Review Article



# Shengmai San: a modern medicine perspective on its remedial effects on Qi and Yin deficiency syndrome in Chinese medicine

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**Abstract:** Shengmai San (SMS, transliterally meaning "the decoction for restoring the pulse" in Chinese) is an herbal formulation for the treatment of conditions of body Qi-Yin deficiency, such as the depletion of Qi and body fluids under conditions of heat-stroke. SMS is comprised of Ginseng Radix (GR, a Qi-invigorating herb), Ophiopogonis Radix (OR, a Yin-nourishing herb) and Schisandrae Fructus (SF, an "astringent" herb). Recent pharmacological studies have revealed the biochemical basis of the Qi-invigorating and Yin-nourishing actions of the component herbs of SMS in relation to the pathological condition of heat-stroke. The pathogenesis of heat-stroke indicates that its major complications include brain ischemic injury, myocardial and respiratory dysfunction. In this regard, GR possesses a Qi-invigorating action which is related to the induction of a glutathione-dependent antioxidant response and the preservation of mitochondrial function, with the resultant protection against ischemia/reperfusion injury in the brain and heart during heat-stroke. OR is a Yin-nourishing herb, which produces immunomodulatory effects. OR can reduce the extent of pulmonary hypertension, edema and inflammation under heat-stress conditions. Although the mechanism underlying the "astringent" action of SF is as yet unknown, we hypothesize that SF may retain body water, with a resultant cooling effect. Recent studies have shown that SF also possesses antioxidant and anti-inflammatory actions, which are likely to synergize the actions of GR and OR. The elucidation of the biochemical basis underlying the pharmacological actions of SMS (and its component herbs) can serve as a paradigm for the modernization of traditional Chinese herbal formulations used in treating disease.

**Keywords:** Shengmai San; Qi-Yin deficiency; heat-stroke

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## The underlying theory in Chinese medicine (CM) for the prevention and treatment of disease: Differentiation of signs and symptoms and the use of herbal formulations

CM views the human body as an organic entity made of various organs that function in a mutually inter-dependent manner (1). The Yin-Yang theory, which originates from ancient Chinese philosophy, is central to the conceptual framework of CM. 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 them determines the physiological status of the human body (2). As such, the interaction between Yin and Yang generates Qi that possesses dual properties, which can be referred to as: (I) the refined and nutritive substances flowing in the body; and (II) the manifestation of organ function. Qi can flow through Meridians and nourishes organs to provide vital energy for supporting physiological activities.

In addition, vital substances (namely, essence, Blood, and body fluids) are fundamental to life and constitute the material and functional basis of the human body (3). Body fluids (such as saliva, gastric juices, sweat and synovial fluid in the joints) are used for nourishing internal organs and moistening joints and skin (4). Blood, a thick red liquid resulting from the combination of dietary nutrients and body fluids, is viewed as one of the basic substances essential for supporting life activities in humans. Blood circulation in the body, which is dependent on the driving action of Qi, offers an important nourishing effect on various organs. According to the Yin-Yang Theory, functional activities of the body (such as Qi) are classified as Yang, while the material basis (such as essence, Blood, and body fluids) of vital functions belongs to Yin (5). The inter-relationship between Qi and Blood exemplifies the importance of a harmony between Yin (Blood) and Yang (Qi) in determining optimal physiological functioning.

According to CM theory, the pathogenesis of a disease is primarily related to a Yin and Yang imbalance in the body, and therefore anything that can disrupt the Yin/Yang balance in the body can be a disease causative factor. The practice of CM emphasizes the prevention of disease. CM theory illustrates that a "Deficiency" in body function (referred to as a sub-healthy body condition in modern medicine) can result from a genetic predisposition, acquired environmental and/or lifestyle factors, as well as aging. To avoid the worsening of an unhealthy or "Deficient" body, it is necessary correct the condition by restoring Yang, Qi, Yin, Blood to their normal levels. As such, a sub-healthy status (a malfunctioning body condition prior to the development of a disease) of an individual should be remedied in a timely manner by using Chinese tonifying herbs/formulations. While Chinese herbs are broadly divided into therapeutic and tonifying groups in terms of their pharmacological actions, tonifying herbs can be further classified into four functional categories: Yang-invigorating, Yin-nourishing, Qi-invigorating and Blood-enriching, with respect to their mode of action in enhancing physiological function under sub-optimal body conditions (6). With regard to the Yin-Yang theory, Qi-invigorating and Blood-enriching actions are classified under the Yang and Yin categories, respectively. In an effort to produce a synergistic effect and/or multiple tonifying actions, the use of herbal formulations, which are comprised of at least two Chinese herbs, is a common approach to restore the physiological functions from the "Deficient" body state.

