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Curcumin in depressive disorders: an overview of potential mechanisms, preclinical and clinical findings

Fernanda Neutzling Kaufmann\textsuperscript{b}, Marta Gazal\textsuperscript{c,d}, Clarissa Bastos\textsuperscript{a}, Manuella Pinto Kaster\textsuperscript{b}, Gabriele Ghisleni\textsuperscript{a}\textsuperscript{*}

\textsuperscript{a}Programa de Pós-Graduação em Saúde e Comportamento – Universidade Católica de Pelotas, Pelotas, Rio Grande do Sul, Brasil.

\textsuperscript{b}Departamento de Bioquímica – Centro de Ciências Biológicas – Universidade Federal de Santa Catarina, Florianópolis, SC, Brasil.

\textsuperscript{c}Centro de Ciências Químicas, Farmacêuticas e de Alimentos – Universidade Federal de Pelotas, Pelotas, RS, Brasil.

\textsuperscript{d}Programa de Biologia Celular e Molecular – Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brasil.

*Corresponding author. Dra. Gabriele Ghisleni, Universidade Católica de Pelotas – UCPel, Programa de Pós-Graduação em Saúde e Comportamento, Rua Gonçalves Chaves 373, sala 324, CEP 96010-280, Pelotas – RS – Brasil. Telephone: +55 (53) 2128-8031, E-mail: ghisleni.g@gmail.com

Abstract

Considering the high prevalence of psychiatric disorders, its social burden and the limitations of currently available treatments, alternative therapeutic approaches targeting different biological pathways have been investigated. Curcumin is a natural compound with multi-faceted pharmacological properties, interacting with several neurotransmitter systems and intracellular signaling pathways involved in mood regulation. Also, curcumin has anti-inflammatory, antioxidant and neurotrophic effects, suggesting a strong potential to manage conditions associated with neurodegeneration,
such as psychiatric disorders. Most literature data focused on the potential of curcumin to counteract behavioral and neurochemical alterations in preclinical models of depression. The findings still need to be further explored and clinical reports share some controversial results that might be associated with its low systemic bioavailability following oral administration. Other psychiatric disorders also have neurochemical alterations similar to those found in depression, including neurotoxicity, oxidative stress and neuroinflammation. Despite the limited number of reports, preclinical models investigated the potential role for curcumin in anxiety, bipolar disorder, post-traumatic stress disorder and autism spectrum disorders. Here, we will summarize the cellular targets of curcumin relevant to psychiatric disorders and its effects in preclinical and clinical studies with depression, anxiety disorders and other psychiatric related conditions.

**Keywords:** Curcumin; Major Depression; Psychiatric Disorders; curcumin properties.

1. Introduction

The efficacy of pharmacological compounds used to manage most of psychiatric disorders is still far from optimal and treatment options are limited in both efficacy and tolerability. Despite the advances made in the past decades, the development of effective and better-tolerated agents to treat conditions such as major depression, bipolar disorder and anxiety disorders reached a plateau. Therefore, therapeutic approaches targeting different biological pathways have been extensively investigated and may represent an improvement in pharmacological therapy for these conditions. Currently, anti-inflammatory, antioxidants and neuroprotective compounds, able to counteract the degenerative processes frequently associated with psychiatric conditions are in the forefront of exploration for treatment or adjuvant therapy. In this review, we will
discuss the most recent research surrounding curcumin, a compound derived from the rhizome *Curcuma longa* used by the traditional Chinese medicine to manage stress and depression-related disorders. The multi-faceted pharmacological properties of curcumin lead to an extensive research in a range spectrum of disorders including cardiovascular, autoimmune, and neurodegenerative diseases, as well diabetes and cancers. The historical use of curcumin in medicine, its chemistry, stability and biological activities, including anti-cancer, anti-microbial, antioxidant, and anti-inflammatory properties were revised by Wang and Qiu, (2013). Here, we will focus in the cellular targets of curcumin relevant to neuroprotection and its effects in preclinical and clinical studies with depression and other psychiatric disorders.

