

Obesity is now a major concern in the Western world, as it can lead to health problems such as diabetes, cardiovascular disease, hypertension and some forms of cancer. Here, Richard A Collins looks at the efficacy of hydroxycitric acid, one of the components in various over-the-counter weight-loss formulations and appetite-suppressor products.

Hydroxycitric acid and weight loss

Losing weight has become a modern-day obsession. Regardless of the personal reasons for wanting to lose weight, there is certainly a need for wider concern about obesity and being overweight. A person whose body mass index (BMI) is greater than 25 kg/m² is defined as overweight, and over 30 kg/m² is regarded as obese. Globally, there are more than one billion overweight adults,¹ of whom at least 300 million are obese.

Childhood obesity is already epidemic in some areas and is on the rise in others. Worldwide, about 22 million children under five years of age are overweight. Obesity and overweight pose a major risk for chronic diseases and disability, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and certain forms of cancer.

In the developed world, several factors contribute to the increase in the number of overweight and obese individuals. Busy schedules do not allow time for cooking healthy meals or participating in regular exercise or sporting activities. Energy-dense food high in saturated fats and sugars are easily and cheaply available.

Without adequate prevention and treatment of obesity, government agencies have suggested that the direct and indirect costs associated with obesity may overwhelm

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the healthcare system.² Obesity places an enormous financial burden on the health service, with the direct costs being at least £500 million per year.³ The cost of obesity-related healthcare varies with the degree of obesity. Overall, the healthcare costs for a person whose BMI is >40 kg/m² are double those of a person of normal weight.⁴

Many diets have been proposed to induce weight loss and it is impossible to review the benefits or otherwise of the vast number of dietary regimes introduced over the decades. For those unable to stick to a diet, there are several pharmacologically active compounds that promote weight loss. For example, sibutramine blocks the re-uptake of serotonin and norepinephrine, both of which help regulate the sense of fullness, and this results in reduced food intake.

In contrast, orlistat is an inhibitor of gastrointestinal lipases. It acts in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue sites of gastric and pancreatic lipases. Thus, the inactivated enzymes are unavailable to hydrolyse dietary fat (ie triglycerides) into absorbable free fatty acids and monoglycerides, which may have a positive effect on weight control. Systemic absorption of the drug is not needed for activity. At the recommended therapeutic dose (120 mg, three times a day), orlistat inhibits dietary fat absorption by approximately 30%.

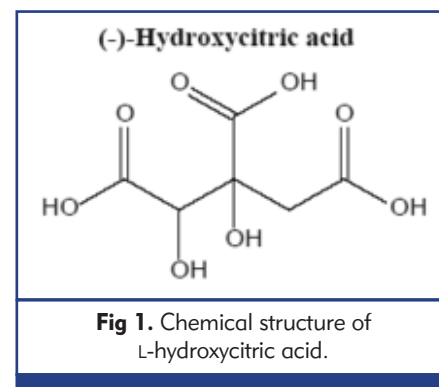
‘Obesity and overweight are factors that pose a major risk for type 2 diabetes, cardiovascular disease, hypertension and stroke’

However, many other compounds that induce weight loss are illegal (amphetamines), dangerous (fenfluramine, ephedra), addictive (phentermine, clobenzorex), experimental (opioid antagonists, amylin) or are indicated for other conditions (fluoxetine [Prozac] – an antidepressant). Few detailed studies on the safety or efficacy of other potentially useful compounds are available.

One of the better-studied compounds is hydroxycitric acid (HCA, Fig 1), the laevorotatory optical isomer (L-hydroxycitric acid or [-]-hydroxycitric acid) of which has been discussed as a potentially safe and effective pharmacological intervention for obesity for at least 30 years.⁵

Hydroxycitric acid

Hydroxycitric acid is purported to be one of the active components in various over-the-



counter weight-loss formulations and appetite-suppressor products. It is obtained from the rind of the fruit of *Garcinia cambogia* (also known as brindal berry, Gorikapuli and, incorrectly, as Malabar tamarind; Fig 2). After harvesting and drying, the rind contains up to 30% by weight of HCA.

Hydroxycitric acid can be purified from the rind by extraction into water at room temperature. The crude extract is loaded on an anion exchange to adsorb HCA, which is eluted with sodium/potassium hydroxide. This fraction is then passed through a cation exchange column to obtain the free acid. The free acid is considered to be the biologically active form. However, the acid is unstable and converts readily to the more stable lactone.

