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Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the risk associated with the consumption of food supplements that contain *Garcinia gummi-gutta* as an ingredient

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Working group

Rosa María Giner Pons (Coordinator), Álvaro Daschner, Francisco José Morales Navas, María del Puy Portillo Baquedano, Magdalena Rafecas Martínez, María José Ruiz Leal, Pau Talens Oliag

Scientific Committee

Carlos Alonso Calleja
Universidad de León

Montaña Cámara Hurtado
Universidad Complutense de Madrid

Álvaro Daschner
Hospital de La Princesa de Madrid

Pablo Fernández Escámez
Universidad Politécnica de Cartagena

Carlos Manuel Franco Abuín
Universidad de Santiago de Compostela

Rosa María Giner Pons
Universitat de València

Elena González Fandos
Universidad de La Rioja

María José González Muñoz
Universidad de Alcalá de Henares

Esther López García
Universidad Autónoma de Madrid

Jordi Mañes Vinuesa
Universitat de València

Sonia Marín Sillué
Universitat de Lleida

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Universidad de Navarra

Francisco José Morales Navas
Consejo Superior de Investigaciones Científicas

Victoria Moreno Arribas
Consejo Superior de Investigaciones Científicas

María del Puy Portillo Baquedano
Universidad del País Vasco

Magdalena Rafecas Martínez
Universitat de Barcelona

David Rodríguez Lázaro
Universidad de Burgos

Carmen Rubio Armendáriz
Universidad de La Laguna

María José Ruiz Leal
Universitat de València

Pau Talens Oliag
Universitat Politècnica de València

Technical Secretary
Vicente Calderón Pascual

Abstract

Garcinia or Malabar tamarind (*Garcinia gummi-gutta*) has traditionally been used as flavouring and has been marketed as a food supplement for decreasing appetite and weight loss.

The rind or pericarp of the garcinia fruit contains α,β-dihydroxy-tricarboxylic acid or hydroxycitric acid (HCA) as an active ingredient, which represents 20-30 % of the dry weight and is responsible for anti-obesity properties attributed to it.

Several authors have linked the consumption of supplements containing *Garcinia gummi-gutta* or hydroxycitric acid to side effects such as hepatotoxicity, nephropathy, cardiovascular toxicity, hypomania or serotonin toxicity and psychosis.

The Scientific Committee deems it necessary for health professionals, researchers and citizens to report the serious adverse effects of food supplements to the corresponding institutions. Furthermore, regulatory authorities must develop post-marketing monitoring systems and enforce

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European Union legislation requiring food business operators to ensure that the food they sell is safe.

There is sufficient clinical evidence to establish a causal association between the consumption of garcinia and the duration of treatment, and the development of acute liver injury, with a clear improvement in liver function after removing the garcinia food supplement.

The progress of patients with depression or occasional episodes of hypomania that consume garcinia should be monitored, as it may worsen their situation. An improvement of manic symptoms has been observed following the removal of the garcinia supplement.

More studies are needed to support the effectiveness and long-term benefits or adverse effects of garcinia supplements in over weight treatment.

Key words

Hydroxycitric acid, food supplements, *Garcinia gummi-gutta*.

1. Introduction

Garcinias are trees or shrubs known for their fruit, which is of nutritional and medicinal interest, that belong to the Clusiaceae family and are native to Asia, Australia, tropical and southern Africa, and Polynesia. Of the 250 species described, the main ones grown in tropical countries are *Garcinia gummi-gutta* (L.) Roxb. (Malabar tamarind), *G. mangostana* L. (mangosteen or purple mangosteen) and *G. indica* Choisy (kokum) (Murthy et al., 2018).

Garcinia or Malabar tamarind is the common name of the botanical species *Garcinia gummi-gutta* (L.) Roxb. (Synonym: *Garcinia cambogia* (Gaertn.) Desr.). It is a species native to southern India that is found in Sri Lanka and Nepal, though it has also been introduced into other tropical and subtropical regions of Asia, including China, Malaysia and the Philippines. Its fruits are small (about 5 cm in diameter with 6-8 grooves), edible and acidic (rich in organic malic and hydroxycitric acids) and are used as a preservative and flavouring agent. The sun-dried rind of the fruits is used as a condiment in curry instead of lime or tamarind in the Malabar regions of India, hence its popular name. The fruit extract has been used traditionally to treat rheumatism and gastrointestinal conditions. In veterinary medicine it has been used to treat oral diseases in cattle (Murthy et al., 2018).

