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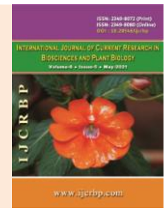

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Garcinia fruit: in the forests and domestic orchards, the prevention of diseases of modernity

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Abstract

The genus *Garcinia* has many varieties of fruit trees, which are found in rural and urban backyards, tropical forests and domestic orchards of several tropical countries. Fruits have a great diversity of metabolites, among which phenolic compounds stand out for their potential antioxidant, anti-inflammatory and other effects, and which have a preventive action on diseases of modernity. This review aimed to associate studies on the metabolic activities of *Garcinia* fruits and their numerous effects on health risk factors, such as obesity, hyperglycemia, inflammatory processes and dyslipidemias. Scientific articles published in English, Portuguese and Spanish were selected, which carried out studies involving the administration of *Garcinia* fruits *in vitro* and *in vivo*, mainly in the last five years. Sixty relevant articles were included in the study. Studies have shown that the *Garcinia* fruit species can be used in body weight control and prevention of cardiovascular disorders, cancer and diabetes mellitus, among other diseases associated with oxidative stress.

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Introduction

Plants of the genus *Garcinia* L. (Family: Clusiaceae Lindl.) can be found in tropical Africa, Asian continent such as Thailand, Myanmar, Philippines, Sri Lanka, Indonesia, New Caledonia, Polynesia and tropical regions of Brazil. *Garcinia* plants are used as ornamentation, food preservative, oil extraction, wood and fresh fruits around the world. Because they are found in rainforest and small farms, considered rich reservoirs of biodiversity, some of them are widely used in many countries for the treatment of various diseases by popular medicine (Espirito Santo et al., 2020; Liu et al., 2016).

Many varieties of *Garcinia* species are fruit trees, e.g., *Garcinia atroviridis* Griff. ex T.Anderson, *G. cochinchinensis* (Lour.) Choisy, *G. cowa* Roxb. ex Choisy, *G. dulcis* (Roxb.) Kurz, *G. forbesii* King, *G. gummi-gutta* (L.) Roxb, *G. livingstonei* T.Anderson, *G. madruno* (Kunth) Hammel and *G. mangostana* L. (Fig. 1), distributed in urban and rural yards, as well as small domestic orchards. Among the fruit plants, the most well-known species are the mangosteen (*G. mangostana*) and *G. gummi-gutta*, also called *G. cambogia* (Hargunani et al., 2020; Semwal et al., 2015).

Fig. 1: Fruit varieties of *Garcinia* species: (a) *Garcinia mangostana*, (b) *G. gummi-gutta (cambogia),* (c) *G. livingstonei,* (d) *G. cowa,* (e) *G. atroviridis,* (f) *G. dulcis,* (g) *G. forbesii,* (h) *G. madruno,* (i) *G. cochinchinensis.*

This genus presents a remarkable diversity of oxidized and prenylated phenolic derivatives, including xanthones, flavonoids, phenolic acids, benzophenones and hydroxycitric acid, responsible for the potential effects observed by the consumption of these plants, such as the so-called diseases of modernity, e.g., obesity, type 2 diabetes mellitus, cancer and cardiovascular disorders (Espirito Santo et al., 2020; Liu et al., 2015).

The antioxidant potential, anti-inflammatory and anti-obesity activities have been observed in extracts of several species of this genus, such as *G. cola* (Oyagbemi et al., 2016), *G. cambogia* (Hargunani et al., 2020), *G. mangostana* (Taher et al., 2016), *G. indica* (Panda et al., 2012), *G. xanthochymus* (Bheemaiah and Kushalappa, 2019), *G. parvifolia* (Hassan et al., 2017), *G. pedunculata* (Sarma et al., 2016), *G. achachairu* (Bagattoli et al., 2016), among others. This review aimed to present studies that have proven beneficial physiological and metabolic effects using the *Garcinia* fruit *in vitro* and *in vivo*.

Materials and methods

The Lilacs-Bireme, SciELO, Medline and Scholar Google databases were consulted. Scientific articles published in English, Portuguese and Spanish were selected, which carried out studies involving the administration of the *Garcinia* fruits *in vitro* and *in vivo*. Sixty relevant articles were included in the study.

