Is there a role for curcumin in the treatment of bipolar disorder?

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Abstract

Curcumin is a polyphenolic nonflavonoid compound extracted from the rhizome of turmeric (Curcuma longa), a plant commonly used in Indian and Chinese traditional medicine to treat rheumatism, cough, inflammation and wounds. Curcumin putative targets, known based on studies of diverse central nervous system disorders other than bipolar disorders (BD) include several proteins currently implicated in the pathophysiology of BD. These targets include, but are not limited to, transcription factors activated by environmental stressors and pro-inflammatory cytokines, protein kinases (PKA, PKC), enzymes, growth factors, inflammatory mediators, and anti-apoptotic proteins (Bcl-XL). Herein, we review previous studies on the anti-inflammatory and anti-oxidant properties of curcumin and discuss its therapeutic potential in BD.

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Introduction

Bipolar disorder (BD) is a chronic, severe and prevalent mental disorder associated with high rates of non-recovery, recurrence, and chronicity [1,2]. Morbidity, mortality, and cost of illness studies indicate that BD is related to significant burden [3,4]. Moreover, for many affected individuals, BD is a progressive and accelerating condition associated with neurostructural changes and cognitive deterioration [5–7]. In addition to brain abnormalities, BD has been linked to several metabolic alterations, including obesity, arterial hypertension, and changes in glucose metabolism [8,9]. In fact, metabolic syndrome and cardiovascular morbidity are one of the most relevant causes of mortality in this population [10].

Evidence-based treatments for BD include the use of lithium, several anticonvulsants, and atypical antipsychotics [11]. Studies evaluating efficacy and effectiveness indicate that most individuals with BD fail to achieve symptomatic remission and functional recovery with existing treatments alone or in combination [12]. Moreover, high rates of treatment discontinuation and switching in BD are consequences of the limited efficacy of available agents [13]. Furthermore, tolerability concerns (e.g., weight gain) are major limitations of current treatments [13].

It is generally accepted that existing treatments for BD are capable of suppressing symptoms but have not been proven to modify the underlying disease course and progression of the illness. In addition to phenotypic/behavioral progression (e.g., shorter symptom-free intervals as a function of episode frequency), pathological progression in BD has been reported at the brain circuits, synaptic, cellular, intracellular, and neurochemical levels [14]. In fact, BD is characterized by progressive neuronal atrophy, cognitive deterioration functioning along with shorter symptom-free intervals and lower treatment response rates [15]. Mechanisms underlying neuroprogression are related to imbalances between neurotoxicity and neuroprotection (i.e., neuroplasticity) [14].

The search for new, more efficient, and safer drugs to treat BD is an unmet need in psychiatry. For instance, the use of complementary and alternative medicines (CAM) offers a potentially interesting resource [16]. Although the development of pragmatic clinical trials for CAM in mood disorders began approximately 20 years ago, their off-label administration dates back to hundreds or thousands of years [17]. Traditional cultures explored which plants were useful for what conditions and passed information on species, preparation, and dose through the ages [17]. There appears to be a high level of patient acceptance of this treatment modality, notwithstanding the relative paucity of evidence supporting their usage, as well as concerns regarding bioavailability and manufacturer quality assurance [18]. Some CAM treatments exhibit neurobiological effects that suggest possible application in BD [19]. For example, over 3000 preclinical reports have described pleotropic properties attributable to the herbal component curcumin [20].

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http://dx.doi.org/10.1016/j.mehy.2013.02.001
Curcumin is a polyphenolic nonflavonoid compound extracted from the rhizome of turmeric (Curcuma longa), a member of the ginger family, and is commonly used as a culinary season in different regions of India, China and other Asiatic countries [21]. In addition to its culinary use, turmeric has been used in these countries as an anti-inflammatory agent [22], being used in traditional Indian medicine for rheumatism, cough, inflammation and wound [23]. Turmeric has been studied in detail and all active ingredients were isolated, including curcumin, which was described as the most effective bioactive component [24]. As curcumin has low toxicity, it has been explored in medicine, based on its anti-oxidants and anti-inflammatory properties. Accordingly, curcumin has been studied in several diseases where inflammation and oxidative stress imbalances are related to the pathophysiological mechanisms, such as, Alzheimer’s and Parkinson’s disease [25], as well as cardiovascular diseases and cancer [20,26,27].

