MEDS Clinical Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2022.030706
ISSN 2616-1907 Vol. 3 Num. 7

Clinical Studies on Curcumin in Improving Mitochondrial Biogenesis

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Keywords: Curcumin, Mitochondria, Mitochondrial Biogenesis

Abstract: Curcumin is a kind of plant polyphenols extracted from the traditional Chinese medicine, turmeric. It is also the most important active ingredient of turmeric. A large body of evidence suggests that this polyphenolic compound is capable of affecting the mitochondrial structure and function, thereby improving mitochondrial biogenesis. This paper combines Chinese and foreign literature to expounds how curcumin can exert anti-inflammatory, anti-oxidation, anti-tumor, protect nervous system and cardiovascular system by improving mitochondrial biogenesis, in order to provide reference for the clinical application of curcumin.

Turmeric is a curry spice [1] and a traditional herbal medicine, with nearly 100 companies worldwide offering a variety of curcumin products, including beverages, tablets, capsules, creams, gels, nasal sprays, extracts and colorants to meet edible and medical needs. There is also a long history of treating inflammatory diseases in China and Southeast Asia. The main ingredients of the product contain three curcumin[2], demethoxycurcumin and didemethoxycurcumin), volatile oil (naphthoquinone, curmerone and gingeroleinone), protein, sugar and resin. Curcumin is a well class of known polyphenols and is the most active component of turmeric. It is used to prevent and treat certain diseases, most of which are attributed to the presence of curcumin. Numerous scientific studies have demonstrated the antioxidant function of curcumin, and in vitro live-cell assays have also shown that curcumin prevents the formation of singlet oxygen (ROS) and reduces the destruction of mitochondrial DNA caused by hydrogen peroxide[3]. Liao et al proposed that curcumin induced mitochondrial [4] mainly by inducing PGC-1 α -related signaling pathway in different mammalian tissues. Clinical experiments have demonstrated that curcumin can trigger mitochondrial biogenesis in both in vitro and in vivo experimental models. At the same time, curcumin as a spice is widely used in the human diet, its side effects and biotoxicity can be basically negligible [5]. Due to its apparent safety profile and multiple therapeutic effects, the clinical efficacy of curcumin in human diseases is receiving increasing attention. Current medical database search for keyword-curcumin shows that there are 14 clinical studies on curcumin. Of these, 114 studies focused on the therapeutic effects of curcumin and its commercial preparations, mainly focusing on mental and psychiatric diseases, digestive system diseases, metabolic diseases,

different types of cancer, inflammation, and skin diseases. Curcumin has excellent antioxidant function in traditional Chinese medicine, strong anti-inflammatory activity, can inhibit inflammation, bacterial proliferation and cell necrosis, can anti-aging, anti-atherosclerosis, reduce blood lipid, hypertension, cancer suppression, and anti-Alzheimer's disease, nerve protection and other effects.

Mitochondria are dynamic double-membrane-bound organelles that play a key role in various cellular functions (e. g., energy production, calcium flux regulation, cellular stress responses (including autophagy and apoptosis), [4]. The process of mitochondria is mainly due to the high ion flux of oxidized phosphorus oxidation, resulting in the formation of singlet oxygen (ROS). The ROS generated within mitochondria, unless completely neutralized, the excess of ROS produces strong oxidation that can cause mitochondria-specific biological responses, i. e., causing mitochondrial oxidative stress [6]. Oxidative stress affects mitochondrial functions, such as biogenesis, ion homeostasis, and antioxidant defense mechanisms, resulting in reduced cellular energy efficiency, altered bioenergetics, cell damage, and apoptotic [7]. Therefore, due to mitochondrial function obstruction and the occurrence mechanism of various inflammatory diseases, malignant tumors, cardiovascular diseases, nervous system degenerative diseases are related to [8,9], mitochondrial function obstruction has become the main reason of various slow diseases in clinic. At the same time, the polyphenolic compounds can affect the structure and function of mitochondria to improve mitochondrial biogenesis, a lot of evidence shows that mitochondria participate in the therapeutic properties of curcumin [3], because curcumin can regulate various mechanisms of mitochondrial entanglement, mainly cell apoptosis (mitochondria-mediated pathway) and respiratory function. This review focuses on some properties of curcumin to specifically illustrate the close relationship between this antioxidant and the induction of mitochondrial ogenesis.

