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Multiple antidepressant potential modes of action of curcumin: A review of its anti-inflammatory, antioxidant, immune-modulating and neuroprotective effects

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Abstract

Curcumin is the principal curcuminoid of the popular Indian spice turmeric and has attracted increasing attention for the treatment of a range of conditions. Research into its potential as a treatment for depression is still in its infancy, although several potential antidepressant mechanisms of action have been identified. Research completed to date on the multiple effects of curcumin is reviewed in this paper, with a specific emphasis on the biological systems that are compromised in depression. The antidepressant effects of curcumin in animal models of depression are summarised, and its influence on neurotransmitters such as serotonin and dopamine is detailed. The effects of curcumin in moderating hypothalamus-pituitary-adrenal (HPA) disturbances, lowering inflammation, and protecting against oxidative stress, mitochondrial damage, neuroprogression and intestinal hyperpermeability, all of which are compromised in major depressive disorder, are also summarised. With increasing interest in natural treatments for depression, and efforts to enhance current treatment outcomes, curcumin is presented as a promising novel, adjunctive or stand-alone natural antidepressant.

Major depression is one of the most common psychiatric disorders in the Western World and is the leading cause of disability (as measured by years lived with a disability). In the year 2000 it was the 4th leading contributor to the global burden of disease and by the year 2020 is projected to be second only to ischemic heart disease in the amount of disability experienced by sufferers (WHO, 2008).

Major depression is a heterogeneous disorder recognised as having a complex and multifactorial aetiology originating from the interaction between environmental and genetic factors. As depicted in figure 1, these lead to a range of disturbances including: neurotransmitter imbalances associated with lowered serotonin, dopamine and noradrenaline, and increased glutamate activity; HPA disturbances typically characterised by increased HPA activity and glucocorticoid resistance; dysregulated inflammatory pathways as evidenced by increased levels of proinflammatory cytokines, acute phase proteins and kynurenine pathway metabolites; increased oxidative and nitrosative damage associated with reduced antioxidant defences; neuroprogression resulting in neurodegeneration, apoptosis, reduced neurogenesis and neuronal plasticity; and mitochondrial disturbances in the form of increased damage to mitochondria and mitochondrial DNA, and lowered ATP production. (Leonard and Maes, 2012; Maes et al., 2009c; Manji et al., 2001; Raison and Miller, 2011). It is these multiple pathways that make the effective treatment of depression difficult, with current therapies achieving far from optimal remission rates of between 20 to 40 percent (Warden et al., 2007). This has motivated a search for alternative pharmacological, psychological, environmental, and even nutraceutical treatment options to enhance current treatment outcomes.

<<<insert Figure 1 near here>

Given the multifactorial nature of depression, an enhancement of treatment efficacy is likely to occur from therapies that target multiple mechanisms. This is likely to be achieved by combining therapies and/or utilising treatments with multiple mechanisms of action. Curcumin, derived from the spice turmeric, is a potential natural substance that may at least partly fulfil this criterion. As demonstrated in figure 2, curcumin has been shown to have a large array of molecular targets of action which may prove to be beneficial for the treatment and prevention of depression and other diseases (Aggarwal and Sung, 2009; Gupta et al., 2012). This has already led to two published brief reviews highlighting the potential antidepressant effects of curcumin (Kulkarni et al., 2009; Kulkarni and Dhir, 2010).<<<**insert Figure 2 near here**>

Interest in the benefits of curcumin has increased dramatically over the past decade with a number of clinical studies currently underway investigating its efficacy for treating and preventing a range of diseases including certain cancers (e.g., http://clinicaltrials.gov/ct2/show/NCT00094445) , Alzheimer's disease (e.g., http://www.anzctr.org.au/trial_view.aspx?id=336793) and musculoskeletal conditions (e.g., http://clinicaltrials.gov/ct2/show/NCT00752154)In addition, at least one unpublished study has been completed investigating the antidepressant effects of curcumin (http://clinicaltrials.gov/ct2/show/NCT01022632), although the outcomes of this study have not yet been released. The research completed to date on the multiple effects of curcumin is reviewed in this paper, with a specific emphasis on the biological systems that are compromised in depression. The antidepressant effects of curcumin in animal models of depression is summarised, and its effect on neurotransmitters, HPA disturbances, inflammation, oxidative stress, mitochondria, neuroprogression and intestinal hyperpermeability, all of which are disturbed in depression, are detailed.

Animal behavioural models of depression

Despite the fact that no animal model is able to incorporate all aspects of depressive symptoms in humans, the forced swimming test (FST) is a reliable and valid tool for screening the antidepressant effects of drugs (Petit-Demouliere et al., 2005). Animals (typically rats and mice) are subjected to two trials where they are forced to swim in an inescapable cylinder filled with water. The time animals spend immobile in the second trial provides a measure of despair, and has been shown to be reduced by antidepressant drugs (Petit-Demouliere et al., 2005).

The tail suspension test (TST) is another animal model of depression that has good reliability and predictive validity (Cryan et al., 2005). In the TST, animals are subjected to the short-term, inescapable stress of being suspended by their tail, with time spent in an immobile posture providing a measure of depressive behaviour. Various antidepressant medications have been shown to reverse immobility and to promote escape-related behaviour (Steru et al., 1985).

Antidepressant effects of curcumin in animal models

The antidepressant effects of curcumin have been evaluated through the FST and TST in over a dozen studies in the past decade. These have consistently demonstrated that both acute (Arora et al., 2011; Chimakurthy and Talasila, 2010; Gilhotra and Dhingra,

2010; Kulkarni et al., 2008; Sanmukhani et al., 2011; Wang et al., 2008) and chronic (Bhutani et al., 2009; Huang et al., 2011; Li et al., 2009; Sanmukhani et al., 2011; Xia et al., 2007; Xu et al., 2005b) administration of curcumin to rats and mice reduces immobility time.

For example, both in the acute models of FST and TST, and the chronic model of FST with a water wheel, curcumin had significant antidepressant-like activity compared with a vehicle control. The effects of curcumin were similar to that of fluoxetine and imipramine although when administered in combination, antidepressant effects were not enhanced (Sanmukhani et al., 2011). Similar results have been found in other animal models of depression, with curcumin having similar antidepressant efficacy to fluoxetine (Li et al., 2009; Wang et al., 2008).

Bilateral olfactory bulbectomy in rats causes changes in behaviour, and in the endocrine, immune and neurotransmitter systems, that lead to many characteristics seen in patients with major depression. Bulbectomy is believed to cause major dysfunction in the cortical-hippocampal-amygdala circuit similar to that seen in people suffering from major depression (Song and Leonard, 2005). Chronic, but not acute administration of antidepressants corrects most of the changes evoked by bulbectomy (Song and Leonard, 2005). A study assessing the effects of curcumin demonstrated that its chronic

administration was also able to reduce immobility time and reverse the behavioural abnormalities induced by bulbectomy (Xu et al., 2005a).