The rind or pericarp of the fruit contains as active ingredient α,β-dihydroxy-tricarboxylic acid or (-)-hydroxycitric acid (HCA), which accounts for 20-30 % of the dry weight, and which is responsible for the anti-obesity properties attributed to it. Moreover, it contains isomers II, III and IV of HCA, polyisoprenylated benzophenones such as gutiferones I, N, J, K, M and N, polyisoprenylated xanthones such as oxygutiferones I, K, K2 and M, and amino acids (Semwal et al., 2015).

Garcinia has traditionally been used as a flavouring agent and has been marketed as a food supplement to reduce appetite, lose weight, lower cholesterol levels and regulate glycaemia.

Several studies have linked the standardised garcinia (GC) extract, which is 50-60 % (-)-HCA, or (-)-HCA itself, with anti-obesity activity, which includes a reduction in intake of food and loss of body fat. These effects are associated with the regulation of serotonin levels, which are related to satiety, as well as metabolic changes, such as an increase in fat oxidation and a decrease in lipogenesis.

A large number of food supplements containing GC/(-)-HCA are currently marketed to reduce weight, despite the possible toxicity associated with their regular use.

The safety of garcinia is therefore questioned. On the one hand, most studies on supplements containing GC have not detected significant toxic effects of GC and/or (-)-HCA. The NOAEL (no observed adverse effect level) of 4000 mg/day for (-)-HCA was estimated by Hayamizu et al. (2002) when they observed no adverse effects in 44 healthy volunteers who received that dose. When they administered sequentially higher doses of up to 3000 mg/day of (-)-HCA for 10 days, they also observed no clinical changes (serum parameters); hence they concluded that the GC equivalent to 3000 mg/day of (-)-HCA was safe in healthy individuals (Hayamizu et al., 2002). Later, in a review by Chuah et al. (2012) a NOAEL of up to 2800 mg/day of (-)-HCA was indicated, suggesting that its use is safe.

It is important to note that the majority of alerts have been related to formulations with multiple ingredients containing GC/(-)-HCA as an active ingredient, as well as other compounds, hence the toxic effect cannot be attributed to a specific ingredient.

However, though there are discrepancies and most studies have limitations, associations have been observed with sufficient scientific evidence of causality between the consumption of GC/(-)-HCA and hepatotoxicity, nephropathy, cardiomyopathy, serotonin toxicity and psychosis, among other things.

Therefore, the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) has been asked to perform a risk assessment associated with the consumption of food supplements containing *Garcinia gummi-gutta* (L.) Roxb. (*G. cambogia*) as an ingredient, to be able to take actions to manage and, occasionally, to reject notifications for the marketing in Spain of those food supplements that exceed the level considered safe.

In this report, we review the evidence of the possible toxicity of the supplements with GC/(-)-HCA.

2. Nutritional Information

From a nutritional point of view, the analysis of garcinia fruits shows a high carbohydrate content. According to Murthy et al. (2018), the composition of the garcinia fruit is as follows: 86.90 % moisture, 0.28 % protein, 0.21 % fat, 8.60 % sugars (of which 5.92 % are reducing agents), 3.10 % fibre, 0.49 % minerals, traces of vitamin C and iron, 2.10 mg of sodium and 169.00 mg of potassium.

On the other hand, the elementary analysis of the garcinia fruit and its commercial products has been shown to contain appreciable amounts of the main nutritional elements Na, K, Mg, Ca, as well as the essential trace elements such as Co, Cr, Cu, Mo , Ni, Se, V, and Zn, hence they are a source of minerals. In addition, the toxic trace elements detected, such as As, Cd and Pb, are within safe limits and at concentrations below tolerable intake values established by FAO/WHO (Food and Agriculture Organization/World Health Organization) (Jamila et al., 2019).

3. Biological activity

The biological activity of garcinia is related to the ability of (-)-HCA to inhibit lipogenesis, triglycerides and cholesterol synthesis, and to stimulate hepatic glycogenesis, promoting energy expenditure. (-)-HCA is a competitive inhibitor of adenosine triphosphate (ATP)-citrate lyase, an enzyme that catalyses the extramitochondrial breakdown of citrate into oxalacetate and acetyl-CoA, thus limiting the availability of acetyl-CoA, a compound that plays a key role in the synthesis of fatty acids in carbohydrate-rich diets.

In *in vitro* studies it has been observed that (-)-HCA inhibits the synthesis of fatty acids (Jena et al., 2002). Specifically, in isolated hepatocytes, (-)-HCA inhibits the synthesis of fatty acids from glucose, but not from acetate. Therefore, (-)-HCA is a lipogenesis inhibitor only if cytoplasmic acetyl-CoA is produced by ATP-citrate lyase. Despite this, the synthesis of fatty acids could continue as long as acetate, another acetyl-CoA precursor, was available. By reducing the synthesis of acetyl-CoA, synthesis of malonyl-CoA is reduced, due to reduction of the negative feedback of carnitine acyltransferase. This causes an increase in lipid transport in the mitochondria and inefficient oxidation, which promotes the formation of ketone bodies, which pass into the bloodstream, thus reaching the brain, where they constitute an energy reserve in the event of fasting (Jena et al., 2002).