2. Anti-inflammatory effects of curcumin

Inflammation is defined as a response generated in the organism to face injury, infection or disease. However, the exacerbation of inflammatory processes is involved in a range of pathological conditions. In this regard, curcumin is capable to interact with a wide variety of molecules involved in inflammatory response and has been evaluated as a potential candidate to counteract this physiological and eventually pathological process (Aggarwal and Harikumar, 2009; Hurley and Tizabi, 2013; Jurenka, 2009).

Human trials revealed that curcumin used as treatment or as adjuvant therapy can ameliorate inflammatory markers in several diseases. Type II diabetes patients receiving curcumin 300 mg/day for 8 weeks improved their general inflammatory state when compared to placebo group (Usharani et al., 2008). Also, peripheral interleukin-1β (IL-1β), interleukin-4 (IL-4) and vascular endothelium growth factor (VEGF) levels were reduced in obese patients treated with curcumin 1 g/day for 4 weeks (Ganjali et al., 2008).
Curcumin treatment was also effective in lowering peripheral inflammatory parameters associated with chronic cutaneous complications (Pahani et al., 2012).

Most of the first studies trying to unravel the beneficial effects of curcumin came from cancer research. Supplementation with curcuminoids (180 mg/day for 8 weeks) significantly diminished peripheral levels of inflammatory cytokines and inflammatory molecules in solid tumor patients undergoing chemotherapy (Panahi et al., 2014). It is well documented that inflammation is a critical component of tumor severity and progression. In this way, studies using curcumin demonstrated that it has a pro-apoptotic activity in neuroblastoma cells and appear to induce apoptosis in a variety of cancers. In fact, curcumin appears to have selectively cytotoxicity in tumor cells when compared to normal cell, an effect that probably result from differences in metabolism between normal and malignant cells (Basnet and Skalko-Basnet, 2011; Schaffer et al., 2015).

Curcumin presents hypomethylating activity, an important effect in solid and blood cancers since it was demonstrated that this kind of pathologies have aberrant hypermethylation of CpG promoter islands in several tumor suppressor genes, leading to its transcriptional silencing (Liu et al., 2009). Moreover, curcumin presents an overall epigenetic regulatory role, including regulation of histone modifications and microRNAs (Boyanapalli and Kong, 2015). Curcumin acts as a natural selective inhibitor of p300 histone acetyltransferase (HAT), a role that was attributed to its ability to induce apoptosis in cancer cells through the induction of caspase or p53 signaling. This epigenetic mechanism is involved in the control of Alzheimer’s disease related genes, prevention of renal injury and, alleviation of neuropathic pain, diabetes and other metabolic diseases (Pham and Lee, 2012; Lu et al., 2014; Zhu et al., 2014).
One of the most well described intracellular targets for curcumin in different cell types is the nuclear factor-kappa B (NF-κB), a transcriptional factor that regulates the production of inflammatory cytokines and inflammatory responses, and is involved in a wide spectrum of pathologies (Tornatore et al., 2012). Curcumin has an inhibitory effect on NF-κB activation and its downstream signaling (Hatcher et al., 2008). Suppression of NFκB is associated with down regulation of inflammatory cytokines, responsible for tumorigenesis (Aggarwal and Harikumar, 2009). However, curcumin also diminished protein levels of NF-κB in a genetic model of type-2 diabetes (db/db mice) induced by mutation of leptin receptor gene (Lepr<sup>db</sup>) (Jiménez-Flores et al., 2014). Pre-clinical studies have also showed that curcumin intake lowered inflammatory state in a mouse model of obesity (Sarker et al., 2015), inhibited NLRP3 inflammasome activation in LPS-primed macrophages and significantly diminished IL-1β and high mobility group box 1 (HMGB-1) in mice suffering of lethal endotoxic shock (Gong et al., 2015).

