Cocoa
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HISTORICAL NOTE Cocoa originates from Mexico, where the Mayas, Incas and Aztecs considered it the food of the gods. Chocolate, mixed with vanilla and sugar, was first introduced as a beverage in Europe by Columbus and was considered an aphrodisiac and a symbol of wealth and power. The phenolics in chocolate prevent the fat becoming rancid, decreasing the need for added preservatives. This quality was exploited during World War II when at times US troops were rationed three chocolate bars per day during heavy combat as their sole source of nourishment (Waterhouse et al 1996). Whilst an amusing association between countries’ annual chocolate consumption and the number of Nobel laureates per capita has been described, direct correlation between past Nobel prize winners’ chocolate intake and their academic success hasn’t been established (Maurage et al 2013, Messerli 2012).

COMMON NAME
Chocolate, cocoa, cocoa liquor, cocoa mass, baking chocolate, Cacao, Prosthobisa, Actinoca

BOTANICAL NAME/FAMILY
Theobroma cacao (family Sterculiaceae)


Moon SE, et al. Syzygium aromaticum (clove) and Syzygium cumini (cinnamon) bark. Fitoterapia (2001) 72.4


Taguchi Y et al. Protection of oral or intestinal candidiasis in mice by oral or intragastric administration of herbal food, clove (Syzygium aumumum) and mullein (Verbascum thapsus) essential oils. J Ethnopharmacol 133.1–2 (2009): 67–73.


PLANT PARTS USED
Cocoa is produced through a process of fermenting the seeds from the pods of the cacao tree, *Theobroma cacao*. The beans are dried, roasted and crushed to produce high-fat, unsweetened chocolate, which is also called baking chocolate. This intermediate is pressed and alkalised to form cocoa powder, which is then homogenised with sugar and cocoa butter, and sometimes milk, to ultimately form chocolate. Dark chocolate generally contains more than 50% cocoa, whereas mass-produced milk chocolate contains only around 10% cocoa. White chocolate is based on cocoa butter (or theobroma oil) without the cocoa solids.

Although many different types of cocoa beans grow throughout the world, three varieties of cocoa beans are mainly used to make chocolate products: (1) criollo (meaning ‘native’), distributed to the north and west of the Andes; (2) forastero (meaning ‘foreign’), found mainly in the Amazon basin; and (3) trinitario (meaning ‘sent from heaven’) (Bruinsma & Taren 1999).

Cocoa beans from different countries along with postharvesting and processing procedures can have a striking influence on the flavanol content of chocolate and cocoa (Hollenberg et al. 2004). As flavanols impart a bitter, astringent flavour, chocolate often undergoes extensive processing, dilution and the addition of flavour modifiers to improve its palatability, despite these processes having the potential to negatively impact on cocoa’s nutritional and clinical value (McShea et al. 2008). A study that examined the total phenolic content of chocolate found that the antioxidant properties of the artisan-made chocolate were significantly better than those of the factory-produced chocolate (Cervellati et al. 2008), recent attention to flavonoid content has led to the development of commercial processes that protect and preserve the naturally occurring flavonoids, with Cocoapro being developed by Mars and Atocha by the Swiss-based Barry Callebaut.

CHEMICAL COMPONENTS
Cocoa is among the most concentrated sources of the flavanols, catechin and epicatechin, with four times the catechin content of tea (Arts et al. 1999). Chocolate also contains additional flavonoids not found in tea, with high concentrations of oligomeric proanthocyanidins (Lazarus et al. 1999). Dark chocolate has the highest total catechin content, with approximately 53.5 mg/100 g, whereas milk chocolate contains approximately 15.9 mg/100 g (Arts et al. 1999). White chocolate primarily contains cocoa butter with minimal levels of polyphenols. The bioavailability of cocoa flavanols may change depending on the type of sugar used in the chocolate formulation, with maltitol-containing chocolate being associated with reduced flavanol absorption compared to its sucrose-containing equivalent (Rodriguez-Mateos et al. 2012).

In addition to flavanols, cocoa also contains the methylxanthines, caffeine and theobromine, the biogenic amines phenylethylamine, phenylalanine and tyrosine (Bruinsma & Taren 1999) and the cannabinoid-like fatty acid anandamide analogues, N-oleoylthanolamine and N-linoleoylthanolamine (Di Tomaso et al. 1996). Chocolate is also a rich source of minerals, including magnesium, calcium, iron, copper, phosphorus, potassium and zinc (Steinberg et al. 2003) and it is suggested that the presence of methylxanthines, peptides and minerals could synergistically enhance or reduce cocoa’s antioxidant properties (Jail & Ismail 2008).

Food source
Cocoa and chocolate are nutritious foods that contribute to caloric as well as trace mineral intake (Steinberg et al. 2003). Milk chocolate has a relatively low glycaemic index of approximately 40 (Foster-Powell et al. 2002) and this is attributed to the fat in chocolate slowing gastric emptying and thus the rate of subsequent digestion and absorption. The glycaemic effect of milk chocolate can be further reduced by replacing the sucrose with fructose or isomalt (Gee et al. 1991).

MAIN ACTIONS
Antioxidant
Cocoa has been found to have much higher levels of total phenolics and flavonoids, with a correspondingly higher antioxidant capacity per serving, than black tea, green tea or red wine (Lee et al. 2003). It has been suggested that the antioxidant capacity of cocoa polyphenols is greater than synthetic antioxidants and that they have the potential to complement or replace synthetic antioxidants in aqueous and oil-based food applications (Osman et al. 2004). There is, however, tremendous variability in cocoa processing, flavonoid content and measurement of flavonoids.

Cocoa has been consistently shown to confer significant protection against oxidation both in vitro (Martin et al. 2008, Sies et al. 2005, Waterhouse et al. 1996) and in vivo (Kondo et al. 1996). In addition to reducing lipid oxidation, consumption of a flavanol-rich cocoa beverage has been shown to reduce susceptibility of erythrocytes to haemolysis and to increase their ability to buffer free radicals (Zhu et al. 2005).

