Chapter 2

Review of Literature

**Liu et al., (2013)** tested whether curcumin, could protect against rotenone-induced neuronal toxicity in cell and drosophila models of Parkinson’s disease (PD). They used rotenone (a mitochondrial complex I inhibitor) based cell and Drosophila models that resemble some key pathological features of PD. They found that curcumin reduced rotenone induced cell death in SH-SY5Y human neuroblastoma cells and alleviated PD-like symptoms in drosophila via reducing the intracellular and mitochondrial reactive oxygen species (ROS) levels and inhibiting the caspase-3/caspase-9 activity. It was suggested, curcumin is a promising therapeutic compound for PD.

**Jain et al., (2013)** reviewed on the pathophysiology of cerebral malaria (CM) with particular emphasis on scope and promises of curcumin as an adjunctive therapy to improve survival and overcome neurological deficits. It has been observed that curcumin have potent activity against *Plasmodium berghei* with the use of the CM model in mice and it is able to prevent CM and delay death of animals by about 10 days. In addition to having a direct killing effect as an antimalarial, curcumin is also capable to prime the immune system against *P. berghei*. As adjunctive therapy curcumin, with ability to down regulate excessive pro-inflammatory response, reduced the expression of the adhesion molecules and subsequent sequestration of parasitized red blood cells in cerebral endothelium, as a result the survival of CM patients improved. In comparision to many adjunctive therapies which have been studied, curcumin has a supplementary advantage of possessing antimalarial ability of its own. An essential point to be considered for administration of adjunctive therapy using an immunomodulator is that it should be administered together with antimalarial drugs rather than alone in order to delay immunopathology and allow a longer time frame for antimalarial to work.

**Lin et al., (2013)** investigate the effects of curcumin on brain activity in chronic unpredictable stress (CUS) rats. Behavioral and physiological abnormalities can cause CUS that are important to the prediction of symptoms of depression that may be associated with cerebral glucose metabolic abnormalities. Rats were subjected to 3 weeks of CUS and then treated with curcumin orally at a dose of 40 mg/kg/day for one month. After three weeks of CUS body weight, sucrose preference, sucrose
consumption, total distance travelling, and the number of rearing events was significantly decreased. In several parts of the brain, curcumin also induced metabolic alterations showing enhanced glucose metabolism in the right hemisphere. After one month treatment of curcumin, sucrose preference, sucrose consumption, total distance travelling, and the number of rearing events returned to normal levels. Treatment of curcumin also induced strong deactivation of the left primary auditory cortex and activation of amygdalohippocampal cortex. Curcumin was found to ameliorate the abnormalities in the behavior and brain glucose metabolism caused by CUS, which may interpretate for its antidepressive effects.

**Agrawal et al., (2012)** evaluated the neurodegenerative protecting potential of curcumin (CUR), and curcuminoid namely as demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) on 6-hydroxydopamine-(6-OHDA) induced Parkinsonism model in rats. After three weeks of lesion, the behavioral observations, biochemical markers, dopamine quantification (DA), dopamine (D2) receptor binding assay and tyrosine hydroxylase were evaluated using HPLC. The significant protection was observed in pretreated animals against neuronal degeneration compared to lesion animals by normalizing the deranged levels of biomarkers. Curcuminoids were found to shield the neurodegeneration caused by 6-OHDA and it was also found that CUR significantly more potent than DMC and BDMC.

**Xiong et al., (2011)** investigate the mechanism by which curcumin inhibit the generation of β-amyloid (Aβ). Curcumin has been reported to inhibit the generation of Aβ, but the fundamental mechanisms by which this follows remain unknown. It is believed that Aβ play an important role in the pathogenesis of Alzheimer’s disease (AD). The amyloid hypothesis argues that aggregates of β-amyloid trigger a complex pathological cascade that leads to neurodegeneration. B-amyloid is generated by the processing of APP(amyloid precursor protein) by β and γ-secretases. PS1 (Presenilin 1) is a substrate for GSK-3β and is central to γ-secretase activity and both of which are associated in the pathogenesis of AD. They investigate the effects of curcumin on the generation of in cultured neuroblastoma cells and on the *in vitro* expression of PS1 and GSK-3β. They proposed that curcumin decreases β-amyloid production by inhibiting GSK-3β mediated PS1 activation.
Khuwaja et al., (2011) studied the neuroprotective efficacy of curcumin on 6-hydroxydopamine-induced Parkinsonism in rats. The behavioral, neurochemical and immunohistochemical activities were studied. After 3 weeks of lesioning, the behavior activities were increased in a lesioned group as compared to a sham group and these activities were protected significantly with the pretreatment of curcumin (80 mg/kg curcumin for 21 days). A significant protection was observed on lipid peroxidation, glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase, tyrosine hydroxylase and D2 receptor binding in the striatum of lesioned group animals. This study indicates that curcumin, is helpful in preventing parkinsonism.

