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REVIEW

# Ginger and avocado as nutraceuticals for obesity and its comorbidities

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Obesity is a worldwide epidemic and is one of the factors involved in the etiology of type 2 diabetes mellitus. Obesity induces low-grade inflammation and oxidative stress. The treatment for obesity involves changes in diet, physical activity, and even medication and surgery. Currently, the use of nutraceutical compounds is associated with health benefits. Ginger and avocado are used for many people all around the world; however, its effect as a nutraceutical compound is less known by the general population. For this reason, we searched information of the literature to point its effects on distinct mechanisms of defense against the obesity its comorbidities. The present review aimed showing that these nutraceuticals may be useful in obesity treatment. Reports have shown that ginger and avocado induce antioxidant and anti-inflammatory effects by improving enzymatic activity and modulating obesity-related impairments in the anti-inflammatory system in different tissues, without side effects. Furthermore, ginger and avocado were found to be effective in reversing the harmful effects of obesity on blood lipids. In conclusion, on the basis of the positive effects of ginger and avocado in in vitro, animal, and human studies, these nutraceuticals may be useful in obesity treatment.

**KEYWORDS**

diabetes treatment, inflammation, obesity, oxidative stress, phytotherapeutic approach, unhealthy diet

## 1 | INTRODUCTION

Obesity is defined as an excessive accumulation of body fat caused by disparity in energy balance, where a combination of high caloric intake and a sedentary lifestyle results in a significantly increased incidence of health problems, such as diabetes, hypertension, cardiovascular diseases, dyslipidemia, and atherosclerosis (Perez, Sanchez, & Ortiz, 2013; Sasson, Lee, Jan, Fontes, & Motta, 2014). Food intake is controlled by a complex regulatory network that depends on the central regulation of energy homeostasis, and a disturbance in these processes may lead to obesity. The hypothalamus is critical in the regulation of food intake controlling neural circuits, which produce a number of neuropeptides that influence food intake, moreover receives and integrates neural, metabolic, and humoral signals from the periphery (Ropelle et al., 2009). The neurons of the hypothalamus receive information about energy stocks from hormones as insulin and leptin, modulating two subpopulations of neurons in the arcuate nucleus inducing hunger or satiety (Niswender et al., 2003; Schwartz, Woods, Porte Jr., Seeley, & Baskin, 2000). Leptin and insulin sending crucial physiological signal to the hypothalamus regarding of the regulation of the daily pattern of ingestive behavior. When input from these hormones is prejudiced, example insulin and leptin resistance, therefore, the hypothalamus loss feeding behavior pattern and triggers to hyperphagia that favors weight gain (De Souza et al., 2005).

The world average body mass index (BMI) increased from 21.7 kg/m$^2$ in 1975 to 24.2 kg/m$^2$ in 2014 in men (Ezzati et al., 2017), whereas the number of women worldwide with obesity increased from 71 million in 1974 to 375 million in 2014 (Di Cesare et al.,

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2016). Obesity is one of the factors involved in the etiology of type 2 diabetes mellitus, the incidence of which is increasing; more than 400 million people have diabetes, and this number is estimated to reach 600 million in 2040 (Annette, Ramesh, & Reddy, 2017). Moreover, insulin resistance (IR) is a clinical condition that may occur years before the onset of hyperglycemia, which characterizes type 2 diabetes mellitus; IR consists of an increase in insulin concentration and an attenuation of the biological response to insulin, resulting in hyperinsulinemia (Cefalu, 2001).

## 2 | OBESITY AND ITS EFFECTS

Adipose tissue is an endocrine organ, but excess adipose tissue and adipocyte hypertrophy can lead to changes in metabolism, appetite control and satiety, insulin secretion, and sensitivity. Moreover, adipocyte hypertrophy is followed by infiltration of macrophages and increased inflammation with production of proinflammatory adipokines, such as tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β), and interleukin-6 (IL-6) (Alomar et al., 2015; Galic, Oakhill, & Steinberg, 2010; Kintscher et al., 2008), accompanied by an increase in the release of free fatty acids and deregulation of leptin secretion (Galic et al., 2010) and adiponectin (Wree et al., 2012). Increased production of IL-1β cytokines in macrophages and TNF-α is involved in the systemic inflammatory response and has been associated with the development of IR and diabetes in rodents (Dulloo, Jacquet, Solinas, Montani, & Schutz, 2010). This chronic subclinical inflammation, which exerts effects mainly on the brain, liver, muscle, endothelium, and pancreas (Annette et al., 2017), is one of the reasons for the association of obesity with other pathologies (Flehmig et al., 2014; Gregor & Hotamisligil, 2011). Thus, obesity induces hyperexpression of TNF-α and several other inflammatory cytokines (Hotamisligil, Shargill, & Spiegelman, 1993; Marseglia et al., 2015; Spoto et al., 2014). Conversely, studies have shown that reducing body weight and visceral fat is associated with anti-inflammatory effects (Arslan, Erdur, & Aydin, 2010; Dror et al., 2017; Galic et al., 2010).

