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Review

Curcumin in Alzheimer's disease: Can we think to new strategies and perspectives for this molecule?

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ABSTRACT

Population aging is an irreversible global trend with economic and socio-political consequences. One of the most invalidating outcomes of aging in the elderly is cognitive decline, leading to dementia and often related to neurodegenerative disorders. Among these latter, Alzheimer's disease (AD) is the major cause of dementia, affecting more than 30 million of individuals worldwide. To date, the treatment of AD remains a challenge because of an incomplete understanding of the events that lead to the selective neurodegeneration typical of Alzheimer's brains. There is an enormous global demand for new effective therapies and researchers are investigating new fields. One promising strategy is the use of nutraceuticals as integrative, complementary and preventive therapy. Curcumin is one example of natural product with anti-AD properties, with promising potential for prevention, treatment and diagnostic. The limitations in the use of curcumin as therapeutic are represented by its pharmacokinetics profile and the low bioavailability after oral administration. However, curcumin has been the focus of intense research for new drug development. Here we analyzed some new approaches that have been applied in the attempt to improve its use, particularly new formulations, changes in the way of administration, nanotechnology-based delivery systems and the hybridization strategy.

Contents

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1. Introduction

One of the most important demographic trends facing the world is the aging of the population. As the life expectancy has increased, the high prevalence of chronic disabilities represents one of the major causes of upward burden on the economy of Health Services, requiring a long-term clinical management of the affected subjects. Moreover, the morbidity often observed in aged people increases the healthcare costs since requires multiple intervention approaches. Among different comorbidities, cognitive decline leading to dementia remains the most invalidating one, because of the lack of efficacious treatments and its hard impact on both healthcare workers and families.

The major cause of dementia among the elderly is Alzheimer's disease (AD) and current estimations predict that the number of people with dementia will increase and triple by 2050 [1]. For this reason, AD is a growing socio-economic problem worldwide and many researchers are focusing their efforts to come up with a cure. AD is a neurodegenerative disease clinically characterized by progressive loss of memory and cognitive functions. The main microscopic pathological features of AD include accumulation of intracellular fibrillary tangles (NFT) and extracellular senile plaques of β-amyloid peptide (Aβ), chronic neuro-inflammation, synaptic and neuronal loss. From the macroscopic point of view, brain atrophy is consistent with a brain volume and weight decrease [2]. The treatment of AD remains a major challenge because of an incomplete understanding of the events that lead to the selective neurodegeneration typical of Alzheimer's brains. To date, there are not yet effective disease-modifying treatments available, but only therapeutics that slow down the disease progression and control symptoms in the short-term [3,4]. The failure of approved drugs to revert the disease is due to the lack of an early diagnosis for AD: synaptic loss, neuronal loss and brain shrinkage are already significant by the time of symptoms onset and AD diagnosis. There is an enormous global demand for new effective therapies and researchers are investigating different fields. One promising strategy is the cell-based therapy that aims at repopulation and regeneration of neuronal networks in AD brain. Some first clinical trials (NCT01297218 and NCT01696591) concluded that the neuroprotective effect of mesenchymal stem cells intracranial injections (MSCs), frequently reported in AD animal models, was not evident [5], but other trials are ongoing or recruiting patients. Another strategy deeply investigated in the last few years is the immunotherapy targeting Aβ peptide and/or tau protein, the two pathognomonic signs of the disease. Both, Aβ-directed immunization and tau immunotherapy have shown promising results in AD transgenic mouse models [6], but the translation to safe and efficient therapy for humans is still a challenge [7]. In this review we will focus our attention on another approach based on an integrative, complementary and preventive therapy for neurodegenerative disorders with alternative therapeutics, such as nutraceuticals. Natural products have already proven to be a rich source of therapeutics and, by offering a great chemical diversity, they can be of inspiration to create new bioactive compounds. Curcumin is one example of natural product with several properties useful in different clinical fields [8–10], whose antioxidant, Aβ-binding and anti-inflammatory properties make it a potential therapeutic for AD prevention, treatment and diagnostic.

