Lu et al., 2008). In cell culture, treatment with resveratrol protected against MPP^+ toxicity and oxidative damage by modulating the apoptotic markers (Bournival et al., 2009, Gelinas & Martinoli 2002). It has also been demonstrated that resveratrol effectively blocked the proteolytic cleavage of PKCδ and kinase activity induced by MPP^+. In BV-2 microglial cells activated with lipopolysaccharide (LPS), pretreatment with resveratrol suppressed pro-inflammatory cytokine production and nitric oxide release. It could be surmised that resveratrol protects against the dopaminergic neurodegeneration by modulating the PKCδ dependent proapoptotic signaling pathway and the inflammatory response in activated microglia (Gordon , 2010). Resveratrol significantly reversed the toxic effects of MPTP by increasing the levels of dopamine and its metabolites, GSH and activities of GPx and reducing lipid peroxidation along with enhanced behaviour performance indicating that resveratrol could target multiple pathways with therapeutic potential in PD (Anandhan et al., 2010). Interestingly, transfection with SIRT1 siRNA blocked MPP^+-induced apoptosis in SH-SY5Y cells indicating that the toxicity of MPP^+ was mediated via SIRT1 and possibly through the regulation of another pro-apoptotic protein BCL2/Adinovirus E1B 19kDa Interacting Protein 2 (BNIP2). In a similar study, Alvira and colleagues showed that although resveratrol prevented MPP^+ induced death of cortical neurons in culture, the effect was not mediated via SIRT1 activation, since sirtinol - a SIRT1 inhibitor could not attenuate MPP^+ toxicity (Alvira et al., 2007). Furthermore MPP^+ decreased the expression of SIRT1 indicating that the antiapoptotic effects of resveratrol against MPP^+ are independent of the stimulation of SIRT1 and depend on its antioxidant properties.

Other *in vitro* studies have also demonstrated the effects of Resveratrol against different neurotoxins (Chao et al., 2008, Okawara et al., 2007, Outeiro et al., 2007). The therapeutic role of resveratrol has been demonstrated in 6-OHDA induced *in vivo* model of PD. Ultrastructural analysis showed that resveratrol alleviated 6-OHDA-induced chromatin condensation, mitochondrial dysfunction and vacuolization of SN dopaminergic neurons. Resveratrol also reduced the levels of COX-2 and TNF-α mRNA in the SN suggesting that resveratrol exerts its effects via reduced neuroinflammatory reaction (Jin, F. et al., 2008). Oral treatment with resveratrol and its liposomal form prevented oxidative damage, prevented neuronal damage and restored motor behaviour in a 6-OHDA rat model of PD (Khan et al., 2010, Wang, Y. et al., 2011). The study also showed that resveratrol liposome offered better therapeutic effect than free resveratrol due to increased bioavailability. Oxyresveratrol, a polyhydroxylated stilbene from mulberry showed improved protection against 6-OHDA compared to resveratrol owing to its antioxidant activity, blood-brain barrier permeability and water solubility (Chao et al. 2008). Pinostilbene, a methylated derivative of resveratrol showed improved cellular bioavailability and better defense against 6-OHDA neurotoxicity in neuronal cell culture (Chao et al., 2010b). Lee et al. demonstrated that resveratrol protected SH-SY5Y neuroblastoma cells from apoptosis induced by dopamine (Lee, M. K. et al., 2007).

Experiments in rat primary midbrain neuron-glia cultures demonstrated that resveratrol protected dopaminergic neurons against LPS-induced neurotoxicity in a dose and time-dependent manner via inhibition of microglial activation and suppression of release of proinflammatory factors. The anti-inflammatory effects and therapeutic effects against LPS toxicity was attributed to the inhibition of NADPH oxidase-dependent generation of reactive oxygen species and attenuation of translocation of the cytosolic subunit (p47) of NADPH oxidase to the cell membrane. This mechanism was substantiated when resveratrol was not effective in cultures from NADPH deficient mice. This is also related to an attenuation of MAPK and NFκB signalling pathways in microglia (Zhang, F. et al., 2010). Bureau and colleagues demonstrated that resveratrol reduced apoptotic neuronal cell death induced by neuroinflammation in an LPS cell model and strongly decreased the mRNA expression of two proinflammatory genes, IL-1α and TNF-α (Bureau et al., 2008).

Administration of a botanical extract (Regrapex-R) prepared from whole grape *Vitis vinifera* and *Polygonum cuspidatum*, enriched with polyphenols including resveratrol, to a drosophila transgenic model of PD overexpressing alpha-synuclein caused dose-dependent scavenging effects on ROS, protected mitochondria from oxidative damage and improved locomotor dysfunction and extended lifespan (Long et al., 2009). Resveratrol was able to protect neuronal cells in culture against toxicity arising from two aggregation-prone proteins, the AD-involved amyloid-beta (1-42) peptide (Abeta42) and the familiar PD linked alpha-synuclein (A30P) [alpha-syn(A30P)] (Albani et al., 2009).

5. Tea polyphenols

Tea is one of the most frequently consumed beverage of the world. Out of the 2.5 million metric tons of dried tea manufactured annually, ~20 % is green tea, which is mainly consumed in China and Japan and ~78 % is black tea, which is consumed in Western countries (Chen, L. et al., 1997). Although consumption of tea as an ancient beverage and a lifestyle habit has been recognized, its potential pharmacological actions beneficial to human health have been recently reported (Weinreb et al., 2004). Human epidemiological and

animal experiments indicate that consumption of green and black tea might protect the brain against aging and reduce the incidence of dementia, AD and PD, which might be one of the mechanistic factors underlying the significantly lower rates of age-related neurological disorders among Asians compared to European or American populations (Mandel, S. A. et al., 2008). Green tea is non-fermented and contains mainly catechins that accounts for 30-40% of its dry weight. Catechins are polyphenols that have been suggested to contribute to the therapeutic properties of green tea. On the contrary, black and red teas are extensively fermented and oolong tea is semi-fermented which catalyzes the oxidation and polymerization of catechins thereby reducing their content to 3-10 % of dry weight. The catechins from green tea are polyphenols representing flavonoids. The eight major catechins of green tea are (+)-catechin (C), (+)-catechin gallate, (+)-gallocatechin, (+)-gallocatechin gallate, (-)-epicatechin (EC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin gallate (EGCG) (+ and – represent *cis* and *trans* isomers respectively). EGCG is the most abundant catechin (Higdon & Frei 2003). Green tea in addition to catechins contain 2-3% of caffeic acid and 1-6% of amino acids (theanine constitutes about 50% amino acid content) (Higdon & Frei 2003).

5.1 Absorption

The *in vivo* metabolism of green tea catechins has been very well documented in humans and laboratory animals (Li, C. et al., 2000, Pietta et al., 1998). In humans, orally administered catechins are absorbed, metabolized and largely excreted within 24 h. Catechins were detected in rat plasma and bile as free or sulphated and glucuronidated conjugates (Harada et al., 1999). The bioavailability of green tea polyphenols *in vivo* depends on the route of administration. After intragastric administration of decaffeinated green tea (DGT) (200 mg/kg) in rats, 13.7 % of EGC and 31.2 % of EC were shown in the plasma, but only 0.1% of EGCG was bioavailable (Chen, L. et al. 1997). Intravenous injection of DGT (25 mg/kg) showed that, the beta-elimination half-lives of EGCG, EGC, and EC were 212, 45, and 41 min respectively (Chen, L. et al. 1997). Recent studies have suggested that the EC metabolites such as epicatechin glucuronide and 3'–O-methylated epicatechin glucuronide formed after oral ingestion in rats were detectable in the brain (Abd El Mohsen et al., 2002). The results from the distribution study suggest that EGCG is mainly excreted through bile, and that EGC and EC are excreted through both the bile and urine (Spencer 2003).

5.2 Antioxidant functions of tea polyphenols

There is growing evidence that catechins exert protective role in neurodegeneration. Several studies have suggested that the potential curative and therapeutic effects of tea polyphenols could be attributed to their free radical scavenging capacity. Catechins are powerful hydrogen donating antioxidants and scavengers of reactive oxygen and nitrogen species *in vitro* (Lee, S. et al., 2000, Matsuoka et al., 1995, Oliver et al., 1990). Tea polyphenols may also regulate antioxidant enzymes like SOD and catalase in mouse striatum (Levites et al., 2001). Progressive iron accumulation in SN pars compacta of PD patients is well established and is considered to be a major contributor to oxidative stress (Gerlach et al., 1994, Riederer et al., 1989). Green tea polyphenols can stoichiometrically bind ferric iron to form an inactive iron polyphenol complex (Grinberg et al., 1997). In rat brain tissue, green tea and black tea extracts were shown to inhibit lipid peroxidation promoted by iron ascorbate in homogenates of brain mitochondrial membranes (Levites et al., 2002b). EGCG inhibited

paraquat-induced MDA production in rat liver microsomes by scavenging superoxide radicals and by iron chelating activity (Liou et al., 2001).

5.3 Functions of tea and its constituent polyphenols in PD

Several prospective studies have assessed the association between coffee/tea consumption and PD risk, but the results are inconsistent. Kandinov and colleagues carried out a retrospective study on 278 consecutive PD patients and assessed the data on smoking and coffee or tea consumption and found that disease progression was not affected by cigarette smoking, tea or coffee consumption (Kandinov et al., 2007). In contrast, the same group demonstrated that cigarette smoking, coffee and tea drinking may protect against PD and delay the onset of disease (Kandinov et al., 2009). According to their study in human patients, while consumption of more than 3 cups of tea per day delayed the onset of motor symptoms by 7.7 years, coffee consumption advanced the age of PD onset by 4.8 years. In a related study, Barranco Quintana and colleagues compiled data from human studies carried out by different groups and observed a clear protective effect of tea consumption and this protective effect was more evident in the Chinese populations (Barranco Quintana et al., 2009). They also suggest that the low rate of tea consumption among persons with PD could provide valuable insight into the pathology. A population based study in ethnic Chinese to understand the role of environmental factors and dietary intake demonstrated that while there was a dose-dependent protective effect of PD in coffee and tea drinkers and smokers, a history of exposure to heavy metals increased the risk of PD (Tan, E. K. et al., 2003). Tan et al. observed that while black tea, a caffeine-containing beverage, showed an inverse association with PD risk, green tea drinking was unrelated to PD (Tan, Louis C. et al., 2008). A study among Finnish subjects indicated that coffee drinking is associated with a lower risk of PD and increased tea consumption is associated with a lower risk of PD (Hu et al., 2007). Since most of these studies are based on survey among PD patients, it would be difficult to draw significant conclusions.

