Anti-inflammatory components from functional foods for obesity

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Abstract

Obesity defined as excessive fat accumulation that may impair health has been described throughout human history, but it has now reached epidemic proportions with the WHO estimating that 39% of the world's adults over 18 years of age were overweight or obese in 2016. Obesity is a chronic low-grade inflammatory state leading to organ damage with an increased risk of common diseases including cardiovascular and metabolic disease, non-alcoholic fatty liver disease, osteoarthritis and some cancers. This inflammatory state may be influenced by adipose tissue hypoxia and changes in the gut microbiome. There has been an increasing focus on functional foods and nutraceuticals as treatment options for obesity as drug treatments are limited in efficacy. This chapter summarises the importance of anthocyanin-containing fruits and vegetables, coffee and its components, tropical fruit and food waste as sources of phytochemicals for obesity treatment. We emphasise that preclinical studies can form the basis for clinical trials to determine the effectiveness of these treatments in humans.

161 words

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Obesity – the extent of the problem

Obesity is often referred to as a global health challenge. The literature on the epidemiology, causes, co-morbidities and potential treatments of obesity is enormous. As an example, a PubMed search from 2013-2019 for "obesity" lists about 125,000 references. This chapter will provide a background on the disease risk in obesity and the role of inflammation before examining some examples of functional foods that may reduce obesity by their anti-inflammatory actions.

The World Health Organisation defines overweight and obesity as abnormal or excessive fat accumulation that may impair health [1] and provides the key facts on overweight and obesity that are listed in Table 1.

Table 1. Key facts on overweight and obesity (World Health Organisation)

Worldwide obesity nearly tripled since 1975
In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these, over 650 million were obese
39% of adults aged 18 years and over were overweight in 2016, and 13% were obese
Most of the world's population live in countries where overweight and obesity kills more people than underweight
41 million children under the age of 5 were overweight or obese in 2016
Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016
Obesity is preventable

The increase in the number of people with overweight and obesity has been described as an epidemic or even as a pandemic of the late 20th and 21st century [2]. However, obesity has been described through the ages, starting with prehistoric statuettes from 30,000 years ago such as the Venus of Willendorf [3] and including members of the Ptolemy dynasty who ruled Egypt from 305-30BC [4]. Physicians from the Greco-Roman and Byzantine world described

the aetiology and clinical manifestations of obesity with suggestions for therapy including a Mediterranean-like diet with an active lifestyle [5]. In European art, overweight and obesity were indications of health, beauty and vitality [6]. In 1980, there were 921 million overweight and obese people; this had increased to 2.1 billion in 2013, about 29% of the world's total population in 2013 of 7.3 billion with the proportion of adult males with a body mass index of 25 or greater increasing from 28.8% in 1980 to 36.9% and an increase from 29.8% to 38.0% in adult females [7]. The trends in mean body mass index as a measure of under- or over-nutrition from 1975-2014 have been reported for adults aged over 18 years in 200 countries [8]. Over these 4 decades, global prevalence of underweight has decreased from 13.8% to 8.8% in men and from 14.6% to 9.7% in women. However, the prevalence of obesity increased from 3.2% to 10.8% in men and from 6.4% to 14.9% in women. Severe obesity with BMI $\geq$35 kg/m^2 occurred in 2.3% of the world's men and in 5.0% of the world's women; the corresponding figures for morbid obesity with BMI $\geq$40 kg/m^2 were 0.64% in men and 1.6% in women. Obesity is clearly a current worldwide occurrence in adults.

Obesity is not restricted to adults, but occurs widely in children and adolescents. Analyses of data sources with measurements of height and weight on 128.9 million children and adolescents aged 5 years and older from 1975 to 2016 have shown that the prevalence of obesity increased from 0.7% in 1975 to 5.6% in 2016 in girls, and from 0.9% in 1975 to 7.8% in 2016 in boys, with accelerated increases in east and south Asia [9]. This study also highlighted the co-existence of underweight and obesity in the world's children and adolescents with 75 million girls and 117 million boys being underweight, along with 50 million girls and 74 million boys being obese in 2016.

