Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
www.phytojournal.com
JPP 2020; 9(2): 2005-2008
Received: 12-01-2020
Accepted: 16-02-2020

Bhagyasree Prathipati
Research Scholar, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India

Dr. P Rohini
Assistant Professor, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India

Corresponding Author:
Dr. P Rohini
Assistant Professor, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India

Curcumin: A review on neuroprotection

Bhagyasree Prathipati and Dr. P Rohini

Abstract
Treatment based on traditional medicine is very popular in developing world due to inexpensive properties. There is a growing interest in herbal medicine. Curcumin a hydrophobic poly-phenol is derived from turmeric, the rhizome of the herb *Curcuma longa* L. Neurodegenerative diseases have become a major challenge for public health because of their incurable status. Curcumin has an outstanding safety profile and a number of pleiotropic actions with potential for neuroprotective efficacy, including anti-inflammatory, antioxidant, and antiprotein- aggregate activities. Because of its pleotropic actions on the central nervous system, including preferential binding to amyloid proteins, Curcumin is being touted as a promising treatment for age-related brain diseases. This review article aims at gathering information predominantly on neurodegenerative diseases.

Keywords: Turmeric, curcumin, neurodegenerative disease, neuroprotection

Introduction
Turmeric is a spice that has received much interest from both the medical/scientific worlds as well as from the culinary world. Turmeric is commonly called as "golden spice" or "spice of life" (D Shrishail *et al*., 2013) [8]. Curcuma longa, commonly known as turmeric, is a perennial herb that belongs to Zingiberaceae family with 133 different species available worldwide. Curcuma has been reported to be used in Ayurveda, Siddha, and Unani system of medicines from Vedic times. Turmeric also has special religious significance in Hinduism. It is used as a cooking spice, cosmetic agent, dying agent, and also in medicinal practice to treat various ailments like skin infections and liver and gastrointestinal disorders (Yallapu MM *et al*., 2012) [48]. Curcuma longa has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory (Lestari, M.L *et al*., 2014) [23], antimutagenic, antimicrobial (Reddy, R.C *et al*., 2005) [36] and anticancer properties (Wright, L.E *et al*., 2013) [47]. While in India, its average consumption is estimated to be about 4 g/day (Tapsell LC *et al*., 2006). Curcumin content in turmeric of turmeric is variable. Curcumin, a polyphenol, has been shown to target multiple signaling molecules while also demonstrating activity at the cellular level, which has helped to support its multiple health benefits (Gupta, S.C *et al*., 2013) [14]. It has been shown to benefit inflammatory conditions (Aggarwal, B.B, Harikumar, K.B. 2009) [1], metabolic syndrome (Panahi, Y *et al*., 2016) [33], pain (Kuptniratsaikul, V *et al*., 2014) [19], and to help in the management of inflammatory and degenerative eye conditions (Mazzolani, F, Togni, S 2013) [27]. In addition, therapeutic contributions of curcumin in many neurological diseases have been proven in several studies (Goozee KG *et al*., 2016) [13]. Lower incidence rate of many neurodegenerative diseases in Indians can be attributed to the regular intake of turmeric in their routine diet (Krishnaswamy K *et al*., 2008) [17].

History of Curcumin
Pelletier and Vogel made the remarkable scientific discovery of curcumin by isolating the yellow colored pigment from the rhizomes of turmeric in 1815. In 1842 they synthesized pure curcumin. Later in 1973, Roughly and Whiting described its detailed chemical structure. Later, chemists discovered that turmeric paper can be used to test the alkalinity of substance, as the turmeric's orange-yellow root powder color changed into reddish brown color when treated with alkaline chemicals. Great enthusiasm in curcumin research started after researchers came to know about the botanical history of Curcuma longa from the book, "Maude Greve's book—A Modern Herbal". Though various Indian medical systems use turmeric from ancient times, German scientists started detailed research in early 1920s, as they identified the therapeutic potential of oils extracted from the roots of Curcuma herb in 1926. Curcumin is extracted from turmeric by column chromatography, soxhlet apparatus, pulse ultrasonic, and microwave-based extraction methods (Priyadarsini KI., 2014) [24].