By depleting monoamines and increasing oxidative stress, reserpine is a drug that increases pain and depressive symptoms. An investigation into the protective effects of curcumin on the reserpine-induced pain-depression dyad in rats demonstrated that curcumin was effective in ameliorating a number of behavioural changes induced by reserpine (Arora et al., 2011). Finally, depressive-like behaviours characterised by a decrease in sugar consumption and an increase in immobility time were induced by 3 weeks of corticosterone injections in rats. Concurrent treatment with curcumin reduced depressive-like behaviours, demonstrated by a 46% increase in sucrose consumption and a 57% reduction in immobility time compared with rats receiving corticosterone injections alone (Huang et al., 2011).

Based on the studies reviewed, in animal models of depression, oral and intraperitoneal curcumin appear to have potent antidepressant properties with effects similar to antidepressants such as the serotonin reuptake inhibitor fluoxetine and the tricyclic imipramine.

Depression and immuno-inflammation

Interest in the association between major depression and inflammation was triggered by studies demonstrating increased levels of inflammatory mediators in depression. This led to the development of inflammatory models of depression and prompted initial comparisons between the symptoms of depression and 'sickness behaviours' such as anorexia, soporific effects, reduction of locomotor activity and exploration, anhedonia and cognitive disturbances (Dantzer et al., 2011; Raison et al., 2006). These were later confirmed to be distinct conditions, with sickness behaviour an adaptive, acute state, whereas depression is a disabling, progressive disorder (Maes et al., 2012a)

Three recent meta-analyses have all confirmed that depression is associated with elevated levels of pro-inflammatory cytokines and other inflammatory mediators. Howren et al. (2009) concluded that depression in clinic and community samples was associated with high levels of C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6). In a meta-analysis by Dowlati et al. (2010), levels of tumour necrosis factor-α (TNF-α) and IL-6 were significantly higher in depressed patients than controls. Finally, a meta-analysis by Liu et al. (2012) demonstrated that the blood levels of soluble interleukin-2 receptors (sIL-2R), TNF-α and IL-6 were all significantly higher in patients with major depressive disorder than in controls. There is also evidence that major depression is characterised by a Th-1-like cell-mediated response,

as evidenced by increased production of interferon-γ (IFN-γ), increased IFN-γ/IL-4 ratios and increased neopterin levels (Maes et al., 1994; Myint et al., 2005).

Further support for the relationship between depression and inflammation is provided by a meta-analysis on the anti-inflammatory effects of antidepressant medications, which concluded that antidepressants reduced levels of cytokines IL-1β and possibly IL-6, but not TNF-α (Hannestad et al., 2011). The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine, which has rapid antidepressant effects in treatment-resistant patients with major depressive disorder, also has anti-inflammatory effects (Loix et al., 2011; Mathew et al., 2012)

While increased inflammation is not found in all patients with depression, it is argued that its effects may be relevant to a subset of patients (Raison and Miller, 2011). Researchers have also become increasingly interested in the impact of inflammation on kynurenine pathway metabolites which have both neurotoxic and neuroprotective qualities (Dantzer et al., 2011; Maes et al., 2011c).

Immuno-inflammatory effects of curcumin

Effects of curcumin on inflammatory pathways

Extensive research using a wide range of *in vitro* models has indicated that curcumin can reduce the inflammatory response by regulating the production of a range of

inflammatory molecules (Basnet and Skalko-Basnet, 2011; Srivastava et al., 2011). Research performed in animals also provides strong evidence for the beneficial effects of curcumin in various diseases associated with inflammation including inflammatory bowel disease, obesity, cardiovascular disease and certain cancers (Gupta et al., 2012).

Evidence of anti-inflammatory effects in human studies is accumulating and has so far been promising. For example, in a clinical trial on osteoarthritis patients, the administration of a patented form of curcumin (Meriva®) significantly reduced a number of inflammatory markers including IL-1β, IL-6, and the erythrocyte sedimentation rate (ESR) (Belcaro et al., 2010). In another randomised clinical trial, curcumin (BCM-95®) given to patients with rheumatoid arthritis significantly reduced the ESR to levels similar to that obtained from the non-steroidal anti-inflammatory drug, diclofenac sodium (Chandran and Goel, 2012). Further evidence of the anti-inflammatory effects of curcumin was demonstrated in a randomised, double-blind, placebo-controlled study on patients with overt type 2 diabetic nephropathy where curcumin administration reduced serum levels of TGF-β and IL-8, and urinary IL-8 (Khajehdehi et al., 2011). Finally, in another study on patients with type 2 diabetes, curcumin lowered levels of IL-6 and TNF-α significantly more than placebo (Usharani et al., 2008).

COX-2 selective inhibitors are a form of non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, an enzyme responsible for the production of prostaglandin E_2 (PGE_2). PGE_2 is a pro-inflammatory chemical messenger involved in pain, fever and swelling. In normal conditions, COX-2 is not expressed in most cells, but elevated levels are found during inflammation which, in turn, stimulates the production of PGE_2. As a co-factor, COX-2 is associated with the increased expression of IDO (Basu et al., 2006; Cesario et al., 2011; Lee et al., 2009) and with inflammatory cytokines (Abbasi et al., 2012).

Studies in the area of depression have provided evidence of increased PGE_2 production and COX-2 expression in depressed people. For example, increased concentrations of PGE_2 in the saliva of patients with major depressive disorder were identified (Ohishi et al., 1988). Moreover, increased levels of PGE_2 were reported both in the CSF and serum of depressed patients (Calabrese et al., 1986; Linnoila et al., 1983). Increased expression of the genes encoding for COX-2 were also found in the peripheral blood cells of patients with recurrent depression (Galecki et al., 2012). The antidepressants fluoxetine and amitriptyline also inhibit cytokine-induced PGE_2 production by inflammatory cells (Yaron et al., 1999). Recent interest in the potential of COX-2 inhibitors to augment antidepressant therapies also show promise, with a number of positive findings from animal models of depression and from preliminary human clinical trials (Muller and Schwarz, 2008).

In a six-week double-blind, placebo-controlled trial, depressed patients treated with a combination of fluoxetine and the COX-2 inhibitor, celecoxib, experienced greater improvement in mood compared with those treated with a combination of fluoxetine and placebo (Akhondzadeh et al., 2009). In a double-blind, add-on study using the noradrenergic reuptake inhibitor reboxetine as the antidepressant, Muller et al. (2006) obtained a similar outcome. The combination of reboxetine and celecoxib led to significantly greater improvements compared with the reboxetine-alone treated group. Also, in an open-label pilot study, the mixed COX-1/COX-2 inhibitor acetylsalicylic acid accelerated the antidepressant effect of fluoxetine and increased the response rate in depressed non-responders to fluoxetine (Mendlewicz et al., 2006). More recently, celecoxib enhanced the efficacy of the serotonergic antidepressant sertraline in 40 depressed patients. Patients in the celecoxib and sertraline group experienced a significantly greater response (95%) and remission (35%) rate compared with those receiving placebo and sertraline (50% response and 5% remission) (Abbasi et al., 2012).

