THE EFFECT OF THE BIOACTIVE COMPOUND CURCUMIN ON CONDITIONS AFTER ISCHEMIC STROKE: A SYSTEMATIC REVIEW

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ABSTRACT

Ischemic stroke is a common degenerative disease in Indonesia caused by interrupted or restricted blood supply to part of brain, preventing it from getting oxygen and nutrients. Without sufficient blood supply, brain cells begin to die. Various treatments for ischemic stroke patients have been developed and implemented, but are still ineffective in treating or preventing brain damage. Curcumin is one of the bioactive compounds which mostly found in turmeric which is one of the main spices resource in Indonesia that has many benefits as a medicine. People have been making use of curcumin as a medicine for various diseases, one of which is stroke. Therefore, this systematic review analysed qualitatively the effect of curcumin on the brain condition after ischemic stroke. The method used in this study was a systematic review of 8 databases in the last 10 years, from 2012 to August 2022. Study included was only experimental study on rats. Based on 19 articles gathered, there was a decrement in ROS, COX-2, iNOS, NF-kB, TNF-α, IL-6, Bax, Caspase-9, Caspase-3, ICAM-1, MMP-9, neurological deficit score, and an increment in BCL-2, glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) in rats receiving curcumin intervention either orally or intravenously. Curcumin affects the ischemic brain in a number of ways, namely as an antioxidant, anti-inflammatory, anti-apoptotic, Blood-Brain-Barrier (BBB) protector, increasing neurogenesis, and reducing neurological deficits. It is concluded that curcumin has an elevating effect in protecting brain condition after an ischemic stroke.

Keywords: curcumin, ischemic stroke, brain ischemia, neurogenesis, deficit neurologic

INTRODUCTION

Stroke is a condition where an artery transporting blood to the brain ruptured or blocked, causing brain cells deprived from oxygen and died (WHO, 2020a). Stroke is the second predictor causing death and the third predictor to disability around the world (Feigin et al., 2017). Every year more than 15 million people suffering from stroke, with a third ended in death and a third ended with permanent disability (WHO, 2011). The prevalence of stroke in Indonesia increases from 7 per mill in 2013 to 10.9 per mill in 2018 (Kementrian Kesehatan, 2018).

Stroke can be divided into three categories based on the types of stroke, namely transient ischemic attack (TIA), ischemic stroke and hemorrhagic stroke (WHO, 2020a). Around 80% of strokes occurred are ischemic in nature (Krishnamurthi et al., 2013). Ischemic stroke happen when blood flow blocked by a blood clot which occur in the brain. These blood clots usually occur due to atherosclerosis or thickening of the walls of blood vessels due to accumulated fat (WHO, 2020b). These clots then block the supply of oxygen and nutrients to brain cells, causing hypoxia, free radicals and inflammation (Jia et al., n.d.; Oh et al., 2019). Ischemic stroke leads to many complications like memory loss, motor dysfunction, fatigue, mental state change, and Alzheimer (Béjot et al., 2016). In addition, the incidence of ischemic stroke is associated with continuous treatment, inflicting unfavorable consequences in terms of socio-economic to a country (Béjot et al., 2016; Rusek & Czuczwar, 2021). Death due to stroke in young adults are currently starting to increase significantly, especially in developing countries in which the incidence of stroke is indeed common (Feigin et al., 2017).

Ischemic stroke usually treated by using thrombolysis and thrombectomy therapy which aim to restore blood flow in the brain, protect tissue and maintain brain function (Marler, 1995; Patel et al., 2020; Wang et al., 2023). However, these

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treatments are limited in that their effectiveness depends on time after the event (Cassella & Jagoda, 2017). In addition, in control of free radical and oxygen level before and after thrombolysis is very crucial to save patient (Shi et al., 2020). Currently, there are no treatment that can prevent, delay/stop neurodegeneration that occur in ischemic stroke patient (Briggs et al., 2016).

Curcumin is an active compound in turmeric obtained from *Curcuma longa Linn* powder (Zhao et al., 2010). Curcumin may useful as a treatment for ischemic stroke that causes brain cell death and clinical deficits (Dirnagl et al., 1999; Lapchak & Araujo, 2007). Evidence shows that inflammation, oxidative damage and misfolded protein amyloid are the main factors of brain damage in ischemic stroke (Pluta et al., 2019; Pluta & Ułamek-Kozioł, 2021). Curcumin plays a role in 2 main key activities in stopping neural degeneration in ischemic stroke, namely free radicals production and immune system activation (Lapchak, 2010; Moskowitz et al., 2010). Research in patients in hospital show that there were no severe side effects from curcumin use but some patients develop mild diarrhea and nausea (Chh-Hung & Ann-Lii, 2007).

Curcumin is a bioactive compound with a potential to be a treatment for ischemic strokes and an interesting subject to be studied further. Thus, this paper aim to review various literatures with a narrative synthesis in interpreting some of the latest empirical literature regarding to the effect of curcumin on ischemic stroke.

METHODS

Data Sources and Article Search Methods

This study was systematic review research that would answer the question: "How is the effect of curcumin on ischemic stroke?" Search articles using 8 databases: Pubmed, Medline, Research Gate, Science Direct, Springer Link, Proquest, EbscoHost, and Google scholar. Keywords use to search articles were "Curcumin, stroke, ischemic stroke, ischemic brain, brain damage, and neuroprotection".

Inclusion and Exclusion Criteria

The criteria for articles excluded in this study included articles with irrelevant topics, articles not available for open access, the year of publication exceeding ten years, the type of document in the form of review articles, notes or letters, and poor methodology. Articles that pass the exclusion process would be selected with inclusion criteria in the form of duplication, articles must be in English, experimental research, discussing ischemic stroke, and the experimental animals used are rats. The study used was only an experiment in mice because the application of the research in humans is still very limited. Additionally, homogeneous study participants may minimize the possibility of bias due to species differences.

Based on the selection, 37 articles were obtained that met the criteria. After further review, 19 articles were found suitable for this study because the complete article content and research reviewed curcumin's neuroprotection effects, including its effect as antioxidant, anti-inflammatory, anti-apoptotic, and BBB protectant.