Ranjithkumar et al., (2011) studied the ameliorative effect of curcumin against excitotoxin induced brain damage in rats. Excitotoxins, the ultimate brain layer, that have a bland taste, which stimulate the neuron brain cells and lead to exhaustion. To measure the damage induced by excitotoxin, the mitochondrial enzymes and histopathological examination was carried out. The biochemical changes resulting from curcumin also correlated well with its ability to ameliorate the changes induced by excitotoxin. The positive effects of curcumin show as a promising class of compounds for the protection of brain.

Chiu et al., (2011) studied the differential distribution of i.v. curcumin formulations in the rat. The i.v administration of prepared formulation namely as liposomal curcumin, polymeric nanocurcumin and polylactic glycolic acid copolymer (PLGA)–curcumin in rats passes the blood–brain barrier. The therapeutic amounts reaches in damaged areas in the brain with tolerable safety, preferentially localize in the hippocampus, the striata, and brain stem. The curcumin availability at specific brain sites may have antioxidant, anti-inflammatory, positive neurogenesis and neuroplasticity activity. These result support clinical applications of curcumin for remediation of neuropathic disorders.

Lin et al., (2011) investigate whether curcumin has neuroprotective effects after traumatic spinal cord injury (SCI) SCI in 39 male Sprague-Dawley rats after spinal cord hemisection. Specimens were tested for histologic, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL), and immunohistochemical staining. The Basso, Beattie, and Bresnahan scores for the
affected hindlimb after hemisection were significantly improved in the curcumin-treated group compared with the vehicle group. Immuno-histochemistry of NeuN revealed remarkable neuronal loss in the vehicle group after hemisection. Curcumin significantly protected neurons after SCI in comparison with vehicle. Curcumin significantly improved neurologic deficit 7 day after spinal cord hemisection and inhibited apoptosis and neuron loss, quenched astrocyte activation.

Lee et al. (2011) synthesized $[^{18}F]$ fluoropropylcurcumin ($[^{18}F]$ FP-curcumin), which demonstrated excellent binding affinity for β-amyloid (Aβ) aggregates and good pharmacokinetics in normal mouse brains. Though, its original brain uptake was poor. Alzheimer’s disease is characterized by the accumulation of β-amyloid (Ab) plaques and neurofibrillary tangles (NFTs) in the brain. Therefore, pegylated curcumin derivatives or fluorine-substituted 4, 4'-bissubstituted were synthesized and evaluated. Radioligand $[^{18}F]$ 1-(4-fluoroethyl)-7-(40-methyl)curcumin was found to have an appropriate partition coefficient, and its tissue distribution in normal mice demonstrated improved brain permeability compared to that of $[^{18}F]$FP-curcumin.

Yadav et al., (2011) have studied neuroprotective effect of curcumin. The efficacy of curcumin was studied in arsenic induced cholinergic dysfunctions in rats. Rats treated with sodium arsenite, exhibited a significant decrease in the learning activity, assessed by passive avoidance response associated with decreased binding of $^3$H-QNB, known to label muscarinic–cholinergic receptors in hippocampus and frontal cortex as compared to controls. Learning and memory performance was increased by the simultaneous treatment with arsenic and curcumin as compared to arsenic treated rats. This result associated with increased binding of $^3$H-QNB in hippocampus, frontal cortex and activity of acetylcholinesterase in hippocampus and frontal cortex. The results of the present study suggest that curcumin significantly modulates arsenic induced cholinergic dysfunctions in brain.

