ANSES

In this guide

This is a discussion paper. It does not reflect the views of the Committee. It should not be cited.

14. It should be noted that paragraphs 16 and 17 were summarised from the relevant webpage of ANSES (ANSES, 2025) rather than information from their opinion which is published in French.

15. The ANSES assessment highlighted 38 cases of adverse effects reported between 2009 and March 2024 (as identified in the French nutrivigilance scheme). They further “identified several drug interactions that can lead to an increase in adverse effects or cause medicines to lose their efficiency.”, from their analysis of other vigilance systems and literature review.

16. From their review of the literature, adverse effects were observed in people with various health issues like psychiatric disorders, pancreatitis or hepatitis, diabetes, obesity or hypertension. Those on certain medications that affect liver function, antiretroviral treatments or antidepressants were also seen to be negatively affected by consumption of G. cambogia. Those without any previous medical problems were also reported to have severe health effects following consumption of G. cambogia.

17. The FSA have commissioned a translation of the ANSES opinion, it is not an official ANSES translation. The following paragraphs provide a summary of the approach used by ANSES and their conclusions. The full ANSES opinion is attached in Annexes A and B of this paper.

18. ANSES’ goal was to review the existing data on the physicochemical [and toxicological] properties of *G. cambogia* Desr*.,* and analyse clinical cases from literature and vigilance reports to draw conclusions.

Classification and Taxonomy

19. G. gummi-gutta (L.) N. Robson is commonly known as the Malabar tamarind tree. In the scientific literature or on the labelling of marketed products it is referred to as G. cambogia Desr., It belongs to the Clusiaceae family and has 18 genera. The genus Garcinia was found to include nearly 404 species.

20. The French regulations allow the use of the fruit, fruit peel, and gum resin from *G. gummi-gutta*, as well as the fruit, fruit pulp, and pericarp (rind) of *G. mangostana* in food supplements.

21. ANSES observed that researchers and regulatory bodies utilise the name *G. cambogia* for *G. gummi-gutta*, which creates confusion. As such in their assessment, *G. cambogia* Desr., denotes *G. gummi-gutta*.

Botanical data and geographical distribution

22. ANSES described that the species of the genus *Garcinia* is widespread in tropical regions. *G. cambogia* Desr., is native to India, Sri Lanka and Nepal but has been introduced to other subtropical areas in Asia including China, Malaysia, Indonesia and the Philippines, as well as to West Africa and Polynesia.

Traditional uses of the plant and associated economic activities

23. ANSES found that the Indian populations had historic use of G*. cambogia* Desr., in several applications: medicinal, culinary, crafts and construction.

24. The fruits are edible; however, they are too acidic to eat raw and are processed into marmalade, vinegar or dried to use in condiments. The pericarp [rind] is sun-dried and are sold as is or ground into powder. It is traditionally used as a spice to act as a flavour enhancer and/or a preservative. Other food uses for the rind include non-alcoholic drinks and syrup. The bark has been used to produce fermented alcoholic drinks, whilst the seeds can be extracted for vegetable oil.

25. In Indian folk medicine, *G. cambogia* Desr., has been used to treat oedema, delayed menstruation, digestive disorders (in particular, chronic diarrhoea). The emetic properties of *G. cambogia* Desr., have been described as treatment for intestinal parasites. Various decoctions have been described to treat rheumatism and management of cardiovascular conditions.

26. It was found that the literature attributed these food and medicinal uses to other species of *Garcinia*, thus it is difficult to definitively associate them with *G. cambogia* Desr.

27. In 2014-2015, the Indian industry was reported to have an annual use of ~300 tonnes (dry weight) of G*. cambogia* Desr., fruit. Exported quantities ranged from 100 to 5,000 tonnes per year between 2005-2015, where more than half was destined for the United States of America, and the remainder exported to South Korea, Japan, Germany and Australia.

Chemical composition of the plant

28. The pericarp of *G. cambogia* Desr., contains 10 to 30% organic acids, calculated as citric acid equivalents, including less than 1% citric, oxalic, tartaric, and acetic acids; more than 4% malic acid; and up to over 15% HCA. It was identified that other *Garcinia* ssp., also contained HCA though typically at lower levels.

29. HCA ($C_6H_8O_8$) is a derivative of citric acid that has an additional hydroxyl group on the second carbon, creating two chiral centres at positions C-2 and C-3. HCA exists as four stereoisomers: (-)-HCA (2*S*,3*S*), (+)-HCA (2*R*,3*R*), (+)-*allo*-HCA (2*S*,3*R*) et (-)-*allo*-HCA (2*R*,3*S*).