However, experiments in cell and animal models have clearly indicated the therapeutic effects of tea extracts and its constituent catechin, EGCG against PD. These curative properties might be due to their ability to act as antioxidants, modulators of intracellular neuronal signalling, metabolism, cell survival/death genes, and mitochondrial function (Mandel, S. A. et al. 2008, Mandel, S. A. et al., 2011). With reference to PD therapy, EGCG has a dual therapeutic effect *in vivo (*Kang et al., *2010)*. Firstly, EGCG is a naturally occurring catechol-O-methyl transferase (COMT) inhibitor which strongly inhibited human liver COMT-mediated O-methylation of L-DOPA in a dose-dependent manner and decreased the accumulation of 3-O-methyldopa in the plasma and striatum *in vivo* following oral administration of L-DOPA + carbidopa. In addition, EGCG also protected against glutamate-induced oxidative cytotoxicity in hippocampal cultures through inactivation of the NFκB-signaling pathway *in vitro* and against kainic acid-induced oxidative damage and neurodegeneration in the hippocampus *in vivo*.

Many studies related to therapeutic effects of tea polyphenols in PD have been carried out in the Parkinsonian model involving the neurotoxin 6-OHDA and have obtained varied results. Rats treated with black tea either prior to or after 6-OHDA provided significant protection in terms of behavioural and motor functions, antioxidant levels, apoptotic markers, dopaminergic neuronal numbers and expression of tyrosine hydroxylase (TH). However, the degree of improvement in motor and neurochemical deficits was more

prominent in 6-OHDA rats pre-treated with the extract (Chaturvedi et al., 2006). Green tea polyphenols protected SH-SY5Y neuroblastoma cells against apoptosis induced by 6-OHDA as evidenced by lowered apoptotic markers, restoration of mitochondrial integrity, decreased oxidative damage and intracellular free Ca^{2+} and inhibition of auto-oxidation of 6-OHDA. Further, the cells were protected against 6-OHDA-induced increase in levels of NO and protein nitration, and over-expression of neuronal NOS (nNOS) and iNOS. These results indicate that green tea polyphenols ameliorate 6-OHDA toxicity via attenuation of the ROS-NO pathway (Guo et al., 2005). The same group confirmed these effects against 6-OHDA *in vivo* in mid brain and striatum again emphasizing the involvement of the ROS-NO pathway (Guo et al., 2007). In order to identify the active ingredient against 6-OHDA, five catechins [EGCG, ECG, EGC, EC and (+)-C] representing the most prominent tea polyphenols were compared with regard to their effects on 6-OHDA-induced apoptosis in PC12 cells and the protective effects of the five catechins were in the order ECG > EGCG > EC > (+)-C > EGC and the antiapoptotic activities appear to be structurally related to the 3-gallate group (Jin, C. F. et al., 2001, Nie et al., 2002). In a related study, it was showed that EGCG protected against 6-OHDA via stimulation of PKC and modulation of cell survival/cell cycle genes such as Bax, Bad, Mdm2, Bcl-2, Bcl-w, and Bcl-x(L) and also by potent antioxidant and iron chelating actions thereby preventing nuclear translocation and activation of cell death promoting NFκB (Levites et al., 2002a). Since the stability and bioavailability of EGCG are restricted, Chao et al. generated and tested a pro-drug representing a fully acetylated EGCG (pEGCG) in a PD cell model (Chao et al., 2010a). They found that pEGCG displayed improved protection compared to EGCG against 6-OHDA toxicity in SH-SY5Y neuroblastoma cells probably via activation of Akt pathway and reduced caspase-3 activity. In contrast, when Leaver et al. administered rats with EGCG for 14 days followed by exposure to 6-OHDA, they observed that EGCG produced subtle symptomatic relief in lesioned animals and could not prevent neuronal damage to a significant extent (Leaver et al., 2009).

Tea extracts and EGCG have displayed therapeutic effect in other toxic models of PD. Tea extract and EGCG protected against MPTP mediated dopamine loss and neurotoxicity *in vivo* and this effect could be mediated by inhibition of NOS (Choi et al., 2002, Kim, J. S. et al., 2010, Li, R. et al., 2006). In a related study, it was demonstrated that green tea extract and EGCG protected against MPTP neurotoxicity via antioxidant effects and inhibition of monoamine oxidase-B (MOAB) (Levites et al. 2001). Mechanistically, green tea polyphenols can ameliorate neuronal damage via inhibitory effects on dopamine transporters (DAT), through which they block MPP^+ uptake and protect dopaminergic neurons against MPP^+-induced injury (Pan, T. et al., 2003). Similarly, Hou et al. (2008) demonstrated that EGCG attenuated cell death in PC12 cells induced by the herbicide and PD toxin paraquat (PQ) by maintaining mitochondrial membrane potential, inhibiting caspase-3 activity and down regulating the expression of pro-apoptotic protein second mitochondrial-derived activator of caspase (SMAC) in cytosol. However, in rotenone-treated mesencephalic cultures and organotypic striatal cultures, EGCG protected striatal slices to a limited extent by counteracting NO production by rotenone but was not significantly effective against rotenone toxicity in mesencephalic cultures (Moldzio et al., 2010).

Green tea could also protect against environmental toxin-induced cell injury and neuroinflammation with implications for PD. Tai and Truong (2010) reported that EGCG reduced dichlorodiphenyl-trichloroethane (DDT)-induced cell death in dopaminergic SH-

SY5Y cells suggesting that EGCG might activate a protective mechanism that might alleviate organochlorine pesticide-induced cell injury. Likewise, EGCG also inhibited LPS-activated microglial secretion of NO and TNF-α through the down-regulation of iNOS and TNF-α expression thereby protecting against neuroinflammation and injury in dopaminergic neurons (Li, R. et al. 2004). The antioxidant property of EGCG is also beneficial against protein aggregation in PD. Iron induces toxic aggregation of monomeric alpha synuclein leading to neurodegeneration in dopaminergic neurons. In the MPTP model, iron accumulation is also linked to NO-dependent mechanism. Mandel et al. showed that EGCG prevented the accumulation of iron and alpha-synuclein in SN thereby preventing neuronal damage (Mandel, S. et al., 2004). However, green tea and its constituent polyphenols could not protect PC12 cells against L-glutamate and MPP^+ (Mazzio et al., 2001).

6. Conclusions

Most of the drugs currently used in PD therapy replenish the brain dopamine and provide symptomatic relief during early PD. However, many patients develop motor complications with chronic treatment. Further, these drugs do not slowdown or prevent the progression of the disease since their ability to prevent neuronal damage has not been comprehensively validated in humans. Therefore, novel therapies with possible curative properties are being exploited for adjunctive therapy. It is well documented that neurodegeneration in PD is contributed by several interrelated disease pathways but the molecular mechanisms of their relationships and their chronology have not been completely understood. Therefore, any molecule(s) with therapeutic potential in PD should be simultaneously effective against multiple pathways. In this regard, several *in vitro* and *in vivo* studies using PD models have tested natural antioxidants and molecules for their ability to protect against neurodegeneration with implications for therapy. The most prominent are the polyphenolic antioxidants obtained from plant sources. Most of these compounds display antioxidant, anti-inflammatory and anti-cancer properties, cross the blood-brain barrier and prevent neuronal damage in neurological disorders. Recent studies strongly support the clinical application of these compounds in PD. The current chapter explores the therapeutic potential of polyphenols such as curcumin, resveratrol and tea polyphenols in PD. These three polyphenols share common biological properties including antioxidant function, low toxicity and therapeutic benefits in the brain of different PD models. The available data indeed indicate that these polyphenols could have therapeutic potential in PD. Although several studies have been carried out in the recent years, the biological properties and health benefits of these polyphenols have not been completely understood. However, the most important limiting factor for the therapeutic application of these compounds in PD is their limited bioavailability *in vivo*. Further, the delivery of compounds specifically to mid-brain dopaminergic neurons for maximum therapeutic effect has not been completely standardized. Apart from this, studies are also needed to test the safety and efficacy in humans to translate the experimental results for therapeutic application in PD patients.

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8. References

Abd El Mohsen MM, Kuhnle G, Rechner AR, Schroeter H, Rose S, Jenner P & Rice-Evans CA (2002) Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. *Free Radic Biol Med*. Vol. 33, No. 12, (Dec 15 2002):pp. (1693-1702), 0891-5849 (Print)

Adams BK, Cai J, Armstrong J, Herold M, Lu YJ, Sun A, Snyder JP, Liotta DC, Jones DP & Shoji M (2005) EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. *Anticancer Drugs*. Vol. 16, No. 3, (Mar 2005):pp. (263-275), 0959-4973 (Print)

Aggarwal BB, Bhatt, I.D., Ichikawa, H., Ahn, K.S., Sethi, G., Sandur, S.K., Natarajan, C., Seeram, N., Shishodia, S. (2006) Curcumin–biological and medicinal properties. in: *Turmeric: the genus Curcuma,* (ed.), pp (297-368), Taylor and Francis GroupLondon

Agullo G, Gamet-Payrastre L, Manenti S, Viala C, Remesy C, Chap H & Payrastre B (1997) Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: a comparison with tyrosine kinase and protein kinase C inhibition. *Biochem Pharmacol*. Vol. 53, No. 11, (Jun 1 1997):pp. (1649-1657), 0006-2952 (Print)

Albani D, Polito L, Batelli S, De Mauro S, Fracasso C, Martelli G, Colombo L, Manzoni C, Salmona M, Caccia S, Negro A & Forloni G (2009) The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by alpha-synuclein or amyloid-beta (1-42) peptide. *J Neurochem*. Vol. 110, No. 5, (Sep 2009):pp. (1445-1456), 1471-4159 (Electronic)

Albani D, Polito L, Signorini A & Forloni G (2010) Neuroprotective properties of resveratrol in different neurodegenerative disorders. *Biofactors*. Vol. 36, No. 5, (Sep 2010):pp. (370-376), 1872-8081 (Electronic)

Alessi DR, Cuenda A, Cohen P, Dudley DT & Saltiel AR (1995) PD 098059 is a specific inhibitor of the activation of mitogen-activated protein kinase kinase in vitro and in vivo. *J Biol Chem*. Vol. 270, No. 46, (Nov 17 1995):pp. (27489-27494), 0021-9258 (Print)

Alladi PA, Mahadevan A, Yasha TC, Raju TR, Shankar SK & Muthane U (2009) Absence of age-related changes in nigral dopaminergic neurons of Asian Indians: relevance to lower incidence of Parkinson's disease. *Neuroscience*. Vol. 159, No. 1, (Mar 3 2009):pp. (236-245), 0306-4522 (Print)

Almeida QJ, Hyson HC (2008) The evolution of pharmacological treatment for Parkinson's disease. *Recent Pat CNS Drug Discov.* 2008 Jan;Vol 3, No. 1, (Jan 2008): pp. (50-54).