In animal experiments, chronic oral administration of (-)-HCA to rats significantly reduces food intake in the first hour after administration, as well as body weight and cholesterol, triglyceride

and fatty acid concentrations. Upon assessing the acute and chronic effects of (-)-HCA on energy metabolism in mice (Ishihara et al., 2000), it was observed that oral administration of a 10 mg dose increased the serum concentration of free fatty acids and glycogen concentration in skeletal muscle. Chronic administration of 20 mg of (-)-HCA for 25 days improved endurance exercise, possibly due to the reduction in glycogen consumption caused by increasing lipid oxidation. In a cross-sectional study in which six sedentary women received 250 mg of (-)-HCA for 5 days, 2 hours before exercise, (-)-HCA reduced the respiratory quotient and glycogen use over 1 hour's exercise and increased the sports activity time until exhaustion against the placebo (Lim et al., 2003). In six athletes who received the same dose, an increase in fat oxidation and a decrease in carbohydrate oxidation were observed, compared to the placebo (Lim et al., 2002).

(-)-HCA's hepatotoxicity mechanism is not completely elucidated. A study conducted in Houston (United States) by Asghar et al. (2007) showed that treating obese rats for 90 days with a dietary supplement of up to 2500 mg/kg b.w./day ((-)-HCA-SX, 50 % (-)-HCA calcium and potassium salt, more soluble and with greater bioavailability than calcium salt) reduced food intake, weight gain, inflammation, oxidative stress and insulin resistance, without causing adverse effects. Another study in rodents showed that the oral LD_{50} of (-)-HCA-SX was greater than 5000 mg/kg. However, upon assessing the effect of long-term GC in obese mice, contradictory results were observed (Kim et al., 2013). Supplementation with GC regulated weight control, significantly reducing the accumulation of visceral fat and adipocyte size by inhibition of fatty acid synthesis and increased β-oxidation of fatty acids, but increased hepatic collagen accumulation, lipid peroxidation, mRNA levels of genes related to oxidative stress (superoxide dismutase and glutathione peroxidase) and the inflammatory response. In addition, mice supplemented with GC showed liver failure, with elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Oxidative stress plays an important role in the progression of steatohepatitis and hepatocellular injury. In fact, reactive oxygen species can damage DNA, lipids and proteins, inducing necrosis and apoptosis of hepatocytes and promoting the inflammatory response. Clouatre and Preuss (2013) proposed that (-)-HCA protects against liver toxicity associated with the administration of ethanol and dexamethasone, and keeps ALT, AST and alkaline phosphatase (ALP) levels close to normal. The administration of GC (1 % w/w) for 16 weeks to C57BL/6J mice susceptible to developing obesity, fed a high-fat diet (45 % kcal from fat), did not cause inflammation or hepatotoxicity, but reduced the markers of inflammation in the brain, intestine, kidney and serum.

The Semwal et al. (2015) review includes a study that indicates that GC, administered at doses of 778 and 1244 mg/kg b.w./day for 13 weeks, causes marked testicular atrophy and toxicity in male Zucker rats. However, diets containing 389 mg/kg b.w./day did not cause these toxic effects, which indicates that the dose was NOAEL. Given the controversy over testicular toxicity related to (-)-HCA in animal studies, Hayamizu et al. (2008) investigated the effect of (-)-HCA on serum sex hormone levels, observing that GC (1667.3 mg/day equivalent to 1000 mg (-)-HCA/day) administered for 12 weeks to humans (n= 44), did not cause significant changes in the serum levels of the sex hormones testosterone, oestrone and oestradiol, and haematology and serum parameters did not indicate significant adverse effects. In a previous study, the administration of a dose of 5000 mg/day of GC (3000 mg/day of (-)-HCA) to healthy volunteers (24 women, 24 men), for 12 weeks, caused

an increase, which was not of great magnitude but which was significant, of the serum levels of inhibin B and follicle stimulating hormone in men; in women there were no significant changes in sex hormones, nor in the menstrual cycle, and no adverse effects were observed, suggesting that these high garcinia doses sustained for 12 weeks were safe (Ishii et al., 2003).

Oral administration of the garcinia fruit (1000 mg/kg b.w./day) for 5, 10 and 15 days protected gastric mucosa against indomethacin-induced injury in rats, possibly by reducing the production of hydrochloric acid and acidity, via inhibition of vagus nerve stimulation, and by promoting the defence mechanisms of the gastric mucosa (Semwal et al., 2015).