Curcumin is being recognized and used worldwide in many different forms for multiple potential health benefits. For example, in India, turmeric—containing curcumin—has been used in curries; in Japan, it is served in tea; in Thailand, it is used in cosmetics; in China, it is used as a colorant; in Korea, it is served in drinks; in Malaysia, it is used as an antiseptic; in Pakistan, it is used as an anti-inflammatory agent; and in the United States, it is used in mustard sauce, cheese, butter, and chips, as a preservative and a coloring agent, in addition to capsules and powder forms. Curcumin is available in several forms including capsules, tablets, ointments, energy drinks, soaps, and cosmetics (Gupta, S.C *et al*., 2013) [14]. Curcuminoids have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized As Safe" (GRAS) (Gupta, S.C *et al*., 2013) [14], and good tolerability and safety profiles have been shown by clinical trials, even at doses between 4000 and 8000 mg/day (Basnet, P, Skalko-Basnet, N., 2011) [2] and of doses up to 12,000 mg/day of 95% concentration of three curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin (Lao, C.D *et al*., 2006) [21]. Curcumin has been reported to have a low absorption rate, high biotransformation rate in intestines, and fast elimination rate from the systemic circulation (Rachmawati H *et al*., 2013) [35].

Structure and synthesis of Curcumin

Turmeric contains 2–9% curcuminoids, depending upon its biological origin and soil fertility and its place of cultivation. Curcuminoids include compounds like curcumin (77%), demethoxycurcumin (17%), and bis-demethoxycurcumin (3%) (Goel A *et al*., 2008) [12]. The chemical structure of curcumin shows symmetry to molecule formula $C_{21}H_{20}O_6$ (1E, 6E): 1,7-bis(4-hydroxy- 3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with molecular weight of 368.38 g/mol. This molecule has three functional groups attached in its structure: o-Methoxy phenolic groups present in the two aromatic ring systems, associated with a seven carbon attachment comprising α, β-unsaturated β-diketone group, which show keto-enol tautomerism (Priyadarsini KI., 2014) [34].