Investigation into the biological activities of curcumin have demonstrated that it can down-regulate COX-2 expression and PGE_2 synthesis (Hong et al., 2004; Lee et al., 2011; Moriyuki et al., 2010; Plummer et al., 1999), therefore providing an alternative natural option as a COX-2 inhibitor. While further human clinical studies are required in this area, the promising antidepressant findings of pharmaceutical COX-2 inhibitors

provides another potential mechanism of action of for the antidepressant effect of curcumin.

Effects of curcumin on immune pathways

<<<insert Figure 3 near here>

IDO is an enzyme expressed in multiple cell types including macrophages, dendritic cells, astrocytes and microglia and is strongly activated by the pro-inflammatory cytokine IFN-γ and to a lesser extent TNF-α, IL-1, and IL-6. IDO can also be induced by lipopolysaccharides (LPS) (Chen and Guillemin, 2009; Stone et al., 2012). As shown in Figure 3, IDO is important in depression as it reduces serotonin synthesis by catabolising tryptophan, the primary amino-acid precursor of serotonin, into kynurenine pathway metabolites. The role of serotonin in depression is already well recognised; however, accumulating research shows that a number of kynurenine pathway metabolites can impact on several mechanisms associated with depression (Maes et al., 2011c; Maes et al., 2007). For example, excess levels of the NMDA agonist and kynurenine pathway metabolite, quinolinic acid (QUIN), are excitotoxic, leading to degenerative changes in the central nervous system. It can increase the generation of free radicals and induce lipid peroxidation. The damaging effects of QUIN can also contribute to mitochondrial degeneration and in experimental models QUIN has anxiogenic effects (Stone et al., 2012). Excess QUIN levels were found in depression

(Raison et al., 2010; Steiner et al., 2011), and in neurological conditions such as Alzheimer's disease, Parkinson's disease and multiple sclerosis (Kincses et al., 2010; Zádori et al., 2009).

Another kynurenine pathway metabolite and NMDA antagonist, kynurenic acid (KYNA), is considered neuroprotective and inversely regulates dopaminergic activity. Its balance with QUIN is important as it is considered protective against the excitotoxicity of QUIN (Myint, 2012). KYNA levels were found to be low in depression (Maes et al., 2011b; Myint et al., 2007) and, more recently, were observed to be particularly low in patients with somatization (Maes et al., 2011b; Maes and Rief, 2012). KYNA levels were also associated with an increased risk of depression in people undergoing IFN-α treatment for hepatitis C virus (Wichers et al., 2005).

Research into the effects of curcumin on IDO expression is only preliminary. However, studies identified to date have been positive. One study demonstrated that curcumin significantly inhibited the expression and activity of IDO in IFN-γ-stimulated bone marrow dendritic mice cells (Jeong et al., 2009). In a study on cancer cells induced by IFN-γ, curcumin was also reported to inhibit the expression of IDO (Zhang et al., 2008). Finally, in an *in vitro* and *in vivo* investigation, curcumin delivered to mice significantly attenuated LPS-induced increases in IDO expression in bone marrow-derived dendritic cells (Jung et al., 2010).

Further evidence of curcumin's immuno-modulating effects are demonstrated by its ability to lower Th-17 autoimmune responses (Kanakasabai et al., 2012; Xie et al., 2009) which have recently been shown to be upregulated in major depression (Chen et al., 2011). Curcumin also decreases the expression of Th-1 cytokines (e.g., IFN-γ, TNF-α) and increases the expression of Th-2 cytokines (e.g., IL-4 and IL-10) (Bereswill et al., 2010; Zhang et al., 2006). This may prove to be beneficial for the treatment of depression given consistent findings of increased Th-1-like cell-mediated responses in major depression (Maes, 2011; Maes et al., 1994; Myint et al., 2005).

Several studies have also investigated the influence of curcumin on the lipopolysaccharide (LPS)-induced immune response. One such study revealed that the systemic administration of LPS to rabbits increased core temperature and hypothalamic levels of glutamate and hydroxyl radicals along with increased plasma levels of TNF-α, IL-1β, and IL-6. Pre-treatment with curcumin one hour before an intravenous dose of LPS significantly reduced the LPS-induced overproduction of circulating TNF-α, IL-1β, and IL-6, and brain glutamate, PGE2, and hydroxyl radicals (Huang et al., 2008).

Depression and neurotransmitters

The monoamine-deficiency theory is the most recognised and investigated causative model of major depression. It is postulated as the primary mechanism of action of

popular pharmaceutical antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), is to increase the availability of monoamines such as serotonin, noradrenaline (i.e., norepinephrine) and, possibly, dopamine. According to this theory, the underlying pathophysiological basis of depression is a depletion of these neurotransmitters in the central nervous system (Maletic et al., 2007).

Serotonin is the most extensively studied neurotransmitter in depression, with evidence of its deficiency emerging from studies using tryptophan depletion (which reduces central serotonin synthesis) (Toker et al., 2010), studies demonstrating abnormalities in serotonin receptors in depressed patients (Carr and Lucki, 2011), research showing increased availability of monoamine oxidase, an enzyme that metabolises serotonin and other monoamines in the brain of depressed people (Meyer et al., 2006), and evidence of abnormalities in the expression of the enzyme tryptophan hydroxylase, which is involved in serotonin synthesis (Matthes et al., 2010). The monoaminergic theory has prompted research into the potential of curcumin in altering neurotransmitters such as serotonin, dopamine and noradrenaline. A selection of these studies is reviewed.

Effects of curcumin on serotonin, dopamine and noradrenaline

Both animal and *in vitro* studies conducted over the past decade have now confirmed that curcumin is able to influence levels of serotonin, dopamine and noradrenaline in the

central nervous system. For example, in a chronic unpredictable mild stress (CUMS) model with rats, curcumin reduced serum corticosterone levels and attenuated CUMS-induced reductions of serotonin (Li et al., 2009). Curcumin administered to mice for 21 days prior to the FST was also shown to markedly attenuate FST-induced decreases in concentration of serotonin, the serotonin metabolite 5-hydroxyindoleacetic acid, noradrenaline and dopamine, as well as increases in serotonin turnover (Xia et al., 2007). Similar results were found following the acute administration of curcumin to mice one hour prior to the FST. Curcumin dose-dependently increased serotonin, and at higher doses increased dopamine levels. However, no changes in noradrenaline levels were found. The researchers demonstrated that curcumin was able to inhibit the monoamine oxidase enzymes (both MAO-A, and at higher doses MAO-B) and when co-administered with piperine, a bioavailability enhancing agent, the effects of curcumin on pharmacological, biochemical, and neurochemical activities were potentiated (Kulkarni et al., 2008). Similar findings were obtained when rats were subjected to chronic unpredictable stress. Curcumin treatment for 21 days significantly reversed the chronic unpredictable stress-induced behavioural (increase in immobility period), biochemical (increase in monoamine oxidase activity) and neurochemical (depletion of brain monoamine levels, except noradrenaline) alterations. The combination of piperine with curcumin again showed significant potentiation of its anti-

immobility, neurotransmitter enhancing (serotonin and dopamine) and MAO-A effects compared to curcumin administration alone (Bhutani et al., 2009).

