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Review

Green Tea Induces the Browning of Adipose Tissue—Systematic Review

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Abstract: Several foods and nutrients are being studied extensively because they have a positive effect on thermogenesis and the browning of white adipose tissue. Therefore, this study aims to evaluate, through a systematic review, the effect of green tea for inducing browning of adipose tissue. The systematic review was built following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyze. We searched the following electronic databases: PubMed (Medline), Science Direct, Scopus, and Web of Science. We included ten experimental articles that used green tea to treat induced obesity in rodents. Green tea reduced the weight of white and brown adipose tissue, positively regulated gene expression and microRNA that regulate the metabolism of adipose tissue, and morphological changes were identified as beige tissue. According to the results found, the factors involved in this induction to browning are PPARγ, PGC-1α, UCP1, CPT, and PRDM16. Therefore, green tea promotes the browning of adipose tissue in rodents. It is important to emphasize the need for studies in obese humans to identify whether the same metabolic response occurs.

Keywords: *Camellia sinensis*; green tea; obesity; beige adipose tissue; browning

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1. Introduction

Adipocytes are cells specialized in the storage of lipids as triacylglycerol in their cytoplasm [1]. In mammals, there are two types of adipose tissue: white (WAT) and brown (BAT) [2].

The mature white adipocyte stores the triglycerides in a single large lipid molecule that occupies 85–90% of the cytoplasm and pushes the nucleus and a thin layer of the cytosol to the cell periphery [3]. The brown adipose tissue aims to maintain body temperature since it has a greater number of mitochondria and the ability to metabolize large energetic substrates to produce heat [1,2].

The main difference between BAT and WAT is the presence or absence of the uncoupling protein-1 (UCP-1) activity, located in the inner mitochondrial membrane of the

brown adipose tissue cells [3]. Uncoupling protein 1 (UCP1) participates in adaptive thermogenesis by decoupling the production of adenosine triphosphate from the lipids and carbohydrates catabolic pathways. The derived energy is released by the brown adipocytes as heat diffusing throughout the body, to the BAT rich vascularization [4].

Browning is characterized by the brown-like phenotype acquisition by white adipocytes [3]. The subcutaneous depots of WAT are the most common location for browning as these adipocytes are predominantly smaller and have a greater potential to differentiate [4]. Adrenergic stimulation initiates the thermogenic pathway. PGC1-α is a key factor to drive browning as it stimulates mitochondrial biogenesis and UCP1 transcription [3]. UCP1 and PR domain containing 16 (PRDM16) are consistent to identify the presence of beige adipocytes within the white adipocytes [5,6].

In recent years, a wide variety of pharmacological and nutritional compounds have been studied as agents of browning in humans and experimental models. In the present study, we focused on discussing recent in vitro and in vivo findings, though some problems in translating animal to human data exist [7].

Recently, beige adipocytes have been reported in the scientific literature. These are adipocytes that are located in the WAT, but resemble the brown adipocyte phenotype. The appearance of beige adipose tissue is due to the "browning", a process characterized by an increase in the WAT mitochondria density and metabolic function [5].

Nutrients are being studied extensively because they have a positive effect on thermogenesis and browning of WAT, such as capsaicin, vitamins A, D and E, omega 3, resveratrol, safflower, and flaxseed oils [4–7]. Green tea is studied due to its different mechanisms of anti-obesity action [8]. This study aims to evaluate, through a systematic review, the effect of green tea to induce browning of adipose tissue.

2. Methods

2.1. Data Sources and Search Strategy

The systematic review was constructed following the recommendations of PRISMA–Preferred Reporting Items for Systematic Reviews and Meta-Analyses [9]. This systematic review is registered in PROSPERO, and is available under number CRD42020179027.

A search was performed in the following electronic databases: PubMed (Medline), Science Direct, Scopus, and Web of Science. The search for articles published in all years until February 2020 was delimited. The following MESH terms were used: green tea, catechin, Camellia sinensis, browning, brown adipose tissue, white adipose tissue. Boolean operators "AND" and "OR" were used to cross the terms as follows: (green tea OR Camellia sinensis OR catechin) AND (brown adipose tissue OR white adipose tissue).

2.2. Selection and Study Eligibility

The evaluation of titles, abstracts, and complete papers was carried out following the steps of identification, screening, eligibility, and inclusion in February 2020. The articles selection was carried out by two researchers adopting the following inclusion criteria: experimental studies in animals (i.e., rats and mice) induced to obesity and exposed to the infusion of green tea, green tea extract or catechins; research on obese humans who consumed the infusion of green tea, green tea extract or catechins; and studies that evaluated the induction of browning of adipose tissue and published in English.

