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CURCUMIN NANOFORMULATIONS AND THEIR THERAPEUTIC APPLICABILITY TO DEPRESSIVE DISORDER

NANOFORMULAÇÕES DE CURCUMINA E SUA APLICABILIDADE TERAPÊUTICA AO TRANSTORNO DEPRESSIVO

NANOFORMULACIONES DE CURCUMINA Y SU APLICABILIDAD TERAPÉUTICA AL TRASTORNO DEPRESIVO

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ABSTRACT

Depressive disorder is one of the most prevalent multifactorial psychiatric syndromes, recognized as a global public health problem. Recent research with the nanostructured systems of curcumin has aroused the interest of the scientific community, for emerging neuroprotective effects with potential applicability in biological systems. Curcumin is a natural substance, considered for therapy in various diseases, including neuropsychiatric such as depressive disorder. This is a systematic review, with articles published in PubMed, Scielo and Science Direct, filtered from 2014-2021. The inclusion criteria started from a guiding question, combined with the DeSs indexes for the search: depression, curcumin, nanoparticles, antidepressant agent, linked to Boolean operators to combine the terms of your search and the StArt system to exclude duplicates. Twenty-two articles were included, and approximately 60-70% of them showed some therapeutic potential of reduced curcumin in nanoformulation applicable to the biological system. It was possible to verify that nanostructured curcumin exhibits differentiated properties that increase antioxidant and antidepressant action and low cytotoxicity. Its therapeutic potential is able to interfere in neuro-inflammatory processes. The perspective is the development of drugs with controlled delivery of bioactive such as curcumin, with multiple organic functions. The increased bioavailability of curcumin may promote neurogenesis in the cortico-hippocampal region and function as adjuvants in antidepressant treatment.

KEYWORDS

Depression. Curcumin. Nanoparticles. Antidepressant Agent.

RESUMO

O transtorno depressivo é uma das síndromes psiquiátricas multifatorial das mais prevalentes, reconhecida como problema de saúde pública mundial. Recentes pesquisas com os sistemas nanoestruturados de curcumina, tem despertado interesse da comunidade científica, por despontar efeitos neuroprotetores com potencial de aplicabilidades em sistemas biológicos. A curcumina é uma substância natural, cogitada para terapia em várias doenças, que inclui as neuropsiquiátricas como o transtorno depressivo. Trata-se de uma revisão sistematizada, com artigos publicados na *PubMed, Scielo* e *Science Direct,* filtrados de 2014-2021. Os critérios inclusão partiu de uma pergunta norteadora, aliada aos indexadores *DeSs* para busca, na língua inglesa: depression, curcumin, nanoparticles, antidepressant agent, vinculados aos operadores booleanos para combinar os termos de sua pesquisa e o sistema StArt para excluir duplicidades. Foram inclusos 22 artigos, sendo que aproximadamente 60-70% deles evidenciaram algum potencial terapêutico da curcumina reduzida em nanoformulações aplicáveis ao sistema biológico. Foi possível verificar que curcumina nanoestruturada exibe propriedades diferenciadas que aumentam a ação antioxidante, antidepressiva e baixa citotoxicidade. Desponta seu potencial terapêutico capaz de interferir em processos neuro-inflamatórios. A perspectiva é o desenvolvimento de medicamentos de entrega controlada de bioativos como a curcumina, com múltiplas funções orgânicas. O aumento da biodisponibilidade da curcumina pode promover neurogênese na região córtico-hipocampal e funcionar como adjuvantes no tratamento antidepressivo.

PALAVRAS-CHAVE

Depressão. Curcumina. Nanopartículas. Agente Antidepressivo.

RESUMEN

El trastorno depresivo es uno de los síndromes psiquiátricas multifactoriales más prevalentes, reconocido como un problema de salud pública mundial. Investigaciones recientes con los sistemas nanoestructurados de la curcumina han despertado el interés de la comunidad científica, por los emergentes efectos neuroprotectores con potencial aplicabilidad en sistemas biológicos. La curcumina es una sustancia natural, considerada para la terapia en diversas enfermedades, incluidas las neuropsiquiátricas, como el trastorno depresivo. Esta es una revisión sistemática, con artículos publicados en PubMed, Scielo y Science Direct, filtrados desde 2014-2021. Los criterios de inclusión partieron de una pregunta orientadora, combinada con los índices DeSs para la búsqueda: depresión, curcumina, nanopartículas, agente antidepresivo, vinculados a operadores booleanos para combine los términos de su búsqueda y el sistema StArt para excluir duplicados. Se incluyeron veintidós artículos, y aproximadamente el 60-70% de ellos mostraron algún potencial terapéutico de curcumina

reducida en nanoformulaciones aplicables al sistema biológico. Se pudo verificar que la curcumina nanoestructurada exhibe propiedades diferenciadas que aumentan la acción antioxidante y antidepresiva y baja citotoxicidad. Su potencial terapéutico es capaz de interferir en procesos neuroinflamatorios. La perspectiva es el desarrollo de fármacos con liberación controlada de bioactivos como la curcumina, con múltiples funciones orgánicas. La mayor biodisponibilidad de la curcumina puede promover la neurogénesis en la región cortico-hipocampal y funcionar como adyuvantes en el tratamiento antidepresivo.

PALABRAS CLAVE

depresión, curcumina, nanopartículas, agente antidepresivo.

