



ANTI-OBESITY EFFECT OF GREEN TEA CATECHINS IN HIGH-FAT DIET-INDUCED OBESE MICE

LOGAN WHITFIELD^{1*}, MARTA CASTELLANOS², SOFIE DUBOIS³

Affiliation

¹Department of Pharmacology, Shenandoah Valley College of Pharmacy, Harrisonburg, USA

²Department of Pharmacology, Cantabrian Coast Centre for Drug Development, Torrelavega, Spain

³Department of Pharmacology, Kempen Centre for Pharmaceutical Analysis, Geel, Belgium

*Corresponding author: Logan Whitfield, l.whitfield@svcp.edu

ORCID iD: Logan Whitfield 0000-0001-3499-2958; Marta Castellanos 0000-0001-4221-4742; Sofie Dubois 0000-0001-3054-9377

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1. INTRODUCTION

Obesity is now one of the commonest metabolic conditions worldwide, and the search for safe, inexpensive agents that limit fat accumulation has turned many researchers towards dietary polyphenols. Green tea, made from unfermented leaves of *Camellia sinensis*, is consumed daily by hundreds of millions of people and has been linked in observational work to better cardiometabolic health [1]. Its distinctive polyphenols, the catechins, have attracted special attention. Among them, (-)-epigallocatechin-3-gallate (EGCG) is the most abundant and, in most experiments, the most active [1, 2]. When laboratories began to feed mice high-fat diets

Abstract

Green tea catechins, especially epigallocatechin gallate, are among the most studied natural products in experimental obesity research. This review, which reports no new data, brings together published work on their effects in mice fed high-fat diets. It describes catechin chemistry and pharmacokinetics, the design and limits of the diet-induced obesity model, reported effects on body weight, fat mass, liver fat and glucose handling, proposed mechanisms including reduced energy absorption, increased fat oxidation and gut microbiota change, and safety at high doses. Findings are broadly consistent across rodent studies, but doses are often far above human tea intake, housing and reporting practices vary, and translation to people has been modest.

and to add catechins to the mix, the early results looked strikingly positive.

That enthusiasm needs to be read against what has happened in human trials. Meta-analyses of green tea and catechin-cafeine preparations suggest small effects on body weight, with wide variation

between studies and some dependence on habitual caffeine intake and ethnicity [3, 4]. A Cochrane review found only small, statistically non-significant weight loss in overweight adults [5]. Long supplementation in postmenopausal women did not change adiposity [6]. Such mixed human findings make the animal literature especially important to examine closely, because it supplies the mechanistic rationale and the dose-response information on which clinical studies were designed [2, 7]. Their pooled outcome, a small effect that is hard to separate from caffeine, is the context in which the mouse data should be judged.

This review is a narrative synthesis of published experimental studies on green tea catechins in mice made obese by high-fat feeding, with some reference to rats and to human data for context. It does not present new experiments and does not claim to have counted the literature systematically. The sections that follow describe the chemistry and kinetics of catechins, the strengths and weaknesses of the diet-induced obesity model, the main outcomes reported, the mechanisms proposed, and the question of safety and dose translation. Evidence is judged mainly on consistency across independent laboratories and on whether the doses used bear any relation to human exposure [2, 8]. Readers wanting a mechanistic overview first may turn directly to the sections on mechanisms and on safety. Where a figure is quoted, it comes from the cited paper and no data have been re-analysed here.

A word on scope may help. Studies using purified EGCG, mixed catechin preparations and whole green tea extract are all considered, but they are not interchangeable. Whole extracts contain caffeine, which has its own effects on energy expenditure, and the ratio of catechins varies with cultivar, processing and extraction [2, 9]. Where a conclusion depends on that distinction, the text says so. Contributions from the caffeine component are discussed where relevant, since several of the studies cited cannot exclude them from the observed result, a limitation shared with human work [9].

