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ANTIHYPERLIPIDAEMIC EFFECT OF GARCINIA CAMBOGIA EXTRACT IN HIGH-FAT DIET-FED RATS

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Abstract

Garcinia cambogia extract, standardised to hydroxycitric acid, is widely sold for weight control and is often reported to lower body fat and blood lipids in rodents fed high-fat diets. This review summarises published literature on the chemistry, proposed mechanisms, high-fat diet study designs, reported effects on weight and lipids, and safety of the extract in animals and humans. It reports no new experimental data. Rodent studies are broadly consistent in direction but variable in size and often poorly reported, human trials show little or no clinically useful benefit, and case reports of liver injury argue for caution in interpreting the animal findings.

1. INTRODUCTION

Walk into almost any pharmacy and there is a shelf of weight-loss supplements, and *Garcinia cambogia* is rarely missing from it. The dried rind of the fruit, also known as Malabar tamarind, has long been used in South Indian cooking as a souring agent and preservative, and its principal acid, (−)-hydroxycitric acid, was isolated and characterised in the 1960s [1, 2]. Commercial extracts are standardised to this compound, usually as calcium, potassium or mixed salts, and are sold on the promise that they reduce appetite and body fat [3, 4]. The promise rests on a combination of biochemical rationale, rodent experiments and a mixed set of human trials.

Obesity and dyslipidaemia are linked to heart disease and type 2 diabetes, so an oral agent that lowers body fat or blood lipids would be useful if it were safe and effective. Rodents

fed a high-fat diet are the usual first test of such an agent, because they gain weight, accumulate visceral fat and develop raised cholesterol and triglycerides in a way that loosely resembles human metabolic syndrome [5, 6]. The model is cheap and fast, which is both its strength and, as discussed later, its weakness. Many natural-product papers use it, and the quality of reporting varies a great deal.

This article reviews the published literature on the antihyperlipidaemic and anti-obesity effects of *G. cambogia* extract and hydroxycitric acid in rats and mice fed high-fat diets. It reports no new experiments and no new data. The sections cover the chemistry and proposed mechanisms, the design of high-fat diet studies, the reported effects on body weight, fat and lipids, the safety findings in animals and humans, and the limits of the evidence. Human trials are included where they help interpret the animal findings [7, 8].

Traditional use offers some reassurance and some misdirection. The rind has been eaten in curries for generations at low quantities, a pattern very different from taking grams of concentrated extract daily for weight loss [1, 4]. Food-level exposure to the acid is therefore not strong evidence for the safety of a supplement at pharmacological doses, a distinction relevant to both the animal and human literature reviewed here [9, 10].

A note on terms. Hydroxycitric acid exists as several stereoisomers, and only the (−) form from *Garcinia* is biologically active against the target enzyme. Extracts differ in how much of this form they contain and in the salt used, which influences solubility and absorption [1, 4]. When papers refer to a *Garcinia* extract without giving its hydroxycitric acid content, comparison across studies becomes guesswork, a point that recurs throughout this review. Certificates of analysis from suppliers are therefore worth requesting and citing.

2. PHYTOCHEMISTRY AND PROPOSED MECHANISMS

The fruit rind contains organic acids, mainly hydroxycitric acid and its lactone, along with garcinol and related polyisoprenylated benzophenones, xanthones and flavonoids [1, 4]. Hydroxycitric acid can make up a substantial part of the dry rind, but the proportion depends on the species, region and processing. The free acid converts partly to the lactone on heating, and the lactone is much less active, so the way an extract is dried and stored changes its potency. This chemistry explains why commercial products are standardised and why unstandardised crude extracts in animal studies are hard to compare [1, 3].

The best-supported mechanism is inhibition of ATP citrate lyase. This cytosolic enzyme cleaves citrate into acetyl-CoA and oxaloacetate and so supplies the two-carbon units for fatty acid and cholesterol synthesis. Watson and colleagues showed that hydroxycitrate is a competitive inhibitor of the enzyme, and Lowenstein later reported reduced fatty acid synthesis in rat liver after dosing [11, 12]. Sullivan and colleagues extended this to whole-animal studies, finding that rats given hydroxycitrate accumulated less lipid when fed a meal after fasting [13]. The effect depends on the animal being in a lipogenic state, which is relevant to feeding design.