In the central nervous system (CNS), curcumin reduced interleukin-23 (IL-23) and interleukin-17 (IL-17) levels in a model of retinal ischemia (Zhang et al., 2015), while in cerebral ischemia it was able to decrease the infarct area and IL-1β, tumor necrosis factor (TNF-α), cyclooxygenase-2 (COX-2) and prostaglandin-2 (PGE-2) levels via activation of peroxisome proliferator-activated receptor gamma (PPARγ) (Liu et al., 2013). Moreover, it was demonstrated that curcumin inhibited Toll-like receptor 2 and 4 (TLR-2/4) and NF-κB in rats submitted to permanent focal cerebral ischemia (Tu et al., 2014). In neurodegenerative disorders, the multi-faceted effects of curcumin, lead to the interest in evaluating its use in Alzheimer’s disease and Parkinson's disease. In Alzheimer’s disease curcumin treatment was capable to reduce Aβ accumulation in the brain and improved cognitive and synaptic dysfunction (reviewed by Venigalla et al., 2015). Curcumin also counteracted the down-regulated mRNA
expression of glial fibrillar acidic protein (GFAP) and diminished the number of hypertrophic astrocytes in the hippocampus of Aβ(1-40)-treated rats Wang et al., (2013). A curcumin analog, demethoxycurcumin, decreased hippocampal pro-inflammatory IL-1β and GFAP in a rat model of Alzheimer’s disease (Ahmed and Gilani, 2011). Beyond that, in vitro studies have shown that curcumin can influence Aβ metabolism, aggregation and dramatically suppress IL-1β, IL-6 and TNF-α production in Aβ-exposed microglia via mitogen-activated protein kinase (MEK1/MEK2) and p38 pathways (Ono et al., 2004; Shi et al., 2015). Also, curcumin treatment protected dopaminergic neurons from degeneration in a Parkinson's disease model and reduced pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) (Fu et al., 2015; Ojha et al., 2012).

3. Antioxidant effects of curcumin

Several works consistently demonstrated that curcumin has a potent antioxidant activity in vitro and in vivo (Ak and Gulcin, 2008; Menon and Sudheer, 2007). In fact, curcumin reduced lipid peroxidation in morphine-induced hippocampal toxicity, in hydrogen peroxide- (H₂O₂) induced liver and spleen damage, in iron-overloaded rats, as well as in rats with diabetic neuropathy (Al-Rubaei et al., 2014; Attia et al., 2012; Badria et al., 2015; Motaghinejad et al., 2015). Curcumin attenuated intracellular production of reactive oxygen species (ROS) and protected mitochondria from oxidative stress (Wei et al., 2006; Zhu et al., 2004). Also, animals intoxicated by gentamicin and receiving curcumin treatment showed reduced levels of the enzyme inducible nitric oxide synthase (iNOS), and peroxynitrite levels were decreased in a model of diabetic rats receiving a combined curcumin and gliclazide treatment (Attia et al., 2012; Manikandan et al., 2011). Some of these effects are probably related to
mechanisms such as activation of heme oxygenase-1, maintenance of glutathione metabolism or by ROS scavenging and activation of the nuclear factor erythroid 2-related factor 2 (Nrf2), (Greco and Fiskum, 2010; Jiang et al., 2011; Sood et al., 2011).

The activity of antioxidant enzymes can also be modulated by curcumin treatment. Curcumin was capable to counteract oxidative stress profile by diminishing superoxide dismutase (SOD), catalase (CAT) and reducing glutathione (GSH) serum levels in rat damaged liver (Al-Rubaei et al., 2014). On the other hand, a phytochemical mixture containing curcumin was associated with increased SOD and GSH levels in the liver of diabetic rats (Parmar et al., 2015). In a primary culture of cortical neurons exposed to oxyhemoglobin neurotoxicity, curcumin enhanced SOD and glutathione peroxidase (GSH-Px) activity (Li et al., 2015). Besides that, curcumin administration decreased Aβ peptide- induced mitochondrial dysfunction by normalizing SOD and CAT activity and by inhibiting glycogen synthase kinase-3β (GSK-3β) in cultured cells (Huang et al., 2012).

4. Effects on neurotrophic factors and synaptic plasticity

An epidemiologic study conducted in Asia with elderly subjects identified a better cognitive performance in individuals who had consumed curry in the diet (Ng et al., 2006). In fact, curcumin showed to be protective and reverse cognitive impairments in different animal models through mechanisms involving important intracellular signaling pathways involved in neuroplasticity and cell survival (Dong et al., 2012).

