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Review

Effects of Mitochondrial Dysfunction via AMPK/PGC-1α Signal Pathway on Pathogenic Mechanism of Diabetic Peripheral Neuropathy and the Protective Effects of Chinese Medicine*

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ABSTRACT Diabetic peripheral neuropathy (DPN) is a progressive neurodegenerative disease of peripheral nervous system with high energy requirement. The adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) axis plays a key role in regulating mitochondrial energy metabolism. Increasing preclinical evidences have shown that inhibition of AMPK/PGC-1α pathway leading to mitochondrial dysfunction in neurons or Schwann cells contributes to neuron apoptosis, distal axonopathy and nerve demyelination in DPN. Some Chinese medicine formulae or extracts from herbs may have potential neuroprotective effects on DPN via activating AMPK/PGC-1α pathway and improving mitochondrial function.

KEYWORDS monophosphate-activated protein kinase, peroxisome proliferator-activated receptor-γ coactivator 1α, sirtuins, diabetic peripheral neuropathy, Chinese medicine

Diabetes mellitus (DM) is one of the leading causes of deaths in many countries and it has become an increasing and serious health burden globally. Individuals with both type 1 and type 2 DM are at high risk of developing diabetic peripheral neuropathy (DPN),[1,2] a major cause of recurrent lower extremity infection, foot ulcer and amputation. Putative pathophysiologic mechanisms of DPN include enhanced polyol pathway activity, increased advanced glycation-end products, activation of protein kinase C, accumulations of reactive oxygen species (ROS)[3,4] and neurotrophic deficiency[5,6] characterized by neuron apoptosis, axonal degeneration or nerve demyelination.

DPN is a progressive neurodegenerative disease of peripheral nervous system with high energy requirement. Mitochondrial dysfunction has been suggested as an important contributor to the pathogenesis of DPN.[7] Abnormal mitochondrial function and bioenergetics in peripheral nerve may cause impaired axonal plasticity, diminishment of collateral sprouting, axonal degeneration and disorder of nerve regeneration.[7-11] The term of "mitochondrial dysfunction" widely used in literature has embodied diverse concepts, for example, changes in mRNA level of mitochondrial markers, proteins level, mitochondrial electron transfer chain, mitochondrial transmembrane potential, enzymatic activity of components of mitochondrial oxidation,[12] and mitochondrial trafficking.[13] Besides, both hyperglycemia and dyslipidemia may cause mitochondrial dysfunction in DPN.[7,13]

As an intracellular energy sensor and modulator, the adenosine monophosphate-activated protein kinase (AMPK) is activated in response to cell energy depletion. Proteins of peroxisome proliferator-activated receptor-γ coactivator 1 (PGC-1) family of transcriptional coactivators coordinate physiological adaptation on many tissues especially in response to high demands for energy supply. Of the members in the family, PGC-1α plays various roles in mediating gluconeogenesis, glycolysis, lipogenesis, mitochondrial fatty acid oxidation and mitochondrial respiratory efficiency. Under nutrient starvation, AMPK/PGC-1α pathway is activated to promote adenosine triphosphate (ATP)

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production. AMPK/PGC-1 α signaling pathway plays a crucial role in survival and degeneration of neurons.[14] Mitochondrial bioenergetics profiles are found to be impaired with down-regulation of expression of AMPK/PGC-1 α in dorsal root ganglia (DRG) neurons under diabetic condition.[15] AMPK activators can prevent the abnormal molecular changes as well as behavioral abnormalities in experimental DPN.[16]

This review focuses on recent advances of the influence of mitochondrial dysfunction on pathogenesis of DPN through the AMPK/PGC-1 α signaling pathway. Recently, the protective effects of Chinese medicine (CM) on DPN have become a hot topic. CM may help improve the mitochondrial function by regulating the signaling pathway on energy metabolism, thus CM may have therapeutic effects on DPN. Therefore, the present paper also reviews current studies and evidence regarding the neuroprotective effects of CM on DPN, with an emphasis on the interactions between AMPK/PGC-1 α signaling pathway and mitochondrial function.

