The mitohormetic response as part of the cytoprotection mechanism of berberine

Berberine induces mitohormesis and mechanisms

Xiaofei Zhu 1,2,3*, Yihui Wei 1, Beibei Yang 1, Xiaoxiao Yin 1 and Xiaofang Guo 4

Abstract

It was well-known that Berberine, a major bioactive compound extracted from natural plants Coptis chinensis, has anti-diabetic effects for decades in China. Other types of pharmacological activities, such as anti-inflammatory, antimicrobial, hypolipidemic, and anti-cancer effects, have also been examined. At cellular level, these pharmacological activities were mostly an inhibitory effect. However, the cytoprotective effect of berberine was also observed in various types of cells, such as neurons, endothelial cells, fibroblasts, and β-cells. The paradoxical result may be closely associated with characteristics and distribution of berberine within cells, and they can be explained mechanically by mitohormesis, one particular form of hormesis. Here, we reviewed the mitohormetic response and assessed the berberine-induced effects and the possible signaling pathway involved. These findings may contribute to better clinical applications of berberine and indicate that some mitochondria-targeted conventional drugs should be considered carefully in clinical application.

Keywords: Berberine, Mitohormesis, Reactive oxygen species, Nicotinamide adenine dinucleotide, Mitochondrial unfolded protein response

Introduction

At a cellular level, mitochondria play a critical role in cell’s adaptation to external stressors, such as chemical toxicants, xenobiotics, and pathogens. These potentially damaging stressors could induce mitochondrial stress response by targeting pathways directly or indirectly involved in energy production and signaling required for survival. When the strength of stressors exceeded the adaptive capacity of cells, it could cause mitochondria-mediated cell death (Valera-Alberni and Canto 2018; Lan et al. 2019). In toxicology, this biphasic dose response, called as “hormesis,” was observed in many natural active ingredients from traditional Chinese medicine (Wang et al. 2018; Liu et al. 2019). This phenomenon indicated that conventional “toxic” drugs may have beneficial effects on cells. Evidence from both in vivo and in vitro studies has indicated that mild or sublethal mitochondrial stress from chemicals, especially some mitochondria-targeted drugs, showed beneficial effects on cells and organisms against larger subsequent stresses-induced damages or death (Cox et al. 2018; Obata et al. 2018; Yuyun et al. 2012; De Haes et al. 2014). This response activated by a moderate mitochondrial stress has been named mitohormesis, and it can maintain cellular homeostasis and extend lifespan (Tapia 2006; Yun and Finkel 2014).

