

REVIEW ARTICLE



Awareness on the possible adverse effects of *Garcinia cambogia*: A scientific approach

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The modern popular ideology is that plant-based products do not have adverse effects. Hence, people are fond of using herbal products of their choice to treat their own ailments or anyone else. As majority of the population are not aware of herbal toxicity concept, the use of formulated single or combined medicinal and/or nutritional plant extracts or isolated compounds to treat chronic diseases are increasingly popular due to the widespread concerns regarding the adverse effects of pharmaceutical drugs. Awareness from the scientific community to bring society to its senses regarding the safety issue of a herbal product is rare. *Garcinia gummi-gutta* (more popularly known by the synonym *Garcinia cambogia* in commercial preparations), belonging to the family of Clusiaceae (alt. Guttiferae) is a popularly consumed weight-loss nutraceutical. This review aims to highlight the possible adverse effects of *G. cambogia*. For the said purpose, 147 articles were collected from PubMed, Web of Science and Google scholar. Literature review revealed a plethora of beneficial actions. Investigational outcomes and clinical evidences hint the possible adverse effects likely to be linked with the use of *G. cambogia*. However, the use of *G. cambogia* as an anti-obesity agent is advisable as long as the therapeutic value outweighs the adverse effect.

Keywords: *Garcinia cambogia*, *Garcinia gummi-gutta*, herbal toxicity, nutraceutical, obesity, weight-reducing drug.

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Introduction

Obesity, in simple terms, is defined as a chronic metabolic disorder leading to over-accumulation of fats in the adipose tissue.¹ Sometimes, obesity is also described as a condition when the body fat is greater than 25% and 30% of the total body mass in men and women respectively.² Clinically, obesity is defined as a body mass index (BMI) equal to or greater than 30 kg/m².^{3,4} As per BMI, obesity is further classified as class 1 obesity (30.0–34.9 kg/m²), class 2 obesity (35.0–39.9 kg/m²) and class 3 obesity

(+40 kg/m²).⁵

There are two categories of obese individuals, i.e. metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO).⁶ The MUO are more susceptible to develop obesity and related comorbidities.^{7,8} Whereas, MHO have lesser visceral adiposity, lesser adverse metabolic disturbances and lower cardiovascular risk factors than MUO. Despite these facts, MHO individuals are also still unsafe in comparison to normal-weight individuals.⁹

Epidemiologically, the number of people affected by obesity worldwide has doubled within almost a 30-year span, i.e. from 1980 to 2008.² In low-income countries, obesity is highly prevalent in middle-aged people. However, in developed countries, obesity is predominant in kids and teenagers. It is noteworthy that nowadays, even in developing countries, the numbers of obese youngsters are increasing.⁵ Moreover; a study revealed that children are also largely affected by obesity, and could possibly develop metabolic syndromes later in life.¹⁰ Obesity in poor countries is linked with higher education.¹¹ Obesity in rich countries is linked with poor living standards and low-quality education.^{12, 13}

Obesity is a heterogeneous disorder and induced by a number of factors. Although it is difficult to pinpoint the exact origin due to countless mechanisms coming into play, it can, however, be summarised in the following texts. Overconsumption of calorie-dense foods while limiting physical activity is one of the most notable cause for obesity.^{14,15} The consumption of snacks (apart from breakfast, lunch and dinner) in the evening and late at night increases the BMI of an individual and is directly linked with obesity.¹⁶ Over ingestion of sugars, fats and sodas combined with insufficient intake of dietary fibre, fruits and vegetables is another cause for obesity. In older people, obesity is prevalent with irregular consumption of whole wheat cereals.¹⁷ A study in Iran associates the particular metabolic disorder with a family history of obesity, unusual work timings, sleep deficiency, consumption of psychotropic medicines and the use of other pharmaceuticals particularly those undergoing regular chemotherapy-based treatments.¹⁸ Menopause is regarded as a high-risk time for weight gain which can further develop to obesity.¹⁹ A study showed that the absence of a specific group of beneficial bacteria called Bacteroidetes in the human gut is linked with obesity.²⁰