## Shengmai San—formulation principle and therapeutic indications

According to CM theory, formulating a prescription with different herbs is based on the specific therapeutic roles (namely "Monarch", "Minister", "Assistant" and "Guide" in the terminology of Chinese Medicine) of each component herb and their interaction, in order to produce a synergistic effect, as well as minimize potential adverse side effects. "Monarch" refers to the component herb which is responsible for the principal therapeutic action directed against the pathological cause(s) and treatment of the main symptoms. "Minister" plays a relatively less important role than that of "Monarch" and involves an enhancement of the action of "Monarch" and treatment of the particular complication(s) of the disease and its minor symptoms. "Assistant" serves a pharmacological role to minimize the side effects of "Monarch" and "Minister", to synergize the action of "Monarch" and to treat the minor symptoms. "Guide", the herb which usually possesses a mild pharmacological action, is used for facilitating the delivery of the active herbal components to target organs.

Shengmai San (SMS, transliterally meaning "the decoction for restoring the pulse" in Chinese) is an herbal formulation used for the treatment of Qi-Yin deficiency conditions such as the depletion of Qi and body fluids in the presence of heat-stroke (7). Body fluids (which are Yin in nature) originate from the "Heart" while a significant portion of Qi is generated from the "Lung". In this regard, excessive sweating under high temperature can reduce the volume of body fluids and hence impair the Yin in the "Heart", with resultant manifestations of dryness of mouth and tongue, dysphoria, thirst, and a weak and asthenic pulse. In addition, spontaneous sweating under heat stress can consume the Qi in the "Lung", with a consequent shortness of breath and lassitude. Therefore, the symptoms of Qi-Yin deficiency in CM are analogous to conditions associated with heat exhaustion and/or heat-stroke in modern medicine.

SMS, which contains Ginseng Radix (GR, a Qi-invigorating herb), Ophiopogonis Radix (OR, a Yin-nourishing herb) and Schisandrae Fructus (SF, an "astringent" herb), is formulated based on the CM theory of "Monarch", "Minister", "Assistant" and "Guide" for treating Qi-Yin deficiency, particularly in the "Heart" and "Lung" (7). Based on the CM pharmacopeia, GR, which is the "Monarch" in SMS, mainly invigorates Qi in the "Lung" and "Heart". OR, which is the "Minister" in SMS, can

 

**Table 1** Comparisons between Qi-Yin deficiency and heat-stroke in the context of Chinese medicine and Western medicine

| Deficiency syndrome | Chinese medicine | Western medicine |
|---|---|---|
| Qi-deficiency/heat-stroke | • Over-consumption of Qi in the "Lung" | • Acute lung inflammation |
| | • Shortness of breath and lassitude | • Pulmonary edema and injury arising from heat-stroke |
| Yin-deficiency/heat-stroke | • Reduction of the volume of body fluid | • Circulatory failure |
| | • Dryness of mouth and tongue | • Circulatory shock |
| | • Dysphoria | • A weak pulse and myocardial ischemia under conditions of heat-stroke |
| | • Thirsty | |
| | • A weak and asthenic pulse | |

nourish Yin in the "Lung" and "Heart" by removing "Heat", with a subsequent promotion of body fluid generation. SF, which is the "Assistant" and "Guide" in SMS, can produce an astringent action in the "Lung" and "Heart" (preventing excessive loss of body fluid). Instead of using a single herb, the mixture of GR, OR and SF can act synergistically to treat Qi-Yin deficiency states. With hundreds of years of clinical experience, the efficacy of SMS has been confirmed.

