EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2021,16 (01) 01-04
(*FORMERLY: CAPSULA EBURNEA*)

Commentary

WHAT'S IN CURCUMIN'S MIND? THE POTENTIAL ROLE OF CURCUMINOIDS IN THE TREATMENT OF ALZHEIMER'S DISEASE

Paola Marzullo, Silvestre Buscemi

Department of Biological, Chemical and Pharmaceutical Sciences and Technologies -STEBICEF, University of Palermo

ARTICLE INFO

Article history:
Accepted 22 January 2021
Revised 07 February 2021
Published 15 February 2021

Keywords:
Curcumin, Alzheimer's Disease, amiloyd peptide.

ABSTRACT

Neurodegenerative diseases (NDs) are one of major public health problems and their impact is continuously growing. Curcumin has been proposed for the treatment of several of these pathologies, such as Alzheimer's disease (AD) and Parkinson's disease (PD) due to the ability of this molecule to reduce inflammation and aggregation of involved proteins. Nevertheless, the poor metabolic stability and bioavailability of curcumin reduce the possibilities of its practical use. In this review will be highlighted recent results on curcumin and curcuminoids in the search of new effective therapeutics agents against NDs, with particular emphasis on AD.

1. Introduction

In the last two century, natural products have attracted the attention of researchers for their pharmacological importance in prevention and healthcare of several diseases.[1] In 1815 Vogel isolated from rhizome of Curcuma Longa, an East Indian plant, a yellow pigment named Curcumin.[2] Other minor components extracted from turmeric, known as curcuminoids, are demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin.[3] After the first extraction of Curcumin, several studies showed various biological activities of this molecule. As well as other polyphenol compounds,[4] curcumin is a molecule provided by mother nature with anti-inflammatory[5] and antioxidant proprieties.[6] In addition, it has an important chemotherapeutic[7] and hypoglycemic activity.[8] Several evidences support the protective role of this molecule in chronic neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases.[9] In this review we focused our attention on curcumin and its related compounds as modulator agents of pathogenic pathway correlated to Alzheimer's disease.

Worldwide 50 million of people have dementia and Alzheimer's disease is the most common form. A lot of efforts have been made to discover drugs able of preventing the onset of the disease but unfortunately some of these have not given the desired results.

To date, the therapeutic strategy consists only in relieving the associated symptoms and therefore in delaying cognitive decline. The main class of drugs in use today are acetylcholinesterase inhibitors (e.g. Donezepil or Tacrine), antagonists of glutamate NMDA receptor (Memantine), antioxidants, anti-inflammatory agents and agonist of nicotinic or muscarinic receptors.[10]

The pathogenic cause of neurodegenerative diseases is the accumulation of unfolded and aggregate proteins in the brain with consequent loss of biological functions.[11] The extracellular aggregation of amyloid-β and the intracellular accumulation of phosphorylated Tau in neurofibrillary tangles (NFTs) were detected in patients with Alzheimer's disease.

Normally, Aβ proteins are generated from transmembrane amyloid precursor protein (APP) by proteolytic cleavage of α and γ- secretase. Accumulation of Aβ-42 disordered peptide, observed in the brain of patients with Alzheimer's disease, is a consequence of different metabolism of APP involving β-secretase rather than α-secretase. This monomeric toxic species is prone to self-assembly to form oligomers and lather amyloid fibrils.[12] Important evidences suggest that oligomeric/pre-fibrillar Aβ-peptide is the primary toxic species in amyloids.[13]

Alzheimer's disease is classified as tauopathies for the pathological accumulation of protein Tau, a microtubule-associated protein, essential for microtubule stabilization, axonal transport and to maintain the shape of cell.[14]

* *Corresponding author*: Paola Marzullo,paola.marzullo@unipa.it
DOI: 10.3269/1970-5492.2021.16.1
 ISSN: 2279-7165 - Available on-line at www.embj.org

Under pathological conditions, Tau can be subjected to post-translational modifications, phosphorylation or acetylation, with reduction of its affinity for microtubule and self-aggregation to form soluble oligomers (TauO). These can assembly into paired helical filaments (PHFs) and PHFs can aggregate into insoluble neurofibrillary tangles (NFT) considered pathological hallmark of Alzheimer's disease.[15] Like Aβ-oligomers, TauO are considered toxic species and their formation is accompanied by neuronal loss.[16]

2. Curcumin, curcuminoids and AD

Curcumin is one of the main elements of the diet of Southeast Asian populations and it has been used for centuries as a medicine especially for the anti-inflammatory, analgesic, antiseptic or antimalarial activity.[17] In particular, the increased intake of curcumin by these populations explains the lower incidence of Alzheimer's disease in these countries compared to western ones.