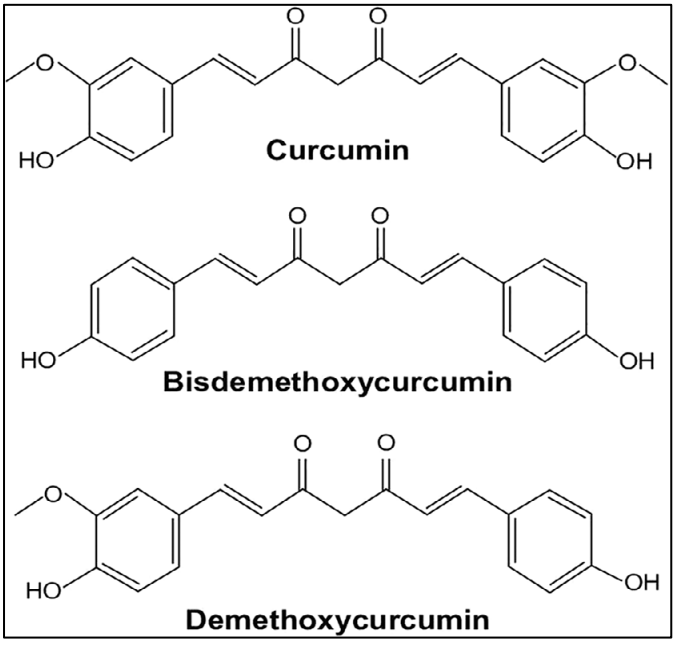

Fig 1: Chemical structure of curcumin

Chemist Lampe synthesized curcumin using carbomethoxy feruloyl chloride and ethyl acetoacetate (Lampe V, Milobedzka J., 2006) [20]. A new preparatory process of curcumin was developed by Pabon, 2010 [32] using acetylacetone and substituted aromatic aldehydes in the presence of boron trioxide (B_2O_3), trialkyl borate, and n-butylamine and then stabilized the preparatory method with some minor modifications. Pabon's preparatory method has been used extensively and has a good yield. In this method, 2,4-diketones reacts with substituted aromatic aldehydes and undergoes Knoevenagel condensation with boron complex to avoid precipitation. In anhydrous environment, curcumin gets separated easily using polar aprotic solvents. Under mild acidic environment, the boron complex breaks into curcumin that can be separated by washing continuously and precipitated by column chromatography (Pabon HJJ., 2010) [32].

Neuroprotective effects of Curcumin

Many neurodegenerative diseases of aging involve the accumulation of protein aggregates, oxidative damage, and inflammation. Curcumin is a pleiotropic molecule, which not only directly binds to and limits aggregation of misfolded proteins in many neurodegenerative diseases Although curcumin corrects dysregulation of several pathways, it may exert multiple effects via a few molecular targets. Curcumin is a drug of interest in the management of various neurodegenerative discussed below.

- **Alzheimer's disease (AD):** Alzheimer's disease (AD) is a progressive fatal neurodegenerative disorder involving chronic CNS inflammation leading to significant oxidative damage (Friedlich and Butcher, 1994; Montine *et al*., 1999; Smith *et al*., 1997) [11, 28, 45]. The classical pathology of AD involves neurodegeneration and the accumulation of protein aggregates to form two major lesions: neurofibrillary tangles (NFTs) extracellularly and senile plaques intracellularly along with progressive loss of neurons and dendritic spines in the hippocampal and cortical regions. The most important symptoms in AD include decline in cognitive and motor performances, dementia and memory loss (Cheng KK *et al*., 2012) [5]. Accumulation of insoluble alpha-beta amyloid protein leads to senile plagues and hyperphosphorylation of tau proteins at multiple sites results in neurofibrillary tangles (Oddo S *et al*., 2003) [30]. Senile plaques and amyloid fibrils form chaperone protein plaques that damage the neuronal structure and its synaptic connections.

Curcumin, because of its strong anti-inflammatory activity, binds with Aβ (Amyloid beta), and prevents protein aggregation and also destabilize the preformed fibril by metal binding (Baum L, Ng A 2004; Daniel S *et al*., 2004; Ono K *et al*., 2004) [4, 9, 31]. Thus, altogether it reduces the progression of neuronal damage in AD brains (Shukla PK *et al*., 2003) [43]. Curcumin has known to possess potent antioxidant and free radical scavenging activity (Hamaguchi T *et al*., 2010; Nimse SB, Pal D, 2015) [11, 29]. Oxidative stress increases the concentration of metals like copper, zinc, or iron in the brain. When the concentrates of these metals reaches more than 1 mM, their affinity toward Aβ increases. This results in increase in peptide aggregation and enhanced plague formation, which ultimately leads to disease progression (DeToma AS *et al*., 2012) [10]. Curcumin because of its free radical scavenging and protein aggregation inhibition could be a potential therapeutic value in AD.

- **Parkinson's disease:** Parkinson's disease (PD) is one of the major neurodegenerative diseases characterized by