Whilst the antioxidant activity of cocoa is well established, questions remain around best forms for maximal bioavailability and dosing frequency (Fisher & Hollenberg 2006).

Cocoa powder dissolved in milk as one of the most common ways of cocoa powder consumption seems to have a negative effect on the absorption of polyphenols; however, statistical analyses have shown that milk does not impair the bioavailability of flavonoids (Keogh et al. 2007, Roura et al. 2007). High-flavonoid cocoa products may lead to greatly
enhanced flavonoid bioavailability in humans (Tomas-Barberan et al. 2007). A feeding study demonstrated that procyanidins were remarkably stable in the stomach environment and thus most ingested procyanidins reach the small intestine intact and are available for absorption or metabolism (Rios et al. 2002). Epicatechin and its metabolites reach maximal levels 2 h after either chocolate or cocoa intake, with rapid excretion in the urine (Baba et al. 2000) and dimeric procyanidins have been detected in human plasma as early as 30–60 min after the consumption of flavanol-rich beverages providing 0.25–0.50 g/kg cocoa/kg body weight (Holt et al. 2002, Zhu et al. 2005). Human studies have confirmed that the polyphenols in chocolate are indeed bioavailable and able to increase the antioxidant capacity of plasma, with one study reporting that ingestion of 80 g of procyanidin-rich chocolate increased plasma epicatechin concentrations 12-fold, significantly increased plasma total antioxidant capacity by 31% and significantly decreased 2-thiobarbituric acid-reactive substances by 40% after 2 h, with levels returning to normal within 6 h (Rein et al. 2000a). Similarly, a 2012 study identified that both dark chocolate and high-antioxidant dark chocolate had a peak total antioxidant capacity 2 h post-ingestion, with the high-antioxidant dark chocolate showing raised levels for over 5 h post-ingestion (Lettieri-Barbato et al. 2012).

There is evidence that the polyphenols are not the only antioxidants in chocolate, as suggested by a study that found that consumption of chocolate containing 200 mg of polyphenols, as well as chocolate with less than 10 mg of polyphenols, reduced faecal free radical production (Record et al. 2003). Furthermore, similar reductions in markers of lipid peroxidation have been observed after daily consumption of 75 g of dark chocolate and dark chocolate enriched with cocoa polyphenols, as well as with white chocolate, which contains very little polyphenols (Mursu et al. 2004).

In a crossover study in 23 healthy subjects, cocoa powder and dark chocolate were seen to modestly reduce low-density lipoprotein (LDL) oxidation susceptibility while increasing serum total antioxidant capacity and high-density lipoprotein (HDL) cholesterol concentrations (Wan et al. 2001), and another crossover trial of 25 healthy subjects found that supplementation with 36.9 g of dark chocolate (30 g of cocoa powder drink) for 6 weeks reduced LDL oxidisability (Mathur et al. 2002). Similar results were seen in a randomised, double-blind crossover trial that found that high-flavanol cocoa drink providing 187 mg flavan-3-ols/100 mL significantly reduced lipid peroxidation, compared with a low-flavanol cocoa drink providing only 14 mg/100 mL (Wiswedel et al. 2004).

In contrast to these studies a further randomised, double-blind, placebo-controlled study of 21 healthy adults, however, found that intake of high-flavonoid (213 mg procyanidins, 46 mg epicatechin) dark chocolate bars for 2 weeks did not alter resistance to LDL oxidation, total antioxidant capacity, 8-isoprostanes, blood pressure, lipid parameters, body weight or body mass index (BMI), despite increasing plasma epicatechin concentrations and improving endothelium-dependent flow-mediated dilatation of the brachial artery (Engler et al. 2004).

**Lipid-modifying**

A 3-week clinical supplementation trial of 45 non-smoking, healthy volunteers consuming high-polyphenol chocolate found a significant increase in serum HDL cholesterol with dark and high-polyphenol chocolate (11.4% and 13.7%, respectively), whereas white chocolate consumption resulted in a small decrease in HDL. Markers of lipid peroxidation decreased 11.9% in all three study groups, suggesting that, while cocoa polyphenols may increase the concentration of HDL cholesterol, chocolate fatty acids may modify the fatty acid composition of LDL, making it more resistant to oxidative damage (Mursu et al. 2004).

A new soluble cocoa fibre product rich in soluble dietary fibre and antioxidant polyphenols diminished the negative impact of the cholesterol-rich diet in an animal model of dietary-induced hypercholesterolaemia (Ramos et al. 2008). Similarly, in an animal model of hypercholesterolaemia a cholesterol- and triglyceride-lowering effect along with a reduction of biomarkers of oxidative stress and increasing faecal bulking was seen after 3 weeks of consuming a fibre-rich cocoa product (Bravo et al. 2008).

It appears that chronic intake of cocoa-based products is required for effects, as an acute dosing study using 100 g of either dark chocolate (55% dry cocoa solids) or high-antioxidant dark chocolate (66% dry cocoa solids) did not significantly affect total cholesterol levels 5 h afterwards, although triacylglycerol was significantly increased in both products after 1 h (Lettieri-Barbato et al. 2012).

**Effects on microcirculation and nitric oxide**

Flavanols have been shown in several in vitro or ex vivo studies to modify the production of proinflammatory cytokines, the synthesis of eicosanoids, the activation of platelets and nitric oxide (NO)-mediated mechanisms (Selmi et al. 2008). A double-blind, dose-finding study found that flavanol-rich cocoa increased circulating NO species in the plasma of male smokers, with maximal effects seen with ingestion of 176–185 mg flavanols (Heiss et al. 2005). Another double-blind trial found that ingestion of a high-flavanol cocoa drink, but not a low-flavanol one, enhanced NO bioactivity and increased plasma concentrations of nitroso compounds and flow-mediated dilatation of the brachial artery (Sies et al. 2005). Similarly, ingestion of flavanol-rich cocoa is associated with acute elevations in levels of circulating NO species, enhanced flow-mediated dilatation response of conduit arteries and an augmented microcirculation, with these effects being...
mimicked by ingestion of chemically pure epicatechin. Moreover, chronic consumption of a cocoa-flavanol-rich diet has been associated with augmented urinary excretion of NO metabolites (Schroeter et al 2006).