Hydroxycitric acid should be distinguished from citric acid, which has a similar structure but is a substrate for the enzyme rather than an inhibitor. The additional hydroxyl group is what allows the molecule to bind the active site while resisting cleavage, and this structural feature has been used to explain why the compound competes with citrate rather than being metabolised [11, 12]. Sources of the extract also vary, as *G. cambogia* is usually used, but *G. indica* and *G. atroviridis* contain the same acid in different proportions [1, 4].

A second proposed action concerns appetite. In rats, hydroxycitrate reduced food intake in some studies, and the effect was attributed to altered glycogen and energy status or to changes in brain serotonin availability [14, 15]. The human data are less convincing. Mattes and Bormann reported little consistent effect on appetite measures, which fits the view that animals respond more clearly than people [16]. Ishihara and colleagues added another strand by showing that chronic

hydroxycitrate feeding in mice spared carbohydrate and increased lipid oxidation during exercise, hinting at an effect on substrate use beyond lipogenesis [17].

A caveat concerns human lipid biochemistry. In adults eating a mixed diet, de novo lipogenesis from carbohydrate contributes only a small share of body fat, and it rises mainly when carbohydrate intake is very high [18]. Rodents are more lipogenic, so an inhibitor of the pathway can produce larger effects in them than in humans. A high-fat diet, moreover, supplies preformed fat and suppresses hepatic lipogenesis, which makes the rationale for ATP citrate lyase inhibition in these models weaker than usually assumed [5, 6]. Other reported effects, such as altered adipocyte gene expression in obese women, are intriguing but come from small studies [19].

Pharmacokinetic information is thin. Hydroxycitric acid is a hydrophilic tricarboxylic acid that crosses membranes poorly, and it is partly lost as the lactone and by chelation with divalent cations in the gut, particularly calcium and magnesium, so absorption from some salts is limited [1, 4]. Studies of the compound in rats suggest rapid clearance, with a plasma half-life measured in hours, though most work used non-specific assays [3, 15]. Administration before meals is advised on commercial labels, a recommendation consistent with the idea that the compound must be present when citrate is being exported from mitochondria during lipogenesis [11, 13].

3. HIGH-FAT DIET MODELS

Diet-induced obesity models differ in strain, diet composition, duration and sex. C57BL/6J mice gain weight, become hyperinsulinaemic and develop glucose intolerance on a diet rich in fat, as Surwit and colleagues showed in 1988, while Wistar and Sprague-Dawley rats show greater variation in weight gain between individuals [5, 20]. Diets with 40 to 60 percent of energy as fat are common, and the source of the fat, whether lard, beef tallow or vegetable oil, changes the metabolic picture [6]. Bray and Popkin made the broader point that dietary fat intake does influence adiposity, which supports the use of such diets even though the relationship in humans is more complex [21].

The control diet matters as much as the high-fat one. Purified formulations such as AIN-93 define the composition tightly, while many laboratories use grain-based chow whose composition varies by batch and which contains plant phytochemicals that can affect lipid metabolism [6, 22]. If the high-fat diet is purified and the control diet is chow, the comparison confounds fat with everything else in the diet. A well-designed experiment matches the two diets except for fat and fibre, and that detail is easy to miss when reading methods sections [5, 22].

Animals are normally fed the diet for several weeks before treatment to induce obesity, and then the extract is given by oral gavage or mixed into the diet. Gavage allows accurate dosing but is stressful, while dietary admixture lets intake vary with the palatability of the extract, which is itself sour [6, 23]. The dose is often given in milligrams of extract per kilogram, and conversion to a human equivalent using body surface area, following the approach of Reagan-Shaw and colleagues, shows that many rodent doses correspond to far more than the recommended human intake [24]. This does not invalidate the findings, but it limits their clinical meaning.