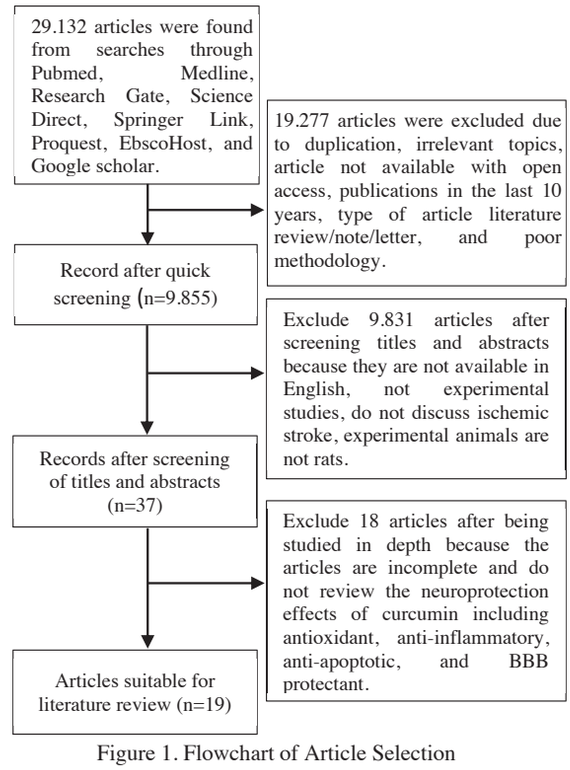

Figure 1. Flowchart of Article Selection

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Table 1. Summary of Experimental Study of Curcumin in Mice

No	Study	Method	Dosage	Duration (week/s)	Result	Outcome	Reference
1	An experimental study using Female Sprague Dawley rats	Rats divided into five groups: normal group, untreated ischemic stroke (CIR) group, ischemic group with empty PLGA-PEG, FC (curcumin free) 5 mg/kg body weight, and NC (nano-encapsulated curcumin) 5 mg/kg body weight, containing 200 g of curcumin, administered orally	FC: 5 mg/kg body weight, NC: 5 mg/kg body weight, contains 200 g of curcumin		NC treatment group provided better neuroprotection by lowering ROS and preventing apoptosis than other groups ($p<0.01$) NC treatment group significantly decreased COX-2 and iNOS expression ($p<0.05$) NC treatment group significantly prevented the activation of caspase 3 and 9 NC treatment group significantly decreased lipid peroxidation ($p<0.05$) Nano-Curcumin (NC) is more effective in preventing cerebral ischemia than the Free-Curcumin (FC) form	Antioxidant Anti-apoptosis anti-inflammatory	(Mukherjee et al., 2019)
2	**An experimental study using mice**	Mice divided into three groups, namely the negative control group, the treatment group induced ischemic stroke using the middle cerebral artery occlusion (MCAO) and vehicle (VEH) methods, and the ischemic stroke group given curcumin (100, 200, 300, and 400 mg/Kg) through injection.	(100, 200, 300, and 400 mg/kg)		Curcumin group had a significant decrement in infarct volume compared to the VEH group ($p<0.005$) A dose of curcumin 300 mg/kg had the most significant effect on reducing infarct volume Curcumin-treated mice significantly inhibited increased expression of Bax, Caspase-3, and decreased expression of Bcl-2 (Anti-apoptotic)	Anti-apoptosis	(Xie et al., 2018)
3	An experimental study using Male SHR rats	SHR rats divided into control group (saline) and the curcumin group (100 mg/kg/day)	100 mg/kg body weight /day	Four weeks	Treatment group given curcumin significantly slowed the occurrence of ischemic stroke ($p<0.05$) Curcumin can significantly reduce the value of ROS in treatment group ($p<0.05$) Curcumin increases plasma nitrate/nitrite levels and plasma SOD activity	Antioxidant	(Lan et al., 2018)
4	An experimental study using Spraguee Dawley rats	Rats divided into four treatment groups: vehicle + sham, curcumin (50 mg/kg) + sham, vehicle + MCAO, and curcumin (50 mg/kg) + MCAO. Each group consisted of 14 rats	50mg/kg body weight		Curcumin lowers the neurological deficit score	BBB Protectant	(Shah et al., 2016)

No	Study	Method	Dosage	Duration (week/s)	Result	Outcome	Reference
5	An experimental study using Male Wistar rats	Rats divided into four groups: control group (SO), ischemic group not given curcumin, treatment group (curcumin 25 mg/kg BW), and treatment group (curcumin 50 mg/kg BW) orally	25 mg/ body weight, 50 mg/ body weight	a week	COX-2 levels significantly decreased in the treatment group given curcumin 25 mg and 50 mg TNF-α levels in the treatment group given curcumin 50 mg were significantly lower than in the ischemic group not given curcumin	anti-inflammatory	(Alcântara et al., 2017)
6	An experimental study using male Sprague-Dawley rats	Mice divided into six groups: sham group, I/R group, Curcumin group, Curcumin + I/R group, I/R + siRNA group, and I/R + scrRNA group. Each group consisted of 8 mice. Curcumin is given by injection	300 mg/kg body weight	a week	Curcumin effectively reduced ROS and MDA levels in the treatment group ($p<0.05$) compared to the ischemic group	Antioxidant	(Jia et al., 2017)
7	An experimental study using Male Sprague-Dawley rats	Mice divided into five groups: untreated sham-operated, PBS-treated MCAO, nave Ex-treated MCAO, Free-cur treated MCAO, and Ex-cured (exosomes) treated MCAO	10 µg/mL curcumin intravenous injection		Curcumin significantly decreased mitochondria-induced apoptosis Curcumin-treated mice inhibited Bax expression and significantly decreased Caspase-3, and caspase-9 Curcumin significantly reduces ROS levels Curcumin can significantly reduce tight junction protein	Anti-apoptosis Antioxidant BBB Protectant	(He et al., 2020)
8	An experimental study using Male SHR rats	Rats divided into four groups: sham group, ischemic/reperfusion group, solvent (dimethyl sulfoxide) control group, and curcumin treatment group	100 mg/kg	a week	The group given curcumin experienced a significant decrease in retinal cell apoptosis	Anti-apoptosis	(Wang et al., 2017)
9	An experimental study using female Wistar Hannover rats	Rats divided into five groups: (1) curcumin group orally administered before ischemia and intraperitoneally after ischemia, (2) curcumin group intraperitoneally after ischemia, (3) curcumin group orally before ischemia, (4) ischemic group, (5) sham group	300 mg/kg BW Oral and intraperitoneal	Three weeks	Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) significantly higher in the curcumin I group ($p<0.05$) IL-6 and TNF-α significantly lower in the curcumin-treated group compared to the ischemic group ($p<0.05$) The treatment group given curcumin had a significantly lower apoptotic index compared to non curcumin group	Antioxidant anti-inflammatory Anti-apoptosis	(Altinay et al., 2017)