In an animal study on the effects of curcumin on serotonin (5-HT) receptors, the antidepressant-like effects of curcumin in the FST were related to the serotonergic system, possibly due to an interaction with 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors (Wang et al., 2008). Further evidence of the monoamine effects of curcumin has been demonstrated in rats submitted to a bilateral olfactory bulbectomy. The administration of curcumin completely reversed induced reductions in serotonin and noradrenaline in the hippocampus and frontal cortex (Xu et al., 2005a). Curcumin also reversed reseperine-induced reductions in dopamine, noradrenaline and serotonin in rats (Arora et al., 2011). Pre-treatment with curcumin reversed haloperidol-induced reductions of dopamine, noradrenaline and serotonin in rats (Bishnoi et al., 2008). In a follow-up study, the co-administration of piperine significantly enhanced the effect of curcumin on these monoamines (Bishnoi et al., 2011).

Collectively, these animal studies provide strong support for the monoaminergic effects of curcumin. Curcumin enhances levels of serotonin and dopamine and, to a lesser extent, noradrenaline, following exposure to acute and chronic stress. The studies reviewed in this section indicate that curcumin has an inhibitory effect on monoamine

oxidase and influences 5-$HT_{1A/1B}$ and 5-HT_{2C} receptors, all of which play a role in depression.

Effects of curcumin on glutamate

Glutamate is the major excitatory synaptic neurotransmitter in the central nervous system and plays a vital role in the regulation of synaptic plasticity, learning, and memory (McEntee and Crook, 1993). Increasing research has demonstrated altered levels of glutamate in plasma, cerebrospinal fluid (CSF) and various areas of the brain in people with depression. An increasing number of reports also suggest potential antidepressant effects of anti-glutamatergic agents, such as ketamine, amantadine, and riluzole (Gao and Bao, 2011; McNally et al., 2008).

Curcumin inhibited the release of glutamate evoked by exposing synaptosomes to the K^+ channel blocker 4-aminopyridine (4-AP) (Lin et al., 2011). Because the inhibitory effect of curcumin on glutamate release was completely abolished by the antidepressant fluoxetine, it was concluded that these two substances may use a common intracellular mechanism to inhibit glutamate release from rat prefrontal cortex nerve terminals. When the effects of curcumin and fluoxetine were compared, curcumin had significantly greater inhibitory effects on glutamate release than fluoxetine (Lin et al., 2011).

Depression and HPA disturbances

The hypothalamic, pituitary and adrenal (HPA) axis plays a significant role in the body's stress response and is initiated by the secretion of corticotrophin releasing hormone (CRH) and arginine-vasopressin (AVP) from the hypothalamus. This, in turn, activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which then stimulates the secretion of glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. These glucocorticoids impact on their receptors and are involved in the negative feedback control of CRH and AVP release from the hypothalamus (Zunszain et al., 2011).

Abnormalities in the activity of the HPA axis have long been observed in major depression (Pariante and Lightman, 2008). This has been characterised by heightened cortisol secretion in patients presenting with melancholic depression, and reduced levels in people presenting with atypical depression (Gold and Chrousos, 2002). Increasing research has also demonstrated that depression is associated with a hypersecretion of CRH and impairment in the responsiveness to glucocorticoids, a phenomenon known as glucocorticoid resistance (Pariante and Lightman, 2008). Depression is also associated with an increased size and activity of the pituitary and adrenal glands (Nemeroff et al., 1992).

Effects of curcumin on HPA disturbances

A few studies have examined the effect of curcumin in regulating HPA disturbances, namely its effect in moderating the hypersecretion of corticosterone and subsequent neuroprotection. For example, rats subjected to 3 weeks of corticosterone injections exhibited depressive-like behaviours, as demonstrated by a significant decrease in sucrose consumption and an increase in immobility time in the FST. These behaviours were significantly reduced in those rats treated concurrently with curcumin (Huang et al., 2011). In a study on rats exposed to 4 weeks of chronic unpredictable mild stress, curcumin was able to moderate increases in serum corticosterone at levels similar to those obtained by fluoxetine (Li et al., 2009). In a final study, exposure of corticosterone to rat neurons decreased mRNA levels for three serotonin receptor subtypes, 5-HT_{1A}, 5-HT_{2A} and 5-HT_4. Pre-treatment with curcumin one hour prior to corticosterone exposure reversed this effect on 5-HT_{1A} and 5-HT_4 receptors, but not for the 5-HT_{2A} receptor. Moreover, curcumin significantly reduced neuronal loss, indicating that it could protect cells from corticosterone-induced toxicity. Curcumin also inhibited corticosterone-induced morphological changes such as increases in soma size, dendritic branching and dendritic spine density, and elevated synaptophysin expression in cortical neurons. The antidepressant fluoxetine also provided a protective effect against the toxicity of corticosterone and reversed corticosterone-induced down-regulation of mRNA levels for three receptors: 5-HT_{1A}, 5-HT_{2A} and 5-HT_4 (Xu et al., 2011).

In sum, these studies highlight the potential protective effects of curcumin on stress-induced cortisol production. HPA imbalances in depression may prove to be at least partly ameliorated by curcumin, although further studies are required.

Depression and neuroprogression

Neurogenesis is the process by which new neurons are formed from populations of neural stem or progenitor cells residing in discrete regions of the CNS (Abdipranoto et al., 2008). Recent research into neuroanatomy and neurochemistry has increasingly demonstrated that major depression is associated with impaired neurogenesis, neuronal plasticity, and subsequent neurodegeneration. This is indicated by stress-induced alterations to the number and shape of neurons and glia in the brain regions of depressed patients (Duman, 2009). Depression is also associated with a decrease in proliferation of neural stem cells (Eyre and Baune, 2012).

Neuronal plasticity is influenced by a range of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which is the most abundant and widely distributed neurotrophin in the central nervous system (Martinowich and Lu, 2008). BDNF plays a role in regulating a large array of functions including neuronal survival, growth and proliferation, and levels usually are low in people suffering from major depression (Duman, 2009; Lee and Kim, 2010). Chronic administration of several classes of antidepressants, including monoamine oxidase inhibitors, SSRIs, tricyclic agents, and

SNRIs increases BDNF levels (Duman and Monteggia, 2006; Sen et al., 2008). The detrimental effects of early life and chronic stress on BDNF, and evidence of increased levels of BDNF following physical exercise and electroconvulsive therapy, provides further support for a role of BDNF in the pathogenesis of depression (Martinowich et al., 2007; Nagahara and Tuszynski, 2011).