Dietary components also affect the inflammatory profile. Saturated fatty acids such as palmitate or long-chain saturated fatty acids activate receptors leading to increased phosphorylation of the main intracellular inflammatory pathway signals, including JNK and IKK. On the other hand, it has been reported that the unsaturated fatty acid palmitoleate is incapable of inducing the release of TNF-α or other inflammatory signals (Lancaster et al., 2018). In addition, obesity and a high-fat diet alter the composition of the intestinal microbiota involved in systemic inflammation and increase the intestinal absorption of microbial products derived from the intestine. This increases the concentration of circulating lipopolysaccharides, leading to metabolic endotoxemia (Cani et al., 2007; Sonnenburg & Backhed, 2016), which can initiate inflammation of adipose tissue and activation of macrophages in a toll-like receptor 4-dependent manner (Caesar, Tremaroli, Kovatcheva-Datchary, Cani, & Backhed, 2015).

As described above, it has long been known that obesity is related to inflammation. Moreover, obesity is also associated with the oxidative stress mechanism. In fact, obesity induces oxidative stress as a consequence of an imbalance in the redox system due to the excess of free radicals, reactive oxygen species (ROS), and/or antioxidant disruption (Schieber & Chandel, 2014). The possible contributors to increased ROS in obesity include hyperglycemia (Aronson & Rayfield, 2002), high accumulation of ectopic fat (Beltowski, Wojcicka, Gorny, & Marciniak, 2000), vitamin and mineral deficiencies (Ortega et al., 2012), chronic inflammation (Fernandez-Sanchez et al., 2011), hyperleptinemia (Bouloumie, Marumo, Lafontan, & Busse, 1999), impairment of mitochondrial function (Pennathur & Heinecke, 2007), and increased of the NADPH oxidase pathway (DeVallance, Li, Jurczak, Cifuentes-Pagano, & Pagano, 2019). In addition, endogenous and exogenous antioxidant compounds are inversely related to body fat and visceral obesity and induce cell damage in obese individuals (Chrysohoou et al., 2007). Oxidative stress may in turn stimulate white adipose tissue deposition and increase preadipocyte proliferation, adipocyte differentiation, and mature adipocyte size, ultimately altering food intake (Higuchi et al., 2013). Furthermore, ROS are involved in controlling body weight, exerting effects on hypothalamic neurons that control satiety and hunger (Horvath, Andrews, & Diano, 2009). This link between oxidative stress and obesity has been demonstrated in animal models; for example, obese rodents have a high degree of lipid peroxidation and $H_2O_2$ production in adipose tissue, whereas the expression and activity of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), are downregulated (Furukawa et al., 2004). Finally, clinical studies have established correlations of biomarkers and end products of oxidative stress (lipid peroxidation and protein carbonylation) with BMI, supporting this obesity-induced oxidative stress hypothesis in humans (Sankhla et al., 2012; Vincent & Taylor, 2006).

As classical pharmaceutical products are not sufficient to reduce obesity and related diseases, the use of bioactive compounds, known as nutraceuticals, may be an additional strategy. Because these compounds can modulate metabolism and reduce inflammation, oxidative stress, risk of diabetes, dyslipidemia, and risk of cardiovascular and neurodegenerative diseases, they may be used to prevent and treat obesity and its comorbidities (Bluher, 2013).

## 3 | GINGER AS A NUTRACEUTICAL

Ginger (*Zingiber officinale* Roscoe), described in 1807 by William Roscoe, is one of the most widely used spices in the world. Belonging to the family Zingiber aceae, it contains a variety of phytochemicals, such as phenols and flavonoids (Palatty, Haniadka, Valder, Arora, & Baliga, 2013). The chemical constituents of ginger can be divided into volatiles and nonvolatiles (Govindarajan, 1982); volatiles consist mainly of several terpenoids, whereas the nonvolatile compounds include gingerol, zingerone (Butt & Sultan, 2011), and 12-dehydrogingerdione (Zhao et al., 2019). Among the medicinal properties of ginger, the following properties stand out: anti-inflammatory (Grzanna, Lindmark, & Frondoza, 2005; Li, McGrath, Nammi, Heather, & Roufogalis, 2012), antiemetic (Palatty et al., 2013; Zick et al., 2008), anticancer (Pereira,

Haniadka, Chacko, Palatty, & Baliga, 2011), antilipidemic (Alizadeh-Navaei et al., 2008; Naidu et al., 2016), and hypoglycemic (Lee et al., 2015).