## Clinical manifestations of Qi-Yin deficiency syndrome and the effect of SMS treatment

As mentioned earlier, the syndrome of Qi-Yin deficiency is similar to pathological conditions prevalent in heat exhaustion or heat-stroke. Heat exhaustion refers to a pathological condition associated with exposure to high temperatures at high humidity or strenuous physical activity, resulting in a severe loss of water and electrolytes from the body due to profuse sweating. Heat exhaustion will develop into heat-stroke if no remedial actions (e.g., cooling down and rehydration) are taken. Heat stroke is a life-threatening condition characterized by a high core body temperature (≥40 ℃) and dysfunction of the central nervous system, with a subsequent delirium, convulsions and coma. Heat-stroke occurs when the heat stress surpasses the thermoregulatory response in the body. Under conditions of high ambient temperature, blood is preferentially shunted to skeletal muscle and skin with a reduced volume of blood supplied to visceral organs in an effort to dissipate heat. In this regard, the severe water loss (produced by profuse sweating) in heat-stroke will result in an insufficient blood volume to support the circulation in the body, leading to circulatory shock, intracranial hypertension, encephaloedema and ischemic injury to various organs (notably, brain, heart and lung) (8-11). Hyperpyrexia, as in the case of fever during a viral infection, can trigger a systemic inflammatory response due to interaction among endothelial cells, lymphocytes and epithelial cells, leading to the release of an array of pro-inflammatory cytokines (12,13). Hyperpyrexia also decreases the DNA synthesis, increases protein degradation, disrupts membrane permeability and reduces aerobic respiration (14). The circulatory shock and cerebral ischemia arising from heat-stroke have been found to be associated with an increased production of reactive oxygen species (ROS), presumably due to pathological changes in cellular energy metabolism and the reduced expression of antioxidant proteins. Interestingly, various complications of heat-stroke appear to resemble those of Qi-Yin deficiency. As such, acute lung inflammation, pulmonary edema and injury arising from heat-stroke are quite analogous to the Qi deficiency in the "Lung", as described in terms of CM (15). The circulatory failure, circulatory shock, weak pulse and myocardial ischemia under conditions of heat-stroke are described as Yin deficiency in "Heart" (*Table 1*). With regard to its clinical management, SMS would seem to provide an appropriate treatment for heat-stroke and its associated complications.

The pathogenesis of heat-stroke is such that its major complications include brain ischemic injury, myocardial and respiratory dysfunction. Recent clinical studies have shown that SMS treatment can ameliorate the extent of Qi-Yin deficiency syndrome in relation to the cardiopulmonary system. As such, SMS can enhance the vitality and reduce the mortality rate in patients with acute myocardial infarction (16,17). SMS can also improve the survival and endothelial function in relaxing arterial blood vessels in patients with coronary heart disease (18,19).

Moreover, SMS treatment can increase the body's functional capacity, as assessed by the New York Heart Association functional classification (a commonly used assessment for the severity of heart failure symptoms) (20), and reduce the extent of blood coagulation (21) in patients with chronic heart failure. The protective effect of SMS in patients with chronic or pulmonale heart failure has also been reported recently (22). In this regard, SMS can augment pulmonary gas exchange in patients following tourniquet-induced ischemia-reperfusion (23) and improve respiratory function in patients with chronic obstructive pulmonary disease (24).

## Biochemical mechanism underlying the pharmacological actions of SMS

Recent experimental studies have demonstrated that heat-stroke is associated with increased oxidative stress, an inflammatory response, endoplasmic reticulum stress induced by unfolded proteins as well as pathological changes in energy metabolism. The pharmacological actions afforded by SMS are likely attributed to an adaptive response against different forms of heat-stroke-related stress.

### *Antioxidation*

Exposure of rats to high environmental temperatures (as in heat-stroke) can lead to a burst of free radical production, an increase in lipid peroxidation, and a down-regulation of antioxidant systems (25). In this regard, SMS was found to protect against oxidative injury in hydrogen peroxide-challenged PC12 cells (26), in ischemic-reperfused mouse forebrain (27) and in scopolamine-challenged mice (28). The protection against oxidative damage in the brain was paralleled by the induction of an antioxidant response, as evidenced by increased levels of reduced glutathione (GSH) and elevated superoxide dismutase (SOD) activity (28). Similarly, SMS attenuated right ventricular dysfunction in mice subjected to chronic intermittent hypoxia (29) and adriamycin-induced cardiomyopathy in rats (30). The SMS-induced cardioprotection was invariably associated with an induction of antioxidant enzymes such as SOD, glutathione peroxidase and heme oxygenase 1.