The effect of (-)-HCA on the reduction of glucose uptake and postprandial glycaemia in rodents has been observed (Thazhath et al., 2016). Thus, in a double-blind randomised cross-sectional trial with twelve healthy individuals and eight patients with type 2 diabetes who received an intraduodenal infusion of (-)-HCA (2800 mg) for 60 minutes, followed by an intraduodenal glucose infusion (60 g) for 120 minutes, (-)-HCA showed no effect on blood glucose in diabetic patients. In healthy subjects, (-)-HCA caused a modest reduction in blood glucose and the stimulation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon but had no effect on glucagon-like peptide type 1 (GLP-1), insulin, or glucose absorption (Thazhath et al., 2016).

Histological analysis of the liver and serum biochemical parameters in chicken embryos showed that the administration of (-)-HCA, from 0.1 to 50.0 mg/kg, was safe, suggesting that supplementation with (-)-HCA It would be safe in animals and humans (Peng et al., 2018).

Li et al. (2019) provide a new approach to understanding the (-)-HCA fat reduction mechanism in animals and humans by researching its effect on the regulation of glycolipid metabolism at the biochemical level. These researchers observed that treating broiler chickens with (-)-HCA decreased lipid deposition through activation of the AMPK pathway, causing a decrease in the expression of genes related to lipogenesis and potentiation of genes related to lipolysis. (-)-HCA decreased lipid accumulation and triglyceride content by reducing fatty acid synthase and increasing phosphorylation of acetyl-CoA carboxylase, thus enhancing its inhibition. (-)-HCA accelerated the aerobic metabolism of carbohydrates by increasing the activities of phosphofructokinase-1, and pyruvate, succinate and malate dehydrogenases. Moreover, (-)-HCA increased the gene expression of adiponectin receptor 1 (AdipoR1) and increased levels of phospho-AMPKα, coactivator-1α of peroxisome proliferator-activated receptor gamma (PGC-1α), nuclear respiratory factor-1 (NFR-1) and mitochondrial protein A transcription factor (TFAM). These data indicate that (-)-HCA is able to reduce lipid accumulation, improve glucose catabolism and accelerate energy metabolism in broiler chickens, possibly through activation of the adiponectin-AMPK signalling pathway. These results support its use as a feed additive, in order to control the defecation of fats and the prevention of diseases related to metabolic disorders in broiler chickens.

3.1 Anti-allergenic effects

There are some studies that describe anti-allergic effects.

The addition of *G. cambogia* to fresh skipjack tuna (*Katsuwonus pelamis*) inhibited histamine production and could thus reduce the risk of scombroidosis (Thadhani et al., 2002).

In a murine study, isogarcinol, extracted from the species *G. mangostana*, was able to lower the delayed hypersensitivity response, demonstrating immunosuppressive activity (Nakatani et al., 2002). An extract of the same species was shown to have potent anti-allergic activity by reducing the synthesis of PGE_2 and inhibiting the release of histamine (Cen et al., 2013).

A compound from *G. nujiangensis* also caused, in a murine experiment, the suppression of mastocyte activation and inhibition of histamine release and pro-inflammatory mediators. In an asthma model, it inhibited the synthesis of pro-allergenic cytokine and histamine (Lu et al., 2016).

4. Indications

The standardised extract from the rind of the garcinia (GC) fruit at 50-60 % (-)-HCA is used as an adjuvant in the treatment of excess weight, together with a hypocaloric diet and aerobic exercise, in hyperlipidaemias and to increase stamina in aerobic exercises (Vanaclocha and Cañigueral, 2019). GC and/or (-)-HCA are active ingredients in various weight loss food supplements. (-)-HCA is marketed in the form of salts (Ca, Mg, K and mixtures thereof) with different properties; some of them improve glucose tolerance.

Though there is preclinical evidence that suggests that oral consumption of (-)-HCA reduces food intake and body weight, it has not been observed in most human studies. Onakpoya et al. (2011) assessed the effectiveness of (-)-HCA to reduce weight in humans through a systematic review using data from nine randomised clinical trials. Although the meta-analysis revealed that (-)-HCA (average dose 1000-3000 mg of GC) caused weight loss with a small significant difference from the placebo group and caused minimal side effects, mainly mild gastrointestinal ones, the methodological quality of the studies was poor and most were short-lived (2-12 weeks), factors make it impossible to draw firm conclusions. Evidence suggests that GC (1000-2800 mg/day of (-)-HCA) may cause short-term weight loss, but the magnitude of the effect is small, and the clinical importance seems questionable.