In consumer products, the free acid is often stabilised by forming potassium, sodium or calcium salts of HCA. The calcium and magnesium salts of HCA are only sparingly soluble in water and are not well absorbed in the gastrointestinal tract.

In a recent study, the peak plasma level of hydroxycitrate was 8.4 µg/mL two hours after the oral administration of 2 g *G. cambogia* extract to normal subjects.⁶ Hydroxycitric acid can be broken down by bile acids and fats in the intestine and can bind to fibre, pectin and other substances in the diet or secreted during digestion.

Hydroxycitric acid is an extremely popular dietary supplement. Between March 2000 and September 2003, 225 tonnes of HCA, *G. cambogia* and *G. cambogia* extract were imported into the United States.⁷

Safety

G. cambogia extracts are usually standardised to contain 50% (w/w) HCA. The recommended daily dose of *G. cambogia* extract is 4500–6000 mg per day (ie 2250–3000 mg HCA per day). Since 1994, dietary supplements have been regulated by the Dietary Supplement Health and Education Act in the USA. For dietary supplements marketed before October 1994, no proof of safety is required for them to remain on the market.

Despite this, distributors in the USA include contraindications for using HCA in persons with diabetes, Alzheimer's disease or dementia or in those who are pregnant or lactating. Potential drug interactions include interference with anti-arrhythmics and calcium-channel blockers, antagonism of β-adrenoreceptor blockers, potentiation of cardiac glycosides, increased risk of hypokalaemia, and risk of arrhythmia when combined with depolarising muscle relaxants or terfenadine.

Studies failed to demonstrate any changes in hepatic and testicular peroxidation, DNA fragmentation, histopathological changes, haematology or clinical chemistry in rats whose feed was supplemented with 5% (w/w) HCA-containing commercial product (60% potassium-calcium salt) for 90 days.^{8,9}



Fig 2. *Garcinia cambogia*, is a small to medium-sized evergreen tree native to south-east Asia, particularly southern India and Sri Lanka, where it thrives in moist forests. The precise identity of the tree is unclear, as different taxonomic sources indicate that *G. cambogia* could be one of several separate species – *G. quaesita*, *G. zeylanica* or *G. hanburyi*. The tree is a member of the Guttiferae family that includes the mangosteen and St John's wort. The tree produces an orange-sized fruit that varies in colour from yellowish to purple. The sour-tasting fruit and rind are also used as a condiment and to cure fish.

In Indian traditional medicine, *G. cambogia* is prescribed for oedema, delayed menstruation, constipation, rheumatism and intestinal parasites.

Proposed actions

Hydroxycitric acid has several proposed actions that may be useful in promoting weight loss, including inhibition of fatty acid synthesis, appetite suppression and the increase of thermogenesis/fat oxidation

Inhibiting fatty acid synthesis

Hydroxycitric acid is a potent competitive, reversible inhibitor of ATP-citrate lyase (also known as ATP citrate synthase, citrate cleavage enzyme) *in vitro*, and an inhibitor of fatty acid synthesis in rat liver *in vivo*.^{10,11} ATP citrate lyase is a cytosolic enzyme required for the synthesis of fatty acids and catalyses the following reaction: citrate + CoA + ATP → oxaloacetate + acetyl-CoA + ADP + phosphate.

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Acetyl-CoA is the basic building block of fatty acids. It is produced by oxidation of glucose obtained from carbohydrates in the diet via the tricarboxylic acid (TCA) cycle or by oxidation of fatty acids. Both activities take place in the mitochondria and cytoplasmic acetyl-CoA is ultimately derived from citrate exported across the mitochondrial membrane (Fig 3).

Inhibiting production of acetyl-CoA would also be expected to deplete the concentrations of subsequent metabolites in the fatty acid synthetic pathway. The second metabolite in the pathway, formed from acetyl-CoA, is malonyl-CoA. This is an inhibitor of the enzyme carnitine acyltransferase, which is needed for the oxidation of fat. Therefore, it is proposed that reducing malonyl-CoA formation with HCA might stimulate fat metabolism.