The non-inclusion criteria were: studies that did not use green tea, the association of green tea with other substances, herbal medicines or caloric restriction, review articles with humans or other animal species, experimental studies in genetically modified animals, experimental studies in which the method of obesity induction has not been the diet, animals submitted to physical exercise, even if voluntary, exposure to cold, studies that used beta-adrenergic system suppressant medication, and in vitro studies.

Then, the screening was carried out, and the duplicate records were eliminated. In the next stage, the articles' eligibility was considered, bearing in mind the methodology, by eliminating those that did not correspond to experimental studies. After reading the entire

consulted articles content, the records in the chosen databases were counted according to the inclusion criteria.

2.3. Data Extraction and Analysis

Each included article was read thoroughly, and pertinent information was extracted. Data extracted from each study were: the animal species, the green tea form of administration, the green tea dosage, extract or catechins, total catechins, duration, and the main results obtained.

The articles' quality assessment was carried out according to the ARRIVE guidelines—Animals in Research: Reporting Experiences at Vivo [10]. To assess the articles' adequacy to the ARRIVE Guidelines a scoring system (0–no; 1–yes) was used for the 20 listed items.

3. Results

The systematic review flow diagram is shown in Figure 1. The systematic search strategy retrieved 1781 records from the databases: PubMed (94), Science Direct (1423), Web of Science (250), and Scopus (14). Titles and abstracts were assessed and initially, 25 studies were considered eligible. After full-text review, 10 articles were deemed eligible. Human studies were not found.

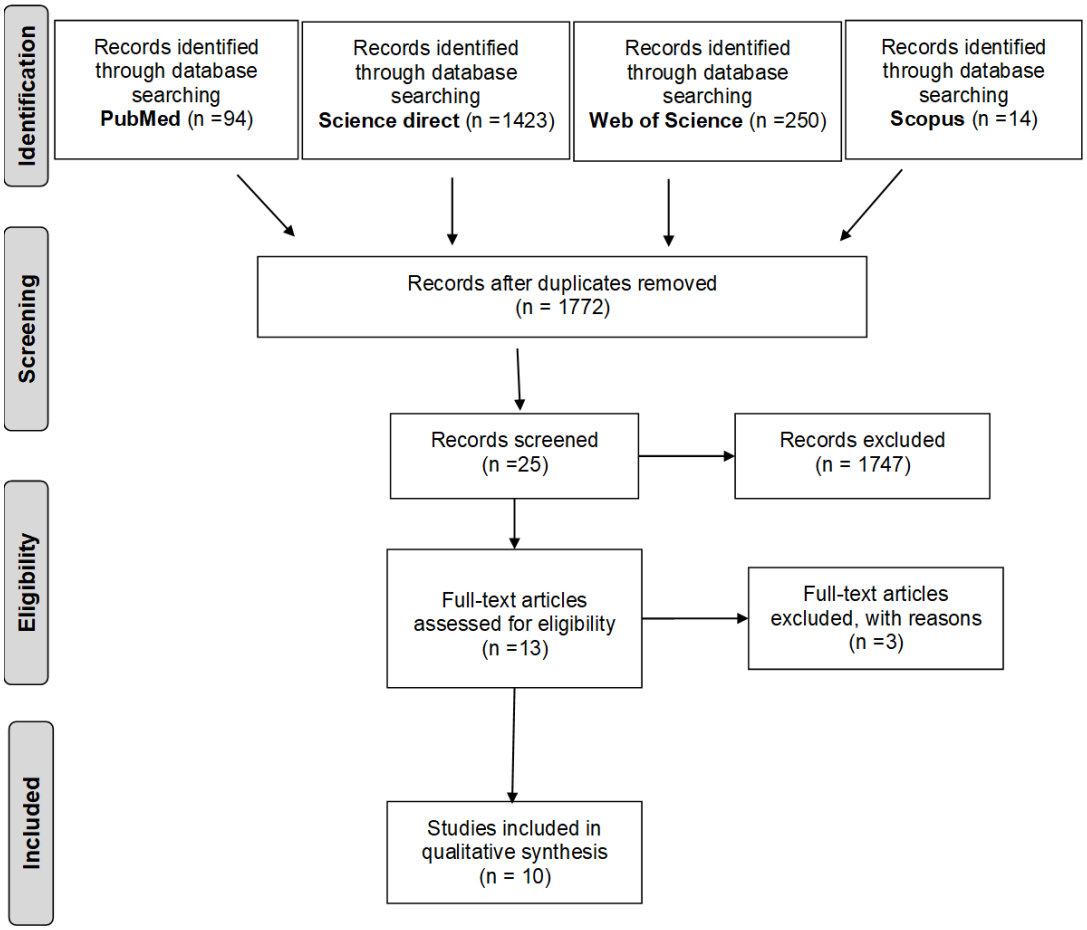

Figure 1. Flowchart of the selection stages of articles (adapted from PRISMA). Source: Own authorship.