Obesity is associated with many complex complications. Obesity is damaging to cardiovascular health and contributes to the development of atherosclerosis and acute myocardial infarction.^{2,16,23} Obesity plays a major role in the development of type-2 diabetes.^{16,21,22} Obese individuals are more likely to develop hypertension.²⁴⁻²⁸ Obesity is also associated with infertility, stroke, arthritis, neuroinflammation and hypothyroidism.^{1,4,30-32}

Out of many drugs, there are six commonly prescribed potent antiobesity medications and they all come with a variety of adverse effects. Phentermine causes dry mouth, insomnia, dizziness and irritability. Orlistat causes faecal urgency, oily stool, flatus with discharge and faecal incontinence. Phentermine/topiramate extended-release causes paresthesias, dizziness, dysgeusia, insomnia, constipation and dry mouth. Lorcaserin causes headache, dizziness, fatigue, nausea, dry mouth and constipation. Naltrexone/bupropion sustained-

release causes nausea, vomiting, constipation, headache, dizziness, insomnia and dry mouth. Liraglutide causes nausea, vomiting, diarrhoea, constipation, dyspepsia and abdominal pain.^{33,34} Currently, the public are aware of the dangers accompanied with the use of conventional drugs. Nutraceuticals seem to provide a solution for the inevitable adverse effects of pharmaceuticals. Hence the consumption of herbal preparations is one practice followed to evade the harmful effects arising from pharmacotherapy.

Garcinia gummi-gutta (L.) N. Robson, commonly known as Malabar-tamarind or brindleberry, is a member of the family Clusiaceae (alt. Guttiferae), is one such medicinal plant whose fruit rinds are harvested for its antiobesity property.³⁵⁻³⁷ It is still more popularly known by its old scientific name *Garcinia cambogia* (Gaertn.) Desr. because of widespread use of the name in commercial products. (-)-Hydroxycitric acid (HCA, Figure 1) is the main active phytochemical of the fruits of *G. cambogia*.^{38,39} It effectively inhibits ATP citrate lyase which causes a decrease in acetyl-CoA upon which synthesis of fatty acid and lipogenesis are suppressed.⁴⁰ The methanolic extract of *G. cambogia* was found to contain xanthochymol (Figure 2).⁴¹ The diethyl ether extract of *G. cambogia* was found to contain garcinol (Figure 3), guttiferone I (Figure 4), guttiferone J (Figure 5), guttiferone K (Figure 6), guttiferone M (Figure 7), guttiferone N (Figure 8), oxy-guttiferone K (Figure 9).⁴²

HCA is considered to be safe when tested in rats.⁴³ A novel water-soluble calcium/potassium salt of HCA, i.e. Super CitriMax was found to have relatively high bioavailability and fewer signs of toxicity in rats.^{44,45} *G. cambogia* has been investigated and proven to be a potent antiobesity agent with weight-reducing efficiency in animal models.⁴⁶⁻⁶⁵ A study concluded that *G. cambogia* inhibited the accumulation of lipids in 3T3-L1 cells.^{66,67} *G. cambogia* contains phytochemicals which can down-regulate genes linked with obesity.^{68,69}

Recent study reported that pear pomace extract and *G. cambogia* extract jointly prevent adipogenesis and boosted lipolysis in 3T3-L1 cells.⁷⁰ Further, the weight-reducing property of *G. cambogia* had also been clinically validated in humans.⁷¹⁻⁸⁵ The satiety inducing property had also been reported.⁸⁶ Another study reported that the extract obtained from the fruits of *Citrus junos* accelerates the anti-adipogenic action of *G. cambogia*.⁸⁷ A combination of physical exercise and *G. cambogia* is found to increase the endurance of an athlete allowing higher expenditure of calories thereby promoting weight loss.⁸⁸ A randomized study in Iraq reported that orlistat in combination with *G. cambogia* rather than orlistat administered alone was found to result in better cardio-metabolic parameters.⁸⁹

Furthermore, in 2002, the antiulcer activity of *G. cambogia* was reported twice.^{90,91} In 2007, anti-

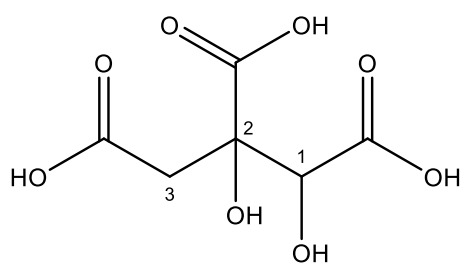


Figure 1 | (-)-Hydroxycitric acid (HCA).