1 INTRODUCTION

Depressive disorder is a heterogeneous and chronic disorder, with psychological and physiological manifestations that modify behavior, it is a debilitating disease of worldwide prevalence. The neurobiology of depressive disorder (DD) involves neuronal, monoaminergic, biochemical, reactive oxygen species and neurogenesis systems. In particular, the process of neurotransmitters has received more attention from researchers regarding pathogenesis in search of therapeutic alternatives (BARBARA et al., 2017; LABANCA et al., 2021).

Inhibitory drugs for serotonin and norepinephrine reuptake are widely used in depression therapy. However, there are clinically relevant adverse effects that pose a challenge to researchers in search of drug substances with a better pharmacokinetic profile. The current therapeutic approach still needs more effective and resolute alternatives in the intervention of patients with neuropsychiatric diseases (BARBARA et al., 2017; ASADI et al., 2020).

Phytochemicals with neuroprotective potential, found in spices and medicinal plants, have also been the subject of studies by nanomedicine, especially bioactives that can reduce the risk and treat some psychiatric and neurodegenerative diseases. Recent research using nanostructured systems that encapsulate curcumin has aroused the interest of the scientific community, due to its applicability in biological systems with neuroprotective effects. Curcumin is a natural substance, considered for therapy in neuropsychiatric diseases such as depressive disorder (HURLEY et al., 2014; HE et al., 2016; LABANCA et al., 2021).

Studies for new antidepressants are of economic interest, given the prevalence of depressive disorder and its difficulty in tolerating and undesirable effects of current drugs. Nanomedicine is an emerging science that represents a strong alternative in the drug industry, related to the development of smart delivery systems in nanoformulations. Several researches have been carried out, with the objective of producing drugs with controlled direction for drug release (GHALANDARLAKI et al., 2014; HE et al., 2016).

Nanotechnology is a science that studies the properties of materials at reduced sizes from 1 to 100 nanometers, designs and develops technological products and processes by manipulating nanoscale particles. The objective of which is the creation of encapsulated substances, with procedures from the handling of submicron molecules, individual atoms and synthesis of nanostructured systems with clinical applications (GHALANDARLAKI et al., 2014).

The prefix nano is derived from the Greek and means "dwarf", an indicator of measurements that can be represented by 1nm (one nanometer), equivalent to one billionth of a meter. Nanotechnological research proposes major innovations and advances in numerous areas, such as nanomedicine, bionanotechnology and others. Nanotechnology represents the link of convergence of the physical, biological and digital world, due to the breadth of advances it is considered the technology of the future and the fourth pharmaceutical-industrial revolution (HE et al., 2016; FAKHRAEI et al., 2018).

Nanoscale drug technology is a dynamic and innovative approach. That employs research efforts and increases industrial interest in nanoproducts, with a safe, reliable profile and with production less aggressive to the environment, known as green synthesis, in these methods, the use of polluting chemical reagents is minimal, constituting a sustainable methodology (RAI et al., 2015; ESSA et al., 2020).

Among the nanoproducts with therapeutic potential, the encapsulation of curcumin nanoparticles (NPs-cur) stands out, which aims to break with the limitation of bioavailability and solubility of lipophilic compounds, in systems that control the release of drugs in the target. *Curcuma longa* Lin (Zingiberaceae) is widely recognized for its properties: antiviral, antibacterial, anti-inflammatory, anticarcinogenic, antioxidant, antifungal. Curcumin is one of the most researched natural compounds for nanoencapsulation for therapeutics with a neuroprotective effect (GHALANDARLAKI et al., 2014; HURLEY et al., 2014; RAI et al., 2015).

Therefore, the aim of this study is to describe curcumin nanoformulation, their applicability and antidepressant and neuroprotective potential.

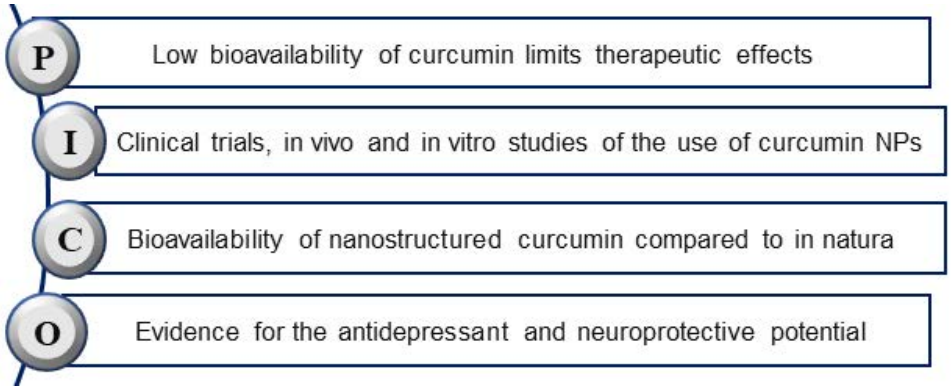
2 METHODS

This research is characterized by a systematic review, applying pre-established inclusion criteria to search for original articles in the SciELO, ScienceDirect and PubMed databases. It was considered a time window of eight years, filtering publications from 2014-2021.

Inclusion criteria were: results of clinical trials, in vitro and in vivo research, which used biosynthesis as a method for producing nanoformulation with curcumin encapsulation. Although nanomedicine involves biosynthesis with the eukaryotic system, in this research, only research that used turmeric longa as a reducing agent to produce nanostructured systems with therapeutic purposes, aimed at the potential for treating CNS disorders, neuropsychiatric such as DD.