Alvira D, Yeste-Velasco M, Folch J, Verdaguer E, Canudas AM, Pallas M & Camins A (2007) Comparative analysis of the effects of resveratrol in two apoptotic models: inhibition of complex I and potassium deprivation in cerebellar neurons. *Neuroscience*. Vol. 147, No. 3, (Jul 13 2007):pp. (746-756), 0306-4522 (Print)

Alwi I, Santoso T, Suyono S, Sutrisna B, Suyatna FD, Kresno SB & Ernie S (2008) The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Med Indones*. Vol. 40, No. 4, (Oct 2008):pp. (201-210), 0125-9326 (Print)

Anandhan A, Tamilselvam K, Vijayraja D, Kumar NA, Rajasankar S & Manivasagam T (2010) *Resveratrol attenuates oxidative stress and improves behaviour in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) challenged mice*,

Anderson DW, Bradbury KA & Schneider JS (2006) Neuroprotection in Parkinson models varies with toxin administration protocol. *Eur J Neurosci*. Vol. 24, No. 11, (Dec 2006):pp. (3174-3182), 0953-816X (Print)

Barclay LR, Vinqvist MR, Mukai K, Goto H, Hashimoto Y, Tokunaga A & Uno H (2000) On the antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity. *Org Lett*. Vol. 2, No. 18, (Sep 7 2000):pp. (2841-2843), 1523-7060 (Print)

Barranco Quintana JL, Allam MF, Del Castillo AS & Navajas RF (2009) Parkinson's disease and tea: a quantitative review. *J Am Coll Nutr*. Vol. 28, No. 1, (Feb 2009):pp. (1-6), 1541-1087 (Electronic)

Baur JA & Sinclair DA (2006) Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov*. Vol. 5, No. 6, (Jun 2006):pp. (493-506), 1474-1776 (Print)

Ben-Shachar D, Zuk R & Glinka Y (1995) Dopamine neurotoxicity: inhibition of mitochondrial respiration. *J Neurochem*. Vol. 64, No. 2, (Feb 1995):pp. (718-723), 0022-3042 (Print)

Bharath S, Hsu M, Kaur D, Rajagopalan S & Andersen JK (2002) Glutathione, iron and Parkinson's disease. *Biochem Pharmacol*. Vol. 64, No. 5-6, (Sep 2002):pp. (1037-1048), 0006-2952 (Print)

Bharti AC, Donato N & Aggarwal BB (2003) Curcumin (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation in human multiple myeloma cells. *J Immunol*. Vol. 171, No. 7, (Oct 1 2003):pp. (3863-3871), 0022-1767 (Print)

Bhat NR, Zhang P, Lee JC & Hogan EL (1998) Extracellular signal-regulated kinase and p38 subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-alpha gene expression in endotoxin-stimulated primary glial cultures. *J Neurosci*. Vol. 18, No. 5, (Mar 1 1998):pp. (1633-1641), 0270-6474 (Print)

Biasutto L, Marotta E, Garbisa S, Zoratti M & Paradisi C (2010) Determination of Quercetin and Resveratrol in Whole Blood—Implications for Bioavailability Studies. *Molecules*. Vol. 15, No. 9, 2010):pp. (6570-6579), 1420-3049

Bierhaus A, Zhang Y, Quehenberger P, Luther T, Haase M, Muller M, Mackman N, Ziegler R & Nawroth PP (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*. Vol. 77, No. 4, (Apr 1997):pp. (772-782), 0340-6245 (Print)

Bishnoi M, Chopra K, Rongzhu L & Kulkarni SK (2010) Protective Effect of Curcumin and its Combination with Piperine (Bioavailability Enhancer) Against Haloperidol-Associated Neurotoxicity: Cellular and Neurochemical Evidence. *Neurotox Res*. Vol., No. (Nov 13 2010):pp. 1476-3524 (Electronic)

Blanchet J, Longpre F, Bureau G, Morissette M, DiPaolo T, Bronchti G & Martinoli MG (2008) Resveratrol, a red wine polyphenol, protects dopaminergic neurons in MPTP-treated mice. *Prog Neuropsychopharmacol Biol Psychiatry*. Vol. 32, No. 5, (Jul 1 2008):pp. (1243-1250), 0278-5846 (Print)

Boege F, Straub T, Kehr A, Boesenberg C, Christiansen K, Andersen A, Jakob F & Kohrle J (1996) Selected novel flavones inhibit the DNA binding or the DNA religation step of eukaryotic topoisomerase I. *J Biol Chem*. Vol. 271, No. 4, (Jan 26 1996):pp. (2262-2270), 0021-9258 (Print)

Bors W, Heller W, Michel C & Saran M (1990) Flavonoids as antioxidants: determination of radical-scavenging efficiencies. *Methods Enzymol*. Vol. 186, No. 1990):pp. (343-355), 0076-6879 (Print)

Bournival J, Quessy P & Martinoli MG (2009) Protective effects of resveratrol and quercetin against MPP+ -induced oxidative stress act by modulating markers of apoptotic death in dopaminergic neurons. *Cell Mol Neurobiol*. Vol. 29, No. 8, (Dec 2009):pp. (1169-1180), 1573-6830 (Electronic)

Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev*. Vol. 56, No. 11, (Nov 1998):pp. (317-333), 0029-6643 (Print)

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*. Vol. 206, No. 2, (Jan 17 1995):pp. (533-540), 0006-291X (Print)

Bureau G, Longpre F & Martinoli MG (2008) Resveratrol and quercetin, two natural polyphenols, reduce apoptotic neuronal cell death induced by neuroinflammation. *J Neurosci Res*. Vol. 86, No. 2, (Feb 1 2008):pp. (403-410), 1097-4547 (Electronic)

Butterfield D, Castegna A, Pocernich C, Drake J, Scapagnini G & Calabrese V (2002) Nutritional approaches to combat oxidative stress in Alzheimer's disease. *J Nutr Biochem*. Vol. 13, No. 8, (Aug 2002):pp. (444), 1873-4847 (Electronic)

Chan MM, Huang HI, Fenton MR & Fong D (1998) In vivo inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties. *Biochem Pharmacol*. Vol. 55, No. 12, (Jun 15 1998):pp. (1955-1962), 0006-2952 (Print)

Chanas SA, Jiang Q, McMahon M, McWalter GK, McLellan LI, Elcombe CR, Henderson CJ, Wolf CR, Moffat GJ, Itoh K, Yamamoto M & Hayes JD (2002) Loss of the Nrf2 transcription factor causes a marked reduction in constitutive and inducible expression of the glutathione S-transferase Gsta1, Gsta2, Gstm1, Gstm2, Gstm3 and Gstm4 genes in the livers of male and female mice. *Biochem J*. Vol. 365, No. Pt 2, (Jul 15 2002):pp. (405-416), 0264-6021 (Print)

Chao J, Lau WK, Huie MJ, Ho YS, Yu MS, Lai CS, Wang M, Yuen WH, Lam WH, Chan TH & Chang RC (2010a) A pro-drug of the green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) prevents differentiated SH-SY5Y cells from toxicity induced by 6-hydroxydopamine. *Neurosci Lett*. Vol. 469, No. 3, (Jan 29 2010a):pp. (360-364), 1872-7972 (Electronic)

Chao J, Li H, Cheng KW, Yu MS, Chang RC & Wang M (2010b) Protective effects of pinostilbene, a resveratrol methylated derivative, against 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y cells. *J Nutr Biochem*. Vol. 21, No. 6, (Jun 2010b):pp. (482-489), 1873-4847 (Electronic)

Chao J, Yu MS, Ho YS, Wang M & Chang RC (2008) Dietary oxyresveratrol prevents parkinsonian mimetic 6-hydroxydopamine neurotoxicity. *Free Radic Biol Med*. Vol. 45, No. 7, (Oct 1 2008):pp. (1019-1026), 0891-5849 (Print)

Chaturvedi RK, Shukla S, Seth K, Chauhan S, Sinha C, Shukla Y & Agrawal AK (2006) Neuroprotective and neurorescue effect of black tea extract in 6-hydroxydopamine-

lesioned rat model of Parkinson's disease. *Neurobiol Dis*. Vol. 22, No. 2, (May 2006):pp. (421-434), 0969-9961 (Print)

Chen A & Xu J (2005) Activation of PPAR{gamma} by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. *Am J Physiol Gastrointest Liver Physiol*. Vol. 288, No. 3, (Mar 2005):pp. (G447-456), 0193-1857 (Print)

Chen C, Yu R, Owuor ED & Kong AN (2000) Activation of antioxidant-response element (ARE), mitogen-activated protein kinases (MAPKs) and caspases by major green tea polyphenol components during cell survival and death. *Arch Pharm Res*. Vol. 23, No. 6, (Dec 2000):pp. (605-612), 0253-6269 (Print)

Chen CJ, Raung SL, Liao SL & Chen SY (2004) Inhibition of inducible nitric oxide synthase expression by baicalein in endotoxin/cytokine-stimulated microglia. *Biochem Pharmacol*. Vol. 67, No. 5, (Mar 1 2004):pp. (957-965), 0006-2952 (Print)

Chen J, Tang XQ, Zhi JL, Cui Y, Yu HM, Tang EH, Sun SN, Feng JQ & Chen PX (2006) Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2-mitochondria-ROS-iNOS pathway. *Apoptosis*. Vol. 11, No. 6, (Jun 2006):pp. (943-953), 1360-8185 (Print)

Chen JC, Ho FM, Pei-Dawn Lee C, Chen CP, Jeng KC, Hsu HB, Lee ST, Wen Tung W & Lin WW (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*. Vol. 521, No. 1-3, (Oct 3 2005):pp. (9-20), 0014-2999 (Print)

Chen L, Lee MJ, Li H & Yang CS (1997) Absorption, distribution, elimination of tea polyphenols in rats. *Drug Metab Dispos*. Vol. 25, No. 9, (Sep 1997):pp. (1045-1050), 0090-9556 (Print)

Chen YR & Tan TH (1998) Inhibition of the c-Jun N-terminal kinase (JNK) signaling pathway by curcumin. *Oncogene*. Vol. 17, No. 2, (Jul 16 1998):pp. (173-178), 0950-9232 (Print)

Cheng TC, Lin CS, Hsu CC, Chen LJ, Cheng KC & Cheng JT (2009) Activation of muscarinic M-1 cholinoceptors by curcumin to increase glucose uptake into skeletal muscle isolated from Wistar rats. *Neurosci Lett*. Vol. 465, No. 3, (Nov 20 2009):pp. (238-241), 1872-7972 (Electronic)

Cheynier V (2005) Polyphenols in foods are more complex than often thought. *Am J Clin Nutr*. Vol. 81, No. 1 Suppl, (Jan 2005):pp. (223S-229S), 0002-9165 (Print)

Choi JY, Park CS, Kim DJ, Cho MH, Jin BK, Pie JE & Chung WG (2002) Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate. *Neurotoxicology*. Vol. 23, No. 3, (Sep 2002):pp. (367-374), 0161-813X (Print)

Coffer PJ, Jin J & Woodgett JR (1998) Protein kinase B (c-Akt): a multifunctional mediator of phosphatidylinositol 3-kinase activation. *Biochem J*. Vol. 335 (Pt 1), No. (Oct 1 1998):pp. (1-13), 0264-6021 (Print)