In a model of traumatic brain injury, curcumin supplementation was able to reduce oxidative damage and normalize cognitive impairment, and levels of brain derived neurotrophic factor (BDNF), synapsin I, cAMP response element-binding protein (CREB), protein kinase B (AKT) and Ca²⁺/calmodulin-dependent protein kinase
II in the hippocampus of mice (Wu et al., 2006; Wu et al., 2011). Curcumin-fortified diet improved cognition and neurogenesis in aged rats (Dong et al., 2012) and in a rodent model of Alzheimer’s disease. This effect depended on activation of AKT/GSK-3β signaling pathway, increased levels of protein kinase RNA-like endoplasmic reticulum kinase (PERK) and BDNF (Hoppe et al., 2013; Zhang et al., 2015). Curcumin also increased memory performance in both adult and D-galactose-induced aged mice by increasing levels of phosphorylated CREB and BDNF in the subgranular zone of dentate gyrus and preventing the reduction of cell proliferation and neuroblast differentiation (Nam et al., 2014).

In a rat model of Parkinson’s disease (PD), curcumin treatment also improved spatial learning and memory ability, increasing BDNF, tropomyosin receptor kinase B (TrkB) and phosphoinositide 3-kinase (PI3K) protein levels in hippocampus (Yang et al., 2014). The levels of BDNF and synaptophysin in lateral amygdala were also enhanced after curcumin treatment, which was accompanied by antidepressant-like behavior in rats exposed to the preclinical model of depression induced by chronic unpredictable mild stress (Zhang et al., 2014).

Rat cortical neurons treated with curcumin had enhanced cell viability. In this model, MAPK and PI3k appear to be the signaling downstream BDNF activation underlying curcumin effects (Wang et al., 2008; Wang et al., 2010). A recent study has showed that curcumin prevented the reduction of neural stem cells increasing hippocampal cell proliferation in a model of bisphenol-A treated animals, an endocrine-disrupting synthetic xeno-estrogen. These effects occurred via Wnt signaling, increasing genes such as Wnt-1, Wnt-3, disheveled, β-catenin and ameliorating learning and memory performance (Tiwari et al., 2015).
5. Role of curcumin in major depressive disorder

The potential beneficial effects of curcumin in the pathophysiology of major depression are probably related to its ability in modulate neurobiological substrates strongly associated with the disease. Besides its anti-inflammatory, and antioxidant properties described above, other biological effects of curcumin are intimately involved in the etiology of major depression, including: inhibition of monoamine oxidase (MAO) (Kulkarni et al., 2008; Wang et al., 2008), serotonin and dopamine release (Li et al., 2009; Seo et al., 2015; Xu et al., 2005a), regulation of hypothalamus pituitary adrenal (HPA) axis and modulation of neurotrophic factors and hippocampal neurogenesis and neuroplasticity (Huang et al., 2011; Liu et al., 2014; Xu et al., 2006; Zhang et al., 2012). Based in these findings research is focusing attention for the potential antidepressant properties of this compound (Kulkarni et al., 2009; Noorafshan et al., 2015; Panahi et al., 2015; Seo et al., 2015).

5.1. Preclinical studies

Both acute and chronic curcumin administration to rats and mice consistently reduced immobility time in behavior despair models such as the forced swimming test (FST) and tail suspension test (TST), an indicative of antidepressant-like effect (Kulkarni et al., 2009; Liu et al., 2014; Lopresti et al., 2012; Noorafshan et al., 2015; Panahi et al., 2015; Seo et al., 2015; Wang et al. 2008; Wang et al., 2014; Xu et al. 2005a). Chronic curcumin treatment also alleviated behavioral and neurochemical alterations in other preclinical models with face and construct validity, including the olfactory bulbectom (OB) (Rinwa et al., 2013; Xu et al., 2005a), chronic stress models (Buthani et al., 2009; Jiang et al., 2013; Li et al., 2009; Lin et al., 2013; Liu et al., 2014; Xu et al., 2005a; Zhang et al., 2014), pharmacological models including chronic
corticosterone administration (Huang et al., 2011), reserpine-induced monoamine depletion (Arora et al., 2011), lipopolysaccharide (LPS) administration (Wang et al., 2014), and also in genetic models such as the Wistar Kyoto rats (Hurley et al., 2013).

