



Understanding Benefits of Curcumin on Cognitive Function from Molecular Aspect: A Review

A. A. A. Putri Laksmidewi^{1*} and Richard Suherlim²

¹*Department of Neurology, Division of Neurobehavior, Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia.*

²*Department of Neurology, Neurology Resident, Faculty of Medicine, Udayana University, Sanglah Hospital, Denpasar, Bali, Indonesia.*

Authors' contributions:

This work was carried out in collaboration between both authors. Author AAAPL managed the conception of the review. Author RS managed the literature searches. Author RS wrote the first draft of the manuscript. Author AAAPL help in writing the final manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2021/v19i730340

Editor(s):

(1) Dr. Ashish Anand, G. V. Montgomery Veteran Affairs Medical Center, USA.

Reviewers:

(1) Nene Bi Semi Antheleme, Felix Houphouet-Boigny University, Ivory Coast.

(2) Che Norma Mat Taib, Universiti Putra Malaysia, Malaysia.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/69618>

Mini-review Article

Received 10 April 2021

Accepted 17 June 2021

Published 30 June 2021

ABSTRACT

Cognitive function has a significant impact on individuals' quality of life. Over time, human cognitive function tends to decline. The importance of cognitive function in everyday life has led many researchers to seek alternative treatments to maintain and improve cognitive function. Some studies show that curcumin can improve cognitive function and prevent cognitive decline in humans. This review focuses on the benefits of curcumin on cognitive function and the mechanism of how it works from molecular aspect. According to some studies, one of the factors leading to cognitive decline is chronic low-grade systemic inflammation. This review will focus on antioxidant, anti-inflammatory, neuroprotective effects, and β amyloid aggregation inhibition properties of curcumin that can improve cognitive function or delay cognitive decline. It is important to understand the basic reasons why curcumin can have benefits on cognitive function, this can be seen from the mechanisms that are reflected in the biomolecular aspect.

*Corresponding author: E-mail: putri_laksmidewi@unud.ac.id;

Keywords: Curcumin; alternative; molecular aspect; cognitive function.

INTRODUCTION

The cognitive function consists of some vital domains including attention, executive function, memory, visuospatial, dan language. These domains have a significant impact on individuals' quality of life. According to a study in China by Ren et al. in 2016, the prevalence of people with cognitive decline was 40% higher in people older than 80 years old [1]. It suggests that aging is positively correlate with cognitive decline in human.

Pharmacology treatments to prevent and stop cognitive decline are still very limited. It encourages researchers to struggle looking for novel treatments, that are effective and safe to improve cognitive function, especially in elderly patients and patients with dementia Alzheimer. Among some other alternative medicine, turmeric with its curcumin content is one of the traditional herbs which has a potential benefit on cognitive function.

Some studies show that curcumin can improve cognitive function and prevent cognitive decline in humans. This article aims to review the mechanism of curcumin's benefit on cognitive function based on the molecular aspect.

2. COGNITIVE DECLINE IN POPULATION

Cognitive function is essential to maintain a good quality of life as an individual gets older. In the past few decades, human life expectancy has greatly increased, so people get to live longer. Despite its great impact, it makes the number of people with neurodegenerative disorders such as age-related dementia also greatly increased. In 2014 there were 5,2 million patients diagnosed with Alzheimer dementia, this number is estimated to be 13,8 million in 2050 if there are no significant actions done to slow the trend [2].

Studies conducted on older people show that the cognitive declining process associated with aging in healthy individuals take a very long time. This process occurs over a span of decades. It was influenced by various factors related to the individual such as education level, social economy, and living environment [3]. Nutrition is also a substantial factor that needed to be considered has a significant role in the process of cognitive decline in old age.

A study in China in 2016 demonstrates that the prevalence of dementia in South Asia is

significantly lower compared with the prevalence of other regions. It was thought to be associated with high curry consumption in South Asia. Curry use turmeric as one of the main ingredients which contain curcumin, a substance to be expected has benefit on cognitive function. In 2006, there was a study conducted in Singapore that also verify that individuals age between 60-93 years old who frequently eat curry have a better MMSE score compared with those who does not eat curry [4].

3. CURCUMIN PHARMACOLOGY

Curcumin is the main bioactive component of turmeric (*Curcuma longa L*) which is a member of *Zingiberaceae* family [5]. Turmeric is widely found in Indonesia; it grows well in lowlands and highlands. Balinese people use turmeric as one of their main cooking spices. Turmeric is used in many dishes such as traditional betutu chicken, sate lilit, and as a seasoning in grilled fish or many other recipes. Indonesian people also have traditional yellow rice (nasi kuning) that often served in celebration. (Fig. 1) The yellow color was obtained from turmeric.