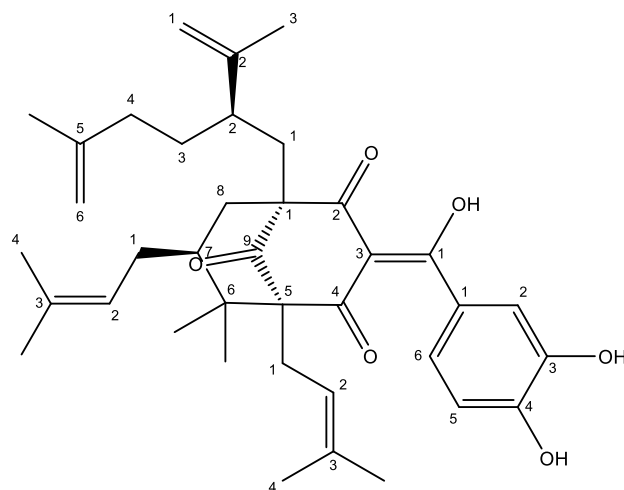


Figure 2 | Xanthochymol.

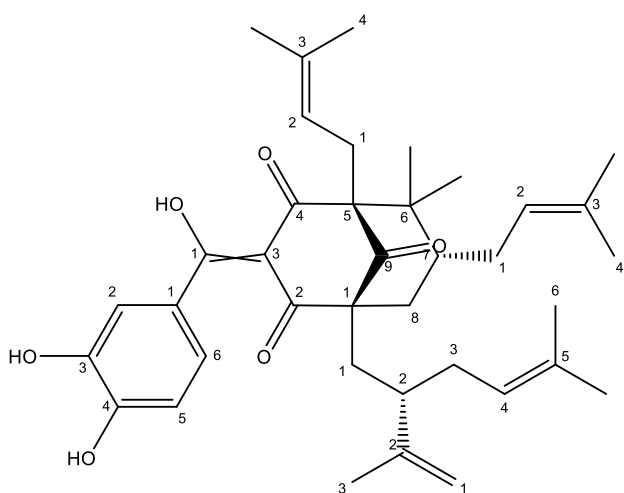


Figure 3 | Garcinol.

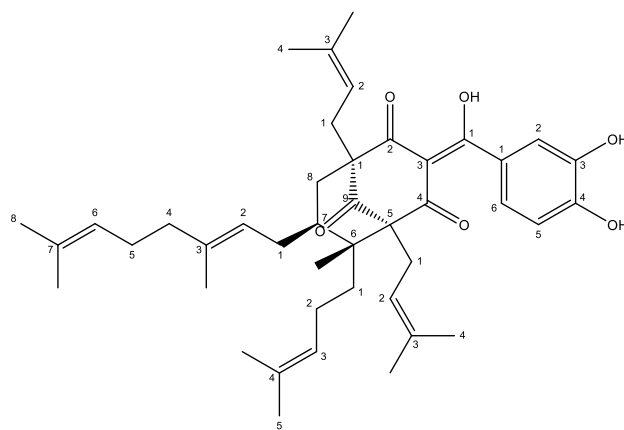


Figure 4 | Guttiferone I.