No	Study	Method	Dosage	Duration (week/s)	Result	Outcome	Reference
10	An experimental study using male Sprague–Dawley rats	Mice divided into three groups: CI (cerebral ischemic) given curcumin, vehicle group, and sham. Curcumin was started an hour after stroke and continued once a day for seven days	300 mg/kg by intraperitoneal injection	a week	• Curcumin can significantly reduce the post-stroke neurologic deficit	Reduce neurological deficit	(Liu et al., 2016)
11	An experimental study using male Sprague-Dawley (SD) rats	Rats divided into three groups: the sham group, the vehicle group, and the curcumin-treated group. Curcumin was administered intraperitoneally 30 minutes before surgery MCAO/R	300 mg/kg BW	1 week	Curcumin protects mice from impaired BBB permeability due to ischemic damage The group given curcumin before surgery significantly decreased MMP-9 and NF-κB levels	BBB protectant anti-inflammatory	(Wu et al., 2021)
12	An experimental study using male Wistar rats	Rats divided into four groups: the sham group was given a vehicle, the sham group was given curcumin, the ischemic stroke group was given a vehicle, and the ischemic stroke group was given curcumin	300 mg/kg BW by intraperitoneal injection		In the curcumin-treated MCAO group, infarct size decreased significantly The ischemic group treated with curcumin improved the neurological deficit score Curcumin significantly decreased ICAM 1 . expression Curcumin significantly decreased MMP-9 expression Curcumin significantly inhibits caspase-3 expression Curcumin reduces NF-κB expression	Reduce neurological deficit BBB Protectant Anti-apoptosis Anti-inflammatory	(Li et al., 2017)
13	An experimental study using adult male C57BL/6 mice	Mice divided into three groups: sham, ICH + vehicle, and ICH + curcumin	100 mg/kg		Curcumin significantly improves neurological scores	Reduce neurological deficit	(Liu et al., 2016)
14	An experimental study using male C57BL/6 mice	Mice assigned to 4 groups: sham, CI (cerebral ischemic), curcumin treatment 1, and curcumin treatment 2 + DKK1 (a blocker of Wnt receptor, 200 ng/d, icv)	Curcumin treatment 1 = 50, 100 mg/kg/day Curcumin treatment 2 = 100 mg/kg/day		Curcumin increases proteins expression involved in neurogenesis Significantly decreased T lymphocytes in the brain. Reduces T lymphocytes infiltration to the brain	Neurogenesis	(X. Yang et al., 2020)

No	Study	Method	Dosage	Duration (week/s)	Result	Outcome	Reference
15	An experimental study using male Sprague-Dawley rats	Experiments were carried out in 2 groups: MCAO (middle cerebral artery occlusion) and MCAO + CCM (curcumin)	50 mg/kg		Curcumin reduces TNF-α and IL-6 in brain Increase levels of Bcl-2 and reduce levels of Ac-p53 and Bax expression	Anti-apoptosis Anti-inflammatory	(Miao et al., 2016)
16	An experimental study using adult male Swiss albino mice	Mice divided into four groups with ten rats each: 1) sham, 2) control (stroke group), 3) vehicle, and 4) CUR treatment group.	100 mg/kg		IL-6, NF-κB, MCP-1, and Bax levels lower in CUR group than in the control group An increase in BCL-2 in the CURgroup compared to the control group.	Anti-apoptosis Anti-inflammatory	(Hussein et al., 2020)
17	An experimental study using adult male C57BL/6J mice	Mice divided into three groups: sham, MCAO+vehicle, and MCAO+curcumin (n=8). All mice were used to measure infarct volume, neurobehavioral tests, white matter injuries, and protein expression	150 mg/kg BW	3 weeks	Curcumin inhibits the activation of the NF-κB pathway Curcumin lowers the pyroptosis-related proteins, namely IL-1β	Anti-inflammatory	(Ran et al., 2021)
18	An experimental study using male albino Wistar strain rats	Male albino rats divided into three groups with 6 in each group: 1) sham, 2) MCAO (Middle Cerebral Artery Occlusion), 3) MCAO + CUR	25mg/kg BW		The use of curcumin decreased IL-6 and TNF-α significantly. MMPs decreased significantly after CUR treatment. p53 and Bax proteins decreased significantly Bcl-2 increased on CUR treatment	Anti-apoptosis Anti-inflammatory	(Zhang et al., 2017)
19	An experimental study using adult male mice C57BL/6	Experimental animals divided into three groups: 1) sham, 2) stroke plus vehicle, 3) stroke plus curcumin groups. A total of 80 mice, 23 mice for infarct volume measurement. 42 mice for behavioural tests and immunohistochemical examination. 15 mice for measurement of mRNA or protein expression	150mg/kg immediately after ischemia and 24 hours later	1,5 weeks	Post-treatment curcumin reduced cerebral ischemic damage significantly within three days after dMCAO Curcumin treatment reduces the expression of pro-inflammatory cytokines, including TNF-α and IL-6	Anti-inflammatory	(Liu et al., 2017)

RESULTS AND DISCUSSION

From the results of the literature review, curcumin has a significant effect on ischemic stroke. Curcumin shows a number of roles that affect a brain with ischemic stroke, namely as an antioxidant, anti-apoptotic, anti-inflammatory, BBB protector, neurogenesis, and reducing neurological deficit.

Of the 19 articles reviewed, there were 5 articles which stated that curcumin has a high antioxidant content and can prevent significant nerve cell damage. The antioxidant properties of curcumin are characterized by a decrease in Reactive Oxygen Species (ROS) and lipid peroxidase, and an increase in superoxide dismutase (SOD) observed in this study. There were 10 articles that stated that the bioactive compound curcumin has significant anti-inflammatory properties. This anti-inflammatory property was inferred from the results of the research articles that showed a decrease in iNOS, COX-2, NF-B, TNF-, IL-1β, MMPs, an increase in IL-4, IL-10, and IGF-1. 9 articles showed positive results that curcumin has significant anti-apoptotic properties against brain cells as indicated by a decrease in the enzymes caspase 10, p53 and bax, caspase-9 and an increase in Bcl-2. A total of 3 articles showed the results that curcumin was able to protect blood brain barrier (BBB) significantly by reducing degradation of tight junctions, production of MMP-9 and ICAM-1. In addition, 3 articles stated that curcumin can reduce neurological deficits and 1 article stated that curcumin has a positive effect on neurogenesis.

