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How Schisandrae Fructus Benefits the Body: Mechanisms in Traditional Chinese Medicine and Modern Medicine

Kam Ming Ko*, Hoi Yan Leung

Division of Life Science, Hong Kong University of Science & Technology, Hong Kong SAR, China
Email: *bcrko@ust.hk

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Abstract

Schisandrae chinensis Fructus (SF) is a commonly used herb in Traditional Chinese Medicine (TCM). According to TCM theory, SF can invigorate Qi in the liver and other visceral organs through the meridian system. Furthermore, the liver's pivotal role in regulating the functions of various visceral organs helps explain how SF can promote holistic health benefits. The main active ingredient of SF, schisandrin B (Sch B), has been found to improve mitochondrial ATP production and enhance glutathione redox status in multiple organs. This could account for the overall protective effects of Sch B on organs. Due to its stronger impact on liver function, the positive influence of Sch B on different organs may be facilitated by signal molecules originating from the liver.

Keywords

Schisandrae chinensis Fructus, Schisandrin B, Mitochondrial Glutathione Redox Status, Liver

1. Introduction

Schisandrae chinensis Fructus (SF), also known as Wu-Wei-Zi (the fruit of five tastes), is believed to invigorate Qi in the five visceral organs (*i.e.*, the five Zang) in traditional Chinese medicine (TCM) [1]. In the Five-Element Theory, the predominant sour taste of SF suggests that it may have a stronger impact on the "liver" [2]-[4]. In TCM, the "liver" is considered an organ that plays the role of a General, governing the flow of Qi and storing the blood in the body [5]. In a holistic view, the "liver" is closely linked to other visceral organs through the meridian system. (**Figure 1**). These inter-organ relationships have been studied and applied in Traditional Chinese Medicine (TCM) treatments, such as acupuncture

and herbal prescriptions, for treating various diseases [5] [6]. In modern medicine, the liver performs various functions, including metabolism, detoxification, and breaking down toxic substances. Additionally, the liver communicates with various organs such as the digestive system, heart, lungs, kidneys, and brain through liver-derived signal molecules in the blood (**Figure 2**) [5] [7]. In this theoretical paper, we aimed to propose the mechanism underlying the overall health benefits of SF from both Chinese medicine and modern medicine perspectives.

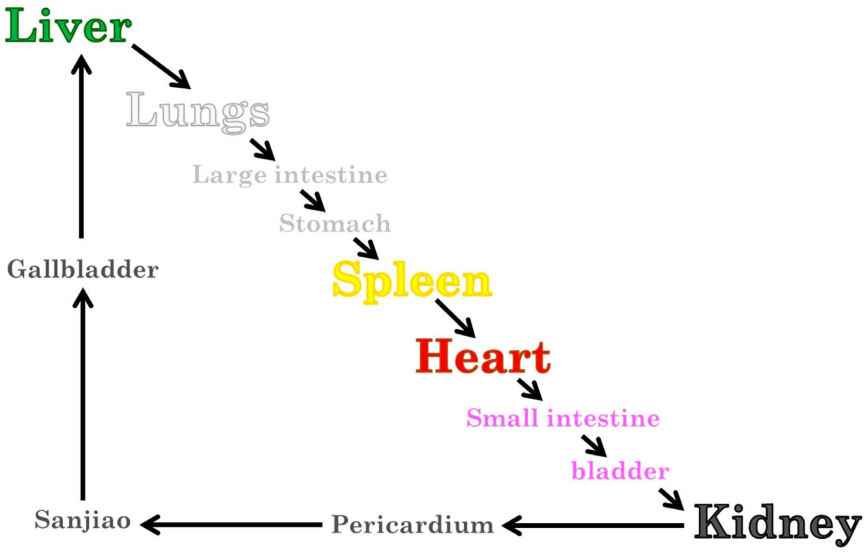

Figure 1. "Zang and Fu" organs are connected by the Meridians and Collaterals system, providing pathways for Qi and blood to circulate throughout the body. This forms a comprehensive network that links the visceral organs into a holistic entity.

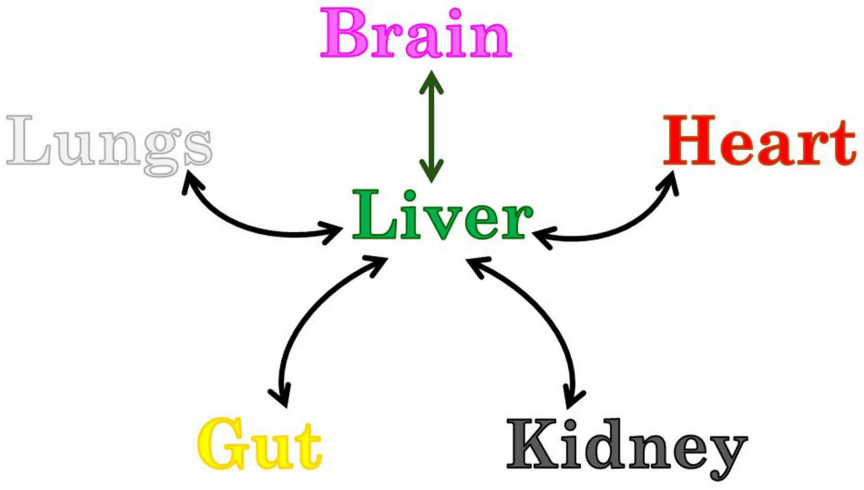

Figure 2. The liver interacts functionally with the brain, heart, lungs, kidneys, and gut.