The antidepressant-like effects of curcumin were similar to those observed after treatment with classical antidepressants including fluoxetine and imipramine (Li et al., 2009; Sanmukhani et al., 2011; Wang et al., 2008). Indeed, most studies discuss that curcumin inhibitory effects on MAO-A and MAO-B activities increase serotonin and dopamine synaptic availability or restored monoamine levels in several brain regions, an effect related to antidepressant activity (Arora et al., 2011; Kulkarni et al., 2008; Wang et al., 2008; Xu et al., 2005a; Xu et al., 2005b). Moreover, the antidepressant-like effects of curcumin in the FST were mediated, at least in part, by an interaction with serotonin 5-HT$_{1A/1B}$ and 5-HT$_{2C}$ receptors (Wang et al., 2008). The co-administration of piperine seems to act as a bioavailability-enhancing agent, potentiating the effects of curcumin in the chronic unpredictable mild stress model of depression (Kulkarni et al., 2008).

Besides the effects on monoaminergic system, chronic administration of curcumin also counteracted the increased corticosterone levels, and other physiological changes induced by chronic unpredictable mild stress in rats, such as abnormal adrenal weight and glucocorticoid receptors expression (Li et al., 2009; Xu et al., 2011). In addition, curcumin inhibited glutamate release in synaptosomes (Lin et al., 2011), and an in vivo study indicated that curcumin exerts antidepressant-like effect by activation of GluN2B NMDA receptor subunits (Zhang et al., 2013). The antidepressant potential of curcumin was also related to its anti-inflammatory properties described above (Tizabi et al., 2014). In fact, curcumin treatment for 7 days prevented the depressive-like behavior and anhedonic behavior induced by systemic LPS administration in mice. This
effect was associated with its ability to reduce the levels of pro-inflammatory cytokines, iNOS and COX-2 mRNA expression in areas involved in mood regulation such as the hippocampus and prefrontal cortex (Wang et al., 2014). Additionally, chronic curcumin treatment significantly reversed the anhedonic behavior and the hypolocomotion in rats submitted to the chronic mild stress model of depression, an effect associated with its anti-inflammatory potential (Jiang et al., 2013).

The antidepressant effects of curcumin also involve its ability to enhance protein levels and expression of BDNF (Xu et al., 2006; Xu et al., 2007), by a mechanism dependent on the activation of intracellular targets including the MAPK/ERK pathway (Liu et al., 2014; Zhang et al., 2012). Furthermore, curcumin appears to prevent neuronal and biochemical alterations induced by chronic unpredictable mild stress in the lateral amygdala, including the expression of the synapse-associated proteins PSD-95 and synaptophysin (Zhang et al., 2014). These neuronal and biochemical alterations induced by curcumin suggest a potential use for this compound to counteract neuronal dysregulation and alterations in neuroplasticity related to the depressive-like behaviors caused by chronic stress.

5.2. Clinical

The chronic supplementation with curcumin (1000 mg/day) for six weeks was capable to reduce the Hamilton Depression Rating Scale (HDRS-17) and Montgomery-Asberg Depression Rating Scale (MADRS) scores in patients. Furthermore, curcumin decreased inflammatory cytokines IL-1β and TNFα levels, increased plasma BDNF levels, and decreased salivary cortisol concentrations in depressed patients compared with placebo group (Yu et al., 2015). In another study, treatment with curcumin (1000 mg/day) for 8 weeks was significantly more effective than placebo, improving mood-
related symptoms, particularly in individuals with atypical depression (Lopresti et al., 2014). Also, in a randomized controlled trial by Sanmukhani et al. (2014) a comparable efficacy was obtained after curcumin monotherapy (1000 mg/day) and fluoxetine monotherapy, according to the response rates measured by the HDRS-17. However, fluoxetine/curcumin combination was not found to have a superior efficacy compared with monotherapy with either of the agents (Sanmukhani et al., 2014).