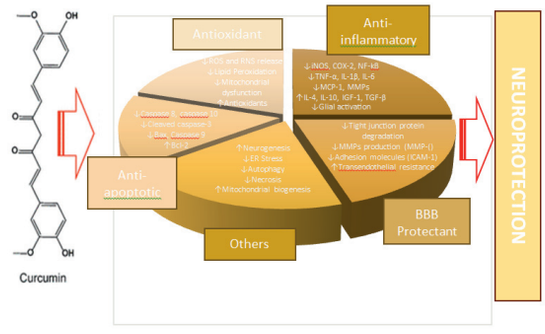

Figure 2. Curcumin Roles in Ischemic Stroke

Ischemic stroke is a condition of blood flow decrement caused by blockage due to embolism or thrombus in the blood vessels of the brain. Blockage of cerebral blood vessels leads to oxygen and glucose deficiency which causes an imbalance of ion in the cells. This condition causes an increase in glutamate secretion, triggering toxic to neuron cells or commonly called excitotoxic which results in cell damage.

Curcumin is a bioactive compound that can prevent damage to neuron cells as a result of ischemic stroke. It has high antioxidant properties, anti-inflammatory properties, anti-apoptosis, and is able to protect the blood brain barrier (BBB). In addition, many studies showed that curcumin plays role in promoting neurogenesis and as neuroprotection useful for repairing brain cells in ischemic stroke patients (Li et al., 2016; Li et al., 2015; Rusek & Czuczwar, 2021; Ułamek-Kozioł et al., 2020).

Curcumin as an antioxidant

Ischemic stroke can trigger an increase in level of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) which increasing oxidative stress in brain cells, thereby triggering neurodegeneration (Daniel et al., 2018; Y. Wang et al., 2019). In addition, post-ischemic stroke involved glutamate excitotoxicity, causing calcium overload, resulting in mitochondrial function (Scholpa & Schnellmann, 2017). Mitochondrial dysfunction caused increased oxidative stress, increased catalase and superoxide dismutase (SOD)

enzymes, lipid peroxidation, DNA damage, and cell death (Awad, 2011; Subedi & Gaire, 2021).

Curcumin given after ischemic stroke was significantly able to prevent mitochondrial dysfunction by preventing glutamate excitotoxicity and preventing an increase in intracellular calcium. Curcumin was also able to reduce oxidative stress level by suppressing the number of ROS, RNS, and NO, thereby preventing neurodegeneration in brain nerve cells (Subedi & Gaire, 2021).

Curcumin as inti-inflammation response

Blockage of blood vessels in the brain which then developed into an ischemic stroke caused ion imbalance leading to excess glutamate in nerve cells (Godínez-Rubí et al., 2013). Excessive glutamate triggered an increase in intracellular calcium (Gaire et al., 2014). This condition caused increased iNOS production and pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and MMPs. This condition may exacerbate neuroglial cell activation, causing inflammation (Wang et al., 2019).

Curcumin is a bioactive compound with anti-inflammatory properties that is able to lessen inflammation mediators, such as proinflammatory cytokines, chemokines and adhesion molecules residing in brain. Curcumin can inhibit glial cell activation as well as the production of IL-1β, IL-6, TNF-α, NF-kB, MMPs (Li et al., 2015; Peng et al., 2021; Zhou et al., 2020). It can also significantly boost the production of anti-inflammatory cytokines namely IL-4, IL-10, and IGF-1. Therefore, it has a positive effect in suppressing the risk of brain inflammation due to ischemic stroke (Liu et al., 2017).

Curcumin as anti-apoptosis

Apoptosis is a common condition of cell death that can be caused as ischemic stroke (Uzdensky, 2019). High ROS exposure and excess calcium (Ca^{2+}) cause increased oxidative stress and damage to the mitochondrial membrane so that Bax from the cytosol goes to the mitochondria (Sarmah et al., 2019; Sekerdag et al., 2018). High oxidative stress affected the production of pro-apoptotic proteins and inhibition of anti-apoptotic protein Bcl-2. In addition, high ROS exposure caused damage to mitochondria function and triggered the activity of cytochrome c which released to cytosol and causes the formation of apoptosomes. Apoptosome formation caused procaspase-9 to be activated which triggered procaspase-3 to undergo activation. Activated caspase 3 can affect DNA fragmentation (Bavarsad et al., 2019). This is what then causes brain cell death.

Curcumin is a bioactive compound that can prevent cell death due to ischemic stroke. Pro-apoptotic proteins, namely Bax, Bak, and Caspase 3 and 9 were significantly inhibited by curcumin (Xie et al., 2018). In addition, curcumin also activated the Bcl-2 and reduced translocation of cytochrome c to cytosol to attenuate brain cell death activity (Li et al., 2017).

Curcumin protects Blood Brain Barrier (BBB)

Blood Brain Barrier (BBB) damage can cause brain cell damage after an ischemic stroke. BBB damage is characterized by tight junction proteins (ZO-1, claudin-5, occludin) damage located in cerebral blood vessels between endothelial cells. Tight junction proteins serve as gateways for immune cells and fluids (Jiang et al., 2018). Ischemic stroke followed by microglial cell activation leads to increased production of proinflammatory cytokines, thereby activating intercellular and vascular cell adhesion molecules (ICAM and VCAM) (Jiang et al., 2018). Adhesion molecules helped in the entry of immune cells into brain nerve cells (Yang et al., 2009). This process caused the degradation of the binding of tight junction proteins causing the BBB to become separated and edema to occur in brain cells.

Curcumin can provide protection to Blood Brain Barrier by increasing protein of tight junction. Curcumin also significantly decreased the enzyme matrix metalloproteinase (MMP) which was proteolytic towards the basement membrane (Dang et al., 2013; Wang et al., 2019), as well as VCAM and ICAM adhesion molecules, thereby preventing leukocyte infiltration in brain cells (Wicha et al., 2020). Decreased expression of VCAM and ICAM can also prevent inflammation of cerebral blood vessels thereby reducing the rate of brain injury (Funk et al., 2013). Thus, curcumin effectively has neuroprotective properties after ischemic stroke.

