



Yang/Qi-invigorating herbs for the prevention and/or treatment of diabetic complications

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Abstract: Based on traditional Chinese medicine (TCM) theory, Yang and Qi are the driving forces of physiological functions in the body, by the virtue of their role in regulating mitochondrial function. While the biochemical basis of Yang-invigoration primarily involves a stimulation of mitochondrial adenosine triphosphate generation capacity (GC) via fluidizing the mitochondrial inner membrane, Qi-invigoration elicits a glutathione-dependent antioxidant response, presumably via activating nuclear factor (erythroid-derived 2)-like 2 (the master regulator of antioxidant gene expression). In this regard, Yang-invigorating herbs can increase mitochondrial ATP production whereas Qi-invigorating herbs preserve the structural integrity of mitochondria in the presence of oxidative stress. Accumulating evidence has shown that type 2 diabetes, which is mainly caused by over-nutrition, is associated with mitochondrial dysfunction. As a result of mitochondrial lesions and the pathogenesis of diabetes, complications, such as cardiomyopathy and nephropathy, are major causes of morbidity and mortality in patients with diabetes. Since mitochondria are the primary target of Yang- and Qi-invigoration, the possible beneficial effects of Yang- and Qi-invigorating herbs in the prevention and/or treatment of diabetic cardiomyopathy and nephropathy warrant further investigation. The identification of active compounds isolated from Yang- and Qi-invigorating herbs and the elucidation of the biochemical mechanism(s) underlying their beneficial actions on mitochondrial function could not only provide a rational basis for developing herbal health products but also help to establish biomarkers for the quality control of Yang/Qi-invigorating herbal products.

Keywords: Chinese tonifying herbs; Yang-invigoration; Qi-invigoration; mitochondria; ATP generation; glutathione status; diabetic complications

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The Yin-Yang theory in traditional Chinese medicine (TCM)

TCM views the human body as an organic entity made up of various organs that function in a mutually interdependent manner (1). The Yin-Yang theory, which originated from ancient Chinese philosophy, is central to the conceptual framework of TCM. According to the Yin-Yang theory, the functioning of the human body is governed by the interplay of two complementary, but opposing, forces, namely, Yin

and Yang. The dynamic equilibrium between Yin and Yang determines the physiological status of the human body (2). Any disturbance in the balance of Yin and Yang can lead to various pathological conditions. For example, an excess of Yin can lead to an over-consumption of Yang and, conversely, a relative excess of Yin or Yang is referred to as Yang deficiency or Yin deficiency, respectively. Therefore, within this conceptual framework, TCM classifies bodily structures, explains clinical symptoms, and guides the

treatment of diseases on the basis of the Yin-Yang theory (3).

According to TCM theory, the interaction between Yin (postnatal essence or Yin Qi) and Yang (prenatal essence or Yang Qi) generates Zheng Qi (i.e., “the Qi of the body”) which maintains life activities and defends against pathogens, as well as allowing adaptive changes in the body in response to internal and/or external factors. Zheng Qi can flow through meridians and thereby energize physiological activities. TCM theory also states that aging and aging-associated disorders can result in a gradual depletion of Zheng Qi and the complete deprivation of Zheng Qi (which is mainly due to the exhaustion of prenatal essence) will ultimately result in death (4). As the prenatal essence is inherited from parents and hence cannot be replenished after birth, a sufficient supply of postnatal essence is needed to minimize the utilization of prenatal essence for the generation of Zheng Qi. According to TCM theory, Blood, a thick red liquid circulating in circulatory vessels, is viewed as one of the basic substances essential for supporting vital activities in humans. Blood circulation in the body is dependent on the driving action of Qi and it exerts a strong nourishing effect on various organs. The inter-relationship between Qi and Blood exemplifies the importance of a harmony between Yin (Blood) and Yang (Qi) in determining optimal physiological function.

