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Editorial

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Beneficial Effects of Supplementation on Endothelial Function: What Mechanisms?

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Recently, much attention has been given to supplementation, and supplements are now used worldwide. In western countries, focusing on auxiliary effects on nutritional and physiological functions, vitamins, minerals, and herbs are treated as "dietary supplements" and "food supplements." Some supplements were authorized as health function foods by the Ministry of Health, Labour and Welfare in Japan before their authorization in other countries. However, due to the wide distribution of foods, including supplementation, standardization of supplementation and international unification of display are required. The function of supplementation should be scientifically revealed at the molecular level. In addition, it is clinically important to determine whether supplementation prevents the onset of diabetes, hypertension, cardiovascular disease, and cancer, and whether it has anti-aging effects for the establishment of evidence-based supplementation. From the viewpoint of the significance of supplementation, methods for evaluating the biological regulation functions and clinical evidence of supplementation are strongly required. In a clinical setting, the assessment of endothelial function is established as a surrogate marker for the degree of atherosclerosis, evaluation of therapy for atherosclerosis, and prediction of cardiovascular events[1-3].

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis, leading to the development and maintenance of atherosclerosis, which results in cardiovascular and cerebrovascular outcomes[4]. It is well known that the degree of endothelial dysfunction is a marker of future cardiovascular events in patients with hypertension, diabetes mellitus, coronary artery disease, and peripheral arterial disease[1-3]. Thus, it is important to select appropriate interventions for the prevention of endothelial dysfunction in patients with atherosclerosis or augmentation of endothelial function even in healthy subjects. Supplementation therapy is one of the interventions for beneficial effects on endothelial function. Several investigators have shown that supplementation, including L-arginine (a substrate of nitric oxide [NO]), tetrahydrobiopterine (a cofactor of NO), antioxidants vitamin C, and other polyphenols with antioxidant properties, such as red wine, chocolate, coffee, tea, fruits, and vegetables, improves or augments endothelium-dependent vasodilation in patients with cardiovascular disease and healthy subjects[5-8].

In this issue, Fujisue, *et al.*[9] reported that the administration of royal jelly, a substance selected by honeybees at 690 mg per day for 4 weeks, increased reactive hyperemia index as an index of endothelial function in 100 healthy subjects using a double-blinded, randomized placebo-controlled study design, suggesting royal jelly-induced augmentation of endothelial function. It is thought that the augmentative effects of royal jelly on endothelial function are due to its muscarine receptor agonist effect that activates the endothelial NO synthase (eNOS)/NO/cGMP pathway, enhancement of insulin signaling that activates the eNOS)/NO/cGMP pathway, and inhibition of angiotensin-converting enzyme activity, resulting in an increase in NO production. Royal jelly is composed of a mixture of properties, including moisture, protein, sugar, ether extract, ash, vitamins, minerals, and amino acids[9].

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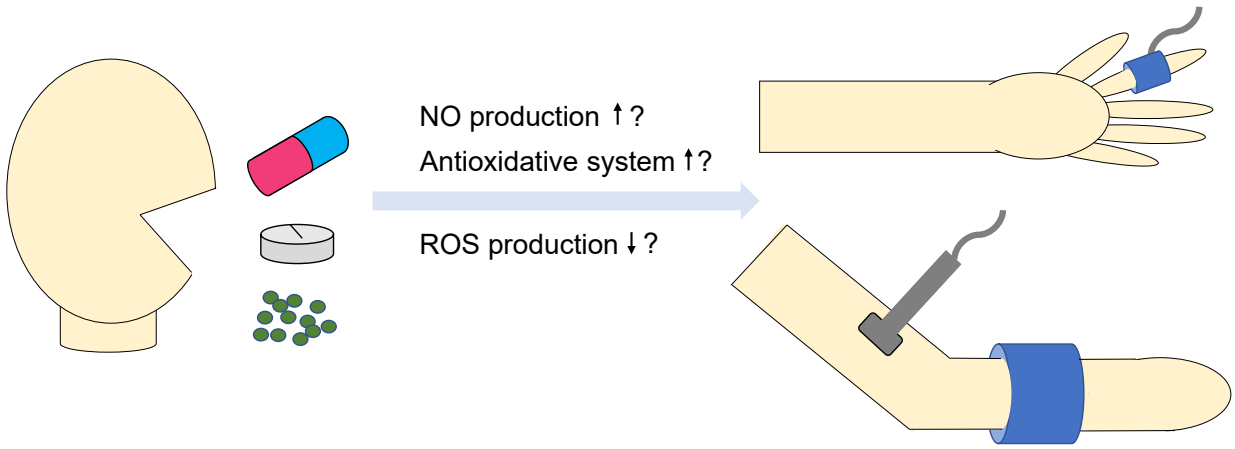

Fig. 1. Beneficial Effects of Supplementation on Endothelial Function: What Mechanisms?
NO indicates nitric oxide. ROS inducates reactive oxygen species.

Therefore, it is expected that royal jelly inhibits the degradation of NO through the inhibition of reactive oxygen species (ROS), leading to the augmentation of endothelial function.

A balance between released NO and ambient levels of ROS also plays a critical role in the maintenance of endothelial function. Endothelial dysfunction is, at least in part, due to the inactivation of NO by ROS. We have shown that one mechanism of endothelial dysfunction is an increase in ROS in patients with renovascular hypertension, who are ideal models of excess angiotensin II and angiotensin II-related increase in ROS and oxidative stress[10]. Measurement of NO or oxidative stress markers, 8-hydroxy-2'-deoxyguanosin, isoprostanes, and malondialdehyde-modified low-density lipoprotein, and assessment of the antioxidant system, such as superoxide dismutase, glutathione peroxidase, and catalase, would enable a more specific conclusion concerning the role of administration of royal jelly in NO bioavailability and endothelial function to be drawn.

Future studies are needed to determine the precise mechanisms by which supplementation therapy, including royal jelly, improves endothelial function in patients with atherosclerosis or augments endothelial function in healthy subjects **(Fig. 1)**.

Conflict of Interest

No conflict of interest.

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