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Sericin improves heart and liver mitochondrial architecture in hypercholesterolaemic rats and maintains pancreatic and adrenal cell biosynthesis

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ABSTRACT

Hypercholesterolaemia is well known to be associated with mitochondrial dysfunction, subsequently leading to multiple organ failure. Similar to other natural products, sericin is a candidate for adjunctive therapy in hyperlipidaemic conditions. However, the cholesterol-lowering mechanisms of sericin are multifactorial and controversial. Here, a high-cholesterol-fed rat model with or without sericin treatment was established using a dosage of 1000 mg/kg/day for 30 days. Blood lipid profiles, oxidative stress markers (superoxide dismutase, SOD; malondialdehyde, MDA; nuclear factor erythroid 2-related factor, Nrf-2), dysmorphic mitochondria in relation to fission (dynamin-related protein-1; Drp-1) and fusion (guanosine triphosphatase mutated in dominant optic atrophy; OPA-1) markers and biosynthetic markers (aquaporin, AQP-1; tubulin-4 β , Tb4B) in the pancreas and adrenal gland were evaluated. The results showed that sericin reduced blood cholesterol and increased high-density lipoprotein (HDL) by acting against oxidative stress. Hypocholesterolaemic and antioxidant conditions further preserved heart and liver mitochondrial architecture; however, this protection was not exhibited in the kidney, where a high level of renal mitophagy, indicating by LC-3 up-regulation, was presented. The steps of ultrastructural alteration of mitochondria from degenerative changes to necrosis were also demonstrated. Sericin also conserved AQP-1 and Tb4B levels in the exocrine pancreatic acinar cells and zona glomerulosa cells, which were positively correlated with serum lipase, HDL, antioxidative markers and mitochondrial integrity. The present study revealed that sericin not only has antioxidant capacity but also balances pancreatic and adrenal cell biosynthesis, especially lipase activity, which may have played an important role in improving lipid dysregulation in the hypercholesterolaemic rat model, leading to the reduction of dysmorphic mitochondria, particularly in the heart and liver.

1. Introduction

Mitochondrial dysfunction has been claimed to be an important phenomenon in dietary-induced hypercholesterolaemia, leading to organ insufficiency or failure, particularly in the heart, liver and kidney [1–3]. Our recent study showed that short-term sericin consumption alleviates mitochondrial dysfunction in the heart and liver due to its antioxidative property, which further lowered the blood cholesterol level without hypoglycaemic effect in a hypercholesterolaemic and diabetic rat model [4]. Our previous study also demonstrated that sericin reduces the severity of microvesicular steatosis in the liver. Studies of the cholesterol-lowering mechanism of sericin have mainly focused on the gastroduodenal level, for example, absorption site

effects and intracellular tracking [5,6]. However, the roles of sericin during the events after cholesterol absorption, such as its entry into the blood circulation, a high persistence of blood cholesterol and then cellular deposition, remain controversial.

Catabolic enzymes and hormones are important for regulating the blood cholesterol level in association with accelerating internal metabolism. It is well understood that lipase, in both serum and tissue, promotes lipolysis, reduces blood cholesterol and triglyceride and maintains a normal blood lipid profile [7–9]. Taking these findings together, glucocorticoids are well described to affect serum lipids and induce hyperlipidaemia [10–12] in relation to the increased metabolic availability of fatty acids. Dysregulation of their synthesis leads to many features of metabolic syndrome, disordered lipid metabolism, hepatic

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Table 1
Blood lipid, kidney and antioxidative profiles in high cholesterol-fed rats with and without sericin treatment.

Group	Serum chemistry						Serum oxidative markers	
	Cholesterol (mg/dL)	HDL (mg/dL)	Lipase (U/L)	BUN (mg/dL)	Creatinine (mg/dL)	ALT (U/L)	SOD	MDA
With sericin	77.66 ± 4.41 ^a	72.0 ± 1.57 ^a	42.0 ± 0.42 ^a	16.15 ± 0.71	0.26 ± 0.01	45.33 ± 1.58	2487.3 ± 240.1	9.20 ± 0.92
Without sericin	234.16 ± 3.34 ^{a,b}	50.0 ± 1.35 ^a	37.5 ± 0.47 ^a	15.71 ± 0.59	0.30 ± 0.00	39.50 ± 1.35	1333.6 ± 66.4	8.76 ± 1.02
Normal chow-fed rats	66.34 ± 5.32 ^b	84.11 ± 7.22 ^b	NA	19.98 ± 5.98	0.44 ± 1.11	59.19 ± 5.55	NA	NA

Abbreviation; HDL: high-density lipoprotein, BUN: blood urea nitrogen, ALT: alanine transaminase, SOD: super oxide dismutase, MDA: malondrialdehyde, NA: not available, superscript a or b: matched of significant difference by Kruskal-Wallis test.