Common outcome measures include body weight, food intake, weights of epididymal or retroperitoneal fat pads, serum total cholesterol, triglycerides, HDL and LDL cholesterol, and liver histology. Serum LDL is frequently calculated with the Friedewald equation, originally designed for human plasma, which is less well validated in rodents because much cholesterol in rats and mice is carried in HDL [6, 25]. Risk-of-bias tools for animal studies ask for details of randomisation, blinding and sample size, yet many papers in this area omit them, and unblinded measurement of fat pads is a recognised source of bias [26].

Choice of sex and age also affects results. Male rodents are used far more often because they gain weight more readily and avoid oestrous cycle variation, yet female animals respond differently to both the diet and many treatments, so conclusions drawn only from

males may not describe half the population [5, 6]. The Zucker rat study used developing males and reported testicular effects that could not have been detected in females, a reminder that safety conclusions are sex specific [27]. Young animals still growing may respond to a lipogenesis inhibitor differently from adults who have reached a stable weight.

Pair feeding is the control that answers the taste problem, yet it is rare. If treated animals eat less because the extract is unpalatable, any loss of weight or fat could result from lower energy intake and not from enzyme inhibition [14, 23]. Studies that report food intake generally find a small reduction, which cannot be separated from a true anorectic effect without pair-fed controls. Calorimetry, which measures energy expenditure and respiratory exchange ratio, would also test the claim of altered substrate use suggested by the exercise work in mice [6, 17].

4. REPORTED EFFECTS IN RODENTS

Representative animal and human findings are collected in table 1, and fig. 1 shows the number of entries by type of evidence. The earliest rat work found that hydroxycitrate lowered fatty acid synthesis and body fat accumulation, and the later high-fat diet studies largely repeated the pattern [13]. Kim and colleagues fed C57BL/6J mice a high-fat diet with *G. cambogia* extract and reported reduced visceral adiposity, lower body weight gain and improved serum lipids, along with changes in expression of genes involved in fat metabolism [23]. Such results are consistent across several laboratories, though not uniformly strong.

Lipid findings are more variable than weight findings. Reductions in serum triglycerides and total cholesterol are common, and a lowering of LDL with some rise in HDL is sometimes reported, but the effects are inconsistent between papers and often modest [3, 23]. Reviewers of the toxicology and efficacy literature have noted that outcomes differ with dose, diet, strain and extract composition, so a simple summary of efficacy is not possible [3, 9]. The pattern fits what one would expect if the extract had a real but limited effect, magnified in some designs and invisible in others.

Table 1: Representative findings for hydroxycitric acid and Garcinia cambogia extract

Study type	Reported finding	Ref.
ATP citrate lyase Enzyme studies	Hydroxycitrate competitively inhibits the enzyme that supplies acetyl-CoA	[11]
Rat liver Fatty acid synthesis	Lower hepatic lipogenesis and less lipid accumulation after dosing	[12, 13]
Mice, exercise Chronic feeding	Carbohydrate spared and lipid oxidation increased during exercise	[17]
Rats, appetite Feeding studies	Reduced food intake and weight gain in some experiments	[14, 15]
C57BL/6J mice High-fat diet	Less visceral fat and weight gain; improved serum lipids	[23]
Zucker rats High dose	Fat accumulation suppressed but testis toxicity observed	[27]
Mice, high-fat diet Hepatic outcomes	Reduced adiposity but more hepatic collagen and inflammation	[28]
Rats, 90-day study Standardised salt	No adverse effects on organ weights or clinical chemistry reported	[29]
Obese adults Randomised trial	No significant difference in weight loss versus placebo	[7]
Meta-analysis Randomised trials	Small short-term weight difference of doubtful clinical relevance	[8]
Case reports Supplement users	Acute liver injury described, often with multi-ingredient products	[30, 31]