progressive loss of dopaminergic neurons in substantia nigra compacta (SNpc), deposition of α-synuclein and Lewy bodies (Sekar S *et al*., 2018; Mani S *et al*., 2018) [26, 41]. High levels of free radicals and compromised mitochondrial functions are found to be the main causes of neuronal death in PD brains (Chidambaram SB *et al*., 2018) [6]. The neurotoxin 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) selectively damages mitochondrial complex I of electron transport chain, triggering oxidative stress, and thereby producing dopaminergic degeneration (Sathiya S, Babu CS, 2015) [38]. In recent studies, curcumin possesses antioxidant, anti-inflammatory, anti-apoptotic activities, and therapeutic potential in neurodegenerative disorders (Liu Z *et al*., 2011) [25]. Curcumin shields dopaminergic neurons against MPTP-induced neuronal damage. It also causes increase of dopamine (Zhang N *et al*., 2018) [49] and tyrosine hydroxylase (TH), by inhibiting the glial fibrillary acidic protein (GFAP) and iNOS protein expression (Sharma N, Nehru B, 2018) [42]. In several investigations, transgenic PD model of Drosophila showed that curcumin reduces the levels of lipid peroxidation and protein carbonyl aggregates in the brains (Siddique YH *et al*., 2014) [44].

- **Huntington's disease:** Huntington's disease (HD) is an inherited, autosomal, neurological neurodegenerative disorder, characterized by the choreiform movements (Scattoni *et al*., 2007) [40], selective degeneration of striatum spiny GABAergic neurons in basal ganglia which leads to motor and cognitive impairments (Lin and Beal, 2006; Kumar *et al*., 2012) [24, 18], mood disorders, psychiatric disturbances (Kent 2004) [16]. HD is primarily characterized by the expansion of a polymorphic cytosine-adenine-guanine (CAG) trinucleotide repeat chain encoding N-terminal region of poluglutamine tract within the huntingtin gene (htt) (Bates, 2003) [3]. Curcumin, because of its ability to cross the BBB, (Lee WH *et al*., 2013) [22] has been investigated for its therapeutic effects against various motor neurodegenerative disorders. Curcumin has been shown to reverse the polyQ-induced apoptosis and neuronal dysfunction in motor areas of HD patients (Saudou F *et al*., 1998) [39]. Thus, curcumin is seen as potential therapeutic candidate in polyQ disease patients (Chongtham A, Agrawal N 2016) [7].

Conclusion

Numerous studies have been conducted to test the potential of Curcumin to prevent or treat different neurological diseases. However, several reports have raised questions about its safety and efficacy, especially at high doses, which may be harmful. Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its anti-oxidant and anti-inflammatory mechanisms. Neurodegenerative diseases are age-related complicated disorders with complex neuropathological characteristics. Neuronal damage and cognitive deficits or impairment of motor coordination are the major problems in these diseases. Because of its pleotropic actions on the nervous system, including anti-amyloid, anti-inflammatory, and anti-oxidant properties, Curcumin is a promising candidate for targeting protein misfolding neurological diseases. Furthermore, it is safe and inexpensive, readily available and can effectively penetrate the blood-brain barrier and neuronal membranes. We have provided detailed information on the anti-amyloid properties of Curcumin in major neurodegenerative disorders, such as alzheimer's disease, parkinson's disease and huntington's disease. Collectively, the information available from reviewing the literature on the therapeutic potential of Curcumin can provide helpful insights into the potential clinical utility of Curcumin for treating neurological diseases.