5. Dosage

It is recommended to not exceed a daily dose of 3000 mg of standardised extract at 50-60 % (-)-HCA (dose equivalent to 1500-1800 mg of (-)-HCA), administered orally and in three shots, 30-60 minutes before the three main meals. The different supplements marketed in Spain containing GC and/or (-)-HCA, either in the form of tablets, capsules, sachets or vials, have different compositions and GC or (-)-HCA content, with recommended daily allowances involving a minimum intake from 30 mg to a maximum of 2070 mg of (-)-HCA.

Fibre-rich diets decrease the absorption of (-)-HCA (Vanaclocha and Cañigueral, 2019).

6. Safety

At European level, there is heterogeneity across countries with regards to safety in terms of specific standards for substances used as ingredients in food supplements, other than vitamins or minerals. In the specific case of plants or plant extracts, there is a procedure (Article 8 of Regulation (EC) No. 1925/2006) (EU, 2006) that allows a substance to be controlled for a certain period, if the avail-

able scientific information is insufficient. In the United States, dietary supplements do not require a review or authorisation by the FDA (Food and Drug Administration) before they are marketed, but if the FDA finds a supplement that is not safe, it can be recalled, or the manufacturer can be ordered to do so.

Consumption of supplements containing GC/(-)-HCA has been linked to toxic effects, but it has not been confirmed that garcinia is responsible because most have compound formulations. However, various adverse effects associated with the consumption of GC/(-)-HCA food supplements have been described, including hepatotoxicity, rhabdomyolysis, nephropathy, cardiovascular toxicity, hypomania and serotonin toxicity and psychosis.

The most important effects are detailed below.

6.1 Hepatotoxicity

The United States' drug-induced liver injury network (DILIN) identifies dietary supplements among the most common causes of drug-induced hepatotoxicity (Lunsford et al., 2016). Cavalieri and D'Agostino (2017) confirmed that hepatitis, cholestasis accompanied by jaundice, pruritus, marked elevation of ALP and mild elevation of ASP and ALT are clinical evidence of drug-induced hepatotoxicity (DILI) and of herb-induced hepatotoxicity (HILI). In a prospective study conducted in the United States, herbal and food supplements were implicated in 10 % of DILI cases (Crescioli et al., 2018).

In several double-blind, placebo-controlled trials, which used up to 2800 mg (-)-HCA/day, no adverse effects related to treatment were reported. Soni et al. (2004) indicated that there was sufficient qualitative and quantitative scientific evidence, including animal and human data, which suggested that an (-)-HCA intake of up to 2800 mg/day was safe for human consumption.

Sharma et al. (2010) reported that the FDA warned consumers about the serious adverse effects associated with the consumption of one of the most widely used dietary supplements in the United States for weight loss and bodybuilding. The supplement contained, among other ingredients, *Garcinia cambogia, Cissus quadrangularis*, caffeine, ephedra and green tea. To do so, it was based on 23 cases of liver damage, including one death and one liver transplant. This resulted in the withdrawal of the supplement from the market (Sharma et al., 2010). These same authors (Sharma et al., 2010) reported the first case of hepatotoxicity due to this same food supplement in a 19-year-old male with no significant medical history, who presented at a medical centre with a two-day history of fever, fatigue, myalgia, arthralgia and an erythematous rash on the lower extremities. The patient had started taking this supplement the previous week to burn fat and build muscle. He was a non-smoker, nor did he consume alcohol or take medications. The initial examination indicated toxicity, jaundice, high fever, abnormal levels of AST, ALT, ALP and total bilirubin (BT), as well as severe leukocytosis. His liver appeared normal in size and texture and there was no evidence of stones, ascites or biliary ductal dilation, but the biopsy suggested cholangitis, probably secondary to an infectious or drug-mediated injury. GC has been associated with a pattern of hepatocellular and cholestasic injury. The patient improved with a supportive therapy and the withdrawal from the GC-containing supplement. Liver function gradually recovered and returned to normal 14 weeks after

the onset of symptoms. The absence of any other aetiology indicated this nutritional supplement as being responsible for the possible hepatotoxicity. Two other similar cases, one of hepatocellular toxicity and another with cholestasic liver toxicity secondary to the use of said supplement, had been described previously.

The formulation of this food supplement has varied over the years. The first reports of acute liver injury related to this food supplement were part of a series of cases of four transplant centres of patients who developed severe hepatitis after taking supplements containing ephedra and its active ingredient ephedrine. After eliminating the ephedra content, new cases of hepatotoxicity were reported. Despite the reformulation of the food supplement, in 2015, a new case of hepatotoxicity was reported with elevation of AST, ALT, BT levels, impaired coagulation and renal failure. Subsequently, García-Cortés et al. (2016) published a review of food supplements that induce hepatotoxicity which included the mentioned food supplements. At least 28 cases of liver damage induced by this complement have been reported. The episodes occur after weeks of consumption and show a hepatocellular pattern of liver damage (25/28) and high levels of transaminases. Only a few cases showed cholestasis (3/28). In five reported cases of hepatotoxicity induced by this food supplement, the pattern of liver injury was not specified. In these reports, six patients developed induced acute liver failure; of those, three received a liver transplant. Another patient underwent an exploratory laparotomy for liver transplantation, and after being diagnosed with an intestinal infarction, the transplant was aborted, and the patient died.