1. Curcumin Induces a Mitochondrial Development Mechanism

The mechanism of curcumin-induced mitochondriogenesis has shown that curcumin indirectly increases the expression of mitochondrial biogenesis genes in obese liver steatosis mice, including NRF1 and mitochondrial transcription factor A (Tfam), which are responsible for the activity of the lower mitochondrial respiratory chain (MRC) complex I and the [10] production of ATP. In vitro experiments, Lu et al. demonstrated that curcumin could improve mitochondrial biogenesis by increasing mitochondrial membrane potential, so as to improve mitochondrial cell necrosis and apoptosis[11], and reduce cell damage and AD progression. In addition, Zhang Jing[12] et al. used the heat oxidative stress response of broilers induced by high temperature to give different degrees of curcumin in the control group, thus proving that curcumin can significantly reduce the liver ROS content of heat stress, and increase the amount of DNA copy of mitochondrial membrane potential, thus changing the degree of heat oxidation and reduction of mitochondria. Nrf translocation was induced and PGC-1 α was increased in LLC-PK1 cells treated with gentamicin in in vitro experiments. This evidence suggests that curcumin can induce the mitochondrial biogenesis of [13,14] in vitro through Nrf by acting as a master regulator of the redox cellular environment. At the same time, providing curcumin (400 mg / kg day-1) preserves the morphology, structure and increases the number of mitochondria before exposure to gentamycin.

2. Curcumin Acts on the Mitochondria

2.1 Anti-inflammatory

The key factor in anti-inflammatory inflammation is the reduction in mitochondrial function.

Usually, the number of mitochondria and their function decline as you age. As the cellular energy decreases during this process, the inflammatory compounds leak out from the mitochondria, and more cellular debris forms within the cell. The process of processing these cell debris, called autophagy. When the resulting cellular debris cannot be removed by autophagy, decreased mitochondrial function triggers chronic inflammation.Curmeric, which has a unique anti-inflammatory effect, protects and optimizes mitochondrial function and retains autophagy. It can help the immune system to properly process and discard cellular waste. It helps to reduce inflammation and promote overall cell health. Curcumin has been shown to be highly pleiotropic molecules interacting with multiple inflammatory molecular targets. Curcumin exerts an anti-inflammatory effect by preventing K flow and interfering with downstream events, including efficient spatial arrangement of mitochondria, ASC oligomerization and puncta production, thereby preventing the NLRP triinflammasome, [15]. Wang Long [16] et al. established a NASH model in rats and evaluated the protective effect of curcumin by histological observation: the average mitochondrial length and width of NASH were significantly greater than that of normal and NASH-treated curcumin rats. The regulation of curcumin can promote the mitochondrial biogenesis, control the mitochondrial dysfunction and the necrosis of hepatocytes, thus alleviating the oxidative damage in the liver. Recent evidence suggests that improved mitochondrial dysfunction induced during nephrotoxicity appears to be a key mechanism for curcumin protection and indirectly reducing ROS production, [17], and that curcumin also reduces the expression of NF- β B and TNF- α, TGF- β, extracellular matrix collagen type IV, cellulose, and growth factors (e. g., CTGF). These proteins are closely involved in the inflammatory response. In vitro and in vivo studies, especially in clinical trials, suggest that curcumin can be a potential therapeutic agent in many chronic diseases, such as inflammatory bowel disease, pancreatitis, chronic preuveitis, arthritis [18], and much more.

2.2 Antioxidant

Antioxidative oxidative stress plays an important role in the development mechanism of various lesions, such as myocardial ischemia, cerebral ischemia-reperfusion damage, ischemia and shock, damage of neuronal cells, hypoxia, and cancer. Curcumin exhibits differential antioxidant activity [19] in several in vitro and in vivo models, for example, preventing lipid peroxidation in various cells including erythrocytes, rat brain homopheities, rat liver microsomes, liposomes, and macrophages. Curcumin is a bi-functional antioxidant, [20]. Its protective function is attributed to the induction of the main regulatory system of antioxidant response speed, that is, it produces antioxidant response nuclear erythrocyte source (Nrf), controls mitochondrial function, reduces inflammatory response, and then protects antioxidant enzymes and reduces oxide stress. It exerts antioxidant activity directly and indirectly by scavenging reactive oxygen species and inducing antioxidant reactions, respectively, reducing the production of active substances and upregulating antioxidant enzymes. Extensive scientific evidence indicates that curcumin is able to improve lipid peroxidation and oxidative stress between different tissues, with significant antioxidant activity. Priyanka et al [21] also evaluated the protective effects of various doses of curcumin on hypoxia-induced alterations. The results showed that hypoxia significantly altered important parameters of adipocyte biology, such as reactive oxygen species production (43.53%), increased lipid and protein oxidation (376.6% and 566.6% +), decreased antioxidant enzymes (superoxide lyase and lactase) status, decreased inflammatory marker secretion (TNF α, IL 6, IL 1°, and IFN γ) and decreased mitochondrial function (mitochondrial quality, membrane potential, permeability transition aperture integrity and superoxide generation), while curcumin improved this state.