Curcumin is often regarded as pleiotropic compound whose the putative mechanisms of action are directed to several targets [28], such cell proteins, including transcription factors (ATF-3, AP-1, STAT-3, NF-kB), protein kinases (PKA, PKC), enzymes, growth factors, inflammatory mediators, and anti-apoptotic proteins (i.e., Bcl-XL) [21]. Because several of these targets have been implicated in the pathophysiology of BD [29–31] or in the mechanisms of action of current mood stabilizers [32,33], we postulated that curcumin could have therapeutic potential for the treatment of BD. In this work, we review current evidences of the anti-inflammatory and anti-oxidant properties of curcumin and propose that these effects may offer advantage for BD therapeutics.

Neurotrophins, oxidative species and inflammation in bipolar disorder: possible targets for curcumin

Although the pathophysiology of BD remains elusive, in the last decade, findings from different modalities of research have converged to demonstrate alterations in neuroplasticity, neuronal interconnectivity, apoptosis regulation, cell survival and resilience as critical processes in the patho-etiology and neuroprogression of BD [34]. The balance between neuronal survival and death is regulated or influenced by several mediators. Alterations in levels of these substances in the periphery have been postulated as possible biomarkers of BD [35]. The reproduction of abnormalities in neurotrophins, inflammatory mediators and oxidative species in independent studies lead to the postulation that this combination can be considered a viable biosignature and marker of progression in BD [35]. Throughout this section, we discuss these mediators and report the effects of curcumin on these potential therapeutic targets.

Neurotrophins

Neurotrophins are a family of proteins involved in neuronal development, survival and neuronal functioning. The neurotrophin called brain-derived neurotrophic factor (BDNF) is considered a key mediator of neuroplasticity, being implicated in processes such as neuronal differentiation, survival and synaptic plasticity [36]. Decreased serum BDNF levels in acute mood episodes of either polarity in BD were recently confirmed in a comprehensive meta-analysis [37]. Furthermore, clinical recovery is associated with a corresponding increase in BDNF levels [38]. The pathophysiological role of BDNF BD has been reviewed in detail elsewhere [38,39]. Several effective treatments for BD, such as lithium, electroconvulsive therapy and atypical antipsychotics are known to increase BDNF levels [40–42]. Moreover, polymorphisms of the BDNF gene were shown to confer vulnerability to develop BD [43–45]. A special attention has been given to the Val66Met polymorphism, as it appears to be significantly associated with greater risk for BD [43].

Curcumin and BDNF

Several preclinical studies revealed that curcumin is able to: (i) induce widespread increases in brain BDNF levels; (ii) enhance the expression of this neurotrophin and (iii) modulate the second messengers in BDNF signaling pathway [46].

Induction of stress and activation of hypothalamus–pituitary–adrenal (HPA) axis in animals promotes a reduction in BDNF levels. Curcumin restored BDNF levels in the hippocampus and prefrontal cortex of rats when compared to control animals submitted to corticosterone-induced animal models of depression [47]. In addition, administration of curcumin completely reversed the alterations in BDNF and its mRNA expression in the hippocampus of pigs submitted to stress [47]. The BDNF signaling pathway in the hippocampus has been implicated in the neurogenesis and neuroprotection machinery that maintains homeostasis and ensure neuronal survival in humans [48]. The hippocampus is also suggested as a major target for curcumin’s anti-stress activity in rodents and humans [49].

Studies in primary neuronal cultures found that curcumin enhanced neuronal survival by 21% by day 6 when compared to control cells [50]. To investigate if the BDNF receptor activation was involved in these neuroprotective effects, Wang and cols [50] blocked the BDNF receptor TrkB with a specific antibody. The application of an anti-TrkB IgG inhibited curcumin’s effects upon neuronal survival in vitro [50]. Curcumin also stimulates the synthesis of BDNF in a dose-dependent manner [50]. In addition, curcumin increased the phosphorylation of TrkB, indicating that the BDNF/TrkB signaling pathway was activated by this compound. Two well-known downstream mediators of BDNF intracellular effects, MAPK–ERK and PI-3K/AKT were also investigated as putative curcumin targets. Curcumin treatment led to the phosphorylation (i.e., activation) of both mediators, thereby indicating that this substance act on important points in the BDNF signaling cascade [50]. Furthermore, curcumin upregulates cAMP response element-binding (CREB) phosphorylation, a pathway known to regulate BDNF transcription, in cortical neurons reaching a maximum effect after 6 h [50]. Finally, pretreatment with curcumin reverses the downregulation of BDNF and phosphorylated-TrkB induced by glutamate in cultured cortical neurons [51].