Conseil G, Baubichon-Cortay H, Dayan G, Jault JM, Barron D & Di Pietro A (1998) Flavonoids: a class of modulators with bifunctional interactions at vicinal ATP- and steroid-binding sites on mouse P-glycoprotein. *Proc Natl Acad Sci U S A*. Vol. 95, No. 17, (Aug 18 1998):pp. (9831-9836), 0027-8424 (Print)

D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C & Masella R (2007) Polyphenols, dietary sources and bioavailability. *Ann Ist Super Sanita*. Vol. 43, No. 4, 2007):pp. (348-361), 0021-2571 (Print)

Dale WM & Russell C (1956) A study of the irradiation of catalase by ionizing radiations in the presence of cysteine, cystine and glutathione. *Biochem J*. Vol. 62, No. 1, (Jan 1956):pp. (50-57), 0264-6021 (Print)

Davis RJ (1999) Signal transduction by the c-Jun N-terminal kinase. *Biochem Soc Symp*. Vol. 64, No. 1999):pp. (1-12), 0067-8694 (Print)

Dickinson DA, Iles KE, Zhang H, Blank V & Forman HJ (2003) Curcumin alters EpRE and AP-1 binding complexes and elevates glutamate-cysteine ligase gene expression. *FASEB J*. Vol. 17, No. 3, (Mar 2003):pp. (473-475), 1530-6860 (Electronic)

Dikshit M, Rastogi L, Shukla R & Srimal RC (1995) Prevention of ischaemia-induced biochemical changes by curcumin & quinidine in the cat heart. *Indian J Med Res*. Vol. 101, No. (Jan 1995):pp. (31-35), 0971-5916 (Print)

Duvoix A, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E, Dicato M & Diederich M (2005) Chemopreventive and therapeutic effects of curcumin. *Cancer Lett*. Vol. 223, No. 2, (Jun 8 2005):pp. (181-190), 0304-3835 (Print)

Ejaz A, Wu D, Kwan P & Meydani M (2009) Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *J Nutr*. Vol. 139, No. 5, (May 2009):pp. (919-925), 1541-6100 (Electronic)

Finkel T, Deng C-X & Mostoslavsky R (2009) Recent progress in the biology and physiology of sirtuins. *Nature*. Vol. 460, No. 7255, 2009):pp. (587-591), 0028-0836

Frankel EN, Waterhouse AL & Kinsella JE (1993) Inhibition of human LDL oxidation by resveratrol. *Lancet*. Vol. 341, No. 8852, (Apr 24 1993):pp. (1103-1104), 0140-6736 (Print)

Fremont L (2000) Biological effects of resveratrol. *Life Sci*. Vol. 66, No. 8, (Jan 14 2000):pp. (663-673), 0024-3205 (Print)

Frozza RL, Bernardi A, Paese K, Hoppe JB, da Silva T, Battastini AM, Pohlmann AR, Guterres SS & Salbego C (2010) Characterization of trans-resveratrol-loaded lipid-core nanocapsules and tissue distribution studies in rats. *J Biomed Nanotechnol*. Vol. 6, No. 6, (Dec 2010):pp. (694-703), 1550-7033 (Print)

Fukumoto LR & Mazza G (2000) Assessing antioxidant and prooxidant activities of phenolic compounds. *J Agric Food Chem*. Vol. 48, No. 8, (Aug 2000):pp. (3597-3604), 0021-8561 (Print)

Gamet-Payrastre L, Manenti S, Gratacap MP, Tulliez J, Chap H & Payrastre B (1999) Flavonoids and the inhibition of PKC and PI 3-kinase. *Gen Pharmacol*. Vol. 32, No. 3, (Mar 1999):pp. (279-286), 0306-3623 (Print)

Ganguli M, Chandra V, Kamboh MI, Johnston JM, Dodge HH, Thelma BK, Juyal RC, Pandav R, Belle SH & DeKosky ST (2000) Apolipoprotein E polymorphism and Alzheimer disease: The Indo-US Cross-National Dementia Study. *Arch Neurol*. Vol. 57, No. 6, (Jun 2000):pp. (824-830), 0003-9942 (Print)

Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, Steward WP, Gescher AJ & Berry DP (2004) Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. *Br J Cancer*. Vol. 90, No. 5, (Mar 8 2004):pp. (1011-1015), 0007-0920 (Print)

Gelinas S & Martinoli MG (2002) Neuroprotective effect of estradiol and phytoestrogens on MPP+-induced cytotoxicity in neuronal PC12 cells. *J Neurosci Res*. Vol. 70, No. 1, (Oct 1 2002):pp. (90-96), 0360-4012 (Print)

Gerlach M, Ben-Shachar D, Riederer P & Youdim MB (1994) Altered brain metabolism of iron as a cause of neurodegenerative diseases? *J Neurochem*. Vol. 63, No. 3, (Sep 1994):pp. (793-807), 0022-3042 (Print)

Gordon,R. (2010). Resveratrol Protects Dopaminergic Neurons in Parkinson's Disease Models by Modulating the PKC-delta Apoptotic Signaling Pathway & Microglial Activation (24:763.5) Proceedings of FASEB meeting, 0892-6638, conference location, April, 2010

Grinberg LN, Newmark H, Kitrossky N, Rahamim E, Chevion M & Rachmilewitz EA (1997) Protective effects of tea polyphenols against oxidative damage to red blood cells. *Biochem Pharmacol*. Vol. 54, No. 9, (Nov 1 1997):pp. (973-978), 0006-2952 (Print)

Guo S, Bezard E & Zhao B (2005) Protective effect of green tea polyphenols on the SH-SY5Y cells against 6-OHDA induced apoptosis through ROS-NO pathway. *Free Radic Biol Med*. Vol. 39, No. 5, (Sep 1 2005):pp. (682-695), 0891-5849 (Print)

Guo S, Yan J, Yang T, Yang X, Bezard E & Zhao B (2007) Protective effects of green tea polyphenols in the 6-OHDA rat model of Parkinson's disease through inhibition of ROS-NO pathway. *Biol Psychiatry*. Vol. 62, No. 12, (Dec 15 2007):pp. (1353-1362), 1873-2402 (Electronic)

Gupta NK & Dixit VK (2011a) Development and evaluation of vesicular system for curcumin delivery. *Arch Dermatol Res*. Vol. 303, No. 2, (Mar 2011a):pp. (89-101), 1432-069X (Electronic)

Gupta NK & Dixit VK (2011b) Bioavailability enhancement of curcumin by complexation with phosphatidyl choline. *J Pharm Sci*. Vol. 100, No. 5, (May 2011b):pp. (1987-1995), 1520-6017 (Electronic)

Han X, Shen T & Lou H (2007) Dietary Polyphenols and Their Biological Significance. *International Journal of Molecular Sciences*. Vol. 8, No. 9, 2007):pp. (950-988), 1422-0067

Harada M, Kan Y, Naoki H, Fukui Y, Kageyama N, Nakai M, Miki W & Kiso Y (1999) Identification of the major antioxidative metabolites in biological fluids of the rat with ingested (+)-catechin and (-)-epicatechin. *Biosci Biotechnol Biochem*. Vol. 63, No. 6, (Jun 1999):pp. (973-977), 0916-8451 (Print)

Harborne JB & Williams CA (2000) Advances in flavonoid research since 1992. *Phytochemistry*. Vol. 55, No. 6, (Nov 2000):pp. (481-504), 0031-9422 (Print)

Harikumar KB & Aggarwal BB (2008) Resveratrol: a multitargeted agent for age-associated chronic diseases. *Cell Cycle*. Vol. 7, No. 8, (Apr 15 2008):pp. (1020-1035), 1551-4005 (Electronic)

Harish G, Venkateshappa C, Mythri RB, Dubey SK, Mishra K, Singh N, Vali S & Bharath MM (2010) Bioconjugates of curcumin display improved protection against glutathione depletion mediated oxidative stress in a dopaminergic neuronal cell line: Implications for Parkinson's disease. *Bioorg Med Chem*. Vol. 18, No. 7, (Apr 1 2010):pp. (2631-2638), 1464-3391 (Electronic)

Higdon JV & Frei B (2003) Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. *Crit Rev Food Sci Nutr*. Vol. 43, No. 1, 2003):pp. (89-143), 1040-8398 (Print)

Hou RR, Chen JZ, Chen H, Kang XG, Li MG & Wang BR (2008) Neuroprotective effects of (-)-epigallocatechin-3-gallate (EGCG) on paraquat-induced apoptosis in PC12 cells. *Cell Biol Int*. Vol. 32, No. 1, (Jan 2008):pp. (22-30), 1065-6995 (Print)

Hu G, Bidel S, Jousilahti P, Antikainen R & Tuomilehto J (2007) Coffee and tea consumption and the risk of Parkinson's disease. *Mov Disord*. Vol. 22, No. 15, (Nov 15 2007):pp. (2242-2248), 0885-3185 (Print)

Huang Q, Wu LJ, Tashiro S, Gao HY, Onodera S & Ikejima T (2005) (+)-Catechin, an ingredient of green tea, protects murine microglia from oxidative stress-induced DNA damage and cell cycle arrest. *J Pharmacol Sci*. Vol. 98, No. 1, (May 2005):pp. (16-24), 1347-8613 (Print)

Huang TS, Lee SC & Lin JK (1991) Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells. *Proc Natl Acad Sci U S A*. Vol. 88, No. 12, (Jun 15 1991):pp. (5292-5296), 0027-8424 (Print)

Huguet AI, Manez S & Alcaraz MJ (1990) Superoxide scavenging properties of flavonoids in a non-enzymic system. *Z Naturforsch C*. Vol. 45, No. 1-2, (Jan-Feb 1990):pp. (19-24), 0939-5075 (Print)

Hung CW, Chen YC, Hsieh WL, Chiou SH & Kao CL (2010) Ageing and neurodegenerative diseases. *Ageing Res Rev*. Vol. 9 Suppl 1, No. (Nov 2010):pp. (S36-46), 1872-9649 (Electronic)

Ishikawa Y & Kitamura M (2000) Anti-apoptotic effect of quercetin: intervention in the JNK- and ERK-mediated apoptotic pathways. *Kidney Int*. Vol. 58, No. 3, (Sep 2000):pp. (1078-1087), 0085-2538 (Print) 0085-2538 (Linking)

Iwunze MO & McEwan D (2004) Peroxynitrite interaction with curcumin solubilized in ethanolic solution. *Cell Mol Biol (Noisy-le-grand)*. Vol. 50, No. 6, (Sep 2004):pp. (749-752), 0145-5680 (Print)

Jagatha B, Mythri RB, Vali S & Bharath MM (2008) Curcumin treatment alleviates the effects of glutathione depletion in vitro and in vivo: therapeutic implications for Parkinson's disease explained via in silico studies. *Free Radic Biol Med*. Vol. 44, No. 5, (Mar 1 2008):pp. (907-917), 0891-5849 (Print)