Double-blind, crossover intervention studies in both humans and rats suggest that an increase in the circulating NO pool following flavanol consumption is correlated with decreased arginase activity as the availability of l-arginine can be a rate-limiting factor for cellular NO production by nitric oxide synthase (NOS) (Schnorr et al 2008).

Cardioprotection
A significant reduction in experimentally induced myocardial infarct size was observed following treatment with the cocoa-derived flavanol (−)-epicatechin in vivo. Test animals who were 48 h and 3 weeks post permanent coronary occlusion experienced a 52% and 33% reduction in myocardial infarct size respectively (Yamazaki et al 2010). The left ventricular scar area strain was improved following (−)-epicatechin treatment, suggesting possible cardioprotective mechanisms. (Arranz et al 2013).

Inhibits platelet activation
Numerous dietary intervention studies in humans and animals indicate that flavanol-rich foods and beverages might exert cardioprotective effects with respect to vascular function and platelet reactivity (Keen et al 2005). Acute doses of flavanols and oligomeric procyanidins from cocoa have been observed to inhibit platelet activation (Pearson et al 2002, Rein et al 2000b) and have an aspirin-like effect on primary haemostasis 2 and 6 h after consumption (Hermann et al 2006, Pearson et al 2002, Rein et al 2000b), with the effects being similar to, but less profound than, aspirin (Pearson et al 2002). Similar results have been observed in longer studies with lower doses of cocoa flavanols, with a double-blind, controlled trial demonstrating significantly lower platelet aggregation and significantly higher plasma ascorbic acid concentrations after supplementation with cocoa flavanols (234 mg cocoa flavanols and procyanidins/day) over 28 days (Murphy et al 2003).

In a randomized controlled trial (RCT) of 30 healthy volunteers, 100 mg of dark chocolate, but not white or milk chocolate, was found to significantly inhibit collagen-induced platelet aggregation (Innes et al 2003). The alteration of eicosanoid synthesis has been suggested as a plausible mechanism by which procyanidins can decrease platelet activation, and this has been observed in an in vitro study of the effect of procyanidin on aortic endothelial cells, as well as in a randomised, blinded, crossover study of high-procyanidin chocolate (4.0 mg/g) (Schramm et al 2001).

Diabetes — glycaemic control
Pretreatment with a cocoa extract high in polyphenols was seen to normalise body weight, plasma glucose levels, total cholesterol, triglycerides and HDL levels in streptozotocin-diabetic rats (Ruzaidi et al 2008). The supplementation of 0.5% epicatechin in drinking water of non-obese diabetic mice reduced the incidence of hyperglycaemia (16.6% of treated vs 66.7% of control mice), significantly increased plasma insulin levels (0.392 mcg/L in treated vs. 0.129 mcg/L in controls) and lowered glycosylated haemoglobin levels (5.2% in treated vs 7.4% in controls) (Fu et al 2013). In prediabetes, cocoa polyphenol extract is able to inhibit insulin receptor activity, as well as prevent the development of obesity in mice given a high-fat diet (Miri et al 2013).

In humans, short-term administration of flavonoid-rich dark chocolate significantly improved insulin sensitivity and endothelial function in healthy and hypertensive subjects (Grassi et al 2008a), while a double-blind, placebo-controlled crossover study found that flavanol-rich dark chocolate but not flavanol-free white chocolate ameliorated insulin sensitivity and beta-cell function, decreased blood pressure and increased flow-mediated dilation in hypertensive patients with impaired glucose tolerance (Grassi et al 2008a). Similar results were obtained from another small RCT that found that high-flavanol cocoa reversed vascular dysfunction in diabetic patients (Balzer et al 2008). In contrast to these findings, a double-blind, crossover study found that daily consumption of flavanol-rich cocoa for 2 weeks was not sufficient to reduce blood pressure or improve insulin resistance in human subjects with essential hypertension (Muniyappa et al 2008). Similarly, a randomised crossover study determined that the short-term (5-day) intake of cocoa flavanols (30–900 mg per day) did not have any effect on glucose metabolism in 20 obese participants at risk of insulin resistance; however markers of oxidative stress, inflammation and haemostasis were significantly reduced (Stote et al 2012).

Psychological effects
Chocolate is purported to have a range of psychological effects, including enhanced arousal and cognitive function, stimulation of feelings of wellbeing and euphoria, as well as initiating cravings. The orosensory aspects of chocolate, including its taste, smell and texture, certainly contribute to chocolate’s positive appeal. Chocolate contains large amounts of fat in the form of cocoa butter, which melts at body temperature, producing a pleasurable melt-in-the-mouth experience. Chocolate also often contains large amounts of sugar and thus satisfies the seemingly innate preference for sweet, high-fat foods (Bruinsma & Taren 1999).

In addition to unique sensory properties, chocolate also contains many pharmacologically active substances. Several endogenous biogenic amines with sympathomimetic properties are found in chocolate, most notably tyramine and phenylethylamine (Hurst et al 1982). Phenylethylamine is an amphetamine analogue structurally related to...
methyleneoxy-methamphetamine that may act to potentiate dopaminergic and noradrenergic neurotransmission and modulate mood (Bruinsma & Taren 1999).

Cocoa is also known to contain methylxanthines, including caffeine and theobromine, both of which are stimulants. Although the stimulatory and sympathomimetic effects of caffeine are well documented, the psychological effects of theobromine are less certain.

A group of biologically active constituents, including N-oleoylthelantholamine and N-linoleoylthelantholamine, have been identified in chocolate and appear to be related to anandamide, the ‘internal bliss’ chemical, which is the endogenous lipoprotein that binds cannabinoid receptors within the brain (Di Tomaso et al 1996). Although it has been suggested that these compounds may elicit heightened sensitivity and euphoria by directly activating cannabinoid receptors or by increasing anandamide levels (Bruinsma & Taren 1999), measurements have suggested that their amount in cocoa is several orders of magnitude below those required to reach the blood and cause observable central effects (Di Marzo et al 1998).