Curcumin improves neurogenesis

Administration of curcumin can significantly improve neurogenesis in brain hippocampal cells (Sun et al., 2020). Curcumin is neuroprotective and has a high antioxidant content. Increased hippocampal neurogenesis is evidenced by the ability of curcumin to initiate continuous proliferation of Neural Stem Cells (NSC) and form new neurons (Sun et al., 2020). The role of curcumin in enhancing neurogenesis consisted of various ways including activating the Wnt/β-catenin signaling pathway. In addition, curcumin can also increase gene expression that play a role in cell proliferation (nesin, pax6, and reelin), neuron differentiation (Stat3, neuregulin, neurogenin, neuroD1, and neuroligin), and can activate extracellular signal regulated kinases and p38 kinases (Tiwari et al., 2014; X. Yang et al., 2020).

Encapsulated curcumin nanoparticles were more effective in the neurogenesis process compared to directly-consumed curcumin because curcumin has low bioavailability in brain cells (Tiwari et al., 2014). The administration of 30 mg/kg body weight curcumin showed positive results for the optimal neurogenesis process (Sun et al., 2020).

Curcumin reduces neurological deficits

Ischemic stroke is a condition of blockage of blood vessels in the brain that can cause neurological function disorders (Luo & Rubinsztein, 2013). Neurological deficits were caused by decreased neuronal function due to inflammation, high level of ROS, and apoptosis in brain nerve cells (Joshi & Johnson, 2012). Curcumin has significant anti-inflammatory, antiapoptotic, and antioxidant properties, thus it can reduce neuronal dysfunction in the brain which can prevent a more severe functional decline in the body.

Based on this review of 19 articles, the main finding is that curcumin has an absolute effect to post-ischemic stroke brain conditions. Curcumin is a bioactive compound with significant anti-inflammatory, antiapoptotic, and antioxidant properties. This results in agree to previous studies stating curcumin as a traditional medicine has anti-inflammatory, anti-infective, antitumor, antibacterial, and antioxidant properties, and is believed to have a positive effect on ischemic stroke (Goozee et al., 2016; Hagl et al., 2015; Manca et al., 2015; Park et al., 2021; Rusek & Czuczwar, 2021). The anti-inflammatory, anti-oxidant and neuroprotective properties contained in curcumin help control ischemic stroke by preventing more severe brain impact (Ułamek-Kozioł et al., 2020). Limitation of this study are this article did not investigate the side effects of curcumin or the specific dose amount that can be beneficial in stroke circumstances. More research is needed to determine the appropriate dosage for ischemic stroke patients.

CONCLUSIONS

The bioactive compound curcumin has a positive effect in maintaining post-ischemic stroke conditions in rats. The drawback of this research is that it does not carry out a quantitative meta-analysis. In the future, it is hoped that clinical trial studies in humans can be carried out so that the effective dose and side effects of curcumin can be determined.

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REFERENCES

Alcântara, G. de F. T., Simões-Neto, E., da Cruz, G. M. P., Nobre, M. E. P., Neves, K. R. T., de Andrade, G. M., Brito, G. A. de C., & Viana, G. S. de B. (2017). Curcumin reverses neurochemical, histological and immuno-histochemical alterations in the model of global brain ischemia. *Journal of Traditional and Complementary Medicine*, *7*(1), 14–23. https://doi.org/10.1016/j.jtcme.2015.10.001

Altinay, S., Cabalar, M., Isler, C., Yildirim, F., Celik, D. S., Zengi, O., Tas, A., & Gulcubuk, A. (2017). Is chronic curcumin supplementation neuroprotective against ischemia for antioxidant activity, neurological deficit, or neuronal apoptosis in an experimental stroke model? *Turkish Neurosurgery*, *27*(4), 537–545. https://doi.org/10.5137/1019-5149.JTN.17405-16.0

Awad, A. S. (2011). Effect of Combined Treatment With Curcumin and Candesartan on Ischemic Brain Damage in Mice. *Journal of Stroke and Cerebrovascular Diseases*, *20*(6), 541–548. https://doi.org/10.1016/J.JSTROKECEREBROVASDIS.2010.03.008

Bavarsad, K., Barreto, G. E., Hadjzadeh, M. A. R., & Sahebkar, A. (2019). Protective Effects of Curcumin Against Ischemia-Reperfusion Injury in the Nervous System. *Molecular Neurobiology*, *56*(2), 1391–1404. https://doi.org/10.1007/s12035-018-1169-7

Béjot, Y., Daubail, B., & Giroud, M. (2016). Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. *Revue Neurologique*, *172*(1), 59–68. https://doi.org/10.1016/j.neurol.2015.07.013

Briggs, R., Kennelly, S. P., & O'Neill, D. (2016). Drug treatments in Alzheimer's disease. *Clinical Medicine, Journal of the Royal College of Physicians of London*, *16*(3), 247–253. https://doi.org/10.7861/clinmedicine.16-3-247

Cassella, C. R., & Jagoda, A. (2017). Ischemic Stroke: Advances in Diagnosis and Management. *Emergency Medicine Clinics of North America*, *35*(4), 911–930. https://doi.org/10.1016/J.EMC.2017.07.007

Chh-Hung, H., & Ann-Lii, C. (2007). Clinical studies with curcumin. *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*, *12*(579), 471–480. https://pubmed.ncbi.nlm.nih.gov/17569225/

Dang, Q. B., Lapergue, B., Tran-dinh, A., Diallo, D., Moreno, J., Mazighi, M., Romero, I. A., Weksler, B., Michel, J., Amarenco, P., & Meilhac, O. (2013). *High-density lipoproteins limit neutrophil-induced damage to the blood – brain barrier in vitro*. *August 2012*, 575–582. https://doi.org/10.1038/jcbfm.2012.206

Daniel, B. J., Balla, J., & Bereczki, D. (2018). Heme Oxygenase-1: Clinical Relevance in Ischemic Stroke. *Current Pharmaceutical Design*, *24*(20), 2229. https://doi.org/10.2174/1381612824666180717101104

Dirnagl, U., Iadecola, C., & Moskowitz, M. A. (1999). Pathobiology of ischaemic stroke: an integrated view. *Trends in Neurosciences*, *22*(9), 391–397. https://doi.org/10.1016/S0166-2236(99)01401-0

Feigin, V. L., Norrving, B., & Mensah, G. A. (2017). Global Burden of Stroke. *Circulation Research*, *120*(3), 439–448. https://doi.org/10.1161/CIRCRESAHA.116.308413