Jang EM, Choi MS, Jung UJ, Kim MJ, Kim HJ, Jeon SM, Shin SK, Seong CN & Lee MK (2008) Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat-fed hamsters. *Metabolism*. Vol. 57, No. 11, (Nov 2008):pp. (1576-1583), 1532-8600 (Electronic)

Jeyapaul J & Jaiswal AK (2000) Nrf2 and c-Jun regulation of antioxidant response element (ARE)-mediated expression and induction of gamma-glutamylcysteine synthetase heavy subunit gene. *Biochem Pharmacol*. Vol. 59, No. 11, (Jun 1 2000):pp. (1433-1439), 0006-2952 (Print)

Jiao Y, Wilkinson Jt, Christine Pietsch E, Buss JL, Wang W, Planalp R, Torti FM & Torti SV (2006) Iron chelation in the biological activity of curcumin. *Free Radic Biol Med*. Vol. 40, No. 7, (Apr 1 2006):pp. (1152-1160), 0891-5849 (Print)

Jiao Y, Wilkinson Jt, Di X, Wang W, Hatcher H, Kock ND, D'Agostino R, Jr., Knovich MA, Torti FM & Torti SV (2009) Curcumin, a cancer chemopreventive and

chemotherapeutic agent, is a biologically active iron chelator. *Blood*. Vol. 113, No. 2, (Jan 8 2009):pp. (462-469), 1528-0020 (Electronic)

Jin CF, Shen SR, Sr. & Zhao BL (2001) Different effects of five catechins on 6-hydroxydopamine-induced apoptosis in PC12 cells. *J Agric Food Chem*. Vol. 49, No. 12, (Dec 2001):pp. (6033-6038), 0021-8561 (Print)

Jin F, Wu Q, Lu YF, Gong QH & Shi JS (2008) Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. *Eur J Pharmacol*. Vol. 600, No. 1-3, (Dec 14 2008):pp. (78-82), 1879-0712 (Electronic)

Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA & Sartor RB (1999) Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. *J Immunol*. Vol. 163, No. 6, (Sep 15 1999):pp. (3474-3483), 0022-1767 (Print)

Kandinov B, Giladi N & Korczyn AD (2007) The effect of cigarette smoking, tea, and coffee consumption on the progression of Parkinson's disease. *Parkinsonism Relat Disord*. Vol. 13, No. 4, (May 2007):pp. (243-245), 1353-8020 (Print)

Kandinov B, Giladi N & Korczyn AD (2009) Smoking and tea consumption delay onset of Parkinson's disease. *Parkinsonism Relat Disord*. Vol. 15, No. 1, (Jan 2009):pp. (41-46), 1353-8020 (Print)

Kang KS, Wen Y, Yamabe N, Fukui M, Bishop SC & Zhu BT (2010) Dual beneficial effects of (-)-epigallocatechin-3-gallate on levodopa methylation and hippocampal neurodegeneration: in vitro and in vivo studies. *PLoS One*. Vol. 5, No. 8, 2010):pp. (e11951), 1932-6203 (Electronic)

Kantengwa S & Polla BS (1991) Flavonoids, but not protein kinase C inhibitors, prevent stress protein synthesis during erythrophagocytosis. *Biochem Biophys Res Commun*. Vol. 180, No. 1, (Oct 15 1991):pp. (308-314), 0006-291X (Print)

Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF & Gibson GE (2009) Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. *Neurochem Int*. Vol. 54, No. 2, (Feb 2009):pp. (111-118), 0197-0186 (Print)

Khan MM, Ahmad A, Ishrat T, Khan MB, Hoda MN, Khuwaja G, Raza SS, Khan A, Javed H, Vaibhav K & Islam F (2010) Resveratrol attenuates 6-hydroxydopamine-induced oxidative damage and dopamine depletion in rat model of Parkinson's disease. *Brain Res*. Vol. 1328, No. (Apr 30 2010):pp. (139-151), 1872-6240 (Electronic)

Khopde SM, Priyadarsini KI, Guha SN, Satav JG, Venkatesan P & Rao MN (2000) Inhibition of radiation-induced lipid peroxidation by tetrahydrocurcumin: possible mechanisms by pulse radiolysis. *Biosci Biotechnol Biochem*. Vol. 64, No. 3, (Mar 2000):pp. (503-509), 0916-8451 (Print)

Kim H, Kim YS, Kim SY & Suk K (2001) The plant flavonoid wogonin suppresses death of activated C6 rat glial cells by inhibiting nitric oxide production. *Neurosci Lett*. Vol. 309, No. 1, (Aug 17 2001):pp. (67-71), 0304-3940 (Print)

Kim JS, Kim JM, O JJ & Jeon BS (2010) Inhibition of inducible nitric oxide synthase expression and cell death by (-)-epigallocatechin-3-gallate, a green tea catechin, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *J Clin Neurosci*. Vol. 17, No. 9, (Sep 2010):pp. (1165-1168), 1532-2653 (Electronic)

Kim SJ, Son TG, Park HR, Park M, Kim MS, Kim HS, Chung HY, Mattson MP & Lee J (2008) Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *J Biol Chem*. Vol. 283, No. 21, (May 23 2008):pp. (14497-14505), 0021-9258 (Print)

Klinge CM, Blankenship KA, Risinger KE, Bhatnagar S, Noisin EL, Sumanasekera WK, Zhao L, Brey DM & Keynton RS (2005) Resveratrol and estradiol rapidly activate MAPK signaling through estrogen receptors alpha and beta in endothelial cells. *J Biol Chem*. Vol. 280, No. 9, (Mar 4 2005):pp. (7460-7468), 0021-9258 (Print)

Kobuchi H, Roy S, Sen CK, Nguyen HG & Packer L (1999) Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway. *Am J Physiol*. Vol. 277, No. 3 Pt 1, (Sep 1999):pp. (C403-411), 0002-9513 (Print)

Kong AN, Yu R, Chen C, Mandlekar S & Primiano T (2000) Signal transduction events elicited by natural products: role of MAPK and caspase pathways in homeostatic response and induction of apoptosis. *Arch Pharm Res*. Vol. 23, No. 1, (Feb 2000):pp. (1-16), 0253-6269 (Print)

Kovacic P & Somanathan R (2010) Multifaceted approach to resveratrol bioactivity: Focus on antioxidant action, cell signaling and safety. *Oxid Med Cell Longev*. Vol. 3, No. 2, (Mar-Apr 2010):pp. (86-100), 1942-0994 (Electronic)

Kumar A, Naidu PS, Seghal N & Padi SS (2007) Effect of curcumin on intracerebroventricular colchicine-induced cognitive impairment and oxidative stress in rats. *J Med Food*. Vol. 10, No. 3, (Sep 2007):pp. (486-494), 1096-620X (Print)

Kumar V (2006) Potential medicinal plants for CNS disorders: an overview. *Phytother Res*. Vol. 20, No. 12, (Dec 2006):pp. (1023-1035), 0951-418X (Print)

Lamuela-Raventos RM, Romero-Perez AI, Waterhouse AL & de la Torre-Boronat MC (1995) Direct HPLC Analysis of cis- and trans-Resveratrol and Piceid Isomers in Spanish Red Vitis vinifera Wines. *Journal of Agricultural and Food Chemistry*. Vol. 43, No. 2, 1995):pp. (281-283), 0021-8561

Lao CD, Ruffin MTt, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL & Brenner DE (2006) Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med*. Vol. 6, No. 2006):pp. (10), 1472-6882 (Electronic)

LaVoie MJ, Ostaszewski BL, Weihofen A, Schlossmacher MG & Selkoe DJ (2005) Dopamine covalently modifies and functionally inactivates parkin. *Nat Med*. Vol. 11, No. 11, (Nov 2005):pp. (1214-1221), 1078-8956 (Print)

Lavoie S, Chen Y, Dalton TP, Gysin R, Cuenod M, Steullet P & Do KQ (2009) Curcumin, quercetin, and tBHQ modulate glutathione levels in astrocytes and neurons: importance of the glutamate cysteine ligase modifier subunit. *J Neurochem*. Vol. 108, No. 6, (Mar 2009):pp. (1410-1422), 1471-4159 (Electronic)

Leaver KR, Allbutt HN, Creber NJ, Kassiou M & Henderson JM (2009) Oral pre-treatment with epigallocatechin gallate in 6-OHDA lesioned rats produces subtle symptomatic relief but not neuroprotection. *Brain Res Bull*. Vol. 80, No. 6, (Dec 16 2009):pp. (397-402), 1873-2747 (Electronic)

Lee H, Kim YO, Kim H, Kim SY, Noh HS, Kang SS, Cho GJ, Choi WS & Suk K (2003) Flavonoid wogonin from medicinal herb is neuroprotective by inhibiting inflammatory activation of microglia. *FASEB J*. Vol. 17, No. 13, (Oct 2003):pp. (1943-1944), 1530-6860 (Electronic)

Lee MK, Kang SJ, Poncz M, Song KJ & Park KS (2007) Resveratrol protects SH-SY5Y neuroblastoma cells from apoptosis induced by dopamine. *Exp Mol Med*. Vol. 39, No. 3, (Jun 30 2007):pp. (376-384), 1226-3613 (Print)

Lee S, Suh S & Kim S (2000) Protective effects of the green tea polyphenol (-)-epigallocatechin gallate against hippocampal neuronal damage after transient global ischemia in gerbils. *Neurosci Lett*. Vol. 287, No. 3, (Jun 30 2000):pp. (191-194), 0304-3940 (Print)

Levites Y, Amit T, Youdim MB & Mandel S (2002a) Involvement of protein kinase C activation and cell survival/ cell cycle genes in green tea polyphenol (-)-epigallocatechin 3-gallate neuroprotective action. *J Biol Chem*. Vol. 277, No. 34, (Aug 23 2002a):pp. (30574-30580), 0021-9258 (Print)

Levites Y, Weinreb O, Maor G, Youdim MB & Mandel S (2001) Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration. *J Neurochem*. Vol. 78, No. 5, (Sep 2001):pp. (1073-1082), 0022-3042 (Print)

Levites Y, Youdim MB, Maor G & Mandel S (2002b) Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures. *Biochem Pharmacol*. Vol. 63, No. 1, (Jan 1 2002b):pp. (21-29), 0006-2952 (Print)

Li C, Lee MJ, Sheng S, Meng X, Prabhu S, Winnik B, Huang B, Chung JY, Yan S, Ho CT & Yang CS (2000) Structural identification of two metabolites of catechins and their kinetics in human urine and blood after tea ingestion. *Chem Res Toxicol*. Vol. 13, No. 3, (Mar 2000):pp. (177-184), 0893-228X (Print)

Li R, Huang YG, Fang D & Le WD (2004) (-)-Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury. *J Neurosci Res*. Vol. 78, No. 5, (Dec 1 2004):pp. (723-731), 0360-4012 (Print)

Li R, Peng N, Du F, Li XP & Le WD (2006) Epigallocatechin gallate protects dopaminergic neurons against 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity by inhibiting microglial cell activation. *Nan Fang Yi Ke Da Xue Xue Bao*. Vol. 26, No. 4, (Apr 2006):pp. (376-380), 1673-4254 (Print)