Chocolate craving, which is reported to be the most common food craving (Weingarten & Elston 1991), is more common in women, with fluctuations occurring with hormonal changes just before and during the menses (Rozin et al 1991). The basis for chocolate craving, however, remains undetermined, but it is suggested that aroma, sweetness, texture and calorie content are likely to play a more important role in chocolate cravings than pharmacological factors (Bruinsma & Taren 1999, Michener & Rozin 1994, Rozin et al 1991, Smit et al 2004).

In 2013, a randomised, placebo-controlled trial (n = 72) identified that ingesting a cocoa treatment (500 mg polyphenols) daily for 30 days significantly improved self-rated calmness and contentedness compared to placebo (Pascual et al 2013). This effect was not observed after acute treatment, and cognition was unaffected both acutely and after 30 days.

Modulation of immune function and inflammation
The procyanidin fraction from cocoa demonstrates immunomodulatory function in vitro, with stimulation of tumour necrosis factor-alpha (Mao et al 2002) and modulation of the secretion of the cytokine transforming growth factor (Mao et al 2003), as well as inhibiting induced nuclear transcription of human interleukin-1β (IL-1β) (Mao et al 2000a), phytol-o-melagglutinin-induced stimulation of IL-2 (Mao et al 1999) and mitogen-stimulated secretion of IL-4 (Mao et al 2000b) in peripheral blood mononuclear cells in vitro. In vivo cocoa intake has been shown to modulate intestinal immune responses in young rats (Ramos-Puig et al 2008), while cocoa polyphenols have been shown to reduce leukotriene synthesis through inhibition of human 5-lipoxygenase in humans (Sies et al 2005).

In vivo rat studies have also shown that a diet supplemented with 10% (w/w) cocoa for 7 weeks resulted in significantly reduced serum immunoglobulin A (IgA), IgG2b and IgM levels compared to those fed an isocaloric unsupplemented diet (Pérez-Berezo et al 2012). Additionally gut IgA and IgM levels were significantly reduced to approximately 30% and 50% of control animals, respectively.

Anti-inflammatory
While flavanols are known to modify the production of proinflammatory cytokines, the synthesis of eicosanoids, the activation of platelets and NO-mediated mechanisms (Selmi et al 2008), evidence for any beneficial effects of cocoa flavanols in providing a meaningful anti-inflammatory action has been gathered predominantly from in vitro experiments and only more recently have in vivo studies been conducted.

An in vivo study of induced colon carcinogenesis found that a cocoa-rich diet reduced NF-κB levels and the expression of proinflammatory enzymes, including cyclooxygenase-2 and iNOS (Rodríguez-Ramiro et al 2013). A study which investigated the effects of cocoa supplementation on trigeminal nerve inflammation identified that 1% (w/w) and 10% (w/w) cocoa repressed MKP-1 and -3, as well as resulted in reduced MAPK proteins, all of which indicates a reduced inflammatory response (Cady & Durham 2010). This study was conducted using immunofluorescence as the main indicative biomarker.

More recently, a randomised, crossover study of 20 obese volunteers confirmed that beverages containing cocoa flavanols (30–900 mg flavanol per day) produced a dose-dependent effect on the inflammation marker C-reactive protein and also significantly reduced IL-6 concentrations (Stote et al 2012).

Altered cellular signalling
Flavonoids have been shown to modulate tumour pathology in vitro and in animal models, and the pentamer Procyanidin fraction isolated from cocoa is reported to slow the growth of cultured human aortic endothelial cells (Kenny et al 2004a), as well as inhibit the proliferation of human dermal microvascular endothelial cells in vitro through inhibition of tyrosine kinase ErbB2 expression. This has led to the suggestion that polyphenols may influence endothelial growth signalling in vitro, with potential beneficial effects for specific neoplasias in which cells overexpress ErbB2 (Kenny et al 2004b).

Inhibition of dental caries
Cocoa contains substances that protect against dental caries (Palenik et al 1977, s’Gravenmade et al 1977) and in vitro experiments have shown that monomeric polyphenols and tannins from cocoa may interfere with glucosyltransferase activity of...
Streptococcus mutans and reduce plaque formation (Kashket et al. 1985). Similar results were reported in hamsters, with a marked caries-inhibitive effect found with a water extract of cocoa (Straloffs 1966). Cocoa bean husk, while not used in cocoa or chocolate, demonstrates antibacterial properties attributed to its unsaturated fatty acids and antilactoferrin transerase activities attributed to epicatechin polymers, as well as being shown both in vitro and in vivo to possess significant antiplaque activity (Matsumoto et al. 2004).

Antitussive

It has been suggested that theobromine, a methylxanthine derivative present in cocoa, may form the basis for a new class of antitussive drugs, as it has been shown to effectively inhibit citric acid-induced cough in guinea pigs in vivo, as well as suppress capsaicin-induced cough in a human double-blind trial (Usmani et al. 2005). The observation that theobromine inhibits capsaicin-induced sensory nerve depolarisation of the guinea pig and human vagus nerve suggests that its antitussive action may be mediated peripherally through an inhibitory effect onafferent nerve activation.

Skin antiageing and photoprotection

Cocoa and, more specifically, cocoa-derived flavanols have multiple beneficial effects on skin integrity, according to several clinical trials.

Long-term cocoa ingestion appears to lead to an increased resistance to UV-induced erythema and a lowered transepidermal water loss. In a crossover design study in 10 healthy women, a single dose of cocoa rich in flavanols (329 mg) was found to enhance dermal blood flow by 1.7-fold and elevate oxygen saturation of haemoglobin at 1 mm skin depth 1.8-fold 2 h after consumption, while there was no effect seen after consumption of low-flavanol cocoa (27 mg) (Neukam et al. 2007).

In a study using a model of ex vivo human skin explants, cocoa polyphenols were seen to exhibit a positive action on several indicators of skin elasticity and skin tonus, and an enhancing effect of cocoa butter on activity of cocoa polyphenol was observed (Gasser et al. 2008).