### 3.1 | Ginger as antiobesity nutraceutical

Many studies show that ginger may influence body weight reduction by increasing thermogenesis, release of catecholamines (Pulbutr, Thunchomnang, Lawa, Mangkhalathon, & Saenubol, 2011), and lipolysis in white adipose tissue (Ahn & Oh, 2012; Mansour et al., 2012; Pulbutr et al., 2011). In addition, analysis of cellular respiration in human skeletal myotubes revealed that ginger extract increased the rate of palmitate-induced oxygen consumption, suggesting that fatty acid oxidation was increased (Misawa et al., 2015). Moreover, ginger produces a hypoglycemic effect in diabetic animals, in addition to reducing accumulation of liver fat in animals that have been fed a high-fat diet, as it improves insulin sensitivity, activates peroxisome proliferator-activated receptor gamma, and reduces acetyl-CoA carboxylase and fatty acid synthase activities (Okamoto et al., 2011; Rahimlou, Yari, Hekmatdoost, Alavian, & Keshavarz, 2016). Finally, ginger reduces circulating levels of proinflammatory cytokines (Isa et al., 2008; Saravanan, Ponmurugan, Deepa, & Senthilkumar, 2014; Shalaby & Saifan, 2014).

Ginger is a functional dietary agent for weight control and prevention of metabolic disorders (Al-Amin, Thomson, Al-Qattan, Peltonen-Shalaby, & Ali, 2006; Chrubasik, Pittler, & Roufogalis, 2005; Goyal & Kadnur, 2006; Matsuda et al., 2009; Nammi, Sreemantula, & Roufogalis, 2009; Okamoto et al., 2011); supplementation with 75-mg/kg/day 6-gingerol has been shown to reduce body weight (Naidu et al., 2016; Saravanan et al., 2014). A decrease in food intake, body weight, and fat accumulation was reported after supplementation with 500-mg/kg/day *Z. officinale* (Kaur & Kulkarni, 2001). In a clinical trial, a higher dose of 2,000-mg/kg/day ginger supplementation caused a decrease in hip circumference (Honarvar et al., 2019). The mechanism through which ginger can control appetite seems to be through serotonin modulation and binding to 5-HT2c receptors, which regulate satiety (Goyal & Kadnur, 2006; Mansour et al., 2012; Palatty et al., 2013). The ethanolic extract of ginger diminishes weight gain in mice with a high fat diet (Kim, Kim, Mun, Jeong, & Cha, 2018) and in animal models of diabetes (Al Hroob, Abukhalil, Alghonmeen, & Mahmoud, 2018). Ginger extract containing gingerol, the most active compound in the plant, reduced adipocyte differentiation and increased insulin-sensitive glucose uptake (Sekiya, Ohtani, & Kusano, 2004; Tzeng, Liou, Chang, & Liu, 2015). In aged rats, 6-gingerol improved HOMA-IR, whereas this effect was not observed in young rats (Li et al., 2019). Ginger may have a therapeutic effect on plasma lipids by elevating the hepatic activity of the enzyme cholesterol 7α-hydroxylase, which is responsible for the biosynthesis of bile acids, thus stimulating the conversion of cholesterol to bile acids and facilitating excretion (Ahn & Oh, 2012). For example, 0.4-g/kg/day reduced total cholesterol and increased HDL similar to the effect of atorvastatin, a standard cholesterol-lowering drug, in a hyperlipidic diet (Nammi et al., 2009). Diabetic rats supplemented with 0.050-g/kg/day zingerone showed a decrease in total cholesterol, triglyceride, and LDL levels and an increase in the HDL level (72). Ethanolic ginger extract administration (400 or 800 mg/kg/day) in diabetic rats decreased total cholesterol, triglyceride, and LDL levels and increased the serum HDL level (Al Hroob et al., 2018). Ten weeks of ginger supplementation (8,000-mg/kg diet, high hydrostatic pressure) in rats on a high-fat diet resulted in elevated HDL and decreased total cholesterol and serum triglyceride levels (Kim et al., 2018).