Restoration of Yin-Yang balance in sub-healthy conditions

While exhaustive sexual activity and the Yin-Yang imbalance of body functioning can cause an over-consumption of prenatal essence, the maintenance of an optimal Yin-Yang balance for body functions (in particular that of the “Spleen” for digestion and absorption) and a healthy lifestyle (diet and physical exercise) is crucial in acquiring sufficient postnatal essence, and thereby in preserving the prenatal essence in humans. In this regard, the use of Chinese tonifying herbs aims to re-establish the Yin-Yang balance in the body and thereby prevent the over-consumption of prenatal essence. In addition, any internal or external causes of diseases (i.e., pathogenic factors) can be classified as Yin or Yang on the basis of their pathological characteristics. Various modalities of interventions (therapeutic and tonifying) in TCM, including the use of herbal formulations and acupuncture, can also exert Yin/Yang-modulatory actions, thereby producing beneficial effects in Yin/Yang-deficiency disorders (3). While Chinese herbs are broadly divided into therapeutic and tonifying

groups in terms of their pharmacological actions, tonifying herbs can be further divided into four functional categories: Yang-invigorating, Yin-nourishing, Qi-invigorating and Blood-enriching, with respect to their mode of action in enhancing physiological functions under sub-optimal body conditions (5). With regard to the Yin-Yang theory, Qi-invigorating and Blood-enriching actions are classified under the Yang and Yin categories, respectively.

Differing modes of action of Yang and Qi-invigorating herbs

Various body functions are dependent on cellular activities, which are manifestations of Yang and Qi. In this regard, mitochondria (the “powerhouse” of the cell) generates ATP that energizes a wide range of cellular activities. To keep up with their ATP generation capacity (ATP-GC), a glutathione-dependent antioxidant system in mitochondria is in place to protect respiratory complexes against reactive oxygen species (ROS) arising from mitochondrial electron transport (6,7). With this in mind, the stimulation of mitochondrial ATP generation by the Yang/Qi-invigorating action of Chinese tonifying herbs may involve an increase in electron transport and/or the induction of a glutathione antioxidant response which can safeguard mitochondrial ATP-GC.

The pharmacological basis of Yang-invigoration has been demonstrated by our laboratory, wherein Yang-invigorating herbal extracts consistently increase mitochondrial ATP-GC both *ex vivo* in mouse hearts and *in vitro* in H9c2 cells (5,8). A recent study in our laboratory has further compared the capacity of Yang-invigorating and Qi-invigorating herbal extracts (*Table 1*) to stimulate mitochondrial ATP-GC and increase cellular reduced glutathione (GSH) levels in cultured H9c2 cardiomyocytes (10). Qi-invigorating herbal extracts were found to increase mitochondrial ATP-GC in H9c2 cells after a long (24 h) versus a short (4 h) incubation, as was the case for Yang-invigorating herbal extracts (*Table 1*). The experimental result points to the possibility that Yang-invigorating and Qi-invigorating herbs stimulate mitochondrial ATP-GC via different mechanisms of action. In this connection, an earlier study in our laboratory has demonstrated that β -sitosterol, an active component of *Cistanches Herba* (a Yang-invigorating tonifying herb), can fluidize mitochondrial inner membrane and stimulate mitochondrial ATP-GC in cultured C2C12 myocytes (9). This postulation is strengthened by the observation that

Table 1 Effects of Yang- and Qi-invigorating Chinese tonifying herbs on ATP-GC and reduced glutathione (GSH) levels in cultured H9c2 cardiomyocytes [modified from (9)]

Pharmaceutical name	ATP-GC		GSH level	
	4 h	24 h	4 h	24 h
Yang				
Eucommiae Cortex	↑	↓	–	↑
Cibotii Rhizoma	↑	–	–	↑
Dipsaci Radix	↑	–	–	–
Cynomorii Herba	↑	↑	–	–
Cistanches Herba	↑	↑	–	↑
Cuscutae Semen	↑	↑	–	↑
Epimedii Herba	↑	–	–	–
Morindae Radix	↑	–	–	↑
Qi				
Ginseng Radix	↑	↑	–	↑
Pseudostellariae Radix	↑	↑	–	↑
Quinquefolii Radix	↓	↑	↑	↑
Codonopsis Radix	–	↑	–	↑
Astragali Radix	–	↑	↑	↑
Atractylodis Rhizoma	↓	↑	–	↑
Jujubae Fructus	↑	↑	–	↑
Fici Simplicissimae Radix	–	↑	↑	↑
Dioscoreae Oppositae Radix	–	↑	–	↑