There is evidence to suggest that dietary flavanols from cocoa contribute to endogenous photoprotection, improve dermal blood circulation and affect cosmetically relevant skin surface and hydration variables in women. A 12-week RCT, comparing high-flavanol (326 mg/day containing epicatechin [61 mg/day] and catechin [20 mg/day]) and low-flavanol (27 mg/day containing 6.6 mg epicatechin and 1.6 mg catechin) cocoa consumption found that high-flavanol consumption led to significantly reduced ultraviolet-induced erythema (by 15% and 25%, after 6 and 12 weeks of treatment). The high-flavanol group also experienced increased skin density, skin hydration and skin thickness along with increased blood flow in cutaneous and subcutaneous tissues, and significantly decreased skin roughness and scaling, compared with no change in the low-flavanol group (Heinrich et al. 2006).

Antineurodegenerative

The major flavonoids of cocoa, epicatechin and catechin, protected cellular membrane from amyloid beta-protein-induced neurotoxicity in vitro, suggesting that cocoa may have antineurodegenerative effects (Heo & Lee 2005). This is supported by a study that found that 1-year administration of a cocoa polyphenolic extract (Acticoa powder) affects the onset of age-related cognitive defects, urinary free dopamine levels and lifespan in old Wistar-Unilever rats (Bisson et al. 2008a, b). Daily oral administration of Acticoa powder was also seen to protect rats from cognitive impairments after heat exposure by counteracting the overproduction of free radicals (Rozan et al. 2007). A 2012 human study confirms that the effects are also seen clinically. The study of 90 elderly men and women with mild cognitive impairment identified that the consumption of 520–990 mg cocoa flavanols daily for 8 weeks improved the outcome of cognitive function assessments, including verbal fluency test and the trail-making test compared to those taking low (45 mg daily) flavanols (Desideri et al. 2012).

OTHER ACTIONS

Acticoa powder has been observed to protect rats from prostate carcinogenesis (Bisson et al. 2008a) and prostate hyperplasia as well as improve established prostate hyperplasia in an animal model (Bisson et al. 2007). The clinical significance of these findings is yet to be determined.

CLINICAL USE

Cardiovascular disease

There is evidence to support that the flavanols in cocoa can be absorbed, are bioactive and may be responsible for the cardiovascular benefits associated with regular cocoa consumption. Several mechanisms have been proposed to explain this positive influence, including metabolic, antihypertensive, anti-inflammatory and antioxidant effects, along with decreased platelet activation and function, effects on serum lipids, insulin sensitivity, immune function and vascular endothelial function (Ding et al. 2006, Eo 2008, Lippi 2008).

A 2012 Cochrane review performed a meta-analysis of 20 studies involving 856 mainly healthy adults, and found that flavanol-enriched cocoa exhibited a small but statistically significant blood pressure-lowering effect compared to controls in short-term trials of 2–18 weeks’ length (Reid et al. 2012).

Additionally, two recent systematic reviews and meta-analyses on the effects of chocolate, cocoa and flavanols on major cardiovascular disease risk factors found benefits on markers of vascular function, insulin resistance and cholesterol (Hooper et al. 2012, Shrime et al. 2011). In addition to significant
anthypertensive benefits, these reviews reported significant effects on LDL (−0.07 mmol/L; 95% confidence interval (CI) −0.13, 0.00 mmol/L) and HDL (±0.03 mmol/L; 95% CI 0.00, 0.06 mmol/L), cholesterol (Hooper et al 2012) and insulin resistance (−0.94 points; 95% CI −0.59, −1.29) (Shrime et al 2011).

The impact of other chocolate constituents must be considered when evaluating the effects of chocolate on cardiometabolic health. An animal study found that the chronic supplementation of two chocolate preparations with equivalent composition aside from fibre and polyphenol content resulted in significant differences in systemic inflammatory markers, liver weight and endothelial activation markers (Yakala et al 2013).

Of the epidemiological studies conducted thus far, inverse associations between dietary polyphenols and mortality from coronary heart disease have also been identified. Small, short-term intervention studies have indicated that cocoa-containing foods may provide many cardiovascular benefits, including reducing blood pressure, inhibiting platelet function, preventing lipid oxidation, reducing LDL, increasing HDL, improving endothelial function, increasing insulin sensitivity, reducing insulin resistance and reducing inflammation.

A meta-analysis of 133 trials on flavonoid-rich foods and cardiovascular risk found that chocolate increased flow-mediated dilatation after acute (3.99%; 95% CI 0.62, 2.28; two studies) intake and reduced systolic (−5.88 mmHg; −9.55, −2.21; five studies) and diastolic (−3.30 mmHg; −5.77, −0.83; four studies) blood pressure (Hooper et al 2008, Innes et al 2003). A 2006 systematic review of 136 experimental, observational and clinical studies on cocoa products and the risk of cardiovascular disease concluded that stearic acid may be neutral, while flavonoids are likely protective against cardiovascular mortality. The review found that multiple short-term, randomised feeding trials suggest cocoa and chocolate may exert beneficial effects on cardiovascular risk, with a meta-analysis finding that flavonoids may lower risk of cardiovascular mortality (relative risk = 0.87; 95% CI 0.71–0.92), comparing highest and lowest tertiles (Ding et al 2006).

While there are no published long-term RCTs or prospective intervention studies of cocoa with hard clinical end points (Hooper et al 2008, Maron 2004), the cardiovascular benefits of cocoa are evident in a 15-year epidemiological study of 470 elderly men, which found that cocoa intake was inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality. This study found a 50% reduction in cardiovascular-related death and all-cause mortality in men with the highest tertile of cocoa intake compared to the lowest tertile, suggesting that the pharmacological actions described for cocoa do, in fact, translate into reduced cardiovascular risk and other positive clinical outcomes (Buijsse et al 2011).