Ten experimental articles were found in induced obesity rodents that used green tea is shown in Table 1. Of these, five used the C57BL/6J mouse [11–15], followed by three using the Sprague Dawley rats [16–18], a single study using the Swiss mice [19], and another study using the New Zealand black [20].

Table 1. Experimental studies in rodents that use green tea for browning.

Author/Year	Specie	Type of Diet	Method of Administration	Administered Dose	Catechin Content	Duration	Results
Chen et al. 2017 [15]	Rats (Sprague Dawley) induced obesity by diet	High-energy diet	Green Tea Extract	77.5 mg·kg^{-1} per day of extract of green tea 155 mg·kg^{-1} per day of extract of green tea	83.5% of catechins	8 weeks	eWAT → adipocytes were much smaller in the supplemented group compared to the high calorie diet; Significant increase in the expression of PPAR-γ, PRDM-16, BMP-7, FGF-21 and PGC-1α and reduction in TLE-3 in supplemented groups.
Klaus et al. 2005 [19]	Mice (New Zealand black–NZB) induced obesity by diet	High-fat diet (17% protein, 15% lipids and 42% carbohydrates)	EGCG	0.5% e 1% de TEAVIGO ™	94% of EGCG	4 weeks (induction obesity) + 4 weeks (treatment)	There were no changes in gene expression in BAT; WAT → SCD1 expression was reduced in groups supplemented with EGCG.
Lee et al. 2017 [13]	Mice (C57BL/6J) induced obesity by diet	High-fat diet (60% lipids)	EGCG	0.2% added in the diet	-	8 weeks (induction obesity) + 8 weeks (treatment)	The weights of WAT and BAT were decreased by 45% and 34%, respectively, in the group supplemented with EGCG compared to the high-fat group; BAT → EGCG in the diet significantly increased the expression of UCP1, UCP2, PRDM16, PGC-1α, NRF1, TFAM and CPT-1β and decreased of ACC2, compared to the high-fat group.
Mi et al. 2017 [10]	Mice (C57BL/6J) induced obesity by diet	High-fat and high fructose diet (45% lipids and 10% fructose)	EGCG	2 g EGCG per liter of water	-	16 weeks	BAT → EGCG intake restored average cell size and distribution; increased Sirt1 and Cpt2 and reduced Fasn; WAT → EGCG prevented HFFD-induced adipocyte hypertrophy and the uneven size distribution common to iWAT and eWAT; EGCG increased Sirt, PGC-1α and Cpt2 and reduced PPARγ and Fasn.
Neyrinck et al. 2017 [11]	Mice (C57BL/6J) induced obesity by diet	High-fat diet (60% lipids)	Green Tea Extract	0.5% extract of green tea added in the diet	60% of catechins 30% of EGCG	8 weeks	sWAT → GTE supplementation reduced the weight, the size of the adipocytes, significantly increased the expression of PPARγ, PGC-1α, Prdm16 and Cited1; BAT → GTE supplementation promoted normalization of weight and reduced size of lipid droplets in cells; significant reduction in the expression of C/EBPα and aP2; up-regulation of PGC-1α, Vegfa165; Beige adipocytes were defined by their multilocular lipid droplet morphology.

Table 1. *Cont.*

Author/Year	Specie	Type of Diet	Method of Administration	Administered Dose	Catechin Content	Duration	Results
Nomura et al. 2008 [16]	Rats (Sprague Dawley) induced obesity by diet	High-fat diet (60% fat)	Green Tea catechin	5 g catechins per kilo of feed	81.5% of catechins (EGCG–40.6%, ECG–23.1%, EGC–12.4%, EPI–9.2%)	8 weeks	BAT–weight reduction in supplemented animals Control group supplemented with GTC showed UCP1 mRNA expression 70% higher than animals fed a control diet; High-fat group showed similar mRNA expressions from the three UCPs.
Otton et al. 2018 [12]	Mice (C57BL/6) induced to obesity by diet	High-fat diet (20% protein, 36% carbohydrates and 34% lipids)	Green Tea Extract	500 mg·kg^{-1} of body weight per day	30% of catechins	4 weeks (inducation obesity) + 12 weeks (treatment)	BAT → weight and adipocyte reduction; sWAT and eWAT → weight and adipocyte reduction; eWAT → In the OB + GT group, only miR-802 was increased and 3 miRNAs were reduced (miR-335, miR-221, miR-155).
Santana et al. 2015 [18]	Swiss mice induced obesity by diet	High-fat diet	EGCG	50 mg·kg^{-1} of body weight per day	-	8 weeks	It did not promote changes in the hyperlipidic group supplemented with EGCG.
Yan et al. 2013 [17]	Rats (Sprague Dawley) induced obesity by diet	High fat diet (15% saturated fat and 1% cholesterol)	Green Tea Catechin	100 mg·kg^{-1} of body weight per day	50%–EGCG, 22%–ECG, 18%–EGC and 10%–EPI	6 weeks	sWAT and vWAT →GTCs increased the PPARγ and UCP-1; BAT → PPAR level increased, significantly increased the expression of CPT1, AOX, and UCP-1.
Zhou et al. 2018 [14]	Mice (C57BL/6) induced by diet to obesity	High-fat diet (60% lipids)	EGCG	1% EGCG of the diet composed	-	4 weeks	BAT→ increased expression of UCP1, PGC-1α and PRDM16 in the HFD + EGCG group.