Despite the increasing prevalence of overweight and diabetes, life expectancy at birth has increased from 59 to 71 years over the same time-frame [10]. This apparently protective

relationship is likely to be casual, rather than causal, as body mass index changes in children do not appear to be protective. Also, the increases in obesity have not been evenly spread in the world, as the poor are more likely to be obese in high income countries but this group is usually underweight in low-income countries leading to increased global inequalities in the prevalence of obesity [10], making a protective effect of obesity on life expectancy less likely.

As part of the Global Burden of Disease study, patterns of death and disability-adjusted life years were determined in people with high body-mass index from 195 countries from 1990-2015 [11]. In 2015, high body mass index was estimated to contribute to 4 million deaths each year and 120 million disability-adjusted life years. More than two-thirds of deaths were related to cardiovascular disease, but the improvements in survival from cardiovascular disease have reduced the rate of increase of mortality in people with high body-mass index. Diabetes was the second leading cause, contributing to 0.6 million deaths per year and 30.4 million disability-adjusted life years. Less than 10% of deaths in 2015 were associated with chronic kidney disease or cancers [11].

The World Health Organisation has summarised that an increased body mass index is a risk factor for the non-communicable diseases that are listed in Table 2 [1].

Table 2. Risk factors with increased body mass index (World Health Organisation)

Cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012
Diabetes
Musculoskeletal disorders (especially osteoarthritis – a highly disabling degenerative disease of the joints)
Some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon)

Obesity has been defined as a disease of chronic low-grade inflammation [12] which will be further discussed in the next section. Co-morbidities with obesity include

cardiovascular disease, diabetes, some cancers, non-alcoholic fatty liver disease (NAFLD) and osteoarthritis. There is a clear relationship between obesity and cardiovascular disease, with increasing incidence of cardiovascular disease with increasing obesity and length of duration of obesity [13]. However, obese patients with high cardiorespiratory fitness, known as metabolically healthy but obese or fat-but-fit, showed reduced cardiovascular risk. This may be one of the reasons for an obesity paradox, where overweight or mildly obese patients with cardiovascular disease showed a better prognosis [13]. Obesity and type 2 diabetes are both characterised by defects in insulin action produced by increased plasma concentrations of free fatty acids and so are commonly observed in the same patients [14]. The increased flux of free fatty acids from increased abdominal fat is likely to be the cause of the increased incidence of NAFLD in obese patients [15]. Further, both diabetes and obesity are associated with an increased risk of cancers which could be initiated by the increased pro-inflammatory environment that characterises both diabetes and obesity [16]. Increased adiposity increases the release of a wide range of adipokines from adipocytes; together with increased mechanical loading, the pro-inflammatory cytokines such as leptin and visfatin are likely to be important in the development of osteoarthritis in obese and older patients [17]. Thus, the major common mechanism in obesity and its co-morbidities is systemic inflammation.

Inflammation in obesity

Obesity has been described as a low-grade, chronic inflammation orchestrated by metabolic cells in response to excess nutrients and energy [18]. As described by these authors, this inflammation is different from classic inflammation producing redness, swelling, heat and pain, which is essential for the repair, remodelling and renewal of tissues. The inflammatory trigger in the development of obesity is the consumption of foods causing an increased production and secretion of an array of inflammatory cytokines, known as adipokines, by

adipocytes, causing increased infiltration of immune cells such as macrophages into the metabolic tissues, including adipose, liver, muscle, pancreas and brain. Obesity-induced inflammation differs from classic inflammation in that it is moderate, creates a pro-inflammatory environment and is sustained by the constant stimulus of chronic nutrient intake. This metabolic inflammation (or metaflammation) then interferes with normal metabolism and disrupts insulin signalling to produce insulin resistance and lipolysis, so disrupting glucose and lipid homeostasis [18]. The precise triggers of metabolic inflammation could include intestinal antigens including lipopolysaccharides, components of foods such as free fatty acids, or signals associated with dying or stressed adipocytes including leptin and other adipokines, or hypoxia which could involve hypoxia-inducible factor 1α [19].