**Hyperlipidaemia**

While the lipid content of chocolate is relatively high, around one-third of the lipid in cocoa butter is composed of the fat, stearic acid, which exerts a neutral cholesterolaemic response in humans by an unknown mechanism (Kris-Etherton et al 1993, Steinberg et al 2003). Cocoa butter, however, is considered a high-calorie fat because it has a high digestibility with a digestible energy value of 37 kJ/g in humans (Shahkhalili et al 2000). The results of a randomised, double-blind, crossover design supplementation study suggest that the addition of calcium to chocolate can significantly reduce the absorption of cocoa butter, thus reducing the absorbable energy value of the chocolate by approximately 9% while at the same time reducing the plasma LDL cholesterol level and leaving the plasma HDL cholesterol level and taste of the chocolate unchanged (Shahkhalili et al 2001).

A systematic review and meta-analysis of 10 clinical trials (n = 320) found that dark chocolate significantly reduced serum LDL by 5.90 mg/dL (95% CI −10.47, −1.32 mg/dL) and total cholesterol levels by 0.35 mmol/L (95% CI −0.64, −0.05 mmol/L) compared to low or nil cocoa control (Tokedo et al 2011). No statistically significant effects on HDL or triglycerides were found (difference in means [95% CI] −0.16, 0.08), and −0.28 mmol/L [−0.75, 0.18], respectively.

Since then, a double-blind RCT of 152 healthy adults (aged 40–70 years) reported that 850 mg theobromine, a non-flavonoid constituent of cocoa, independently increased serum HDL concentrations by 0.16 mmol/L compared to placebo (Neufingerl et al 2013). In this study, the use of cocoa in addition to theobromine supplementation (total 1000 mg theobromine) did not have a significant effect on HDL.

Cocoa bran may also have a use in hypercholesterolaemia, as well as constipation, because this low-fat, high-fibre material has been shown in a randomised, controlled, double-blind study to increase faecal bulk similarly to wheat bran and reduce the LDL/HDL cholesterol ratio, with no effect on LDL cholesterol oxidation (Jenkins et al 2000).

**Blood pressure**

A 2012 Cochrane review of 20 studies involving 856 mainly healthy adults found that flavanol-enriched chocolate supplementation over 2–18 weeks reduced mean systolic blood pressure by 2.77 mmHg (95% CI −4.72, −0.82) and mean diastolic blood pressure by 2.20 mmHg (95% CI −3.46, −0.93; n = 19) (Reid et al 2012). These modest effects for flavanol-containing dark chocolate have been observed in various populations, including normotensive people with mild hypercholesterolaemia (Erdman et al 2008), overweight adults (Davison et al 2008, Faridi et al 2008), patients with newly
diagnosed essential hypertension (Grassi et al. 2005b), patients with untreated upper-range prehypertension and stage 1 hypertension without concomitant risk factors (Taubert et al. 2007a) and healthy people (Grassi et al. 2005a, Vlachopoulos et al. 2007), including male soccer players (Fraga et al. 2005).

While cocoa appears to have mild antihypertensive actions, this is complemented by positive effects on other cardiovascular risk factors, such as serum lipids, blood glucose and vascular function. These benefits are evident from the results of various clinical trials. For example, an RCT using 100 g of dark chocolate containing approximately 500 mg of polyphenol consumed daily for 15 days found reductions in diastolic blood pressure by $-11.9 \pm 7.7$ mmHg, decreases in serum LDL cholesterol from 3.4 to 3.0 mmol/L, improvements in flow-mediated dilation, and reductions in insulin resistance and increased insulin sensitivity in patients with newly diagnosed essential hypertension (Grassi et al. 2005b). An 8-week double-blind, placebo-controlled crossover study found that consumption of a cocoa flavanol-containing dark chocolate bar with added plant sterols lowered serum lipids and blood pressure in a normotensive population with elevated cholesterol (Allen et al. 2008). Yet another study found that 12 weeks of supplementation with high-flavanol cocoa led to reduced insulin resistance, diastolic blood pressure and mean arterial blood pressure and improved endothelial function independently of exercise in overweight and obese subjects (Davison et al. 2008).

**Use in children**

In children, 7 g dark chocolate once daily for 7 weeks ($n = 124$) did not significantly affect blood pressure compared to controls ($n = 70$), with mean systolic pressure differing by 1.7 mmHg (95% CI $-0.6$ to 4.1) and mean diastolic pressure differing by $-1.2$ mmHg (95% CI $-3.6$ to 1.3) (Chan et al. 2012). This study did conclude that, whilst providing dark chocolate appeared feasible and acceptable in a school setting, further studies would be required to clarify possible cardiovascular benefits of dark chocolate supplementation in children.

**Vascular function**

In a 2008 meta-analysis it was found that acute and chronic intake of chocolate increases flow-mediated dilation (Hooper et al. 2008). A 30-day double-blind RCT in 41 medicated diabetic patients which compared thrice-daily dosing of flavanol-rich cocoa with a nutrient-matched control found that vascular function was significantly improved in the cocoa-treated group, as measured by flow-mediated dilation of the brachial artery (Balzer et al. 2008). More recently, a randomised, placebo-controlled crossover study found that women, but not men, also experienced significant reductions in arterial stiffness (augmentation index (AI) reduced by 83% and AI at 75 beats / min reduced by 129%) following 4-weeks of high-flavanol cocoa and dark chocolate treatment (West et al. 2014). Given that the women in this study had higher AI at baseline, the clinical relevance of this finding is unclear.

A review of evidence from both animal and human studies suggests that human ingestion of the flavanol epicatechin is, at least in part, causally linked to the reported beneficial effects on vascular function (Schroeter et al. 2006), while results from a controlled trial suggest that formation of vasodilative NO contributes to beneficial vascular effects (Taubert et al. 2007b).

Improved vascular function after cocoa consumption has been demonstrated in a number of clinical trials involving congestive heart failure patients (Flammer et al. 2012), hypercholesterolaemic postmenopausal women (Wang-Polagru et al. 2006), heart transplant recipients (Flammer et al. 2007), diabetics (Balzer et al. 2008) and healthy subjects (Fardis et al. 2008, Grassi et al. 2012, Vlachopoulos et al. 2007) and people with coronary artery disease (Horn et al. 2013).