On the other hand, in a review by Márquez et al. (2012) a total of 13 studies were analysed that reported on the medium-term effects of the administration of 1500-4667 mg/day of GC (dose range equivalent to 900-2800 mg/day of (-)-HCA) in a total of 930 subjects. None of the studies indicated serious adverse effects attributable to the intake of GC/(-)-HCA, the main side effects being nausea and headache. In general, there were no differences among the treated patients. Only one of the studies included leg cramps, heartburn, diarrhoea, flatulence, increased appetite, headaches, and menstrual disorders.

In a trial involving 60 overweight Brazilian women, randomised into two groups (2400 mg/day of GC or placebo) for 60 days, liver transaminase analysis and creatinine clearance showed no signs of acute toxicity during treatment; gastric discomfort, increased evacuation and nausea were reported as adverse effects (Vasques et al., 2014).

Al-kuraishy and Al-Gareeb (2016) studied the effect of orlistat (a drug for treating obesity by selective and reversible inhibition of gastric and pancreatic lipases), alone and in combination with GC, on visceral adiposity index in obese patients. For this, 99 obese male patients were randomized to three groups of 33 subjects each: a first group received orlistat (120 mg/day), a second GC group in capsules (166 mg/day) and a third group was treated with both. The combination of orlistat and GC improved the cardiometabolic profile and visceral adiposity index compared to orlistat alone, but patients treated with GC reported side effects: headache (12 patients), heartburn (9), constipation (5), abdominal pain (4), flatulence (2) and diarrhoea (3).

Lunsford et al. (2016) described the first known case of fulminant liver failure associated with a GC dietary supplement, increasing concern about these products' risk. A 34-year-old Hispanic male

with nausea, vomiting, abdominal pain, dark urine, and elevated AST, ALT and BT values indicated having taken only one GC supplement at the rate of 2 capsules three times a day (480 mg of GC/day) before meals over the previous 5 months. Liver biopsy showed submassive necrosis with collapse of the liver architecture that affected 70 % of the liver parenchyma, consistent with severe drug-induced liver injury. He received a liver transplant and recovered without incident.

A study by Crescioli et al. (2018) described four case studies of adverse reactions after consumption of food supplements containing GC. They also reviewed clinical evidence of hepatotoxicity in patients taking supplements with GC. From a total of 1510 reports gathered in the Emergency Department of the Italian Natural Products Health Surveillance System (January 2000-October 2017), 24 case reports and 8 case series were selected, reporting adverse effects after consuming GC. Of the total of 32 studies, 17 described cases of acute liver injury, liver failure and hepatotoxicity in patients who consumed GC dietary supplements. The authors used various algorithms and scales to assess the causality between the observed effects and GC consumption. Clinicians use the World Health Organization (WHO) criteria (The use of the WHO-UMC system for standardised case causality assessment. https://www.who-umc.org/media/2768/standardisedcase-causality-assessment.pdf), and the recently-updated specific hepatotoxicity scale of the Council for International Organizations of Medical Societies (CIOMS) as a tool to confirm the HILI diagnosis. In four studies, the CIOMS criterion was used, with a total of 1 possible, 2 certain and 12 probable cases. Elinav et al. (2007), using WHO criteria, diagnosed 3 cases as certain, 6 as probable, and 3 as possible. Using the DILIN study criteria, 2 cases were classified as probable, 2 possible and 5 highly related to GC use.

Below is a description of each of the four cases that reported acute hepatotoxicity (according to the CIOMS criterion):