References

1. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int. J Biochem. Cell Biol. 2009; 41:40-59.
2. Basnet P, Skalko-Basnet N. Curcumin: An anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules. 2011; 16:4567-4598.
3. Bates G. Huntingtin aggregation and toxicity in Huntington's disease. Lancet. 2003; 361:1642–1644.
4. Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. J Alzheimers Dis. 2004; 6:367–377.
5. Cheng KK, Yeung CF, Ho SW, Chow SF, Chow AHL, Baum L. Highly stabilized curcumin nanoparticles tested in an *in vitro* blood–brain barrier model and in Alzheimer's disease Tg2576 mice. AAPS J. 2012; 15:324–336.
6. Chidambaram SB, Bhat A, Ray B *et al*. Cocoa beans improve mitochondrial biogenesis via PPARγ/PGC1α dependent signaling pathway in MPP+ intoxicated human neuroblastoma cells (SH-SY5Y). Nutr Neurosci, 2018, 1–10.
7. Chongtham A, Agrawal N. Curcumin modulates cell death and is protective in Huntington's disease model. Sci Rep. 2016; 6:18736.
8. Shrishail D, Harish KH, Ravichandra H, Tulsianand G, Shruthi SD. Turmeric: nature's precious medicine. Asian J Pharm Clin Res. 2013; 6:10–16.
9. Daniel S, Limson JL, Dairam A, Watkins GM, Daya S. Through metal binding, curcumin protects against lead- and cadmium induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain. J Inorg Biochem. 2004; 98:266–275.
10. DeToma AS, Salamekh S, Ramamoorthy A, Lim MH. Misfolded proteins in Alzheimer's disease and type II diabetes. Chem Soc Rev. 2012; 41:608–621.
11. Friedlich AL, Butcher LL. Involvement of free oxygen radicals in Bamyloidosis: an hypothesis. Neurobiol. Aging. 1994; 15:443–455.
12. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol. 2008; 75:787–809.
13. Goozee KG, Shah TM, Sohrabi HR *et al*. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. Br J Nutr. 2016; 115:449–465.
14. Gupta SC, Patchva S, Aggarwal BB. Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials. AAPS J. 2013; 15:195–218.
15. Hamaguchi T, Ono K, Yamada M. Review: Curcumin and Alzheimer's disease. CNS Neurosci Ther. 2010; 16:285–297.
16. Kent A. Huntington's disease. Nurs. Stand. 2004; 18:45–51.