Li X, Jankovic J & Le W (2010) Iron chelation and neuroprotection in neurodegenerative diseases. *Journal of Neural Transmission*. Vol., No. 2010):pp. (1-5), 0300-9564

Lim GP, Chu T, Yang F, Beech W, Frautschy SA & Cole GM (2001) The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci*. Vol. 21, No. 21, (Nov 1 2001):pp. (8370-8377), 1529-2401 (Electronic)

Liou HH, Chen RC, Chen TH, Tsai YF & Tsai MC (2001) Attenuation of paraquat-induced dopaminergic toxicity on the substantia nigra by (-)-deprenyl in vivo. *Toxicol Appl Pharmacol*. Vol. 172, No. 1, (Apr 1 2001):pp. (37-43), 0041-008X (Print)

Long J, Gao H, Sun L, Liu J & Zhao-Wilson X (2009) Grape extract protects mitochondria from oxidative damage and improves locomotor dysfunction and extends lifespan in a Drosophila Parkinson's disease model. *Rejuvenation Res*. Vol. 12, No. 5, (Oct 2009):pp. (321-331), 1557-8577 (Electronic)

Lu F, Zahid M, Wang C, Saeed M, Cavalieri EL & Rogan EG (2008) Resveratrol prevents estrogen-DNA adduct formation and neoplastic transformation in MCF-10F cells. *Cancer Prev Res (Phila)*. Vol. 1, No. 2, (Jul 2008):pp. (135-145), 1940-6215 (Electronic)

Luo Y, Hattori A, Munoz J, Qin ZH & Roth GS (1999) Intrastriatal dopamine injection induces apoptosis through oxidation-involved activation of transcription factors AP-1 and NF-kappaB in rats. *Mol Pharmacol*. Vol. 56, No. 2, (Aug 1999):pp. (254-264), 0026-895X (Print)

Mandel S, Maor G & Youdim MB (2004) Iron and alpha-synuclein in the substantia nigra of MPTP-treated mice: effect of neuroprotective drugs R-apomorphine and green tea polyphenol (-)-epigallocatechin-3-gallate. *J Mol Neurosci*. Vol. 24, No. 3, 2004):pp. (401-416), 0895-8696 (Print)

Mandel SA, Amit T, Kalfon L, Reznichenko L & Youdim MB (2008) Targeting multiple neurodegenerative diseases etiologies with multimodal-acting green tea catechins. *J Nutr*. Vol. 138, No. 8, (Aug 2008):pp. (1578S-1583S), 1541-6100 (Electronic)

Mandel SA, Amit T, Weinreb O & Youdim MB (2011) Understanding the Broad-Spectrum Neuroprotective Action Profile of Green Tea Polyphenols in Aging and Neurodegenerative Diseases. *J Alzheimers Dis*. Vol., No. (Mar 2 2011):pp. 1875-8908 (Electronic)

Matsuoka Y, Hasegawa H, Okuda S, Muraki T, Uruno T & Kubota K (1995) Ameliorative effects of tea catechins on active oxygen-related nerve cell injuries. *J Pharmacol Exp Ther*. Vol. 274, No. 2, (Aug 1995):pp. (602-608), 0022-3565 (Print)

Matter WF, Brown RF & Vlahos CJ (1992) The inhibition of phosphatidylinositol 3-kinase by quercetin and analogs. *Biochem Biophys Res Commun*. Vol. 186, No. 2, (Jul 31 1992):pp. (624-631), 0006-291X (Print)

Mattivi F, Reniero F & Korhammer S (1995) Isolation, Characterization, and Evolution in Red Wine Vinification of Resveratrol Monomers. *Journal of Agricultural and Food Chemistry*. Vol. 43, No. 7, 1995):pp. (1820-1823), 0021-8561

Mattson MP, Son TG & Camandola S (2007) Viewpoint: mechanisms of action and therapeutic potential of neurohormetic phytochemicals. *Dose Response*. Vol. 5, No. 3, 2007):pp. (174-186), 1559-3258 (Electronic)

Mazzio E, Huber J, Darling S, Harris N & Soliman KF (2001) Effect of antioxidants on L-glutamate and N-methyl-4-phenylpyridinium ion induced-neurotoxicity in PC12 cells. *Neurotoxicology*. Vol. 22, No. 2, (Apr 2001):pp. (283-288), 0161-813X (Print)

Mishra B, Priyadarsini KI, Bhide MK, Kadam RM & Mohan H (2004) Reactions of superoxide radicals with curcumin: probable mechanisms by optical spectroscopy and EPR. *Free Radic Res*. Vol. 38, No. 4, (Apr 2004):pp. (355-362), 1071-5762 (Print)

Moldzio R, Radad K, Krewenka C, Kranner B, Duvigneau JC, Wang Y & Rausch WD (2010) Effects of epigallocatechin gallate on rotenone-injured murine brain cultures. *J Neural Transm*. Vol. 117, No. 1, (Jan 2010):pp. (5-12), 1435-1463 (Electronic)

Molina MF, Sanchez-Reus I, Iglesias I & Benedi J (2003) Quercetin, a flavonoid antioxidant, prevents and protects against ethanol-induced oxidative stress in mouse liver. *Biol Pharm Bull*. Vol. 26, No. 10, (Oct 2003):pp. (1398-1402), 0918-6158 (Print)

Motterlini R, Foresti R, Bassi R & Green CJ (2000) Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radic Biol Med*. Vol. 28, No. 8, (Apr 15 2000):pp. (1303-1312), 0891-5849 (Print)

Muthane U, Yasha TC & Shankar SK (1998) Low numbers and no loss of melanized nigral neurons with increasing age in normal human brains from India. *Ann Neurol*. Vol. 43, No. 3, (Mar 1998):pp. (283-287), 0364-5134 (Print)

Mythri RB, Harish G, Dubey SK, Misra K & Bharath MM (2011) Glutamoyl diester of the dietary polyphenol curcumin offers improved protection against peroxynitrite-mediated nitrosative stress and damage of brain mitochondria in vitro: implications for Parkinson's disease. *Mol Cell Biochem*. Vol. 347, No. 1-2, (Jan 2011):pp. (135-143), 1573-4919 (Electronic)

Mythri RB, Jagatha B, Pradhan N, Andersen J & Bharath MM (2007) Mitochondrial complex I inhibition in Parkinson's disease: how can curcumin protect mitochondria? *Antioxid Redox Signal*. Vol. 9, No. 3, (Mar 2007):pp. (399-408), 1523-0864 (Print)

Nie G, Cao Y & Zhao B (2002) Protective effects of green tea polyphenols and their major component, (-)-epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells. *Redox Rep*. Vol. 7, No. 3, 2002):pp. (171-177), 1351-0002 (Print)

North BJ & Verdin E (2004) Sirtuins: Sir2-related NAD-dependent protein deacetylases. *Genome Biol*. Vol. 5, No. 5, 2004):pp. (224), 1465-6914 (Electronic)

Ohara K, Mizukami, W., Tokunaga, A., Nagaoka, S., Uno, H., and Mukai (2005) Kinetic Study of the Mechanism of Free-Radical Scavenging Action in Curcumin: Effects of Solvent and pH. *Bull Chem Soc Jpn*. Vol. 78, No. 4, 2005):pp. (615-621), 0009-2673

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*. Vol. 73, No. 4, (Feb 15 2007):pp. (550-560), 0006-2952 (Print)

Oliver CN, Starke-Reed PE, Stadtman ER, Liu GJ, Carney JM & Floyd RA (1990) Oxidative damage to brain proteins, loss of glutamine synthetase activity, and production of free radicals during ischemia/reperfusion-induced injury to gerbil brain. *Proc Natl Acad Sci U S A*. Vol. 87, No. 13, (Jul 1990):pp. (5144-5147), 0027-8424 (Print)

Ono K & Yamada M (2006) Antioxidant compounds have potent anti-fibrillogenic and fibril-destabilizing effects for alpha-synuclein fibrils in vitro. *J Neurochem*. Vol. 97, No. 1, (Apr 2006):pp. (105-115), 0022-3042 (Print)

Outeiro TF, Kontopoulos E, Altmann SM, Kufareva I, Strathearn KE, Amore AM, Volk CB, Maxwell MM, Rochet JC, McLean PJ, Young AB, Abagyan R, Feany MB, Hyman BT & Kazantsev AG (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease. *Science*. Vol. 317, No. 5837, (Jul 27 2007):pp. (516-519), 1095-9203 (Electronic)

Pallas M, Casadesus G, Smith MA, Coto-Montes A, Pelegri C, Vilaplana J & Camins A (2009) Resveratrol and neurodegenerative diseases: activation of SIRT1 as the potential pathway towards neuroprotection. *Curr Neurovasc Res*. Vol. 6, No. 1, (Feb 2009):pp. (70-81), 1875-5739 (Electronic)

Pallas M, Verdaguer E, Tajes M, Gutierrez-Cuesta J & Camins A (2008) Modulation of sirtuins: new targets for antiageing. *Recent Pat CNS Drug Discov*. Vol. 3, No. 1, (Jan 2008):pp. (61-69), 1574-8898 (Print)

Pan MH, Huang TM & Lin JK (1999) Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos*. Vol. 27, No. 4, (Apr 1999):pp. (486-494), 0090-9556 (Print)

Pan MH, Lin-Shiau SY & Lin JK (2000) Comparative studies on the suppression of nitric oxide synthase by curcumin and its hydrogenated metabolites through down-regulation of IkappaB kinase and NFkappaB activation in macrophages. *Biochem Pharmacol*. Vol. 60, No. 11, (Dec 1 2000):pp. (1665-1676), 0006-2952 (Print)

Pan T, Jankovic J & Le W (2003) Potential therapeutic properties of green tea polyphenols in Parkinson's disease. *Drugs Aging*. Vol. 20, No. 10, 2003):pp. (711-721), 1170-229X (Print)

Pandey N, Strider J, Nolan WC, Yan SX & Galvin JE (2008) Curcumin inhibits aggregation of alpha-synuclein. *Acta Neuropathol*. Vol. 115, No. 4, (Apr 2008):pp. (479-489), 0001-6322 (Print)

Peeyush KT, Gireesh G, Jobin M & Paulose CS (2009) Neuroprotective role of curcumin in the cerebellum of streptozotocin-induced diabetic rats. *Life Sci*. Vol. 85, No. 19-20, (Nov 4 2009):pp. (704-710), 1879-0631 (Electronic)

Pietta PG, Simonetti P, Gardana C, Brusamolino A, Morazzoni P & Bombardelli E (1998) Catechin metabolites after intake of green tea infusions. *Biofactors*. Vol. 8, No. 1-2, 1998):pp. (111-118), 0951-6433 (Print)