Oxidative stress

An excessive production of reactive oxygen species (ROS) or deficiency in antioxidant mechanisms leads to oxidative stress, which, in turn, may promote apoptosis or necrosis [52], along with brain damage [14]. Several lines of evidences relate oxidative stress mechanisms to BD [53,54]. Previous studies demonstrate both reduction and overactivity of defenses against oxidative damage as well as increases in ROS [54]. Although the findings are heterogeneous, alterations in antioxidant enzymes, such as an increase in superoxide dismutase (SOD) in both depressive and manic episodes were demonstrated (2). Catalase was found to be increased in mania [55] and decreased in euthymia (2). Markers of lipid peroxidation, like thiobarbituric acid reactive substances (TBARS), as well as nitric oxide (NO), have also been shown to be increased in major mood episodes of BD, regardless of polarity [54]. Post mortem brain investigations revealed that SOD and catalase expression are consistently decreased in the hippocampus of BD patients [56]. Furthermore, a down-regulation of several mitochondrial-related genes, such as the ATP synthase and cytochrome-c oxidase genes in the hippocampus [57] and dorsolateral prefrontal cortex of BD patients were reported [53]. These reductions in gene expression could lead to mitochondrial dysfunction, shifting metabolism...
towards anaerobic energy production, leading to an overproduction of ROS.

**Anti-oxidant actions of curcumin**

There is consistent evidence that, in the presence of an oxidative challenge, curcumin can exhibit antioxidant properties and act as a ROS scavenger [58–60]. In an animal model of alcohol-induced neuropathy, curcumin treatment markedly decreases elevated levels of endogenous nitric oxide [61]. In addition, curcumin treatment for 21 days before transport, which was used as a stressor, effectively prevented stress-induced elevation in NO production in the hippocampus of pigs [47]. Curcumin treatment also attenuated the stress induced up-regulation in the enzyme NOS along with an increase in mRNA expression of NOS to levels that were not significantly different from a healthy control group [47].

Cellular effects of oxidative stress also can be antagonized by curcumin, as it prevented DNA damage in a model of alcoholic neuropathy [61].

There is interplay between pathways involved in oxidative stress and those related to inflammation. Inhibition of NOS in activated macrophages can result in an anti-inflammatory effect [62].

**Inflammation**

The immune and the central nervous system are widely interconnected and influence each other on a bidirectional way. Inflammatory markers directly influence neurotransmitter function [63] and neural plasticity pathways [64]. The role of inflammation in the pathophysiology of mental disorders has been studied for decades and data supporting this association is convincing [65]. In BD, increases in pro-inflammatory markers, such as C-reactive protein (CRP), soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are observed in mania and in depression [66]. Changes in some of these markers, such as sIL-2R and IL-6, have also been associated with treatment or symptomatic improvement [66]. In euthymia, a few studies found differences between patients and controls [67,68]. Length of illness was also associated with altered levels of pro-inflammatory markers, with a decrease in IL-6 and an increase in TNF-α in late compared with early stages of BD [69].

**Effects of curcumin in inflammation**

*Prostaglandins pathway.* Cyclooxygenase is a prostaglandin H synthase, which converts arachidonic acid released by membrane phospholipids in prostaglandins. Two isoforms of prostaglandin H synthase, COX-1 and COX-2 have been identified. COX-1 is constitutively expressed in many tissues, but COX-2 is regulated by several factors, including mitogens, cytokines and growth factors [70]. There is a consistent body of evidence that curcumin is a potent modulator of pro-inflammatory enzymes (cyclooxygenases [COX] and lipoxygenases) and inflammatory transcription factors involved in transduction of signal of inflammatory mediators, like IL-1[alpha] and IL-6 [71]. Curcumin is not only able to inhibit COX-2 but also to down-regulate COX-2 gene expression [72].