30. In *G. cambogia* Desr., this compound [HCA] appears in the (2S,3S) or (-)-HCA configuration and serves as a competitive inhibitor of ATP-citrate lyase, an enzyme that drives fatty acid synthesis. Each stereoisomer can cyclise to a γ-lactone. In *G. cambogia Desr.,* HCA occurs in both its non-lactonic form and its lactonic form, known as garcinia lactone or (2S,3S)-3-hydroxy-5-oxo-2,3,4,5-tetrahydrofuran-2,3-dicarboxylic acid. From the literature, it was described that the lactonic form of (2S,3S)-HCA inhibits ATP citrate lyase less effectively than the non-lactonic form. It is also less bioavailable.

31. Industrial processes generally stabilise HCA as a single, double, or triple salt to prevent its cyclisation into the lactone form. The most common are calcium, magnesium, or potassium salts because they offer greater stability, higher solubility, and lower hygroscopicity compared to sodium salts.

32. The fruit of *G. cambogia* Desr., contains 6.25% carbohydrates, 3.25% protein, less than 0.0060% amino acids, and 0.34% lipids. The dried pericarp of *G. cambogia* Desr., contains 14.4 mg vitamin C. The bark has also been reported to contain certain B-group vitamins: 48 µg vitamin B1, 275 µg vitamin B2, 45 µg vitamin B3 and 8.8 µg vitamin B12 per 100 g. The dried fruit bark also contains minerals: 2.8 mg sodium, 26.6 mg potassium, 12.7 mg calcium, 14.4 mg magnesium, 9 mg iron and 5.3 mg phosphorus per 100g.

33. *G. cambogia* Desr., has been described to contain polyisoprenylated benzophenones (precursors of xanthones). Studies have isolated garcinol, isogarcinol from the plant’s bark and fruit. Both compounds have been shown to have antitumour, antimicrobial, antioxidant, anti-inflammatory, and central nervous system effects, especially *in vitro* and in animal models. Other isolated polyisoprenylated benzophenones are presented in Appendix 2a and 2b of the ANSES Opinion (see Annex A).

34. The xanthone content of the fruit was estimated to be 1.96%. The total phenol content is estimated to be 3.26%. Flavone heterosides (apigenin, luteolin) and flavanols (kaempferol, quercetin) have been detected in *G. cambogia* Desr., fruits.

35. Glycosylated derivatives of caffeic acid (caffeoyl glucose), esterified with quinic acid (dicaffeoyl-quinic acid) as well as *p*-coumaroyl-quinic acid have also been detected in fruits.

Regulatory status in different fields of use and geographic regions

United States

36. Several clinical trials had not revealed any health risks, and G. cambogia Desr., was used as an ingredient in food supplements, most notably in the Hydroxycut® range sold in the U.S. in the early 2000s. However, shortly after they were marketed, reports of hepatic, muscular, cardiac and neurological damage, sometimes serious, were reported in the United States and Canada. In 2009, the United States Food and Drug Administration (US FDA) requested the withdrawal of G. cambogia Desr., from Hydroxycut® preparations. It should be noted that consumers continued to use these products for several years following withdrawal from the market, due to remaining stock or illegal sales.

Europe

37. Several European Union member states, including Belgium, Italy, and Hungary, have authorised the use of *Garcinia cambogia* Desr., in food supplements. Between 2008 and 2010, applicants submitted requests to the European Food Safety Authority (EFSA) for the evaluation of health claims related to the species *G. cambogia* Desr., including in extract form. These health claims relate to weight control, reducing fat storage and hunger, controlling blood sugar and cholesterol levels. These are said to still be awaiting assessments. In addition, HCA is also the subject of a health risk assessment by EFSA, which is yet to be published.

France

38. The French National Agency for the Safety of Medicines and Health Products (ANSM), classifies *G.cambogia* Desr., as a medical product due to its

hypoglycaemic and lipid-lowering effects associated with HCA. However, given the lack of proven therapeutic benefit and an unfavourable benefit/risk ratio due to adverse effects reported in the U.S. and Canada, the ANSM Director General issued a ban on 12 April 2012. The decision prohibits the import, preparation, prescription, and dispensing of preparations containing *G. cambogia*, as well as its use in humans.

39. The French “plants” decree which establishes the list of plants authorised for use in food supplements and their conditions of use, does not include G. cambogia Desr.,; however, the General Directorate for Competition, Consumer Affairs and Fraud Control (DGCCRF) registered it by mutual recognition under the incorrect name G. gummi-gutta (L.) Roxb. The latter appears on the list of plants permitted in food supplements.