Based on the recommendations of the Joanna Briggs Institute (JBI), the guiding question for the P.I.C.O strategy was defined, as shown in Figure 1.

Figure 1 – P.I.C.O Strategy



Source: Elaborated by the authors.

The delimitation of the P.I.C.O served to define the eligibility criteria for the selection of published articles. Being a, Population (P) – Problem of low oral bioavailability of curcumin. Intervention (I) - potential of curcumin and its antidepressant, anxiety and neuroprotective potential. Comparison (C) difference in bioavailability levels of in natural turmeric compared to absorption of nanoencapsulated or conjugated curcumin. Results (O) Benefits of curcumin nanostructure experienced for the treatment of depressive disorder.

Studies were selected by the evaluators, based on specific descriptors (DeCs) in English: depression, curcumin, nanoparticles, antidepressant agent, linking Boolean "and/or" operators to minimize excess and the State of the Art through Systematic Review (StArt) specificity system to identify duplication.

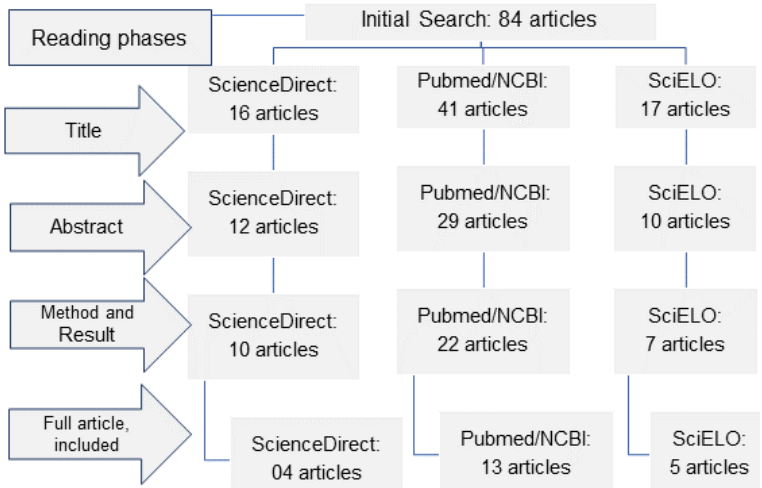
Then, the limitations of the articles and possible inconsistency in the results (heterogeneity), mode of intervention, comparison and inaccuracies were evaluated. The pre-established criteria were first submitted to the guiding question of the study: what is the applicability of nanoformulation with curcumin in biological systems with antidepressant and neuroprotective potential?

During the searches, in parallel, the titles were analyzed, duplicates were excluded by the StArt, followed by the reading of the abstracts and methodologies, soon after the articles were selected, in view of the guiding question elaborated by the P.I.C.O.

3 RESULTS

Twenty-two articles that met the pre-established criteria were included in this research, in search of research results on curcumin nanoencapsulation applicable to biological systems with therapeutic potential for depressive disorder, available in the databases (Figure 2).

Figure 2 – Eligibility flowchart of articles included in the systematized review



Source: elaborated by the authors

Table 1 represents a cutout among the selected publications, which summarized research that used turmeric as a reducing agent in several types of nanostructured systems, nanoparticle (NPs) sizes and study design, applicability and therapeutic potential pointed out by the researchers. Totaling 10 articles with more direct results in relation to nanoformulation with curcumin with antidepressant and neuroprotective potential.

Table 1 – Characterization of the main articles related to nanoformulations with curcumin with therapeutic and neuromodulatory potential

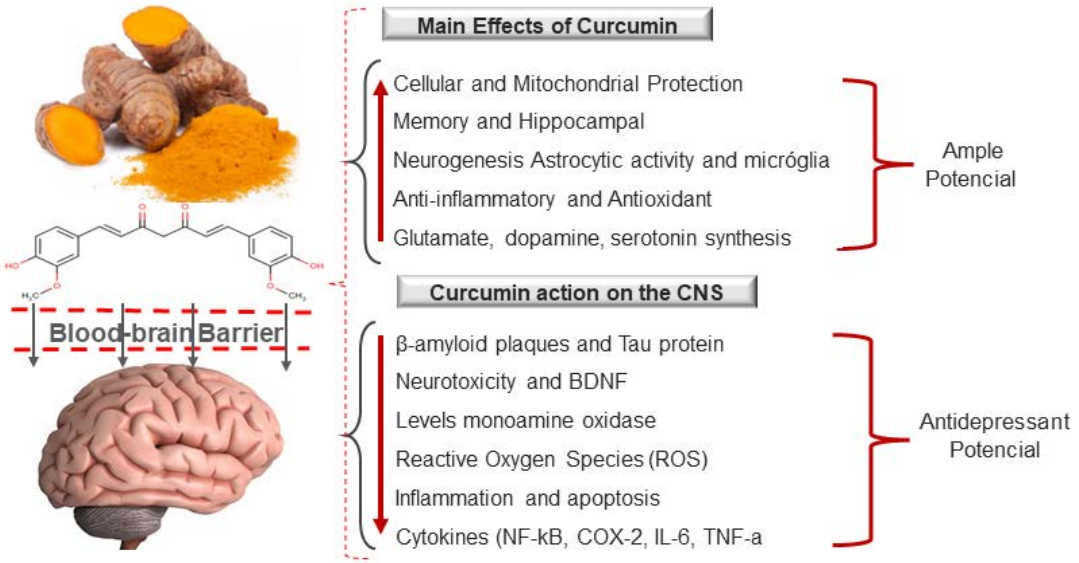
Reference	Drawing Size NPs	Result / Activity and potential
Yusuf et al., 2016	In vivo. PLGA 90-160nm	Antidepressant, catalytic potential and neuroprotective activity
Szymusiak et al., 2016	In vivo ---	Pure turmeric (400mg/kg) and NPs-cur (20mg/kg). Increased curcumin in the CNS confirmed by spectrometry and chromatography.
He et al., 2016	RCT Cur/SLNs 58nm	Western blot and immunofluorescence revealed that Cur/SLNs-HU-211 increases the expression of CB1, p-MEK1 and p-ERK1/2. Exhibited antidepressant activity and protects corticostriatal neurons