Growing scientific evidences show a protective effect of curcumin against Aβ-amyloid plaque formation, but the mechanism of action is not fully clarified. Some studies have classified curcumin as an inhibitor of Aβ-aggregation, other as a disaggregating and destabilizing of amyloid fibrils.[18] In addition, curcumin has shown to inhibit Aβ-oligomerization but no fibril formation.[19] A recent study evidenced that curcumin doesn't inhibit fibril formation during the aggregation process of Aβ-40 but enriches the population of "off-pathway" non-toxic oligomers and prefibrillar proteins.[20]

Curcumin also exerts protective action on pathological aggregation of protein Tau and therefore it has a neuroprotective role in Alzheimer's, Parkinson's and frontotemporal dementia diseases. Curcumin inhibits the oligomerization of tau, disintegrates tau oligomers, inhibits β-sheet formation of and disaggregates tau filaments.[21,22] Moreover, in vitro studies have shown an antiaggregant ability on α-synuclein a protein involved in Parkinson's disease.[23] The neuroprotective effect of curcumin is certainly due to its ability to mitigate inflammation and oxidative stress, known to be key factors in the progression of neurodegenerative disorders.[24]

In view of the important biological proprieties of Curcumin, organic chemists identified curcumin's structure and Lampe et al., for the first time, synthetized it in 1913.[25] In the last century, different research teams designed derivatives of curcumin with the aim to creating a correlation between chemical and biological aspects and to enhance its bioavailability.[26]

Despite the relevant biological activities of curcumin numerous studies revealed a low oral bioavailability due to its poor solubility in water, low permeability and absorption, fast metabolism and excretion in vivo. Oral administration of curcumin in rats (500 mg/kg) showed 1% of bioavailability in rat plasma.[27] In the same way, several clinal studies have revealed extremely low serum levels after oral administration.[28] Curcumin's bioavailability improves when it is injected intravenously in rats.[29]

The gastrointestinal tract with the mucus layer and epithelium tight junction represents a first physical barrier to limit oral absorption.[30] The poor bioavailability is also due to a metabolic pathway of curcumin. It is conjugated with sulphate or glucuronide in an enzymatic reaction involving glucuronidases and sulfotransferases found in liver, kidney and intestinal mucosa.

Thus O-glucoronide or O-sulphate have been the principal curcuminoid metabolites identified in plasma following oral administration in rats. Also, bio-reduction products such as dihydrocurcumin or tetrahydrocurcumin and their conjugate are formed by alcohol dehydrogenase and identified with HPLC and mass spectrometry.[31] The β-diketone moiety of curcumin, at room temperature and in a neutral or alkaline pH, is the most susceptible component to hydrolytic reaction and several degradation products are identified. The serum quantity of reduction products (ferulic acid, ferulic aldehyde, vanillin, vanillic acid and feruloylmethane) is less than conjugated product. Probably in biofluids the β-keto function is not free but bound to proteins and therefore is not hydrolysable.[32] Curcumin is also photoreactive and when it is exposed to light it can undergo photodegradation to give similar products to those of hydrolytic degradation.[33] Preclinical evidences suggest a potential therapeutic use of curcumin in neurodegeneration but several clinical trials not give desired effects probably due to difficult of curcumin, following oral administration, to cross the blood-brain barrier (BBB).[34] To improve the lower bioavailability in the brain, researches developed different pharmaceutical strategies such as new formulation and new delivery system. Most of new delivery systems have a central hydrophobic pocket in which curcumin binds trough hydrophobic interaction. This macromolecular system also preserve curcumin from degradation reaction as well as enhance its absorption and distribution.[33]

A recent paper reported exosomes from curcumin-treated (primed) cells as valid carrier to release selectively curcumin in the brain. This delivery system increases the percentage of curcumin that across the BBB through receptor-mediated transcytosis. Following an injection in AD mice model they observed a reduction of Tau phosphorylation trough inhibition of AKT/GSK pathway.[34] Liposomes modified with penetrating agents also facilitate the passage of curcumin trough the BBB and are evaluated as new therapeutic approach to carry Curcumin and other Aβ/Tau aggregation inhibitor in the brain.[35]

The nanotechnology has given other important results in drug delivery of curcumin. Giacomelli et al. developed a novel nanocarrier named lipid-core nano-capsules (LNC).[36] Age female mice treated with intracerebroventricular injection of Aβ42 are used as Alzheimer's disease model. After 14 days, the administration of curcumin loaded nano-capsules displayed significant neuroprotection against Aβ-toxicity compared to control group treated with free curcumin.