2.3 Anti-tumor

At present, three anti-tumors have been confirmed that the mitochondria of malignant bacteria are different from the general bacteria in terms of structure and function, and their biggest feature is the excessive formation of ROS, which can use the change of gene expression and the change of gene expression and the regulation of information channels to improve the genome instability. Oxidative damage targeting both the mitochondrial compartment and nuclear DNA can then cause the effects of cell oxidative phosphorylation, thus increasing the formation of mitochondria-specific ROS, thus maintaining the "vicious circle" between mitochondrial ROS, gene body function imbalance and tumorigenesis. Changes in bioenergetics are necessary for cancer development. Therefore, the control of mitochondrial bioenergy and kinetics can be used as potential cancer therapies. Phenol derivatives[22]such as curcumin can realize their own anti-tumor function by interfering with inflammatory pathways such as apoptosis and oxidation process to induce malignant tumor cell decomposition, necrosis and inhibitory effect of malignant cancer cells, which is very common in clinical use. Medical data have confirmed that curcumin has anti-proliferative functional [23] against various cancer cells, involving colon cancer, bladder cancer, breast cancer, lung cancer, prostate cancer, cervical cancer, ovarian cancer, skin cancer and other malignant cancers. Curcumin can induce the isolation of malignant breast cancer cells, accompanied by swelling of mitochondria and fused [24] normal breast cells, curcumin is more cytotoxic to malignant breast cancer cells, cell death is induced paracellular detachment. Deprolapse is characterized by a vacuolation process that begins with physical expansion of the mitochondria and endoplasmic reticulum, independent of the caspase protease pathway.

2.4 Protection of the Nervous System

Protection of mitochondrial biogenesis in the nervous system is particularly important in modern neurochemistry because of mitochondrial ions and ROS homeostasis, defects in energy production and morphology causing the widespread development of human diseases. In the context of neurodifferentiation, Martine Uittenbogaard and Anne Chiaramello[25] (Department of Anatomy and Regenerative Biology, George Washington University School of Medicine and School of Health Sciences, USA) comprehensively describe the role of mitochondrial biogenesis on neuronal differentiation, indicating that mitochondrial dysfunction is a major source of neurodegenerative diseases and neurodevelopmental disorders. Studies show that [26], curcumin has comparable neural and mitochondrial protective properties against broad-spectrum neurotoxic compounds and disease injury-associated NDs. Increasing evidence suggests that mitochondrial dysfunction and its associated mutations, in the form of oxidative / nitroso stress and neurotoxic compounds, play a major role in the pathogenesis of various NDs. Curcumin also attenuates oxidative stress, cognitive dysfunction, and amyloid [27] accumulation in neuronal tissues in animal models of Alzheimer's disease. Other studies have shown that curcumin can significantly improve memory and [28], reverse changes in PSD-95 levels, and modulate brain plasticity.

2.5 Protect the Cardiovascular System

Five to protect the cardiovascular system cardiovascular disease mechanism, often deeply affected by the common influence of inflammation and oxidative stress, and curcumin due to its own resistance to inflammation, antioxidant function, in the prevention and treatment of atherosclerosis, heart hypertrophy, heart failure, coronary aneurysm, chronic diabetes cardiovascular complications and myocardial infarction, plays an important role. Curcumin can also change the mitochondrial morphology and function of H 9 c cardiomyocytes under oxidative stress

conditions, mainly reflected in enhanced mitochondrial membrane potential, promoting ATP formation, enhanced mitochondrial ATPase vitality, and maintaining the true morphological structure of mitochondria, [29], and thus improving mitochondriogenesis.Curcumin can also delay vascular aging and reduce atherosclerotic cardiovascular diseases. Takano et al. [30] deeply investigated the effect of curcumin during long oral administration (7 weeks) on capillary senescent cells and slow inflammatory damage in HFD animals, indicating that curcumin can reduce SA- β -Gal activity in mice, thus reducing the accumulation of senescent cells in the aorta. Other studies have shown that curcumin can also be used as an adjuvant therapy for the prevention and treatment of diabetic cardiomyopathy, [31], curcumin can inhibit protein kinase C (PKC) - α and- β -mitogen active protein kinase (MAPK) pathway, reduce the level of plasma glucose stimulation and reduce the antioxidant response, and thus reduce the hypertrophy of heart cells, cardiac fibrosis.