Bergman and colleagues investigated the efficacy and safety of 5-week curcumin (500 mg/day) supplementation for patients with MDD in a randomized, double blind, placebo-controlled clinical trial. In their study, they failed to find any significant differences in improvement of depression symptoms measured by HAMD and MADRS between curcumin and placebo together with antidepressants (escitalopram or venlafaxine), although curcumin demonstrated a trend to relieve the depressive symptoms faster in comparison to placebo group treated with antidepressants (Bergman et al., 2013). However, in a recent open-label comparative trial, 111 subjects were allocated to standard antidepressive therapy plus curcumin/piperine combination (1000–10 mg/day) or standard antidepressive therapy alone, for a period of 6 weeks. In this study, the Beck Depression Inventory II (BDI-II) and Hospital Anxiety and Depression Scale (HADS) scores were reduced in both study groups and the total HADS scores were significantly reduced in patients treated with curcuminoids versus standard antidepressants (Panahi et al., 2015). On the other hand, a recent study showed that chronic treatment with curcumin (1 g/day) or placebo for a period of 30 days did not exert any significant impact on BDI scales (Esmaily et al., 2015). Most of the clinical studies with curcumin were evaluated in a recent meta-analysis including six clinical trials. The results supported that curcumin administration reduces depressive symptoms in patients with MDD (Al-Karawi et al., 2016). However, due to the low
systemic bioavailability of curcumin in humans following oral administration and the small number of clinical trials, its efficacy for MDD alone or as an adjuvant therapy still need to be explored.

6. Other psychiatric disorders

Disturbance in neurotransmitters, inflammatory processes, defects in neurogenesis and synaptic plasticity, mitochondrial dysfunction, and redox imbalance are observed in several pathologies affecting the CNS including psychiatric and neurodevelopmental disorders. However, for most of these conditions preclinical and clinical studies with curcumin are scarce or even absent.

Anxiety disorders are characterized by a state of high arousal and negative valence resulting in increased vigilance in the absence of an immediate threat (Calhoon et al., 2015). According to the American Psychiatric Association, these heterogeneous conditions include diseases such as social anxiety disorder, obsessive-compulsive disorder, and panic disorder. In common they all share extreme or pathological anxiety states (Benammi et al., 2014). Although little is known about the anxiolytic properties of curcumin, anxiety and depression share many biological substrates and several preclinical studies suggest a pharmacological potential of these compound in anxiety-related behaviors.

Treatment with curcumin extract (10 and 20 mg/kg, i.p.) for 5 days significantly prevented anxiety-like effects in mirror chamber, plus maze, zero maze paradigms in 72-h sleep-deprived mice. The mechanism involved in the protective effects of curcumin was dependent on the inhibition of nitric oxide (NO) and oxidative damage (Kumar and Singh, 2008). In another animal study, anxiolytic effects of curcumin (30 mg/kg, i.p.) in the dark light box and elevated plus maze were observed in rats acutely
intoxicated with lead (Benammi et al., 2014). This data suggested that a possible modulation of monoaminergic neurotransmission was involved in this effect, similarly to the mechanisms involved in the antidepressive-like effects of curcumin (Kulkarni et al., 2008). Curcumin treatment had also shown a protective effect in quinpirole- induced model of obsessive-compulsive disorder, by affecting brain monoamine levels in rats (Chimakurthy and Murthy, 2010).

In a chronic unpredictable mild stress the protective effects of curcumin were compared to sertraline on behavioral parameters, including anxiolytic profile (Noorafshan et al., 2013). Moreover, the anxiolytic properties of curcumin were also evaluated in acute stress models. Pre-treatment with curcumin (20 mg/kg) prevented the hyperlocomotion and anxiogenic state in restraint stress mice, as well as 1-week curcumin (200 mk/kg/day) treatment prevented memory deficit induced by acute immobilization stress in rats (Gilhotra and Dhingra, 2010; Haider et al., 2015). The beneficial effects of curcumin in anxiety-related behaviors were also attributed to its inhibitory effect of iNOS and decrease in NO levels (Haider et al., 2015). Also, curcumin reduced anxiety-like behavior in rodents and enhanced brain synthesis of docosahexaenoic acid, an omega-3 fatty acid strongly linked to anxiety.

