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**File: ■ Chocolate (*Theobroma cacao*)**  
**■ Flavan-3-ols**  
**■ Metabolic Syndrome**

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**RE: Flavan-3-ols Improve Metabolic Syndrome Risk Factors**

Osakabe N. Flavan 3-ols improve metabolic syndrome risk factors: evidence and mechanisms. *J Clin Biochem Nutr.* May 2013;52(3):186-192.

Flavan-3-ols, a type of polyphenols, are found in various plant foods. Chocolate (*Theobroma cacao*) is abundant in flavan-3-ols, including the flavan-3-ol monomers (+)-catechin and (–)-epicatechin and oligomers. Recent studies suggest that chocolate or flavan-3-ols have a positive influence on human health through their antioxidant, anti-inflammatory, and antithrombotic properties. Evidence also suggests that cocoa products containing flavan-3-ols may help prevent cardiometabolic disorders. In this review article, the author, Naomi Osakabe, from Shibaura Institute of Technology in Saitama, Japan, focuses on the ability of flavan-3-ols to improve the risk factors for the metabolic syndrome, thereby reducing the risk for cardiovascular disease.

Epidemiological evidence suggests that flavan-3-ol monomers reduce the risk for coronary heart disease<sup>1,2</sup> and that the ingestion of chocolate reduces the risk for stroke.<sup>3</sup> A meta-analysis of 5 studies<sup>4</sup> showed that the multivariable relative risk for stroke was 0.83 for the highest quartile of chocolate consumption (median, 62.9 g weekly) compared with the lowest quartile (no chocolate).

Numerous randomized, controlled trials have studied the effects of chocolate or cocoa products on the risk factors for metabolic syndrome, including hypertension, vascular endothelial dysfunction, dyslipidemia, and glucose intolerance. The authors cite 7 meta-analyses of chocolate intervention trials, with the number of subjects ranging from 173 in an analysis of 5 studies to 1,297 subjects in an analysis of 42 studies. In the latter analysis,<sup>5</sup> insulin resistance was improved by the consumption of chocolate or cocoa due to significant reductions in serum insulin. That analysis also reported improved flow-mediated dilatation, reduced diastolic blood pressure and mean arterial pressure, and marginally significant improvements in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels. Those beneficial effects of cocoa products on metabolic syndrome risk factors are confirmed in short-term intervention trials, says Osakabe. "However, further larger and longer-duration trials are required to confirm the potential cardiovascular benefits of cocoa flavan-3-ols."

Numerous reports on the bioavailability of flavan-3-ols report that the monomers such as (–)-epicatechin and (+)-catechin are well absorbed and are metabolized mainly in the small intestine or liver, forming metabolites through the action of transferase enzymes. In contrast, says Osakabe, numerous studies in animals and humans demonstrate that *polymeric* epicatechins such as procyanidins are not absorbed. For example, in a study on rats conducted by the author and colleagues,<sup>6</sup> "only about 0.5% of the epicatechin dimer, procyanidin B2, is absorbed, with the majority passing unaltered into the large intestine where it is catabolized by colonic microflora to a diverse range of phenolic acids."

Despite the reported low bioavailability of some of the flavan-3-ols, a number of in vitro studies have reported improvements in metabolic syndrome risk factors following their ingestion. In studies using cell culture or isolated organs, the nitric oxide radical, a potent endothelium dilatation factor, and endothelial nitric oxide synthase were increased by adding flavan-3-ols from various sources.<sup>7-9</sup> "However," cautions Osakabe, "almost all these investigations lacked physiological significance as the parent compounds rather than the metabolites were used at high[er] levels than those achieved in blood following oral administration of flavan-3-ols." The cited in vitro studies "suggest that absorbed procyanidins, catechins or phenolic acids contributed only a portion of the improvement in metabolic syndrome risk factors," writes Osakabe.

In a study of more than 1,000 American men and women, a negative correlation was shown between the frequency of chocolate consumption and body mass index (BMI).<sup>10</sup> In an animal study conducted by Osakabe,<sup>11</sup> the repeated ingestion of flavan-3-ols influenced energy expenditure in rats: after 2 weeks with either a normal diet or one containing 0.2% flavan-3-ols derived from cacao, total oxygen consumption increased significantly in the flavan-3-ols group compared with the control group. As a result, total energy expenditure also increased significantly in the flavan-3-ols group.

Other studies<sup>12</sup> have demonstrated that flavan-3-ols prevented glucose intolerance and obesity by promoting translocation of glucose transporter 4 and phosphorylation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) in the plasma membrane of skeletal muscle and brown adipose tissue, prompting Osakabe to suggest, "Improvement of dyslipidemia or lowering of BMI in RCT [randomized, controlled trials] or epidemiological studies may also be induced by this mitochondrial biogenesis promoting effect."

Osakabe concludes, "Flavan-3-ols may improve hypertension, dyslipidemia, insulin resistance, and obesity induced by inappropriate daily habits," but more studies are needed to identify the mechanisms responsible for those effects.

—Shari Henson

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Referenced article can be found at [https://www.jstage.jst.go.jp/article/jcbrn/52/3/52\\_12-130/\\_article](https://www.jstage.jst.go.jp/article/jcbrn/52/3/52_12-130/_article).

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