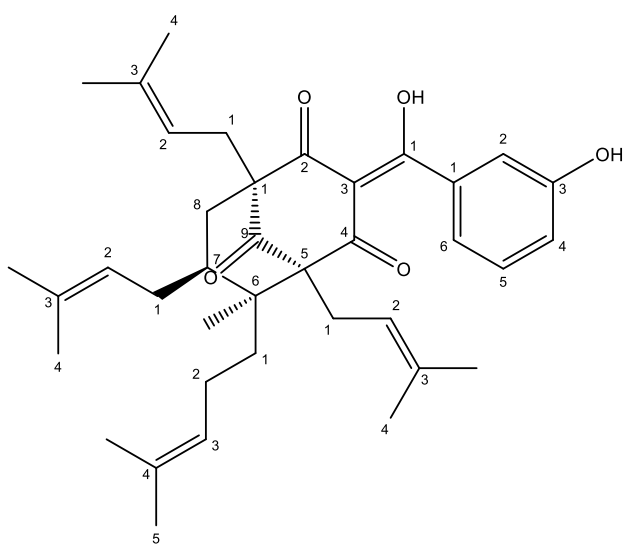


Figure 5 | Guttiferone J.

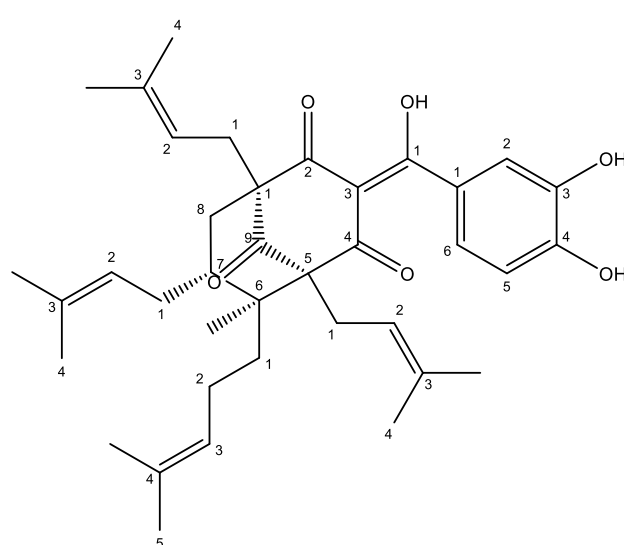


Figure 6 | Guttiferone K.

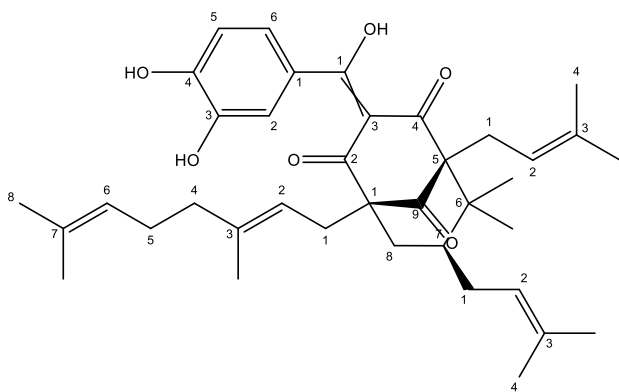


Figure 7 | Guttiferone M.

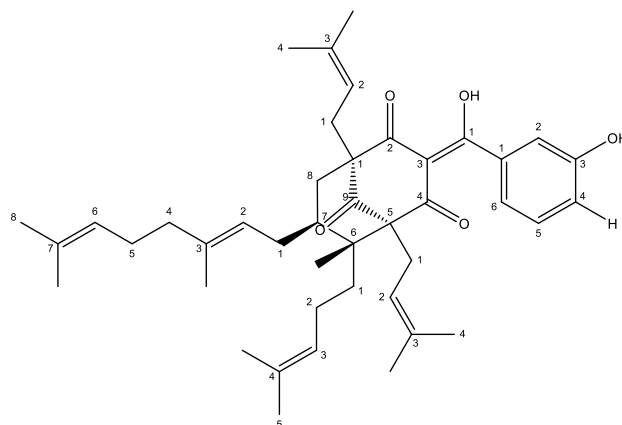


Figure 8 | Guttiferone N.