40. Data from the Téléicare database show that the DGCCRF registered 340 food supplements containing *G. cambogia* Desr., between April 2016 and January 2023. Based on the information gathered from these products, the average HCA intake was 752 mg/day for products that contained only *G. cambogia* Desr. The range was 1.25 – 2,850 mg/day, with 747 mg/day as the median. For multi-ingredient dietary supplements (MIDS) containing HCA, the average HCA intake was 255 mg/day. The range was 0 – 2,070 mg/day, with 150 mg/day as the median.

41. HCA analyses were conducted separately by Service commun des laboratoires and shared between the DGCCRF and customs. The HCA intake was calculated to consider the manufacturer’s advice for use. The average daily intake was 412 mg/day. The range was 21 – 2,000 mg/day, with a median of 203 mg/day.

42. Seventy-four percent [of the registered 340 food supplement products] combined *G. cambogia* with other ingredients that are known to cause liver toxicity in experimental models and clinical studies. These included: green tea containing epigallocatechin gallate; curcuma containing curcumin; red yeast rice containing monacolin K and coumarin. The Plants Working Group (WG) identified other substances that were suspected to be hepatotoxic (as suggested by the literature). These included: conjugated linoleic acid (unspecified isomers), hydroxyanthracene derivatives, forskolin, salicin, methyl salicylate and salicylated derivatives, *Equisetum arvense* [horsetail], gingerol, ginsenosides, gymnemic acid, and parsley. The Plants WG and Human Nutrition Expert Committee further noted that 89% [of the registered 340 food supplement products] contained at least one other ingredient that is known to be hepatotoxic: chromium, caffeine or

piperine.

Adverse effects linked to the consumption of G. cambogia Desr

Data from French vigilance systems

43. Since launching in 2009 and up to March 2024, ANSES has received 38 reports of adverse reactions likely linked to food supplements containing *G. cambogia* (or *G. gummi-gutta*), the products labels did not display the full scientific names. All admissible cases (n=35/38) were hepatic, cardiovascular and digestive. Of the 35 reported cases, 18 had sufficient information to assess the product's causal relationship with the observed adverse effects. The number of reports where the causal relationship of the product was very likely was (n = 1/18), likely (n = 7/18), possible (n = 8/18), doubtful (n = 1/18) or excluded (n = 1/18). The reader is referred to Table 2 of Annex A of TOX/2025/41 for additional information. It should be noted that the majority of the products are MIDS (n=16/18), with the remaining 2 stated to contain *G. cambogia* only.

44. The reported cases with a possible causal relationship associated with hepatic effects were further analysed by ANSES. Five of the six reported liver damage cases involved cytolytic hepatitis. In each case, the person either took *G. cambogia* alongside another potentially hepatotoxic ingredients in the supplement or used a hepatotoxic drug at the same time. In addition, all consumers have co-morbidities, or even risk factors for liver damage (obesity, significant and rapid weight loss).

45. Six additional case reports from the pharmacovigilance system were provided by the French ANSM. Three of which had enough information for the Nutrivigilance WG to assess the causal relationship of *G. cambogia* consumption with the observed adverse effects. The Nutrivigilance WG determined that 2 of the 6 cases had a possible or a very likely causal relationship.

46. Twenty out of 30 additional case reports from the toxicovigilance system were reviewed by the Nutrivigilance WG, they identified that the adverse effects were mostly cardiovascular (n=8/20; tachycardia) and digestive effects (n=6/20; abdominal pain, vomiting). Other effects included general symptoms (n=5/20; dizziness, malaise, fatigue, excessive sweating, dilated pupils) and skin reactions (itchy erythema).

Data from other vigilance system

Europe

47. In October 2020, ANSES contacted its European counterparts to gather more data on adverse effects potentially linked to the consumption of food supplements containing *G. cambogia* or *G. gummi-gutta* (under their truncated names). Of the 37 countries contacted, 21 responded. Table 6 of Annex A of TOX/2025/41 provides additional information. In brief, most of the 21 respondents (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, Slovakia, Spain, Switzerland) were not aware of any cases of adverse reactions related to *G. cambogia* (truncated names).

48. In Belgium, the Federal Public Service for Public Health, Food Chain Safety and the Environment authorises the use of "gum-resin (from the whole fruit or the pericarp)" of *Garcinia* in food supplements. Companies have currently notified and obtained authorisation for over 300 such products on the Belgian market. In Hungary, manufacturers have used this plant in food supplements on the market for over 20 years, and in 2020, they notified 152 products containing it. Some of these contain HCA at a dose higher than the 1,000 mg considered acceptable in Hungary. In these two countries, despite the notification of several hundred dietary supplements containing *G. cambogia*, authorities have not received any reports of adverse reactions.