Funk, J. L., Frye, J. B., Davis-Gorman, G., Spera, A. L., Bernas, M. J., Witte, M. H., Weinand, M. E., Timmermann, B. N., Mcdonagh, P. F., & Ritter, L. (2013). Curcuminoids Limit Neutrophil-Mediated Reperfusion Injury in Experimental Stroke by Targeting the Endothelium. *Microcirculation*, *20*(6), 544–554. https://doi.org/10.1111/MICC.12054

Gaire, B. P. rasa., Moon, S. K., & Kim, H. (2014). Scutellaria baicalensis in stroke management: nature's blessing in traditional Eastern medicine. *Chinese Journal of Integrative Medicine*, *20*(9), 712–720. https://doi.org/10.1007/s11655-014-1347-9

Godínez-Rubí, M., Rojas-Mayorquín, A. E., & Ortuño-Sahagún, D. (2013). Nitric oxide donors as neuroprotective agents after an ischemic stroke-related inflammatory reaction. *Oxidative Medicine and Cellular Longevity*, *2013*. https://doi.org/10.1155/2013/297357

Goozee, K. G., Shah, T. M., Sohrabi, H. R., Rainey-Smith, S. R., Brown, B., Verdile, G., & Martins, R. N. (2016). Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. *British Journal of Nutrition*, *115*(3), 449–465. https://doi.org/10.1017/S0007114515004687

Hagl, S., Kocher, A., Schiborr, C., Kolesova, N., Frank, J., & Eckert, G. P. (2015). Curcumin micelles improve mitochondrial function in neuronal PC12 cells and brains of NMRI mice - Impact on bioavailability. *Neurochemistry International*, *89*, 234–242. https://doi.org/10.1016/j.neuint.2015.07.026

He, R., Jiang, Y., Shi, Y., Liang, J., & Zhao, L. (2020). Curcumin-laden exosomes target ischemic brain tissue and alleviate cerebral ischemia-reperfusion injury by inhibiting ROS-mediated mitochondrial apoptosis. *Materials Science and Engineering C*, *117*(August), 111314. https://doi.org/10.1016/j.msec.2020.111314

Hussein, Y. A., Al-sarraf, A. M., & Alfalluji, W. L. (2020). Modulation of oxidative stress, inflammatory and apoptotic response by curcumin against cerebral ischemia reperfusion injury in a mouse model. *Interdisciplinary Neurosurgery: Advanced Techniques and Case Management*, *21*(April), 100741. https://doi.org/10.1016/j.inat.2020.100741

Jia, G., Tan, B., Ma, J., Zhang, L., Jin, X., & Li, C. (2017). Prdx6 Upregulation by Curcumin Attenuates Ischemic Oxidative Damage via SP1 in Rats after Stroke. *BioMed*

Research International, 1–9. https://doi.org/10.1155/2017/6597401

Jia, J.-M., Chowdary, P. D., Gao, X., Ci, B., Li, W., Mulgaonkar, A., Plautz, E. J., Hassan, G., Kumar, A., Stowe, A. M., Yang, S.-H., Zhou, W., Sun, X., Cui, B., & Ge, W.-P. (n.d.). *Control of cerebral ischemia with magnetic nanoparticles*. https://doi.org/10.1038/nmeth.4105

Jiang, X., Andjelkovic, A. V., Zhu, L., Yang, T., Bennett, M. V. L., Chen, J., Keep, R. F., & Shi, Y. (2018). Blood-brain barrier dysfunction and recovery after ischemic stroke. *Progress in Neurobiology*, *163–164*, 144–171. https://doi.org/10.1016/J.PNEUROBIO.2017.10.001

Joshi, G., & Johnson, J. A. (2012). The Nrf2-ARE pathway: a valuable therapeutic target for the treatment of neurodegenerative diseases. *Recent Patents on CNS Drug Discovery*, *7*(3), 218–229. https://doi.org/10.2174/157488912803252023

Kementrian Kesehatan. (2018). *Hasil Utama Riset Kesehata Dasar (RISKESDAS)* (Vol. 44, Issue 8). https://doi.org/10.1088/1751-8113/44/8/085201

Lan, C., Chen, X., Zhang, Y., Wang, W., Wang, W. E., Liu, Y., Cai, Y., Ren, H., Zheng, S., Zhou, L., & Zeng, C. (2018). Curcumin prevents strokes in stroke-prone spontaneously hypertensive rats by improving vascular endothelial function. *BMC Cardiovascular Disorders*, *18*(1), 1–10. https://doi.org/10.1186/s12872-018-0768-6

Lapchak, P. A. (2010). A critical assessment of edaravone acute ischemic stroke efficacy trials: Is edaravone an effective neuroprotective therapy? *Expert Opinion on Pharmacotherapy*, *11*(10), 1753–1763. https://doi.org/10.1517/14656566.2010.493558

Lapchak, P. A., & Araujo, D. M. (2007). Advances in ischemic stroke treatment: neuroprotective and combination therapies. *Expert Opinion on Emerging Drugs*, *12*(1), 97–112. https://doi.org/10.1517/14728214.12.1.97

Li, W., Suwanwela, N. C., & Patumraj, S. (2016). Curcumin by down-regulating NF-kB and elevating Nrf2, reduces brain edema and neurological dysfunction after cerebral I/R. *Microvascular Research*, *106*, 117–127. https://doi.org/10.1016/j.mvr.2015.12.008

Li, W., Suwanwela, N. C., & Patumraj, S. (2017). Curcumin prevents Reperfusion injury following ischemic stroke in rats via inhibition of NF-κB, ICAM-1, MMP-9 and caspase-3 expression. *Molecular Medicine Reports*, *16*(4), 4710–4720. https://doi.org/10.3892/mmr.2017.7205

Li, Y., Li, J., Li, S., Li, Y., Wang, X., Liu, B., Fu, Q., & Ma, S. (2015). Curcumin attenuates glutamate neurotoxicity in the hippocampus by suppression of ER stress-associated TXNIP/NLRP3 inflammasome activation in a manner dependent on AMPK. *Toxicology and Applied Pharmacology*, *286*(1), 53–63. https://doi.org/10.1016/j.taap.2015.03.010

Liu, S., Cao, Y., Qu, M., Zhang, Z., Feng, L., Ye, Z., Xiao, M., Hou, S. T., Zheng, R., & Han, Z. (2016). Curcumin protects against stroke and increases level of Notch intracellular domain. *Neurological Research*, *38*(6), 553–559. https://doi.org/10.1080/01616412.2016.1187804

