Flavan 3-ols improve metabolic syndrome risk factors: evidence and mechanisms

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Flavan 3-ols, a type of polyphenolic substance, are distributed in a number of plant foods and supplements such as cacao beans, red wine, beer, berries, apples, black soy bean and French maritime pine bark. Of these foods, chocolate is the most abundant flavan 3-ols containing food. As shown in Fig. 1, these include the flavan 3-ol monomers, (+)-catechin and (−)-epicatechin, and the oligomers, B-type flavan 3-ols, such as procyanidin B2 (dimer), procyanidin C1 (trimer), and cinnamtannin A2 (tetramer) that are linked by C4–C8 bonds. It has been reported that chocolate contains oligomers ranging from dimers to decamer flavan 3-ols. Recent studies have suggested that chocolate or flavan 3-ols have a positive influence on human health, due to antioxidant, anti-inflammatory, and anti-thrombotic effects. There is also evidence that cacao products containing flavan 3-ols have the potential to contribute to the prevention of cardiometabolic disorders. This review focuses on recent advances in research on the ability of flavan 3-ols to reduce the risk of cardiovascular disease as a result of improving metabolic syndrome risk factors and these mechanisms.

Key Words: flavan 3-ols, chocolate, cardiovascular diseases, metabolic syndrome, risk factors

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Inverse Association of Chocolate Intake and the Risk of Developing Cardiovascular Diseases

The Kuna, an indigenous group who lives predominantly on small islands off the coast of Panama consume a large amount of natural cocoa drinks, and are nearly free of hypertension and cardiovascular disease. In contrast, Kuna who migrate to Panama urban sites lose this advantage, as they are no longer able to maintain their habit of drinking cocoa. Recent epidemiological evidence suggests that ingestion of flavan 3-ols monomers reduces the risk of coronary heart disease. These reports showed a strong inverse association between intake of (+)-catechin and (−)-epicatechin as flavan 3-ols monomers and death from coronary heart disease. Epidemiological evidence also suggests that ingestion of chocolate reduces the risk of cardiovascular diseases such as stroke and cardiometabolic disorders. Buitrago-Lopez et al. using six cohort studies and one cross-sectional study showed that the highest level of chocolate consumption was associated with a 37% reduction in cardiovascular disease (relative risk 0.63, 95% CI 0.44–0.90) and a 29% reduction in stroke compared with the lowest levels (Fig. 2). Larsson et al. also reported a meta-analysis of 5 studies that showed the multivariable relative risk of stroke was 0.83 (95% CI 0.70–0.99) for the highest quartile of chocolate consumption (median 62.9 g/week) compared with the lowest quartile (median 0 g/week). Based on observational evidence, these results suggested that the level of chocolate consumption was associated with a substantial reduction in the risk of cardiovascular disorders.

Association of Ingestion of Chocolate and Metabolic Syndrome Risk Factors

Numerous randomized, controlled trials (RCT) have investigated the effects of chocolate or cocoa products, especially dark chocolate, on metabolic syndrome risk factors such as hypertension, vascular endothelial dysfunction, dyslipidemia, and glucose intolerance. As shown in Table 1, seven meta-analyses of chocolate intervention trials have been reported recently. Hooper et al. analyzed the data of 1297 subjects in 42 acute or short-term chronic RCTs and showed that insulin resistance (HOMA-IR: −0.67; 95% CI: −0.98, −0.36) was improved by consumption of chocolate or cocoa due to significant reductions in serum insulin. They also reported that flow-mediated dilatation (FMD) improved after chronic (1.34%; 95% CI: 1.00%, 1.68%) and acute (3.19%; 95% CI: 2.04%, 4.33%) chocolate ingestion. Reducions in diastolic blood pressure (BP: −1.60 mmHg; 95% CI: −2.77, −0.43 mmHg) and mean arterial pressure (−1.64 mmHg; 95% CI: −3.27, −0.01 mmHg), and marginally significant improvements in LDL (−0.13 mmol/l; 95% CI: 0.03 mmol/l; 95% CI: −0.01, 0.06 mmol/l) were also observed in the study. These data are consistent with the beneficial effects of cocoa products on metabolic syndrome risk factors shown in...
Fig. 1. Chemical structures of flavan 3-ols in chocolate.\(^{(1-3)}\)

Fig. 2. Relative risks for cardiovascular disease, heart failure, and stroke in adults with higher levels of chocolate consumption compared with lower levels. Reproduced from (14) with permission.
### Table 1. Effect of chocolate on cardiovascular health: systematic reviews and meta analyses

| Study Authors | Journal | Year | Title | n (study) | n (subjects) |
|---------------|---------|------|-------|-----------|--------------|
| Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A | *Am J Clin Nutr*  | 2012; 95: 740–751 | Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials | 42 | 1297 |
| Shrime MG, Bauer SR, McDonald AC, Chowdhury NH, Coltart CE, Ding EL | *J Nutr* | 2011; 141: 1982–1988 | Flavonoid-rich cocoa consumption affects multiple cardiovascular risk factors in a meta-analysis of short-term studies | 24 | 1106 |
| Tokedoe OA, Gaziano JM, Djoussé L | *Eur J Clin Nutr* | 2011; 65: 879–886 | Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis | 10 | 320 |
| Ried K, Sullivan T, Fakler P, Frank OR, Stocks NP | *BMC Med* | 2010 Jun 28; 8: 39 | Does chocolate reduce blood pressure? A meta-analysis | 13 | 288 |
| Jia L, Liu X, Bai YY, Li SH, Sun K, He C, Hui R | *Am J Clin Nutr* | 2010; 92: 218–225 | Short-term effect of cocoa product consumption on lipid profile: a meta-analysis of randomized controlled trials | 8 | 215 |
| Desch S, Schmidt J, Kobler D, Sonnadabend M, Eitel I, Sareban M, Rahimi K, Schuler G, Thiele H | *Am J Hypertens* | 2010; 23: 97–103 | Effect of cocoa products on blood pressure: systematic review and meta-analysis | 10 | 297 |
| Taubert D, Roesen R, Schönig E | *Arch Intern Med* | 2007; 167: 626–634 | Effect of cocoa and tea intake on blood pressure: a meta-analysis | 5 | 173 |

**Fig. 3.** Structure of (−)-epicatechin metabolites. (A) 3'-O-Methyl-(−)-epicatechin, (B) (−)-epicatechin-7-O-glucuronide, (C) 3'-O-Methyl-(−)-epicatechin-7-O-glucuronide, (D) (−)-epicatechin-3'-O-glucuronide, (E) 4'-O-Methyl-(−)-epicatechin-3'-O-glucuronide. Chemicals A, B and C were obtained from rat urine, D and E were obtained from human.
short-term intervention trials. However, further larger and longer-duration trials are required to confirm the potential cardiovascular benefits of cocoa flavan-3-ols.

Bioavailability of Flavan 3-ol

Numerous reports have investigated the bioavailability of flavan 3-ols. Flavan 3-ols monomers, such as (−)-epicatechin and (+)-catechin are well absorbed, and are metabolized mainly in the small intestine or liver, forming sulfate, glucuronide or methylated metabolites through the action of sulfotransferases (SULT), uridine-5'-diphosphate glucuronosyltransferases (UGTs) and catechol-O-methyltransferases (COMT), respectively. Non-metabolized flavan 3-ol monomers are therefore rarely detected in the blood. We provided evidence that the chemical structure of (−)-epicatechin glucuronide, a major metabolite of (−)-epicatechin, was different between human and rats (Fig. 3). The antioxidative activities of those metabolites was also shown to be reduced in metabolites derived from human biomaterials.

In contrast, there are numerous feeding studies on animals and humans that demonstrate polymeric epicatechin as procyanidins are not absorbed. For example, we showed that 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 including 3-(3-hydroxyphenyl)propionic acid and 4-O-methylgallic acid. These acids are then absorbed into the circulatory system and excreted in the urine. It is possible that the biological effects of procyanidins described above are attributable to these phenolic acids, although there is a lack of detailed information in this area.

Flavan 3-ols Bioactivity: In Vitro Studies

As described above, despite the bioavailability of flavan 3-ols being very low, there has been a large number of in vitro studies to examine improvements in metabolic syndrome risk factors following the ingestion of these compounds. Studies using cell culture or isolated organs showed that the nitric oxide (NO) radical, a potent endothelium dilatation factor, and endothelial nitric oxide synthase were increased by the addition of flavan-3-ols. However, almost all these investigations lacked physiological significance as the parent compounds rather than the metabolites were used at high levels than those achieved in blood following oral administration of flavan-3-ols. Several recent studies have investigated flavan-3-ols-conjugated metabolites in mammals and microbial degradation products, with one study showing that O-methylated epicatechin inhibited NADPH oxidase in the endothelium. Phenolic acids, which are metabolites of colonic fermentation, have also been reported to possess certain bioactivities. Unfortunately, biological significance was also not achieved in these studies due to the high dose of metabolites used in the experiments. Taken together, these studies suggest that absorbed procyanidins, catechins or phenolic acids contributed only a portion of the improvement in metabolic syndrome risk factors.

Table 2. Chocolate consumption frequency predicts lower BMI: regression results

| Adjustment model | Chocolate consumption frequency, association with BMI |
|------------------|------------------------------------------------------|
|                  | δ (SE) | p value |
| Unadjusted       | −0.142 (0.053) | 0.08 |
| Age and sex adjusted | −0.126 (0.053) | 0.02 |
| Age, sex and activity adjusted | −0.130 (0.052) | 0.01 |
| Age, sex and calorie adjusted | −0.146 (0.059) | 0.01 |
| Age, sex and satfat adjusted | −0.190 (0.059) | 0.001 |
| Age, sex, satfat and CES-D adjusted | −0.191 (0.059) | 0.001 |
| Age, sex, satfat, fruite and vegetable, and CES-D adjusted | −0.201 (0.060) | 0.001 |
| Age, sex, satfat, fruite and vegetable, and CES-D and calories adjusted | −0.208 (0.060) | 0.001 |

Fig. 4. VO2 (A), VCO2 (B) and energy expenditure (C) in rats fed control or 0.2% flavan 3-ols containing diet. Values are mean and SD. Significantly different from control, *p<0.05.
A study in over 1000 American men and women showed a negative correlation between the frequency of chocolate consumption and body mass index (BMI) (Table 2). Taub et al. (46) also reported that ingestion of chocolate stimulated mitochondrial biogenesis of skeletal muscle in patients with type 2 diabetes or heart failure. We showed recently that repeated ingestion of the flavan 3-ols fraction influenced energy expenditure in rats. (47) In that study, the animals were fed for 2 weeks with either a normal diet or one containing 0.2% flavan 3-ols derived from cacao. At the end of the experimental period, energy expenditure was estimated by an indirect calorimetric method that measured oxygen consumption (VO₂) and carbon dioxide excretion (VCO₂) for 22 h. As shown in Fig. 4, total O₂ consumption was increased significantly in the flavan 3-ols group compared with controls. As a consequence, total energy expenditure also increased significantly in the flavan 3-ols group. We observed that repeated ingestion of flavan 3-ols reduced mean blood pressure to the same degree as that reported in published meta-analyses. In contrast, a single administration of flavan 3-ols in rats was shown to cause an immediate elevation in blood pressure and heart rate leading to increased blood flow and recruitment of capillaries in skeletal muscle (Table 3). In addition, studies by Yamashita et al. (49) demonstrated that flavan 3-ols prevented glucose intolerance and obesity by promoting translocation of glucose transporter type 4 (GLUT4), resulting acceleration of glucose uptake. AMPK might be activated peroxisome-proliferator-activated receptor coactivator 1 (PGC1α) which was the key factor of mitochondrial biogenesis. Improvement of dyslipidemia or BMI lowering activity seen in RCT or epidemiological studies also might be induced by such mitochondria biogenesis promoting effect.

### Flavan 3-ols Bioactivities—a New Angle of Observation

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4 and phosphorylation of AMP-activated protein kinase (AMPK) in the plasma membrane of skeletal muscle and brown adipose tissues.

These results in recent reports are summarized in Fig. 5. A hypertensive effect is produced by the oral administration of flavan-3-ols that induced expression of endothelial nitric oxide synthase (eNOS), while this effect is unclear in a point whether this effect was produced by metabolites of monomers in circulating blood or oligomers that remained in the gastrointestinal tract. In skeletal muscle, enhancement of energy expenditure is induced by metabolites of monomers in circulating 3-ols that induced expression of endothelial nitrogen oxide synthase (eNOS), while this effect is unclear in a point whether this effect was produced by metabolites of monomers in circulating lipids or oligomers that remained in the gastrointestinal tract.

Several epidemiological studies may also be induced by this mitochondrial biogenesis promoting effect. On the basis of these results, recent studies have attempted to define the mechanism responsible for the beneficial effects of flavan-3-ols from a new perspective.

Conclusion
In conclusion, flavan-3-ols may improve hypertension, dyslipidemia, insulin resistance, and obesity induced by inappropriate daily habits. However, further studies are required to elucidate the mechanisms responsible for the risk reduction of cardiovascular diseases caused by flavan-3-ols.

Conflict of Interest
No potential conflicts of interest were disclosed.

References

1 Hammerstone JF, Lazarus SA, Mitchell A, Rucker R, Schmitz HH. Identiﬁcation of ﬂavan-3-ol isomers in cocoa (Theobroma cacao) and chocolate using high-performance liquid chromatography/mass spectrometry. J Agric Food Chem 1999; 47: 490–496.
2 Hatano T, Miyatake H, Natsume M, et al. Proanthocyanidin glycosides and related polyphenols from cacao liquor and their antioxidant effects. Phytochemistry 2002; 59: 749–758.
3 Sanbongi C, Osakabe N, Natsume M, Takizawa T, Gomi S, Osawa T. Anti-oxidative polyphenols isolated from theobroma cacao. J Agric Food Chem 1998; 46: 454–457.
4 Mao TK, Van De Water J, Keen CL, Schmitz HH, Gershwin ME. Cocoa flavanols and proanthocyanins promote transforming growth factor-β1 homeostasis in peripheral blood mononuclear cells. Exp Biol Med 2003; 228: 93–99.
5 Keen CL, Holt RR, Oteiza PI, Fraga CG, Schmitz HH. Cocoa antioxidants and cardiovascular health. Am J Clin Nutr 2005; 81 (Suppl): 298S–303S.
6 Aron PM, Kennedy JA. Flavan-3-ols: nature, occurrence and biological activity. Mol Nutr Food Res 2008; 52: 79–104.
7 Martinez-Micaelo N, González-Acuña N, Ardevol A, Pinent M, Blay MT. Proanthocyanids and inﬂammation: molecular targets and health implications. Biofactor 2012; 38: 257–265.
8 Selmi C, Mao TK, Keen CL, Schmitz HH, Eric Gershwin M. The anti-inﬂammatory properties of cocoa ﬂavanols. J Cardiovasc Pharmacol 2006; 47 (Suppl 2): S163–S171.
9 De Curtis A, Amore C, Donati MB, De Gaetano G, Iacoviello L. A proanthocyanidin extract prolongs bleeding time but does not prevent thrombosis in rats. J Thromb Haemost 2003; 1: 199–200.
10 Corti R, Flammer AJ, Hollenberg NK, Lüscher TF. Cocoa and cardiovascular health. Circulation 2009; 119: 1433–1441.
11 McCullough ML, Chevaux K, Jackson L, et al. Hypertension, the Kuna, and the epidemiology of ﬂavanoids. J Cardiovasc Pharmacol 2006; 47: S103–S109.
12 Arts IC, Hollman PC, Feskens EJ, Bueno de Mesquita HB, Kromhout D. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: the Zutphen Elderly Study. Am J Clin Nutr 2001; 74: 227–232.
13 Arts IC, Jacobs DR Jr, Harnack LJ, Gross M, Folsom AR. Dietary catechins in relation to coronary heart disease death among postmenopausal women. Epidemiology 2001; 12: 668–675.
14 Buitrago-Lopez A, Sanderson J, Johnson L, et al. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ 2011; 343: d4488.
15 Larsson SC, Virtamo J, Wolk A. Chocolate consumption and risk of stroke: a prospective cohort of men and meta-analysis. Neurology 2012; 79: 1223–1229.
16 Taubert D, Roesen R, Lehmann C, Jung N, Schömig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. JAMA 2007; 298: 49–60.
17 Desch S, Kohler D, Schmidt J, et al. Low vs. higher-dose dark chocolate and blood pressure in cardiovascular high-risk patients. Am J Hypertens 2010; 23: 694–700.
18 Engler MB, Engler MM, Chen CY, et al. Flavanoid-rich dark chocolate improves endothelial function and increases plasma epicatechin concentrations in healthy adults. J Am Coll Nutr 2004; 23: 197–204.
19 Schroeter H, Heiss C, Balzer J, et al. (−)-Epicatechin mediates beneﬁcial effects of ﬂavan-3-ol-rich cocoa on vascular function in humans. Proc Natl Acad Sci USA 2006; 103: 1024–1029.
20 Baba S, Osakabe N, Kato Y, et al. Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility and has beneﬁcial effects on plasma HDL–cholesterol concentrations in humans. Am J Clin Nutr 2007; 85: 709–717.
21 Baba S, Natsume M, Yasuda A, et al. Plasma LDL and HDL cholesterol and oxidized LDL concentrations are altered in normo- and hypercholesterolemic humans after intake of different levels of cocoa powder. J Nutr 2007; 137: 1436–1441.
22 Grassi D, Nocicione S, Lippi C, et al. Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 2005; 46: 398–405.
23 Grassi D, Lippi C, Nocicione S, Desideri G, Ferri C. Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons. Am J Clin Nutr 2005; 81: 611–614.
24 Taubert D, Roesen R, Schömig E. Effect of cocoa and tea intake on blood pressure: a meta-analysis. Arch Intern Med 2007; 167: 626–634.
25 Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008; 88: 38–50.
26 Desch S, Schmidt J, Kohler D, et al. Effect of cocoa products on blood pressure: systematic review and meta-analysis. Am J Hypertens 2010; 23: 97–103.
27 Ried K, Sullivan T, Fakler P, Frank OR, Stocks NP. Does chocolate reduce blood pressure? A meta-analysis. BMC Med 2010; 8: 39.