2. CATECHIN CHEMISTRY AND PHARMACOKINETICS

Green tea contains four principal catechins: epicatechin, epicatechin gallate, epigallocatechin and EGCG. Together they can account for a substantial fraction of the dry weight of the leaf, and EGCG usually makes up about half of the catechin total [1, 2]. The gallate esters are generally more potent than the non-gallated forms in cell-free and cellular assays, which is one reason EGCG is studied so heavily. Catechins are polyphenols with multiple hydroxyl groups, so they are good antioxidants in vitro, but they are also chemically fragile: in neutral or mildly alkaline solution they oxidise and epimerise within hours, and cooking, brewing and storage can alter the profile [1, 2]. Variation in tea cultivar, harvest time and brewing also means that the same nominal dose of tea can deliver very different amounts of EGCG [1, 2].

Oral bioavailability is low in both people and rodents. In healthy volunteers who drank green tea or took EGCG, plasma levels peaked within a few hours and fell away over the following day, and EGCG circulated largely in its free form while the smaller catechins appeared mostly as glucuronide and sulfate conjugates [10, 11]. Intestinal and hepatic metabolism, efflux transporters, and degradation by the gut microbiota all contribute to low systemic exposure. Repeated dosing in volunteers showed substantial inter-individual variation, and taking EGCG on an empty stomach produced considerably higher plasma concentrations than taking it with food, which has direct bearing on safety [11, 12].

Practical details of exposure are easily overlooked. Catechins are lost during diet manufacture, particularly where pellets are heated, and further oxidation can occur during storage in warm or humid rooms, so the amount actually eaten may be well below the nominal inclusion level [1, 2]. Authors seldom assay the diet at the time of feeding. Analysis of catechins in diets and in biological samples is usually performed by high-performance liquid chromatography with ultraviolet or electrochemical detection, and plasma samples need stabilisation with

antioxidants because EGCG degrades quickly after collection [10, 11]. Incomplete control of these points helps explain why identical nominal doses give different outcomes between laboratories [10, 13, 14].

In mice the pharmacokinetic picture is similar in outline, but the quantitative relationship to human dosing is less straightforward. Mice have faster metabolism and a different gut microbial community, and the way the catechin is delivered, whether mixed into the diet, dissolved in drinking water or given by gavage, affects peak concentration and tissue distribution [14, 15]. Diet admixture produces low, sustained exposure that resembles habitual intake, whereas gavage of a large bolus gives a high peak that may be more relevant to toxicity than to nutrition. Many papers report the dose as a percentage of diet or in milligrams per kilogram, but few measure plasma or tissue catechin concentrations [13, 14, 15].

The route and schedule of dosing change the exposure a mouse actually receives, even when the daily amount is nominally identical. Mixing catechins into the diet spreads intake across the night-time feeding period and tends to give low, sustained plasma concentrations [13, 14]. Oral gavage delivers the whole dose at once, producing a sharper peak, and the same bolus given to fasted animals has been linked to liver injury at doses that were tolerated when the compound was taken with food [15]. Human work points the same way, since plasma levels after a fixed dose are higher in the fasted state than after a meal [10, 11]. For this reason, a study that reports only milligrams per kilogram per day cannot be compared fairly with another unless the vehicle, timing and feeding status are also stated. Dietary admixture also carries a practical risk, because catechins degrade in moist food, so the amount eaten may fall below the amount weighed in unless diets are replaced frequently.

A part of the activity of catechins in the gut may not depend on absorption at all. Unabsorbed catechins remain in the intestinal lumen for hours, where they can interact with dietary lipid, digestive enzymes and bacteria. Experiments suggest that EGCG can bind lipid droplets and enzymes involved in fat

digestion, which would reduce the energy extracted from food [16]. This local action may help explain why a compound with poor systemic availability can nevertheless alter body composition, and it is one reason why plasma levels alone are an incomplete guide to biological activity [2, 16]. Such luminal effects also raise the possibility that results depend on whether the catechin is given with or between meals, a variable that animal protocols rarely control [2, 16].

Caffeine complicates the interpretation of studies using tea extracts. In humans, a green tea extract rich in catechins and caffeine increased 24-hour energy expenditure and fat oxidation, and the effect exceeded what an equivalent amount of caffeine alone produced, which led to the proposal that catechins prolong sympathetic stimulation by inhibiting catechol-O-methyltransferase [9]. Rodent work with decaffeinated preparations helps separate the effects, but many mouse studies still use extracts that contain caffeine [2, 13]. Dosing in the human study used a specific commercial extract, so the finding applies strictly to that preparation and its caffeine content, not to catechins as a class [2, 9].