Morphological Abnormalities of Mitochondria in DPN

Earlier studies have observed the morphological alterations of mitochondria induced by hyperglycaemia *in vivo* or *in vitro*. In DRG of DPN animals, both DRG cell bodies and nerve roots display morphological changes in mitochondrial cristae structures,[17,18] for example, swollen cristae of mitochondria, increased numbers of mitochondria and elevated mitochondrial density in the axons. In cultured DRG neurons, high glucose generates ROS coupled with enlargement of mitochondria and unstability of mitochondrial membrane potential (MMP).[19] High glucose also decreased the number of mitochondria and promoted the fragmentation of mitochondria through the activation of pro-apoptotic proteins and the mitochondrial fission protein dynamin-regulated protein 1.[20] Mitochondria fission was proposed to be a kind of self-defense mechanism in neurons. The appropriate self-defense mechanism leads to imbalance between fission/fusion and causes mitochondria damage. In the nerve terminal from sympathetic ganglia of diabetic mice, the ultrastructure alterations of synaptic vesicle was observed coupled with aggregates of hyperchromatic and small mitochondria.[21] Furthermore, changes of mitochondrial morphology were also confirmed in human peripheral nerve biopsies. In intraepidermal nerve fibers from patients with DPN, the number of mitochondrial was the same with that of control participants despite mitochondria volume enlarged in DPN.[22] The results of these studies indicated that changes in the numbers of mitochondria are different in diverse peripheral nervous tissues with an imbalance between fission/fusion of mitochondria in DPN. Mitochondrial ultrastructural damages occur in the peripheral nervous tissues of both diabetic animals and patients with DPN.

Changes in Mitochondria Proteome and Mitochondria DNA in Experimental DPN

Normal mitochondrial activity in peripheral nerve depends on the function of a series of mitochondrial proteins that maintain the metabolism homeostasis of neurons and Schwann cells (SCs). Totally 197 proteins were reported in mitochondria with 127 proteins of them were involved in metabolism process.[23] The mitochondrial proteins profiles change significantly in DPN animals.[10] The expressions of nearly half of the mitochondrial proteins were observed to be either inappropriately down-regulated or up-regulated in DRG of diabetic rats.[24] Abnormal mitochondrial oxidative phosphorylation exists in the sciatic nerve (SN) of diabetic rats including increased expression of complexes Ⅰ, Ⅲ, Ⅳ and Ⅴ and elevated level of mitochondrial ρ-GTPase 1 (Miro1, a protein modulating mitochondrial electron transport chain). While these changes were not found in other nervous tissues.[23] Thus, SN may be the most vulnerable nervous tissue in DPN. Guilford, et al[25] reported that complex Ⅲ subunit Core-2 and voltage-dependent anion channel increased significantly in streptozotocin (STZ)-induced diabetic mice. Akude, et al[9] analyzed the protein profiles in mitochondria by using stable isotope labeling with amino acids in cell culture. The results showed that the activity of respiration and mitochondrial complex (complex Ⅰ, complex Ⅳ, the Krebs cycle enzyme and citrate synthase) in DRG from diabetic rats significantly decreased. At present, results from the limited studies indicate that the abnormal mitochondria proteome contributes to DPN via impairment in oxidative phosphorylation and respiratory chain activity. Although the changes of mitochondrial proteome have been observed in DPN models, the exact mechanism remains a mystery. With the development of proteome technology, the mitochondrial proteomic studies will help to

understand the exact content and functional changes of mitochondrial protein in DPN.

A diminishment of mitochondrial DNA (mtDNA) copy number and content was reported in experimental DPN models.[18,26,27] Mitochondrial transcriptional factor A (TFAM), a nuclear DNA encoding protein, can regulate the replication and transcription of mtDNA in peripheral DRG neurons of diabetic rodent animals. Nerve conduction velocity, mechanical allodynia, and thermal nociception was reported to be prevented in diabetic TFAM transgenic mice, indicating up-regulating TFAM expression can improve DPN.[26] Furthermore, TFAM expression can be regulated by PGC-1α. Choi, et al[27] found that the expression of TFAM was reduced in DRG neurons from PGC-1α gene knockout mice. Similarly, both the expression of TFAM and nuclear respiratory factor-1 (NRF-1) gene decreased in diabetic PGC-1α (-/-) neurons compared to that in diabetic PGC-1α (+/+) neurons, parallel with reduction of mtDNA. Hence, TFAM is an important regulator of mtDNA which may have influence on pathogenesis of DPN through PGC-1α related pathway. Moreover, diabetes-induced oxidative stress can affect mtDNA and then lead to the mutations of mitochondrial genome.[28] However, it is still not clear how the proteins encoded by mtDNA play the role in the pathogenesis of DPN yet. Most of the proteins that are known to be related to mitochondrial dysfunction in DPN are encoded by nuclear genes, not mtDNA