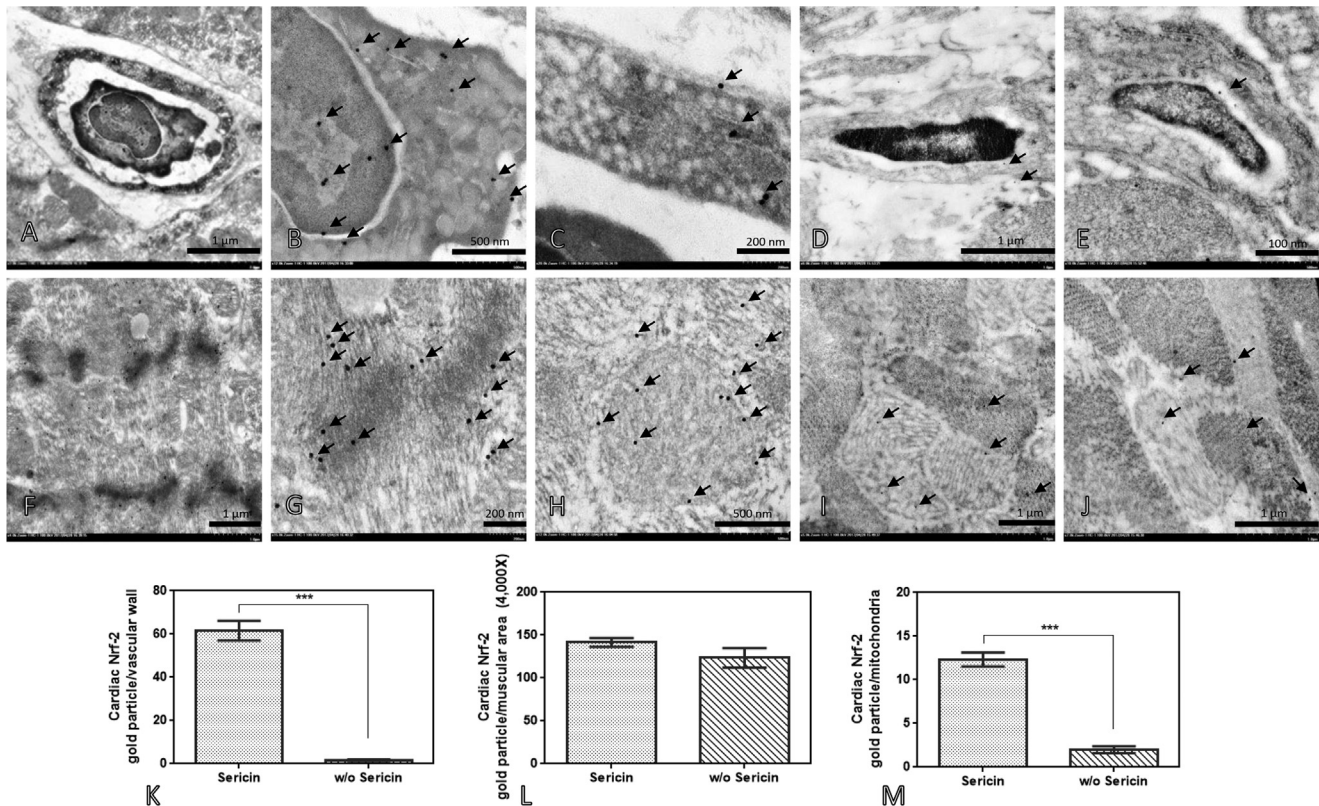


Fig. 1. Electron micrographs of heart with Nrf-2 immunogold labeling. The positive Nrf-2 gold particle (arrow) was observed throughout of the heart, but it mainly deposited in the wall of small blood vessels (A-E), myocytes (F-G) and mitochondria (H-J). Nrf-2 gold labelled in those mentioned tissues in the rats with (A-C and G-H) or without (D-E, F and I-J) sericin treatment is shown. Bar graphs also demonstrated the difference of Nrf-2 expression in the vascular wall (K), muscular area (L) and mitochondria (M) between treated and untreated rats.

steatosis, obesity, hyperglycaemia, insulin resistance and muscle wasting [13–15].

Against this background, in the present study, it was postulated that, due to the antioxidant capacity of sericin, it may equilibrate the synthesis of some lipid catabolic enzymes, especially lipase, and subsequently alleviate hypercholesterolaemic conditions. Blood lipid profiles, oxidative stress markers (superoxide dismutase, SOD; malondialdehyde, MDA and nuclear factor erythroid 2-related factor, Nrf-2), dysmorphic mitochondria in the heart, liver and kidney dysmorphic mitochondria both fine morphological changes and the expression of fission (dynamamin-related protein-1; Drp-1) and fusion (guanosine triphosphatase mutated in dominant optic atrophy; OPA-1) proteins, and biosynthetic markers (aquaporin, AQP-1 [16]; tubulin-4 β , Tb4B [17]) in the pancreas and adrenal gland were examined and compared between high-cholesterol-fed rats with and without sericin treatment. Moreover, the present study highlighted potential dynamic ultrastructural mitochondrial changes induced by hypercholesterolaemia, from degenerative stages to necrosis.

2. Materials and methods

2.1. Sericin extraction

Cocoons of the silkworm *Bombyx mori* were provided by Chul Thai Silk Co., Ltd., Petchaboon Province, Thailand. Sericin was extracted from fresh cocoon shells by autoclaving in purified water at 120 °C for 60 min. The supernatant was then filtered, frozen and finally lyophilised.

2.2. Ethics statement

All animal experiments were approved and certified by the Faculty of Medicine, Chulalongkorn University Animal Care and Use Committee, Bangkok, Thailand (Approval No. 16/2558). Eight-week-old Sprague-Dawley rats were procured from the National Laboratory Animal Centre, Mahidol University, Thailand. They were housed in a strict hygienic conventional system under a 12-h dark/light cycle and

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