The nutrient and immune systems are fundamentally related as survival relies on both the ability to store and harness energy and to sense and fight infection. Both respond to danger signals and share many of the signalling networks. We suggested that, in metabolic disease, the initiation of multiple redundant mechanisms in response to an increase in nutrients limits endogenous nutrient output and exogenous nutrient intake with a similar set of molecules and signalling pathways as in innate immunity [20]. Studies on the convergence of these pathways show that many levels are involved, including receptors, organelles, kinase pathways and gene expression [12]. These evolutionally conserved interactions are essential for the maintenance of healthy organs, including adipose tissue, as well as overall health, especially in chronic non-communicable diseases such as obesity [12].

The gut microbiome

The bacteria in the gastrointestinal tract, concentrated in the colon, are essential for many functions including protection from pathogens, digesting otherwise indigestible carbohydrates, synthesising essential vitamins and modifying the immune system. The

intestinal microbiota is diverse, with at least 1000 different species providing around $2x10^{13}$ bacteria, similar to the number of cells in the adult human [21]. The healthy human microbiome is dominated by bacteria of two phyla, *Bacteroidetes* and *Firmicutes* together with about 90% of the total number of bacteria, although there can be marked variation of the *Bacteroidetes*/*Firmicutes* ratio in healthy subjects which may result from differences in nutrition or geography [22]. Further, the role of individual bacterial families is far from clear as maybe 50% of these families remain functionally uncharacterised [22]. Changes to this complexity during the development and maintenance of obesity include decreased *Bacteroidetes* and increased *Firmicutes*, but these changes are highly individualised, and depend on dietary composition and a wide range of lifestyle factors including breastfeeding, exercise, stress, use of antibiotics, sleep disturbances and cold exposure [23]. Many physiological responses have been associated with obesity-associated microbiota including host energy harvesting, insulin resistance, inflammation and fat deposition, together with regulation of adiposity, energy balance, and central appetite and food reward signalling [24]. Metabolic, immune and defence systems are strongly influenced by the gut microbiome, directly influencing human health in conditions such as obesity and metabolic diseases, undernutrition and eating disorders, inflammatory bowel disease and colorectal cancer [25]. Further, changes in the intestinal microbiota and changes in intestinal permeability may provide the triggers of the persistent low-grade systemic inflammation that characterises obesity [26]. Increased intestinal permeability allows bacterial components such as lipopolysaccharides into the body where they may disrupt vagal afferent signalling to the brain and then increase body weight [27].

The intestinal microbiota is important in host energy metabolism and clearly affects the bidirectional communication between the brain and the gut, referred to as the microbiome-gut-brain axis. These changes in the microbiome are important in metabolic disorders as diverse as

anorexia nervosa, cachexia, and severe malnutrition such as kwashiorkor, as well as obesity, and also after interventions such as bariatric surgery [28]. Short-chain fatty acids such as acetate, propionate and butyrate produced by colonic bacteria influence host energy metabolism and appetite by multiple mechanisms [28]. The gut microbiota is important in energy harvesting by producing these short-chain fatty acids, in particular from polysaccharides such as cellulose, xylan and pectin which cannot be metabolised by human digestive enzymes, so termed as prebiotics. Prebiotics increase the growth of the selected intestinal microbiota including *Bifidobacterium* and *Lactobacillus*; this reduces the production of liposaccharides, increases the integrity of the gastrointestinal barrier and may prevent obesity [29].