Mitochondrial Dysfunction in Myelin

Myelin sheath is a lipid membrane wrapped in the surface of an axon, which has multiple functions such as protection, nutrition and insulation of the neuronal axon. The segmental or diffuse myelin sheath shrinkage and demyelination commonly existing in DPN can lead to nerve action potential conduction disorders.[23,29] The process maintaining the peripheral axon and nerve fiber growing consumes a large amount of ATP from mitochondria.[7,30,31] The mitochondria in myelin may be an important organelles to maintain metabolic homeostasis in peripheral neurons and SCs. In central nervous system, mitochondria are able to enter and move within the myelin sheath, and accumulate in the cytoplasmic ridges along the sheath of glial cells.[32] In peripheral nervous system, SCs play an essential role in myelination.[33,34] It boosts the axonal regeneration. Mitochondrial dysfunction in SCs may be associated with demyelination and axon degeneration.[35] Ino, et al[36] raised a neurons-to-SCs mitochondria signal during myelination. Stimulation of SN increases extracellular ATP and then sends messages from neurons to SCs mitochondria for the regulation of myelination. Additionally, deficiency of some neurotrophic factors synthesized by SCs is closely related to aberrant mitochondrial bioenergetics as measured by oxygen consumption rate in sensory neurons in high glucose incubation.[37] At present, there are few studies focusing on the relationship between mitochondrial energy regulation pathway and process of myelin formation or demyelination in DPN. Much effort is needed to clarify the role of myelin mitochondria in peripheral neuropathies.

Mitochondrial Dysfunction via AMPK/PGC-1α Signal Pathway in DPN

AMPK/PGC-1α is a crucial signal pathway in the energy metabolism regulation of biological cells. The cellular energy status is sensed by AMPK/PGC-1α signal pathway that directly modulates the biogenesis and function of mitochondria. In the last decade, the strong correlation between AMPK/PGC-1α pathway and diabetes has been found.[38] Energy starvation launches this pathway by increasing the ratio of AMP/ATP. AMP and AMPK crosslinking switches the catabolic metabolism and stimulates the synthesis of ATP.[39] Similarly, the loss of mitochondrial function related to damage of AMPK/PGC-1α signal pathway in peripheral nervous system also plays a key role in the onset and progression of DPN.[7] Activating the AMPK/PGC-1α axis may be conducive to the preservation of mitochondrial function in the peripheral nervous system under hyperglycaemia.[40]

The ubiquitous intracellular kinase AMPK consists of a catalytic α-subunit and regulatory β- and γ-subunits. In normal nutritional status,[41] energy consuming elevates AMP/ATP ratio and boosts the binding of AMP to the γ-subunit in sequence.[42] The combination leads to the activation of the kinase through enhancing phosphorylation of the α-subunit. Then the activation of AMPK induces phosphorylation of PGC-1α which impacts on mitochondrial function and biogenesis positively, and meanwhile off energy-consuming processes.[39] AMPK not only senses metabolic stress but also integrates many physiological signals to restore energy homeostasis. As a result, catabolic

and anabolic pathways are balanced. Nerve tissue meets high energetic demands for growth of neurons, neurite outgrowth and neurotransmission, which is also vulnerable to energy expenditure. In general, AMPK is activated by low glucose and inhibited by high glucose. Hyperglycaemia or insulin signal damage causes the failure of mitochondrial function by inducing silence of AMPK which may contribute to vascular complications of diabetes.[43] High glucose stress decreases the AMP/ATP ratio via excess flux of glucose. When the energetic demands increasing in neurons, this pathway inhibited by hyperglycaemia is under reaction with down-regulated AMPK activity. The maladaption of energy metabolism finally causes neuron damage.[7] The phosphorylation level of AMPK in SN was also found to be lower in diabetic rats than that in the normal control rats.[44] Activation of AMPK is beneficial to nerve regeneration after peripheral nerve injury and neuropathic pain owing to regulating the neuron excitability.[45] High glucose exposure impairs the phosphorylation and activity of AMPK in neurons accompanied with enhanced generation of mitochondrial specific superoxide and mitochondrial membrane depolarization.[46] Therefore, the relationship between activity of AMPK and mitochondrial function is very close.