3. THE HIGH-FAT DIET MODEL

The standard experimental subject is the male C57BL/6J mouse. Early work showed that this strain, when fed a diet high in fat and sucrose, becomes obese, hyperinsulinaemic and hyperglycaemic, unlike some other inbred strains that remain relatively lean [17]. Later characterisation traced this susceptibility to physiological and molecular features such as altered insulin secretion and adipose tissue responses [18]. Diets in current use provide 45 or 60 percent of energy as fat, usually from lard or similar, and are given for 8 to 20 weeks. Weight gain, increased fat mass, fatty liver, impaired glucose tolerance and raised serum lipids follow in a matter of weeks, which makes the model convenient for testing interventions [19, 20].

Convenient does not mean perfect, and the model has recognised weaknesses. Human obesity develops over years, in response to a complex mixture of foods and settings, whereas the mouse is given a purified high-fat

diet that is unlike any human diet [20]. The choice of control diet matters greatly: a chow control differs from the high-fat diet in fibre, phytochemical content and ingredients, not just fat, so differences between groups may be due to something other than fat. Matched purified control diets, such as the AIN-93 formulations, allow cleaner comparisons [20, 21]. Response varies between animals, with some becoming obese and others resisting, so group sizes must allow for wide scatter [19, 22].

The age and sex of the animals deserve similar attention. Most experiments use male mice starting at six to eight weeks of age, since females are partly protected against diet-induced obesity and show smaller and more variable weight gain, a difference linked to oestrogen and fat distribution [19, 20]. Using only males simplifies analysis but limits generality, and there is little published work on catechins in female or aged obese mice. Group sizes of eight to ten animals are common, though experiments with wide response scatter may need more to detect a modest effect, and formal calculation based on pilot variance is the recommended approach [19, 22].

Housing conditions have a larger effect than is often appreciated. Laboratory mice are usually kept at 20 to 22 °C, which is below their thermoneutral zone, so they spend considerable energy maintaining body temperature. Studies of optimal housing temperature argue that mice kept near 30 °C better mimic the thermal environment of humans, and that obesity and energy expenditure results can change substantially with temperature [23]. Because catechins have been proposed to influence thermogenesis and energy expenditure, the thermal environment is directly relevant to the claims made for them, yet it is seldom reported in detail [23, 24]. Even small shifts of a couple of degrees can alter weight gain on a high-fat diet, so a bare statement of room temperature adds little unless cages, bedding and nesting material are also described [23, 24]. Reporting both raw and adjusted values would let readers judge the effect of the adjustment [24].

Measuring energy metabolism properly in mice is technically demanding. Indirect calorimetry gives oxygen consumption and carbon dioxide production, but expressing results per animal, per gram of body weight or per gram of lean mass can lead to different conclusions, and the appropriate approach is to use statistical adjustment for body composition rather than simple ratios [24]. Many catechin studies report only body weight and food intake, which cannot distinguish between reduced intake, reduced absorption and increased expenditure. The studies that do measure calorimetry, faecal energy or both provide the most informative evidence, and their findings are summarised in table 1, with the grouping of the entries shown in fig. 1 [16, 24].

Reporting quality has been a concern across animal research. Reporting standards, of which the ARRIVE guidelines are the best known, and calls for better experimental conduct set out items such as randomisation, blinding, sample size justification, animal characteristics and housing, which allow readers to judge risk of bias [8, 25]. Reviews of animal studies have found that many papers omit these details. In the catechin literature, randomisation and blinding are often unstated, and sample size is rarely justified, which limits confidence in modest effects [22, 25]. Together with unstated housing details, these gaps make it hard to compare results from different centres on an equal footing [23].