Berberine (Ber) is a botanical alkaloid isolated mainly from the root and bark of several plants, such as Coptidis rhizoma and Hydrastis canadensis. According to the ancient records of traditional Chinese medicine listed in The Divine Farmer’s Classic of Materia Medica (Shen Nong Ben Cao Jing), Coptidis rhizoma can be used to treat dysentery and diarrhea. Ber is one of the main active ingredients in Coptidis rhizoma, accounting for 5.2–7.7% (Huang and JNM 1986; Berberine 1991). Clinical trials revealed that Ber also exhibits antimicrobial and anti-inflammatory activities in infectious diseases. It is a non-prescription drug used to treat gastrointestinal infections in China (Qu 2006). Moreover, other pharmacological...
effects of Ber, such as anti-diabetic, anti-obesity and anti-
cancer, have been also unravelled (Yan et al. 2017; Pang et al. 2015; Kong et al. 2004). However, there were con-
fllicting results reported in the literature that opposite ef-
cfects of Ber exhibited in different type of cells, such as protective effect on neuronal cells (Zhang et al. 2017) or
apoptosis-induced effect on cancer cells (Bao et al. 2015; Yan et al. 2017). Even in same type of cells, for example,
cancer cells, it was also found that the effects of Ber was
opposite. These phenomena were discussed and attributed
to hormetic effect of Ber (Bao et al. 2015). But in these
studies, a common results was demonstrate that Ber at
low dose could exerted a cytoprotection effect in all types
of cells, including cancer cells (Bao et al. 2015; Gao et al.
2011; Guo et al. 2016; Yan et al. 2017; Zhu et al. 2017).
Actually, mitohormesis is a biological response activ-
ated by a potentially external stressors in mitochondria.
The mitochondrial stress response leads to an improve-
ment in diseases and health and viability within a cell via
mitonuclear communication (Yun and Finkel 2014). The
mechanism of this interplay between mitochondria and
nuclear were involved in a broad and diverse cytosolic and
nuclear signalling pathways, including reactive oxy-
gen species (ROS) (Ristow 2014), the mitochondrial un-
folded protein response (UPRm) (Iovaisi et al. 2014),
and mitochondrial metabolites (Toyama et al. 2016;
Canto et al. 2015). As an important target and a major
subcellular localization of Ber at low dose (Serafim et al.
2008; Pereira et al. 2007), mitochondria play a key role
in activity of Ber (Yan et al. 2017). This may be partly
explained the different effect in different energy-
demanded cells, such as cancer cells, which may be asso-
ciated with different sensitivities to Ber. As similar to
functions of another mitochondrial-targeted drug met-
formin (Wang et al. 2017), Ber could induce mitochon-
drial stress response against stress-induced cellular
damage through multiple pathways, such as mitochon-
drial respiratory chain-mediated ROS production (Turner et al. 2008; Lenaz 2001) and Nrf2 signalling pathway
(Zhang et al. 2017; Jiang et al. 2019), AMPK signalling
pathway (Turner et al. 2008). These pathways also cross-
talk with mitonuclear communication signalling pathways
in mitochondrial stress response. Here, the possible cyto-
protection mechanism of Ber via mitohormesis were
reviewed.

Cellular uptake and subcellular location of Ber
Ber is a hydrophilic compound with high solubility in
basic solution and low permeability. Under physiological
conditions, it mainly exists in a positively charged pro-
tonated form. In normal water solution, only a few Ber
particles are converted to aldehyde or alcohol-type, and
these possess lipophilic properties. In this way, it was
difficult for Ber to rapidly and passively diffuse through
cell membranes (Berberine 1991; Zhang et al. 2014). However, as a substrate of organic cation transporter 1
(OCT1; SLC22A1 gene) and organic cation transporter 2
(OCT2; SLC22A2 gene), Ber could be taken up into cells
at a relatively fast rate (Nies et al. 2008; Shi et al. 2018).
OCT2 is also expressed in the central nervous system.
This may explain how Ber can penetrate the blood-brain
barrier and so play a protective role in neurons (Sun et al. 2014). In living cells, the Ber first accumulated on
the mitochondria due to its physicochemical properties.
As the amount of uptake increased, Ber could accumu-
late in the cytoplasm or nucleus, possibly because of sat-
uration in the mitochondria. The subcellular location
may partially explain the paradoxical results in cell fate
(Serafim et al. 2008; Mikes and Dadák 1983). For
example, it has recently been reported that Ber at low dose
range (1.25–5 μM) could promote cancer cell prolifera-
tion and significantly attenuate the anticancer activity of
chemotherapeutic agents in combination drug regimens
(Bao et al. 2015).

Pathway of berberine-induced mitohormetic response

ROS signaling pathways
The mitochondria are not only the main powerhouse of
bioenergy but also a source of ROS. The majority of
ROS are products of the mitochondrial respiratory chain,
especially at the site of respiratory chain complex I and
III (Turrens 2003). However, an increase in ROS did not
mean that it was harmful to cell survival. Several studies
have shown that, under physiological conditions, as sig-
nalling molecules, the transient increase in ROS could
induce some transcriptional changes in the nucleus by
mitohormetic response to regulate cell adaption to an
unfriendly environment (Obata et al. 2018; Zarse et al.
2012; Ristow 2014).