It has also been found that flavanol-rich cocoa enhanced several measures of endothelial function to a greater degree among older than younger healthy subjects, leading to the suggestion that the vascular effects of flavanol-rich cocoa may be greater among older people in whom endothelial function is more disturbed (Fisher & Hollenberg 2006).

There is evidence to suggest that the improved vascular function with flavanol-rich cocoa occurs acutely and in a sustained and dose-dependent manner, with a maximal flow-mediated dilatation at 2 h after a single-dose ingestion of flavanol-rich cocoa seen in a trial involving individuals with smoking-related endothelial dysfunction (Heiss et al. 2007). Similar acute results were seen in a double-blind RCT involving 22 heart transplant recipients in which flavonoid-rich dark chocolate was seen to induce coronary vasodilation, improve coronary vascular function, decrease platelet adhesion and reduce serum oxidative stress 2 h after consumption compared to cocoa-free control chocolate (Flammer et al. 2007). Further evidence for acute effects comes from a study in which dark chocolate, but not white chocolate, was observed to significantly improve endothelial and platelet function in healthy smokers, with increased flow-mediated dilatation, increased total antioxidant status and reduced shear stress-dependent platelet function seen 2–8 h after ingestion (Hermann et al. 2006).

The above findings are contrasted by a 6-week double-blind, placebo-controlled, fixed-dose, parallel-group clinical trial of 101 healthy older adults that compared consumption of a 37 g dark chocolate bar or 237 mL of artificially sweetened cocoa beverage with placebo. This study failed to demonstrate the predicted beneficial effects of short-term dark chocolate and cocoa consumption on neuropsychological or cardiovascular health-related variables (Crews et al. 2008).
Whether sugar-free cocoa products have different effects to those containing sugar has also been investigated. A single-blind, crossover RCT of 45 healthy adults suggested that endothelial function improved significantly more with sugar-free than with regular cocoa (Faridi et al 2008). Despite this, Njike et al (2011) found that both sugar-free and sugar-sweetened cocoa beverages improved endothelial function compared to sugar-sweetened placebo, in a double-blind crossover RCT of 44 healthy, overweight (BMI 25–35 kg/m²) adults. The same study found no significant changes for blood pressure, BMI, lipids or blood glucose levels for these cocoa beverages compared to placebo (Njike et al 2011).

**Cardiac ischaemia**
A prospective analysis of the self-reported chocolate consumption habits of 33,372 Swedish women over a mean follow-up of 10.4 years suggested that high chocolate consumption may be associated with a lower risk of stroke (Larsson & Virtamo 2011). There is evidence suggesting that cocoa flavanols may help in reducing cardiac ischaemia, with an animal study finding that epicatechin pretreatment confers cardioprotection in the setting of ischaemia-reperfusion injury and that the effects are independent of changes in haemodynamics, sustained over time, and accompanied by reduced levels of indicators of tissue injury (Yamazaki et al 2008). Human studies suggest that cocoa consumption may have clinical benefits for cerebrovascular ischaemic syndromes, including dementias and stroke with dietary intake of flavanol-rich cocoa being associated with a significant increase in cerebral blood flow velocity in 34 healthy elderly humans (Sorond et al 2008). It is further suggested that the prospect of increasing cerebral perfusion with cocoa flavanols is extremely promising, with implications for stroke and dementia (Fisher et al 2006).

**Premenstrual syndrome**
Magnesium deficiency may contribute to premenstrual syndrome symptoms, which may be improved by chocolate or cocoa powder, which contain a high concentration of magnesium (100 mg/100 g in chocolate and 320 mg/100 g in cocoa powder). There is also some evidence to suggest that serotonin levels are low premenstrually, and it is possible that premenstrual chocolate cravings are the body’s attempt to raise central nervous system (CNS) concentrations of serotonin (Bruinsma & Taren 1999).

**Enhanced cognitive function**
A recent systematic review of RCTs on the neurocognitive effects of chocolate or cocoa concluded that neither cocoa nor chocolate exerted cognitive effects in chronic or subchronic administration (Scholey & Owen 2013). Despite this, the review acknowledged that some specific physiological functions underlying cognition did appear affected, including cerebral blood flow and region-specific brain activity (Crews et al 2008, Francis et al 2006).

Previously, a double-blind study suggested that improvements in cognitive function following chocolate consumption are due to the methyloxanthine content of chocolate, with 11.6 g of cocoa powder producing identical improvements in cognitive function and the mood construct ‘energetic arousal’ as a mixture of caffeine (19 mg) and theobromine (250 mg) (Smit et al 2004).

A randomised, single-blinded, cross-over study determined that consuming 35 g dark chocolate (720 mg cocoa flavanols) improved visual contrast sensitivity and spatial memory and reduced time required to detect motion compared to 35 g white chocolate (trace flavanols) in a group of 50 healthy young adults (Field et al 2011).

Consumption of a 65 g chocolate bar was shown to significantly decrease driving accuracy and reduce collisions compared to an equicaloric snack of cheese and biscuits or no snack in a small controlled trial of 12 volunteers (Smith & Rich 1998).

**Motor function in Parkinson’s disease**
A 2012 crossover study compared the effects of a single dose of dark chocolate (200 g) containing 80% cocoa with the equivalent cocoa-free white chocolate in 26 adults diagnosed with moderate non-fluctuating Parkinson’s disease (Wolz et al 2012). The study found that the single dose of dark chocolate did not result in any significant improvement in Parkinson’s disease motor function. As a number of cocoa components, such as xanthine derivatives, are thought to have anti-Parkinson activity, quantifying plasma concentration of these compounds in this population may help to explain the observed effects from this study.

**Colonic health and constipation**
Cocoa mass has been suggested to have beneficial effects on metabolism of colonic microbiota (Mäki-vuokko et al 2007) and cocoa husk rich in dietary fibre may assist paediatric patients with idiopathic chronic constipation. This is supported by an RCT that found that benefits seem to be more evident in paediatric constipated patients with slow colonic transit time (Castillejo et al 2006). Similarly, a double-blind, crossover RCT (n = 22) found that daily intake of high-flavanol cocoa over 4 weeks resulted in significant increases in faecal bifidobacterial and lactobacilli microflora and reduced clostridia compared to low-flavanol cocoa (Tsounis et al 2011).