### 3.2 | Ginger as anti-inflammatory nutraceutical

The anti-inflammatory potential of ginger and its compounds has also been reported; zingerone decreases NFκB levels, besides down-regulating other cytokines such as IL-1β, IL-6, and TNF-α. Ginger supplementation (500 mg/kg) in mice with a hyperlipidic diet was able to decrease the serum levels of IL-6 and TNF-α (Ahmad et al., 2018). Zingerone also decreases nephritis by decreasing the levels of TNF-α (Alibakhshi, Khodayar, Khorsandi, Rashno, & Zeidooni, 2018), IL-1β, and IL-6 in the kidneys of diabetic rats supplemented with ethanolic extract of *Z. officinale* (Al Hroob et al., 2018). Ginger extract and 6-gingerol are capable of decreasing TNF-α levels in the adipose tissue of animals fed a hyperlipidic diet (Nammi et al., 2009). Ginger can also decrease the expression of mRNAs from genes related to adipogenesis and proinflammatory cytokines, such as peroxisome proliferator-activated receptor gamma, TNF-α, IL-6, and MCP1, in addition to increasing AMPK activity in rats on a hyperlipidic diet (Kim, Kim, et al., 2018; Suk et al., 2017).

### 3.3 | Ginger as antioxidant nutraceutical

Antioxidant effects have also been reported for ginger and its extracts, derived mainly from its high content of polyphenols, which neutralize free radicals (Mukherjee, Mandal, Dey, & Mondal, 2014). Supplementation with 100, 200, and 400 mg/kg of ginger extract for 10 days reduced acetic acid-induced protein carbonylation in the colon of animals, reducing the colonic mucosal lesions (El-Abhar, Hammad, & Gawad, 2008). Diabetic animals treated with ginger extracts showed reduced protein carbonylation, as the extracts positively modulate the activity of the enzyme aldolase reductase 2, thus normalizing the polyol pathway and preventing oxidative stress under hyperglycemic conditions (Saraswat et al., 2010). The isolated compounds 6-gingerol and 6-shogaol also showed positive effects in response to *Z. officinale* in the prevention of protein glycation, suggesting that regular consumption of ginger root extract may attenuate the progression of diabetic complications (Zhu, Zhao, Wang, Ahmedna, & Sang, 2015).

One of the main bioactive derivatives present in ginger, 6-shogaol, inhibited the production of ROS and increased the levels of total glutathione, heme oxygenase-1, and quinone oxidoreductase 1 through the activation of nuclear factor erythroid 2-related factor

2 (Park, Oh, Lee, Lee, & Kim, 2016). Furthermore, 6-gingerol protected pancreatic β cells from oxidative stress, reducing ROS production (Son, Miura, & Yagasaki, 2015), possibly by increasing the activity of the antioxidant enzymes SOD3 and CAT (Lee et al., 2015). In rat heart tissue, *Z. officinale* supplementation resulted in an increased activity of SOD, CAT, and the glutathione antioxidant system, leading to lower isoproterenol-induced oxidative damage (Ansari, Bhandari, & Pillai, 2006). In alloxan-induced diabetic animals, zingerone increased the activity of GSH, SOD, CAT, and GPx enzymes in the liver, thus reducing peroxidative damage (Ahmad et al., 2018). Aged mice supplemented with 6-gingerol showed increased activity of GSH and SOD enzymes and expression of CAT, GPx1, SOD1, SOD2, and SOD3 (Li et al., 2018). Finally, zingerone is also capable of decreasing cisplatin-induced nephrotoxicity by decreasing MDA levels and increasing GSH, GPx, and CAT activity (Alibakhshi et al., 2018).

### 3.4 | Ginger as a neuromodulator nutraceutical

Increasing epidemiological evidence shows that obesity is closely related to brain dysfunction and early onset of Alzheimer's disease. Ginger supplementation (100 or 200 mg/kg) reduced neuroinflammation and cognitive deficits in a rat model of neuroinflammation by increasing the antioxidant enzymes GSH, GPx, and SOD, as well as by reducing the levels of NO (Zhang et al., 2018). In vitro, the administration of 12-dehydrogingerdione in lipopolysaccharides-activated microglial cells decreases TNF-α and IL-6 secretion, in addition to decreasing the expression of iNOS and COX-2 and inhibiting the production of NO by suppressing the NfKb and Akt/IKK signaling pathways (Zhao et al., 2019). Recognition memory was also improved by ginger extract via ERK/CREB activation, resulting in increased learning and memory (Lim et al., 2014). Administration of 100-mg/kg/day *Z. officinale* to animals treated with methylene dioxy-methamphetamine attenuated apoptotic cell death and improved learning memory (Mehdizadeh et al., 2012). Finally, in a dementia model, pretreatment with 6-gingerol was able to increase brain-derived neurotrophic factor signaling and reverse memory damage in aversive and spatial memory (Kim, Seo, Lee, Park, & Jang, 2018).