2. Curcumin and its potential in alzheimer's disease

Curcumin is a natural product found in turmeric (*Curcuma longa*), a spice herb member of the ginger family (*Zingiberaceae*). Its chemical name is 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione, also named diferuloylmethane, and it constitutes the 2–5% of the turmeric root. Dried turmeric root was a traditional remedy of Chinese medicine and Ayurvedic indian medicine since ancient times; it was used in the treatment of different pathologies such as skin diseases, wounds, rheumatisms, asthma, allergies, sinusitis, hepatic disorders, intestinal worms, generic inflammation and oxidative stress conditions [11]. Commercially available curcumin is a combination of three molecules, together called curcuminoids. Curcumin is the most representative (60–70%), followed by demethoxycurcumin (DMC, 20–27%) and bisdemethoxycurcumin (BDMC, 10–15%). Curcuminoids differ in potency and efficacy, with no clear supremacy of curcumin over the other two compounds or the whole mixture, thus suggesting that DMC and BDMC significantly contributed to the curcuminoid mixture effectiveness, that is not only due to curcumin. This concept is well reviewed by Ahmed and Gilani [12] in the context of Alzheimer's disease. The authors listed numerous papers that have demonstrated the neuroprotective potential of curcuminoids *in vitro* and *in vivo*, suggesting that curcuminoids act through multiple mechanisms as a mixture, but the contribution of the single components is distinct for activity and potency. For example, curcumin is more effective in inhibiting acetilcholinesterase activity [13], in protecting PC12 cells and HUVEC cells against Aβ [14,15], whereas DMC and BDMC have a stronger antioxidant activity measured with the DPPH (1,1-diphenyl-2-picrylhydrazyl) assay [15] and an higher IC_{50} in the inhibition of Aβ 1–42 fibrillogenesis [16].

Concerning the potential effects of curcumin, in particular in AD, it can prevent AD development thanks to its anti-inflammatory [17–21] and antioxidant properties [22–24]. *In vitro* studies have shown that curcumin can bind Aβ, thus influencing the peptide aggregation and inhibiting fibrils formation and elongation [25]. Moreover, curcumin can enhance Aβ cellular uptake [26] avoiding plaques deposition and preventing cellular insults induced by the peptide [16] and it can also downregulate Aβ production through BACE1 (beta-site APP-cleaving enzyme) expression [27]. *In vivo*, curcumin is able to rescue the distorted neuritic morphology near Aβ plaques [28], to decrease Aβ serum level as well as Aβ burden in the brain, especially in the neocortex and in the hippocampus, and to attenuate inflammation and microglia activation in AD mouse models [29]. Furthermore, curcumin can modulate tau protein processing and phosphorylation avoiding NFTs formation [recently reviewed by [30,31]] (Fig. 1).

Interestingly, curcumin has been shown to have a potential in the diagnostic field. Thanks to its fluorescent properties and Aβ-binding ability, curcumin has been also suggested as a detection agent for the early diagnosis of plaques deposition in the brain [32].

These findings were very promising; however, despite curcumin has a very safe nutraceutical profile with low side-effects and it has been reported to be well tolerated at doses up to 8 g per day in humans, the attempts to use curcumin in a therapeutic field were discouraging because the translation of these studies in clinical trials was not very successful [33]. Moreover, doubts about curcumin potential therapeutic use have recently raised because its classification as a PAINS (pan-assay interference compounds) candidate. PAINS are compounds that show activity in multiple assay, not through a specific interaction with the target, but by interfering with the assay readout. Curcumin has numerous PAINS-type characteristics such as redox activity, metal chelation properties, auto-fluorescence and covalent protein labeling [34]. For this reason, results obtained with methods that can involve PAINS-like behaviors, need to be verified with other techniques to be confirmed. The classification of curcumin as a PAINS candidate is a very recent issue, and published data regarding the bioactivity of curcumin have to be read with a critical view. The limitations in the use of curcumin as therapeutic are represented by its pharmacokinetics profile. Curcumin is nearly insoluble in water, has a short half-life and a low bioavailability [35]. After oral administration it is