Table 1: Selected published studies of green tea catechins in obesity and metabolic research

Study type	Reported finding	Ref.
Dietary tea catechins mice on high-fat diet	Lower body fat and hepatic fat; liver enzymes of lipid catabolism increased.	[13, 14]
Dietary EGCG mice on high-fat diet	Less weight gain and fatty liver; improved glucose tolerance.	[14, 16]
EGCG in diet energy balance study	Greater faecal energy loss and increased fat oxidation.	[16, 24]
Intraperitoneal EGCG rats	Reduced food intake and body weight with endocrine changes.	[26, 27]
EGCG in diabetic rodents glucose handling	Lower blood glucose and insulin; improved diabetic state.	[27, 28]

Study type	Reported finding	Ref.
Green tea with probiotic mice on high-fat diet	Altered gut microbiota, lipid metabolism and inflammation.	[29, 30]
High-dose oral EGCG mice by gavage	Liver injury and mortality at the highest doses.	[15, 31]
Catechin-caffeine extract healthy men	Raised 24-hour energy expenditure and fat oxidation.	[4, 9]
Green tea preparations adults with overweight	Small weight loss, mostly non-significant.	[3, 5]
Green tea extract for one year postmenopausal women	No change in adiposity.	[6, 32]

4. EFFECTS ON BODY WEIGHT AND METABOLISM

A consistent finding in the early rodent studies was that catechin-supplemented high-fat diets produced less body fat. Mice fed a high-fat diet with tea catechins mixed in showed lower body weight, lower visceral and subcutaneous fat, and less hepatic fat than mice fed the diet alone, and the effect increased with dose over a modest range [13]. Dietary EGCG at about 0.3 percent in mice given a high-fat diet for several months reduced weight gain, and also improved fatty liver and glucose tolerance [14]. Other groups using higher concentrations reported lower weight gain within four weeks [16]. The direction of effect is thus reproducible, although the size varies a great deal [13, 14, 16]. Experiments in which treatment began after obesity was established are fewer, and report smaller or slower changes [13, 14].

Effects are not limited to weight. Studies report reduced fasting glucose and insulin, improved glucose tolerance, lower serum triglycerides and cholesterol, and less hepatic steatosis after catechin treatment of obese or diabetic rodents [14, 27, 28]. EGCG supplementation in rodents with diabetes alleviated hyperglycaemia and hyperinsulinaemia in one report [27], and green tea lowered blood glucose in a diabetic mouse strain in another [28]. Hepatic benefits seem especially consistent, and the liver is the organ that sees the highest concentration of absorbed catechins, so a direct hepatic effect is plausible [13, 14]. Such metabolic changes

may run in parallel with the weight effect rather than depend on it, and a few studies report glucose benefits at doses that left body weight unchanged [27, 28]. Liver fat is usually the outcome with the most consistent response.

It is worth asking how much of the weight effect comes from eating less. Some studies show lower food intake after treatment, and intraperitoneal EGCG in rats reduced both intake and body weight in an early report, with changes in hormones that regulate appetite [26]. Yet in mice given catechins by diet, intake was often similar between groups, and body weight differences were attributed to other mechanisms [13, 16]. Palatability is an obvious confounder, since catechins are astringent and bitter, and pair-feeding controls are the cleanest way to deal with it. Few papers include them [16, 26]. Studies of this kind are at their most convincing when body composition is measured directly, because weight alone cannot separate fat loss from changes in water or lean tissue [7, 24].

Where fat is lost matters as much as how much. Several studies of dietary catechins and EGCG report smaller visceral and epididymal fat pads, and some also show reductions in subcutaneous depots, but the relative effect on different depots is rarely compared in a statistically careful way [7, 13, 14]. Visceral fat is more closely linked with insulin resistance and fatty liver in people, so a preferential loss from that depot would be metabolically meaningful. The mouse epididymal pad is the usual surrogate, although it has no exact human counterpart, and its behaviour on a high-fat diet may not mirror that of human intra-abdominal fat [20, 33].

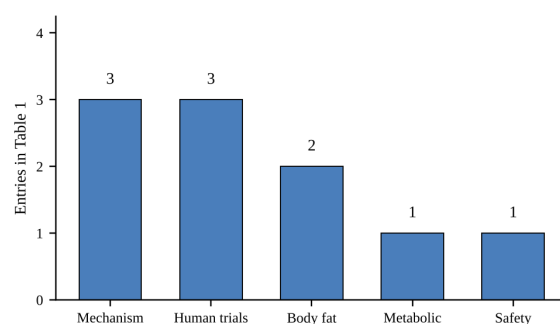


Fig. 1: Number of entries in table 1 by type of evidence

The human translation has been disappointing compared with these preclinical signals. Controlled trials of green tea extracts report small average weight loss, wide differences between individuals, and little effect on fat mass in some populations [3, 5, 6]. A randomised trial of EGCG supplementation in obese adults did not show a clear improvement in insulin sensitivity [32]. Several explanations are offered: the doses in mice, scaled to humans, are often much larger than those achievable with tea; the diet of the mouse is artificial; and human weight is regulated by behaviour and environment in ways the cage cannot reproduce [2, 7, 34]. None of these invalidates the animal work, but together they caution against reading it as a prediction of clinical benefit.