The descriptors used for research articles in the databases were as follows: "*Garcinia* fruit", "antioxidant", "antimutagenic", "anti-inflammatory", "anti-hyperglycemic", "weight loss and obesity and anti-hyperlipidemic".

Results and discussion

Many studies have shown the beneficial physiological and metabolic effects of *Garcinia* species. Table 1 presents a summary of the species used, useful part, effects and mechanisms of action.

Garcinia and weight control

The significant increase in the prevalence of overweight and obesity in increasingly younger adults has aroused the concern of researchers and professionals, due to the damage and health problems caused by excess adiposities, such as diabetes, hyperlipidemia, hypertension, and cardiovascular diseases (Marques et al., 2018; Seidell and Halberstadt, 2015).

Scientific evidence links weight and obesity control with adequate consumption of fruits and vegetables (Yazew and Daba, 2020). The World Health Organization says that the minimum daily intake of 400 g of fruits and vegetables is an important factor in preventing obesity and related chronic disorders (Ness, 2004).

Table 1. Beneficial physiological and metabolic effects of *Garcinia* species.

Name scientific	Parts	Activities and effects	References
G. pedunculata	Pulp	Weight reduction	Sarma et al. (2016)
		Antihyperglycemic and antioxidant effects	Ali et al. (2017)
		Decrease in triglycerides and LDL-c	Sarma et al. (2016)
G. brasiliensis	Pulp	Reduction of adiposity and obesity	Moreira et al. (2017)
	Pulp	Antioxidant activity	Infante (2013)
G. mangostana	Pulp and leaves	Weight reduction	Watanabe et al. (2018)
		Anti-inflammatory capacity	Xie et al. (2015)
		Decrease inflammatory markers	Udani et al. (2009)
	Pericarp	Hypoglycemic effect	Taher et al. (2016)
		Decrease in triglycerides and LDL-c	Abuzaid et al. (2017)
		Antitumor effect	Mohamed et al. (2017); Ovalle-Magallanes et al. (2017)
G. cambogia	Pulp	Decrease visceral adiposity, adipocyte size and reduction body weight	Kim et al. (2013) Oluyemi et al. (2007)
		Control plasma lipids and reduction oxidative stress	Amin et al. (2011)
		Improvement in lipid profile	Sripradha et al. (2016);
		Decrease levels plasma leptin and proinflammatory cytokine	Sripradha and Magadi (2015)
G. indica	Pulp	Hypoglycemic effect	Kirana and Srinivasan (2010)
		Antioxidants effects	Mishra et al. (2006)
	Peels	Hepatoprotective activity	Panda et al. (2012)
G. kola	Pulp	Hypoglycemic effect	Farahna et al. (2017)
G. atrovirids	Pulp and leaves	Antihyperlipidemic activity	Al-Mansoub et al. (2017)
		Protection against atherosclerosis	Amran et al. (2009)
		Antioxidant activity	Nursakinah et al. (2012)
G. brasiliensis	Pulp and peels	Antioxidant activity	Infante (2013); Naves (2014)
G. achachairu	Pulp	Antioxidant activity in the ABTS, DPPH and FRAP assays	Virgolin (2015)
		Inhibition of cell tumor growth	Bagattoli et al. (2016)
G. lanceifolia	Pericarp	Antioxidant activity in the ABTS and DPPH models	Gogoi et al. (2015)
G. xanthochymus	Pericarp	Antioxidant activity in the ABTS and DPPH models	Gogoi et al. (2015)
G. morella	Pulp	Anti-proliferative action	Choudhury et al. (2018)
G. opaca	Pulp	Antitumor effect	Jabit et al. (2009)
G. garderiana	Pulp and leaves	Antiproliferative and antioxidant activity	Demenciano et al. (2020)
`	Pulp and peels	Hepatoprotective activity	Abu Bakar et al. (2015); Gogoi et al. (2017)

Consumption of some species of *Garcinia* has been associated with weight control and adiposity levels. The methanolic extract of the *G. pedunculata* pulp (200 mg kg^{-1} of body weight) was administered to obese rats induced by a high-fat diet, which caused a weight reduction of about 60 % compared to the control group that received the same hypercaloric diet without fruit extract for 60 days (Sarma et al., 2016). Similarly, the ethanolic extract of *G. brasiliensis* reduced the indicators of adiposity and obesity (Lee Index) in animals treated with a high-fat diet after 8 weeks (Moreira et al., 2017). The use of *G. mangostana* extract for 26 weeks in obese adult women with insulin resistance promoted an improvement in body weight compared to the control group, but the values were not significant (Watanabe et al., 2018).