Numerous animal studies have demonstrated that HCA can reduce weight gain and that inhibiting fat synthesis is the likely mechanism for the observed effect. For example, male rats ($n=24$) had restricted access to food (10 g/day) for 10 days followed by *ad libitum* energy-rich diet for the next 10 days. Half of the rats were supplemented with HCA (3 g/day). Overall, HCA reduced body weight regain after substantial body weight loss; an effect the authors presumed to be due to the inhibiting effect of HCA on lipogenesis.¹² In human studies, however, ingestion of HCA at 6–30 times the recommended dose did not increase fat oxidation.¹³

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Appetite suppression

Regulation of appetite is a complex process that is not fully understood. It consists of both central and peripheral elements and involves the integration by the brain of a variety of signals from peripheral organs transmitted by neurotransmitters, peptides, hormones and metabolites.¹⁴ Most anorectic drugs act by central mechanisms and have many disadvantages that include limited effectiveness, side effects on the central nervous system, the development of tolerance, abuse potential, and rebound hyperphagia (over-eating) on discontinuation of treatment.

Several appetite-modulating agents have been tested in animals that act by peripheral mechanisms and do not produce tolerance or rebound hyperphagia, which suggests that peripherally acting anorectic drugs may provide new therapeutic approaches to disorders of appetite regulation in humans. A patent for the use of HCA as an appetite suppressant and an inducer of weight loss was issued in 1998.¹⁵

Early studies on obese rats and mice indicated that HCA decreased food intake and body weight gain. Body lipid levels decreased but body protein levels remained unchanged. In contrast, citrate had no such effect.¹⁶ In genetically obese Zucker rats, administration of HCA in the diet for 39 days reduced food intake and body weight but had no effect on percentage of body fat.¹⁷

A study compared 42 adults taking 1.2 g/day HCA for 12 weeks with 47 adults taking placebo on weight loss and appetite suppression. Both groups lost weight, with the HCA group showing a significantly greater reduction (3.7 ± 3.1 kg vs 2.4 ± 2.9 kg). However, there was no difference in appetite variables and the study did not support a satiety effect of HCA.¹⁸ The lack of effect of HCA on satiety was supported in a separate trial on 11 overweight males receiving 500 mg HCA per day for two weeks.^{19,20} Furthermore, satiety was unaffected in 24 adults receiving 900 mg/day HCA for two weeks compared with placebo, while 24-hour energy intake was decreased by 15–30%.²¹

Peripheral and central increases in serotonin after feeding are implicated in satiety. An HCA-containing commercial dietary supplement up-regulated the

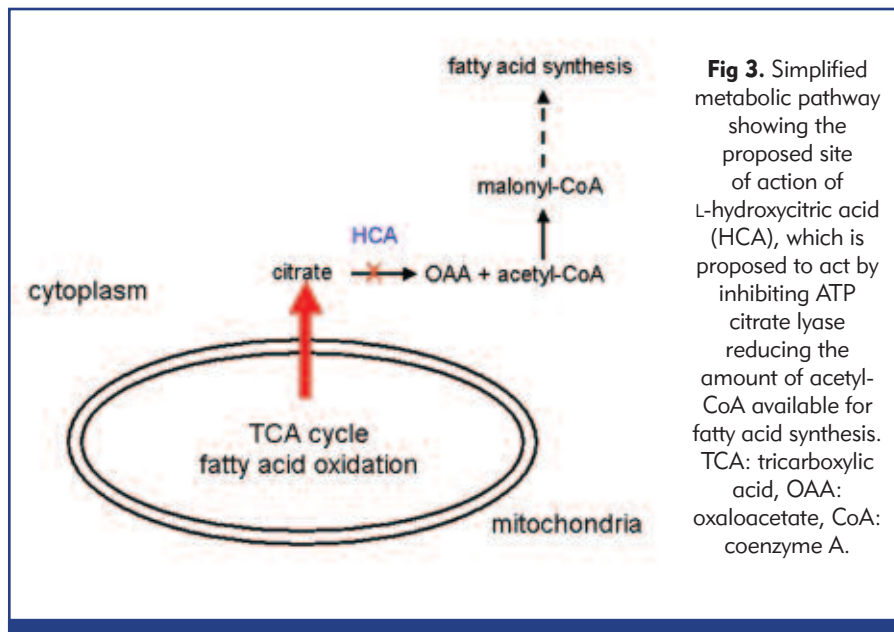


Fig 3. Simplified metabolic pathway showing the proposed site of action of L-hydroxycitric acid (HCA), which is proposed to act by inhibiting ATP citrate lyase reducing the amount of acetyl-CoA available for fatty acid synthesis. TCA: tricarboxylic acid, OAA: oxaloacetate, CoA: coenzyme A.