A further reason for caution is that the outcomes measured differ between laboratories. Some report body weight only, some include magnetic resonance or dissection measures of fat pads, and some add histology of liver and adipose tissue. Adipocyte size, macrophage infiltration and crown-like structures offer richer evidence of tissue-level change than weight alone, and studies that include them tend to agree that catechins reduce adipose inflammation [7, 33]. Comparing results across studies is easier when a minimal common set of measures is reported, which is one of the aims of reporting guidelines [8, 25].

5. PROPOSED MECHANISMS

Four mechanisms recur in the literature, and they are not mutually exclusive. The first is reduced energy absorption: in mice fed a high-fat diet with EGCG, faecal energy loss increased, consistent with impaired digestion or absorption of dietary fat [16]. The second is increased fat oxidation, with higher expression of hepatic enzymes of fatty acid beta-oxidation after catechin feeding [13, 16]. The third is increased energy expenditure, supported by human calorimetry with catechin-caffeine mixtures but less clearly shown in mice [9, 24]. The fourth is modulation of the gut microbiota and inflammation, which has attracted much newer work [29, 30, 33]. Which of these dominates probably depends on dose, duration and diet [2, 7].

Much of the intracellular signalling has been traced to AMP-activated protein kinase, a cellular energy sensor that switches on catabolic pathways such as fatty acid oxidation and switches off anabolic ones such as lipogenesis [35]. Catechin treatment has been reported to activate this kinase in liver, muscle and adipose tissue in rodents, with downstream suppression of lipogenic gene expression and increased oxidative capacity [7, 35]. The evidence is mostly correlative, based on phosphorylation of the kinase and its targets, and few studies use genetic models to prove the pathway is necessary. Catechins also inhibit several lipogenic enzymes in vitro, though the concentrations needed are higher than those found in tissue after oral dosing [2, 7].

Appetite and endocrine effects have also been described. Intraperitoneal EGCG reduced food intake and lowered circulating insulin, leptin and other hormones in rats, suggesting a central or endocrine component [26]. Since dietary administration often shows less effect on intake, the relevance of this route to oral exposure is unclear. Inflammation links obesity with insulin resistance, and the idea that chronic low-grade inflammation of adipose tissue drives metabolic disease is well established [33]. Catechins reduce inflammatory markers in several rodent studies, which would add to metabolic benefit independently of weight [7, 33]. Reported effects on appetite hormones in particular should be treated as hypothesis-generating until they are repeated with dietary dosing and appropriate controls [26, 27]. Reproducibility of these measures between laboratories remains to be shown [29, 30].

Hepatic lipid handling is the best documented target. After catechin feeding, the mRNA and activity of enzymes such as acyl-CoA oxidase and medium-chain acyl-CoA dehydrogenase, which control fatty acid beta-oxidation, were raised in mouse liver, and the effect fitted the observed reduction in hepatic and body fat [13]. Other reports describe lower expression of lipogenic genes and less liver triglyceride [14, 35]. Because the liver is exposed to relatively high catechin concentrations after absorption through the portal vein and is also the site of conjugation, it is a plausible

primary site of action, though adipose tissue and muscle may contribute [10, 13].

The gut microbiota is a more recent focus. Mice fed a high-fat diet together with green tea powder and a probiotic strain showed altered microbiota composition, changes in lipid metabolism and lower inflammation compared with the diet alone [29]. Fermented green tea extract likewise reduced obesity-related changes in diet-induced obese mice and shifted bacterial communities [30]. These observations are interesting, but microbiota data are descriptive and sensitive to housing, cage effects and diet, so they show association more than cause. Poorly absorbed catechins reach the colon in quantity, where bacterial transformation yields smaller phenolic metabolites that may themselves be active [29, 30].