↑, significantly increased; –, no significant change; ↓, significantly decreased. ATP-GC, ATP-generation capacity.

the Yang-invigorating herbal extract-induced stimulation of ATP-GC is completely abrogated by cholesterol (a biomembrane stabilizer). Presumably, the fluidization of mitochondrial inner membrane by active components of Yang-invigorating herbal extracts can activate enzymes involved in electron transport (9), resulting in the increase in mitochondrial ATP-GC under the described experimental conditions.

On the other hand, Qi-invigorating herbal extracts were found not able to stimulate mitochondrial ATP-GC following a 4 h incubation, whereas all of them stimulated ATP-GC in H9c2 cells following incubation for 24 h (Table 1). The stimulation of mitochondrial ATP-GC was associated with an increase in cellular GSH levels. Regression analysis showed a positive significant

correlation between the degrees of mitochondrial ATP-GC stimulation and the extents of cellular GSH increase in Qi-invigorating herbal extract-pre-incubated H9c2 cells. The observation that co-incubation of H9c2 cells with inhibitors of glutathione synthesis and glutathione regeneration abolished the stimulatory effect of Qi-invigorating herbal extracts on mitochondrial ATP-GC further confirms that the increase in mitochondrial ATP-GC is secondary to an enhancement of cellular GSH status. This is consistent with earlier findings that glutathione antioxidant status plays a crucial role in maintaining mitochondrial structural and functional integrity (11,12). Recently, studies on antioxidant phytochemicals have revealed that various phytochemicals (such as curcumin, catechin, resveratrol and schisandrin B) can serve as direct free radical scavengers and/or induce a nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-driven expression of antioxidant proteins/enzymes (13,14). With respect to the mechanism underlying the enhancement of cellular GSH levels by Qi-invigorating herbs, Qi-invigorating herbs may enable the maintenance of cellular GSH levels by free radical scavenging activities and/or increasing the expression of glutathione-related proteins/enzymes.

Protection against diabetic cardiomyopathy by Yang/Qi-invigoration

Cardiomyopathy is a major cause of morbidity and mortality in patients with diabetes. Recent studies have shown that mitochondrial dynamics and mitophagy (a cellular event involving the removal of dysfunctional mitochondria are sensitive to nutrient availability and hence their dysregulation is associated with diabetes. As such, the induction of mitochondrial fusion [which is mediated by mitofusin 1 (Mfn1), mitofusin 2 (Mfn2) and optic atrophy 1 (Opa1)] via the up-regulation of Mfn2 was found to alleviate high-fat diet (HFD)-induced insulin resistance and adiposity in diabetic rodents (15). The induction of mitochondrial fusion by incubation with insulin can also enhance energy GC and increase the rate of oxygen consumption in cultured cardiomyocytes (16). In contrast, increased mitochondrial fission [which is mediated by dynamin-related protein 1 (Drp1), mitochondrial fission factor (Mff) and fission 1 (Fis1)] was observed in coronary endothelial cells isolated from diabetic mouse hearts (17). Over-nutrition, as occurs with high glucose and lipid diets, can cause an excessive production of ROS during mitochondrial oxidative phosphorylation in cardiomyocytes, with resultant oxidative

damage to mitochondria. An impairment in mitophagy was found to be associated with cardiomyopathy, probably due to an increased number of dysfunctional mitochondria in the heart (18). Mitophagy involves the fusion of fragmented mitochondria with autophagosomes, in which LC-3/p62 are crucial regulators of the process (18). The restoration of mitophagy by pharmacological intervention was found to improve the cardiomyopathy in diabetic mice (19). The aforementioned findings suggest that the control of mitochondrial quality (i.e., functional integrity) is critical in the pathogenesis of cardiomyopathy.