49. In contrast, Germany (which recorded at least 167 notified products containing *G. cambogia* in 2020), along with Italy, Norway, Slovenia, and the Netherlands, have reported cases. The effects were primarily hepatic (n=13), followed by cardiovascular (n=8), psychiatric (n=6), and neurological issues (n=6).

50. In 2018, the Slovenian National Institute of Public Health published information relating to dietary supplements for weight control, specifying the risks and benefits of the ingredients frequently used in their composition. Regarding *G. cambogia*, liver damage is mentioned.

51. In 2019, the Spanish Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) published a report on the risks linked to consuming dietary supplements containing *G. gummi-gutta* (AESAN, 2019). The report emphasised the existence of sufficient clinical evidence connecting the consumption of *G. gummi-gutta* to the occurrence of hepatic events. This agency

also stressed the need to monitor psychiatric disorders (manic attacks, psychoses) reported in the literature in connection with the consumption of this plant.

Canada

52. From the 1st of January 1965 to 31st of August 2023, 93 reports involving at least one product containing one of the following ingredients: ‘ *garcinia*', '*garcinia gummi-guta*', '*garcinia gummigutta*', '*garcinia gummi- guta extract*', '*garcinia gummi-guta fruit*', '*garcinia gummi-gutta gum resin*' (names registered in the database), were recorded. The average age was 42 [note that 12% of the data did not have information on age], and over 80% were women. The mean BMI where available (62% missing data) was 29.9 (± 5.2) kg/m^2. The commonly reported adverse reactions included general symptoms (headache, dizziness), digestive issues (abdominal pain, nausea, vomiting), cardiovascular problems (palpitations, high blood pressure), and psychiatric or neurological effects. Of these 93 reports, 4 were reports of liver damage.

United States

53. According to the US FDA-Medwatch database, authorities had received 40 adverse reaction reports up until the 14th of December 2023 [the start date was not provided]. Of these 40 adverse reaction reports, 35 involved women. The average age (with 17% of data missing) was 43 years (± 12.9). The adverse effects reported were mainly of a hepatic, digestive and cardiovascular nature. The Plants WG and the Human Nutrition Expert Committee reviewed the cases submitted by all foreign vigilance systems but could not establish a causal relationship due to a lack of information.

Data published in the literature

54. The clinical cases reported in the literature up to October 2024 were mainly hepatic effects (n = 35). Psychiatric (n = 8), cardiovascular (n = 3), digestive (n = 3), muscular (n = 2) and metabolic (n = 2) disorders were the subject of several publications. Authors of these publications utilised *G. cambogia* and did not further allow for accurate scientific identification.

Hepatotoxicity

55. Thirty-six cases of liver damage have been published, observations by ANSES are detailed in Appendix 3 of Annex B of TOX/2025/41. Readers are also referred to Table 9 of Annex A of TOX/2025/41 for further information.

56. In brief, hepatitis of the cytolytic type were observed (86%), followed by cholestatic hepatitis (8%) and mixed hepatitis (6%). Grade 2 hepatitis was observed with elevation of transaminases (greater than 3 times the normal range) in the majority of cases; however, some were life-threatening (n=6), or even fatal (n=1). 60% of the reported cases involved women aged 37 years on average (35 years as the median; 19 – 64 years age range).

57. In 20 of the 36 publications, co-morbidities were reported, including hypertension, heart or kidney failure, diabetes, haemochromatosis, allergy, hypothyroidism, adenoma, chronic pain, dyslipidaemia, or hepatic steatosis. Authors of the publications identified risk factors for certain pathologies, including high BMI, hypocaloric diets, intense physical activity, a history of hepatitis, rapid and significant weight loss, alcohol use, and smoking.

58. In 29 of the 36 publications, the composition of the food supplements was of sufficient detail to identify other ingredients. Within these 29, 24 involved dietary supplements containing *G. cambogia* in combination with other hepatotoxic ingredients: caffeine, piperine or chromium. Most cases involving multi-ingredient products have been reported in the United States in people who have consumed products from the Hydroxycut® range. The composition of Hydroxycut® products in reported cases is often vague or entirely unknown.

59. Besides these occasional published cases, research teams have also analysed database records of liver damage linked to toxic drugs or plant-based products.