Most of the absorbed curcumin is metabolized in the liver and intestines. Curcumin reaches peak serum level after 1-2 hours post oral intake and gradually decreasing in 12 hours [6]. Majority of curcumin is excreted through the biliary system and passed with stool, only a small part is excreted through urine [7].

There are some experimental studies using curcumin on human to assess its effect on cognitive function. The results obtained are still not conclusive, there are many confounding factors that influence the results and make them inconsistent such as the difference in the age of participants, the characteristics of comorbidities, duration of the studies, and dosage of curcumin used in the studies. However, most of those results stated that curcumin was beneficial to improve cognitive function [8-12].

4. CURCUMIN MOLECULAR ASPECT

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a lipophilic polyphenol. Curcumin can pass blood brain barrier because it has high lipid solubility and hydrophobic nature. Curcumin has a high level of pleiotropic activity including antiinflammation,

antioxidant, antimicrobial, and antiangiogenetic. According to some studies, one of the factors leading to cognitive decline is chronic low-grade systemic inflammation [4,5,13]. This review will focus on the antiinflammation and antioxidant properties of curcumin that can improve cognitive function or delay cognitive decline.

Curcumin has a strong antioxidant effect comparable to vitamin C or vitamin E. Curcumin is a scavenger of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). Curcumin can also inhibit oxidative damage such as lipid peroxidation in various experimental animals. This substance can also activate the enzymatic antioxidant responses by activating the genes encoding superoxide dismutase, catalase, glutathione peroxidase and glutathione transferase [13].

In the human body, there is an endogenous antioxidant system called KEAP1-NRF2-ARE that activated by a mild-moderate level of free radicals [4]. In a normal state, NRF2 is inactive because it was bonded to KEAP1. Mild-moderate stress condition disconnect the bond between *Kelch-like-ECH-associated protein 1* (KEAP 1) and *nuclear factor E2-related factor 2* (NRF2) thereby releasing phosphorylated NRF2. This phosphorylated NRF2 then undergoes nuclear translocation and induces transcription of the *antioxidant response element* (ARE). *Antioxidant response elements* will increase the synthesis of antioxidant enzymes, one of which is *glutamate cysteine ligase catalytic subunit* (GCLC). Glutamate cysteine ligase catalytic is an enzyme that plays a role in the synthesis of glutathione (GSH). Decreased levels of GSH are associated

with the emergence of neurodegenerative diseases such as Alzheimer's dementia and Parkinson's disease in the elderly [4,14].

The strong antioxidant effect of curcumin is based on its molecular structure as it can binds to KEAP1. Curcumin acts as an electrophile and binds to KEAP1 via a sulfhydryl group which causes cysteine modification and stabilizes NRF2. Stabilization and separation of NRF2 will induce the ARE phase II antioxidant gene, which will activate an enzyme that synthesizes GSH to prevent neurodegenerative diseases and cognitive decline [4]. Curcumin also activates ARE gene expression via PKC δ and P38 [14].

The antiinflammation effect of curcumin is obtained from its potency to suppress proinflammatory transcription factors like nuclear factor kB (NF-kB), protein-1 activator, and transcription activator protein 3 (SAT3). These transcription factors have a substantial role in mediating inflammation response through modulation of inflammatory cytokines production [5].

Nuclear factor kB (NF-kB) is known as a regulator of the inflammatory process and is very sensitive to oxidative stimuli. This system slowly loses its integrity as people get older, resulting in a continuous transcription of NF-kB which induces low-grade chronic systemic inflammation. It induces the production of some proinflammatory proteins like TNF- α , IL-1 β , and IL-6. Studies show that proinflammation cytokines level like TNF- α , IL-1 β , dan IL-6 in the central and peripheral nervous system are higher in older people [4].



Fig. 1. Turmeric and Indonesian traditional yellow rice

Table 1. Curcumin Effect on Cognitive Function Experimental Studies on Human [8-12]

No	Researchers	Number of Participants (people)	Age of Participants (years old)	Participants Characteristic	Duration and Type of Study	Curcumin Dose	Results
1	Smith SRR, et al. [8]	160	40-90	Without cognitive impairment	12 months; RCT double-blind	Biocurcumax 1500 mg/day	Curcumin delays cognitive decline
2	Cox, et al. [9]	60	65-80	Without cognitive impairment	4 weeks; RCT double-blind	Longvida 400 mg/day	Curcumin improves working memory and sustained attention after 1 hour and 4 weeks consumption
3	Small GW, et al. [10]	40	50-90	Without cognitive impairment	18 months; RCT double-blind	Theracurmin 2x90 mg	Curcumin improves cognitive function
4	Parker JRS, et al. [11]	39	45-74	Without cognitive impairment	12 weeks; RCT	Longvida 2000 mg /day	Curcumin does not improve cognitive function
5	Kucukgoncu, et al. [12]	12	30-50	Schizophrenia	8 weeks; pilot study	Curcumin 180 mg/day	Curcumin improves working memory
6	Baum, et al. [9]	34	> 50	Probable or possible alzheimer dementia	6 months; RCT double-blind	Curcumin 1 gr or 4 gr/day	There is no difference between case and control group