Mitohormesis, which refers to a phenomenon wherein mild oxidative stress in mitochondria can protect the cell/tissue against subsequent perturbations, is proposed to promote longevity and protect against aging-associated diseases (20). For instance, caloric restriction, physical exercise or treatment with phytochemicals have been shown to induce a mitohormetic response via modulating mitochondrion-related and bioenergetics-sensitive signaling regulators, such as 5' adenosine monophosphate-activated protein kinase (AMPK), sirtuin(s) as well as the target of rapamycin (mTOR) (21). AMPK and sirtuin(s), which act antagonistically with mTOR, can activate a number of transcription factors regulating mitochondrial function, such as peroxisome proliferator-activated receptor gamma coactivator (PGC1) α and β , peroxisome proliferator-activated receptors (PPAR) α and γ and Forkhead box O3 (Foxo3) (21). While PGC 1 α and β can regulate the expression of *Mfn2* (22), which in turn can improve the insulin signaling cascade (15), the induction of PPAR α can facilitate fatty acid β -oxidation (23). Emerging evidence has also shown a possible correlation between mitohormetic signaling and the maintenance of mitochondrial functional integrity. As such, recent studies have shown that the activation of PPAR γ and/or Foxo3 can induce BNIP3/LC-3/p62-mediated mitophagy in heart tissues (24). In addition, a small degree of mitochondrial uncoupling (i.e., the uncoupling of oxidative phosphorylation) can reduce ROS production in mitochondria and thereby attenuate the oxidative damage. In support of this, a recent study has shown that Nrf2, the master regulator of antioxidant response plays a role in mitohormesis (induced by a small degree of mitochondrial uncoupling) in skeletal muscle of transgenic mice deficient in oxidative phosphorylation capacity (25).

Recent studies in our laboratory have shown that Cistanches Herba and Cynomorii Herba (two Yang-invigorating herbs) can fluidize the mitochondrial inner

membrane, causing a small increase in ROS production. This increase in ROS generation can induce a small degree of uncoupling effect which serves as a retrograde signal for the induction of an antioxidant response in the cultured H9c2 cardiomyocytes (26,27). In this connection, the induction of the glutathione-dependent antioxidant response elicited by Cistanches Herba and Cynomorii Herba was found to be associated with cyto- and cardio-protection against oxidative stress in cultured menadione-intoxicated H9c2 cardiomyocytes as well as in ischemic/reperfused rat hearts (26,27). In addition, Cistanches Herba and Cynomorii Herba can induce a mitohormetic response, via activation of the AMPK/PGC-1 pathway. As such, Cistanches Herba can cause a redox-sensitive induction of mitochondrial uncoupling and activation of AMPK/PGC-1 in C2C12 Myotubes and reduce the body weight of HFD-fed obese mice (9). Ursolic acid, the active ingredient of Cynomorii Herba, can induce mitochondrial biogenesis through the activation of AMPK/PGC-1 in C2C12 myotubes and increase the exercise endurance capacity in mice (28). Ginsenoside Rg1, which is one of the active ingredients in Ginseng Radix (a Qi-invigorating herb), was found to reduce oxidative stress and the degree of cardiomyopathy in streptozotocin-injected diabetic rats via the induction of an antioxidant response (29). A Yin-nourishing and Qi-invigorating herbal formula, namely Shengmai San, was found to reduce the extent of myocardial fibrosis in streptozotocin-diabetic rats (30), presumably via the activation of mitohormetic AMPK and sirtuin 1 signaling pathways (31).

Protection against diabetic nephropathy by Yang/Qi-invigoration

The kidneys, which are highly sensitive to hemodynamic and metabolic alterations, are susceptible to microvascular damage in patients with diabetes. Diabetic nephropathy, one of the major microvascular complications of diabetes, is characterized by albuminuria, a reduction in glomerular filtration rate and ultimately a decline in renal functions (i.e., end-stage renal disease) (32). Recent studies have shown that oxidative stress and inflammation arising from hyperglycemia play critical roles in the pathogenesis of diabetic nephropathy (33). As described in the previous section, oxidative stress originates mainly from the excessive production of ROS arising from mitochondrial oxidative phosphorylation. The oxidant-induced damage in the glomerulus can induce leukocyte infiltration, with