60. As part of the US Drug Induced Liver Injury Network (DILIN), Vuppalanchi *et al*., (2022) published their analysis of the 22 cases related to *G, cambogia* hepatotoxicity. Five of the twenty-two cases could be attributed to *G. cambogia* alone, in combination with green tea (n=16/22) or *Withania somnifera* [ashwagandha] (n=1/22). Statistical tests comparing control groups—patients with liver injury linked to green tea supplements without *G. cambogia* (n=57) or to other herbal supplements (n=103) showed that liver damage caused by *G. cambogia* and green tea was clinically indistinguishable. Patients who developed liver damage from dietary supplements containing *G. cambogia* showed a significantly higher frequency of the HLA-B*35:01 allele compared to those whose liver injuries were linked to other herbal supplements or conventional

medications. The authors concluded that this association suggested a mode of action that is mediated by the immune system.

61. Bessone *et al*., (2022) analysed the Latin America-Drug Induced Liver Injury (LATINDILI) database, they found that out of 367 cases, 8% were attributed to herbal food supplements. *Camellia sinensis* [green tea], Herbalife® products, and *G. cambogia*—mostly used for weight loss—were the most frequently identified as causes.

Psychiatric disorders

62. Four of the eight cases involved people with a history of psychiatric disorders. This was identified to be a potential risk factor, although adverse reactions have also occurred in individuals without any known psychiatric history. The studies reviewed as part of the ANSES opinion are summarised in Table 2.

Table 2 - Summary of data on psychiatric disorders linked to the consumption of G. cambogia Desr., reported in the literature (reproduced from the ANSES Opinion, 2025).

Author, date	**Sex, age**	**Psychiatric history**	**Treatments**	**Consumption and context of use**	**Effects**	**Score assigned by the authors**
Narasimha, 2013	Man, 23 years old.	None.	No information.	Hydroxycut® containing caffeine, guarana, G. cambogia, Gymnema sylvestre, glucomannan, green tea and willow bark.	Mania.	Linked to Hydroxycut® but authors suspect caffeine and guarana.

Beecheno, 2016	Woman, 33 years old.	None.	None.	Graviola® + spray containing levocarnitine, chromium, lipoic acid and dried fruit extracts from G. cambogia, leaves of Gymnema sylvestre, tea leaves and seeds of Avena sativa.	Psychosis	Naranjo 5, "probable" level accordi to WHO (positive reintroductio
Hendrickson, 2016	Man, 50 years old.	Type I bipolar disorder.	None.	Food supplement based on G. cambogia. Diet or even exercise context.	Severe manic bipolar disorder (DSM-5)*.	None.
Hendrickson, 2016	Man, 25 years old.	None.	No information.	Food supplement based on G. cambogia. Diet or even exercise context.	Severe manic bipolar disorder (DSM-5)*.	None.

Hendrickson, 2016	Woman, 34 years old.	Type II bipolar disorder, hypomania induced by selective serotonin reuptake inhibitors.	Aripiprazole, bupropion and topiramate.	Food supplement based on G. cambogia. Diet or even exercise context.	Severe manic bipolar disorder (DSM-5)*.	None
Cotovio, 2017	Woman, 51 years old.	Stabilised type I bipolar disorder and occasional episodes of hypomania or moderate depression.	Valproic acid and paroxetine.	Product contains G. cambogia calcium, chromium and potassium.	Hypomanic episode.	Probable according to the authors (suggestive developmen

Nguyen, 2019	Woman, 22 years old.	Traumatic episode in adolescence.	Subdermal etonogestrel implant.	Garcinia cambogia Plus®, containing G. cambogia extract with 60% HCA, and Cleanse and Detox®, containing raspberry ketone, liquorice root, pumpkin seeds, buckthorn root, cascara (Rhamnus purshiana), mango, rhubarb, citrus pectin, L. acidophilus, and Cape aloe.	Mania with psychosis.	Naranjo 3, level "Possib according to WHO.
Guu, 2020	Woman, 20 years old.	History of overweight (BMI=25.6) and early-onset type 2 diabetes.	Metformin.	G. cambogia extract.	Autoimmune psychosi.	None.

*Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders.

Cardiovascular disorders

63. Two cases of cardiomyopathy and one case of giant cell myocarditis have been reported in the literature. They are detailed in Appendix 3 of Annex B of TOX/2025/41.

64. The Plants WG and the Human Nutrition Expert Committee noted that both cases of cardiomyopathy involved women with no prior medical history. The clinical observations were deemed to be severe; one led to cardiac arrest, and the other caused high blood pressure with cardiac dysfunction, requiring ongoing cardiology follow-up.

Digestive disorders

65. The Plants WG and Human Nutrition Expert Committee noted that acute lithiasis pancreatitis often occurs in cases of obesity and diabetes. These three cases of pancreatitis occurred in people with diabetes and hypertension. Two of the three cases involved a history of obesity and chronic hepatitis C. They are detailed in Appendix 3 of Annex B of TOX/2025/41.

