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Schisandrin B Elevates Plasma Glutathione Redox Status and Modulates Hepatokines for Extrahepatic Metabolic Regulation

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Abstract

Schisandrin B (Sch B), a bioactive lignan derived from *Schisandrae chinensis Fructus*, exhibits well-documented tissue-protective properties, yet its systemic metabolic effects mediated by liver-derived factors remain elusive. This study investigated the capacity of Sch B to modulate systemic redox status and hepatokine secretion in a mouse model. Following oral administration of Sch B, treated animals demonstrated a significantly elevated plasma glutathione (GSH/GSSG) ratio, reflecting a robust enhancement of systemic antioxidant capacity essential for extrahepatic tissue protection. Concurrently, Sch B induced a highly favorable reprogramming of circulating hepatokines by downregulating angiopoietin-like proteins 3 and 4 (ANGPTL3 and ANGPTL4) while upregulating the insulin-sensitizing hormone adropin. Because ANGPTL3/4 act as lipase inhibitors, this coordinated shift theoretically promotes an atheroprotective lipid profile alongside enhanced energy expenditure and glucose homeostasis. Collectively, these findings demonstrate that Sch B exerts beneficial systemic metabolic effects through coupled redox enhancement and hepatokine regulation, underscoring its potential as a therapeutic agent for metabolic disorders.

Keywords

Schisandrin B, Plasma, Glutathione Redox Status, Hepatokines

1. Introduction

Schisandrae Chinensis Fructus (SF), a cornerstone of traditional Chinese medicine (TCM), is recognized for its ability to invigorate "Qi" within the Liver zang and other "visceral organs" via the meridian system [1]. In TCM, the Liver's piv-

otal role as a "General" organ, orchestrating the functions of numerous other visceral organs, provides a theoretical framework for SF's broad health-promoting effects [2]. The principal bioactive compound within SF, schisandrin B (Sch B), has demonstrated promising effects, including improved mitochondrial ATP production and enhanced glutathione redox status across various organs [3] [4]. These findings suggest that Sch B's organ-protective properties may stem from its influence on cellular energy metabolism and antioxidant defense. Given Sch B's pronounced impact on liver function, it is plausible that its beneficial effects on other organs are mediated by signaling molecules originating from the liver. This study investigates whether Sch B can positively alter plasma glutathione redox status and modulate the levels of hepatokines—liver-secreted proteins that influence cardiometabolic function—to exert its regulatory effects on extrahepatic tissues.

2. Materials and Methods

2.1. Reagents

Reduced glutathione (GSH), oxidized glutathione (GSSG), and glutathione reductase (GR) were purchased from Sigma Chemical Co. (St. Louis, MO). Mouse ELISA assays for ANGPTL3, ANGPTL4, and adropin were obtained from Wuhan Fine Biotech Co., Ltd. (FineTest) (Wuhan, P.R. China). Sch B was bought from Shaanxi Jiahe Phytochem Co., Ltd. (Xian, P.R. China).

2.2. Animal Care

Thirty adult male ICR mice were randomized into three groups of 10: Control, Sch B (10 mg/kg), and Sch B (30 mg/kg). They were maintained under a 12-hour dark/light cycle at an ambient temperature of approximately 22˚C with ad libitum access to food and water. Experimental protocols were approved by the Research Practice Committee at the Hong Kong University of Science and Technology (AEP-2023-0062).

2.3. Animal Treatment

Animals were randomly divided into groups of ten each. In the treatment groups, mice were intragastrically administered Sch B (suspended in water) at a daily dose of 10 or 30 mg/kg for 15 doses within 3 weeks. Control animals received water only. The pharmacological doses used in this study are consistent with those in the previous study of Sch B. Long-term, low doses of Sch B (0.001 - 0.03 g/kg for 15 days, corresponding to human equivalent doses) were shown to protect against cerebral ischemia-reperfusion injury in rats [5]. Twenty-four hours after the last dose, animals were euthanized by cervical dislocation, and blood samples were collected via cardiac puncture, and plasma samples were obtained after centrifugation (2000 × g, 10 min, 4˚C) of blood samples. In each group, two plasma samples were pooled into one for subsequent biochemical analysis due to the small volume of plasma obtained from one animal. Biochemical analyses were done in a non-biased manner with established protocols. A blinding approach was not

adopted in dosing, tissue processing, and endpoint readouts.