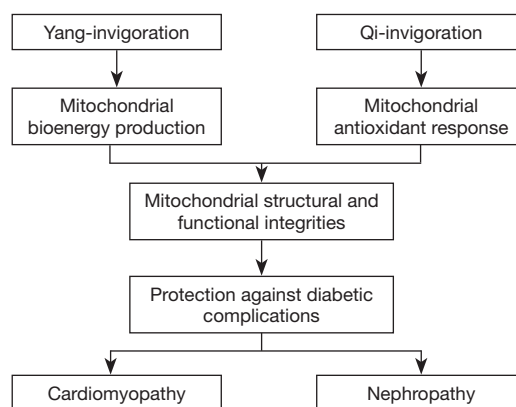


Figure 1 Yang/Qi-invigoration protects against diabetic cardiomyopathy and nephropathy.

a resultant inflammatory response (33). Transforming growth factor- β 1, one of the pro-inflammatory mediators secreted by renal cells upon interaction with leukocytes, has been identified as the key factor involved in the pathogenesis of diabetic nephropathy (34). TGF- β 1 can promote the de-differentiation of epithelial-mesenchymal cells (which normally possess a highly polarized structure for efficient reabsorption of solutes and proteins from the renal tubule into peritubular capillaries), which in turn reduces cell polarity and hence the capability of reabsorption of solutes in the nephron (35). The tubular dysfunction ultimately leads to albuminuria, polyuria and glycosuria. TGF- β 1 can also facilitate the accumulation of components of the extracellular matrix (such as collagen, fibronectin and laminin) in the glomerulus, with resultant glomerulosclerosis and tubulointerstitial fibrosis (36).

Recent studies exploring the possible cause-and-effect relationship between oxidative stress and diabetic nephropathy have demonstrated that the induction of a Nrf2-driven antioxidant response can ameliorate pathological manifestations of diabetic nephropathy in experimental animals whereas, conversely, the deletion of the *Nrf2* gene can augment the severity of diabetic nephropathy (37). In an effort to attenuate the progression of oxidant-mediated diabetic nephropathy, interventions with antioxidant and anti-inflammatory activity may offer a reasonable approach. Given that both Yang- and Qi-invigorating herbs can induce a glutathione-dependent antioxidant response, they should prove effective in the prevention and/or treatment of diabetic nephropathy. A previous finding in our laboratory has shown that a Yang-invigorating herbal health product (namely, VI-28) can protect against gentamicin-induced nephrotoxicity

in rats associated with increases in the level/activities of GSH, superoxide dismutase, Se-glutathione peroxidase and glutathione S-transferases, all of which are regulated by Nrf2 (38). With regard to compounds isolated from Qi-invigorating herbs, ginsenoside Rg1 (alone or in combination with astragaloside IV) can suppress oxidative stress and reduce the severity of nephropathy in streptozotocin-diabetic rats via the inhibition of TGF- β 1/Smads signaling cascades (39). Similarly, schisandrin B, an active ingredient isolated from *Schisandra Fructus* (also regarded as an herb that can invigorate the Qi of the five viscerae), can alleviate hyperglycemia-induced renal injury in streptozotocin-diabetic mice, by suppressing inflammation and oxidative stress (40).

Conclusions

In conclusion, the health-promoting actions of, Yang-invigorating herbs are mediated, at least in part, by increasing mitochondrial ATP-GC, likely by fluidizing the mitochondrial inner membrane, whereas Qi-invigorating herbs increase mitochondrial ATP-GC via the induction of a glutathione-dependent antioxidant response, which can indirectly preserve the functional integrity of mitochondria (Figure 1). These observations strongly support the view that mitochondria are the primary target of Yang- and Qi-invigoration. The possible beneficial effects of Yang- and Qi-invigorating herbs in the prevention and/or treatment of diabetic cardiomyopathy and nephropathy warrants further investigation. Future studies should be focused on identifying active compounds from Yang- and Qi-invigorating herbs in relation to their action in enhancing mitochondrial ATP-GC and glutathione antioxidant

status. The molecular mechanisms underlying Yang- and Qi-invigoration can then be elucidated. Consequently, biomarkers can be established for implementing quality control for Yang/Qi-invigorating herbs and related herbal health products.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/lcm.2019.03.01>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are 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.

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