Ber could inhibit mitochondrial respiration by target-
ing complex I (Turner et al. 2008), which led to leakage
of electrons that cause a higher rate of reactive oxygen
production in the mitochondria (Lenaz 2001). ROS
could transduce signals to the nucleus by triggering the
oxidation of several reactive Cys residues in redox-
dependent manner (Truong and Carroll 2012). The
redox modification of proteins could translocate to and
accumulate in the nucleus to induce host-antioxidant
defense genes, such as the mammalian Kelch-like ECH-
associated protein 1 (KEAP1)–nuclear factor erythroid
2-related factor 2 (NRF2) (Taguchi et al. 2011). Ber was
also proposed as a potential anti-aging agent (Zhao et al.
2013) and exhibited a neuroprotective effect via the
ROS-mediated pathway (Zhang et al. 2017). In this way,
transient rise in ROS levels induced by a low dosage of
Ber may protect cells through a potential feedback
mechanism involved in anti-oxidative defence or stress
defence pathways, such as Nrf2 signaling pathway, to
resist larger subsequent stress-induced damage (Jiang et al. 2019).

**Metabolite signaling pathways**

Adenosine triphosphate (ATP) is an important metabolite produced by mitochondria through oxidative phosphorylation (OXPHOS). Decreases in ATP levels can increase the ratio AMP/ATP and activate the adenosine monophosphate (AMP) sensor, the AMP-activated protein kinase (AMPK), which is a master regulator of cellular metabolism. The phosphorylated-activation of a downstream signaling pathway via AMPK can enhance mitochondrial energy harvesting by decreasing ATP consumption (Herzig and Shaw 2017), and maintain mitochondrial homeostasis by promoting mitophagy and mitochondrial fission (Egan et al. 2011; Toyama et al. 2016). Ber could active AMPK pathway by inhibiting mitochondrial respiration, which increased the ratio of AMP/ATP (Turner et al. 2008). Pharmacological activation of AMPK by Ber had protective effects against cellular senescence and apoptosis and exhibit therapeutic efficacy in metabolic and neurodegenerative conditions as well as other aging-related diseases (Zhang et al. 2016; Han et al. 2016; Wang et al. 2011; Zhao et al. 2014).

Nicotinamide adenine dinucleotide (NAD⁺) is also an important metabolite. As a key cofactor of multiple dehydrogenases, the levels of NAD⁺ and the ratios of NAD⁺/NADH are primarily maintained by mitochondria via the tricarboxylic acid (TCA) cycle and OXPHOS function. During energy deficits, NAD⁺ levels become elevated, which can be protective against disease and increase lifespan in mice (Canto et al. 2015; Zhang et al. 2016). NAD⁺ is also an essential co-substrate of sirtuins, such as SIRT1, which promoted mitochondrial biogenesis, and its function was closely associated with lifespan (Imai and Guarente 2014). Therefore, elevation of NAD⁺ levels by medication may be an effective strategy for aging-related diseases (Houtkooper and Auwerx 2012). Ber may induce an increase of intracellular NAD⁺ levels by moderately inhibiting OXPHOS, which was similar to energy deficits (Turner et al. 2008; Yin et al. 2008). Ber may also increase intracellular NAD⁺ concentrations indirectly through AMPK activation, so regulating the expression and activity of nicotinamide phosphoribosyl transferase (NAMPT), a key rate-limiting enzyme in NAD⁺ synthesis, which could increase sequential SIRT1 activity (Brandauer et al. 2013; Cantó et al. 2009).

**Unfolded protein response signaling pathways**

The mitochondrial unfolded protein response (UPRmt) is a stress response pathway that maintains mitochondrial homeostasis, specifically proteostasis. The UPRmt could be induced by intramitochondrial damage. Its activation has been shown to elicit a retrograde signaling pathway from mitochondria to the nucleus, which results in the expression of proteases, chaperonins, and other stress response genes to restore mitochondrial protein homeostasis. Multiple stressors have been shown to be involved in the activation of UPRmt, such as perturbation of OXPHOS, impairment of mitochondrial ribosomes, and high levels of ROS (Jovaisaite et al. 2014; Zhao et al. 2002).