sWAT—subcutaneos White Adipose Tissue, eWAT—epididymal White Adipose Tissue, vWAT—visceral White Adipose Tissue BAT—Brown Adipose Tissue, EGCG—Epigallocatequinagalate, ECG—epicatechin gallate, EGC—epigallocatechin (EGC), EPI—epicatechin, GT—Green Tea, GTE—Green tea extract, HFD—High-fat diet, GTC—Green Tea catechin, OB—Obese.

Eight of these studies used the high-fat diet with the fat percentage ranging from 15 to 60% [12–15,17,18,20]. One of the studies did not report the percentage [19]. The other studies submitted the animals to hypercaloric [16] and high-fat diets, 45% fat combined with 10% fructose [11].

The green tea was administered in the form of an extract [12,13,16]. Only isolated epigallocatechin [11,14,15,19,20] and the combination of green tea catechins [17,18] were also administered in animals. Green tea extract was added to the diet at a concentration of 0.5% [12]. The dose was also administered per kilo of weight, 77.5 mg, and 155 mg [16], and 500 mg [13].

The dose of EGCG ranged from 0.2 to 1% added to the diet [14–16,20]. The dose of 50mg per kilo of the animal's weight was supplemented in the work of Santana et al. (2015). The two-gram dose was diluted in per liter of water offered to the animal [11]. Catechins were administered at a dose of 100 mg per kilo of the animal's weight [18] and five grams of catechin per kilo of feed [17]. The total concentration of catechins in the studies ranged from 30 to 100% of the extract [12,13,15,17,18,20].

The study duration ranged from 4 to 16 weeks. Only three studies did not give the diet concomitantly to treatment [13,14,20]. Obesity induction was conducted in two studies for 4 weeks. In one, the animals were subjected to treatment with green tea extract for 12 weeks, maintaining the consumption of a high-fat diet [13]. In other, they submitted the animals to treatment for 4 weeks with EGCG but did not maintain their food intake [20]. Researchers induced obesity for 8 weeks and subjected the animals to treatment for another 4 weeks with EGCG while maintaining the high-fat diet [14].

Supplementation with green tea extract (GTE) reduced the weight and the size of the adipocytes in the subcutaneous adipose tissue [12], and reduced the weight and size of adipocytes of subcutaneous, epididymal, and brown tissue [13]. The weights of WAT and BAT were decreased by 45% and 34%, respectively, in the group supplemented with EGCG compared to those in the control group [14]. Catechins also reduced the weight of brown adipose tissue [17].

Supplementation with green tea extract (GTE) significantly increased the expression of PPARγ (Peroxisome proliferator type gamma), PGC-1α (Peroxisome proliferator Co-activator 1-alpha), PRDM16 and CITED1 in subcutaneous adipose tissue [12]. In brown adipose tissue, GTE supplementation promoted normalization of weight and reduced size of lipid droplets in cells; a significant reduction in the expression of C/EBPα and aP2; positive regulation of PGC-1α, and Vegfa165 [12]. The epididymal white adipose tissue supplemented with green tea extract showed lower adipocytes compared to a high-calorie diet. In the supplemented groups, significant expression increases in PPAR-γ, PRDM-16, BMP-7 (Bone Morphogenetic Protein 7), FGF-21 (Fibroblast Growth Factor 21) and PGC-1α were recorded, as well as reduced TLE-3 (transducin-like enhancer protein-3) [16].

After 12 weeks, the green tea extract promoted an epididymal tissue miR-802 increase, and a 3 miRNAs reduction (miR-335, miR-221, miR-155) in the supplemented obese group [13].

EGCG at a concentration of 0.2% of the diet significantly increased the expression of UCP1 (Uncoupling Protein 1), UCP2 (Uncoupling Protein 2), PRDM16, PGC-1α, NRF1 (Nuclear Respiratory Factor 1), TFAM (Mitochondrial Transcription Factor A), and CPT-1β (Carnitine Palmitoyltransferase I beta), and decreased ACC2 (Acetyl-CoA carboxylase 2) compared to the high-fat group. Beige adipocytes were also identified, defined by their lipid droplets multilocular morphology after EGCG supplementation [14]. EGCG added to 1% of the diet increased the expression of UCP1, PGC-1α, and PRDM16 in the high-fat group supplemented in brown adipose tissue [15].