### *Anti-inflammation*

Studies using an experimental model of heat-stroke have shown that a high environment temperature (43 ℃) can activate inducible nitric oxidase, which catalyzes the generation of nitric oxide in the brain, with a subsequent increase in plasma levels of pro-inflammatory cytokines (such as interleukin-1β, interleukin-6 and tumor necrosis factor-α) (31,32). SMS treatment was found to protect against heat-stroke which is paralleled by the suppression of releases of nitric oxide and associated pro-inflammatory cytokines in rats (31). The anti-inflammatory action of SMS was also demonstrated in brains of rats with endotoxin (i.e., lipopolysaccharide)-induced shock (33) and in rats with doxorubicin-induced myocardial toxicity (34). SMS treatment was shown to inhibit the expression of toll-like receptor-2 as well as the release of interferon-γ and interleukin 6 in doxorubicin-treated rats (34).

### *Heat shock response and unfolded protein response*

In response to heat stress, the induction of heat shock proteins (HSPs, also called molecular chaperones) serves to repair unfolded/misfolded proteins during hyperthermia (35). In this regard, SMS treatment can attenuate heat-stroke-associated injury (such as that in cerebral ischemia and hypotension) through the induction of heat shock protein 72 (36). In addition, SMS protected against endoplasmic reticulum stress and the associated caspase 12-mediated cell death by triggering an unfolded protein response in the myocardium of doxorubicin-treated rats (37). SMS also produced a protective effect on endoplasmic reticulum stress and cell apoptosis in oxygen/glucose-deprived PC12 cells and in mice with permanent middle cerebral artery occlusion-induced brain injury (38).

### *Improvement in energy metabolism*

In the light of the protective action of SMS in ischemia/reperfusion injury and doxorubicin-induced myocardial toxicity, recent metabolomics studies have investigated the mechanism(s) underlying the cardioprotective effects of SMS. In addition to the well-established antioxidant action of SMS, SMS treatment was also found to up-regulate enzymes involved in glucose oxidation, in the tricarboxylic acid cycle and in ATP synthesis in ischemic-reperfused rat hearts, suggesting an improvement in aerobic respiration and ATP generation (39). Consistent with this, another metabolomics study has shown that SMS can promote glycogenolysis, glycolysis and amino acid utilization in myocardial tissue of doxorubicin-treated rats, which further supported an enhancement of myocardial energy metabolism by SMS under pathological conditions (40).

 

This postulation is strengthened by the observation that SMS treatment improved blood glucose, cholesterol and triglyceride levels and ameliorated myocardial fibrosis in diabetic rats (41,42) and produced a reduction in hepatic lipid content in obese high cholesterol-fed rats (43).

### *Regulation of mitochondrial dynamics*

The mitochondrion is considered to be a coordinator of cell survival and death by virtue of its functional role in cellular energy generation and programmed cell death. As mentioned earlier, SMS can augment energy generation and protect against apoptosis, suggesting the possibility that SMS can modulate mitochondrial function. SMS suppressed cell apoptosis in the myocardium of mice with hypercholesterolemia (44) and mice with chronic intermittent hypoxia (45), presumably through inhibition of mitochondrial permeability transition pore formation (46) and activation of the opening of mitochondrial $K_{ATP}$ channels (47,48). In addition, recent research has indicated that mitochondrial dynamics (i.e., the equilibrium among mitochondrial fission, mitochondrial fusion and mitophagy) regulate mitochondrial bioenergetics and determine the cell's fate in response to any change in energy status. SMS was found to activate adenosine monophosphate kinase (AMPK, an important regulator of cellular energy metabolism) (49) and inactivate dynamin-related protein 1 (a key protein involved in mitochondrial fission) (50), with a resultant inhibition of mitochondrial fission that can further develop into mitophagy and the associated autophagic cell death in ischemic-reperfused rodent hearts. SMS treatment also ameliorated the extent of autophagic cell death and cerebral ischemia/reperfusion injury in mice via the modulation of AMPK, mammalian target of rapamycin and c-Jun N-terminal kinase (51,52).