UPRmt can be pharmacologically activated by antibiotics, such as tetracyclines and phenicols, in living organisms (worms, flies, and mammals), which leads to UPRmt-dependent increases in longevity and health span (Quiros et al. 2016; Moullan et al. 2015). It has also been reported that this pharmacological treatment can have protective effects in several neuromuscular disorders, such as amyotrophic lateral sclerosis and Guillain-Barré syndrome (Zhu et al. 2002; Zhang et al. 2009). Ber could accumulate not only in mitochondria to influence energy metabolism but also bind to DNA or RNA to regulate gene expression (Yuan et al. 2015). This may be closely associated with the dosage used at the cellular level (Yan et al. 2017). At low doses, Ber may disturb OXPHOS and bind to mtDNA to activate UPRmt, which may contribute to cytoprotective effects, whereas it was reverse at high dose (Bao et al. 2015; Yan et al. 2017; Turner et al. 2008; Bhadra et al. 2008).

In addition, elevation of NAD⁺ levels may activate the UPRmt in both mammals and nematodes partly through NAD⁺-driven activation of SIRT1 (Zhang et al. 2016; Mouchiroud et al. 2013; Gariani et al. 2015). Elevated NAD⁺ levels and overexpression of SIRT1 robustly increased the protein levels of the mammalian UPRmt homolog Hsp60 and UPRmt protease CLPp (Khan et al. 2014; Calabrese 2008). This may be how Ber exerts its cytoprotective effects by activating the UPRmt through Ber-mediated elevation of NAD⁺ levels or upregulation of SIRT1 expression (Zhu et al. 2017; Turner et al. 2008; Yin et al. 2008).

**Conclusion**

Hormesis is a biphasic dose response to a chemical agent, which was first proposed and used in the toxicology field. In biology, it also means to an adaptive response activated by a low dose of stress stimuli, such as caloric restriction and phytochemicals, in cells and organisms to maintain homeostasis, whereas it has a harmful effect at higher doses (Calabrese 2008; Mattson 2008). The mitochondria are key to nutrient metabolism and bioenergy production and essential to cellular homeostasis. It was proposed and supported experimentally that sublethal mitochondrial stress should cause a beneficial hormetic response called mitohormesis (Wang et al. 2018; Obata et al. 2018). As a bioactive component from traditional Chinese medicine,
Ber showed a protective effect on cells in harsh environments, which was associated with a mitohormetic response (Serafim et al. 2008; Bao et al. 2015; Gao et al. 2011; Guo et al. 2016; Yan et al. 2017; Zhu et al. 2017).

Here, we review the current understanding of possible retrograde signaling pathways involved in berberine-mediated mitohormesis. A low dose of Ber could target mitochondria through the physicochemical properties of its positively charged form. Ber mildly inhibited electron transport chain (ETC) by accumulating in mitochondria and causing a decrease in the efficiency of energy produced of OXPHOS (i.e., ATP) and a moderate increase of ROS and NAD⁺ (Turner et al. 2008; Lenaz 2001; Yin et al. 2008; Brandauer et al. 2013; Cantó et al. 2009). This could lead to a mitohormetic response in the following signaling pathways: (1) ROS-mediated redox pathway, (2) AMP/ATP-induced AMPK pathway, (3) NAD⁺/NADH-mediated Sirtuins pathway (i.e., SIRT1), and (4) UPRmt pathway. In a sense, upstream of these pathways originated from energy stress (ATP deficits), and signal interactions existed downstream of these pathways, such as AMPK-regulated NAD⁺ increase (Brandauer et al. 2013; Cantó et al. 2009) and SIRT1-regulated UPRmt-relative gene expression (Mouchiroud et al. 2013) (Fig. 1). All of these pathways could ultimately enhance the adaptiveness of cells to adverse circumstances by upregulating transcription involved in resolving metabolic adaptation, the antioxidant response, and cell survival.