Neuroprotective effects of curcumin

Preliminary investigations into the neuroprotective effective of curcumin have provided evidence of its ability to enhance BDNF and attenuate stress-induced neurodegeneration. Repeated corticosterone injections were shown to significantly decrease BDNF levels in the hippocampus and frontal cortex of rats, which curcumin was able to significantly ameliorate (Huang et al., 2011). In another study, rats exposed to a range of daily stressors over a 20-day period were administered either 3 doses of curcumin orally or the antidepressant imipramine. Curcumin administration at higher doses reversed the stress-induced decrease in hippocampal neurogenesis in stressed rats at levels similar to imipramine treatment. Curcumin also reversed the stress-induced decrease in BDNF and 5-HT_{1A} mRNA levels across all hippocampal subfields. These effects were similar to those obtained from imipramine (Xu et al., 2007). Further evidence for the neuroprotective effects of curcumin was demonstrated in a recent study where pre-treatment with curcumin reversed the effect of corticosterone-induced

neuronal changes in rats (Xu et al., 2011). Curcumin also attenuated quinolinate-induced excitotoxicity on primary cultures of human neurons (Braidy et al., 2011).

Depression and mitochondrial disturbances

Mitochondria are intracellular organelles found in most eukaryotic cells which generate most of the cell's supply of adenosine triphosphate (ATP). They are also involved in a range of other processes, such as signalling, cellular differentiation, cell death, as well as the control of the cell cycle and cell growth (McBride et al., 2006). Because of the brain’s significant energy demands, high concentrations of mitochondria are found in this region making the brain susceptible to reductions in aerobic metabolism (Pieczenik and Neustadt, 2007).

Malfunction in the biochemical cascade and damage to the mitochondrial electron transport chain can lead to mitochondrial dysfunction or disease which has been implicated in a range of neuropsychiatric disorders such as depression, bipolar disorder and schizophrenia (Gardner and Boles, 2011; Rezin et al., 2009). In depression, mitochondrial disturbances such as deletions of mitochondrial DNA (Gardner and Boles, 2008a; Shao et al., 2008) and lower activities of respiratory chain enzymes and ATP production (Gardner et al., 2003) have been found. Gardner and Boles (2008a; b) also showed that in depressed individuals with somatic complaints, the majority had lowered ATP production rates in biopsied muscles. Further support for mitochondrial dysfunction in depression is demonstrated by increased rates of depression in patients with mitochondrial disorders. For example, the lifetime diagnosis of depression in patients with mitochondrial disorders was 54% (Fattal et al., 2007). Greater rates of depression were also detected in adolescents with mitochondrial disorders (Koene et al., 2009).

It has been argued that because depression is associated with increased oxidative and nitrosative stress, increased inflammatory pathways, and lowered antioxidant defences, this may be a major cause of mitochondrial dysfunction in major depression (Gardner and Boles, 2011; Maes et al., 2012c). Kynurenine pathway metabolites such kynurenic acid, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, which are dysregulated in major depression, can also impair mitochondrial ATP production (Baran et al., 2003).

Effects of curcumin on mitochondrial function

Altering the pathogenic cascade associated with mitochondrial dysfunction in major depression may be a potential avenue to enhance treatment outcomes in depression. Curcumin, with its numerous molecular effects, may be a useful option with a number of studies demonstrating protective effects on mitochondria. Curcumin was able to attenuate oxidative damage in rat cortical neurons by reducing intracellular production of reactive oxygen species (ROS) and protecting mitochondria from oxidative damage (Zhu et al., 2004). Treatment with curcumin also lowered aluminium-induced oxidative stress and mitochondrial dysfunction in the rat brain, likely by several mechanisms such as activation of Heme oxygenase-1, maintenance of glutathione metabolism or by scavenging ROS (Sood et al., 2011). Curcumin and its analogues were also able to inhibit ROS-induced lipid peroxidation and protein damage in mitochondria (Wei et al., 2006). Nuclear factor erythroid 2-related factor 2 (Nrf2), which mediates neuroprotection against mitochondrial complex I and II inhibitors, is also activated by curcumin (Greco and Fiskum, 2010; Jiang et al., 2011)

Depression and nitric oxide

Nitric oxide (NO) is an intercellular messenger in the brain, synthesised from the amino acid L-arginine by the enzymatic action of nitric oxide synthase (NOS). Three NOS isoforms are known to exist in mammals — neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) (Alderton et al., 2001). NO plays an important role in various physiological and pathological processes, and there has been increasing interest in its role in depression and other mental health conditions (Dhir and Kulkarni, 2011; McLeod et al., 2001; Pinto et al., 2008). According to Dhir & Kulkarni (2011), support for a role of NO in the pathogenesis of major depression is provided by studies showing that levels of plasma NO and its metabolites are elevated in suicidal and depressed patients (Lee et al., 2006; Suzuki et al., 2001), evidence that decreasing or blocking the synthesis of NO can induce antidepressant-like effects (Joca and Guimaraes, 2006), research demonstrating that NO modulates the production of neurotransmitters such as noradrenaline, serotonin, and dopamine (Dhir and Kulkarni, 2011), and evidence of lower levels of nNOS in the locus coeruleus of people suffering from major depression than in normal controls (Karolewicz et al., 2004). Further indirect evidence for NO involvement in major depression is derived from the characterisation of circulating antibodies against NO-epitopes. Highly reactive substances such as NO-tyrosine, NO-tryptophan and NO-arginine are formed by nitration reactions, and increased IgM antibody levels against these NO-adducts have been found in depressed patients (Maes et al., 2008b; Maes et al., 2011d). These results suggest that increased NO and/or activation of nitration reactions and consequent increases in nitrated containing proteins may be involved in the pathophysiology of depression (Maes et al., 2011a).

Effects of curcumin on nitric oxide

Several studies have now confirmed that curcumin can regulate levels of nitric oxide. Immobilisation-induced restraint stress lasting six hours significantly increased plasma nitrite levels in mice, which was attenuated by intraperitoneal delivery of curcumin. This effect was enhanced when curcumin was jointly delivered with aminoguanidine, an iNOS inhibitor, thereby suggesting curcumin's possible inhibitory effect on iNOS (Gilhotra and Dhingra, 2010). In cultured human neurons, quinolinic acid induced nNOS activity and consequently increased nitrite levels. Curcumin dose-dependently decreased nNOS activity in human neurons (Braidy et al., 2010). Further evidence of curcumin's nitric oxide inhibitory effect was demonstrated in a study on rats subjected to 72 hours of sleep deprivation. This led to increases in nitrite levels, along with several markers of oxidative damage. Intraperitoneal treatment with curcumin for 5 days had anxiolytic effects and restored nitrite levels. This effect was, however, abolished by pre-treatment with L-arginine, a precursor to nitric oxide, but only with the lower dose of curcumin of 10mg/kg. The researchers concluded that nitric oxide modulation is involved in the protective effect of curcumin in ameliorating sleep deprivation-induced behavioural alterations and oxidative damage (Kumar and Singh, 2008).