Products of the intestinal microbiota induce activation of tissue macrophages and this low-grade inflammation contributes to metabolic diseases such as obesity and other metabolic disorders [30, 31]. Thus, changes to the microbiota through treatments including faecal transplantation and prebiotics are logical approaches to the treatment of these metabolic diseases [32]. Faecal microbiota transplantation has already shown the importance of intestinal dysbiosis in disease states such as infections with *Clostridium difficile* and inflammatory bowel disease [33]. Faecal microbiota transplantation is a potential method to delineate the effects of intestinal microbiota on the metabolic syndrome [34]. This could be an innovative option to treat human obesity [35] as studies in murine models showed that faecal transplantation from an obese human twin produced obesity in contrast to the lack of weight gain with faecal transplantation from the lean human twin [36]. However, there is no current information to show that this treatment improves human obesity [37]. Further, the gut microbiome may be heavily involved in obesity-associated diseases such as the development of NAFLD [38] as well as other chronic liver diseases including chronic hepatitis B and C, and cirrhosis [39].

However, the effectiveness of faecal microbiota transplantation in these common liver diseases in humans remains to be proved.

Hypoxia

As adipose tissue mass expands, hypoxia develops and this reduction in oxygen underlies the switch from oxidative metabolism to anaerobic glycolysis [40] with increased macrophage infiltration and the development of insulin resistance leading to hyperglycaemia [40]. Gaseous oxygen is essential for all aerobic organisms [41] and deficiency of oxygen leads to widespread cellular adaptations, mostly driven by transcription factors such as the hypoxia-inducible factors (HIFs). HIFs are important in hypothalamic control of the regulation of body weight, glucose homeostasis and liver metabolism [42] and inhibition of HIFs decreases adverse diet-induced metabolic phenotypes so that HIFs may be drug targets for metabolic diseases [43]. Hypoxic adipocytes produce a wide range of protein factors, the adipokines, that alter many physiological functions such as appetite, insulin sensitivity and blood pressure, important in the development of obesity, diabetes, NAFLD and dyslipidaemia [44]. Despite this close relationship between hypoxia, adipokine secretion and chronic systemic inflammation, intermittent hypoxia during rest or exercise may lead to improved exercise tolerance, metabolism and systemic arterial pressure as a treatment strategy to increase weight loss and improve obesity-associated disease [45]. One example is the improved body composition, physical fitness, pulmonary function and heart rate variability following 12 weeks' hypoxic training compared to normoxic training in obese 65-70 year old Korean men [46].

Current and future treatments of obesity

Drug treatments for obesity are characterised by their relatively small changes in body weight, usually less than 10%, which are often not sustained [47]. More effective compounds

may be unimolecular dual agonists, for example at receptors for glucagon-like peptide 1 and glucagon or glucose-dependent insulinotropic polypeptide, or triple agonists for all three peptide receptors [47]. Peptide-mediated delivery of nuclear hormones, for example covalently bound glucagon-like peptide 1-dexamethasone or -oestradiol, and glucagon-triiodothyronine, may be more acceptable as the nuclear hormone is only released in cells with the peptide receptors, so reducing the adverse effects in other tissues [47]. An alternative treatment protocol may involve functional foods, defined as foods that provide nutrition as well as being able to prevent or reverse disease states [48], or nutraceuticals, defined as pharmaceutical-grade and standardised nutrients derived from foods such as prebiotics and probiotics [49]. In obesity, these functional foods and nutraceuticals are likely to be anti-inflammatory so as to be effective in a disease state of chronic low-grade inflammation. This concept is supported by the effectiveness of selective semi-synthetic anti-inflammatory compounds including protease-activated receptor 2 antagonists [50], complement 3a and 5a receptor antagonists [51] and phospholipase A_2 group IIA inhibitors [52] to reduce abdominal obesity. While using foods to treat an inflammatory state produced by increased food intake sounds counter-intuitive, plants produce a wide range of secondary metabolites that may have developed to protect the plants. The hypothesis is that this protective role could potentially be translated to decreasing chronic inflammatory states in humans such as obesity. There are also practical reasons for testing functional foods since the production of these foods is likely to be sustainable and adherence to dietary treatment will probably be higher than with pharmaceutical agents.