As important intracellular organelle of nutrient and energy metabolism, mitochondria have an essential role in controlling the fate of cells, such as cell death and immunity (Mehta et al. 2017; Orrenius et al. 2007). In this way, mitochondria are central platforms to support cell function and maintain cell homeostasis. Given probable mitohormetic effect of drug related to low dosage, some mitochondria-targeted conventional drugs should be interrogated dialectically in clinic applications, such as statins (Marcheggiani et al. 2019; Bouitbir et al. 2012). Moreover, mitochondria-targeted agents, such as rotenone and metformin, also exhibit protective effects on cellular survival and extending lifespan at a low concentration via ROS-mediated mitohormetic signaling pathways (Yuyun et al. 2012; De Haes et al. 2014). This implied that mitochondria-targeted agents may produce a beneficial effect in aging-relative diseases via mitohormesis (Marcheggiani et al. 2019; Bouitbir et al. 2012; Liu et al. 2019).

![Fig. 1 Overview of Ber-mediated mitohormesis signaling. Ber mainly accumulated in the mitochondria after entering cells through organic cation transporter (OTC1/2) or passive diffusion. In mitochondria, Ber could target enzymes and other proteins associated with the electron transfer chain or mtDNA to disrupt energy homeostasis and induce translation stress. This can induce mitohormetic response via (1) ROS-mediated redox pathway, (2) AMP/ATP-induced AMPK pathway, (3) NAD⁺/NADH-mediated Sirtuins pathway (i.e., SIRT1), and (4) UPRmt pathway to regulate and maintain mitochondria homeostasis for the ability of cells to adapt to adverse circumstances](image-url)
Abbreviations
AMP: Adenosine monophosphate; AMPK: AMP-activated protein kinase; ATP: Adenosine triphosphate; Ber: Berberine; ETC: Electron transport chain; FOXO: Forkhead box protein O; NAD: Nicotinamide adenine dinucleotide; NAMPT: Nicotinamide phosphoribosyltransferase; OCT: Oxidative cation transporter; OXPHOS: Oxidative phosphorylation; ROS: Reactive oxygen species; SIRT1: SirT1-1; TCA: Tricarboxylic acid; UPRmt: mitochondrial unfolded protein response

Acknowledgements
We thank Graduate innovative Practice Base for clinical medicine of Xinxiang Medical University for support. We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Authors’ contributions
XZ and XG: Substantial contributions to the conception of the work, revising the article critically for important intellectual content, final approval of the submitted version, both agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YW and XZ: Drafting the article, final approval of the version to be published. By and XY: Searching literatures and collecting some related information. All authors read and approved the final manuscript.

Funding
This work was supported by grants from the National Natural Science Foundation of China (No. 81373135, No.81771690), The Training Plan of Young Key Teachers in Universities of Henan Province (No. 2014GGJS-097).

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Clinical Immunology, School of Laboratory Medicine, Xinxiang Medical University, Xinxiang 453003, China. 2Henan Collaborative Innovation Center of Molecular Diagnosis and Laboratory Medicine, Xinxiang Medical University, Xinxiang 453003, China. 3Henan Key Laboratory of Immunology and Targeted Drugs, Xinxiang Medical University, Xinxiang 453003, China. 4Department of Microbiology, School of Basic Medical Sciences, Xinxiang Medical University, Xinxiang 453003, China.