In a clinical double blind crossover randomized trial, curcumin (1 g/day) administration for 30 days in obese individuals reduced anxiety levels without producing an antidepressant effect when compared to placebo group (Esmaily et al., 2015). Since depression and anxiety share many neurobiological events including oxidative stress, neuroinflammation, as well as modulation of monoamines content in brain, these initial data point to a potential use of curcumin to treat anxiety- related disorders. However, the mechanisms involved in these effects should be evaluated in
preclinical trials and more clinical studies need to be conducted to further reinforce this notion.

The potential use of curcumin in bipolar disorder was proposed in revision papers by Brietzke et al., (2013) and Ong et al., (2015), especially due to its anti-inflammatory, antioxidant and neurotrophic properties. In preclinical models, ketamine administration is capable to induce hyperlocomotion and other behavioral and neurochemical changes in rats that resemble schizophrenia-like states and the manic episode of bipolar disorder. In fact, these behavioral and neurochemical alterations are normalized by antipsychotics and mood stabilizers traditionally used to treat schizophrenia and bipolar disorder, respectively (Frohlich and Van Horn, 2014; Ago et al., 2012; Ghedim et al., 2012). Treatment with curcumin reversed the both behavioral and neurochemical alterations in this model (Gazal et al., 2014). On the other hand, dietary curcumin also impaired fear memory consolidation and reconsolidation in rats, findings that may have important clinical implications for treatment of post-traumatic stress disorder (PTSD) (Monsey et al., 2015). Central administration of propionic acid in rodents is capable to induce behavioral and neurochemical alterations resembling autistic spectrum disorders, including impairment in social interaction, stereotypy, anxiety, depression, learning and memory dysfunction, oxidative stress, and mitochondrial dysfunction (Bhandari and Kuhad, 2015). Treatment with curcumin for 4 weeks significantly restored both behavioral and neurochemical effects of propionic acid, suggesting a potential for a potential for autism spectrum disorders.

7. Perspectives

Given the multifactorial nature of psychiatric disorders, an enhancement of treatment efficacy is likely to occur from therapies that target multiple mechanisms. In
this line, curcumin has a wide variety of pharmacological properties including anti-antioxidant, anti-inflammatory, modulator of transcription factors and enzymes that include MAO, iNOS and COX-2, growth factors such as BDNF, and signaling transducing pathways. Thanks to all these activities, curcumin is positioned as an interesting compound and it has been used in several clinical trials.

One important limitation for the clinical use of curcumin is its low absorption rates in the intestine and a rapid metabolism (Liu et al., 2016). A study performed in rats to evaluate the pharmacokinetics of curcumin demonstrated that its elimination half-life is 28.1±5.6 min for 500 mg/kg, p.o. and 44.5±7.5 min 10 mg/kg, i.v. and a bioavailability of only 1% after oral administration (Yang et al., 2007). Therefore, many curcumin formulations contain ingredients that are intended to improve its bioavailability and effectiveness against different diseases. The co-administration of curcumin with piperine or quercetin seems to enhance curcumin bioavailability. In this line, many recent studies are also proposing novel strategies to administrate this compound, such as encapsulation in liposomes, polymeric nanoparticles or lipid complexes in order to improve bioavailability and consequently its beneficial effects (Pulido-Moran et al., 2016).

The efficacy of curcumin as a neuroprotective agent in several preclinical models has created considerable excitement mainly due to its low toxicity and cost, suggesting that this compound might be a worthy candidate for prophylactic intervention in different psychiatric disorders. However, the potential beneficial effect of curcumin in other psychiatric and neurodevelopmental conditions still needs to be explored.

References:


