Human intervention studies have tended to focus on markers of inflammation, platelet activation, and endothelial function (Ellam and Williamson, 2013; Gu and Lambert, 2013). Consumption of dark chocolate, flavanol-rich cocoa preparations and purified cocoa flavanols (i.e. (–)-epicatechin) have been shown to enhance flow-mediated dilation of peripheral blood vessels and decrease blood pressure both in healthy subjects as well as those with increased risk of CVD (West *et al.*, 2014; Berends *et al.*, 2015). In animal models and *in vitro* studies, cocoa and cocoa-derived components have been shown to enhance endothelial nitric oxide synthase levels and increase intracellular nitric oxide levels. Given the role of nitric oxide in vasodilation, it is likely that this mechanism accounts in part for improvements in vascular endothelial function and reduced blood pressure observed in human intervention studies.

Although studies both in humans and in animal models have shown that pure EC can reduce blood pressure, the importance of other cocoa components has been suggested by some studies. For example, dietary supplementation of spontaneously hypertensive rats with soluble cocoa fibre (SCF) has been reported to decrease both systolic and diastolic blood pressure (Sanchez *et al.*, 2010). Given the complex nature of chocolate as a food product, it is likely that multiple bioactive components interact to produce the overall health beneficial effects reportedly associated with chocolate consumption. Further studies are needed to determine the relative contribution of each and the mechanisms of interaction.

## 22.7 Obesity and metabolic syndrome

Obesity (body mass index $\geq 30\,kg/m^2$) is a growing public health problem worldwide and has been linked to the development of a number of chronic diseases including diabetes, cancer, fatty liver disease and others. Metabolic syndrome (MetS) comprises a cluster of metabolic abnormalities, which has been defined by the International Diabetes Foundation as including central obesity and at least two of the following: low high-density lipoprotein (HDL) cholesterol, high triacylglycerols, high systolic or diastolic blood pressure and increased fasting glucose (Ford, 2005; Cherniack, 2011).

A growing number of epidemiological, human intervention and laboratory animal studies have shown that consumption of chocolate and cocoa can mitigate obesity and symptoms of MetS. For example, a cross-sectional study of 1108 adults from San Diego, California, found that chocolate consumption was inversely associated with body mass index (Golomb *et al.*, 2012). Although other studies have observed similar effects in other populations (O'Neil *et al.*, 2011), some population-based studies have shown an opposite trend. For example, a prospective study of more than 12 000 subjects in the Atherosclerosis Risk in Communities cohort found a direct correlation between chocolate intake and body weight gain (Greenberg and Buijsse, 2013). The reasons for these different

results are not clear, but may be the result of differences in background diet, chocolate products consumed or subject genetics. Additional studies are needed.

Studies of cocoa and cocoa polyphenols in animal models have tended to support the obesity preventive effects of chocolate. For example, Yamashita *et al*. (2012) found that treatment of high fat-fed C57BL6/J mice with a PaC-rich cocoa liquor extract (0.5 and 2.0%) for 13 weeks promoted glucose transporter 4 translocation and significantly reduced body weight, blood glucose, insulin and total cholesterol levels in obese mice. In addition, phosphorylation of AMP-activated protein kinase α was enhanced by PaCs (2%) in skeletal muscle adipose tissue and liver.

In another recent study, Min *et al*. (2013) found that C57BL/6 mice fed a high fat diet containing cocoa polyphenol extract for five weeks significantly reduced body weight and epididymal fat mass, as well as decreased plasma TG levels.

Studies in our laboratory on the effect of dietary supplementation of high fat-fed mice with cocoa powder failed to find a significant decrease in final body weight or reduction in body fat mass, but did show a reduction in fasting plasma insulin levels and an amelioration of obesity-related fatty liver disease (Gu *et al*., 2014a).

Although a great deal of attention has been paid to the cocoa polyphenols, other components of cocoa have been reported to contribute to the obesity and MetS preventive effects observed in animal models. For example, administration of methylxanthine-rich cocoa extract for four weeks significantly reduced plasma free fatty acid, total cholesterol, triglyceride and oxidative stress biomarker (8-isoprostane) in obese-diabetic rats (Jalil *et al*., 2008).

The effects of SCF have been studied in Zucker fatty rats (Sanchez *et al*., 2010). Zucker fatty rats were fed either standard diet or 5% SCF-enriched diet for seven weeks. The SCF group showed less body weight gain and food intake than the standard group. Lower values of the total cholesterol/HDL-cholesterol ratio, index of insulin resistance and plasma triglyceride levels were observed in those fed a cocoa fibre-enriched diet.

## 22.8 Inflammation

Chronic inflammation plays a causative role in the development of a number of diseases, including arthritis, cancer and diabetes, and represents a mechanistic link between obesity and its comorbidities. There is growing evidence from both observational and experimental studies that consumption of cocoa and chocolate may reduce inflammatory biomarkers, including serum levels of c-reactive protein (CRP) and pro-inflammatory cytokines.

In a study of 4849 Italian subjects free of any chronic disease, 1317 people reported having eaten any chocolate during the past year and 824 ate chocolate regularly in the form of dark chocolate only (Di Giuseppe *et al*., 2008). After