Liu, W., Yuan, J., Zhu, H., Zhang, X., Li, L., Liao, X., Wen, Z., Chen, Y., Feng, H., & Lin, J. (2016). Curcumin reduces brain-infiltrating T lymphocytes after intracerebral hemorrhage in mice. *Neuroscience Letters*, *620*, 74–82. https://doi.org/10.1016/j.neulet.2016.03.047

Liu, Z., Ran, Y., Huang, S., Wen, S., Zhang, W., Liu, X., Ji, Z., Geng, X., Ji, X., Du, H., Leak, R. K., & Hu, X. (2017). Curcumin protects against ischemic stroke by titrating microglia/macrophage polarization. *Frontiers in Aging Neuroscience*, *9*(JUL), 1–10. https://doi.org/10.3389/fnagi.2017.00233

Luo, S., & Rubinsztein, D. C. (2013). BCL2L11/BIM: A novel molecular link between autophagy and apoptosis. *Autophagy*, *9*(1), 104–105. https://doi.org/10.4161/auto.22399

Manca, M. L., Castangia, I., Zaru, M., Nácher, A., Valenti, D., Fernàndez-Busquets, X., Fadda, A. M., & Manconi, M. (2015). Development of curcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring. *Biomaterials*, *71*, 100–109. https://doi.org/10.1016/j.biomaterials.2015.08.034

Marler, J. (1995). *Tissue Plasminogen Activator for Acute Ischemic Stroke*. Journal of Medicine. http://www.nejm.org/doi/pdf/10.1056/NEJM199512143332401

Miao, Y., Zhao, S., Gao, Y., Wang, R., Wu, Q., Wu, H., & Luo, T. (2016). Curcumin pretreatment attenuates inflammation and mitochondrial dysfunction in experimental stroke: The possible role of Sirt1 signaling. *Brain Research Bulletin*, *121*, 9–15. https://doi.org/10.1016/j.brainresbull.2015.11.019

Moskowitz, M. A., Lo, E. H., & Iadecola, C. (2010). The science of stroke: Mechanisms in search of

treatments. *Neuron*, *67*(2), 181–198. https://doi.org/10.1016/j.neuron.2010.07.002

Mukherjee, A., Sarkar, S., Jana, S., Swarnakar, S., & Das, N. (2019). Neuro-protective role of nanocapsulated curcumin against cerebral ischemia-reperfusion induced oxidative injury. *Brain Research*, *1704*(September 2018), 164–173. https://doi.org/10.1016/j.brainres.2018.10.016

Oh, J., Lee, J., Piao, C., Jeong, J. H., & Lee, M. (2019). A self-assembled DNA-nanoparticle with a targeting peptide for hypoxia-inducible gene therapy of ischemic stroke. *Biomaterials Science*, *7*(5), 2174–2190. https://doi.org/10.1039/c8bm01621f

Park, J. Y., Sohn, H. Y., Koh, Y. H., & Jo, C. (2021). Curcumin activates Nrf2 through PKCδ-mediated p62 phosphorylation at Ser351. *Scientific Reports*, *11*(1), 1–12. https://doi.org/10.1038/s41598-021-87225-8

Patel, P., Yavagal, D., & Khandelwal, P. (2020). Hyperacute Management of Ischemic Strokes: JACC Focus Seminar. *Journal of the American College of Cardiology*, *75*(15), 1844–1856. https://doi.org/10.1016/j.jacc.2020.03.006

Peng, Y., Ao, M., Dong, B., Jiang, Y., Yu, L., Chen, Z., Hu, C., & Xu, R. (2021). Anti-inflammatory effects of curcumin in the inflammatory diseases: Status, limitations and countermeasures. *Drug Design, Development and Therapy*, *15*, 4503–4525. https://doi.org/10.2147/DDDT.S327378

Pluta, R., & Ułamek-Kozioł, M. (2021). Genes Associated with Alzheimer's Disease in Post-Ischemic Brain Neurodegeneration. *Cerebral Ischemia*, 31–44. https://doi.org/10.36255/EXONPUBLICATIONS.CEREBRALISCHEMIA.2021.GENES

Pluta, R., Ułamek-Kozioł, M., Januszewski, S., & Czuczwar, S. J. (2019). Amyloid pathology in the brain after ischemia. *Folia Neuropathologica*, *57*(3), 220–226. https://doi.org/10.5114/FN.2019.88450

Ran, Y., Su, W., Gao, F., Ding, Z., Yang, S., Ye, L., Chen, X., Tian, G., Xi, J., & Liu, Z. (2021). Curcumin Ameliorates White Matter Injury after Ischemic Stroke by Inhibiting Microglia/Macrophage Pyroptosis through NF-κ B Suppression and NLRP3 Inflammasome Inhibition. *Oxidative Medicine and Cellular Longevity*, *2021*. https://doi.org/10.1155/2021/1552127

Rusek, M., & Czuczwar, S. J. (2021). The Role of Curcumin in Post-Ischemic Brain. *Cerebral Ischemia*, 149–164. https://doi.org/10.36255/exonpublications.cerebralischemia.2021.curcumin

Sarmah, D., Kaur, H., Saraf, J., Vats, K., Pravalika, K., Wanve, M., Kalia, K., Borah, A., Kumar, A., Wang, X., Yavagal, D. R., Dave, K. R., & Bhattacharya, P. (2019). Mitochondrial Dysfunction in Stroke: Implications of Stem Cell Therapy. *Translational Stroke Research*, *10*(2), 121–136. https://doi.org/10.1007/s12975-018-0642-y

Scholpa, N. E., & Schnellmann, R. G. (2017). Mitochondrial-based therapeutics for the treatment of spinal cord injury: Mitochondrial biogenesis as a potential pharmacological target. *Journal of Pharmacology and Experimental Therapeutics*, *363*(3), 303–313. https://doi.org/10.1124/jpet.117.244806

Sekerdag, E., Solaroglu, I., & Gursoy-Ozdemir, Y. (2018). Cell Death Mechanisms in Stroke and Novel Molecular and Cellular Treatment Options. *Current Neuropharmacology*, *16*(9), 1396–1415. https://doi.org/10.2174/1570159X16666180302115544

Shah, F. A., Gim, S. A., Sung, J. H., Jeon, S. J., Kim, M. O., & Koh, P. O. (2016). Identification of proteins regulated by curcumin in cerebral ischemia. *Journal of Surgical Research*, *201*(1), 141–148. https://doi.org/10.1016/j.jss.2015.10.025