*RCT : Randomized Controlled Trial

The β -diketone group in the molecular structure of curcumin is a Michael's reaction acceptor, when it binds to an inhibitor of nuclear factor kappa-B kinase subunit B (IKK β), so it will inhibit the phosphorylation process IKK subunit of NF-kB and inhibit NF-kB nuclear translocation. Therefore, it will stop the proinflammatory production process through this NF-kB mechanism. Curcumin is also associated with inhibiting NF-kB through its effect on preventing IL-1 β induced IKK phosphorylation by disrupting IKK activity [4,15].

Curcumin also inhibits the expression of glycoprotein 130 which plays a role in the signaling effect of IL-6. Interleukin-6 will induce the production of C reactive protein (CRP) in hepatocytes, which is a biomarker of systemic inflammation. Increased levels of CRP and IL-6 are associated with cognitive decline in obesity and aging [4].

In addition to its anti-inflammatory and antioxidant properties, the mechanism of action of curcumin on neurocognition and neuroprotective effects is still not fully understood. It is suspected that curcumin can

modulate the release of certain neurotransmitters such as brain derived neurotrophic factor (BDNF). Brain derived neurotrophic factor is a widespread neurotrophin in the nervous system that facilitates neurogenesis, synaptogenesis, neuroprotection, neuro-regeneration, synaptic plasticity, neuron survival, neuron growth, memory formation, retention, and retrieval in the frontal cortex and hippocampus. Low BDNF level is associated with various neuropsychiatric diseases and poor memory [16].

The neuroprotective effects of curcumin are acquired through various mechanisms in the central nervous system, which including antioxidant, anti-inflammatory, and BDNF-enhancing properties. Curcumin increases cyclic adenosine monophosphate (cAMP) levels and activates cellular transduction pathways via extracellular signal-regulated kinases (ERKs) and p38 kinase, which are known to be involved in BDNF production, regulation of neuronal plasticity, and stress response. Apart from that, curcumin also increases serotonin. Serotonin has an important role in memory, sleep regulation, learning and behavior [16].