## Qi-invigorating and Yin-nourishing actions of SMS in the context of modern medicine

### *Qi-invigoration by GR*

GR is a very popular Qi-invigorating Chinese tonifying herb for energizing the body (53). According to CM theory, GR can invigorate Qi in several visceral organs, including "Spleen", "Heart", "Lung" and "Kidney". A recent study in our laboratory has revealed that a 24-h incubation of H9c2 cardiomyocytes with Qi-invigorating herbal extracts consistently increase mitochondrial ATP generation capacity and cellular GSH levels in this preparation (54). This finding suggests that Qi-invigoration affects mitochondrial bioenergetics and antioxidant status. Consistent with this, a growing body of evidence has demonstrated an enhancement of mitochondrial function by GR (55,56). GR extracts were found to increase mitochondrial ATP generation capacity in H9c2 cardiomyocytes *in situ* and in rat hearts *ex vivo* (53). The increase in mitochondrial ATP generation capacity by GR has been further demonstrated in cultured CaCo-2 intestinal epithelial cells and in mitochondria isolated from mouse intestine [unpublished data]. Long-term treatment with a GR extract maintained mitochondrial function and reduced oxidative stress in skeletal muscle following exhaustive exercise in rats, as evidenced by an increase in mitochondrial glutathione redox status and a decrease in lipid peroxidation (56). As discussed earlier, heat-stroke as well as ischemia/reperfusion injury in brain/heart can be regarded as a manifestation of Qi-Yin deficiency. A recent study has demonstrated that a Ginseng extract can protect against environmental heat stress in rats (57). In addition, ginsenosides (which are active components in GR) play a vital role in mediating the pharmacological effects of GR, particularly the protection against ischemia/reperfusion injury. Yang *et al.* showed that ginsenoside Rg5 protected against ischemic injury in cardiomyocytes (58). Rg5 also inhibited the opening of mitochondrial permeability transition pore and increased ATP production, resulting in an increased resistance to hypoxia/reoxygenation injury in cardiomyocytes. Rg5 also suppressed cell apoptosis with an increased mitochondrial hexokinase-II binding and a reduced dynamin-related protein 1 recruitment to mitochondria in mouse hearts subjected to isoproterenol-induced ischemia (59). In addition, ginsenoside Rd treatment significantly protected against focal cerebral ischemia in rats, as indicated by a decrease in infarct volume. The neuroprotective effect of Rd was associated with an improvement in neurological function, as evidenced by an improved activity of respiratory chain complexes and aconitase, lowered mitochondrial hydrogen peroxide production and hyperpolarization of mitochondrial membrane potential.

In terms of the formulation principle of SMS, GR serves as the "Monarch" which governs the principal pharmacological action of the formulation. The induction of a glutathione-dependent antioxidant response, the preservation of mitochondrial functional integrity and the protection against ischemia/reperfusion injury in brain/heart by GR are evidence in support of the traditional use

 

of SMS in CM for invigorating the "pulse" in patients with heat-stroke and/or heart failure.

### *Yin-nourishment by OR*

OR is a commonly used Yin-nourishing herbs in various herbal formulations. In the context of preventive health, Yin-nourishing herbs act on the immune system. In support of this, our laboratory has investigated the pharmacological actions of Yin-tonifying herbs which were shown to produce a co-mitogenic effect on concanavalin A-stimulated mouse splenocytes *in vitro* and *ex vivo* (60). Furthermore, OR was found to activate T- and B- lymphocytes in ovalbumin-immunized mice (61) and in porcine parvovirus-inoculated BALB/c mice (62), presumably via the secretion of cytokines (interferon-γ, interleukin-2, interleukin-4 and interleukin-6) by T helper cells. OR can also increase phagocytotic activity and inducible nitric oxide synthase activity in macrophages (63). The polysaccharides isolated from OR can promote the maturation of dendritic cells (which are antigen presenting cells), indicative of an effective immuno-stimulatory action (64). Interestingly, a methanol extract of OR can elicit an anti-inflammatory response in hydrogen peroxide-induced cellular senescence of normal human dermal fibroblasts, presumably by the suppression of the release of cytokines interleukin-6 and interleukin-8 (65). The anti-inflammatory action of OR was further demonstrated in two experimental mouse models of inflammation: xylene-induced ear swelling, as well as carrageenan-induced paw edema (66). The active compound isolated from OR, namely ruscogenin, seems responsible for the anti-inflammatory action. As such, ruscogenin ameliorated monocrotaline-induced pulmonary hypertension in rats via the suppression of nuclear factor (NF)-κB activity, cytokine release and leukocyte infiltration (67). Ruscogenin also reduced infarct size and brain edema in rats with middle cerebral artery occlusion/reperfusion (68) which was associated with inhibition of the NF-κB-mediated inflammatory pathway. The biochemical mechanism underlying the anti-inflammatory action of ruscogenin likely involves a reduced expression intercellular adhesion molecule-1 in leukocytes, with resulting inhibition of leukocyte migration to the inflamed site (69). Given that pulmonary hypertension and cerebral ischemia/reperfusion are common complications of heat-stroke, ruscogenin may be the principal component of OR that contributes to the protective effect of the SMS formulation in heat-stroke.