Received: 27 September 2019 Accepted: 9 January 2020
Published online: 23 January 2020

References
Bao J, Huang B, Zou L, Chen S, Zhang C, Zhang Y, He C. Hormetic effect of berberine attenuates the anticancer activity of chemotherapeutic agents. PLoS One. 2015;10(9):1–13.
Berberine. Bureau CM/MCM/MNM. Handbook of Effective Compositions in Plants. 1. Beijing: People’s Medical Publishing House; 1991. p. 12–8.
Bhadra K, Maiti M, Kumar GS. Berberine-DNA complexation: new insights into the cooperative binding and energetic aspects. Biochim Biophys Acta. 2008;1780(9):1054–61.
Bouitbir J, Charles AL, Echaniz-Laguna A, Kindo M, Daussin F, Auwerx J, Piquard F, Geny B, Zoll J. Opposite effects of statins on mitochondria of cardiac and skeletal muscles: a ‘mitohormesis’ mechanism involving reactive oxygen species and PGC-1. Eur Heart J. 2012;33(11):1397–407.
Brandauer J, Weinberg SG, Andersen MA, Ringholm S, Risis S, Larsen PS, Kristensen JM, Frigas C, Leick L, Fentz J, Jørgensen S, Kiens B, Wojtaszewski JF, Richter EA, Zierath JR, Goodyear LJ, Pilegaard H, Treebak JT. AMP-activated protein kinase regulates nicotinamide phosphoribosyltransferase expression in skeletal muscle. J Physiol. 2013;591(20):5207–20.
Calabrese EJ. Converging concepts: adaptive response, preconditioning, and the Yerkes-Dodson law are manifestations of hormesis. Ageing Res Rev. 2008;7(1):8–20.
Canto C, Gerhart-Hines Z, Feige JN, Lagouge M, Nüesch L, Milne JC, Elliott PJ, Puigserver P, Auwerx J. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature. 2009;458(7241):1056–60.
Canto C, Menzies KJ, Auwerx J. NAD+ metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. Cell Metab. 2015;22:31–53.
Cox CS, McKay SE, Holcombe BA, Christian BE, Scortecci AC, Tsai AJ, Newman LE, Shadel GS. Mitochondrione in mice via sustained Basal Activation of Mitochondrial and Antioxidant Signaling. Cell Metab. 2018;28(5):776–86 e5.
De Haes W, Froozinck L, Van Asche R, Smolders A, Depuydt G, Billen J, Braeckman BP, Schoofs L, Temmerman L. Metformin promotes lifespan through mitohormesis via the peroxioidixin PRDX-2. Proc Natl Acad Sci U S A. 2014;111(12):E2501–9.
Egan DF, Shackelford DB, Milhauya MM, Gelino S, Kohzn RA, Mair W, Vasquez DS, Joshi A, Gwinn DM, Taylor R, Asara JM, Fitzpatrick J, Dillin A, Viollet B, Kundu M, Hansen M, Shaw RJ. Phosphorylation of ULK1 (mTORG1) by AMP-activated protein kinase connects energy sensing to mitochondrial dysfunction. Science. 2011;331:456–61.
Gao N, Zhao TY, Li XJ. The protective effect of berberine on B-cell lipoprotein. J Endocrinol Investig. 2011;34(2):124–30.
Gariani K, Menzies KJ, Ryu D, Wegner CJ, Wang X, et al. Elitizing the mitochondrial unfolded protein response via NAD repletion reverses fatty liver disease. Hepatology. 2015;63:1190–204.
Guo J, Wang L, Wang L, et al. Berberine protects human umbilical vein endothelial cells against LPS-induced apoptosis by blocking JNK-mediated signaling. Evid Based Complement Alternat Med. 2016;2016:6983956.