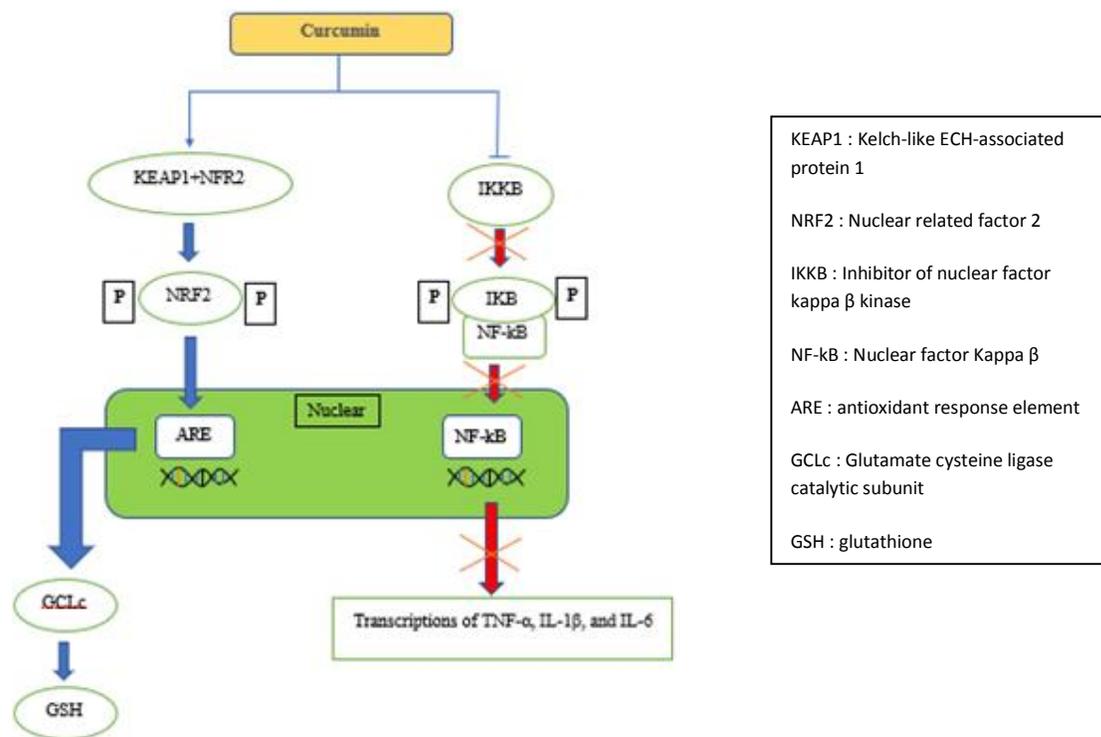


Fig. 2. Curcumin anti-inflammatory and antioxidant pathway

Based on some studies, curcumin can bind to β amyloid ($A\beta$) and tau proteins, as well as inhibit $A\beta$ aggregation. Curcumin contributes to the appearance of a structure similar to the fiber containing salt bridges in $A\beta_{40}$ aggregate. Curcumin interacts with the $A\beta_{40}$ aggregate and changes its toxicity, thereby reducing the toxicity of $A\beta$ on Alzheimer's disease [8,13]. This emphasizes curcumin's benefits on delaying cognitive decline.

CONCLUSION

Curcumin is believed to have the benefit of improving cognitive function because it has antioxidant, anti-inflammatory, neuroprotective effects, and inhibits β amyloid aggregation. There are many clinical trials that have been conducted, but these studies have not yet produced a definitive conclusion because there are still variations in the results. It is important to understand the basic reasons why curcumin can have benefits on cognitive function, this can be seen from the mechanisms that are reflected in the biomolecular aspect. Once we understand, it will be easier to determine whether it is appropriate to use curcumin in daily practice with the purpose to delay cognitive decline.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ren L, Zheng Y, Wu L, Gu Y, He Y, Jiang B, et al. Investigation of the prevalence of Cognitive Impairment and its risk factors within the elderly population in Shanghai, China. *Sci Rep [Internet]*. 2018;8(1):1–9. Available from: <http://dx.doi.org/10.1038/s41598-018-21983-w>
2. Murman DL. The Impact of Age on Cognition. *Semin Hear*. 2015;36(3):111–21.
3. Hayden KM, Reed BR, Manly JJ, Tommet D, Pietrzak RH, Chelune GJ, et al. Cognitive decline in the elderly: An analysis of population heterogeneity. *Age Ageing*. 2011;40(6):684–9.
4. Sarker MR, Franks SF. Efficacy of curcumin for age-associated cognitive decline: a narrative review of preclinical and clinical studies. *GeroScience*. 2018;40(2):73–95.
5. Ross SM. Curcuma longa (Theracumin®): A Bioavailable Form of Curcumin and Its Cognitive Benefits. *Holist Nurs Pract*. 2018;32(4):217–20.
6. Cas MD, Ghidoni R. Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients*. 2019;11(9):1–14.
7. 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;46(1):2–18.
8. Rainey-Smith SR, Brown BM, Sohrabi HR, Shah T, Goozee KG, Gupta VB, et al. Curcumin and cognition: A randomised, placebo-controlled, double-blind study of community-dwelling older adults. *Br J Nutr*. 2016;115(12):2106–13.
9. Voulgaropoulou SD, van Amelsvoort TAMJ, Prickaerts J, Vingerhoets C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Res*. 2019;1725(September).
10. Small GW, Siddarth P, Li Z, Miller KJ, Ercoli L, Emerson ND, et al. Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial. *Am J Geriatr Psychiatry*. 2018;26(3):266–77.
11. Santos-Parker JR, Lubieniecki KL, Rossman MJ, Van Ark HJ, Bassett CJ, Strahler TR, et al. Curcumin supplementation and motor-cognitive function in healthy middle-aged and older adults. *Nutr Heal Aging*. 2018;4(4):323–33.
12. Kocukgoncu S, Guloksuz S, dan Tek C. Effects of Curcumin on Cognitive Functioning and Inflammatory State in Schizophrenia: A Double-Blind, Placebo-Controlled Pilot Trial. *Journal of Clinical Psychopharmacology*. 2019; 39 (2): 182-3.
13. Liczbiński P, Michałowicz J, Bukowska B. Molecular mechanism of curcumin action in signaling pathways: Review of the latest

- research. Phyther Res. 2020;34(8):1992–2005.
14. Shishodia S. Molecular mechanisms of curcumin action: Gene expression. BioFactors. 2013;39(1):37–55.
15. Joe B, Vijaykumar M, Lokesh BR. Biological Properties of Curcumin-Cellular and Molecular Mechanisms of Action. Crit Rev Food Sci Nutr. 2004;44(2):97–111.
16. Sarraf P, Parohan M, Javanbakht MH, Ranji-Burachaloo S, Djalali M. Short-term curcumin supplementation enhances serum brain-derived neurotrophic factor in adult men and women: a systematic review and dose–response meta-analysis of randomized controlled trials. Nutr Res. 2019;69:1–8.

© 2021 Laksmidewi and Suherlim; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/69618>