- Case 1. A 61-year-old woman who presented with symptoms of abdominal pain for 10 days, nausea, progressive weakness, jaundice, dark urine and colic stool. The history indicated cholecystectomy, mixed dyslipidaemia and hypothyroidism (treatment with levothyroxine). There was no history of alcoholism or exposure to hepatotoxins; she denied paracetamol abuse. She reported taking one sachet/day of a dietary supplement containing 60 % GC (-)-HCA, for 2 months to lose weight. The laboratory tests revealed elevated levels of ALT, AST, ALP, BT, albumin and gamma glutamyl transferase (GGT). Four weeks after withdrawal from the supplement, symptoms and liver function tests gradually improved. Four months later, serum levels reverted to normal values. A value of 7 (range 6-8), diagnosed as probably HILI, was obtained.
- Case 2. A 39-year-old woman with symptoms of jaundice, asthenia, loss of appetite and abdominal pain (right hypochondrium). Her anamnesis denoted arterial hypertension, obesity (body mass index, BMI 44.9 kg/m^2) and hiatus hernia. Her medication at admission was methyldopa, domperidone and omeprazole. She also reported having been taking two dietary supplements to reduce weight the month before, recommended by her dietitian. One of them contained, among other ingredients, GC (72 mg (-)-HCA). The main liver markers were altered. After withdrawal from supplements and medications, symptoms and BT levels decreased, and liver function tests gradually improved. After 12 days of hospitalisation, the patient was discharged

without the need for complementary therapies. A diagnosis of acute cholestasic hepatitis was related to the consumption of this supplement, despite the simultaneous use of methyldopa, and high doses of synephrine. A value of 6 was obtained, which is consistent with the probable diagnosis of HILI.

- Case 3. A 47-year-old woman with symptoms of severe abdominal pain (right hypochondrial). Her history indicated hypothyroidism (treated with levothyroxine), high blood pressure (enalapril), and mild obesity. She reported she had been taking 2 capsules/day of a supplement containing 400 mg of 50 % GC (-)-HCA/capsule for 1 month. The laboratory tests revealed slight AST, ALT and BT elevation. During the hospital stay, after the withdrawal from the supplement, the BT levels decreased spontaneously, and her symptoms and liver function tests improved rapidly. Diagnosis of acute hepatitis, and the total score was 6, which is consistent with the probable diagnosis of HILI.
- Case 4. A 52-year-old woman diagnosed with acute hepatitis. She had been taking two supplements (1 capsule/day each) for 1 month to control her weight. One contained 400 mg of 60 % (-)-HCA (240 mg) GC and another, 400 mg of a 50 % extract of chlorogenic acid (200 mg). The laboratory tests revealed slight AST, ALT and BT elevation, and evidence of fatty liver disease was seen. After the withdrawal from the supplements, liver parameters decreased spontaneously, and acute hepatitis resolved completely. The total score was 6, which is consistent with the probable diagnosis of HILI.

The work of Crescioli et al. (2018) suggests a possible causal association between GC consumption and the development of acute liver injury. Though in some cases liver damage progressed more slowly than in others, this association is based on clinical results showing improvement after withdrawal from the food supplements. Symptoms of liver damage were similar in all patients and was also confirmed, in some cases, by liver biopsies.

The duration of GC treatment is very heterogeneous among the cases. However, given the lack of individual factors, such as comorbidities, concomitant treatment and genetic factors, the possible relationship between the duration of GC exposure and the severity of liver damage induced by food supplements could not be assessed.

Sharma et al. (2018) described a case of acute hepatitis due to GC, which was resolved by suspending the intake of the supplement and was aggravated by taking it again. A 57-year-old woman with vomiting and abdominal pain (7/10 severity), not radiating and diffuse, more intense in the upper right quadrant. She denied fever or chills but reported three episodes of non-bloody and non-bilious emesis after pain. She had a history of preserved heart failure. She had been taking vitamins A and D and for 1 month, 2 capsules/day of a supplement containing GC (1400 mg/capsule). Her vital signs were normal, but the analysis revealed high levels of ALT, AST, ALP and BT. When it was suggested to her that she stop taking the supplement, the abdominal symptoms and liver enzyme levels decreased significantly, but 6 months later they reappeared because the patient started taking the same supplement again. The CIOMS/RUCAM scale gave a score of 11, highly probable (score≥ 9), concluding that the aetiology of acute hepatitis of the patient was GC.

6.2 Hypomania

It has been described that (-)-HCA has serotonergic effects and could be involved in cases of severe serotonergic syndrome, hence the appearance of mania has been associated with the consumption of supplements containing GC/(-)-HCA (Hendrickson et al., 2016).

One of the cases of suspected serotonin toxicity is that described by López et al. (2014). A 35-year-old woman stabilised for more than 1 year with the antidepressant escitalopram, and who over the last 2 months had taken a weight loss supplement containing 1000 mg of GC (60 % (-)-HCA), 200 µg chromium, 50 µg potassium and 50 µg calcium, 2 capsules, three times a day. The woman developed tremors, redness and diaphoresis. The escitalopram treatment was discontinued when she was diagnosed with serotonin toxicity, but two weeks later she started with sertraline, another selective serotonin reuptake inhibitor. A week-and-a-half later, she was admitted to accident and emergency with hypertension and tachycardia, anxiety, diaphoresis, bilateral ocular clonus, clonus in the lower extremities and jaw, and stuttering, symptoms consistent with serotonin toxicity according to Sternbach's criteria. There is no definitive proof of cause and effect between GC and serotonin toxicity, but there could be a possible interaction since the patient was stable with escitalopram, symptom-free for an extended period of time, and only developed serotonin toxicity when she began to take the GC supplement.