Depression and oxidative stress

In a review paper, Maes et al. (2011a) confirmed that major depression was accompanied by a decreased antioxidant status and by the induction of oxidative and nitrosative pathways. This was supported by studies showing significantly reduced plasma concentrations of important antioxidants such as vitamin C (Khanzode et al., 2003), vitamin E (Maes et al., 2000; Owen et al., 2005), and coenzyme Q_{10} (Maes et al., 2009b) in depressed patients. Depression was also accompanied by a lowered total antioxidant status (Cumurcu et al., 2009; Sarandol et al., 2007) and reduced antioxidant enzyme activity such as glutathione peroxidase (Maes et al., 2011e). Such deficiencies can impair protection against reactive oxygen species (ROS), causing damage to fatty acids, proteins and DNA (Maes et al., 2011a). In fact, increased levels of malondialdehyde, a measure of lipid peroxidation, were found in depressed patients (Ozcan et al., 2004; Sarandol et al., 2007; Wei et al., 2009), as have increased levels of 8-hydroxy-2-deoxyguanosine (8-OH-dG), a measure of oxidative damage to DNA (Forlenza and Miller, 2006; Maes et al., 2009a).

Further support for an association between oxidative stress and depression is provided by a few studies that demonstrate antioxidant properties of antidepressant medications. However, not all studies have uniformly identified reductions in oxidative markers following antidepressant medications, necessitating further research in this area (Ng et

al., 2008). Clinical studies into the efficacy of antioxidant therapies to alleviate depressive symptoms are lacking although N-acetylcysteine (NAC), a powerful antioxidant, was found to be useful for depressive episodes in bipolar disorder (Magalhaes et al., 2011). Zinc, which serves as a strong antioxidant, also has evidence of antidepressant activity (Szewczyk et al., 2011).

Antioxidant effects of curcumin

Investigations into the pharmacodynamics of curcumin have consistently demonstrated it to be a potent antioxidant (Ak and Gulcin, 2008; Menon and Sudheer, 2007), at least ten times more active as an antioxidant than vitamin E (Ak and Gulcin, 2008). In relation to a selection of the oxidative markers associated with depression, curcumin is able to lower levels of malondialdehyde (Rai et al., 2010), 8-OH-dG (Naik et al., 2011; Rai et al., 2010; Shih and Lin, 1993), and increase the activity of the antioxidant enzymes superoxide dismutase and glutathione peroxidase (Manikandan et al., 2011; Naik et al., 2011). Curcumin also attenuated increased markers of oxidative stress in rats undergoing chronic stress (Bhatia et al., 2011). In recent studies, curcumin also up-regulated Nrf2, a transcription factor that induces the expression of various genes including those that encode for several antioxidant enzymes (Scapagnini et al., 2011; Yang et al., 2009).

Depression and intestinal hyperpermeability

The intestinal epithelium is the largest mucosal surface in the human body and provides an interface between the external environment and the host (Fasano and Shea-Donohue, 2005). Normally, the intestinal epithelium provides a semi-permeable wall which allows nutrients to be absorbed while preventing larger, potentially toxic, antigenic, or pathogenic molecules or organisms from passing into the bloodstream. However, the permeability of the intestinal epithelium can become compromised leading to a condition known as intestinal hyperpermeability or 'leaky gut.' This results in an increased diffusion of antigenic food molecules and translocation of bacteria from the gut into extra-intestinal sites which can then trigger an immune response (Miller, 1997).

Lipopolysaccharides (LPS) are large molecules found in the outer membrane of Gram-negative bacteria and, during a state of intestinal hyperpermeability, are known to translocate into the systemic circulation in greater quantities (Maes et al., 2008a). Once the LPS are translocated into the blood, an inflammatory process is generated and is associated with increased neuroinflammation and secretion of proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α (Dunn, 2006; Henry et al., 2008; Huang et al., 2008; Qin et al., 2007). LPS are also able to activate IDO production leading to increased kynurenine metabolites and tryptophan breakdown (Dobos et al., 2012; Fu et al., 2010; O'Connor et al., 2009).

Research into the relationship between LPS, intestinal permeability and depression has demonstrated that LPS have the capacity to induce depressive behaviour in animals (Henry et al., 2008; Yirmiya, 1996). Interestingly, antidepressants such as fluoxetine and imipramine attenuate behavioural responses to immune challenges, such as LPS (Yirmiya et al., 2001). In a recent study, the reverse was demonstrated where LPS reduced the antidepressant effects of fluoxetine in a chronic, unpredictable mild stress model in mice (Wang et al., 2011).

Investigations into the incidence of intestinal hyperpermeability in patients with major depressive disorder have confirmed an increased translocation of LPS from Gram-negative enterobacteria in depressed patients. This was demonstrated by increased serum IgM and IgA levels directed against LPS of Gram-negative enterobacteria (Maes et al., 2012b; Maes et al., 2008b). Maes and colleagues concluded that depressive disorder was accompanied by increased gut permeability which was associated with an immune response directed against LPS produced by enterobacteria.

Effects of curcumin on the LPS-induced immune response

Several studies have investigated the protective effects of curcumin on LPS administration. In two separate studies, curcumin decreased NO production in LPS-stimulated microglial cells in a dose-dependent manner (Jung et al., 2006; Tocharus et al., 2012). Both pre- and post-treatment with curcumin diminished LPS-induced

dopamine neurotoxicity in a dose-dependent manner. LPS-induced production of many proinflammatory factors and their gene expressions such as TNF-α, NO, PGE_2 and IL-1β was also dramatically reduced following curcumin treatment. Curcumin also decreased LPS-induced activation of two transcription factors - nuclear factor kappaB and activator protein-1 (Huang et al., 2008). The benefits of curcumin may also occur through its ability to reduce the translocation of bacteria into extraintestinal sites, such as mesenteric lymph nodes, liver, spleen, and/or bloodstream (Karatepe et al., 2010)Given the potential of LPS to induce depressive-like behaviour in animals, and an increased translocation of LPS in depressed patients resulting from increased intestinal hyperpermeability, the ameliorating effects on LPS-induced inflammation provides another potential antidepressant mode of action of curcumin.

Conclusion

<<<insert Figure 4 near here>

While clinical trials on the antidepressant effects of curcumin are required to determine the efficacy of this natural substance, this paper highlights the multiple potential antidepressant modes of action of curcumin. As discussed above and summarised in Figure 4, curcumin has been shown through *in vitro* and *in vivo* studies to influence a range of neurotransmitters and hormones commonly observed to be disturbed in major depression. It also has the potential to provide neuroprotective effects, and shows some

promise as a protective agent from stress-induced neurotoxicity. Curcumin's anti-inflammatory and antioxidant effects are already well-recognised and may prove to be another potential mode of action in treating depression.