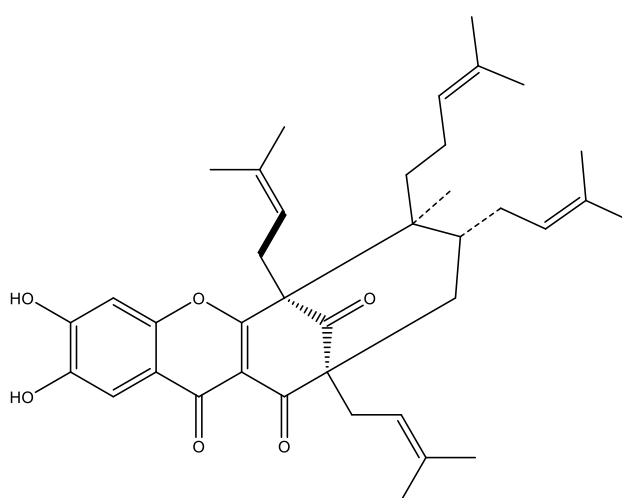


Figure 9 | Oxy-Guttiferone K.

inflammatory activity was first reported. It was again later re-investigated in 2009, 2014 and 2018.^{59,92-94} In 2007, antioxidant activity was first reported. It was again later re-investigated in 2009, 2011 and twice in 2016.^{59,62,95-98} In the year 2009, tumoricidal property was explored and reported.⁹⁹ In 2011, anti-diuretic activity was reported.¹⁰⁰ *G. cambogia* was reported to lower insulin resistance and improve glucose metabolism and also displayed suppression of hunger similar to leptin and improves its signalling.^{101,102} *G. cambogia* lowered blood glucose levels both in animal models as well as in humans.¹⁰³ *G. cambogia* showed potential for ameliorating phosphorus and copper deficiency in animal model.¹⁰⁴ *G. cambogia* effectively ameliorates depleted glycogen levels in human skeletal muscles.¹⁰⁵ *G. cambogia* intensifies the release of serotonin from the cortex of the brain of rats.¹⁰⁶ A study reports that exogenous histamine formation in skipjack was prevented by the addition of *G. cambogia*.¹⁰⁷ Fresh and immobilized biomass of *G.*

cambogia was tested for its arsenic removing property in arsenic-contaminated groundwater and the test results were positive.¹⁰⁸

The genotoxicity of *G. cambogia* was investigated by Lee and Lee in 2007 using Ames test, chromosome aberration test and micronucleus test and results showed that *G. cambogia* does not exhibit genotoxicity.¹⁰⁹ However, the genotoxicity study carried out by Lee and Lee was refuted by Lau et. al. the following year by highlighting several shortcomings in the materials used and methods adopted for evaluation while simultaneously emphasizing on the weakness in statistical analysis.¹¹⁰ *G. cambogia* extract has the potency to inhibit CYP2B6 which is a family of CYP450 enzyme in a timely manner, but HCA alone was not able to significantly inhibit CYP2B6.¹¹¹

Few contradictory reports were also retrieved, suggesting that *G. cambogia* is not as effective in weight lowering property as it is claimed to be.^{77,112-120} None the less, many herbal based companies are

having preparations of *G. cambogia* that are currently on the global market.^{76,121–123} As a result of the immense hype of the weight-reducing potency of the nutraceutical, the adverse effects are going unnoticed and overlooked.

The main aim of this review is therefore to educate the society by highlighting all possible adverse effects of the herbal drug by accessing all of the available research data's and clinical evidences. This article does not aim to discourage anyone from taking the phytomedicine nor disrupt any related business associated with *G. cambogia*. It will rather spread awareness to the masses regarding the lesser-known adverse effects of the nutraceutical.

Materials and Methods

PubMed, Scopus, Web of Science and Google Scholar were accessed to obtain relevant articles. Articles were explored using '*Garcinia cambogia*', 'antiobesity herbal drug', 'weight loss nutraceutical' and 'obesity' as keywords. A total of 147 articles were collected and reviewed. Even though there existed a possibility of compiling the whole profile for the plant like many of the available articles, precautions were taken to maintain the novelty of the review article by focusing on the sole purpose of highlighting only the adverse effects of the nutraceutical. Provisions were made to include all the significant information while excluding all needless texts.