Taken as separate lines of evidence, none of these mechanisms has been shown to account for the whole effect, and some may reflect secondary changes that follow reduced adiposity rather than cause it. Studies that combine calorimetry, faecal energy, tissue gene expression and microbiota in the same animals would resolve more than isolated measurements can [7, 24]. For now, the best-supported statement is that catechins act at several sites, with local gut effects and hepatic fat metabolism more consistently demonstrated than systemic thermogenesis in mice [13, 16]. Combined studies of this type are more expensive, but they are the only route to separating cause from consequence [24, 35].

6. SAFETY AND DOSE TRANSLATION

Dose determines whether catechins look beneficial or harmful. In mice, high oral doses of EGCG given by gavage caused liver injury and, at the extreme, death, with raised transaminases and evidence of oxidative stress, while the same total amount spread through the diet was better tolerated [15]. Commentary on this work warned that polyphenols have been presented too optimistically, and that benefits seen at low doses can reverse at high ones [31]. These findings matter for any study that chooses very large dietary concentrations to obtain a strong effect on body weight [14, 15, 31].

Ranges of exposure that are tolerated in a short experiment may be much less safe when sustained, and the narrowness of the margin between dose and harm is perhaps the main reason for caution [12, 15].

Human reports point the same way. Case series and reviews describe liver injury associated with green tea extracts used as slimming supplements, usually concentrated products taken in large amounts or on an empty stomach, with rare severe cases [36, 37]. A systematic review of the human data concluded that green tea infusions are generally well tolerated, but that concentrated extracts giving high daily doses of EGCG have been linked to raised serum transaminases in some people [12]. A broader safety assessment reached a more nuanced view of beverages and extracts, emphasising differences in matrix, dose and timing [36]. Rodent efficacy studies using doses that approach such levels, scaled to humans, therefore carry a safety question that is seldom discussed [12, 36]. Because the reports concern concentrated products and not brewed tea, they should not be taken as evidence against ordinary tea drinking, which has a long record of use [1, 36].

Translating a mouse dose to a human equivalent requires scaling by body surface area, not body weight. The widely used method multiplies the animal dose by the ratio of species-specific conversion factors, which for mouse to human gives a divisor of about twelve [34, 38]. A dose of several hundred milligrams per kilogram of body weight per day in a mouse corresponds to a human intake of tens of milligrams per kilogram, which for an adult would be several grams of EGCG daily, far beyond the amount in a cup of tea. This simple calculation explains much of the gap between rodent and human results, and papers should present it explicitly [34, 38].

Duration is a second issue. Most mouse studies run for 8 to 16 weeks, a large fraction of the animal's adult life but a short time against the decades over which human obesity builds. The question of whether benefits persist, fade because of adaptation, or are offset by toxicity during longer exposure has rarely been addressed [7, 14]. Food-intake

corrections and the use of diets containing catechins from the start of high-fat feeding, as opposed to treatment of established obesity, also produce quite different clinical meaning: prevention is easier than reversal, and most positive studies test prevention [13, 14, 16]. Choosing prevention designs for convenience is understandable, but it should be acknowledged when results are applied to people already living with obesity [7, 14].

7. LIMITATIONS AND FUTURE DIRECTIONS

Limits of the evidence fall into familiar groups. Doses are often high, exposure is rarely measured, and the preparations differ in catechin ratio and caffeine content [2, 14]. Control diets are not always matched, housing temperature is seldom reported, and energy balance is measured in a minority of studies [20, 23, 24]. Reporting follows such items only partially, and publication bias favouring positive results is likely in a field where a single supplement is tested in many laboratories [8, 22, 25]. Human trials have not confirmed the large effects seen in the mouse [3, 5, 6]. Reviewers should weigh these points when interpreting the pooled picture [7]. Studies of this type would be most valuable if conducted independently and registered in advance, as is now expected in human trials [8]. Lack of dose-response information at low, human-relevant doses is the single most important gap [2, 34].