Plummer SM, Holloway KA, Manson MM, Munks RJ, Kaptein A, Farrow S & Howells L (1999) Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. *Oncogene*. Vol. 18, No. 44, (Oct 28 1999):pp. (6013-6020), 0950-9232 (Print)

Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG & Mohan H (2003) Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radic Biol Med*. Vol. 35, No. 5, (Sep 1 2003):pp. (475-484), 0891-5849 (Print)

Qureshi S, Shah AH & Ageel AM (1992) Toxicity studies on Alpinia galanga and Curcuma longa. *Planta Med*. Vol. 58, No. 2, (Apr 1992):pp. (124-127), 0032-0943 (Print)

Rajeswari A (2006) Curcumin protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Eur Rev Med Pharmacol Sci*. Vol. 10, No. 4, (Jul-Aug 2006):pp. (157-161), 1128-3602 (Print)

Rajeswari A & Sabesan M (2008) Inhibition of monoamine oxidase-B by the polyphenolic compound, curcumin and its metabolite tetrahydrocurcumin, in a model of Parkinson's disease induced by MPTP neurodegeneration in mice. *Inflammopharmacology*. Vol. 16, No. 2, (Apr 2008):pp. (96-99), 0925-4692 (Print)

Ramassamy C (2006) Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. Eur J Pharmacol Vol. 545, No. 1, (Sep 2006): pp (51–64)

Ray B, Bisht S, Maitra A & Lahiri DK (2011) Neuroprotective and neurorescue effects of a novel polymeric nanoparticle formulation of curcumin (NanoCurc) in the neuronal cell culture and animal model: implications for Alzheimer's disease. *J Alzheimers Dis*. Vol. 23, No. 1, (Jan 1 2011):pp. (61-77), 1875-8908 (Electronic)

Raza H, John A, Brown EM, Benedict S & Kambal A (2008) Alterations in mitochondrial respiratory functions, redox metabolism and apoptosis by oxidant 4-hydroxynonenal and antioxidants curcumin and melatonin in PC12 cells. *Toxicol Appl Pharmacol*. Vol. 226, No. 2, (Jan 15 2008):pp. (161-168), 0041-008X (Print)

Revuelta MP, Cantabrana B & Hidalgo A (1997) Depolarization-dependent effect of flavonoids in rat uterine smooth muscle contraction elicited by CaCl2. *Gen Pharmacol*. Vol. 29, No. 5, (Nov 1997):pp. (847-857), 0306-3623 (Print)

Rice-Evans CA & Miller NJ (1996) Antioxidant activities of flavonoids as bioactive components of food. *Biochem Soc Trans*. Vol. 24, No. 3, (Aug 1996):pp. (790-795), 0300-5127 (Print)

Rice-Evans CA, Miller NJ & Paganga G (1996) Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic Biol Med*. Vol. 20, No. 7, 1996):pp. (933-956), 0891-5849 (Print)

Richard T, Pawlus AD, Iglesias ML, Pedrot E, Waffo-Teguo P, Merillon JM & Monti JP (2011) Neuroprotective properties of resveratrol and derivatives. *Ann N Y Acad Sci*. Vol. 1215, No. (Jan 2011):pp. (103-108), 1749-6632 (Electronic)

Riederer P, Sofic E, Rausch WD, Schmidt B, Reynolds GP, Jellinger K & Youdim MB (1989) Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brains. *J Neurochem*. Vol. 52, No. 2, (Feb 1989):pp. (515-520), 0022-3042 (Print)

Rocha-Gonzalez HI, Ambriz-Tututi M & Granados-Soto V (2008) Resveratrol: a natural compound with pharmacological potential in neurodegenerative diseases. *CNS Neurosci Ther*. Vol. 14, No. 3, (Fall 2008):pp. (234-247), 1755-5930 (Print)

Sahu SC & Gray GC (1997) Lipid peroxidation and DNA damage induced by morin and naringenin in isolated rat liver nuclei. *Food Chem Toxicol*. Vol. 35, No. 5, (May 1997):pp. (443-447), 0278-6915 (Print)

Saiko P, Szakmary A, Jaeger W & Szekeres T (2008) Resveratrol and its analogs: defense against cancer, coronary disease and neurodegenerative maladies or just a fad? *Mutat Res*. Vol. 658, No. 1-2, (Jan-Feb 2008):pp. (68-94), 0027-5107 (Print)

Sawada H, Ibi M, Kihara T, Honda K, Nakamizo T, Kanki R, Nakanishi M, Sakka N, Akaike A & Shimohama S (2002) Estradiol protects dopaminergic neurons in a MPP+Parkinson's disease model. *Neuropharmacology*. Vol. 42, No. 8, (Jun 2002):pp. (1056-1064), 0028-3908 (Print)

Scalbert A & Williamson G (2000) Dietary intake and bioavailability of polyphenols. *J Nutr*. Vol. 130, No. 8S Suppl, (Aug 2000):pp. (2073S-2085S), 0022-3166 (Print)

Schroeter H, Bahia P, Spencer JP, Sheppard O, Rattray M, Cadenas E, Rice-Evans C & Williams RJ (2007) (-)Epicatechin stimulates ERK-dependent cyclic AMP response element activity and up-regulates GluR2 in cortical neurons. *J Neurochem*. Vol. 101, No. 6, (Jun 2007):pp. (1596-1606), 0022-3042 (Print)

Schroeter H, Boyd C, Spencer JP, Williams RJ, Cadenas E & Rice-Evans C (2002) MAPK signaling in neurodegeneration: influences of flavonoids and of nitric oxide. *Neurobiol Aging*. Vol. 23, No. 5, (Sep-Oct 2002):pp. (861-880), 0197-4580 (Print)

Schroeter H, Spencer JP, Rice-Evans C & Williams RJ (2001) Flavonoids protect neurons from oxidized low-density-lipoprotein-induced apoptosis involving c-Jun N-terminal kinase (JNK), c-Jun and caspase-3. *Biochem J*. Vol. 358, No. Pt 3, (Sep 15 2001):pp. (547-557), 0264-6021 (Print)

Schroeter H, Williams RJ, Matin R, Iversen L & Rice-Evans CA (2000) Phenolic antioxidants attenuate neuronal cell death following uptake of oxidized low-density lipoprotein. *Free Radic Biol Med*. Vol. 29, No. 12, (Dec 15 2000):pp. (1222-1233), 0891-5849 (Print)

Shankar TN, Shantha NV, Ramesh HP, Murthy IA & Murthy VS (1980) Toxicity studies on turmeric (Curcuma longa): acute toxicity studies in rats, guineapigs & monkeys. *Indian J Exp Biol*. Vol. 18, No. 1, (Jan 1980):pp. (73-75), 0019-5189 (Print)

Sharma S, Kulkarni SK, Agrewala JN & Chopra K (2006) Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *Eur J Pharmacol*. Vol. 536, No. 3, (May 1 2006):pp. (256-261), 0014-2999 (Print)

Shen SC, Lee WR, Lin HY, Huang HC, Ko CH, Yang LL & Chen YC (2002) In vitro and in vivo inhibitory activities of rutin, wogonin, and quercetin on lipopolysaccharide-induced nitric oxide and prostaglandin E(2) production. *Eur J Pharmacol*. Vol. 446, No. 1-3, (Jun 20 2002):pp. (187-194), 0014-2999 (Print)

Shen SQ, Zhang Y, Xiang JJ & Xiong CL (2007) Protective effect of curcumin against liver warm ischemia/reperfusion injury in rat model is associated with regulation of heat shock protein and antioxidant enzymes. *World J Gastroenterol*. Vol. 13, No. 13, (Apr 7 2007):pp. (1953-1961), 1007-9327 (Print)

Shishodia S, Sethi G & Aggarwal BB (2005) Curcumin: getting back to the roots. *Ann N Y Acad Sci*. Vol. 1056, No. (Nov 2005):pp. (206-217), 0077-8923 (Print)

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R & Srinivas PS (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med*. Vol. 64, No. 4, (May 1998):pp. (353-356), 0032-0943 (Print)

Sinha R, Anderson DE, McDonald SS & Greenwald P (2003) Cancer risk and diet in India. *J Postgrad Med*. Vol. 49, No. 3, (Jul-Sep 2003):pp. (222-228), 0022-3859 (Print)

Sofic E, Riederer P, Heinsen H, Beckmann H, Reynolds GP, Hebenstreit G & Youdim MB (1988) Increased iron (III) and total iron content in post mortem substantia nigra of parkinsonian brain. *J Neural Transm*. Vol. 74, No. 3, 1988):pp. (199-205), 0300-9564 (Print)

Spencer JP (2003) Metabolism of tea flavonoids in the gastrointestinal tract. *J Nutr*. Vol. 133, No. 10, (Oct 2003):pp. (3255S-3261S), 0022-3166 (Print)

Spencer JP (2007) The interactions of flavonoids within neuronal signalling pathways. *Genes Nutr*. Vol. 2, No. 3, (Dec 2007):pp. (257-273), 1555-8932 (Print)

Spencer JP, Abd-el-Mohsen MM & Rice-Evans C (2004) Cellular uptake and metabolism of flavonoids and their metabolites: implications for their bioactivity. *Arch Biochem Biophys*. Vol. 423, No. 1, (Mar 1 2004):pp. (148-161), 0003-9861 (Print)

Spencer JP, Rice-Evans C & Williams RJ (2003) Modulation of pro-survival Akt/protein kinase B and ERK1/2 signaling cascades by quercetin and its in vivo metabolites underlie their action on neuronal viability. *J Biol Chem*. Vol. 278, No. 37, (Sep 12 2003):pp. (34783-34793), 0021-9258 (Print)

Srinivasan K (2005) Plant foods in the management of diabetes mellitus: spices as beneficial antidiabetic food adjuncts. *Int J Food Sci Nutr*. Vol. 56, No. 6, (Sep 2005):pp. (399-414), 0963-7486 (Print)

Stridh MH, Correa F, Nodin C, Weber SG, Blomstrand F, Nilsson M & Sandberg M (2010) Enhanced glutathione efflux from astrocytes in culture by low extracellular ca(2+) and curcumin. *Neurochem Res*. Vol. 35, No. 8, (Aug 2010):pp. (1231-1238), 1573-6903 (Electronic)

Sugihara N, Arakawa T, Ohnishi M & Furuno K (1999) Anti- and pro-oxidative effects of flavonoids on metal-induced lipid hydroperoxide-dependent lipid peroxidation in

cultured hepatocytes loaded with alpha-linolenic acid. *Free Radic Biol Med*. Vol. 27, No. 11-12, (Dec 1999):pp. (1313-1323), 0891-5849 (Print)

Suresh D & Srinivasan K (2010) Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. *Indian J Med Res*. Vol. 131, No. (May 2010):pp. (682-691), 0971-5916 (Print)

Tai KK & Truong DD (2010) (-)-Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, reduces dichlorodiphenyl-trichloroethane (DDT)-induced cell death in dopaminergic SHSY-5Y cells. *Neurosci Lett*. Vol. 482, No. 3, (Oct 4 2010):pp. (183-187), 1872-7972 (Electronic)