Schisandrin B (Sch B) is the primary active lignan in SF. It has been demonstrated to provide liver protection [7]-[9], exhibit anti-cancer properties, and safeguard the brain and heart from oxidative damage [10]. Given the diverse spectrum

of pharmacological actions produced by Sch B, the fundamental mechanism involved in eliciting these beneficial responses has yet to be clarified. A recent study in our laboratory has found that Sch B can invigorate Qi by enhancing mitochondrial ATP generation [11]. In accordance with the Qi-invigorating action of SF in the five visceral organs, Sch B increased mitochondrial ATP production in various tissues in mice, which was associated with improved mitochondrial glutathione redox status [11] [12]. This suggests that the beneficial effect of Sch B on mitochondrial function may be connected to the diverse actions of SF on body function, as proposed by both TCM and modern medicine.

1.1. Sch B and Mitochondrial Glutathione

Studies from our laboratory indicate that Sch B treatment protects multiple tissues in rodents from damage or cell death caused by oxidants by improving mitochondrial glutathione redox status [12]-[15]. This is achieved by promoting a cellular glutathione antioxidant response, which helps maintain mitochondrial GSH levels, especially during oxidative stress [7] [15] [16]. Sch B helps maintain mitochondrial glutathione levels, suppressing mitochondrial permeability transition and protecting cells from death [17]-[19]. The molecular mechanism behind the enhancing effect of Sch B on the cellular glutathione antioxidant response involves activating nuclear factor erythroid 2-related factor 2 (Nrf2, a transcription activator) in both hepatocytes and cardiomyocytes [20] [21]. Accordingly, Nrf2 activators have been suggested to provide health benefits by slowing the aging process [22]. A study from our laboratory on male and female mice revealed that long-term Sch B treatment delayed the decline in mitochondrial glutathione levels and ATP production as the mice aged, resulting in an increase in average lifespan [12]. Maintaining optimal levels of mitochondrial GSH is important for preventing age-related diseases and slowing the aging process due to its role in maintaining mitochondrial redox status [23].

Reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide (H_2O_2), are produced by complexes I and III during mitochondrial electron transport [24]. These molecules can attack mitochondrial membranes and proteins or reach the cytoplasm and nucleus, triggering gene-regulatory processes that respond to changes in redox levels [24]. Mitochondrial glutathione (mtGSH) emerges as a key antioxidant in mitochondria, protecting against oxidative damage from reactive oxygen species (ROS). It plays a crucial role in maintaining the proper redox environment within the mitochondria by directly scavenging ROS and supporting other mitochondrial enzymes such as glutathione peroxidase (GPx) 1 and GPx4, glutathione transferases, and glutaredoxin-2, which catalyzes the reversible oxidation and glutathionylation of mitochondrial membrane thiol proteins [23] [25]. The pool of mtGSH is maintained in a reduced state by glutathione reductase, which uses NADPH to reduce oxidized glutathione. Along with the thioredoxin system, specifically mitochondrial thioredoxin 2/thioredoxin reductase 2 (Trx2/TrxR2), mtGSH aids in preserving the redox status of thiols in

mitochondria [23] [25]. Depletion of mtGSH can disrupt the GSH system or the Trx2 system, leading to the oxidation of the dithiol on the active site of Trx2 and making cells more susceptible to ROS-induced cell death [23] [25]. In addition, mtGSH regulates mitochondrial ATP production by influencing the protein sulfhydryl redox states of complexes I and II, which in turn affects electron flow in the electron transport chain [23].

1.2. The Potential Effect of Sch B on Insulin Resistance

Experimental and clinical research suggests that reactive oxygen species (ROS) play a role in causing insulin resistance [26], which is causally related to the development of metabolic syndrome [27]-[29]. Specifically, mitochondrial ROS may contribute to insulin resistance in adipose tissue and skeletal muscle [26]. A preliminary study in our laboratory found that treating mice fed a high-fat diet with Sch B improved glucose intolerance, suggesting an improvement in insulin resistance (unpublished data). Further investigation is needed to determine if Sch B's effect on mice fed a high-fat diet is due to an enhancement of mitochondrial glutathione redox status. Previous research in our laboratory demonstrated that a lignan-enriched SF extract protected rat skeletal muscle from exercise-induced damage. This muscle protection was linked to the enhancement of tissue glutathione status in the liver, but not in skeletal muscle [30]. This finding suggests that the efflux of GSH from the liver to skeletal muscle in SF extract-treated rats may occur during running exercise. Enhancing liver glutathione status with Sch B treatment could improve insulin resistance in skeletal muscle in mice fed a high-fat diet through GSH-mediated reduction in mitochondrial ROS production.

2. Conclusion

In Traditional Chinese Medicine (TCM), Schisandra Fruit (SF) invigorates Qi in the liver and other visceral organs through the meridian system. The liver's pivotal role in regulating the functions of various visceral organs explains why SF can offer overall health benefits. Schisandrin B (Sch B), the primary active ingredient of SF, can enhance mitochondrial ATP generation and improve glutathione redox status in multiple organs. This could explain the overall protective effects of Sch B on various organs. Furthermore, due to the stronger impact of Sch B on liver function, the overall positive effects on different organs may be facilitated by signal molecules originating from the liver. Future studies are warranted to investigate whether Sch B can stimulate the synthesis and release of liver-derived signaling molecules.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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