17. Krishnaswamy K. Traditional Indian spices and their health significance. Asia Pac J Clin Nutr. 2008; 17:265–268.
18. Kumar P, Kalonia H, Kumar A. Possible GABAergic mechanism in the neuroprotective effect of gabapentin and lamotrigine against 3-nitropropionic acid induced neurotoxicity. Eur. J Pharmacol. 2012; 15(674):265–274.
19. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragulpoontawee M, Lukkanapichonchut P, Chootip C *et al*. Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: A multicenter study. Clin. Interv. Aging. 2014; 9:451–458.
20. Lampe V, Milobedzka J. Studien über Curcumin. Ber Dtsch Chem Ges. 2006; 46:2235–2240.
21. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM *et al*. Dose escalation of a curcuminoid formulation. BMC Complement. Altern. Med. 2006; 6:10.
22. Lee WH, Loo CY, Bebawy M, Luk F, Mason RS, Rohanizadeh R. Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol. 2013; 11:338–378.
23. Lestari ML, Indrayanto G. Curcumin. Profiles Drug Subst. Excip. Relat. Methodol. 2014; 39:113–204.
24. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature. 2006; 443:787–795.
25. Liu Z, Hamamichi S, Dae Lee B *et al*. Inhibitors of LRRK2 kinase attenuate neurodegeneration and Parkinson-like phenotypes in Caenorhabditis elegans and Drosophila Parkinson's disease models. Hum Mol Genet. 2011; 20:3933–3942.
26. Mani S, Sekar S, Chidambaram SB, Sevanan M. Naringenin protects against 1-methyl-4-phenylpyridinium-induced neuroinflammation and resulting reactive oxygen species production in SH-SY5Y cell line: An *in vitro* model of Parkinson's disease. Pharmacogn Mag. 2018; 14:458.
27. Mazzolani F, Togni S. Oral administration of a curcumin-phospholipid delivery system for the treatment of central serous chorioretinopathy: A 12-month follow-up study. Clin. Ophthalmol. 2013; 7:939–945.
28. Montine TJ, Markesbery WR, Zackert W, Sanchez SC, Roberts LJ, Morrow JD. The magnitude of brain lipid peroxidation correlates with the extent of degeneration but not with density of neuritic plaques or neurofibrillary tangles or with ApoE genotype in Alzheimer's disease patients. Am. J Pathol. 1999; 155:863-868.
29. Nimse SB, Pal D. Free radicals, natural antioxidants, and their reaction mechanisms. RSC Adv. 2015; 5:27986–28006.
30. Oddo S, Caccamo A, Shepherd JD *et al*. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003; 39:409–421.
31. Ono K, Hasegawa K, Naiki H, Yamada M. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils *in vitro*. J Neurosci Res. 2004; 75:742–750.
32. Pabon HJJ. A synthesis of curcumin and related compounds. Rec Trav Chim Pays Bas. 2010; 83:379–386.
33. Panahi Y, Hosseini MS, Khalili N, Naimi E, Simental-Mendia LE, Majeed M *et al*. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. Biomed. Pharmacother. 2016; 82:L578–582.
34. Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. Molecules. 2014; 19:20091–20112.
35. Rachmawati H, Al Shaal L, Müller RH, Keck CM. Development of curcumin nanocrystal: physical aspects. J Pharm Sci. 2013; 102:204–214.
36. Reddy RC, Vatsala PG, Keshamouni VG, Padmanaban G, Rangarajan PN. Curcumin for malaria therapy. Biochem. Biophys. Res. Commun. 2005; 326:472–474.
37. Roughley PJ, Whiting DA. Experiments in the biosynthesis of curcumin. J Chem Soc, Perkin Trans. 1973; 1(20):2379–2388.
38. Sathiya S, Babu CS. Telmisartan alleviates nitrosative stress in turn dopaminergic degeneration in mice mptp model of parkinsonism–biochemical and histopathological evidences. Int J Pharm Pharm Sci. 2015; 7:97–101.
39. Saudou F, Finkbeiner S, Devys D, Greenberg ME. Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. Cell. 1998; 95:55–66.
40. Scattoni ML, Valanzano A, Pezzola A, March ZD, Fusco FR, Popoli P *et al*. Adenosine A2A receptor blockade before striatal excitotoxic lesions prevents long term behavioural disturbances in the quinolinic rat model of Huntington's disease. Behav. Brain Res. 2007; 176:216–221.
41. Sekar S, Mani S, Rajamani B *et al*. Telmisartan ameliorates astroglial and dopaminergic functions in a mouse model of chronic Parkinsonism. Neurotox Res. 2018; 34:597–612.
42. Sharma N, Nehru B. Curcumin affords neuroprotection and inhibits α-synuclein aggregation in lipopolysaccharide-induced Parkinson's disease model. Inflammo pharmacology. 2018; 26:349–360.
43. Shukla PK, Khanna VK, Khan MY, Srimal RC. Protective effect of curcumin against lead neurotoxicity in rat. Hum Exp Toxicol. 2003; 22:653–658.
44. Siddique YH, Naz F, Jyoti S. Effect of curcumin on lifespan, activity pattern, oxidative stress, and apoptosis in the brains of transgenic Drosophila model of Parkinson's disease. Biomed Res Int. 2014; 2014:606928.
45. Smith MA, Richey Harris PL, Sayre LM, Beckman JS, Perry G. Widespread peroxynitrite-mediated damage in Alzheimer's disease. J. Neurosci. 1997; 17:2653–2657.
46. Tapsell LC, Hemphill I, Cobiac L, Patch CS, Sullivan DR, Fenech M. Health benefits of herbs and spices: the past, the present, the future. Med J Aust. 2006; 21:185.
47. Wright LE, Frye JB, Gorti B, Timmermann BN, Funk JL. Bioactivity of turmeric-derived curcuminoids and related metabolites in breast cancer. Curr. Pharm. Des. 2013; 19:6218–6225.
48. Yallapu MM, Jaggi M, Chauhan SC. Curcumin nanoformulations: a future nanomedicine for cancer. Drug Discov Today. 2012; 17:71–80.
49. Zhang N, Yan F, Liang X, Wu M, Shen Y, Chen M. Localized delivery of curcumin into brain with polysorbate 80-modified cerasomes by ultrasound-targeted microbubble destruction for improved Parkinson's disease therapy. Theranostics. 2018; 8(8):2264–2277.