Reference	Drawing Size NPs	Result / Activity and potential
He et al., 2017	In vivo, In vitro. Cur-Dex 60nm	Neuroprotective activity. Inducing potential for dopaminergic release.
Barbara et al., 2017	In vitro. PLGA, 88-97nm	Anti-amyloidogenic, anti-depressant, anti-inflammatory potential
Fakhraei et al., 2018	RCT, In vivo. 10-100nm	NPs-cur (40-80mg/kg) exhibited neuroprotective, anti-inflammatory, antioxidant effects and modulation of neurotransmitter levels.
Kanchanatawan et al., 2018	RCT, humans Cur-IONPs	Effects of curcumin (500-1500mg/day) adjuvant in DD treatment. There was a significant DS reduction in the test group - MADRS/HAM-
Asadi et al., 2020	RCT, humans	Depressive and diabetic patients. Significant reduction in SD and anxiety (DASS-21) in the test group ($p<0.009$)
Rubab et al., 2021	RCT, in vivo 147,8nm	Curcumin lipid nanocarriers (CUR-NLCs) showed uptake efficiency (91.0%), drug release up to 73% and increased the expression of p-NF-B, TNF- and COX-2 in the brain
Khadrawy et al., 2021	RCT, in vivo Cur-IONP-100nm	NPs-cur-IONPs, with higher bioavailability, reduced oxidative stress, antidepressant effect, increased monoamine levels.

PLGA-poly lactic-co-glycolic acid, nm: nanometer; Cur-IONPs: iron oxide nanoparticles coated with curcumin; AEV/AC: vegetable and chloroformic stearic acid; DASS-21: Depression, Anxiety, Stress Scale; C-SLNs: curcumin encapsulated in solid lipid nanoparticles. SOD: superoxide dismutase; TNF-: Tumor Necrosis Factor Alpha; RCT-DC-H: double-blind randomized clinical trial with humans; DS: Depressive symptoms; MADRS: Montgomery-Asberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; Cur-Dex: Curcumin nanoparticles with Dexabinol.
Source: Elaborated by the authors.

The research that contextualizes this review, it was possible to highlight that curcumin has a broad spectrum of biological activities such as antioxidant, anti-AD, anticarcinogenic, antimutagenic, anti-inflammatory, antidepressant and neuroprotective properties. Thus, it was possible to highlight the recognized bioactivity of curcumin, the main metabolite of turmeric, and its use and therapeutic potential (Figure 3).

Figure 3 – Main effects and potentials of curcumin on biological systems, emphasis on antidepressant potential



Source: Survey data, compilation of information (GHALANDARLAKI et al., 2014; HURLEY et al., 2014; RAI et al., 2015; HE et al., 2016; AFZAL et al., 2021).

4 DISCUSSION

The results of this research contribute to the expansion of knowledge, based on a set of evidence that points to the potential of curcumin, a natural compound, which exhibits pharmacological and therapeutic properties, considered a potent neuromodulator of antidepressant mechanisms and monoaminergic imbalances (serotonin, dopamine, noradrenaline and glutamate).

The neuroprotective action of curcumin seems to act on the hypothalamic-pituitary-adrenal (HPA) axis, in inflammatory disorders, immune pathways, oxidative stress (OS), nitrosative and mitochondria. Considering that, the release of catecholamines increases the synthesis of pro-inflammatory cytokines, such as Interleukin 6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-), which participate in the increase of reactivity in the HPA axis and reduce available serotonin. Figure 3 summarizes potential effects of curcumin, according to Hurley and collaborators (2014), He and collaborators (2016) and Afzal and collaborators (2021).

The increase in research in nanomedicine for the production of compounds and nanoformulation conjugated with curcumin is notorious. The synthesis of nanoformulation applicable to biological systems emerges as an efficient, fast alternative, with almost zero toxicity and undesirable effects, in

relation to traditional methods. Nanoparticles (NPs) are between 1-100 nanometers (nm) and exhibit differentiated physical, chemical and biological properties that are significant and suitable for controlled drug delivery systems. The use of plants, natural compounds, are widely used, mainly due to the feasibility of large-scale production (FAKHRAEI, et al., 2018).

For Yusuf and collaborators (2016), turmeric is very promising due to the applicability of its bioactives, which can serve as a surfactant and particle reducing agent in nanostructured systems. The incorporation of turmeric and its compounds, in these systems, has its effects potentiated, being able to break its limitation related to low solubility, stability and bioavailability. This is due to the chemical structure of turmeric, its phenolic nature and extent of conjugation. Therefore, research results show greater antioxidant and anti-inflammatory action in different experiments, focused on structural subunits, methylene, carbonyls and phenolic hydroxyls, corroborate Poupot and collaborators (2018).