As mentioned earlier, in SMS OR acts as the "Minister", which treats the complication(s) and the minor symptoms of a given pathological condition. Recent studies of the anti-inflammatory activity and the protection against cerebral ischemia/reperfusion injury afforded by OR strongly support the "Minister" role of OR in SMS formulations used for treating the complications of heat-stroke (such as, lung edema, pulmonary hypertension and cerebral ischemia/reperfusion injury).

### *Astringent action by SF*

SF serves as an astringent component in the SMS formulation. The concept of an astringent action in CM refers to the preservation of body fluid (i.e., the prevention of excessive sweating, vomiting, urination and diarrhea) and the maintenance of "*Lung-Qi*" (i.e., prevention of excessive coughing, asthma and palpitations) in the body. The pharmacological action of an astringent agent in modern medicine includes the regulation of blood volume and blood supply to tissues/organs, the reduction of excessive water in tissues/organs and the inhibition of mucous membrane swelling at inflamed sites. We hypothesize that SF can extract water from the extracellular fluid and thereby maintain blood volume, with a resultant cooling effect in the body as well as the prevention of cardiac failure and cerebral stroke. However, the biochemical mechanism underlying the astringent action of SF in relation to the protection against heat-stroke has not as yet been investigated. Despite the unknown mechanism underlying the astringent action of SF, the induction of a heat shock response by SF has been demonstrated. Schisandrin B, the most abundant active lignan in SF, was found to protect against myocardial ischemia/reperfusion injury in rats (70), acetaminophen-induced hepatotoxicity in mice (71) and d-galactosamine-induced liver injury in mice (72) *via* the induction of heat shock protein 25 and 70.

Based on the role of "Assistant" and "Guide" of SF in the SMS formulation, SF would appear to synergize the action of "Monarch" and/or "Minister" to treat the symptoms of pathological conditions. In support of this, accumulating experimental evidence has shown the eliciting of an antioxidant response (73), the induction of an anti-inflammatory response (74) and the preservation of mitochondrial function by schisandrin B (73). In this regard, SF is likely to synergize the pharmacological effect of GR and OR in the SMS formulation. The pharmacological actions of each component herb of SMS in relation to the pathological changes during heat-stroke

 

**Table 2** Pharmacological actions of component herbs in SMS for treating heat-stroke

| Pathological changes during the heat-stroke | Pharmacological actions of component herbs (and its active ingredient) of SMS | | |
|---|---|---|---|
| | GR | OR | SF |
| Oxidative stress in brain and heart | Elicits antioxidant response (56) | – | Elicits antioxidant response (73) |
| A release of pro-inflammatory cytokines | – | Reduces inflammation (65,66) | Reduces inflammation (74) |
| ER stress | – | – | Induces heat shock response (70-72) |
| A reduction of energy production | Increases mitochondrial ATP production (53) | – | – |
| Mitochondrion-mediated cell death | Inhibits the opening of mitochondrial permeability transition pore (59) | – | Preserves mitochondrial functions (73) |

SMS, Shengmai San; GR, Ginseng Radix; OR, Ophiopogonis Radix; SF, Schisandrae Fructus.

are summarized in *Table 2*.

## Future prospects of the research on SMS

Recent advances in molecular technology have enabled an efficient and high throughput analysis of the pharmacological effects of herbal formulations. As such, the next-generation sequencing of mRNA samples from cells/animal tissues can identify changes in gene expression following treatment with SMS, which in turn may facilitate the search for new gene target(s) of SMS treatment. Hopefully, the complete spectrum of pharmacological effects of SMS can eventually be revealed. Meanwhile, as a significant number of SMS-related herbal health and therapeutic products are commercially available, the chemical and functional quality control of the pharmacological effects of these products (in terms of batch-to-batch variations) is a concern for the safe and effective use of the SMS-related products. While an array of chemical markers, which are the active ingredients of the component herbs of SMS, is available, representative biomarker(s) for verifying the effectiveness of SMS products are urgently needed.

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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.2018.09.03). 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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