Results and discussion

The use of herbal nutraceuticals including *G. cambogia* is higher in females when compared to males.¹²⁴ Hence, to spread awareness, scientifically reported adverse effects possibly linked with the use of *G. cambogia* are compiled below.

Rhabdomyolysis was induced in a 54-year-old white female upon the ingestion of a herbal drug named 'body maximizing' where *G. cambogia* was one of the active ingredients alongside vitamin E, magnesium, zinc, chromium, ma huang, guarana, chitosan, *Gymnena sylvestre*, bee pollen, ginseng root, ginger root, lecithin, damiana root, sarsaparilla root, nettle leaf and royal jelly. The patient's serum creatinine kinase (CK) level was 1028 IU/L (normal range: 26–140 IU/L).¹²⁵

Liver toxicity (hepatitis) related to the use of a herbal product was encountered in two individuals with the intake of a weight loss medication called 'Hydroxycut' whose active ingredients included *G. cambogia*. Liver function test of patient 1 revealed that the levels of aspartate aminotransferase, alanine aminotransferase, bilirubin and alkaline phosphatase were 1808 U/L (normal range: 5–50 U/L), 3131 U/L (normal range: 7–40 U/L), 7.8 mg/dL (normal range: 0.0–1.5 mg/dL) and 171 U/L (normal range: 40–150 U/L) respectively. In patient 2, the levels of aspartate

aminotransferase, alanine aminotransferase, bilirubin and alkaline phosphatase were 59 μ /L (normal range: 5–50 U/L), 45 μ /L (normal range: 7–40 U/L), 7.8 mg/dL (normal range: 0.0–1.5 mg/dL) and 530 μ /L (normal range: 40–150 U/L) respectively.¹²⁶

A review article cited a case report on the adverse effect of *G. cambogia* as dizziness, increased appetite, dry mouth, palpitation and increased hepatic enzyme that were induced with a dose of 1.2 g for a period of 3 to 4 days in a 34 and 48 years old female along with one 48 years old male. The same article cited adverse effects reported from clinical trials of *G. cambogia* as nausea and headache induced with a dose of 1.26 g for a period of 4 weeks; headache, upper respiratory tract symptoms and gastrointestinal symptoms induced with a dose of 3 g for a period of 12 weeks; common cold, toothache and diarrhoea induced with a dose of 1.7 g for 12 weeks; nausea and headache induced with a dose of 1.5 g for a period of 8 weeks.¹²⁷ Further, one of the report suggested that HCA causes marked testicular toxicity and impaired spermatogenesis in Zucker obese rats at a daily dose of 778 mg/kg b.w. and 1244 mg/kg b.w.⁵⁶

A 45-year-old obese female suffering from chronic asthma died due to liver failure that had been taking montelukast for the past 5 years and had also previously completed a 7-day course with two herbal supplements wherein *G. cambogia* was an active ingredient in one of the herbal product. As the patient was admitted to hospital with jaundice, the authors made a highly speculative statement that montelukast or *G. cambogia* alone would not be responsible for the patient's death but it might rather be a synergistic action of the two.¹²⁸

A 19-year-old soldier deployed to Iraq had the symptoms of nausea, vomiting and jaundice following the consumption of Hydroxycut.¹²⁹

A study was conducted using C57BL/6J mice. The study revealed that *G. cambogia* resulted in increased accumulation of collagen and lipid peroxidation. The levels of aspartate aminotransferase and alanine aminotransferase, pro-inflammatory markers such as TNF- α and MCP-1, hepatic superoxide dismutase and glutathione peroxidase were also increased.⁵⁵ The study carried out on C57BL/6J mice were refuted by Clouatre *et al.* by questioning the incompleteness of the study. The form of HCA that was not indicated was questioned. A statement was made regarding the source of toxicity. The animal model chosen for the study was also considered inappropriate. The information regarding the test compound was regarded as incomplete.¹³⁰ In the light of the statement made by Clouatre *et al.*, the authors of this article would also like to mention that the anti-inflammatory and antioxidant activity were already positively assessed.^{59,62,92–98}