While at 16 weeks, the 2 $g \cdot L^{-1}$ intake of EGCG restored the average cell size and adipocyte distribution; promoted an increase in PPARγ and a decrease in Cpt2 on brown adipose tissue about the high-fat group. The EGCG also prevented adipocyte hypertrophy induced by a high-fat diet and uneven size distribution; promoted an increase in Sirt, PGC-1α, and Cpt2, as well as a reduction in PPARγ and FASN in white adipose tissue [11].

EGCG for eight weeks, at a dose of 50 mg per kilo of the animal's weight, did not promote changes in the high-fat group, added only in the supplemented control group [19]. EGCG supplemented after obesity induction, reduced the white adipose tissue SCD1 expression. However, there were no changes in gene expression in brown adipose tissue [20].

Green tea catechins promoted a white adipose tissue increase in UCP-1 and PPAR-γ [18], and the brown adipose tissue increased expression of PPAR-γ, CPT1, AOX, and UCP-1 [18]. Catechins in the supplemented control group showed UCP1 mRNA expression 70% higher than animals fed a control diet [17].

All selected articles are experimental studies in rodents. Therefore, the ARRIVE guidelines were chosen to assess the studies' quality. The articles that make up this review reached 55 to 85% of the items recommended by the guidelines (Table 2).

Table 2. Analysis of methodological adequacy according to the ARRIVE guidelines.

Author/Year	Final Score (20 Points)	Percentage of Adequacy by ARRIVE
Chen et al. 2017 [15]	14/21	67%
Klaus et al. 2005 [19]	14/21	67%
Lee et al. 2017 [13]	11/21	52%
Mi et al. 2017 [10]	15/21	71%
Neyrinck et al. 2017 [11]	12/21	57%
Nomura et al. 2008 [16]	14/21	67%
Otton et al. 2018 [12]	17/21	80%
Santana et al. 2015 [18]	13/21	62%
Yan et al. 2013 [17]	13/21	62%
Zhou et al. 2018 [14]	15/21	71%

4. Discussion

The results found in this systematic review suggest that green tea promotes a reduction in the weight of brown and white adipose tissue, and a reduction in the fat droplet of the tissues and influences the expression of genes and microRNA that regulate the metabolism of adipose tissue, in addition to promoting the browning of white adipose tissue.

It is important to note that these experimental results have only been demonstrated in animals, clinical research has not been conducted on obese humans. Browning stimulation is a relatively recent therapy for the treatment of obesity. The maintenance of BAT activity and the browning of WAT has been proposed as effective strategies for the management of obesity.

Animal studies focused on the C57BL/6J mouse [11–15] followed by three articles with Sprague Dawley rats [16–18]. Both Sprague Dawley rats and C57BL6/J mice are animals prone to gaining weight through diet and developing obesity [21]. The Swiss mouse was used in only one study [20], but it is still a species that the high-fat diet also promotes a significant increase in weight, mainly in white adipose tissue [22].

Regarding the species, the work with New Zealand black was unexpected, as this species is used in experimental works for autoimmune models [23]. The authors' choice was based on findings in previous studies that showed NZB mice to be highly susceptible to the development of diet-induced obesity [20].

Most studies used the high-fat diet [12–15,17–20]. The relationship between high-fat diet and browning is already described in the literature. This diet promotes significant positive regulation of PRDM16 in rats. PRDM16 is a transcription factor that activates the differentiation of precursor cells into brown adipose cells [24].

However, little is discussed about the type and percentage of fat used in diets. This regulation is likely to differ when it comes to saturated, monounsaturated, and polyunsaturated fat. Research in this direction needs to be developed, as well as the percentage of dietary fat is another factor that can influence browning. The percentage of fat varied from 15 to 60% in the studies in this review [12–15,17,18,20]. Studies that evaluated the effect of the high-fat diet on browning used the percentage between 35.5 and 60% fat [24–26].

When it comes to the high-calorie, high-fructose diet, there are no reports in the scientific literature about their influence on browning and brown adipose tissue. However, they are effective diets to promote weight gain and metabolic changes [16].

Supplementation with green tea extract (GTE) was able to reduce the weight, the size of the adipocytes in the subcutaneous, epididymal, and brown adipose tissue [12–14], and catechins reduced the weight of brown adipose tissue [17]. These findings can be attributed to the composition of green tea.