In the process of mitochondrial energy metabolism, PGC-1α is a master co-activator, which plays a vital role in coordinating mitochondrial biogenesis and metabolic related gene signal network.[47] The most directive evidence is that over-expression of PGC-1α gene increases the number and enhances the function of mitochondria, on the contrary, depletion of PGC-1α results in mitochondrial dysfunction and metabolic disorders.[48] Besides, one of the important functions of PGC-1α is the detoxification of ROS generated during mitochondrial respiration process.[49] PGC-1α has emerged as a key modulator which can remove the oxidative by-products by means of enhancing the expression of ROS-detoxifying enzymes.[50] Series of studies found that PGC-1α was closely related to some neurodegenerative diseases such as Parkinson's disease,[51] Huntington's disease[52] and Alzheimer's disease.[53] Then a study observed that PGC-1α decreased in the peripheral sensory DRG in diabetic animal models.[15] Moreover, in DRG neurons cultured *in vitro*, down-regulation of PGC-1α leads to mitochondrial dysfunction accompanied by abnormal mitochondrial respiratory chain. Some studies showed that promoting expression of PGC-1α can alleviate injury from oxidative stress in sensory neurons[27] and be benefit for attenuation of glucose-mediated injury in central neurons.[54] In the study of Choi, et al[27] mice lacking of PGC-1α gene developed a mild peripheral neuropathy and then exacerbated by diabetes. The diabetic mice with PGC-1α gene defects exhibited more serous peripheral neuropathy than the control diabetic mice. In DRG derived from both type 1 and type 2 diabetic neuropathy rodent models, the expression and phosphorylation of AMPK/PGC-1α is significantly down-regulated, which has bad effects on the neurite outgrowth.[11] In this signal pathway, PGC-1α can regulate mitochondrial respiratory related proteins and gene expression via NRF1 and TFAM transcription as mentioned above. The study of Choi, et al[27] found that the expression of NRF-1 and TFAM in DRG neurons of DM rats without PGC-1α gene were significantly reduced.

The sirtuins (SIRTs) includes 7 isoforms in mammals. SIRT1-3, a class of NAD^+-dependent deacetylases, were confirmed to involve in regulation of AMPK/PGC-1α axis.[10] SIRTs act as a sensor of NAD^+ levels via NAD^+/NADH ratios under the condition of nutrient consumption.[7,10] Both of SIRT1 and SIRT2 (the cytoplasmic isoforms) can increase the activity of PGC-1α by deacetylation of itself to make tissues suitable for energy changes in different status.[55] Up-regulating expression of upstream SIRT1 enhances activation of AMPK/PGC-1α mitochondrial biogenesis axis and consequently leads to protection of endothelial cells from ROS-mediated mitochondrial injury.[56] SIRT1-modulated regulation of PGC-1α was suggested to dependent on the activation of AMPK. But the molecular interaction between AMPK and SIRTs are still unclear. Similarly, improving expression of SIRT1 can activate AMPK/PGC-1α pathway and may have the effects of protecting cardiomyocytes by ameliorating mitochondrial dysfunction.[47] But diabetes can lower the NAD^+/NADH ratio in nerve[57] and then may suppress of SIRTs/PGC-1α pathway in peripheral nerve system. Significant reduction in the level of SIRT1 was observed in high glucose-exposed neurons with parallel decreasing of PGC-1α and NRF-1.[46] SIRT3 localizes in mitochondria. And its targeted enzymes involve in several mitochondrial energetic metabolism processes, such as respiratory chain, tricarboxylic acid cycle, and fatty acid β-oxidation.[58] SIRT3 was reported to be the key factor in mediating the axoprotective

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effects of NAD^+ during both neurodegeneration-related dying-back processes and axotomy.[59] High glucose concentration also lowers the SIRT3 expression with down-regulation of PGC-1α and AMPK in diabetic myocardium *in vivo* and *in vitro*.[60] Furthermore, SIRT3 level is positively associated with the expression of AMPK and PGC-1α in sciatic nerve in diabetic rats.[61] Recently, SIRTs have become an attractive target for neurodegenerative diseases and metabolic diseases therapy. However, it is very limited of the understanding of SIRTs in pathophysiological mechanism of DPN. The current studies are just the beginning of further exploration to the role of SIRTs in pathogenesis of DPN.