Muscle disorders

66. Two cases of rhabdomyolysis following consumption of Hydroxycut® have been reported in the literature. During periods of consumption (prior to 2009 [when the US FDA requested the withdrawal of G. cambogia from the product – see paragraph 36]), ephedra, caffeine, chromium, G. cambogia and Gymnema sylvestre [gymnema] were part of the composition of Hydroxycut®. These cases involved women who were either overweight or had recently increased their physical activity.

Metabolic disorders

67. Roche *et al*., (2014) reported a case of hypoglycaemia (blood glucose at 33 mg/dl) leading to syncope in a 67-year-old woman. The woman had been taking the following medications: venlafaxine, lisinopril-hydrochlorothiazide and alprazolam. She had started taking a dietary supplement containing *G. cambogia* two days before the onset of hypoglycaemia. The symptoms disappeared after administration of glucose. The author suspected *G. cambogia* because of the temporality of the events and the nonrecurrence of similar events following discontinuation of the product.

68. Bystrak *et al*., (2017) reported a case involving digestive complications in a 56-year-old consumer with diabetes, the patient developed diabetic

ketoacidosis. The authors suggested *G. cambogia* may have triggered ketosis by increasing ketone body production.

69. These studies detailed in Appendix 3 of Annex B of TOX/2025/41.

Other types of disorders

70. A 35-year-old woman with no known medical history or medication use reported an ocular disorder unilateral vision loss and eye pain after taking over 1,500 mg of HCA daily from *G. cambogia* extract for one week (Cho *et al*., 2019). These ocular complications resolved after the extract was discontinued and treatment with topical and oral steroids was initiated.

71. Other publications of adverse reactions suspected to be related to consumption of *G. cambogia* provided little descriptive information on the product label and in general e.g. dose, exposure duration, presence of other hepatotoxic ingredients. Two studies (Sikka *et al*., 2016; Graf *et al*., 2020) reported cases of thrombocytopenia in connection with taking dietary supplements containing *G. cambogia*. Li and Bordelon (2011) reported a case of nephropathy occurring in a 51-year-old woman with no previous medical history in association with one month's consumption of a dietary supplement containing *G. cambogia.*

Clinical trials

72. Several clinical trials have investigated the pharmacological effects of *G. cambogia* (Girola *et al*., 1996; Hayamizu *et al*., 2008; Heymsfield *et al.,* 1998). Most patients either reported no adverse events or showed no significant difference from the control group.

73. Cheng *et al*., (2012) assessed the effects of a single oral HCA supplementation on postprandial glycogen synthesis in skeletal muscle in physically active men. Eight men aged on average 22 years (mean BMI 25.2 kg/m ^{2}) and in apparent good health were dosed with 500 mg of HCA, immediately after exercise. They noted an increase in fat oxidation after HCA supplementation and suggested this may present a risk of increased ketosis in patients with severe diabetes.

74. In another study (phase I observational study), 10 healthy men aged 26-56 years with no digestive disorders received 3,000 mg/day of HCA for 30 days. Although the measured parameters: anthropometric indices, clinical examinations, and serum testosterone levels remained unchanged, two subjects

experienced anorexia and a third reported a headache (Hayamizu *et al*., 2003).

Drug interactions

75. Some reported cases in the literature and in vigilance systems raise suspicions of drug interactions involving *G. cambogia* and other medications.

Effects on P-glycoprotein (P-gp)

76. The Nutrivigilance WG suspects a drug interaction between antiretroviral treatments and the ingredients of the herbal tea blend Thé Catherine®, which includes *G. cambogia*, senna leaves and pods, and *Chrysanthemum morifolium* Ramat (see case no. 2021-129 in Table 4 of Appendix 3 in Annex B of TOX/2025/41). A few days to weeks after starting the product, a 31-year-old woman with stage B3 HIV showed an increase in viral load. Ritonavir and darunavir (medication for HIV/AIDS) act as both substrates and inhibitors of P-glycoprotein (P-gp or MDR1; membrane efflux transporters). Bolla *et al.,* (2021) investigated the effect of garcinol (a polyisoprenyl benzophenone present in *G. cambogia* Desr.,). on the P-gp transporter in rats. Concomitant administration of garcinol to digoxin, a P-gp substrate, decreased the area under the curve of digoxin measured in rat plasma. The authors suggested that this was due to increased expression of the gene encoding P-gp in the brain and digestive tract. Thus, co-administration of Thé Catherine® with ritonavir and darunavir may reduce exposure to these antiviral treatments and therefore contribute to an increase in viral load. An in vitro study on a 95% ethanolic extract of *Garcinia cambogia* in MDR1-MDCK epithelial cells showed an inhibitory effect at the highest dose tested (50 µg/mL) (Husain *et al*., 2023). Boonyong *et al*., (2024) investigated the effects of guttiferone K (a polyisoprenylated benzophenone found in *G. cambogia* Desr.) in Caco-2 cells and its P-gp function. Results showed that guttiferone K could inhibit P-gp.