3. Conclusions

Curcumin, as a polyphenolic compound, can affect the mitochondrial composition and function, and then promote mitochondrial biogenesis, thus playing an anti-inflammatory, antioxidant, anti-malignancy, maintenance of nervous system health and cardiovascular system functions. And because curcumin is a kind of relatively hydrophobic substances, oral bioavailability is low [32], the pharmacokinetic studies confirmed that curcumin oral bioavailability is only one percent, may because it is insoluble in water and gastrointestinal permeability is not enough, namely the solubility is not high, poor stability, very low absorption rate, but in the gastrointestinal is easy to convert into glucoside aldehyde and sulfonic acid complex, so rapid metabolism, short half-life. Clinical trials have shown that even extremely high doses of curcumin (1 gram per day) are harmless to patients. To date, scientific reports on the side effects of curcumin are scarce. However, the exact mechanism by which curcumin induces mitochondrial biogenesis is not fully understood, as most published studies have not investigated[33] for the crucial role of AMPK, NRF1, Nfr, and /or TFAM in biological processes. Studies on the role of curcumin as an inducer of mitochondrial biogenesis in the context of mitochondrial energy disorders are still in its infancy. The induction of mitochondrial biogenesis is valuable clinically in terms of inflammation, neurological degeneration and cardiovascular disease.

References

[1] Cui Dongyue, Li Yuanyuan, Xiao Baoping, Liu Jingwen, Li Jian, Su Wenjin, Li Guiling. Preliminary mechanistic study of curcumin antioxidant effects [J]. Food Safety Guide, 2019 (20): 68-72.

[2] Raghavendhar rk, devanand ll. Curcumin:biological, pharmaceutical, nutraceutical, and analytical aspects [J/OL]. Molecules, 2019, 24(16): 2930.

[3] Trujillo J, Granados-Castro LF, Zazueta C, Andérica-Romero AC, Chirino YI, Pedraza-Chaverr íJ. Mitochondria as a target in the therapeutic properties of curcumin. Arch Pharm (Weinheim). 2014; 347(12):873-84.

[4] Liao Xueyan, Wang Keshun. The protective effect of curcumin on mitochondria in cardiomyocytes under oxidative stress conditions [J]. Journal of Practical Clinical Medicine, 2019, 23 (3): 38-43.

[5] Liu Zhigang. Scientific Opinions on the Re evaluation of Food Additive Plant Carbon Melanin (E153) [J]. Chinese Journal of Food, 2012, 12 (5): 1

[6] Jaenicke L. Biochemistry. The Chemical Reactions of the Living Cell [J]. Angewandte Chemie, 1979, 91(4).

[7] Hernández-Reséndiz S, Buelna-Chontal M, Correa F, Zazueta C. Targeting mitochondria for cardiac protection. Curr Drug Targets. 2013 May 1; 14(5):586-600.

[8] Enns GM. The contribution of mitochondria to common disorders.Mol Genet Metab. 2003; 80(1-2):11-26.

[9] Ferrari CK. Functional foods, herbs and nutraceuticals: towards biochemical mechanisms of healthy aging. Biogerontology. 2004; 5(5):275-89.

[10] Kuo JJ, Chang HH, Tsai TH, Lee TY. Positive effect of curcumin on inflammation and mitochondrial dysfunction in obese mice with liver steatosis. Int J Mol Med.2012 Sep;30(3):673-9.

[11] Lu Shuyan, Yang Li, Dai Xueling, Chang Ping, Jiang Zhaofeng, Huang Hanchang. Inhibition effects of curcumin