A more useful next phase of research would pair realistic doses with measured exposure, matched purified control diets, thermoneutral or at least reported housing and full energy-balance measures [21, 23, 24]. Preventive and therapeutic designs should be distinguished, and safety markers of liver injury ought to be reported alongside efficacy [12, 15]. Studies of catechin metabolites, and of how the microbiota transforms them, would add mechanistic depth [29, 30]. If these steps are taken, the field can say with more confidence whether green tea catechins have a useful place in obesity prevention or are better regarded as a dietary adjunct of modest importance [4, 7]. None of this requires exotic technology; it needs patient, well-reported experiments that can be repeated elsewhere [8, 25].

Statistical design deserves a specific mention. Many catechin studies compare several dose groups with a control by repeated t tests, ignoring multiplicity, and treat each animal as an independent unit even when animals share cages and so share microbiota and feeding behaviour [25]. Cage effects are especially relevant because mice are coprophagic, and group-housed animals converge in microbial community. Using the cage as the experimental unit, or modelling it as a random effect, would be more defensible. Reanalysis of existing datasets with such methods might change the apparent strength of some reported effects, particularly the smaller ones [22, 25].

8. CONCLUSION

Across the rodent literature, green tea catechins, and EGCG in particular, reduce fat gain and hepatic fat in mice fed high-fat diets, and they often improve glucose handling [13, 14, 16]. Likely explanations include reduced energy absorption, increased fat oxidation, and effects on inflammation and the gut microbiota, though each has been shown more convincingly in some studies than in others [16, 29, 35]. Differences between laboratories in diet, housing and dosing appear to explain much of the variation in how large that benefit looks [20, 23].

The effect sizes seen in mice have not carried over to people, partly because the doses are not achievable with tea, partly because the model differs from human obesity, and partly because high doses raise real liver safety concerns [12, 15, 34]. The sensible reading is that catechins are biologically active and worth studying, not that tea or its extracts will reliably treat obesity. Better dosing, controlled housing and transparent reporting would sharpen the answer [8, 23]. Until those steps are taken, claims should stay measured.

9. ABBREVIATIONS

EGCG-Epigallocatechin gallate, HFD-High-fat diet, AMPK-AMP-activated protein kinase, ARRIVE-Animal Research: Reporting of In Vivo Experiments, AIN-American Institute of Nutrition, COMT-Catechol-O-methyltransferase, MRI-Magnetic resonance imaging, CoA-Coenzyme A

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Nil

11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. Khan N, Mukhtar H. Tea polyphenols for health promotion. *Life Sci* 2007;81:519–33.
2. Wolfram S, Wang Y, Thielecke F. Anti-obesity effects of green tea: from bedside to bench. *Mol Nutr Food Res* 2006;50:176–87.
3. Hursel R, Viechtbauer W, Westerterp-Plantenga MS. The effects of green tea on weight loss and weight maintenance: a meta-analysis. *Int J Obes* 2009;33:956–61.
4. Hursel R, Westerterp-Plantenga MS. Catechin- and caffeine-rich teas for control of body weight in humans. *Am J Clin Nutr* 2013;98(6 Suppl):1682S–93S.
5. Jurgens TM, Whelan AM, Killian L, Doucette S, Kirk S, Foy E. Green tea for weight loss and weight maintenance in overweight or obese adults. *Cochrane Database Syst Rev* 2012;(12):CD008650.
6. Dostal AM, Arikawa A, Espejo L, Kurzer MS. Long-term supplementation of green tea extract does not modify adiposity or bone mineral density in a randomized trial of overweight and obese postmenopausal women. *J Nutr* 2016;146:256–64.
7. Huang J, Wang Y, Xie Z, Zhou Y, Zhang Y, Wan X. The anti-obesity effects of green tea in human intervention and basic molecular studies. *Eur J Clin Nutr* 2014;68:1075–87.
8. Macleod MR, Fisher M, O'Collins V, *et al.* Good laboratory practice: preventing introduction of bias at the bench. *Stroke* 2009;40:e50–2.
9. Dulloo AG, Duret C, Rohrer D, *et al.* Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *Am J Clin Nutr* 1999;70:1040–5.
10. Lee MJ, Maliakal P, Chen L, *et al.* Pharmacokinetics of tea catechins after ingestion of green tea and (–)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability. *Cancer Epidemiol Biomarkers Prev* 2002;11:1025–32.
11. Chow HHS, Cai Y, Hakim IA, *et al.* Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res* 2003;9:3312–9.
12. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults: results of a systematic review. *Regul Toxicol Pharmacol* 2018;95:412–33.
13. Murase T, Nagasawa A, Suzuki J, Hase T, Tokimitsu I. Beneficial effects of tea catechins on diet-induced obesity: stimulation of lipid catabolism in the liver. *Int J Obes* 2002;26:1459–64.
14. Bose M, Lambert JD, Ju J, Reuhl KR, Shapses SA, Yang CS. The major green tea polyphenol, (–)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J Nutr* 2008;138:1677–83.
15. Lambert JD, Kennett MJ, Sang S, Reuhl KR, Ju J, Yang CS. Hepatotoxicity of high oral dose (–)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol* 2010;48:409–16.
16. Klaus S, Pültz S, Thöne-Reineke C, Wolfram S. Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *Int J Obes* 2005;29:615–23.
17. Surwit RS, Feinglos MN, Rodin J, *et al.* Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. *Metabolism* 1995;44:645–51.
18. Collins S, Martin TL, Surwit RS, Robidoux J. Genetic vulnerability to diet-induced obesity in the C57BL/6J mouse: physiological and molecular characteristics. *Physiol Behav* 2004;81:243–8.
19. Wang CY, Liao JK. A mouse model of diet-induced obesity and insulin resistance. *Methods Mol Biol* 2012;821:421–33.
20. West DB, Boozer CN, Moody DL, Atkinson RL. Dietary obesity in nine inbred mouse strains. *Am J Physiol* 1992;262:R1025–32.
21. Reeves PG. Components of the AIN-93 diets as improvements in the AIN-76A diet. *J Nutr* 1997;127(5 Suppl):838S–41S.
22. Charan J, Kantharia ND. How to calculate sample size in animal studies? *J Pharmacol Pharmacother* 2013;4:303–6.