Unfortunately, a commonly cited problem associated with curcumin relates to its poor bioavailability via oral ingestion, limiting its potential clinical application (Anand et al., 2007). However, recent efforts to enhance its bioavailability have shown significant promise. For example, blood levels of the patented formulation BCM-95®CG was found to be 6.93 times higher than standard curcumin, and 6.3-fold higher than a curcumin-lecithin-piperine formula (Antony et al., 2008). In another human study on the patented curcumin formula, Meriva®, its total curcuminoid absorption was shown to be 29-fold higher than an unformulated curcuminoid mixture (Cuomo et al., 2011). Curcumin administered with the agent piperine also increases oral bioavailability (Shoba et al., 1998). While no research has yet assessed whether this increased absorption is associated with increased clinical efficacy, it is hoped that these methods of delivery may at least partly overcome problems associated with curcumin's poor oral absorption and therefore enhance its utility in clinical settings.

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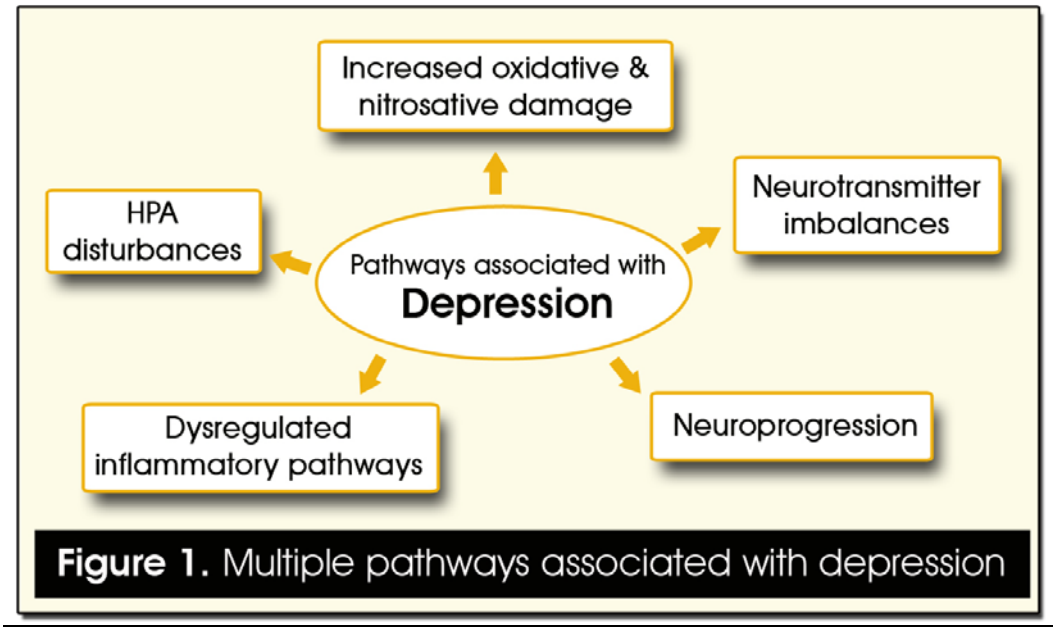