Food as the source of anti-obesity agents

Functional foods are foods that provide basic nutritional requirements along with health benefits [53]. Obesity is a chronic human disease that functional foods may have a role in treating or preventing [48, 54]. Over the past few decades, many animal models have been

developed for the study of anti-obesity effects of many foods and their components [55, 56]. However, the successes in animal trials have not been well translated to overweight or obese humans [48, 57]. Nonetheless, there is widespread interest in functional foods as a viable therapeutic option for obesity and both animal and human trials are continuing to search for a solution to this worldwide problem. Here, we will summarise the findings for some key functional foods and update the literature from our previous review [48] to demonstrate the possibilities with functional foods to treat human overweight and obesity.

Anthocyanins

Anthocyanins are dark-coloured pigments from fruits and vegetables [48] that are produced as secondary metabolites by the plants [58]. These secondary metabolites are produced as a defence mechanism against stress situations including pathogen infection, low nitrogen condition and photo-oxidative damage [58-61]. Sources of anthocyanins include berries, cherries, grapes, plums, dark-coloured vegetables and pigmented grains [48]. Anthocyanins have been proven to be effective in reducing obesity and metabolic syndrome in animal models as well as in humans [48, 62-65]. Some of the proposed mechanisms of actions of anthocyanins as anti-obesity agents are inhibition of lipid absorption, increase in energy expenditure, regulation of lipid metabolism, suppression of food intake, regulation of gut microbiota, amelioration of oxidative stress and resolution of inflammation [66].

Recent studies have extended these observations. Intervention with blackberry and blueberry anthocyanins in high-fat diet-fed mice for 12 weeks resulted in inhibition of body weight gain, reduction in serum and hepatic lipid concentrations, increased faecal acetate and butyrate concentrations and reduced expression of tumour necrosis factor α, interleukin-6 and nuclear factor-κB genes in the pathways to inflammation. These anthocyanins also modulated hepatic lipid and glucose metabolism, and the insulin signalling pathway [67]. In obese rats fed

a high-carbohydrate, high-fat diet, chokeberry and purple maize, both containing cyanidin 3-glucoside, reduced visceral adiposity index, total body fat mass and systolic blood pressure while improving glucose tolerance, liver and cardiovascular structure and function with decreases in plasma triglycerides and total cholesterol [68]. Cyanidin glycosides from fermented chokeberries with reduced bitter taste attenuated increases in weight and serum triglyceride concentrations along with improved glucose tolerance and insulin sensitivity, when treatment was given to high-fat diet-fed mice for 8 weeks [69]. Cyanidin 3-glucoside from Queen Garnet plums and in purified form reduced obesity and metabolic syndrome symptoms in high-carbohydrate, high-fat diet-fed rats [70]. Cyanidin glucoside from Davidson's plum, a native Australian fruit, reduced visceral fat accumulation, total abdominal fat weight, size of retroperitoneal adipocytes, and plasma triglycerides and non-esterified fatty acids, normalised blood pressure, reduced left ventricular stiffness, decreased infiltration of inflammatory cells in both left ventricle and liver, decreased collagen deposition in heart, and reduced both fat vacuoles in liver and obesity-induced degeneration of knee cartilage [71]. Cyanidin and delphinidin improved insulin sensitivity and inhibited oxidative stress, NF-κB and JNK activation and PTP1B overexpression in high-fat diet-fed mice [72]. In high-fat diet-fed mice, boysenberry anthocyanins caused no changes in body weight, systolic or diastolic blood pressure, heart rate and systemic glucose intolerance while increasing nitric oxide in the aorta and improving endothelium-dependent vasodilatation in the iliac artery [73]. Delphinidin did not affect body weight, hyperglycaemia, insulin resistance or histological liver abnormalities induced by high-fat, high-carbohydrate diet in mice [74]. Delphinidin reduced triglyceride accumulation *in vitro* through the modulation of lipid metabolic gene expression but it failed to induce this change in high-fat, high-carbohydrate diet-fed mice [74]. Blueberry supplementation in high-fat diet-fed rats improved gut microbiota through an increase in Gammaproteobacteria abundance and increases in ileal villus height and ileal expression of