On sub-acute consumption of *G. cambogia* extract for about 18 days, the serum troponin levels

of a 48-year-old woman was elevated. Acute necrotizing eosinophilic myocarditis resulted in heart failure requiring extracorporeal membrane oxygenation.¹³¹ Further, sub-chronic consumption of *G. cambogia* along with selective serotonin reuptake inhibitors namely escitalopram and sertraline for 2-3 months, a 35-year-old woman developed serotonin toxicity.¹³²

A week after the consumption of *G. cambogia*, the levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and ferritin of a 42-year-old female were 1277 U/L (normal range: 7–40 U/L), 2792 U/L (normal range: 5–50 U/L), 283 U/L (normal range: 40–150 U/L) and 12,198 mcg/L (normal range: 11–307 mcg/L) respectively.¹³³ The same case was described by Mancano (2015) as awareness to the public regarding drug interactions.¹³⁴

Following the consumption of *G. cambogia*, the levels of alanine aminotransferase, aspartate aminotransferase and bilirubin of a 52-year-old female were found to be 568 U/L (normal range: 7–40 U/L), 723 U/L (normal range: 5–50 U/L) and 10.1 mg/dL (normal range: 0.0–1.5 mg/dL) respectively. The model for end-stage liver disease score that initially was 23 increased to 28. The authors claimed that *G. cambogia* was liable for the progression of the liver disease.¹³⁵

A 34-year-old Hispanic male required liver transplantation after the intake of *G. cambogia* 3 times a day.¹³⁶ A review article that was published in the same year listed *G. cambogia* among a list of dietary supplements that are hepatotoxic.¹³⁷

A 51-year-old female with a 12-year history of type 1 bipolar disorder started consuming *G. cambogia* and was easily irritated and agitated.¹³⁸

A 33-year-old woman consuming *G. cambogia* for weight loss had an acute onset of psychomotor retardation, thought broadcasting, flat affect, persecutory delusions and auditory hallucinations.¹³⁹ An article also reviewed different types of herbals having the potential to induce mania wherein *G. cambogia* was included.¹⁴⁰

A 56-year-old female developed mental confusion with the use of *G. cambogia* at a dose of two tablets taken three times a day. The patient had diabetic ketoacidosis, pancreatitis and elevated troponin levels.¹⁴¹

The levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin of a 57-year-old female consuming *G. cambogia* with no history of liver disorders were 738 U/L (normal range: 7–40 U/L), 856 U/L (normal range: 5–50 U/L), 80 U/L (normal range: 40–150 U/L) and 2.4 mg/dL (normal range: 0.0–1.5 mg/dL) respectively.¹⁴²

Following the consumption of *G. cambogia*, a 36-year-old female had fatigue, anorexia and jaundice. The levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and bilirubin were 5615 U/L (normal range: 7–40 U/L), 5340 U/L

(normal range: 5–50 U/L), 104 U/L (normal range: 40–150 U/L), 7.4 mg/dL (normal range: 0.0–1.5 mg/dL) respectively.¹⁴³ Furthermore, two review articles that were published in the same year reviewed and discussed an array of *G. cambogia* induced liver injury.^{144,145}

A clinical investigation of a 82-year-old male, after the consumption of *G. cambogia*, revealed that the patient had fats deposited around the pancreas that was well-matched with acute pancreatitis.¹⁴⁶ Moreover, a report suggested that a 35-year-old female consumed *G. cambogia* and soon developed nausea, headache, dizziness and swelling of the eyes.¹⁴⁷

The safety of *G. cambogia* is controversial and not properly established. Therefore, it is advisable for a common man to consider taking precautionary measures as simple as consulting a physician or a pharmacist who is expert in the field of plant-based medicines for one's safety.

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Conflict of interest

The authors declare that there are no known conflicts of interest with regards to this work.

Declaration of authors' contribution

All the authors have contributed their time and effort equally.

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