According to the current studies, hyperglycaemia induces the suppression of AMPK or SIRTs in peripheral nerve system,[10,11] and then lowers the expression of PGC-1α which will lead to suboptimal transcriptional of a range of genes (such as NRF-1, NRF-2).[62] The downstream of the signal may include many kinds of mitochondrial proteins that are involved in mitochondrial biogenesis, respiratory chain, and tricarboxylic acid cycle.[11] Impairment of the axis finally causes energy metabolism disorder and oxidative stress injury contributing to loss of neurons and distal fibres, axonopathy, demyelination. Enhancing the axis has been proposed to improve the structural abnormality of both myelinated and unmyelinated fibres in DPN rodent models.[11] However, limited studies just found a causal link between SIRTs/AMPK/PGC-1α and mitochondrial dysfunction in DPN. What the exact roles of downstream proteins is an area in need of investigation. Whether regulation of AMPK/PGC-1α axis can reverse the abnormal mitochondrial morphology is still needed to be confirmed. Further studies should utilize more advanced imaging techniques to detect the morphological changes and observe the mitochondrial trafficking *in vivo* after target treatment.

Target Treatment in CM

Medications targeting to AMPK/PGC-1α axis and promoting the mitochondrial biogenesis recently emerge as a novel and potential therapy of DPN. AMPK activators are proposed to improve experimental DPN.[63] Some chemical medications were found to be neuroprotective on diabetes-induced mitochondrial dysfunction via AMPK/PGC-1α pathway, such as insulin,[64] metformin,[65] fenofibrate.[66] Meanwhile, some CM formula or extracts of herbs were reported to have benefits on stabilizing MMP and inhibiting apoptosis of neurons or SCs.[67,68] More recent studies found that CM could improve mitochondrial dysfunction through AMPK/PGC-1α signal pathway.

Coptis chinensis rhizomes and Its Effective Components

Both watery extract of *Coptis chinensis rhizomes* (CRE) and coptisine which was suggested to be active single compounds of CRE were reported to attenuate tert-butlhydroperoxide-induced cytotoxicity in neuroblastoma cells through increasing the MMP and alleviating ROS production.[69] Berberine is an isoquinoline alkaloids extracted from several CM herbs mainly by CRE to treat metabolic syndrome and diabetes. It has been found to have anti-inflammatory and antioxidant activities[70] *in vitro* and neuroprotective effects in animal models.[69] In the study by Yerra, et al[71] berberine administration could promote both AMPK and SIRT1 expression and increase the level of ATP in sciatic nerve of diabetic rats. Berberine treatment also attenuated the reduction of mitochondrial biogenesis through increasing PGC-1α expression and nuclear localization in neuro 2a (N2A) cells under hyperglycemic condition. Meanwhile, the authors found that berberine could inhibit the generation of ROS induced by high glucose, stabilize the MMP, regulate autophagy markers and improve motor and sensory nerve conduction velocities in diabetic rats. Results of the study indicated that the mitochondrial protective effects of berberine was closely related to AMPK/PGC-1α pathways in DPN.

Extracts from root of *Salvia Miltiorrhiza* Bunge

Salvia Miltiorrhiza Bunge is also a common herb which is used to treat chronic complications of diabetes in CM. Some animal or cell studies have detected the pharmacological effects of *Salvia Miltiorrhiza* Bunge extra on experimental DPN. Salvianolic acid B (Sal B), a bioactive compound extracted from *Salvia Miltiorrhiza* Bunge, was reported to have anti-oxidative stress effects on SCs cultured in high glucose *in vitro* via mitochondrial pathway. Sal B was proposed to prevent mitochondrial membrane depolarization and apoptosis in a dose-dependent manner,[68] although it is unclear whether the neuroprotective effects of Sal B were related to AMPK/PGC-1α signals. But Salvianolic acid A (Sal A), another water-soluble constituent of *Salvia miltiorrhiza* Bunge, was recently proved to improve

the electrophysiological changes and also alleviate the ultramicrostructure damage in sciatic nerves of diabetic rats, for instance, shrunken and swollen axons, derangement of the myelin, cytoplasmic vacuolization and loss of organelles in SCs. In this study, Sal A (1 mg/Kg) treatment could enhance the phosphorylation of AMPK and the expression of PGC-1α, SIRT3 in SNs.[61]

Radix Aconitilateralis

Many CM clinicians use *Radix Aconitilateralis* to treat DPN because it can commonly alleviate the symptoms of numbness, sensation of cold and pain in the extremities. Several recent studies revealed that it may have potential benefits to improve mitochondrial pathway.[72,73] A recent study found that the treatment of *Radix Aconitilateralis* combined with *Rhizoma Zingiberis* could provoke mitochondrial biogenesis in rats with heart failure via SIRT1/PGC-1α axis.[74] The neuroprotective effects of *Radix Aconitilateralis* polysaccharides (RAP) were observed as well in SCs exposed to high glucose concentration. RAP enhanced expression of p-AMPK and PGC-1α in a dose-dependent manner parallel with inhibition of production of intracellular ROS and cell apoptosis.[73] *Radix Aconitilateralis* treatment has been proved to improve the motor nerve conduction velocity and reverse the thermal hypoalgesia in diabetic rats *in vivo*.