28 Tokeda OA, Gazzano JM, Djousse L. Effects of cocoa products/dark chocolate on serum lipids: a meta-analysis. Eur J Clin Nutr 2011; 65: 879–886.
29 Shrim MG, Bauer SR, McDonald AC, Chowdhury NH, Coltart CE, Ding EL. Flavonoid-rich cocoa consumption affects multiple cardiovascular risk factors in a meta-analysis of short-term studies. J Nutr 2011; 141: 1982–1988.
30 Hooper L, Kay C, Abdelhamid A, et al. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr 2012; 95: 740–751.
31 Donovan JL, Manach C, Faulks RM, Kroon PA. Absorption and metabolism of plant secondary metabolites. In: Crozier A, Clifford MN, Ashihara H, eds. Plant Secondary Metabolites: Occurrence, Structure and Role in the Human Diet. Oxford: Blackwell Publishing, 2006; 303–351.
32 Natsume M, Osakabe N, Oyama M, et al. Structures of (−)-epicatechin glucuronide identified from plasma and urine after oral ingestion of (−)-epicatechin: differences between human and rat. Free Radic Biol Med 2003; 34: 840–849.
33 Natsume M, Osakabe N, Yasuda A, et al. In vitro antioxidative activity of (−)-epicatechin glucuronide metabolites present in human and rat plasma. Free Radic Res 2004; 38: 1341–1348.
34 Espín JC, García-Conesa MT, Tomás-Barberán FA. Nutraceuticals: facts
and fiction. Phytochemistry 2007; 68: 2986–3008.
35 Baba S, Osakabe N, Natsume M, Terao J. Absorption and urinary excretion of procyanidin B2 [epicatechin-(4β-8)-epicatechin] in rats. Free Radic Biol Med 2002; 33: 142–148.
36 Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 2005; 81 (1 Suppl): 230S–242S.
37 Appeldoorn MM, Vincken JP, Aura AM, Hollman PC, Gruppen H. Procyanidin dimers are metabolized by human microbiota with 2-(3,4-dihydroxyphenyl)acetic acid and 5-(3,4-dihydroxyphenyl)-γ-valerolactone as the major metabolites. J Agric Food Chem 2009; 57: 1084–1092.
38 Ward NC, Croft KD, Puddey IB, Hodgson JM. Supplementation with grape seed polyphenols results in increased urinary excretion of 3-hydroxyphenylpropionic Acid, an important metabolite of proanthocyanidins in humans. J Agric Food Chem 2004; 52: 5545–5549.
39 Matsui T, Korematsu S, Byun EB, Nishizuka T, Ohshima S, Kanda T. Apple procyanidins induced vascular relaxation in isolated rat aorta through NO/cGMP pathway in combination with hyperpolarization by multiple K+ channel activations. Biosci Biotechnol Biochem 2009; 73: 2246–2251.
40 Fitzpatrick DF, Bing B, Maggi DA, Fleming RC, O’Malley RM. Vasodilating procyanidins derived from grape seeds. Ann N Y Acad Sci 2002; 957: 78–89.
41 Tokoudagba JM, Auger C, Bréant L, et al. Procyanidin-rich fractions from Parkia biglobosa (Mimosaceae) leaves cause redox-sensitive endothelium-dependent relaxation involving NO and EDHF in porcine coronary artery. J Ethnopharmacol 2010; 132: 246–250.
42 Steffen Y, Gruber C, Schewe T, Sies H. Mono-O-methylated flavanols and other flavonoids as inhibitors of endothelial NADPH oxidase. Arch Biochem Biophys 2008; 469: 209–219.
43 Sanee F, Miyaichi Y, Hayashi H. Potentiation of vasoconstrictor response and inhibition of endothelium-dependent vasorelaxation by gallic acid in rat aorta. Planta Med 2002; 68: 690–693.
44 Na HJ, Lee G, Oh HY, et al. 4-O-Methylgallic acid suppresses inflammation-associated gene expression by inhibition of redox-based NF-κB activation. Int Immunopharmacol 2006; 6: 1597–1608.
45 Golomb BA, Kopanski S, White HL. Association between more frequent chocolate consumption and lower body mass index. Arch Intern Med 2012; 172: 519–521.
46 Taub PR, Ramírez-Sanchez I, Ciaraldi TP, et al. Alterations in skeletal muscle indicators of mitochondrial structure and biogenesis in patients with type 2 diabetes and heart failure: effects of epicatechin rich cocoa. Clin Transl Sci 2012; 5: 43–47.
47 Osakabe N. Cacao polyphenol. In: Hatano T, ed. Polyphenols Functional Constituents of Medicinal Plants and Foods, CMC Publishing CO. Ltd, 2012; 231–247.
48 Osakabe N. Polyphenols in Theobroma cacao ameliorate microcirculation: in vivo intravital microscopic observation in rats. J Food Drug Anal 2012; 20 (Suppl 1): 288–291.
49 Yamashita Y, Okabe M, Natsume M, Ashida H. Prevention mechanisms of glucose intolerance and obesity by cacao liquor procyanidin extract in high-fat diet-fed C57BL/6 mice. Arch Biochem Biophys 2012; 527: 95–104.