Shi, J., Yu, W., Xu, L., Yin, N., Liu, W., Zhang, K., Liu, J., & Zhang, Z. (2020). Bioinspired Nanosponge for Salvaging Ischemic Stroke via Free Radical Scavenging and Self-Adapted Oxygen Regulating. *Nano Letters*, *20*(1), 780–789. https://doi.org/10.1021/acs.nanolett.9b04974

Subedi, L., & Gaire, B. P. (2021). Neuroprotective Effects of Curcumin in Cerebral Ischemia: Cellular and Molecular Mechanisms. *ACS Chemical Neuroscience*, *12*(14), 2562–2572. https://doi.org/10.1021/acschemneuro.1c00153

Sun, G., Miao, Z., Ye, Y., Zhao, P., Fan, L., Bao, Z., Tu, Y., Li, C., Chao, H., Xu, X., & Ji, J. (2020). Curcumin alleviates neuroinflammation, enhances hippocampal neurogenesis, and improves spatial memory after traumatic brain injury. *Brain Research Bulletin*, *162*(April), 84–93. https://doi.org/10.1016/j.brainresbull.2020.05.009

Tiwari, S. K., Agarwal, S., Seth, B., Yadav, A., Nair, S., Bhatnagar, P., Karmakar, M., Kumari, M., Chauhan, L. K. S., Patel, D. K., Srivastava, V.,

Singh, D., Gupta, S. K., Tripathi, A., Chaturvedi, R. K., & Gupta, K. C. (2014). Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway. *ACS Nano*, *8*(1), 76–103. https://doi.org/10.1021/nn405077y

Ułamek-Kozioł, M., Czuczwar, S. J., Januszewski, S., & Pluta, R. (2020). Substantiation for the use of curcumin during the development of neurodegeneration after brain ischemia. *International Journal of Molecular Sciences*, *21*(2), 1–17. https://doi.org/10.3390/ijms21020517

Uzdensky, A. B. (2019). Apoptosis regulation in the penumbra after ischemic stroke: expression of pro- and antiapoptotic proteins. *Apoptosis*, *24*(9–10), 687–702. https://doi.org/10.1007/s10495-019-01556-6

Wang, L., Zhang, B., Yang, X., Guo, S., Waterhouse, G. I. N., Song, G., Guan, S., Liu, A., Cheng, L., & Zhou, S. (2023). Targeted alleviation of ischemic stroke reperfusion via atorvastatin-ferritin Gd-layered double hydroxide. *Bioactive Materials*, *20*, 126–136. https://doi.org/10.1016/J.BIOACTMAT.2022.05.012

Wang, S., Ye, Q., Tu, J., Zhang, M., & Ji, B. (2017). Curcumin protects against hypertension aggravated retinal ischemia/reperfusion in a rat stroke model. *Clinical and Experimental Hypertension*, *39*(8), 711–717. https://doi.org/10.1080/10641963.2017.1313854

Wang, Y., Luo, J., & Li, S. Y. (2019). Nano-Curcumin Simultaneously Protects the Blood-Brain Barrier and Reduces M1 Microglial Activation during Cerebral Ischemia-Reperfusion Injury. *ACS Applied Materials and Interfaces*, *11*(4), 3763–3770. https://doi.org/10.1021/ACSAMI.8B20594/SUPPL_FILE/AM8B20594_SI_001.PDF

WHO. (2011). *Stroke, Cerebrovascular accident*. http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html

WHO. (2020a). *Definition of Stroke*. https://www.publichealth.com.ng/world-health-organization-who-definition-of-stroke/

WHO. (2020b). *Definition of Stroke*. https://www.publichealth.com.ng/world-health-organization-who-definition-of-stroke/

Wicha, P., Tocharus, J., Janyou, A., Jittiwat, J., & Chaichompoo, W. (2020). Hexahydrocurcumin alleviated blood – brain barrier dysfunction in cerebral ischemia / reperfusion rats. *Pharmacological Reports*, *72*(3), 659–671. https://doi.org/10.1007/s43440-019-00050-9

Wu, S., Guo, T., Qi, W., Li, Y., Gu, J., Liu, C., Sha, Y., Yang, B., Hu, S., & Zong, X. (2021). Curcumin ameliorates ischemic stroke injury in rats by protecting the integrity of the blood-brain barrier. *Experimental and Therapeutic Medicine*, *22*(1), 5–12. https://doi.org/10.3892/etm.2021.10215

Xie, C. J., Gu, A. P., Cai, J., Wu, Y., & Chen, R. C. (2018). Curcumin protects neural cells against ischemic injury in N2a cells and mouse brain with ischemic stroke. *Brain and Behavior*, *8*(2), 1–12. https://doi.org/10.1002/brb3.921

Yang, C., Zhang, X., Fan, H., & Liu, Y. (2009). Curcumin upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. *Brain Research*, *1282*, 133–141. https://doi.org/10.1016/J.BRAINRES.2009.05.009

Yang, X., Song, D., Chen, L., Xiao, H., Ma, X., Jiang, Q., & Cheng, O. (2020). Curcumin promotes neurogenesis of hippocampal dentate gyrus via Wnt/β-catenin signal pathway following cerebral ischemia in mice. *Brain Research*, *1751*(May 2020), 147197. https://doi.org/10.1016/j.brainres.2020.147197

Zhang, Y., Yan, Y., Cao, Y., Yang, Y., Zhao, Q., Jing, R., Hu, J., & Bao, J. (2017). Potential therapeutic and protective effect of curcumin against stroke in the male albino stroke-induced model rats. *Life Sciences*, *183*, 45–49. https://doi.org/10.1016/j.lfs.2017.06.023

Zhao, J., Yu, S., Zheng, W., Feng, G., Luo, G., Wang, L., & Zhao, Y. (2010). Curcumin improves outcomes and attenuates focal cerebral ischemic injury via antiapoptotic mechanisms in rats. *Neurochemical Research*, *35*(3), 374–379. https://doi.org/10.1007/s11064-009-0065-y

Zhou, J., Wu, N., & Lin, L. (2020). Curcumin suppresses apoptosis and inflammation in hypoxia/reperfusion-exposed neurons via Wnt signaling pathway. *Medical Science Monitor*, *26*, 1–7. https://doi.org/10.12659/MSM.920445