In a study by Farinazzi-Machado et al. (2016), the pulp juice of the yellow mangosteen (*G. cochinchinensis* Choisy), a variety found in the orchard of a Brazilian college, significantly decreased visceral fat in experimental models after 40 days of treatment. Supplementation with *G. cambogia* also caused a significant decrease in visceral adiposity and adipocyte size by inhibiting the activity of fatty acid synthase and mRNA expression in the visceral adipose tissue of mice fed high-fat diets (45 kcal % fat) for 16 weeks (Kim et al., 2013). The ethanolic extract of the same species administered to rats orally at doses of 200 and 400 mg kg^{-1} per day, for 5 weeks, significantly reduced body weight, in the experimental by Oluyemi et al. (2007).

According to Fassina et al. (2015), several studies suggest positive results from the effectiveness of *G. cambogia* on the weight loss process, since the ideal dosage of consumption is not yet well established. Chuah et al. (2013) reported that a substantial amount of hydroxycitric acid, the main component responsible for the anti-obesity effect by reducing lipogenesis and accelerating fat oxidation, is present in the pericarp of the *G. cambogia* fruit.

Garcinia and glycemic control

Diabetes mellitus is a major global health concern that is expected to reach 642 million diabetics by 2040 (IDF, 2015). Despite innovative methods in the management of diabetes mellitus, morbidity and mortality remain high (Akshay Kumar et al., 2017). Studies have shown that several plant-derived natural products with different chemical structures can modulate blood glucose levels through various mechanisms and can be used to treat diabetes (Lee et al., 2018). Taher et al. (2016) described a 28-day administration to diabetic rats (50, 100, and 200 mg kg^{-1}) of an ethanolic extract from the *G. mangostana* pericarp that exhibited a hypoglycemic effect. Similar doses of *G. indica* aqueous extract (100 mg and 200 mg kg^{-1}) promoted a significant reduction in fasting and postprandial hyperglycemia in type 2 diabetic rats, with increased blood levels of erythrocyte glutathione (Kirana and Srinivasan, 2010).

Glutathione, the most abundant thiol that exists as a reduced and oxidized form in cells, plays an important role against oxidative stress. Its intracellular depletion leads to neurodegeneration, myocardial infarction and other cardiovascular complications in diabetes (Mohammedi et al., 2016).

In a study by Ali et al. (2017), streptozotocin-induced diabetic rats showed a significant improvement in hyperglycemia (42 %) and plasma insulin levels, and a decrease in glycated hemoglobin levels when treated with high doses (1000 mg kg^{-1}) of *G. pedunculata* methanolic extract. The aqueous extract of *G. kola* also administered to diabetic rats promoted an improvement in the glucose levels of these animals in relation to those that received distilled water, as demonstrated by Farahna et al. (2017).

Cardiovascular protection

Cardiovascular diseases are responsible for the highest mortality rate worldwide. In their multiple causes, while the main risk factors for these disorders, in addition to obesity, hypertension and smoking, dyslipidemias, which are characterized by increased serum levels of total and LDL cholesterol, and decreased of HDL cholesterol, are among the most significant factors (Guedes, 2016; Guerrero-García and Rubio-Guerra, 2018).

Although alternative mechanisms have been suggested, the simplest chain of events is that high concentrations of triglyceride are a marker for high cholesterol-rich remnants that, when entering into the intima, leads to low-grade inflammation, formation of foam cell, atherosclerotic plaques and, ultimately, cardiovascular disease and increased mortality (Nordestgaard and Varbo, 2014). Therefore, therapeutic actions resulting from the administration of plant extracts have caused a positive impact on plasma lipoproteins levels and, consequently, on the prevention of cardiovascular disorders in several studies (Calvo and Cavero, 2014; Farinazzi-Machado et al., 2017).