Recently, novel nanoparticles loading curcumin made of chitosan and bovine serum albumin were designed. Using these formulations, was observed an increased penetration of curcumin trough BBB and an activation of microglia with a subsequent increase of Aβ-phagocytosis.[37]

To date, also the analysis of several crystalline solid form of curcumin is a great interest research area due to different physicochemical proprieties of polymorphs.[38]

Organic chemists, since the last century, have shown a growing interest in the synthesis of curcumin derivatives with the purpose to improve its biological activity. As mentioned above, curcumin interfere with accumulation of aggregate proteins (Aβ and Tau), inflammation and oxidative stress. The modulation of each of these pathologic pathway required structural features of curcumin. Thus, structure-activity relationship studies are extremely important to identify novel curcumin's derivatives as potential therapeutic agents for neurodegenerative diseases.

In recent years, researches synthetized several curcumin-inspired compounds.[39-42]

These studies are mainly related to applications of curcuminoids that have been found to be important for anti-Aβ activity. Curcumin and its derivatives exert a protective role against disordered Tau-protein but we have few paper about Tau aggregation inhibitors. Unlike Aβ-peptides, Tau lacks hydrophobic residues and therefore its aggregation process doesn't lead to the formation of Π-Π interactions. Instead, tau aggregation inhibitors interact with tau by electrostatic interaction and hydrogen bonding. A recent study designed two ruthenium-curcumin-bipyridine/phenanthroline complex as inhibitors of tau aggregation.[43] In these complexes the metal ion is bound by enolic group of curcumin and by nitrogen atoms of ancillary ligands, bipyridine or phenanthroline. Curcumin inhibits aggregation at nucleation stage while ruthenium complex inhibits the elongation phase reducing longer fibrils.

Oxidative damage plays an important role in neurodegeneration therefore to treat neurodegenerative disorders another pharmacological approach is to develop antioxidant compounds. The antioxidant propriety of Curcumin is due to the abstractable hydrogen of phenol group.[44] This group can reduce, for example, superoxide radicals to generate a less reactive phenoxyl radical resonance stabilized.[45] Ferrari et al. developed analogues of curcumin substituted on central carbon of heptadienone linker and demonstrated the good metal chelating propriety of these complexes.[46] These compounds shown less scavenging propriety because the presence of the substituent on central linker shifts the keto-enol tautomerism towards di-keto form with less stabilization of phenoxyl radical.

3. Conclusion and perspective

Curcumin attracted the attention of many researcher due its potential use for the treatment of neurodegenerative diseases. Many doubt were raised concerning the real activity of this compound and its actual applicability. Nevertheless, many recent studies seems to establish a real therapeutic potential, particularly, by solving issues related to delivery of this molecule to the brain. The use of curcumin or curcuminoids seems quite far to be established for a therapeutic protocol, but the lesson of searching from nature potential drugs is still concrete. Considering the rising numbers of neurodegenerative disease, we hope that this compound could inspire a real solution of this world-wide problem.

4. Acknowledgements

University of Palermo is acknowledged for financial support.