2.4. Measurement of Plasma Glutathione Redox Status

Plasma GSH and GSSG levels were determined enzymatically using DTNB and GR, as previously described [5] [6]. A 140 μL aliquot of the plasma sample was mixed with 60 μL of 10% SSA, and the supernatant was used to measure GSH and GSSG. The plasma glutathione redox status was expressed as the GSH/GSSG ratio.

2.5. Measurement of Plasma Hepatokine Levels

The plasma was used to measure ANGPTL3, ANGPTL4 and adropin levels with the ELISA kits. The ANGPTL levels and adropin were expressed in ng/mL and μg/mL, respectively, and this value was used to estimate the percentage of control for comparison.

2.6. Statistical Analysis

Data, which were expressed as mean ± SD, were analyzed by One-way ANOVA (Fisher's Least Significant Difference (LSD) test) (using five pooled plasma samples in a group) to detect significant differences between groups when $P < 0.05$.

3. Results and Discussion

Previous research has established that Sch B treatment enhances the hepatic GSH to GSSG ratio, thereby improving liver glutathione redox status [3]. Our current findings extend this observation to the systemic circulation, demonstrating that Sch B treatment also significantly improves plasma glutathione redox status, which is mediated by decreasing circulating GSSG levels (data not shown). This elevation of glutathione redox status is crucial, as it sustains the transport of plasma GSH to extrahepatic tissues, such as cardiac and skeletal muscle. The increase in plasma glutathione redox reflects the liver's ability to replenish plasma GSH that has been delivered to tissues [7] [8]. In these tissues, the increased GSH bolsters cellular antioxidant defenses, which are particularly vital for sustaining high-energy metabolic states [7]-[10].

Glutathione, the body's master antioxidant, relies on the delicate balance of its GSH/GSSG ratio as a key indicator of cellular redox health [9]-[11]. Naturally occurring aging in mice is typically characterized by a progressive decline in this ratio, leading to the accumulation of oxidative damage across various tissues [12]. By elevating the GSH/GSSG ratio in the blood, Sch B treatment effectively counteracts this age-related decline in tissue GSH levels. This strengthens the body's capacity to neutralize reactive oxygen species, thereby safeguarding critical tissues such as the brain and cardiovascular system from the damaging oxidative stress associated with elevated metabolic activity. This systemic antioxidant enhancement is further supported by prior research demonstrating that long-term Sch B administration can suppress age-associated reductions in mitochondrial GSH levels in diverse tissues, including the liver, brain, heart, and kidneys, ultimately con-

tributing to an extended average lifespan [13].

Beyond its potent antioxidant effects, Sch B treatment also significantly modulated the hepatokine profile. Specifically, we observed a decrease in the levels of ANGPTL3 and ANGPTL4, accompanied by an increase in adropin (**Table 1**). The dual suppression of ANGPTL3 and ANGPTL4 is particularly noteworthy for its potential cardiovascular benefits [14]. These proteins are known inhibitors of lipoprotein lipase and endothelial lipase; their reduction can therefore maximize the activity of these enzymes, leading to a substantial decrease in plasma triglycerides and circulating low-density lipoprotein cholesterol [15] [16]. Indeed, studies in mouse models have shown that downregulating these specific angiopoietin-like proteins can halt the progression of atherosclerosis, reduce vascular inflammation, and diminish the size of necrotic core areas within arterial plaques [17] [18].

Concurrently, the elevated level of adropin is poised to powerfully stimulate energy utilization and prevent the spontaneous development of obesity and insulin resistance [19] [20]. Adropin complements these effects by functioning as an insulin-sensitizing hormone that protects the liver from excessive fat accumulation [21] [22]. Collectively, these modulated hepatokines orchestrate a significant metabolic shift within the body, promoting a state of enhanced efficiency characterized by increased fat burning and improved glucose utilization.

One limitation of the present study was that only male mice were used. However, prior studies indicated no gender difference in various Sch B-induced pharmacological actions.

Table 1. Effects of Sch B treatment on glutathione redox status and hepatokine levels in plasma of mice. Values given are mean % control ± SD (n = 5). Control values: GSH/GSSG ratio, 3.35 ± 0.31; ANGPTL3 (ng/mL), 7.82 ± 0.44; ANGPTL4 (ng/mL), 3.17 ± 0.79; adropin (μg/mL), 20.1 ± 2.16. *$p < 0.05$, when compared to the control value, using One-way ANOVA (LSD test).