Interestingly, there are evidences for the participation of alterations of arachidonic acid cascade in the pathophysiology of BD [73]. The acid arachidonic cascade is activated by several stimuli such as inflammation and excitotoxicity [73]. In addition, conventional mood stabilizers like lithium, valproic acid and carbamazepine reduce the production of arachidonic acid [32,74]. In a post mortem brain study, the mRNA levels of several components of the arachidonic acid cascade were abnormal in BD patients, including COX-2 levels [73], thereby reinforcing the hypothesis that this pathway is disturbed in BD. Interestingly, the COX-2 antagonist, celecoxib, demonstrated possible efficacy over placebo in reducing depressive symptoms in a randomized controlled trial of individuals with BD [75].

**Microglial activation.** There is some preliminary evidence that curcumin treatment effectively reduces microglial activation. This was demonstrated in a study that examined 49 different transcripts in microglial cells [76]. In this study, curcumin treatment triggered anti-inflammatory signals as shown by induction of IL-4 and peroxisome proliferator activated receptor alpha [76]. Curcumin also blocked gene expression related to pro-inflammatory activation of resting cells such as Toll-like receptor and prostaglandin-endoperoxide synthase-2 [76]. In addition, in a study with a Alzheimer transgenic mouse model, curcumin at low doses reduced microglial activation, as indicated by lower levels of glial fibrillary acidic protein (GFAP), along with a reduction inflammation mediated by microglia in mouse hippocampus and cortex [77]. Taking together, these studies indicate that curcumin attenuates microglial activation, thereby promoting anti-inflammatory and neuroprotective effects.

**Cytokines.** Curcumin reduces inflammatory cytokines, including TNF-α and interleukin-1β in a model of alcoholic neuropathy [61]. TNF-α is a cytokine secreted by monocytes and lymphocytes that kills tumoral cells in vivo. Inflammatory diseases, including BD, are characterized by increases in TNF-α [78] that exert its effects in target cells using two messenger signals such as NFκB. NFκB is a transcription factor located in the cytoplasm. It is activated by several stimuli, including ROS, IL-1, TNF-α. Normally NFκB binds to an inhibitory protein, called IkB. Once activated, the binding between NFκB and IkB is broken and NFκB is transported to the nucleus, where it promoted the transcription of several genes, depending on cell type. In glial cells, it activates the transcription of TNF-α [78]. Curcumin has also been reported to suppress the activity of NFκB in vitro and in vivo, and this suppression has been considered a critical mechanism for protection against incident cancer [79].

Activity of NFκB also has been considered as a relevant modulator of chemokine levels. These cytokines with chemotactic properties exert a critical role in amplification and regionalization of the inflammatory response, because they are able to recruit neutrophils, monocytes and macrophages to the site of inflammation. Some lines of evidence indicate that curcumin inhibits the secretion of chemokines, such as CCL24, through suppression of the NFκB pathway [80]. Increments in serum levels of pro-inflammatory chemokines has been found in euthymic BD patients [80].

**Apoptosis**

Apoptosis or programmed cell death is essential to the maintenance of cellular homeostasis in multicellular organism [81]. It has a crucial role during brain development stages [81]. There is a growing body of evidence that neuropsychiatric disorders are related to deregulation of apoptotic mechanisms, with increased cell death [81,82].

In BD studies have shown increased pro-apoptotic serum activity [83]. Additionally imaging studies show decreased cortical thickness, which might be related to neuronal loss [84]. A *post mortem* study showed significant increases in protein and mRNA levels of the pro-apoptotic factors (Bax, BAD, active Caspase-3 and -9) and significant decreases of levels of the anti-apoptotic factors (Bcl-2, BDNF) [85]. Moreover treatment with Lithium or Valproate affects apoptosis by suppression of caspase-3 activity and stimulates B-cell lymphoma-2 (Bcl-2) expression, which has anti-apoptotic action [86–88].
Effects of curcumin in apoptosis

Curcumin has a role in regulating apoptotic mechanisms. A study showed that curcumin regulated 104 genes out of 214 genes associated with apoptosis in tumor cells [89]. It has also been demonstrated that curcumin inhibits apoptosis in a mice model of Parkinson disease [90] and in iron induced necrosis [91]. The precise role of curcumin in apoptotic mechanism still remains to be fully elucidated, but, because it seems to exert an anti-apoptotic effect, it is a candidate as a possible beneficial medication in BD [92].