Curcumin is the main polyphenolic, hydrophobic bioactive compound in Curcuma longa. Organized chemical structure in diferuloymethane (C21 H20 O6) from 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6--heptadien-3,5-dione, is a lipophilic molecule with rapid permeability in colloidal systems. This tuber contains three main curcuminoids (curcumin, desmethoxycurcumin, bisdesmethoxycurcumin) with pharmacological application. However, curcumin has limitations due to its hydrophobic nature and low water solubility. Nanostructured systems are an alternative to overcome this limitation (SZYMUSIAK et al., 2016; KHADRAWY et al., 2021).

Research in nanobiotechnology that encapsulates curcumin captivates attention, due to the feasibility of pharmacological and medicinal action, with a view to developing a new generation of biogenic nanoproducts, expanding the use of plant materials for therapeutic purposes. Nanoformulation are synthesized with different pharmaceutical forms, and begin to exhibit new characteristics, such as curcumin, which has greater bioavailability and solubility. Allied to the advantages of the bioreductive method and its versatility of synthesis using natural substances such as turmeric (GHALANDARLAKI et al., 2014).

Another important point about drugs in controlled delivery systems refers to the feasibility of more effectively transporting curcumin to the brain, with the aim of increasing levels of neurotransmitters such as monoamines, to minimize depressive and anxiety symptoms. The biogenic synthesis of nanodrugs represents an interesting clinical alternative, due to its simplicity and non-toxicity, low use of polluting reagents, through environmentally friendly methods, and biosynthesis is considered a clean and promising technology (HE et al., 2017; LABANCA et al., 2021).

Studies such as clinical trials (EC) have shown that nanoencapsulated curcumin has broad therapeutic potential in the Central Nervous System (CNS), with antidepressant and anti-inflammatory action, due to its bioactive properties, which significantly increase the response immune response and expression of Brain-Derived Neurotrophic Factor (BDNF) in the hippocampus. Researchers explain that individuals with DD exhibit higher levels of inflammatory markers in their blood compared to those without the depressive disorder and that frequent use of curcumin is able to reduce neuroinflammation (HURLEY et al., 2014; HE et al., 2016; ASADI et al., 2020; AFZAL et al., 2021).

Nanoformulations with turmeric have been studied and recommended for therapeutic use in some organic disorders, in addition to psychiatric ones. In Brazil, the Ministry of Health published the National List of Medicinal Plants of Interest to SUS (RENISUS), recognizing the bioactive properties of curcumin (Figure 1), its pharmacological activities are more potent in nanoformulation, in addition to the benefits of culinary use. Recent European patent (EP3142702B1) describes the smart delivery synthesis (drug delivery) based on biopolymer encapsulated with curcumin and piperine, with proven improvement and efficiency in nanoformulated bioavailability. The action of curcumin is intensified with the addition of piperine (JANGRA et al., 2016; SEZGIN; BAYRAKTAR, 2018).

Nanoscale turmeric is widely tested with the interest of increasing bioavailability and solubility, so that the bioactive can enter the systemic circulation, cross the blood brain barrier (BBB) and potentiate effects on the therapeutic target. Jangra et al. (2016), found that nanoformulation with curcumin combined with piperine, an alkaloid from black pepper, exhibited stabilizing potential in colloidal compounds. It had greater and better therapeutic effects, regarding the bioactivity and bioavailability of curcumin. It's in vivo pharmacokinetics demonstrated that NPs-cur with piperine was able to increase bioavailability and function as an absorption enhancer (SEZGIN; BAYRAKTAR, 2018).

Similarly, the protective effects of curcumin were investigated alone and in combination with piperine against neurobehavioral and neurochemical deficits induced in the hippocampus of mice treated with curcumin powder (100, 200 and 400 mg/kg) and piperine (20 mg/kg). kg, powder). After treatment for seven days, it was possible to verify the relief of neurobehavioral and neurochemical deficits, the co-administration of curcumin with piperine potentiated the neuroprotective action of curcumin (JANGRA et al., 2016).

It is well described in the literature, the demand of researchers about the low bioavailability of curcumin, its malabsorption, rapid metabolism and systemic elimination. Nanotechnology is an emerging field that is changing the modus operandi for drug synthesis in the treatment of diseases, with the use of nanoencapsulated bioactives, such as curcumin. With the aim of breaking the limitation of bioavailability, plasma concentration and cellular permeability to curcumin, through these smart delivery systems to potentiate therapeutic effects (HE et al., 2016; YUSUF et al., 2016).

In fact, the challenge is to increase the stability and bioavailability of curcumin, focusing efforts to develop and adapt the design of curcumin nanoencapsulation, whether by liposomes, micelles, dendrimers and other nanocarriers, combined with the safety of bioactive delivery formulations. An experiment that explored the release of nanoemulsified curcumin showed greater solubility and release than the suspension, reaching an optimization percentage of up to 95%. Confirming that the design used to encapsulate curcuminoid increased its therapeutic action (SHENGNUO et al., 2018).