Effects on cytochrome P450 monooxygenases (CYP)

77. A drug interaction was suspected in a case where a 38-year-old woman developed hypokalaemia and cardiorespiratory arrest with no relevant medical or family history (see case no. 2021 in Table 4 of Appendix 3 in Annex B of TOX/2025/41). The cardiorespiratory arrest due to hypokalaemia occurred two to three days after taking the food supplement Eafit Ultra Slim Burner® (with *G. cambogia*), combined with Maté®, Spasfon®, and Primpéran®. The Nutrivigilance WG highlighted the large number of cofactors potentially

responsible for adverse reactions, including Primpéran® (metoclopramide), known to lengthen the QT interval, and Maté®, which is rich in caffeine, known for its arrhythmogenic effects.

78. In the study by Bolla *et al*., (2021) garcinol exhibited strong inhibitory effects on CYP2D6 (IC50 = 9,5 µM) and CYP1A2 (IC50=7.6 µM). Significant inhibitions were also reported for CYP2C9 (IC50 = 8.0 µM), 2B6 (IC50 = 2.1 µM) and 3A4 (IC50=5.1 µM).

79. Yu *et al*., (2017) examined the inhibitory effects of a *G. cambogia* extract on CYP enzymes. The results showed significant dose-dependent inhibitory effects of *G. cambogia* extract on CYP2B6 activity, effects that did not appear with HCA, which was also tested.

80. An *in vitro* study using recombinant cytochromes found that a hydro-alcoholic extract (95% ethanol) of *G. cambogia* weakly inhibited CYP3A4, with an IC50 around 25 µg/mL (Husain *et al*., 2023). Another in vitro study on human hepatocytes showed that the same type of extract induced over 50% activity of CYP3A4 and CYP1A2 at concentrations below 10 µg/mL (Haron *et al*., 2023).

Effects on nuclear receptors PXR and AhR

81. In an *in vitro* study conducted by (Haron *et al.,* 2023), an activating effect of the nuclear receptors PXR and AhR humans transfected into HepG2 cells (human hepatocytes) were also observed when exposed to a hydro-alcoholic extract (95% ethanol) of *G. cambogia*.

82. Another study describes the agonist effect of the same type of extract on PXR and AhR receptors in HepG2 liver cells and AhR-reporter cells respectively. The authors showed that *G. cambogia* was an activator of PXR and AhR (Husain *et al*., 2023).

Pharmacodynamic reactions

83. A 35-year-old woman developed serotonin syndrome marked by tremors, hot flushes, and diaphoresis after one month of taking a supplement containing *G. cambogia*, chromium, calcium, and potassium. She was also on escitalopram, baclofen, gabapentin, omeprazole, oxycodone, cannabinoids, silodosin, solifenacin, and diphenhydramine. Treatment was changed from escitalopram to sertraline, and the patient kept taking the dietary supplement. One week following change of medication, she was admitted to accident and

emergency with a stammer and excessive sweating. On admission, she had tachycardia, hypertension, clonus, leucocytosis and hypokalaemia. The authors concluded that *G. cambogia* could be involved in a drug-drug interaction context without providing formal evidence (Lopez *et al*., 2014).

84. Roy *et al*., (2004) exposed Sprague-Dawley rats with a calcium-potassium salt of 60% HCA extract from *G. cambogia* (commercially known as Super Citrimax HCA-600-SXS) orally for 8 weeks (5 days a week) at a dose of 10 mg/kg and then performed transcriptomic analysis. A significant increase in the expression of genes encoding the serotonin receptors 5HT2A, 5HT3A, 5HT2B, 5HT4, and 5HT7, with expression levels in abdominal adipose tissue rising by a factor of 1.3.

85. Ohia *et al.,* (2001) utilised the same extract (Super Citrimax HCA-600-SXS) in an *ex vivo* rat model (cortex sections) and it was shown to induce serotonin release at the highest concentration (300 µM) and an inhibition of the reuptake of this neurotransmitter (at 300 and 1 mM; following an 1 h exposure) (Ohia *et al*., 2002).

86. A review was carried out by Leite *et al.,* (2021) on the concomitant use of plants with treatment with warfarin. Between 2016 and 2021, 114 medicinal plants were noted to interact with warfarin. *G. cambogia* (Gaertn.) Desr., (Incorrect designation) was identified as one of the plants that affected platelet activation by lowering adhesion, aggregation, and secretion, which raises the risk of bleeding.