	Control	10 mg/kg	30 mg/kg
GSH/GSSG ratio	100 ± 9.26	129 ± 7.95*	145 ± 4.16*
ANGPTL3	100 ± 5.61	95.2 ± 6.51	82.4 ± 0.93*
ANGPTL4	100 ± 25.0	60.8 ± 9.8*	62.0 ± 3.26*
Adropin	100 ± 10.8	101 ± 17.1	120 ± 9.88*

4. Conclusion

This study provides compelling evidence that Sch B exerts its beneficial metabolic effects through a dual mechanism: direct antioxidant actions and the orchestration of a systemic shift in liver-derived signaling. By enhancing plasma glutathione redox status, Sch B bolsters antioxidant defenses in vital extrahepatic tissues, counteracting age-related oxidative damage. Furthermore, the modulation of key hepatokines, specifically the suppression of ANGPTL3 and ANGPTL4 alongside the elevation of adropin, reveals a sophisticated metabolic regulatory pathway. These combined actions collectively promote a healthier lipid profile, reduce car-

diovascular risk factors, and foster a metabolic environment conducive to energy expenditure and improved insulin sensitivity. These findings underscore the potential of Sch B as a nutraceutical or therapeutic agent for metabolic disorders, highlighting the intricate interplay between liver function and systemic metabolic health.

Conflicts of Interest

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

References

[1] Ko, K.M. and Leung, H.Y. (2024) How Schisandrae Fructus Benefits the Body: Mechanisms in Traditional Chinese Medicine and Modern Medicine. *Chinese Medicine*, **15**, 75-81. https://doi.org/10.4236/cm.2024.153006

[2] Zhang, Y. and Fang, X. (2023) The Pan-Liver Network Theory: From Traditional Chinese Medicine to Western Medicine. *Chinese Journal of Physiology*, **66**, 401-436. https://doi.org/10.4103/cjop.cjop-d-22-00131

[3] Leung, H.Y., Sze, S.C. and Ko, K.M. (2024) Pharmacological Investigation on the Qi-Invigorating Action of Schisandrin B: Effects on Mitochondrial ATP Generation in Multiple Tissues and Innate/Adaptive Immunity in Mice. *Chinese Medicine*, **15**, 15-26. https://doi.org/10.4236/cm.2024.152002

[4] Guo, S., Yu, F., Wang, C., Zhao, W., Li, X., Liu, J., *et al.* (2026) Schisandrin B Confers Multi-Organ Protection via Regulation of Mitochondrial Homeostasis: Mechanistic Integration, Organ-Specific Differences, and Translational Challenges—A Review. *Frontiers in Pharmacology*, **17**, Article ID: 1781376. https://doi.org/10.3389/fphar.2026.1781376

[5] Leung, H.Y., Chiu, P.Y., Poon, M.K.T. and Ko, K.M. (2005) A Yang-Invigorating Chinese Herbal Formula Enhances Mitochondrial Functional Ability and Antioxidant Capacity in Various Tissues of Male and Female Rats. *Rejuvenation Research*, **8**, 238-247. https://doi.org/10.1089/rej.2005.8.238

[6] Tipple, T.E. and Rogers, L.K. (2012) Methods for the Determination of Plasma or Tissue Glutathione Levels. In: *Methods in Molecular Biology*, Humana Press, 315-324. https://doi.org/10.1007/978-1-61779-867-2_20

[7] Vairetti, M., Di Pasqua, L.G., Cagna, M., Richelmi, P., Ferrigno, A. and Berardo, C. (2021) Changes in Glutathione Content in Liver Diseases: An Update. *Antioxidants*, **10**, Article 364. https://doi.org/10.3390/antiox10030364

[8] Ballatori, N., Krance, S.M., Notenboom, S., Shi, S., Tieu, K. and Hammond, C.L. (2009) Glutathione Dysregulation and the Etiology and Progression of Human Diseases. *Biological Chemistry*, **390**, 191-214. https://doi.org/10.1515/bc.2009.033

[9] Lushchak, V.I. (2012) Glutathione Homeostasis and Functions: Potential Targets for Medical Interventions. *Journal of Amino Acids*, **2012**, Article ID: 736837. https://doi.org/10.1155/2012/736837

[10] Vázquez-Meza, H., Vilchis-Landeros, M.M., Vázquez-Carrada, M., Uribe-Ramírez, D. and Matuz-Mares, D. (2023) Cellular Compartmentalization, Glutathione Transport and Its Relevance in Some Pathologies. *Antioxidants*, **12**, Article 834. https://doi.org/10.3390/antiox12040834

[11] Tenchov, R., Sasso, J.M., Wang, X. and Zhou, Q.A. (2024) Aging Hallmarks and Progression and Age-Related Diseases: A Landscape View of Research Advancement.