Muc2. Tumour necrosis factor α and interleukin 1β expression in visceral fat were normalised by blueberry supplementation along with improved insulin sensitivity and hepatic insulin receptor substrate 1 phosphorylation [75]. The positive responses of anthocyanins on adipocytes, endothelial cells, inflammatory cells, hepatocytes, intestinal cells and gut microbiota have been recently reviewed [76]. This review also highlighted the lack of evidence for effects of anthocyanins on other cells, including platelets, skeletal muscle cells, hepatic stellate cells and pancreatic β-cells [76].

Fewer studies have investigated the responses to anthocyanins in humans. In a pilot crossover study, anthocyanin-rich Queen Garnet plum juice reduced ambulatory blood pressure without improving acute cognitive function in younger and older adults [77]. In mildly hypertensive overweight or obese subjects, Queen Garnet plum juice decreased systolic and diastolic blood pressures, and plasma concentrations of insulin, glucose and leptin while increasing plasma concentrations of adiponectin [78]. In an open-label study, the blend of 215 mg anthocyanins and 2.7 g prebiotic fibre daily in obese subjects reduced proportion of *Firmicutes* and increased *Bacteroidetes* with reductions in HbA1c without any changes in body weight [79]. In a randomised, placebo-controlled, crossover study in overweight or obese men, 600 g/day blackberries for seven days reduced average 24-hour respiratory quotient, possibly through increased fat oxidation with no change in glucose area under the curve and reduced insulin area under the curve [80]. In a double-blinded, randomised, placebo-controlled clinical study, blueberries improved insulin sensitivity without changing adiposity, energy intake and inflammatory biomarkers in obese, insulin-resistant men and women [81]. Red orange juice containing anthocyanins, flavone glycosides and hydroxycinnamic acids for 12 weeks reduced body mass index, body weight, waist and hip circumference in overweight healthy human volunteers suggesting its usefulness in obesity management [82].

Coffee components

Coffee, a complex mixture of more than thousand phytochemicals, is a functional food containing alkaloids, phenolic compounds, vitamins, carbohydrates, lipids, minerals and nitrogenous compounds [83]. Coffee has been linked with health benefits [84-86], in some studies through its action on controlling serum concentrations of leptin and adiponectin [87].

Coffee extract in high-carbohydrate, high-fat diet-fed rats improved cardiovascular and hepatic structure and function without reducing obesity [88]. A similar dose of caffeine from this study in obese rats reduced body weight and body fat along with improved cardiovascular and hepatic structure and function [89]. Coffee extract in high-fat diet-fed mice reduced the increase in body weight, prevented the decrease in the concentrations of glutathione and ascorbic acid in lens and prevented the increase in plasma cholesterol and triglycerides. These results were greater in roasted coffee-treated mice than in green coffee-treated mice [90]. Coffee and its components, caffeine and chlorogenic acid, improved liver inflammation without changing body weight, visceral fat, blood glucose and liver steatosis in Tsumura Suzuki obese diabetes mice, a spontaneous model of metabolic syndrome. This effect was seen through the effects on gut microbiota and increase in short-chain fatty acid production [91]. Green coffee bean extract in high-fat diet-fed mice reduced body weight gain, liver steatosis, white adipose tissue weights, fat mass, adipocyte size, plasma lipids and leptin [92]. Effects against metabolic syndrome were also observed with decaffeinated green coffee in diet-induced metabolic syndrome [93]. Chlorogenic acid reduced visceral fat, abdominal circumference, systolic blood pressure, left ventricular diastolic stiffness, ventricular infiltration of inflammatory cells and collagen deposition, inflammation and fat deposition in the liver, and plasma liver enzyme activities without changing plasma lipid profile along with increased diversity of gut microbiota in high-carbohydrate, high-fat diet-fed rats [94].