Researches that investigated the action of cur-NPs synthesized with lactic acid-co-glycolic acid (PLGA) verified that there was complete solubility in water, and the Cur-NPs were monodispersed and exhibited dimensions of 150-200nm. Through biosynthesis and solvent evaporation techniques, it was possible to verify a certain flowering under UV light and break with the limitation of raw curcumin *in natura*. They concluded that PLGA can influence several parameters of nanocarriers in delivery systems and, encapsulate desirable substances, capable of trapping curcumin with more efficient encapsulation (YUSUF et al., 2016; ESSA et al., 2020).

For Yusuf and collaborators (2016), curcumin in PLGA nanocarriers can effectively overcome the limitation of its insolubility in water. Other research also supports that nanoformulations (PLGA-NPs--Cur) have increased solubility, which optimize their application, absorption and promote the most effective neuroprotective therapeutic potential, and their antioxidant activity, capable of reducing oxidative stress (SZYMUSIAK et al., 2016; SHENGNUO et al., 2018).

Nanostructured systems in liposomes, polymers, micelles, nanogels, dendrimers and solid lipids are emerging as useful alternatives that encapsulate concentrations of therapeutic bioactive, concentrating valuable effects on different diseases. Importantly, the efficiency of a drug also depends on its bioavailability at the appropriate location. Reaching the CNS with a treatment substance has always represented a challenge in the face of the inaccessible BBB, which severely restricts the access of many substances or traditional medicines (GHALANDARLAKI et al., 2014).

Considering depressive disorder, there is evidence that curcumin has the potential to reduce serotonergic disturbance, similar to standard antidepressant medication, except that it is free of adverse effects. Depending on the formulation of curcumin, it can increase bioactivity and induce the increase of neurotransmitters (serotonin, dopamine and noradrenaline) in the brain, minimize the action of the monoamine oxidase enzyme, being a positive induction of nanoencapsulated curcumin, which works with a neuroprotective and antidepressant effect, compared to natural curcumin, corroborate Hurley and collaborators (2014) and Barbara and collaborators (2017).

Hurley and collaborators (2014) highlighted that the antidepressant effect of NPs-Cur tested in a WKY-model, with induced depression, was significant and there was a marked expression of BDNF in the hippocampus, which was directly positive for cell survival and neurogenesis in this region, with notorious antidepressant effects, potentiated action and mediator of neurogenesis. Vale recalls that BDNF is a neurotrophin found in high concentrations in the hippocampus and cerebral cortex, considered a key molecule for synaptic plasticity and for the survival of neuronal cells. Analogous research was published by Afzal and collaborators (2021).

The antidepressant effect of NPs-Cur, in an acute condition, still needs clarification. The administration of curcumin, probably, may delay in increasing the expression of BDNF, since the synthesis of new protein may require more time and adjusted doses of the bioactive. The objective is to potentiate the neurochemical effects that interact with curcumin to synthesize serotonin and dopamine (neurotransmitters implicated in the pathophysiology of depression), given that the glutamatergic receptors N-methyl-D-aspartate (NMDA) play an important role in the mechanism of illnesses such as depression. Hurley and collaborators (2014), clarifies that the use of nanoformulations with curcumin stimulate NMDA antagonists and can generate or intensify similar antidepressant and neuroprotective effects.

In the case of studies by He and collaborators (2017), it was found that solid lipid nanoformulations loaded with curcumin and dexanabinol (derived from a synthetic cannabinoid) were able to induce an increase in the monoaminergic neurotransmitter, dopamine and 5- hydroxytryptamine (5-HT), reduce PC12 corticosterone-altered apoptotic cell death in mice. As a result, there was recovery of the depressive behavior expressed by the level of hippocampal neurotransmitters and a clear proliferation of astrocytes, characterizing neuroprotective activity.

Recent research conducted by Khadrawy and collaborators (2021), tested the antidepressant effect of nanoformulations conjugated with curcumin and iron oxide (Cur-IONPs) in animal models. They concluded that treatment with curcuminoid nanoencapsulation attenuated oxidative stress and increased the bioavailability of the bioactive. There was an antidepressant, neuroprotective and antioxidant effect of Cur-IONPs capable of restoring monoaminergic levels. A study by Poupot and collaborators (2018) explain that depressive disorder causes physical, chemical and behavioral changes and impact, mediated by inflammation and oxidative stress. Curcumin has antioxidant and anti-inflammatory action, in these nanoencapsulated systems.

Labanca and collaborators (2021) in their research, also evaluated the neuroprotective effects of solid lipid nanoparticles (NLS) with curcumin. In vivo, oral doses of 40mg/kg were used and they found that there was a reduction in OS, lipid peroxidation and glutathione levels, restoration of SOD activity, and increase in mitochondrial agility. They explained that these NLS compounds have the potential to scavenge free radicals (superoxide anions, lipid peroxidation) suggestive of preventive and therapeutic use in neuropsychiatric disorders. Other studies support that curcumin-based nanoformulation have anti-inflammatory and antioxidant action (LOPRESTI et al., 2014; HE et al., 2016; HE et al, 2017).

An interesting study aimed to develop curcumin-loaded nanostructured lipid carriers (CUR-NLCs) to investigate neuroprotective effects in models of depression and induced anxiety. The nanoformulation, which exhibited a size of 147.8nm, was efficient in incorporating 91.0% and produced rapid sustained drug release reaching up to 73% after 24 h. The results of which improved tissue architecture and suppressed the expression of p-NF-B, TNF- and COX-2 in brain tissues, which were verified by histological and immunohistochemical analyses. CUR-NLCs produced a neuroprotective effect, indicative of the therapeutic potential for depression and anxiety (RUBAB et al., 2021).