Green tea has catechins and caffeine in its composition. Both components have mechanisms to reduce body fat. Green tea catechins can stimulate thermogenesis and oxidation of fat by inhibiting catechol-O-methyl transferase (COMT), an enzyme that degrades norepinephrine. Caffeine also inhibits the degradation of norepinephrine-induced by cyclic intracellular AMP phosphodiesterase (cAMP) [27]. Thus, green tea has anti-obesity effects.

Moreover, green tea increases PPARγ, PGC-1α, PRDM16, Vegfa165, BMP-7 (Morphogenetic Bone Protein 7), FGF-21 (Fibroblast Growth Factor 21), and CITED1. PPARγ activated in adipocytes ensures adequate release of adipocytokines (adiponectin and leptin), which are mediators of insulin action in peripheral tissues. As a result, the insulin sensitivity of the whole body is maintained. In addition to this adipogenic activity, PPARγ is also important in lipid metabolism and regulates genes that participate in the release, transport, and storage of fatty acids such as lipoprotein lipase (LPL) and the CD36 fatty acid transporter [28].

Green tea was able to reveal the expression of adipose tissue marker genes, FGF21, and Cited1 [12,16]. Suggesting the induction of beige adipogenesis [29]. Fibroblast growth factor 21 (FGF21) activates PGC-1α and accelerates the function of brown adipocytes [30]. PGC-1α is highly expressed in brown adipose tissue and skeletal muscle, the two main contributing tissues in adaptive thermogenesis through the adrenergic receptor axis PGC-1α–UCP-1. It can be induced by cold or adrenergic stimuli with improved mitochondrial biogenesis. Based on the findings of this review, it can be expressed through the supplementation of green tea extract in rodents [31].

Another important regulation was the increase in PRDM16. As already mentioned, it is a transcription regulator that controls the brown and beige adipocyte phenotype [24,32]. The increase in vascular endothelial growth factor (VEGFA) is an angiogenic factor in adipose tissue and is important for the development of new vessels. Overexpression of VEGFA in adipose tissue results in an increase in the number and size of blood vessels. In this way, it protects against hypoxia and obesity induced by a high-fat diet and improves insulin sensitivity and glucose tolerance [33].

It is worth mentioning the increase in BMP-7. Originally identified as a bone inducer, it is now recognized as a multifunctional cytokine and has been implicated as a potential therapeutic agent for cardiovascular, metabolic, and degenerative diseases [34]. This bone morphogenetic protein, BMP-7, is overexpressed in leaves of adipose-derived mesenchymal stem cells [35]. While BMP-2, -4, -6, and -7 are capable of inducing a massive accumulation of lipids in brown pre-adipocytes, only BMP-7 has a specific effect on inducing the brown fat specific UCP-1 protein by promoting the increased expression of PRDM16, PGC-1a, PGC-1β, and UCP-1 PPARγ, C/EBPα, and aP2 [34].

Moreover, green tea extract significantly reduced the expression of C/EBPα and aP2 brown adipose tissue and increased C/EBPα in subcutaneous adipose tissue [12,16]. CEBPα has an indispensable role in transcriptional activation and the increase is in line with long-term differentiation. Furthermore, the CEBP DNA-binding protein interacts with the aP2 promoter and elevates the expression of the aP2 gene. aP2 expression is highly induced during adipocyte differentiation [36]. That is, the increase in subcutaneous adipose tissue may indicate tissue differentiation.

The transducin-3 enhancer protein (TLE-3) was reduced after supplementation with the green tea extract. This protein suppresses selective genes from brown and induces selective genes from white adipose tissue. It is involved in a negative browning process

regulatory pathway [16]. A summary of the possible mechanisms for the action of green tea on browning is shown in Figure 2.