Chlorogenic acid treatment reduced hepatic steatosis, inflammation and insulin resistance while suppressing hepatic gene expression of Pparγ, Cd36, Fabp4 and Mgat1 in high-fat diet-fed mice [95]. Other effects of coffee and its components in animal models have been reviewed recently [96].

Moderate coffee consumption (3–4 times daily) was associated with reduced incidence of metabolic syndrome in Korean adults [97]. In a comprehensive study of longitudinal associations in a Danish cohort, an association was found between increased coffee consumption over a 6-year period and decreased concurrent gain in body mass index, fat mass index, body fat percentage and waist circumference [98]. In a randomised clinical trial in metabolic syndrome patients, green coffee extract reduced systolic blood pressure, fasting blood glucose, HOMA-IR, waist circumference and appetite score with no impact on lipid profile and glycated haemoglobin [99]. In a randomised clinical trial in obese women, green coffee bean extract with energy restriction reduced body weight, body mass and fat mass indices, and waist-to-hip circumference ratio. These changes were also accompanied by reductions in serum total cholesterol, low-density lipoprotein, leptin, and plasma free fatty acids and increases in serum adiponectin [100]. The effects of coffee and chlorogenic acid in metabolic syndrome through epidemiological studies have been reviewed recently [101]. Prospective cohort studies have confirmed a link between habitual coffee consumption and reduced all-cause mortality rates with reduced risk of cardiovascular death, type 2 diabetes and liver disease [102]. These outcomes highlight the potential health benefits of coffee and its components.

Tropical fruits

Fruits grown in tropical regions are high in their nutritive values. However, their medicinal properties are unknown for the majority of the tropical fruits [103] as these fruits are

not studied to the same extent as the fruits grown in temperate regions of the world although tropical fruits contain many bioactive compounds [104]. Although some tropical fruits have been commercialised, many of these fruits are still underutilised [103].

As an example of tropical fruits, the genus *Garcinia* from the Clusiaceae or Guttiferae family comprises evergreen, dioecious trees and shrubs that flourish in lowland tropical forests [105]. Most *Garcinia* species are sources of secondary metabolites, including simple organic acids, xanthones, flavonoids, benzophenones, lactones and phenolic acids [106]. The beneficial effects of some of the *Garcinia* species have recently been reviewed [54]. *Garcinia mangostana* xanthones are promising compounds for the development of new drugs that may interact with multiple biological targets for improving cancer, pain, insulin resistance and neurological impairment [107, 108]. In high-fat diet-fed mice, garcinol reduced body weight gain, visceral adipose tissue weight, plasma activity of alanine transaminase, plasma concentrations of total cholesterol and triglycerides, Firmicutes-to-Bacteroidetes ratio in gut microbiome and gut inflammation by increasing *Akkermansia* [109]. Mangosteen pericarp extract decreased concentrations of plasma free fatty acids, hepatic triglycerides and hepatic thiobarbituric acid reactive substances while increasing liver activities of antioxidant enzymes, NADH-cytochrome c reductase and succinate-cytochrome c reductase [110]. In high-fat diet-fed mice, mangosteen exerted anti-obesity effects by activating AMPK and SirT1 and by suppressing PPARγ expression in the liver along with reduced body weight gain, adipose mass, and serum concentrations of triglycerides, total cholesterol and LDL [111]. In high-fat diet-fed rats, *Garcinia cambogia* extract decreased body weight gain, glucose intolerance, and plasma leptin and TNF-α concentrations [112]. In a randomised, controlled pilot trial in obese female patients, mangosteen improved insulin sensitivity [113]. *Garcinia cambogia*, a source of hydroxycitric acid, has been shown to be effective in weight loss [54, 114]. However, there are other tropical fruits such as durian (*Durio zibethinus* Murr.) [115] and jamun (*Syzygium cumini*)

[116, 117] with only very limited evaluation for health benefits and many tropical fruits that have not yet been tested.