Han X, Tai H, Wang X, Wang Z, Zhou J, Wei X, Ding Y, Gong H, Ma C, Zhang J, Qin J, Ma Y, Huang N, Xiang R, Xiao H. AMPK activation protects cells from oxidative stress-induced senescence via autophagic flux restoration and intracellular NAD(+) elevation. Aging Cell. 2016;15(3):416–27.
Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol. 2017;19:121–35.
Houtkooper RH, Auwerx J. Exploring the therapeutic space around NAD+. J Cell Bio. 2012;199:205–9.
Huang L. In: JNM, editor. Chinese Materia Medica Dictionary. 1. School. Shanghai: Shanghai Scientific & Technical Publishers; 1986. p. 2022–30.
Imai S, Guerreiro L, NAD+ and sirtuins in aging and disease. Trends Cell Biol. 2014;24(8):464–71.
Jiang W, Li S, Chen X, Zhang W, Chang Y, He Y, Zhang S, Su X, Gao T, Li C, Jian Z. Berberine protects immortalized line of human melanocytes from H2O2-induced oxidative stress via activation of Nrf2 and Mef2 signaling pathway. J Dermatol Sci. 2019;194(1):236–42.
Joulain V, Mouchiroud L, Auwerx J. The mitochondrial unfolded protein response, a conserved stress response pathway with implications in health and disease. J Exp Biol. 2014;217:137–43.
Khan NA, Auranen M, Paetau I, Pirinen E, Euro L, Forststrom S, Pasila L, Velagapudi V, Carroll CJ, Auwerx J, Suomalainen A. Effective treatment of mitochondrial myopathy by nicotinamide riboside: a vitamin B3. EMBO Mol Med. 2014;6(6):712–31.
Kong W, Wei J, Abidi P, Lin M, Inaba S, Li C, Wang Y, Wang Z, Si S, Pan H, Wang S, Wu J, Wang Y, et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med. 2004;10:344–51.
Lan J, Rollins JA, Zang X, Wu D, Zou L, Wang Y, Zou C, Wu Z, Kapahi P, Rogers AN, Chen D. Translational regulation of non-autonomous mitochondrial stress response promotes longevity. Cell Res. 2019;28(4):1050–62.
Lenaz G. The mitochondrial production of reactive oxygen species: mechanisms and implications in human pathology. IUBMB Life. 2001;53(5–6):159–64.
Liu DQ, Chen SP, Sun J, Wang XM, Chen N, Zhou YQ, Tian YK, Ye DW. Berberine protects against ischemia-reperfusion injury: a review of evidence from animal models and clinical studies. Pharmacol Res. 2019;148:104385.
Marcheggiani F, Cinilli L, Orlando P, Silvestri S, Vogelstang A, Knott A, Bliat T, Weise JM, Tiano L. Modulation of Coenzyme Q10 content and oxidative status in human dermal fibroblasts using HMG-CoA reductase inhibitor over a broad range of concentrations. From mitohormesis to mitochondrial dysfunction and accelerated aging. Aging (Albany NY). 2019;11(9):2565–82.
Mattson MP. Hormesis defined. Ageing Res Rev. 2008;7(1):1–7.
Mehta MM, Weinberg SE, Chandel NS. Mitochondrial control of immunity: beyond ATP. Nat Rev Immunol. 2017;17(10):658–20.
Mikes V, Dadák V. Berberine derivatives as cationic fluorescent probes for the investigation of the energized state of mitochondria. Biochim Biophys Acta. 1983;723(2):231–9.