Figure 1. Multiple pathways associated with depression

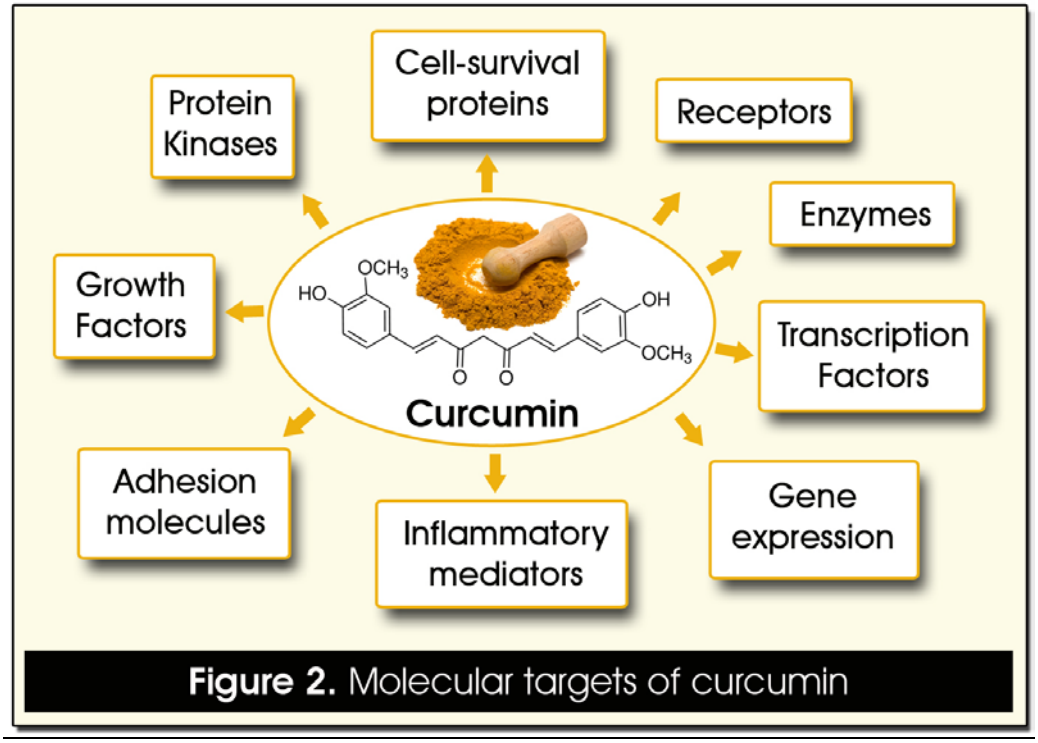

Figure 2. Molecular targets of curcumin

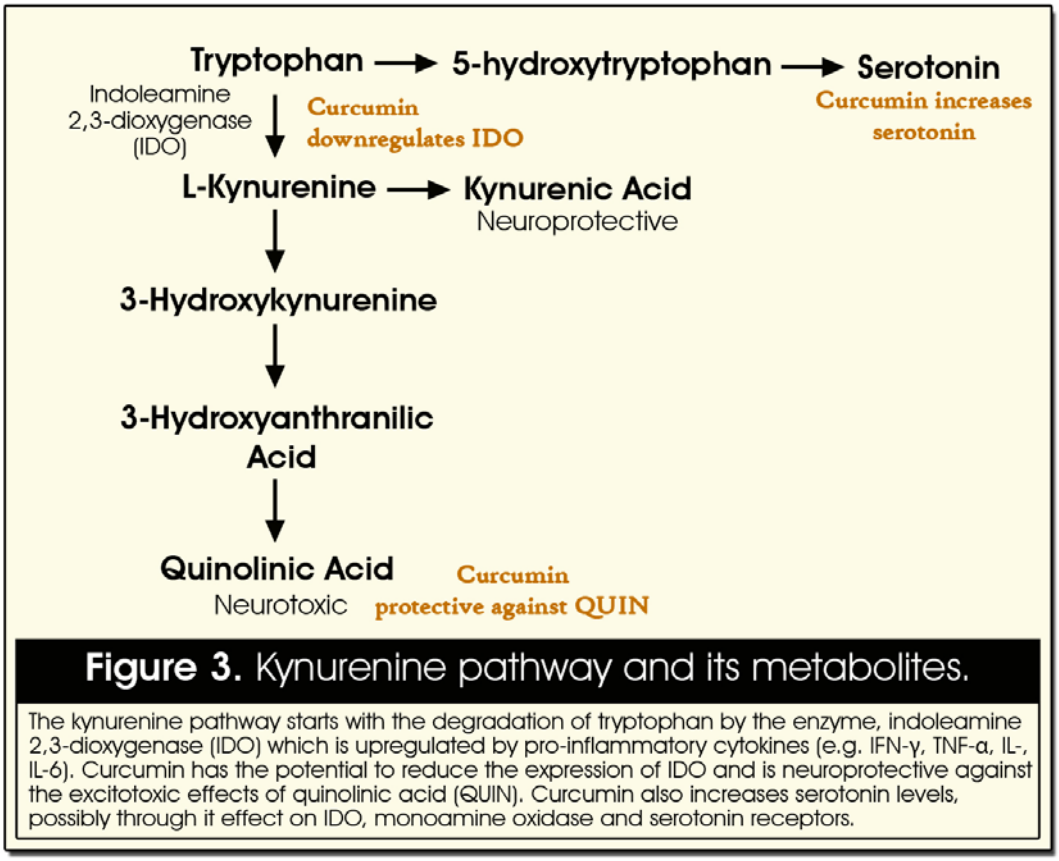

Figure 3. Kynurenine pathway and its metabolites.

The kynurenine pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). Curcumin has the potential to reduce the expression of IDO and is neuroprotective against the excitotoxic effects of quinolinic acid (QUIN). Curcumin also increases serotonin levels, possibly through it effect on IDO, monoamine oxidase and serotonin receptors.

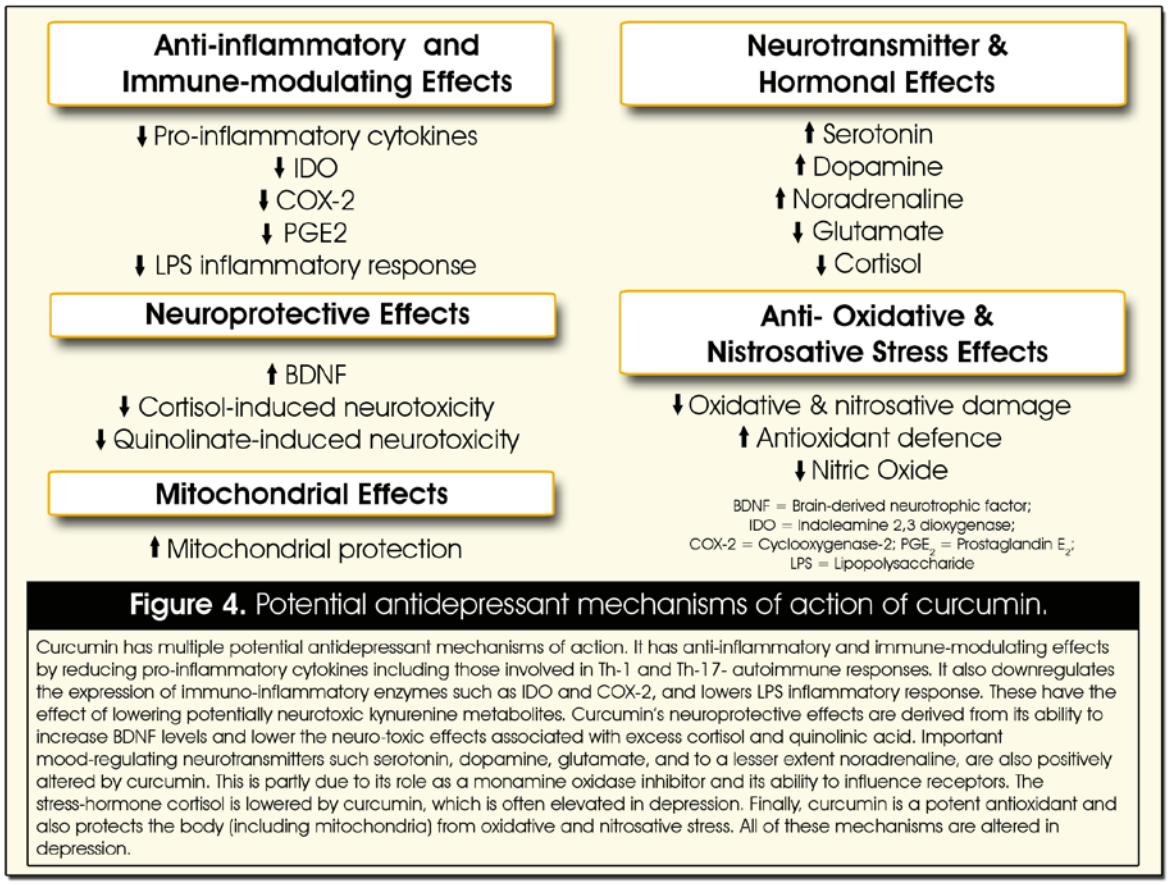

Figure 4. Potential antidepressant mechanisms of action of curcumin.

Curcumin has multiple potential antidepressant mechanisms of action. It has anti-inflammatory and immune-modulating effects by reducing pro-inflammatory cytokines including those involved in Th-1 and Th-17- autoimmune responses. It also downregulates the expression of immuno-inflammatory enzymes such as IDO and COX-2, and lowers LPS inflammatory response. These have the effect of lowering potentially neurotoxic kynurenine metabolites. Curcumin's neuroprotective effects are derived from its ability to increase BDNF levels and lower the neuro-toxic effects associated with excess cortisol and quinolinic acid. Important mood-regulating neurotransmitters such serotonin, dopamine, glutamate, and to a lesser extent noradrenaline, are also positively altered by curcumin. This is partly due to its role as a monamine oxidase inhibitor and its ability to influence receptors. The stress-hormone cortisol is lowered by curcumin, which is often elevated in depression. Finally, curcumin is a potent antioxidant and also protects the body (including mitochondria) from oxidative and nitrosative stress. All of these mechanisms are altered in depression.

Antidepressant Potential Modes of Action of Curcumin