Liua et al., (2010) was conducted the study to observe the effects of curcumin(Cur), demethoxycurcumin(DMC) and bisdemethoxycurcumin (BDMC) on Aβ_{42}, β-amyloid precursor protein (APP) and BACE1. The hallmark of Alzheimer’s disease (AD) is the accumulation of β-amyloid protein (Aβ). Aβ is generated from the β-amyloid precursor protein (APP) through the proteolysis of β-site APP cleaving enzyme 1 (BACE1) and γ-secretase. Aβ_{42} isoform is more easily aggregate and more
toxic to neurons. Curcumin mix showed great promise for AD treatment and prevention due to potent anti-amyloidogenic effect. They found that curcumin was the most active curcuminoid fraction in suppressing Aβ42 production and the order of inhibitory potency of other curcuminoids was DMC > curcumin mix > BDMC. In comparison to other curcuminoids, Cur could reduce APP protein expression and none of curcuminoids affected APP mRNA level. The result indicates that the anti amyloidogenic effect of Cur may be mediated through the modulation of APP.

Purkayastha et al., (2009) studied on injectable formulation of curcumin that crosses the blood–brain barrier and blocks brain tumor formation in mice that had already received an intracerebral bolus of mouse melanoma cells (B16F10). They observed that the solubilized curcumin causes activation of proapoptotic enzymes caspase 3/7 in human oligodendroglioma (HOG) and lung carcinoma (A549) cells, and mouse tumor cells N18 (neuroblastoma), GL261 (glioma), and B16F10. A simultaneous decrease in cell viability is also revealed by MTT [3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide] assays. The result clearly indicated that curcumin in solubilized form effectively blocks brain tumor formation and also eliminates brain tumor cells.

Vareed et al., (2008) examined the pharmacokinetics of conjugate metabolites of curcumin in human volunteers after a single oral dose (10-12 g). Serum samples were assayed for free curcumin, for its glucuronide, and for its sulfate conjugate. In humans, curcumin after oral administration as a single dose generates mainly curcumin glucuronide and curcumin sulfate as metabolite. However, glucuronide conjugate predominates over sulfate conjugate in plasma with no evidence of a mixed conjugate being formed. From the result it was observed that curcumin absorbed after oral administration and could be transported to sites other than the intestinal tract. The ratio of glucuronide to sulfate was 1.92:1.

Ringman et al., (2005) performed a 24 week, randomized, double blinded, placebo-controlled study of two doses of curcumin in persons with mild-to-moderate Alzheimer’s disease(AD). The study was carried out to determine the safety and tolerability of 2000 mg and 4000 mg/day of Curcumin C3 Complex in patients with AD treated for 6 - 12 months. Short term studies in humans suggest safety; curcumin
is a promising agent in the treatment and/or prevention of AD. A direct effect of curcumin in decreasing the amyloid pathology of AD was observed.

Begum et al., (2008) examined the antioxidant, antiinflammatory, or anti-amyloidogenic effects of dietary curcumin and tetrahydrocurcumin (THC), in aged mice. TC and curcumin reduced interleukin- 1β similarly. However only curcumin was effective in reducing amyloid plaque burden, insoluble β -amyloid peptide (Aβ), and carbonyls. Both reduced tris-buffered saline-soluble Aβ and phospho-c-Jun NH2-terminal kinase (JNK) but THC had no impact on plaques or insoluble Aβ. In comparison of THC only curcumin prevented Aβ aggregation. The results indicate that the dienone bridge present in the structure of curcumin is necessary to reduce plaque deposition and protein oxidation in an alzheimer’s model.

Pan et al., (2008) investigated curcumin metabolites by reversed-phase HPLC, after i.p. administration of curcumin (0.1 g/kg) to mice. The two conjugates were observed. Mass spectrometry analysis was used to determine the chemical structures of these metabolites and the result suggested that curcumin was first biotransformed to dihydrocurcumin and THC. These compounds later were converted to monoglucuronide conjugates. The result suggested that glucuronidation compound of curcumin, dihydrocurcumin, and THC are major metabolites of curcumin in-vivo.

Rajeswari (2006) tested that curcumin, acts as a powerful free radical scavenger in-vivo in the brain, and effective in oxidative stress caused by the parkinsonian neurotoxin, 1 methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP). The reduced glutathione levels (GSH), glutathione lipid peroxidation (TBARS), catalase(CAT) and superoxide dismutase (SOD) activity in the striatum (ST) and mid brain(MB) 3rd day and 7th day following MPTP and curcumin administration was measured. MPTP treatment caused a significant depletion in GSH and increased the specific activity of SOD, CAT and lipid peroxidation in both ST and MB on the 3rd and 7th day. After curcumin treatment, MPTP induced GSH depletion and lipid peroxidation in ST and MB was blocked. Curcumin exhibited a synergistic effect on SOD and CAT activities in the ST and MB regions.