ACS Chemical Neuroscience, **15**, 1-30.
https://doi.org/10.1021/acschemneuro.3c00531

[12] Félix, J., Díaz-Del Cerro, E., Garrido, A. and De La Fuente, M. (2024) Characterization of a Natural Model of Adult Mice with Different Rate of Aging. *Mechanisms of Ageing and Development*, **222**, Article 111991.
https://doi.org/10.1016/j.mad.2024.111991

[13] Ko, K.M., Chen, N., Leung, H.Y., Leong, E.P.K., Poon, M.K.T. and Chiu, P.Y. (2008) Long-Term Schisandrin B Treatment Mitigates Age-Related Impairments in Mitochondrial Antioxidant Status and Functional Ability in Various Tissues, and Improves the Survival of Aging C57BL/6J Mice. *BioFactors*, **34**, 331-342.
https://doi.org/10.1002/biof.5520340408

[14] Landfors, F., Henneman, P., Chorell, E., Nilsson, S.K. and Kersten, S. (2024) Drug-target Mendelian Randomization Analysis Supports Lowering Plasma ANGPTL3, ANGPTL4, and APOC3 Levels as Strategies for Reducing Cardiovascular Disease Risk. *European Heart Journal Open*, **4**, oeae035. https://doi.org/10.1093/ehjopen/oeae035

[15] Iglesias, P. (2025) The Endocrine Role of Hepatokines: Implications for Human Health and Disease. *Frontiers in Endocrinology*, **16**, Article ID: 1663353.
https://doi.org/10.3389/fendo.2025.1663353

[16] Jensen-Cody, S.O. and Potthoff, M.J. (2021) Hepatokines and Metabolism: Deciphering Communication from the Liver. *Molecular Metabolism*, **44**, Article 101138.
https://doi.org/10.1016/j.molmet.2020.101138

[17] Cho, D.I., Ahn, J.H., Kang, B.G., Hwang, I., Cho, H.H., Jun, J.H., *et al.* (2025) ANGPTL4 Prevents Atherosclerosis by Preserving KLF2 to Suppress EndMT and Mitigates Endothelial Dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **45**, 1742-1761.
https://doi.org/10.1161/atvbaha.125.322700

[18] Weng, S., Ding, C., Lin, J. and Chai, D. (2026) ANGPTL3 and Residual Atherosclerotic Risk: From Lipid Metabolism to Therapeutic Targeting. *Frontiers in Endocrinology*, **16**, Article ID: 1706091. https://doi.org/10.3389/fendo.2025.1706091

[19] Altamimi, T.R., Gao, S., Karwi, Q.G., Fukushima, A., Rawat, S., Wagg, C.S., *et al.* (2019) Adropin Regulates Cardiac Energy Metabolism and Improves Cardiac Function and Efficiency. *Metabolism*, **98**, 37-48. https://doi.org/10.1016/j.metabol.2019.06.005

[20] Chen, R., Wang, Q., Wang, Y., Wang, Y., Liu, J., Liao, Z., *et al.* (2023) Feeding-Induced Hepatokines and Crosstalk with Multi-Organ: A Novel Therapeutic Target for Type 2 Diabetes. *Frontiers in Endocrinology*, **14**, Article ID: 1094458.
https://doi.org/10.3389/fendo.2023.1094458

[21] Ali, I.I., D'Souza, C., Singh, J. and Adeghate, E. (2022) Adropin's Role in Energy Homeostasis and Metabolic Disorders. *International Journal of Molecular Sciences*, **23**, Article 8318. https://doi.org/10.3390/ijms23158318

[22] Jasaszwili, M., Billert, M., Strowski, M.Z., Nowak, K.W. and Skrzypski, M. (2020) Adropin as a Fat-Burning Hormone with Multiple Functions—Review of a Decade of Research. *Molecules*, **25**, Article 549. https://doi.org/10.3390/molecules25030549