A double-blind RCT performed with 80 patients with comorbid conditions (depression, anxiety and diabetes) verified the antidepressant effects of nanoformulated curcumin supplementation. There was a significant reduction ($p<0.02$) in the mean score related to DD in the group that received supplementation with NPs-Cur, compared to the control (ASADI et al., 2020). A similar study emphasizes that DD is a chronic disease of the modern world, which negatively affects mental health, having OS as one of the causal factors. Curcumin is a potent antioxidant capable of deterring ROS, protecting mitochondrial function and neuro-inflammation (FUSAR-POLI et al., 2020).

Anti-inflammatory actions were cited by Lopresti and collaborators (2014), stating that curcuminoids influence several biological mechanisms associated with DT such as monoaminergic, immuno-inflammatory and hypothalamic-pituitary-adrenal (HPA) axis activity. Through a double-blind RCT, patients with DD who composed the test group, treated with curcumin (500mg) twice a day, were evaluated. The results were verified by the Depressive Symptomatology Inventory (IDS-SR30) and the Spielberger State Trait Anxiety Inventory (STAI) which showed a significant reduction in depressive symptoms (IDS-SR30-$p<0.045$).

As for the preventive effects, the role of curcumin in the treatment of neuropsychiatric and degenerative disorders has been investigated by studies that support the beneficial use of curcumin. Furthermore, the scientific community recognizes the neuro-inflammatory condition, present in neu-

rological disorders, either as an outcome or a causal factor. Neuroinflammation is a pathophysiological feature that actively participates in brain damage. In a recent hypothesis, curcumin is able to alleviate neuroinflammatory and depressive disorders, by activating neurotrophic polypeptides (ERK-Bcl-2-BDNF) in the hippocampus, implicated in the pathophysiology of DD (HE et al., 2016; YUSUF et al., 2016; POUPOT et al., 2018).

Asadi and collaborators (2020) add that the activation of immuno-inflammatory and oxidative-nitrosative stress pathways play a central role in DD-related disorders, on the other hand, there is evidence that supports the hypothesis that curcumin, a polyphenol with antioxidant property, has effectiveness as a monotherapy or adjunct to treat depression. The experiments indicate that potentiation of BDNF expression is one of the relevant factors in combating depression, and the mechanism of the antidepressant effect generated by NPs-Cur can exert inhibitory activity of the monoamine oxidase enzyme and modulate the release of serotonin and dopamine, support Hurley and collaborators (2014) and Barbara and collaborators (2017).

Oxidative stress arises from the imbalance between oxidizing compounds and antioxidant action. For Kanchanatawan and collaborators (2018), the administration of the bioactive curcuminoid can guide the oxidative imbalance. Curcumin is a natural compound, safe and well tolerated, even when combined with an antidepressant drug. They conducted a double-blind, controlled RCT using curcumin in nanoformulated doses of (500-1500 mg/day) which showed a positive and significant difference from the control. The results were verified by primary assessments (Montgomery-Asberg Depression Rating Scale (MADRS) and secondary assessments by the Hamilton Anxiety Rating Scale (HAM-A), considering that this polyphenol has strong properties, efficacy and potential in monotherapy or adjuvant, with antidepressant and antioxidant effects to individuals with DD.

The antioxidant activity of curcuminoid occurs in a special way when it binds compounds such as piperine and or PLGA, and this complex is considered a potent antioxidant due to its reactivity with peroxyl radicals. However, more research is still needed to expand knowledge about the efficacy of nanoformulated curcumin in DD therapy. In this context, it is worth highlighting the results of meta-analyses on curcumin and its therapeutic potential in DD. One of the meta-analyses, carried out in 2016, included six studies summing 377 patients that compared the use of curcumin (test and control) and the other, carried out in 2019, analyzed curcumin as an adjuvant in the treatment of 531 patients in ten RCTs. Both results corroborated that there is an effective potential for curcumin as an antidepressant (AL-KARAWI et al., 2016; FUSAR-POLI et al., 2019).

Prospects emerge that curcuminoids have broad potential for therapeutic applicability, especially when these bioactive compounds are nanoencapsulated in controlled delivery systems. Currently, several nanostructured substances are under investigation, suggestive to treat various neuropsychiatric diseases.

Although evidence suggests an association between depression and inflammation, further clarification is needed on the causal relationship with specific markers of inflammation, underlying cellular mechanisms, and anti-inflammatory and neuromodulator effects. More RCTs needed to expand knowledge on the efficacy of supplementation with curcumin nanoformulation, safe dosage adjustments for antidepressant effects.

The limitations of this research refer to the possible effects of variability of nanoformulation and doses with curcumin. Difficulty in finding RCTs with humans, focused on the guiding question of the present study. And publication bias, language, methodological aspects of primary studies and the difficulty to combine research with the difference of intervention group.

5 CONCLUSION

From this review, it was possible to verify that there is scientific evidence that supports the association between the use of nanostructured curcumin with antidepressant potential. Curcumin is a hydrophobic polyphenolic compound; it has been used to improve various illness conditions such as anxiety and depression. However, the blood-brain barrier (BBB) prevents the entry of curcumin *in natura* into the brain, limiting its therapeutic potential. The use of nanostructured curcumin has the ability to cross the BBB and allow a homogeneous distribution in the brain, positively interfering in the reduction of neuro-inflammation that is the basis of depression.