87. Other authors have studied the toxicity of *G. cambogia* (Gaertn.) based products. Desr., (misnomer) and the mechanisms involved (Di Giacomo *et al*., 2023). Researchers examined several suspected hepatotoxic reactions linked to products containing *G. cambogia* (Gaertn.) Desr., based on reports collected through the Italian Phytovigilance System (IPS). Eight cases of hepatic adverse reactions associated with *G. cambogia* (Gaertn.) Desr., were reported to the IPS over a period of 20 years. One of these cases involves a fatal acute hepatitis in a 45-year-old woman who had taken a dietary supplement containing *G. cambogia* (Gaertn.) Desr., She was also taking montelukast to manage her asthma—a drug known to cause liver toxicity, frequently raising serum transaminase levels and, in rare cases, triggering hepatitis. An *in vitro* study was performed to assess the mechanisms possibly responsible for liver toxicity, focusing on modulation of oxidative stress and Nrf2 expression. Low cytotoxicity was observed. However, its combination with montelukast significantly reduced cell viability, increased intracellular levels of reactive oxygen species, and affected cytoplasmic

expression of Nrf2, suggesting an impairment of antioxidant and cytoprotective defences.

Conclusions of the Plants WG and the Human Nutrition Expert Committee

88. The Plants WG and the Human Nutrition Expert Committee:

- Noted that the EU has not harmonised the lists of authorised plants and plant parts for *G. cambogia* Desr., nor their uses and doses in food supplements, or the related restrictions and warnings. Therefore, they recommended proper characterisation of the raw material, including measuring HCA and conducting a botanical identification utilising appropriate analytical techniques to discriminate between the different species.
- Highlighted that many of the reported studies in the literature and vigilance reports poorly characterise *G. cambogia* Desr., extracts and thus urge operators to clearly define their extracts by detailing the composition and specifying the exact production conditions, including the extraction and purification methods and the solvents used.
- Noted that only HCA has been investigated in clinical studies, other components may contribute to adverse reactions. They recommended conducting studies on constituents found in fruit extracts—particularly benzophenones and polyisoprenylated xanthones to investigate and clarify their potential role in adverse reactions.
- Noted that there is ambiguity in the plant parts present in *G. cambogia* Desr., food supplements.
- Advise individuals with psychiatric disorders, certain cardiometabolic diseases (diabetes, obesity, hypertension), and those with a history of pancreatitis or hepatitis to not consume food products (including supplements) containing *G. cambogia* Desr., based on the information from the literature and various vigilance systems.
- Further advise against the use of food supplements containing *G. cambogia* Desr., in children and pregnant or breastfeeding women [due to the lack of information].
- Recommend not combining the intake of *G. cambogia* Desr., with other hepatotoxic ingredients or foods (such as green tea extract, red yeast rice, turmeric or sources of coumarin).

- Recommended to avoid the use of this plant in combination with drugs known to affect liver function, anti-depressants, and antiretrovirals. More broadly, those taking drugs that are substrates of CYP3A4, CYP2B6, and Pg-P—to avoid consuming food supplements containing *G. cambogia Desr*. They also warn that *G. cambogia* may interact with substrates of CYP1A2, CYP2C9, and CYP2D6, and emphasise that these interactions remain a credible risk.

89. The Plants WG and the Human Nutrition Expert Committee reiterate the opinion of ANSES on slimming diets. Any weight-loss programme requires specialist medical support.

Conclusions of ANSES

90. In brief, ANSES highlighted the inconsistency of the regulatory status of the plant *G. cambogia* Desr., (also known as *G. gummi-gutta* (L.) N. Robson) in France. ANSES further noted that since 2012, the import, preparation, prescription and dispensing of medicines or preparations containing *G. cambogia* Desr., have been prohibited in France, as these preparations have not proven their efficacy and may expose the patient to health risks.

91. Based on the conclusions of the Human Nutrition Expert Committee and the Plants WG, ANSES advises against using *G. cambogia* Desr., products in individuals with psychiatric disorders, cardiometabolic conditions (diabetes, obesity, hypertension), or a history of pancreatitis or hepatitis. Use is also discouraged for those on liver-affecting drugs, antiretrovirals, or antidepressants. Given reports of severe adverse reactions in consumers without prior medical history. ANSES extends its recommendation to the entire population. It advises against consuming food supplements made from this plant or preparations containing it.

92. In general, ANSES highlights the need for European harmonisation regarding authorised plants, plant parts, uses and doses in food supplements, along with related restrictions and warnings.