**OTHER USES**
Chocolate consumption 15 min before exercise has been shown to enhance exercise capacity, spare glycogen stores, delay fatigue and contribute to the recovery of glycogen repletion in healthy subjects (Chen et al 1996).

Milk chocolate has also been shown to be a cheap, effective and palatable form of fatty meal for...
producing gallbladder contraction prior to cholecystography (Harvey 1977).

Cocoa may also be of use in lactose intolerance, with a feeding study of 35 subjects finding that the addition of cocoa significantly reduced breath hydrogen levels, as well as bloating and cramping, with the result being independent of the presence of sucrose and carrageenan (Lee & Hardy 1989).

Cocoa butter is used in the formation of suppositories and pessaries, as well as preparations for rough or chafed skin, chapped lips, sore nipples and various cosmetics (Raintree Nutrition 1996).

There is empirical evidence indicating successful treatment of copper deficiency by adding copper-rich cocoa powder to tube-feeding formulas. It is suggested that, although there are other high-copper-containing foods such as seaweed, oyster and beans, cocoa powder is advantageous due to the ease of adding it to feeding formulas (Tokuda et al 2006, Tokuda 2007).

**DOSAGE RANGE**

There is enormous variability in the polyphenol content of cocoa and chocolate and the flavanols in cocoa exist in a multitude of different stereochemical configurations, thus giving rise to a unique and complex mixture of compounds. Given this complexity, the quantitative analysis of cocoa flavanols can be challenging. It is only through the use of methods that can accurately quantify these flavanols that it will be possible to make meaningful dietary recommendations regarding the consumption of cocoa flavanol-containing foods (Kwik-Uribe & Bektash 2008).

Trials suggest that effective doses are approximately 40–100 g dark chocolate or 15–30 g cocoa powder, providing approximately 200–500 mg polyphenols. Beneficial effects are more likely to result from the use of cocoa powder or dark chocolate containing more than 50–60% cocoa mass.

**TOXICITY**

Cocoa contains caffeine, which is a mild CNS stimulant that can be profoundly toxic in large doses, resulting in arrhythmia, tachycardia, vomiting, convulsions, coma and death. The caffeine content of cocoa is variable, being approximately 0.009% by weight (Kondo et al 1996), with a typical milk chocolate bar containing approximately 10 mg of caffeine, compared to a cup of coffee, which contains approximately 100 mg (Bruinsma & Taren 1999). Fatal caffeine overdoses in adults have been reported, but are rare and typically require ingestion of more than 5 g of caffeine, which would require consumption of more than 50 kg of chocolate (Kerrigan & Lindsey 2005).

**ADVERSE REACTIONS**

It is believed that chocolate is a trigger for migraine, yet there is inconsistent support for this. In one small double-blind, parallel-group study of 12 patients who believed that chocolate could provoke their attacks, chocolate ingestion was more likely than placebo to trigger a typical migraine episode, with the median time until the onset of the attack of 22 hours (Gibb et al 1991). Three other double-blind, placebo-controlled trials suggest that chocolate on its own rarely precipitates migraine (Marcus et al 1997, Moffett et al 1974), with the results of one trial suggesting that chocolate was no more likely to provoke headache than was carob in typical migraine, tension-type or combined headache sufferers (Marcus et al 1997).

One case of paroxysmal supraventricular tachycardia in a healthy 53-year-old female following the consumption of ‘a large amount’ of chocolate has been reported (Parasramka & Dufreane 2012).

Allergy to cocoa has been documented (Taijbee et al 2004) and it has been suggested that workers employed in the processing of cocoa and flour may be at high risk for the development of allergic sensitization and respiratory impairment (Zuskin et al 1998). One case report of cocoa aspiration causing severe aspiration pneumonitis in a 4-year-old has been documented (Lopatka et al 2004).

There is insufficient evidence to determine whether cocoa contributes to acne (Goh et al 2011, Ravenscroft 2005, Smith et al 2007). This may be due to other ingredients, such as fat and sugar content, which are known contributors to acne development and were not adequately controlled for as contributing variables (Smith et al 2007). Further studies which control for these additional factors in chocolate are required to fully evaluate the effects of cocoa on acne. The arginine content of most chocolate formulations may theoretically increase the susceptibility of consumers to cold sores (herpes simplex labialis virus). And sleep may also be adversely affected by high chocolate consumption due to its caffeine content (Lodato et al 2013).

**Practice points/Patient counselling**

- Cocoa has many potential benefits for the cardiovascular system and may reduce blood pressure, improve vascular function, inhibit platelet function and improve the serum cholesterol profile, as well as having beneficial effects on insulin sensitivity. However, further research is required to confirm the benefits.
- Cocoa may act to enhance cognitive function in a similar way to coffee, albeit with one-tenth the caffeine content.
- The most active agents in cocoa are the polyphenols, which are present in high amounts in dark chocolate, with lesser amounts in milk chocolate and minimal amounts in white chocolate.
- Cocoa powder contains minimal fat while dark chocolate contains less fat and sugar than milk or white chocolate. Beneficial effects are more likely to result from the use of cocoa powder or dark chocolate containing more than 50–60% cocoa mass.
SIGNIFICANT INTERACTIONS

Polyphenols may reduce iron absorption, with a cocoa beverage containing 100–400 mg total polyphenols per serving having been shown to reduce iron absorption by approximately 70% (Hurrell et al 1999).

PATIENTS’ FAQs

What will this herb do for me?
Cocoa is a nutritious food that appears to have beneficial effects on blood pressure, cholesterol, blood clotting and psychological wellbeing.

When will it start to work?
Psychological effects of dark chocolate consumption may be evident immediately, whereas beneficial effects on blood pressure and cholesterol may be evident after 2–4 weeks.

Are there any safety issues?
Cocoa powder and dark chocolate are extremely safe and are unlikely to precipitate migraine, acne or dental caries or produce adverse effects from the caffeine content.

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