Behavioral effects of curcumin in preclinical studies

Curcumin has been tested in several animal models of depression showing antidepressant-like properties [93]. This antidepressant profile has been verified in classical predictive models, such as the tail suspension test (TST) and the forced swimming test (FST) [94–100]. Additionally, the effect of curcumin treatment was comparable in magnitude to the effects observed for classical antidepressants, such as fluoxetine and imipramine [97]. Furthermore, curcumin also potentiated sub-therapeutic doses of fluoxetine, venlafaxine and bupropion in the FSR or TST [95]. These behavioral effects of curcumin were accompanied by an increase in brain serotonin and dopamine levels and inhibition of MAO activities [94,95,100]. Conversely, the beneficial effect of curcumin was suppressed by a prior serotonin depletion induced by the tryptophan hydroxylase inhibitor p-chlorophenylalanine [98].

Curcumin also exhibited positive results in models where depression was induced by environmental or pharmacological manipulations. In the chronic unpredictable stress paradigm in rats, repeated curcumin treatment was able to reverse the increase in immobility and in MAO activity as well as the depletion of brain monoamines [101]. In the same way, curcumin ameliorated the low sucrose consumption (an anhedonia-like behavior) and the increase in serum corticosterone levels induced by this paradigm [102]. Furthermore, curcumin promoted decreases in BDNF levels and in the pCREB/CREB ratio [46]. Finally, effective doses of curcumin for behavioral alterations induced by the chronic unpredictable stress paradigm also increased hippocampal neurogenesis similarly to classical antidepressants [49].

Administration of curcumin also reversed the corticosterone-induced depressive behavior in rats, as well as the decrease in sucrose consumption and the immobility time [103]. Additionally, these behavioral effects were accompanied by the reversal of the corticosterone-induced decrease in BDNF levels in hippocampus and frontal cortex [103].

A beneficial effect of curcumin was also described in a pain-depression dyad model [104]. In this model, rats treated with reserpine show a decrease in nociceptive threshold and an increase in immobility time accompanied by a decrease in dopamine, serotonin and norepinephrine along with increased substance P concentration and inflammatory cytokines in cortex and hippocampus. Curcumin ameliorated these behavioral and biochemical alterations induced by reserpine [104].

Finally, curcumin administration was able to reverse the behavioral changes induced by the olfactory bulbectomy animal model of depression – which consists of bilateral removal of the olfactory bulbs inducing neurochemical, neuroendocrine and immune changes mimicking alterations seen in depression. Further, curcumin also reversed the decrease in norepinephrine, serotonin, and dopamine levels in the frontal cortex of rats submitted to this procedure [100].

The effects of curcumin in CNS are not limited to depression models. One study in rats demonstrated that curcumin was able to prevent haloperidol-induced abnormal oro-facial movements [25]. These antidysesthetic effects were shown to be mediated by an induction of gene transcription of Bcl-XL, an antioxidant implicated in the prevention of cell death, in the striatum [25].

Curcumin in clinical trials

Curcumin has been investigated in several preliminary clinical trials for a myriad of inflammatory conditions, neuropsychiatric disorders and cancer [105]. Regarding non-psychiatric conditions, curcumin was tested in the treatment of rheumatoid arthritis in a double-blind crossover study. There was significant improvement in morning stiffness, walking time and joint swelling [106]. A non-controlled study with curcumin in gel treatment of psoriasis showed either resolution or reduction in plaques following 8 weeks of treatment [107]. Two studies have found curcumin to have a positive effect in inflammatory bowel disease, with one randomized controlled trial showing that 6 months of daily doses of curcumin improved symptoms and maintained remission [108,109]. In individuals submitted to kidney transplantation, one study of 43 patients found a positive effect of curcumin on the reduction of acute rejection rates and neurotoxicity over a course of 6 months [110].

The first evidence for a potential role of curcumin in the prevention and treatment of neuropsychiatric conditions came from uncontrolled studies. A large prospective study comparing a rural sample from India and a reference population in the US found lower incidence of Alzheimer’s disease in the Indian population [111]. Among the factors associated with the low incidence of AD, dietary factors and the consumption of natural products were implicated [111]. Curcumin also has been shown to improve spatial memory impairment induced by a human immunodeficiency virus (HIV) cognitive deficit model [112].