Amin et al. (2011) observed that the application of 500 mg day^{-1} of *G. cambogia* for 8 weeks in experimental models resulted in an improvement in plasma lipid levels and a reduction in oxidative stress. Also in experimental models, administration of *G. cambogia* ethanolic extract along with a high-fat diet significantly reduced total plasma cholesterol, triglycerides and non-HDL-C, in addition to increasing HDL-C levels (Sripradha et al., 2016). This species also caused a significant reduction in triglyceride levels in obese women who were treated daily (2.4 g day^{-1}) with the fruit extract for 60 days (Vasques et al., 2014).

The ethanolic extract of *G. mangostana* pericarp significantly decreased the level of triglycerides and LDL in rats after 9 weeks, at doses of 200 mg kg^{-1} and 500 mg kg^{-1} (Abuzaid et al., 2017).

Dehydrated pulp extracts of *G. pedunculata* caused a significant reduction in triglyceride (32 %) and LDL-C (38 %) values in the blood of male Wistar rats (Sarma et al., 2016).

Aqueous and methanolic extracts of *G. atroviridis* presented significant antihyperlipidemic activity in male rats treated for 16 weeks (Al-Mansoub et al., 2014). Working with the same fruit, Amran et al. (2009) showed that co-administration of the methanolic extract with a cholesterol-rich guinea pig diet reduced the serum lipid profile, as well as a reduction in fat deposition in the aorta, which may contribute to a lesser possibility of developing atherosclerosis.

Anti- inflammatory activity

Inflammation (derived from the Latin: *inflammatio*), also known as an inflammatory process, is a biological response of the body against an aggressive agent (González-Chávez et al., 2011). Obesity is one of the many chronic diseases that involve an inflammatory response characterized by an increase in cytokines and proteins of the acute inflammatory phase, e.g., C-reactive protein (CRP) and fibrinogen (Veigas et al., 2012). Specifically, macrophages in adipose tissue have emerged as a critical pathogenic factor for diseases of modernity. The infiltration of macrophages induces a high circulation of pro-inflammatory cytokines in adipose tissue, such as tumor necrosis factor-α (TNF-α) that causes an inflammatory state (Harman-Boehm et al., 2007).

Studies show that the anti-inflammatory action of the *Garcinia* plants must undoubtedly be the presence of numerous phenolic compounds found in expressive concentrations in this genus (Liu et al., 2015; Ramachandran et al., 2014; Swami et al., 2014; Yoshimura et al., 2015).

In the study by Xie et al. (2015), the use of a mangosteen- based beverage in healthy adults showed a significant increase in anti- inflammatory capacity: the CRP level in the group treated with mangosteen decreased significantly from 2.9 mg L^{-1} on the first day to 1.6 mg L^{-1} on the 30th day after consumption of the product.

In a similar study, a mixture of mangosteen juice (*G. mangostana*) administered to individuals between 30-75 years of age, body mass index (BMI) ≥ 30 and ≤ 45 kg/m^2 (obese), and high-sensitivity CRP (hs-CRP) of ≥ 3, resulted in a decrease in these inflammatory markers after 8 weeks (Udani et al., 2009).

Supplementing of the *G. cambogia* extract with a high-fat diet decreased significantly the levels of plasma leptin (p=0.031) and proinflammatory cytokine TNF-α (p=0.013) in experimental models (Sripradha and Magadi, 2015).

Antioxidant activity

Oxidative stress is closely linked to the diseases of modernity. Overproduction of reactive oxygen species (ROS) is considered to have a key role in hyperglycemia, dyslipidemia, and obesity (Liu et al., 2015). The antioxidant efficiency of bioactive compounds derived from plant depends on the structure and concentration. Use of aqueous extracts from *G. indica* fruit peels (800 mg kg^{-1}) in the ethanol-induced hepatotoxicity of Wistar rats promoted significant hepatoprotective activity by restoring depleted levels of glutathione, glutathione peroxidase, catalase, superoxide dismutase and glutathione reductase, after 28 days (Panda et al., 2012).