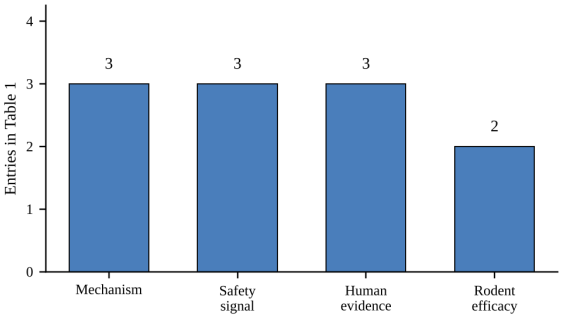


Fig. 1: Number of entries in table 1 by type of evidence

Dose-response data are scarcer than one would hope. Many studies test a single dose, and those that test several often find that the

intermediate dose works as well as the highest, a plateau that suggests the enzyme target is saturated or that absorption is limiting [3, 23]. At very high doses, as in the Zucker rat experiment, benefit is accompanied by harm [27]. A flat or non-monotonic curve like this is hard to reconcile with a simple inhibitor model and may point to uncontrolled variables such as reduced food intake from the sour taste of the extract [9].

Hepatic outcomes deserve attention. Reducing lipogenesis ought to lower liver fat, and some studies show less steatosis in treated animals [3, 23]. Yet Kim and colleagues, in a different set of experiments with mice on a high-fat diet, found that *G. cambogia* attenuated adiposity but increased hepatic collagen accumulation and inflammatory markers, raising the possibility that the extract reduces fat at the cost of liver injury [28]. The conflict between these findings has not been resolved and probably reflects differences in dose, extract and diet. It also gives context to the later human case reports of liver injury [30, 31].

Experiments in genetically obese animals add to the picture. In young Zucker rats, a high dose of *G. cambogia* suppressed fat accumulation but was toxic to the testis, with atrophy of seminiferous tubules reported [27]. This is among the more cited findings in the toxicology literature, and it is relevant to the dose-response question: effects on fat appeared at doses close to those producing testicular damage. Doses used in many diet-induced obesity studies are lower, but the therapeutic margin of the extract in rodents is evidently not wide [9, 27].

Effects on glucose metabolism have received less attention than lipids but deserve mention, because dyslipidaemia in obesity is usually part of a wider insulin-resistant state. Some studies report lower fasting glucose or improved insulin sensitivity in treated mice and rats fed a high-fat diet, while others find no difference, and a few suggest worse glycaemic control at high doses [3, 23, 28]. This inconsistency parallels the human literature, where combination products with chromium or Gymnema reported changes in lipid and glucose indices that cannot be assigned to Garcinia itself [10, 32].

5. SAFETY AND TRANSLATION TO HUMANS

Toxicity studies of standardised extracts have mostly been reassuring. A 90-day study in rats of a calcium-potassium salt of hydroxycitric acid found no adverse effects on body weight, organ weights, haematology, clinical chemistry or histology at the doses tested [29], and complementary work on the same extract described its safety and appetite-suppressing activity [15]. Acute oral toxicity in rodents is commonly screened with stepwise dosing schemes such as the acute toxic class method, which classifies a substance using few animals [33]. Reviews of in vitro and in vivo toxicity conclude that the compound has a reasonable margin at normal doses, with exceptions at very high doses [9].

Human trials are far less encouraging than the animal literature. Heymsfield and colleagues randomised obese adults to Garcinia extract or placebo for twelve weeks with a low-fat diet and found no significant difference in weight loss or fat mass [7]. Other trials from Japan and the United States reported small benefits, including reduced visceral fat in a study using a specific extract, and combination products containing chromium and other extracts have also been tested [32, 34]. A systematic review pooling randomised trials found a small short-term difference in weight in favour of the extract, of doubtful clinical importance, and noted that the best-designed trials were negative [8, 10].