Resveratrol

Resveratrol, a natural polyphenol, is contained in CM herbs named *Rhizoma Polygoni Cuspidali* and exits in many plants. It has attracted more attention due to its neuroprotective properties against diabetes-induced oxidative damage.[75] According to the study by Roy, et al[11] resveratrol can reverse the clinical and pathological features of DPN including thermal hypoalgesia, intraepidermal nerve fibre loss, and reduce myelinated fibre axonal caliber through enhancing the activity of AMPK/PGC-1α pathway mediated neurite outgrowth and axons regeneration.

Other CM Monomers or Compound Formulae

Some other CM monomers or compound formulae were reported to reverse mitochondrial function by stabilizing mitochondrial membrane potential and alleviating oxidative injury in peripheral nerve. A study tested the neuroprotective effects of puerarin, an active ingredient from a CM herbs *Radix Puerariae*, which could significantly decrease mitochondrial depolarized of SCs in glucose fluctuation culture.[76] Puerarin may be benefit for stabilizing mitochondrial potential to protect the mitochondrial function of SCs.[76] Zhang, et al[24] suggested the CM recipe Tang-luo-ning (糖络宁, TLN) comprised of *Astragalus root*, *Fructus corni*, *Rhizoma cibotii*, and *Salvia miltiorrhiza* could ameliorate peripheral nerve conduction velocity through restoring the abnormal mitochondrial protein profiles in diabetic neuropathy rats. But they have not tested whether the neuroprotective properties of TLN due to the improvement of AMPK/PGC-1α pathway.

It is of great significance to find CM medications to be neuroprotective via activating AMPK/PGC-1α pathway. The further aims of studies in DPN may focus on the influence of CM targeting to mitochondrial energy pathway. Additionally, current studies found some extracts of CM herbs to be natural AMPK activators,[77] such as curcumin (polyphenols compounds separated from turemeric),[78] quercetin (exsting in many herbs for example: *Flos sophorae Immaturus*, *Folium Mori*, *Crateagus pinnatifida* Bunge, and also in some vegetables and fruits).[79,80] These compounds may need to be screened for their potential neuroprotective effects on DPN.

Summary and Concluding Remarks

Mitochondrial dysfunction that occurs in sensory neurons and/or SCs contributes to cell apoptosis, distal axonopathy and nerve demyelination in experimental DPN. Silence of AMPK or PGC-1α reduction can cause mitochondrial dysfunction. Increasing preclinical evidences have shown that AMPK/PGC-1α signal pathway plays a crucial role in the development of DPN. In addition, down-regulation of SIRTs also involves in the process of mitochondrial energy metabolism via interaction with AMPK/PGC-1α axis. Some CM formulae or extracts of herbs were observed to have a potential neuroprotective effects on DPN due to activating AMPK/PGC-1α pathway. It is necessary to explore the promising candidate agents of CM for DPN by targeting AMPK/PGC-1α signal pathway. However, there are many limitations in the current studies. Many proteins directly involved in the pathway and the roles of them in DPN are still unclear. It remains to be investigated exact mechanism of the interaction between mitochondrial proteins and the regulation of related gene expression. Subsequent and accurate

mechanisms of upstream and downstream in this pathway are not fully clarified. Thus further studies will be needed. For instance, what are the positive or negative contributors of the axonal regeneration? Whether the mitochondrial energy metabolism abnormality induced by hyperglycemia could be reversed? How to protect the mitochondrial function of peripheral nervous system in diabetes? New techniques will be needed to investigate mitochondrial function and biogenesis in situ *in vivo*. Given that the protective effects of CM on DPN has been proved in limited studies, further exploration should be carried out with emphasis on precise mechanism by which CM improves mitochondrial function.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Zhang Q and Liang XC performed the literature review. Zhang Q drafted the manuscript under Liang XC's guidance and review. Both authors have read and approved the final manuscript.

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