In a study by Sripradha and Magadi (2015), treatment with *G. cambogia* ethanolic extract significantly increased the blood antioxidants, e.g., glutathione (GSH) content and activities of glutathione peroxidase (GPx) and catalase. There was also a decrease in plasma malondialdehyde levels along with a reduction in total oxidant status due to an increase in total antioxidant status in the plasma and liver of rats after supplementation.

There are several varieties of *Garcinia* species that have shown antioxidant activity in *in vitro* models. Infante (2013) identified in the pulp of *G. brasiliensis*, expressive antioxidant activity by the stable DPPH (2,2- diphenyl- 1- picryl- hydrazyl- hydrate) free- radical, micellar model system linoleic acid–β-carotene and ORAC (oxygen radical absorbance capacity) assay. The aqueous and boiled kokam extract (*G. indica*) used in cooking and home remedies, in addition to the commercial kokam syrup, had significant antioxidant effects by ORAC method (Mishra et al., 2006).

The antioxidant activity of the *G. atroviridis* unripe fruits (1.63 mmol l^{-1}), measured by FRAP (ferric reducing antioxidant power) assay, showed a significantly higher level compared to matured fruits (1.47 mmol l^{-1}) (Nursakinah et al., 2012).

The pulp of *G. humilis*, known in Brazil as *G. achachairu*, was characterized by the highest content of phenolic compound and antioxidant activity in the ABTS [(2,2′-azinobis-(3-etilbenzotiazolin-6-sulphonic) acid], DPPH and FRAP assays (Virgolin, 2015).

The extracts of *G. lanceifolia* and *G. xanthochymus* pericarp, collected from the homestead garden, exhibited high potential for free-radical scavenging by the DPPH and ABTS models (Gogoi et al., 2015). The fruit-peel of *Garcinia brasiliensis* offered high antioxidant activity by the DPPH method, as demonstrated by Naves (2014).

Protection against cancer

Many extracts of medicinal plants and their compounds represent an alternative to conventional cancer therapy. A considerable number of studies on the antitumor activities of *Garcinia* species have been reported, and their activities have often attributed to the presence of depsidones, triterpenes, benzophenones and xanthones (Mackeen et al., 2000; Xia et al., 2015). Among them, mangosteen fruit extracts, as well as xanthones extracted from its pericarp, cause an antitumor effect in various types of cancer (Mohamed et al., 2017; Ovalle-Magallanes et al., 2017).

In vitro studies involving chloroform extracts from the *G. morella* pulp showed anti-proliferative action (dose and time-dependent) on breast cancer cells (MCF7, MDAMB231 e SKBR3), with garcinol being the main bioactive component found in this fruit (Choudhury et al., 2018). Bagattoli et al. (2016) observed that the methanolic extract of *G. achachairu* inhibited the growth of tumor cells (B16F10 – murine melanoma) in *in vitro* analysis.

The extract of *G. opaca* fruit presented a cytotoxic effect on three human tumor cell lines, representing breast, lung and prostate tumors, with the extract considered to have a strong and selective activity (Jabit et al., 2009). Antiproliferative activities were also observed in ethanolic extract and the hexane and chloroform fractions of fruits of *G. gardneriana* (Demenciano et al., 2020).

Xanthochymol and isoxanthochymol were isolated from *G. xanthochymus*, *G. mannii*, *G. stauditi*, *G. subeilliptica* and *G. pyrifera*, which exhibited significant growth suppression in the human leukemia cell line (Bheemaiah and Kushalappa, 2019).

The fruit peel and the fresh extract of *G. dulcis* have been shown to be a protective agent for liver damages (hepatoprotective activity) in experimental models and a potential cancer chemotherapeutic agent against liver cancer cells *in vitro*, respectively (Abu Bakar et al., 2015; Gogoi et al., 2017).

Conclusions

Scientific literature has shown that the fruit of *Garcinia* species can be used in the prevention of cardiovascular disorders, cancer and diabetes mellitus, among other diseases associated with oxidative stress, in addition to controlling body weight and its damage to health. These fruits have pharmacologically active constituents, but some are commercially exploited as a fruit crop or for medicinal purposes. Further research must be carried out to assess the mechanism of action of bioactive compounds with beneficial effects for the population.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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