References

1. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs from 1981 to 2014. J Nat Prod. 2016 Mar 25;79(3):629-61.
2 Vogel P. Examen chimique de la racine de Curcuma. Journal de Pharmacie. 1815; (I):289-300.
3 Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007 Nov-Dec;4(6):807-18.
4 Russo GL, Spagnuolo C, Russo M, Tedesco I, Moccia S, Cervellera C. Mechanisms of aging and potential role of selected polyphenols in extending healthspan. Biochem Pharmacol. 2020 Mar; (173):113719.
5 Atami M, Abdolahi M, Soveyd N, Djalali M, Togha M, Honarvar NM. Molecular Mechanisms of Curcumin in Neuroinflammatory Disorders: A Mini Review of Current Evidences. Endocr Metab Immune Disord Drug Targets. 2019;19(3):247-258.
6 Bagheri H, Ghasemi F, Barreto GE, Rafiee R, Sathyapalan T, Sahebkar A. Effects of curcumin on mitochondria in neurodegenerative diseases. Biofactors. 2020 Jan;46(1):5-20.
7 Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer. 2011 Feb 7;10:12.
8 Nishiyama T, Mae T, Kishida H, Tsukagawa M, Mimaki Y, Kuroda M, Sashida Y, Takahashi K, Kawada T, Nakagawa K, Kitahara M. Curcuminoids and sesquiterpenoids in turmeric (Curcuma longa L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. J Agric Food Chem. 2005 Feb 23;53(4):959-63.
9 Lakey-Beitia J, Berrocal R, Rao KS, Durant AA. Polyphenols as therapeutic molecules in Alzheimer's disease through modulating amyloid pathways. Mol Neurobiol. 2015 Apr;51(2):466-79.
10 Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41
11 Walker LC, LeVine H. The cerebral proteopathies: neurodegenerative disorders of protein conformation and assembly. Mol Neurobiol. 2000 Feb-Apr;21(1-2):83-95.
12 Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem. 2017 Jun 20;86:27-68.
13 Glabe CG, Kayed R. Common structure and toxic function of amyloid oligomers implies a common mechanism of pathogenesis. Neurology. 2006 Jan 24;66(2 Suppl 1):S74-8.
14 Naseri NN, Wang H, Guo J, Sharma M, Luo W. The complexity of tau in Alzheimer's disease. Neurosci Lett. 2019 Jul 13;705:183-194.
15 Cook C, Stankowski JN, Carlomagno Y, Stetler C, Petrucelli L. Acetylation: a new key to unlock tau's role in neurodegeneration. Alzheimers Res Ther. 2014 May 29;6(3):29.
16 Lasagna-Reeves CA, Castillo-Carranza DL, Sengupta U, Sarmiento J, Troncoso J, Jackson GR, Kayed R. Identification of oligomers at early stages of tau aggregation in Alzheimer's disease. FASEB J. 2012 May;26(5):1946-59.
17 Prasad S, Aggarwal BB. Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In: Herbal Medicine: Biomolecular and Clinical Aspects. 2nd ed. Edited by I.F.F. Benzie, S. Wachtel-Galor. Cap. 13, CRC Press/Taylor & Francis, 2011.
18 Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem. 2005 Feb 18;280(7):5892-901.
19 Necula M, Kayed R, Milton S, Glabe CG. Small molecule inhibitors of aggregation indicate that amyloid beta oligomerization and fibrillization pathways are independent and distinct. J Biol Chem. 2007 Apr 6;282(14):10311-24.

20 Thapa A, Jett SD, Chi EY. Curcumin Attenuates Amyloid-β Aggregate Toxicity and Modulates Amyloid-β Aggregation Pathway. ACS Chem Neurosci. 2016 Jan 20;7(1):56-68.

21 Rane JS, Bhaumik P, Panda D. Curcumin Inhibits Tau Aggregation and Disintegrates Preformed Tau Filaments in vitro. J Alzheimers Dis. 2017;60(3):999-1014.

22 Ma QL, Zuo X, Yang F, Ubeda OJ, Gant DJ, Alaverdyan M, Teng E, Hu S, Chen PP, Maiti P, Teter B, Cole GM, Frautschy SA. Curcumin suppresses soluble tau dimers and corrects molecular chaperone, synaptic, and behavioral deficits in aged human tau transgenic mice. J Biol Chem. 2013 Feb 8;288(6):4056-65.

23 Pandey N, Strider J, Nolan WC, Yan SX, Galvin JE. Curcumin inhibits aggregation of alpha-synuclein. Acta Neuropathol. 2008 Apr;115(4):479-89.

24 Kim GY, Kim KH, Lee SH, Yoon MS, Lee HJ, Moon DO, Lee CM, Ahn SC, Park YC, Park YM. Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. J Immunol. 2005 Jun 15;174(12):8116-24.

25 Lampe V, Milobedzka J. Studien uber Curcumin. Ber Dtsch Chem Ges. 1913 Apr; 46:2235–2240.

26 Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. Molecules. 2014 Dec 1;19(12):20091-112.

27 Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2007 Jun 15;853(1-2):183-9.

28 Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat. 2014 Jan;46(1):2-18.

29 Sun J, Bi C, Chan HM, Sun S, Zhang Q, Zheng Y. Curcumin-loaded solid lipid nanoparticles have prolonged in vitro antitumour activity, cellular uptake and improved in vivo bioavailability. Colloids Surf B Biointerfaces. 2013 Nov 1;111:367-75.