Regarding clinical trials, Ringman and collaborators [113] conducted a clinical trial to evaluate tolerability and safety of curcumin at dose of 2000 mg/day and 4000 mg/day in patients with mild to moderate AD and healthy controls. In 6 months, randomized, placebo-controlled for individuals with dementia, curcumin, in addition to its clinical effect, increased plasma levels of vitamin E when compared to placebo [114].

Considerations about pharmacokinetics of curcumin

Animal and human studies of curcumin pharmacokinetics revealed that a relatively poor absorption and rapid metabolism of curcumin reduces its bioavailability [115]. Curcumin is rapidly metabolized in animals, conjugated in the liver, and excreted in the feces with minimal amounts found in the urine [115]. Moreover it is sparingly soluble in water, which is one of the reasons for its poor absorption through oral route, being the reason for the use of high doses of this compound in clinical trials (typically more of 1000 mg/day) [22]. In a study by Pan et al. [116], in mice, a curcumin dose of 0.1 g/kg via i.p. route showed a minimum amount in the brain tissue after 1 h (0.4 μg/g). Brain curcumin level peaked at 2.9 (±0.4) nmol/g of tissue, in an analysis following administration of [14C] curcumin (100 mg/kg) via the i.p. route and monitoring for the disappearance of radioactivity associated with the molecule. Radioactive levels declined rapidly in all tissues [117,118]. A phase 1 clinical trial conducted on 25 patients with precancerous lesions showed oral doses of 4, 6, and 8 g curcumin daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 μM respectively, indicating poor absorption of straight curcumin. In addition, curcumin levels peaks in plasma one or two hours following per os administration and declines rapidly, within 12 h [119].
Patients with gallstones or bile duct obstructions should use curcumin with caution, since this compound may cause gallbladder contractions. In a randomized, double-blind, crossover study involving 12 healthy volunteers, 20 mg curcumin produced as much as 29% reduction in gallbladder size, indicating gallbladder contraction [120]. A subsequent study confirmed this finding [121]. Curcumin also inhibits platelet aggregation in vitro and in animal studies [122,123].

Poor absorption and rapid metabolism are a limiting factor for the clinical use of curcumin. To surpass the relatively low bioavailability of this compound, patients need to take high doses of this drug. Although non-toxic, these high doses (as high as 12 g/day) may decrease the tolerability of some patients [21,118]. Nevertheless, curcumin at high doses has shown to be helpful in pancreatic cancer, which indicates that its therapeutic potential could be limited by dosing considerations [21]. These pharmacokinetic obstacles led to the development of curcumin analogs with higher potency, slower metabolism and increased absorption [21]. Examples of curcumin analogs include: 3,5-bis(2-fluorobenzylidene)-4-piperidone (EF24) and 3,5-bis(2-pyridinylmethylidene)-4-piperidone (EF31). Another possible strategy to overcome these pharmacokinetic barriers is the development of a phytosome, complexing curcumin with phosphatidylcholine [71]. The resulting compound has been patented with the name of Meriva [71].

**Future perspectives**

As discussed in previous sections, most beneficial effects of curcumin are supported by preclinical, epidemiological and studies. Interestingly, there are no clinical studies of curcumin in mental disorders to date and the evidences in other medical conditions are still incipient [71]. Curcumin is not the first CAM to be postulated as potentially useful in BD. Substances like L-tryptophan, Omega-3 fatty acids, St. John's Worth, S-adenosylL-metionine (SAMe) and treatments like massage therapy and acupuncture have been proposed [19,124]. Many of these treatments turned out to be ineffective at best and harmful at worst [124].

The history of overstatement of benefit and under delivery of results in the past resulted in scientific skepticism about CAM interventions for the treatment of mental disorders, including BD. The current conceptual models of the patho-etioloogy of BD align with several of the biological targets proposed for curcumin, suggesting that it may have a salutary role in this condition. The unmet needs in BD are notably for agents targeting depressive symptoms/episodes and cognitive impairment. Future clinical trials of curcumin could include either or both of these psychopathological domains as the principle targets of interest.

The development of new curcuminoid formulations would overcome some pharmacokinetic barriers to the clinical use of curcumin. These novel congeners would hopefully have a greater bioavailability and a better prediction of clinical response when compared to the original compound.

**Conflict of interest**

We declare no conflict of interest that may be inherent in this study.

**Acknowledgments**

This work has been supported by FAPESP (Brazil) and CNPq (Brazil).

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