Food waste as source of nutraceuticals

Food waste is an increasing problem in the modern world. One third of all food produced in the world is lost or wasted (~1.3 billion tonnes of food each year) costing the global economy close to $990 billion each year [118]. Much of the food waste, especially from the agriculture and food processing industries, can be a good source of nutraceuticals [119, 120]. As one example, achacha (*Garcinia humilis*) rind as the food waste reduced systolic blood pressure, diastolic stiffness, left ventricular inflammatory cell infiltration and collagen deposition in high-carbohydrate, high-fat diet-fed rats [121]. The responses of achacha rind were greater than the pulp which is the edible part of the fruit, suggesting the increased value of the rind that is generally discarded [121].

Parts of many tropical fruits such as rind, peel, seed, flower and leaf are sources of polyphenols including flavonoids that are also present in many other functional foods, thus suggesting potential health benefits in these waste components of foods [122, 123]. Temperate fruits such as citrus are rich sources of flavonoids and these phytochemicals have shown promising health benefits [124]. Similarly, citrus waste is a readily-available source of similar phytochemicals and can serve as the source of extracting these compounds for the development of nutraceuticals and pharmaceuticals [125-127]. Grape pomace is a waste from wine production and is a rich source of polyphenols including anthocyanins. In high-fat diet-fed rats, grape pomace improved glucose tolerance and insulin sensitivity suggesting the potential for further studies and nutraceutical development [128]. In a prospective, randomised, controlled, parallel-group trial, red wine grape pomace flour decreased systolic and diastolic blood pressure as well as fasting glucose concentrations [129]. Although there are suggestions of

these potential benefits, there are limited high-quality studies confirming the clinical benefits of grape polyphenols [130]. Similarly, many other food wastes are sources of valuable compounds and can serve as alternatives for nutraceutical development [131-135]. These food wastes can provide opportunity for improving public health through the development of sustainable products that can be used for human consumption.

Human trials with functional foods

In our previous review, we summarised the potential health benefits of many functional foods and their components [48]. In that review, we highlighted that there were remarkably few natural products with unambiguous evidence for efficacy in patients with metabolic syndrome, especially obesity [48]. We also highlighted duration and the dose of interventions as the contributing factors in creating difficulties in translation of studies into suitable products. Recently, we reviewed other confounding factors that can create difficulties in suitable translation of functional foods in human studies [136]. These include obtaining adequate funding support for the trial, technical knowledge to initiate the trial, identifying an appropriate placebo, food delivery to participants, food quality, food acceptability, unwanted access to functional foods, compliance, appropriate biomarkers, intake of functional food by the control participants, statistical analysis, the response of the public and the response of the medical community [136].

Conclusions

Overweight and obesity are common disorders throughout the world, increasing the risk of chronic cardiovascular, metabolic and musculoskeletal diseases as well as some cancers. Obesity is described as a chronic, low-grade inflammation. Thus, functional foods delivering adequate amounts of anti-inflammatory compounds would be expected to improve the range of pathophysiological changes in overweight and obese humans. There is much evidence to

support this concept, mostly in animal models but increasingly in clinical trials in humans. The studies in animal models have investigated an interesting range of compounds in functional foods that could provide relevant advances in the currently inadequate treatment of obesity disorders in humans. Further, food waste is an underutilised source of sustainable interventions that could prevent or treat human obesity.

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