30 Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. J Control Release. 2019 Dec 28;316:359-380.

31 Asai A, Miyazawa T. Occurrence of orally administered curcuminoid as glucuronide and glucuronide/sulfate conjugates in rat plasma. Life Sci. 2000 Oct 27;67(23):2785-93.

32 Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The Essential Medicinal Chemistry of Curcumin. J Med Chem. 2017 Mar 9;60(5):1620-1637.

33 Priyadarsini KI. Photophysics, Photochemistry and Photobiology of Curcumin: Studies from organic solutions, bio-mimetics and living cells. J Photochem Photobiol. 2009 Jun;10:81–96.

34 Wang H , Sui H , Zheng Y , Jiang Y , Shi Y , Liang J , Zhao L . Curcumin-primed exosomes potently ameliorate cognitive function in AD mice by inhibiting hyperphosphorylation of the Tau protein through the AKT/GSK-3β pathway. Nanoscale. 2019 Apr 11;11(15):7481-7496.

35 Ross C, Taylor M, Fullwood N, Allsop D. Liposome delivery systems for the treatment of Alzheimer's disease. Int J Nanomedicine. 2018 Dec 12;13:8507-8522.

36 Giacomeli R, Izoton JC, Dos Santos RB, Boeira SP, Jesse CR, Haas SE. Neuroprotective effects of curcumin lipid-core nanocapsules in a model Alzheimer's disease induced by β-amyloid 1-42 peptide in aged female mice. Brain Res. 2019 Oct 15;1721:146325.

37 Yang R, Zheng Y, Wang Q, Zhao L. Curcumin-loaded chitosan-bovine serum albumin nanoparticles potentially enhanced Aβ 42 phagocytosis and modulated macrophage polarization in Alzheimer's disease. Nanoscale Res Lett. 2018 Oct 22;13(1):330.

38 Suresh K, Nangia A. Curcumin: pharmaceutical solids as a platform to improve solubility and bioavailability. Cryst Eng Comm. 2018 May14;20:3277-3296.

39 Reinke AA, Gestwicki JE. Structure-activity relationships of amyloid beta-aggregation inhibitors based on curcumin: influence of linker length and flexibility. Chem Biol Drug Des. 2007 Sep;70(3):206-15.

40 Gagliardi S, Franco V, Sorrentino S, Zucca S, Pandini C, Rota P, Bernuzzi S, Costa A, Sinforiani E, Pansarasa O, Cashman JR, Cereda C. Curcumin and Novel Synthetic Analogs in Cell-Based Studies of Alzheimer's Disease. Front Pharmacol. 2018 Dec 3;9:1404.

41 Konno H, Endo H, Ise S, Miyazaki K, Aoki H, Sanjoh A, Kobayashi K, Hattori Y, Akaji K. Synthesis and evaluation of curcumin derivatives toward an inhibitor of beta-site amyloid precursor protein cleaving enzyme 1. Bioorg Med Chem Lett. 2014 Jan 15;24(2):685-90.

42 Narlawar R, Pickhardt M, Leuchtenberger S, Baumann K, Krause S, Dyrks T, Weggen S, Mandelkow E, Schmidt B. Curcumin-derived pyrazoles and isoxazoles: Swiss army knives or blunt tools for Alzheimer's disease? ChemMedChem. 2008 Jan;3(1):165-72.

43 Liu W, Hu X, Zhou L, Tu Y, Shi S, Yao T. Orientation-Inspired Perspective on Molecular Inhibitor of Tau Aggregation by Curcumin Conjugated with Ruthenium(II) Complex Scaffold. J Phys Chem B. 2020 Mar 26;124(12):2343-2353.

44 Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG, Mohan H. Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Radic Biol Med. 2003 Sep 1;35(5):475-84.

45 Mishra B, Priyadarsini KI, Bhide MK, Kadam RM, Mohan H. Reactions of superoxide radicals with curcumin: probable mechanisms by optical spectroscopy and EPR. Free Radic Res. 2004 Apr;38(4):355-62.

46 Ferrari E, Benassi R, Saladini M, Orteca G, Gazova Z, Siposova K. In vitro study on potential pharmacological activity of curcumin analogues and their copper complexes. Chem Biol Drug Des. 2017 Mar;89(3):411-419.

.