Tan EK, Tan C, Fook-Chong SMC, Lum SY, Chai A, Chung H, Shen H, Zhao Y, Teoh ML, Yih Y, Pavanni R, Chandran VR & Wong MC (2003) Dose-dependent protective effect of coffee, tea, and smoking in Parkinson's disease: a study in ethnic Chinese. *Journal of the neurological sciences*. Vol. 216, No. 1, 2003):pp. (163-167), 0022-510X

Tan LC, Koh W-P, Yuan J-M, Wang R, Au W-L, Tan JH, Tan E-K & Yu MC (2008) Differential Effects of Black versus Green Tea on Risk of Parkinson's Disease in the Singapore Chinese Health Study. *American Journal of Epidemiology*. Vol. 167, No. 5, (March 1, 2008 2008):pp. (553-560),

Thaloor D, Miller KJ, Gephart J, Mitchell PO & Pavlath GK (1999) Systemic administration of the NF-kappaB inhibitor curcumin stimulates muscle regeneration after traumatic injury. *Am J Physiol*. Vol. 277, No. 2 Pt 1, (Aug 1999):pp. (C320-329), 0002-9513 (Print)

Thiyagarajan M & Sharma SS (2004) Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. *Life Sci*. Vol. 74, No. 8, (Jan 9 2004):pp. (969-985), 0024-3205 (Print)

Toniolo R, Di Narda F, Susmel S, Martelli M, Martelli L & Bontempelli G (2002) Quenching of superoxide ions by curcumin. A mechanistic study in acetonitrile. *Ann Chim*. Vol. 92, No. 3, (Mar 2002):pp. (281-288), 0003-4592 (Print)

Tsao R (2010) Chemistry and Biochemistry of Dietary Polyphenols. *Nutrients*. Vol. 2, No. 12, 2010):pp. (1231-1246), 2072-6643

Uchida K, Shiraishi M, Naito Y, Torii Y, Nakamura Y & Osawa T (1999) Activation of stress signaling pathways by the end product of lipid peroxidation. 4-hydroxy-2-nonenal is a potential inducer of intracellular peroxide production. *J Biol Chem*. Vol. 274, No. 4, (Jan 22 1999):pp. (2234-2242), 0021-9258 (Print)

Vajragupta O, Boonchoong P, Watanabe H, Tohda M, Kummasud N & Sumanont Y (2003) Manganese complexes of curcumin and its derivatives: evaluation for the radical scavenging ability and neuroprotective activity. *Free Radic Biol Med*. Vol. 35, No. 12, (Dec 15 2003):pp. (1632-1644), 0891-5849 (Print)

van Acker SA, de Groot MJ, van den Berg DJ, Tromp MN, Donne-Op den Kelder G, van der Vijgh WJ & Bast A (1996) A quantum chemical explanation of the antioxidant activity of flavonoids. *Chem Res Toxicol*. Vol. 9, No. 8, (Dec 1996):pp. (1305-1312), 0893-228X (Print)

Vlahos CJ, Matter WF, Hui KY & Brown RF (1994) A specific inhibitor of phosphatidylinositol 3-kinase, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one (LY294002). *J Biol Chem*. Vol. 269, No. 7, (Feb 18 1994):pp. (5241-5248), 0021-9258 (Print)

Walle T (2011) Bioavailability of resveratrol. *Ann N Y Acad Sci*. Vol. 1215, No. (Jan 2011):pp. (9-15), 1749-6632 (Electronic)

Wang F, Nguyen M, Qin FX & Tong Q (2007) SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. *Aging Cell*. Vol. 6, No. 4, (Aug 2007):pp. (505-514), 1474-9718 (Print)

Wang J, Du XX, Jiang H & Xie JX (2009a) Curcumin attenuates 6-hydroxydopamine-induced cytotoxicity by anti-oxidation and nuclear factor-kappa B modulation in MES23.5 cells. *Biochem Pharmacol*. Vol. 78, No. 2, (Jul 15 2009a):pp. (178-183), 1873-2968 (Electronic)

Wang MS, Boddapati S, Emadi S & Sierks MR (2010) Curcumin reduces alpha-synuclein induced cytotoxicity in Parkinson's disease cell model. *BMC Neurosci*. Vol. 11, No. 2010):pp. (57), 1471-2202 (Electronic)

Wang SL, Li Y, Wen Y, Chen YF, Na LX, Li ST & Sun CH (2009b) Curcumin, a potential inhibitor of up-regulation of TNF-alpha and IL-6 induced by palmitate in 3T3-L1 adipocytes through NF-kappaB and JNK pathway. *Biomed Environ Sci*. Vol. 22, No. 1, (Feb 2009b):pp. (32-39), 0895-3988 (Print)

Wang Y, Xu H, Fu Q, Ma R & Xiang J (2011) Protective effect of resveratrol derived from Polygonum cuspidatum and its liposomal form on nigral cells in Parkinsonian rats. *J Neurol Sci*. Vol., No. (Mar 2 2011):pp. 1878-5883 (Electronic)

Weinreb O, Mandel S, Amit T & Youdim MB (2004) Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases. *J Nutr Biochem*. Vol. 15, No. 9, (Sep 2004):pp. (506-516), 0955-2863 (Print)

Wenzel E & Somoza V (2005) Metabolism and bioavailability of trans-resveratrol. *Mol Nutr Food Res*. Vol. 49, No. 5, (May 2005):pp. (472-481), 1613-4125 (Print)

Wild AC, Moinova HR & Mulcahy RT (1999) Regulation of gamma-glutamylcysteine synthetase subunit gene expression by the transcription factor Nrf2. *J Biol Chem*. Vol. 274, No. 47, (Nov 19 1999):pp. (33627-33636), 0021-9258 (Print)

Williams RJ, Spencer JP & Rice-Evans C (2004) Flavonoids: antioxidants or signalling molecules? *Free Radic Biol Med*. Vol. 36, No. 7, (Apr 1 2004):pp. (838-849), 0891-5849 (Print)

Woo KJ, Lim JH, Suh SI, Kwon YK, Shin SW, Kim SC, Choi YH, Park JW & Kwon TK (2006) Differential inhibitory effects of baicalein and baicalin on LPS-induced cyclooxygenase-2 expression through inhibition of C/EBPbeta DNA-binding activity. *Immunobiology*. Vol. 211, No. 5, 2006):pp. (359-368), 0171-2985 (Print)

Xu Y, Ku B, Cui L, Li X, Barish PA, Foster TC & Ogle WO (2007) Curcumin reverses impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats. *Brain Res*. Vol. 1162, No. (Aug 8 2007):pp. (9-18), 0006-8993 (Print)

Xu YX, Pindolia KR, Janakiraman N, Chapman RA & Gautam SC (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*. Vol. 11, No. 1, 1997):pp. (49-62), 1082-8893 (Print)

Yamamoto H, Schoonjans K & Auwerx J (2007) Sirtuin Functions in Health and Disease. *Mol Endocrinol*. Vol. 21, No. 8, (August 1, 2007 2007):pp. (1745-1755),

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA & Cole GM (2005) Curcumin inhibits formation of amyloid

beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *J Biol Chem*. Vol. 280, No. 7, (Feb 18 2005):pp. (5892-5901), 0021-9258 (Print)

Ye SF, Hou ZQ, Zhong LM & Zhang QQ (2007) Effect of curcumin on the induction of glutathione S-transferases and NADP(H):quinone oxidoreductase and its possible mechanism of action. *Yao Xue Xue Bao*. Vol. 42, No. 4, (Apr 2007):pp. (376-380), 0513-4870 (Print)

Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER & Mizuno Y (1996) Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease. *Proc Natl Acad Sci U S A*. Vol. 93, No. 7, (Apr 2 1996):pp. (2696-2701), 0027-8424 (Print)

Yu S, Zheng W, Xin N, Chi ZH, Wang NQ, Nie YX, Feng WY & Wang ZY (2010) Curcumin prevents dopaminergic neuronal death through inhibition of the c-Jun N-terminal kinase pathway. *Rejuvenation Res*. Vol. 13, No. 1, (Feb 2010):pp. (55-64), 1557-8577 (Electronic)

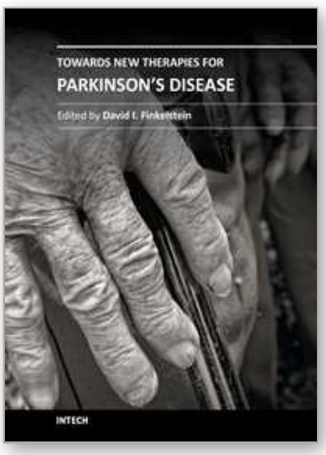
Zbarsky V, Datla KP, Parkar S, Rai DK, Aruoma OI & Dexter DT (2005) Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. *Free Radic Res*. Vol. 39, No. 10, (Oct 2005):pp. (1119-1125), 1071-5762 (Print)

Zhang F, Shi JS, Zhou H, Wilson B, Hong JS & Gao HM (2010) Resveratrol protects dopamine neurons against lipopolysaccharide-induced neurotoxicity through its anti-inflammatory actions. *Mol Pharmacol*. Vol. 78, No. 3, (Sep 1 2010):pp. (466-477), 1521-0111 (Electronic)

Zhang L, Chen J & Fu H (1999) Suppression of apoptosis signal-regulating kinase 1-induced cell death by 14-3-3 proteins. *Proc Natl Acad Sci U S A*. Vol. 96, No. 15, (Jul 20 1999):pp. (8511-8515), 0027-8424 (Print)

Zhu YG, Chen XC, Chen ZZ, Zeng YQ, Shi GB, Su YH & Peng X (2004) Curcumin protects mitochondria from oxidative damage and attenuates apoptosis in cortical neurons. *Acta Pharmacol Sin*. Vol. 25, No. 12, (Dec 2004):pp. (1606-1612), 1671-4083 (Print)

Zhuang H, Kim YS, Koehler RC & Dore S (2003) Potential mechanism by which resveratrol, a red wine constituent, protects neurons. *Ann N Y Acad Sci*. Vol. 993, No. (May 2003):pp. (276-286; discussion 287-278), 0077-8923 (Print)



Towards New Therapies for Parkinson's Disease

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Parkinson's disease (PD) is characterised clinically by various non-motor and progressive motor symptoms, pathologically by loss of dopamine producing cells and intraneuronal cytoplasmic inclusions composed primarily of ?-synuclein. By the time a patient first presents with symptoms of Parkinson's disease at the clinic, a significant proportion of the cells in the substantia nigra have already been destroyed. This degeneration progresses despite the current therapies until the cell loss is so great that the quality of normal life is compromised. The dopamine precursor levodopa is the most valuable drug currently available for the treatment of PD. However for most PD patients, the optimal clinical benefit from levodopa decreases around five to six years of treatment. The aim of the chapters of this book is to work towards an understanding in the mechanisms of degeneration and to develop disease modifying therapies.

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