Mouchnioud L, Houtkooper RH, Moullan N, Katsuya E, Ryu D, et al. The NAD + /sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. Cell. 2013;154:430–41.

Moullan N, Mouchnioud L, Wang X, Ryu D, Williams EG, et al. Tetracyclins disturb mitochondrial function across eukaryotic models: a call for caution in biomedical research. Cell Rep. 2015;10:1681–91.

Nies AT, Herrmann E, Brom M, Keppler D. Vectorial transport of the plant alkaloid berberine by double-transfected cells expressing the human organic cation transporter 1 (OCT1, SLC22A1) and the efflux pump MDRI P-glycoprotein (ABCB1). Naunyn Schmiedeberg's Arch Pharmacol. 2008;376(6):449–61.

Obata F, Fons CO, Gould AP. Early-life exposure to low-dose oxidants can increase longevity via microbiome remodelling in drosophila. Nat Commun. 2018;9(1):975.

Orenius S, Gogvadze V, Zhivotovsky B. Mitochondrial oxidative stress: implications for cell death. Annu Rev Pharmacol Toxicol. 2007;47:143–82.

Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, Gu CJ, Tong XL. Application of berberine on treating type 2 diabetes mellitus. Int J Endocrinol. 2015;2015:905749.

Pereira GC, Branco AF, Matos JA, Pereira SL, Parke D, Perkins EL, et al. Mitochondrially targeted effects of Berberine (natural yellow 18, 5,6-dihydropyrido[1,2-c]imidazole-9,10-dimethoxybenzog)-1,3-benzodioxolo(5,6-a)quinolizinium) on K1735-M2 mouse melanoma cells: comparison with direct effects on isolated mitochondrial fractions. J Pharmacol Exp Ther. 2007;323(2):636–49.

Qu R. Herbology. 1. Shanghai University of Traditional Chinese Medicine Press; 2006.

Quiros PM, Mottis A, Auwerx J. Mitonuclear communication in homeostasis and stress. Nat. Rev. Mol. Cell Biol. 2016;17:23.13–26.

Ristow M. Unraveling the truth about antioxidants: mitohormesis explains ROS-mediated health benefits. Nat Med. 2014;20(7):709–11. https://doi.org/10.1038/nm.3624.

Serafin TL, Oliveira PJ, Sardao VA, Perkins E, Parke D, Holy J. Different concentrations of berberine result in distinct cellular localization patterns and cell cycle effects in a melanoma cell line. Cancer Chemother Pharmacol. 2008;66(6):1007–18.

Shi R, Yang Y, Xu Z, Dai Y, Zheng M, Wang T, Li Y, Ma Y. Renal vectorial transport of berberine mediated by organic cation transporter 2 (OCT2) and multidrug and toxin extrusion proteins 1 (MATE1) in rats. Biopharm Drug Dispos. 2018;39(1):47–58.

Sun S, Wang K, Lei H, Li L, Tu M, Zeng S, Zhou H, Jiang H. Inhibition of organic cation transporter 2 and 3 may be involved in the mechanism of the antidepressant-like action of berberine. Prog Neuro-Psychopharmacol Biol Psychiatry. 2015;56:253–61.

Tabichi K, Ichimura K, Ristow M. Impaired insulin/IGF1 signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal. Cell Metab. 2012;15(4):451–65.

Zhang C, Li C, Chen S, Li Z, Jia X, Wang K, Yao B, Jiang Y, Wang Y, Chen M, Li P, Su H, Wan JB, SMY L, Liu X, He C. Berberine protects against 6-OHDA-induced neurotoxicity in PC12 cells and zebrashift through hormetic mechanisms involving R3K/AKT/Bcl-2 and Nrf2/HO-1 pathways. Redox Biol. 2017:111–11.

Zhang H, Ty C, Wuy, Yu, Gariyan K, Wang X, et al. NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. Science. 2016;352:1436–43.

Zhang C, Chen Y, Deng J, Jia X, Zhou J, Hu L. Solid dispersion of berberine–phospholipid complex/TPGS 1000/SDO2: preparation, characterization, and in vivo studies. Int J Pharm. 2014;465:11–11.

Zhang Z, Zang F, Stuber F, Sherlock J. Improved outcome of EAN an animal model of GBS through amelioration of peripheral and central inflammation by minocycline. J Cell Mol Med. 2009;13(2):341–51.

Zhou H, Halicka HD, LD J, Darzykiewicz Z. Berberine suppresses Gero-conversion from cell cycle arrest to senescence. Aging (Albany NY). 2013;5(8):623–36.

Zhou L, Sun LN, Nie HB, Wang XL, Guan GJ. Berberine improves kidney function in diabetic mice via AMPK activation. PLoS One. 2014;9(11):e113398.

Zhao Q, Wang J, Levichkin M, Stasinopulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. EMBO J. 2006;13(2):341–51.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.