Case reports of liver injury have changed the safety discussion. Reviews of acute liver injury after Garcinia-containing supplements describe a series of patients with hepatocellular damage, in some cases severe enough to need transplantation, although many products also contained other ingredients [30, 31]. Causality is hard to establish, because supplements are mixtures and lack batch traceability, and an individual susceptibility factor is plausible. Even so, the pattern is sufficient for caution and agrees with the hepatic findings in some mouse studies [28, 30]. The extract cannot be described as free of risk, whatever its traditional use as a food ingredient.

Regulatory attention has been limited but not absent. Supplements containing Garcinia are sold as foods or dietary products in many countries and do not undergo the premarket efficacy review applied to medicines, so manufacturing quality and labelling are the responsibility of the producer [10, 30]. Reports of liver injury have prompted warnings in several jurisdictions, and clinicians are advised to ask about supplement use in patients with unexplained hepatitis [30, 31]. For pharmacists, the relevant message is to look for standardised hydroxycitric acid content, avoid multi-ingredient mixtures where possible and counsel patients that evidence of benefit is modest [8, 10].

Put simply, the gap between animals and people has several plausible explanations: rodents rely more on de novo lipogenesis, doses in animals are larger in relation to body mass, and trial participants differ in diet, adherence and baseline adiposity [8, 18, 24]. A further explanation is bioavailability. Hydroxycitric acid is a polar compound absorbed poorly and quickly cleared, and plasma levels in humans after typical doses may fall below those needed to inhibit the enzyme [1, 3]. These possibilities have not been tested head to head, which is a clear opening for pharmacokinetic work.

6. LIMITATIONS AND FUTURE DIRECTIONS

The first limitation is the quality of the underlying papers. Extract identity and hydroxycitric acid content are often not stated, controls are not matched for diet composition, sample sizes are small and blinding is seldom reported [3, 5, 22, 26]. Dosing frequently exceeds a human-equivalent dose, and few experiments pair efficacy outcomes with toxicity endpoints in the same animals [9, 24]. Outcome definitions vary, and lipid assays or calculations such as the Friedewald equation may not suit rodent plasma [6, 25]. As a result the pooled picture is blurred, and conclusions drawn from any single paper should be modest. Journals could help by asking authors to address each risk-of-bias item at submission [26].

Better studies are straightforward to describe. They would use a characterised, standardised extract with stated hydroxycitric acid content, a purified matched control diet, pre-registered endpoints and blinded assessment, and would include liver histology and fibrosis markers alongside lipids [23, 28]. Dose-ranging should span human-equivalent exposures, with pharmacokinetic sampling to link dose and effect [1, 24]. A systematic review of the animal evidence would help estimate the real size of the effect. Until then, the antihyperlipidaemic claims for *Garcinia cambogia* rest on suggestive animal findings and unconvincing human data [7, 8, 10].

7. CONCLUSION

The literature supports a biochemical rationale for Garcinia cambogia extract: hydroxycitric acid inhibits ATP citrate lyase, and in rodents it can lower lipogenesis, visceral fat and serum lipids [11, 12, 13, 23]. Findings in high-fat diet models are consistent in direction but modest, dependent on dose and extract and weakly reported, and some experiments report hepatic or testicular harm at higher doses [27, 28]. The strongest evidence of toxicity comes from high-dose animal work and from human case reports, whereas standardised extracts at moderate doses were well tolerated in a 90-day rat study [29, 30, 31].

For people, the evidence of benefit is weak. Randomised trials and meta-analysis show at most a small short-term effect on weight [7, 8, 10], and the human relevance of the rodent models is limited by differences in lipogenesis, dose and exposure [18, 24]. Future work should use standardised extracts, matched diets, human-equivalent doses and liver endpoints, and should report in enough detail for risk-of-bias assessment [3, 9, 26]. Until such studies exist, the claim that the extract controls dyslipidaemia is better regarded as unproven than disproved.

8. ABBREVIATIONS

HCA-Hydroxycitric acid, HFD-High-fat diet, ACL-ATP citrate lyase, LDL-Low-density lipoprotein, HDL-High-density lipoprotein, OECD-Organisation for Economic Co-operation and Development, AIN-American Institute of Nutrition

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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