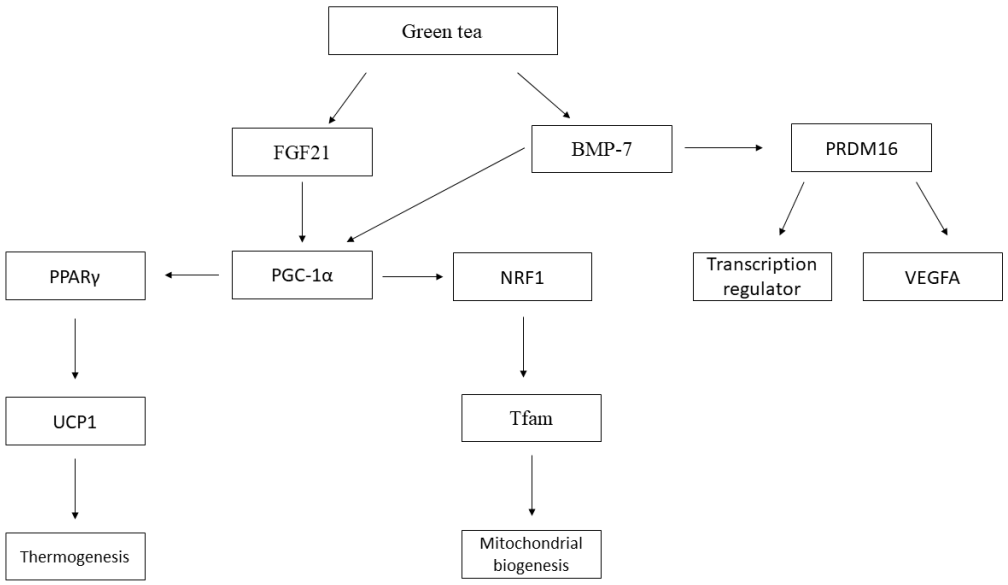

Figure 2. Possible mechanisms by which green tea stimulates the browning of adipose tissue.

Supplementation of catechins in green tea increased UCP-1, PPAR-γ in white adipose tissue and increased expression PPAR-γ, CPT1, AOX, and UCP-1 in brown adipose tissue at a dose of 100 mg·kg^{-1} body weight per day. The concentration of catechins used was 50% EGCG (epigallocatechin gallate), 22% ECG (epicatechin), 18% EGC (epigallocatechin), and 10%–EPI (epicatechin) for six weeks [18]. While 5 g of catechins per kilo of feed in the concentration of 81.5% catechins (EGCG–40.6%, ECG–23.1%, EGC–12.4%, EPI–9.2%) promoted increased expression of UCP1 mRNA by 70% than animals fed a control diet for eight weeks, but there was no difference between the high-fat groups [17].

The difference in the found results can be attributed to the percentage of fat in the high-fat diet. A diet with 15% saturated fat and 1% cholesterol was used, without reporting the total percentage of fat in the diet [18]. In the other study, they used a diet with 60% fat from coconut oil and palm oil. This reinforces the need for experimental research to standardize the type of diet use [17].

EGCG is the catechin present in greater quantity in green tea [37]. The supplementation with this catechin significantly increased the expression of UCP1, UCP2, PRDM16, PGC-1α, and PPARγ in brown adipose tissue [14]. EGCG stimulates PGC-1α and PRDM16, both regulate thermogenesis by stimulating UCP1 expression. UCPs are mitochondrial inner membrane proteins that decouple the oxidative respiratory chain, and three of these proteins have been reported to date. UCP1 is expressed mainly in adipose tissue, UCP2 is expressed ubiquitously in various tissues of the body, and UCP3 is specific for skeletal muscle and brown adipose tissue [11,14].

PGC-1a is known as the main stimulator of mitochondrial biogenesis. It causes the activation of nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (Tfam) that increase the expression of the genes necessary for mitochondrial function [14].

EGCG at a diet concentration of 0.2% significantly increased the expression of CPT-1β (carnitine palmitoyltransferase I β) and decreased of ACC2 in brown adipose tissue. CPT-1β is a rate-limiting enzyme in the regulation of fatty acids uptake and oxidation by the mitochondria in BAT, playing an important role in stimulating BAT thermogenesis. On the other hand, ACC2 inhibits CPT-1β activity by catalyzing the formation of malonyl-coenzyme (CoA) from acetyl-CoA [14]. Thus, green tea regulates thermogenesis by yet another metabolic pathway, CPT-1β.

In white adipose tissue, EGCG promoted increased expression of PGC-1α, CPT2, PPARγ, and SIRT1 (Sirtuin 1) [11]. Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD) dependent deacetylase protein, acting as a regulator of fatty acid oxidation and mitochondrial biogenesis by deacetylating the activated receptors gamma coactivator by peroxisome 1a proliferation (PGC1α). Activation of SIRT1 has been proposed as a key regulator to prevent obesity and obesity-related metabolic dysfunction [38]. Moreover, CPT2 codes for the enzyme carnitine palmitoyltransferase 2. This enzyme is involved in the transfer of long-chain fatty acids (AGCL) from the cytosol to the mitochondria, allowing greater oxidation and energy generation [39].

EGCG also promoted the reduction in FASN in white adipose tissue [11,19]. FASN encodes the enzyme fatty acid synthase (FASN) responsible for the synthesis of fatty acids. The reduction in FASN in white adipocytes from mature mice increases the sympathetic activity and induces the browning of white adipose tissue and improves glucose homeostasis in obese mice [40].

Supplemented EGCG after obesity induction reduced SCD1 expression in white adipose tissue [20]. SDC1 is the gene that encodes stearoyl-CoA desaturase, an enzyme responsible for the synthesis of monounsaturated fatty acids (MUFA) [41]. There are reports in the literature that overexpression of SDC1 increases leptin levels [42]. Corroborating the findings, leptin expression in WAT also decreased due to EGCG supplementation. As the expression of leptin in white fat is highly correlated with fat mass, this decrease may be a consequence of the reduction in the amount of fat, as it may be related to the lower expression of SDC1 [20].