Hendrickson et al. (2016) described three cases of patients (a 50-year-old male with bipolar disorder, a 25-year-old male with no history of psychiatric disorders, and a 34-year-old woman with type II bipolar disorder) who suffered from mania after ingestion of supplements with GC/(-)- HCA, remitted upon withdrawal from said supplements. The authors concluded that, due to mania's multifactor mechanisms, it was impossible to state that GC/(-)-HCA were the cause of the episodes of mania in these three cases. Besides, they indicated that there was an enormous variability in the dose and in the ingredients of the supplements. However, they did consider the risk of these supplements as regards this problem.

Cotovio and Oliveira-Maia (2017) described a case of GC-induced hypomania in a 51-year-old woman with a 12-year history of type 1 bipolar disorder. After 2 years of stability with valproic acid and paroxetine, the patient began with a weight loss supplement that contained GC, calcium, chromium and potassium. After 2 weeks with irritability, agitation, increased energy and insomnia, her psychiatrist diagnosed a hypomanic episode temporally related to the consumption of the food supplement. A week after suspending the supplement and continuing with the other medication, her mood stabilised with the complete remission of all symptoms of hypomania. In this case, the mania improved merely due to the withdrawal from garcinia, suggesting a probable/probable causal association between the consumption of garcinia supplement and the appearance of hypomania. The authors indicated that in other studies, in which the effects had been different, the rest of the components of the garcinia supplement had not been declared or they had observed the outbreak of mania after the administration of a supplement that, in addition to garcinia, contained other stimulants, such as caffeine or guarana. They also pointed out that in other studies, patients, as well as ceasing to take the garcinia supplement, had been treated with neuroleptics and/benzodiazepines, hence the improvement could not be attributed only to the fact they had ceased to take the garcinia supplement.

Nguyen et al. (2019) have described the case of an adult woman without bipolar disorder who developed a case of mania and psychosis after 1 week's treatment with garcinia. After removing the supplement and starting treatment with lithium salts and the neuroleptic quetiapine, the patient showed rapid improvement and was discharged in 8 days.

6.3 Other adverse effects

Another type of toxicity associated with consumption of GC can be observed in patients with pre-existing metabolic disorders. Bystrak et al. (2017) described the case of a 56-year-old insulin-dependent, hypertensive woman with chronic hepatitis C, who developed diabetic ketoacidosis, pancreatitis and cardiomyopathic stress after consuming a GC supplement to lose weight over the last month (1400 mg (-)-HCA/day). As the patient had received chronic treatment without recent dose changes and without previous episodes of pancreatitis, it was suggested that the GC supplement could have had an addictive effect on risk. By applying the algorithm described by Naranjo et al. (1981) to estimate the causality of an adverse drug reaction, a value of 5, probable adverse reaction to the use of GC, was obtained.

In clinical trials for food supplements and functional foods, the population studied tends to be a mixture of healthy individuals and others who are not as healthy, but who are not ill either, who are called "borderline subjects." Given such a heterogeneous population, Hayamizu et al. (2019) propose to assess the effectiveness of the supplements with a new statistical analysis such as the change point regression model (CPRM). After applying CPRM to garcinia data, they obtained clinically interpretable results that can be compared with traditional methods.

With respect to the allergenicity of garcinia, no reports have been published.

Conclusions of the Scientific Committee

The primary method for detecting the potential toxicity of food supplements is post-marketing, through case studies of patients with adverse reactions. Therefore, healthcare professionals, researchers and citizens are required to report serious adverse effects to the relevant institutions. Moreover, the regulatory authorities must develop post-marketing surveillance systems and enforce European Union legislation requiring food operators to ensure that the food supplements they sell are safe.

There is sufficient clinical evidence to establish a causal association between the consumption of garcinia and the duration of treatment, and the development of acute liver injury, with an obvious improvement in liver function after the withdrawal from the garcinia food supplement. The cases described by Lunsford et al. (2016), Crescioli et al. (2018), and Sharma et al. (2018), among others, confirm this fact.

The progress of patients with mild depression or occasional episodes of hypomania who consume garcinia should be monitored, since their situation may be aggravated. The improvement of manic symptoms has been observed after the withdrawal from the garcinia supplement.

More studies are necessary to support effectiveness and long-term beneficial or adverse effects of garcinia supplements in the treatment of excess weight.

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