23. Fischer AW, Cannon B, Nedergaard J. Optimal housing temperatures for mice to mimic the thermal environment of humans: an experimental study. *Mol Metab* 2018;7:161–70.
24. Speakman JR. Measuring energy metabolism in the mouse: theoretical, practical, and analytical considerations. *Front Physiol* 2013;4:34.
25. Crossley NA, Sena E, Goehler J, *et al.* Empirical evidence of bias in the design of experimental stroke studies: a metaepidemiologic approach. *Stroke* 2008;39:929–34.
26. Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. *Endocrinology* 2000;141:980–7.
27. Wolfram S, Raederstorff D, Preller M, *et al.* Epigallocatechin gallate supplementation alleviates diabetes in rodents. *J Nutr* 2006;136:2512–8.
28. Tsuneki H, Ishizuka M, Terasawa M, Wu JB, Sasaoka T, Kimura I. Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. *BMC Pharmacol* 2004;4:18.
29. Axling U, Olsson C, Xu J, *et al.* Green tea powder and *Lactobacillus plantarum* affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutr Metab* 2012;9:105.
30. Seo DB, Jeong HW, Cho D, *et al.* Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. *J Med Food* 2015;18:549–56.
31. Lambert JD, Sang S, Yang CS. Possible controversy over dietary polyphenols: benefits vs risks. *Chem Res Toxicol* 2007;20:583–5.
32. Brown AL, Lane J, Coverly J, *et al.* Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. *Br J Nutr* 2009;101:886–94.
33. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–7.
34. Davidson IWF, Parker JC, Beliles RP. Biological basis for extrapolation across mammalian species. *Regul Toxicol Pharmacol* 1986;6:211–37.
35. Hardie DG. AMPK: a key regulator of energy balance in the single cell and the whole organism. *Int J Obes* 2008;32(Suppl 4):S7–12.
36. Dekant W, Fujii K, Shibata E, Morita O, Shimotoyodome A. Safety assessment of green tea based beverages and dried green tea extracts as nutritional supplements. *Toxicol Lett* 2017;277:104–8.
37. Mazzanti G, Menniti-Ippolito F, Moro PA, *et al.* Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009;65:331–41.
38. Boxenbaum H, D'Souza R. Interspecies pharmacokinetic scaling, biological design and neoteny. *Adv Drug Res* 1990;19:139–95.