Moreover, EGCG promoted morphological changes in adipose tissue as it prevented adipocyte hypertrophy induced by a high-fat diet and uneven size distribution [11]. Furthermore, browning was confirmed and beige adipocytes were identified, defined by their multilocular morphology of lipid droplets after EGCG supplementation [14].

The duration of the studies ranged from 4 to 16 weeks. This wide variation in the study period has a direct impact on the results found. Three-week studies showed an increase in adiposity with the high-fat diet, the percentage of fat accumulated in the liver, and an increase in triglycerides. Only after eight weeks, changes in weight and biochemical parameters were identified [43].

As for the induction method, most studies have induced obesity concomitantly with treatment. Only three studies did not submit the diet to treatment together. Both studies showed positive results for the regulation of brown adipose tissue and the reduction in white adipose tissue. Green tea extract and EGCG were shown to be efficient in the expression of markers involved in browning even with concomitant use or after the induction of obesity [13,14,20].

The main study's innovation was the microRNAs analysis, which has been a trend in current science. Supplementation of green tea extract at a dose of 500 mg·kg^{-1}, with 30% catechins for 12 weeks, promoted a reduction in 3 miRNAs (miR-335, miR-221, miR-155) in the supplemented obese group [13]. MiR-335 is positively regulated in adipocytes by pro-inflammatory cytokines, and this is prevented by catechins in green tea. MiR-155 is significantly increased in atherosclerosis and decreased in NAFLD, type 2 diabetes/insulin resistance (T2DM / IR), and obesity [44]. MiR-221 adipose is over-regulated in obesity [45]. Moreover, the tea extract increased the expression of miR-802 [13]. The expression of miR-802 in obese mice contributed to the induction of obesity and impaired metabolism, while inhibition of miR-802 in obese mice improved glucose tolerance [46]. The green tea was not able to inhibit an increase in miR-802.

In humans who are obese, some studies have shown the benefits of green tea in metabolic health. However, the effects of green tea on brown adipose in obese individuals have not been studied; in healthy individuals increased EE is associated with increased BAT and BAT density [47,48].

The limitation of this review comprises the evident methodological differences observed in the research carried out, such as the great variation in the percentage of fat in

the high-fat diet, the green tea form of preparation and dosage, and the study time. It is important to point out that no studies were found with the infusion of green tea, and it is known that this corresponds to the greatest form of use by humans.

5. Conclusions

The anti-obesity effect of green tea is proposed by different mechanisms. There are mechanisms elucidated by the reduction in body fat via COMT. However, the induction of browning was identified by the morphological changes in the white adipose tissue. However, there is no defined mechanism, but it seems to involve different genes and microRNA expression. According to the results found, the factors involved in this induction to browning are PPARγ, PGC-1α, UCP1, CPT, and PRDM16. The studies do not follow a methodological pattern to evaluate the green tea utilization, including the duration, type of diet, dose administration, way of use, and the genes to be analyzed; therefore, this makes it difficult to outline the mechanism of action, as there are several possibilities. However, the most likely mechanism is the PGC-1α–UCP1 axis. It is important to emphasize the need for studies in obese humans to identify whether the same metabolic response occurs.

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Abbreviations

ACC2	Acetyl-CoA Carboxylase 2
AGCL	Long-Chain Fatty Acids
BAT	Brown Adipose Tissue
BMP-7	Bone Morphogenetic Protein 7
cAMP	Cyclic Adenosine Monophosphate
COMT	Catechol-O-Methyl Transferase
CPT-1	Carnitine Palmitoyltransferase I
Epicatechin	ECG
EGCG	Epigallocatechin 3-gallate
EGC	Epigallocatechin
Epicatechin	PPE
FASN	Fatty Acid Synthase
FGF-21	Fibroblast Growth Factor 21
GTE	Green Tea Extract
HFD	High-fat Diet
IR	Insulin Resistance
MUFA	Monounsaturated Fatty Acids
NAD	Nicotinamide Adenine Dinucleotide

NASH	Non-alcoholic Steatohepatitis
NRF1	Nuclear Respiratory Factor 1
PPARγ	Peroxisome Proliferator Type Gamma
PGC-1α	Peroxisome proliferator Co-activator 1-alpha
SBCAL	Brazilian Society of Science in Laboratory Animals
SIRT1	Sirtuin 1
TFAM	Mitochondrial Transcription Factor A
TLE-3	Transducin-like Enhancer Protein-3
T2DM	Type 2 diabetes
UCP1	Uncoupling Protein-1
UCP2	Uncoupling Protein 2
WAT	White Adipose Tissue

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