expression of serotonin receptor genes in abdominal fat tissues of rats fed low-dose HCA.²² In human subjects receiving 2.8 g HCA per day for eight weeks, serum serotonin concentrations increased by 44.5%.²³

Thermogenesis

Thermogenesis is the metabolism of fat or other compounds to produce heat rather than metabolic energy in the form of ATP. Thermogenesis occurs in specialised fatty tissue known as brown adipose tissue (brown fat). However, it is unclear how HCA exerts any stimulatory effect on brown fat.²⁴ Proposed mechanisms have not been validated and detailed metabolic studies on this interesting hypothesis have not been conducted.

Conversely, oxidation of fat to produce metabolic energy occurs throughout the body. Fat oxidation was increased significantly by short-term administration of HCA (250 mg/day for five days), and carbohydrate oxidation was significantly decreased ($P < 0.05$) during exercise.²⁵ Similar results were obtained in six untrained women receiving an identical course of HCA.²⁶

The effects of HCA on fat oxidation during moderately intensity exercise in untrained men were also examined.²⁷ Six subjects ingested 500 mg HCA or a placebo for five

days and performed endurance exercise. Blood free fatty acid concentrations increased significantly and the respiratory exchange ratio (ratio of the amount of carbon dioxide produced by the body to the amount of oxygen consumed) decreased following HCA ingestion, suggesting that short-term HCA ingestion increases fat oxidation in untrained men.

Evidence from trials

It is generally accepted that evidence of efficacy for pharmacological interventions is demonstrated unequivocally by randomised double-blind, placebo-controlled trial. The fact that such trials have been performed only rarely on compounds ingested with such frequency and at such high doses for a condition that may lead to serious adverse health consequences is mystifying.

Such a trial was performed on 135 overweight men and women receiving 1500 mg HCA per day ($n = 66$) or placebo ($n = 69$) for 12 weeks.²⁸ In addition, both groups were prescribed a high-fibre, low-energy diet. About two-thirds of subjects in each group completed the trial. Subjects in each group lost a significant amount of weight during the 12-week treatment period ($P < 0.001$); however, the between-group weight loss differences were not statistically significant (mean \pm SD: 3.2 ± 3.3 kg vs 4.1 ± 3.9 kg; $P = 0.14$).

There were no significant differences in estimated percentage of body fat mass loss between treatment groups, and the fraction of weight loss as fat was not influenced by the treatment group. The authors concluded that *G. cambogia* failed to produce significant weight loss and fat mass loss beyond that observed with placebo.

An eight-week randomised, double-blind, placebo-controlled trial in 60 moderately obese subjects (BMI > 26 kg/m²) was conducted in which HCA (2.8 g/day in three equal doses, given 30–60 minutes before

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meals) was compared with placebo. All subjects received a 2000 kcal diet/day and undertook supervised walking.

At the end of the trial, body weight and BMI decreased by 5–6% in the HCA group. Food intake, total cholesterol, low-density lipoprotein, triglyceride and serum leptin levels were reduced significantly following HCA supplementation. In contrast, high-density lipoproteins and excretion of urinary fat metabolites increased with HCA. A marginal or non-significant effect was seen in all parameters in the placebo group.²⁹ Similar weight loss and beneficial effects on blood profiles were observed in studies of 82 obese subjects (BMI 30–50.8 kg/m²).²³

Conclusions

Hydroxycitric acid has demonstrable inhibitory effects on the enzyme primarily responsible for fatty acid synthesis *in vitro*. However, equivocal results have been demonstrated in *in vivo* studies in both animals and humans. The pathway(s) responsible for the actions of HCA have not been fully elucidated.

The rationale for taking HCA alone in order to reduce weight is flawed. First, energy consumed as carbohydrates, for example, would not disappear simply because it could not be converted into fat, it would be channelled to other metabolic pathways such as glycogen storage. Second, people become overweight because too much fat is consumed in the diet, not because too much fat is synthesised in the body.

The only sure way of losing excess weight is to reduce energy intake and increase energy expenditure through some form of exercise. The magic potion that allows food to be consumed with no consequences on weight gain has yet to be invented.

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