on A _ (1-42) -induced cell damage and cell apoptosis in the mitochondrial pathway [J]. The Chinese Chinese Journal of Pharmacology and Toxicology, 2017, 31 (02): 138-144.
[12] Zhang Jingfei. The protective effect of curcumin on oxidative damage in animal mitochondria and its antioxidant mechanism [D]. Nanjing Agricultural University, 2015.
[13] Q. Ma, "Role of Nrf 2 in oxidative stress and toxicity," Annual Review of Pharmacology and Toxicology, 2013. 401–426.
[14] M. Negrette-Guzman, W.R. Garcia-Nino, E. Tapia et al., "Curcumin attenuates gentamicin-induced kidney mito-chondrial alterations: possible role of a mitochondrial bio-genesis mechanism," Evidence-based Complementary and Alternative Medicine. 2015, 16, 2015.
[15] Yin H, Guo Q, Li X, Tang T, Li C, Wang H, Sun Y, Feng Q, Ma C, Gao C, Yi F, Peng J. Curcumin Suppresses IL-1β Secretion and Prevents Inflammation through Inhibition of the NLRP3 Inflammasome. J Immunol. 2018; 200(8): 2835-2846.
[16] Wang Yunliang, Shi Rui, Liu Lijuan, et al. Curcumin improves insulin resistance and inflammation in nonalcoholic steatohepatitis cell model [J]. 2013.
[17] Trujillo J, Chirino YI, Molina-Jijón E, Andérica-Romero AC, Tapia E, Pedraza-Chaverrí J. Renoprotective effect of the antioxidant curcumin: Recent findings. Redox Biol. 2013 Sep 17; 1(1):448-56.
[18] Jackson JK, Higo T, Hunter WL, et al. The antioxidants curcumin and quercetin inhibit inflammatory inflammatory processes associated with arthritis [J]. Inflamm Res, 2006, 55:168-175.
[19] Esatbeyoglu T., Huebbe P., Ernst I.M., Chin D., Wagner A.E., Rimbach G.Curcumin—from molecule to biological function. Angewandte Chemie International Edition (in English) 2012; 51:5308-5332.
[20] Reddy S., Aggarwal B.B. Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase.FEBS Letters. 1994; 341: 19–22.
[21] Priyanka A, Anusree SS, Nisha VM, Raghu KG. Curcumin improves hypoxia induced dysfunctions in 3T3-L1 adipocytes by protecting mitochondria and down regulating inflammation.Biofactors. 2014; 40(5):513-23.
[22] Shabaninejad Z, Pourhanifeh M H, Movahedpour A, et al. Therapeutic potentials of curcumin in the treatment of glioblstoma[J]. European Journal of Medicinal Chemistry, 2020, 188:112040.
[23] Jiang Lh, Yin Kx, Ge Mh. Research progress in curcumin's antitumor effect and related mechanisms [J]. Jiangsu Med J (Jiangsu Pharmaceutical), 2018, 44 (7): 830-834.
[24] Yoon MJ, Kim EH, Lim JH, Kwon TK, Choi KS. Superoxide anion and proteasomal dysfunction contribute to curcumin-induced paraptosis of malignant breast cancer cells. Free Radic Biol Med. 2010; 48(5):713-26.
[25] Teresa, Valero. Mitochondrial biogenesis: pharmacological approaches. [J]. Current Pharmaceutical Design, 2014. 20(35):5507-5509.
[26] Bagheri H, Ghasemi F, Barreto GE, Rafiee R, Sathyapalan T, Sahebkar A. Effects of curcumin on mitochondria in neurodegenerative diseases. Biofactors. 2020; 46(1):5-20.
[27] Garcia-Alloza M, Borrelli LA, Rozkalne A, et al. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model [J]. J Neurochem, 2007, 102:1095-1104.
[28] Frautschy SA, Hu W, Kim P, et al. Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology[J]. Neurobiol Aging, 2001, 22:993-1005.
[29] Wu Longmei, Liu Chunyan. The protective effect of curcumin on H2O2-induced oxidative stress injury in H9C2 cardiomyocytes [J]. International Journal of Traditional Chinese Medicine, 2019 (01): 57-61.
[30] Oetikno V, Sari FR, Sukumaran V, et al. Curcumin prevents diabetic cardiomyopathy in streptozotocin-induced diabetic rats: possible involvement of PKC-MAPK signaling pathway [J]. Eur JPharm Sci, 2012, 47(3):604-614.
[31] Fan N, He Z G, Ma P P, et al. Impact of HPMC on inhibiting crystallization and improving permeability of curcumin amorphous solid dispersions [J]. Carbohyd Polym, 2018, 181:543-550.
[32] Bauer D R, Hudson B, Pecora R. Resonance enhance depolarizedrayleigh scattering from diphenylpolyenes [J]. J Chem Phys, 1975, 63: 588-591.
[33] De Oliveira MR, Jardim FR, Setzer WN, Nabavi SM, Nabavi SF. Curcumin, mitochondrial biogenesis, and mitophagy: Exploring recent data and indicating future needs.Biotechnol Adv. 2016; 34(5):813-826.