Depression is commonly controlled with serotonin reuptake inhibitor drugs; however, more effective therapies are still needed to act on the etiopathogenesis of the disease, minimize DS and mitigate side and undesirable effects. The nanoformulation in controlled delivery systems represents a viable alternative, with antidepressant properties.

REFERENCES

AFZAL, A. et al. Therapeutic potential of curcumin in reversing the depression and associated pseudodementia via modulating stress hormone, hippocampal neurotransmitters, and BDNF levels in rats. **Neuroc Res**, v. 46, n. 12, p.3 273-3285, 2021.

AL-KARAWI, D. et al. The role of curcumin administration in patients with major depressive disorder: mini metaanalysis of clinical Trials. **Phytother Res,** v. 30, n. 2, p. 175-183, 2016.

ASADI, S. et al. Beneficial effects of nanocurcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, doubleblind, placebocontrolled clinical trial. **Phytother Res,** v. 34, n. 4 p. 896-903, 2020.

BARBARA, R. et al. Novel curcumin loaded nanoparticles engineered for blood-brain barrier crossing and able to disrupt abeta aggregates. **Int J Pharm,** v. 30 n. 526, p. 413-424, 2017.

ESSA, D. et al. The design of poly (lactide-co-glycolide) nanocarriers for medical applications. **Bioeng Biotechnol**, v. 8, n. 48, p. 422, 2020.

FAKHRAEI, N. et al. Nanocurcumine ameliorates lipopolysaccharide-induced depressive-like behavior in mice. **Rev Pesq Nanomed**, v. 3, n. 2 p. 58-64, 2018.

FUSAR-POLI, L. et al. Curcumin for depression: a meta-analysis. **Crit Rev Food Sci Nutr**, v. 19, p. 1-11, 2019.

GHALANDARLAKI, N. et al. Nanotechnology-applied curcumin for different diseases therapy. **BioMed Res Int**, n. 4 p. 394264, 2014.

HE, X. et al. Antidepressant effects of curcumin and HU-211 coencapsulated solid lipid nanoparticles against corticosterone-induced cellular and animal models of major depression. **Int J Nanomed**, v. 11, p. 4975-4990, 2016.

HE, X. et al. Targeting the endocannabinoid/CB1 receptor system for treating major depression through antidepressant activities of curcumin and dexanabinol-loaded solid lipid nanoparticles. **Cell Physiol Biochem,** v. 42, p. 2281-2294, 2017.

HURLEY, L.L. et al. Antidepressant-like Effects of Curcumin in WKY Rat Model of Depression Is Associated with an Increase in Hippocampal BDNF. **Behav Brain Res**, v. 239, p. 27-30, 2014.

JANGRA, A. et al. Piperine augments the protective effect of curcumin against lipopolysaccharide-induced neurobehavioral and neurochemical deficits in mice. **Inflammation**, v. 39, n. 3, p. 1025-38, 2016.

KANCHANATAWAN, B. et al. Add-on treatment with curcumin has antidepressive effects in thai patients with major depression: results of a randomized double-blind controlled study. **Neurotox Res**, v. 33, p. 621-633, 2018.

KHADRAWY, Y.A. et al. Antidepressant effects of curcumin-coated iron oxide nanoparticles in a rat model of depression. **Eur J Pharmacol**, v. 5, n. 908, p. 174384, 2021.

LABANCA F. et al. Therapeutic and mechanistic effects of curcumin in Huntington's disease. **Curr Neuropharmacol**, v. 19, n. 7, p. 1007-1018, 2021.

LOPRESTI, A.L. et al. Curcumin for the treatment of major depression: randomised, double-blind, controlled study. **J Affect Disord.,** v. 167, n. 1, p. 368-375, 2014.

POUPOT, R. et al. Nanoparticle-based strategies to treat neuro-inflammation. **Materials**, v. 11, n. 270, p. 2-14, 2018.

RAI, M. et al. Three *Phoma* spp. synthesized novel silver nanoparticles that possess excellent antimicrobial efficacy**. IET Nanobiotechnol**, v. 9, n. 5, p. 280-287, 2015.

RUBAB, S. et al. Enhanced neuroprotective and antidepressant activity of curcumin-loaded nanostructured lipid carriers in lipopolysaccharide-induced depression and anxiety rat model. **Int J Pharm.**, v. 15 n. 603, p.120670, 2021.

SEZGIN, V.C.; BAYRAKTAR, O. **Preparation of curcumin- and piperine loaded bopolymer based nano-delivery systems using electrospray. Coating Techniques**. European Patent Number, 3142702B1, 2018.

SHENGNUO F. et al. Curcumin-loaded PLGA-PEG nanoparticles conjugated with B6 peptide for potential use in Alzheimer's disease, **Drug Deliv**, v. 25, n.1, p.1091-1102, 2018.

SZYMUSIAK, M. et al. Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin. **Int J Pharm**, v. 5 n. 11, p. 415-423, 2016.

YUSUF, M. et al. Polysorbate-80-coated, polymeric curcumin nanoparticles for *in vivo* anti-depressant activity across BBB and envisaged biomolecular mechanism of action through a proposed pharmacophore model. **J Microencapsul**, v. 33, n. 7, p. 646-655, 2016

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