## 4 | AVOCADO AS A NUTRACEUTICAL

Avocado (*Persea Americana* Mill.), belonging to the Lauraceae family, is a native fruit of Central and South America (Flores et al., 2019). Avocados are rich in fat (approximately 15% by wt.), containing predominantly monounsaturated fatty acids (MUFA; 9.6% by wt.), which represent 62.8% to 63.6% of the total fatty acids found in avocados (Fulgoni, Dreher, & Davenport, 2013), with a predominance of oleic acid (Duarte, Chaves, Borges, & Mendonca, 2016; Fulgoni et al., 2013). The oil consists of approximately 71% MUFAs, 13% polyunsaturated fatty acids, 16% saturated fatty acids (Dreher & Davenport, 2013), fiber, vitamin B, vitamin K1, vitamin E, magnesium, potassium, and phytochemicals such as carotenoids, phenolics, and phytosterols (Fulgoni et al., 2013; Naveh, Werman, Sabo, & Neeman, 2002). Many of these compounds are antioxidants, including polyphenols, proanthocyanidins, tocopherols, and carotenoids. These antioxidants have shown positive health outcomes in humans and animal models, helping to control weight, reduce the risk of diabetes (Lermangarber, Ichazocerro, Zamoragonzalez, Cardososaldana, & Posadasromero, 1994; Radika, Viswanathan, & Anuradha, 2013), normalize blood cholesterol levels (Carvajal-Zarrabal et al., 2014), and improve hepatic metabolism (Brai, Adisa, & Odetola, 2014; Werman, Neeman, & Mokady, 1991).

### 4.1 | Avocado as antiobesity nutraceutical

Treatment of hypercholesterolemic rats with aqueous solutions and methanolic extracts of *P. americana* leaves (10 mg/kg) for 8 weeks reduced body weight gain by 25% when compared with that in controls (Brai, Odetola, & Agomo, 2007). Supplementation with hydroalcoholic extracts of the fruit (100-mg/kg body weight) for 12 weeks reduced weight gain (24.77%) and BMI (17.92%) in rats fed a high-fat diet (Padmanabhan & Arumugam, 2014). Body weight reduction and improved insulin sensitivity were observed in rats fed a sucrose-rich diet and supplemented with 10–30% avocado oil for 8 weeks (Del Toro-Equihua, Velasco-Rodriguez, Lopez-Ascencio, & Vasquez, 2016). Animals pretreated with an aqueous extract of avocado (100 and 200 mg/kg) for 7 days were protected against CCL4-induced hepatic toxicity, as it reduced the activity of the liver enzymes aspartate aminotransferase and serum alanine aminotransferase and decreased serum bilirubin levels (Brai et al., 2014).

Treatment of hypercholesterolemic rats for 8 weeks with avocado oil (450 and 900 mg/kg/day) partially improved the lipid profile (lower LDL and triglycerides and higher HDL) and increased the activity of the Krebs cycle (Tan, Chong, Hamzah, & Ghazali, 2018). β-sitosterol regulates cholesterol levels (Wu, Molteni, Ying, & Gomez-Pinilla, 2003), decreases the risk of atherogenic plaque formation (Rosenblat, Volkova, & Aviram, 2013), and controls glycemia (Radika et al., 2013). The high concentrations of MUFAs in avocado suggest that an avocado-rich diet results in beneficial effects on blood lipids (Mahmassani, Avendano, Raman, & Johnson, 2018).

### 4.2 | Avocado as antioxidant nutraceutical

Avocado oil has a wide variety of lipophilic antioxidants, which may decrease ROS production in renal mitochondria of STZ-induced diabetic rats (Ortiz-Avila et al., 2013; Ortiz-Avila et al., 2017). Moreover, supplementation with aqueous extracts of avocado induced a decrease in the protein carbonylation in an animal model of liver fibrosis (Brai et al., 2014). Supplementation of mice with β-sitosterol increased the activities of antioxidant enzymes such as SOD, CAT, and GSH, lowering lipid damage (Yin et al., 2018). Avocado oil is also rich in carotenoids, which have the ability to remove cellular superoxide ions ($O_2^{-}\bullet$) suggesting that, in addition to β-sitosterol, the carotenoids of avocado oil also have a protective role against oxidative damage (Foss et al., 2004; Galano, Vargas, & Martinez, 2010; Han, Zhang, & Skibsted, 2012).

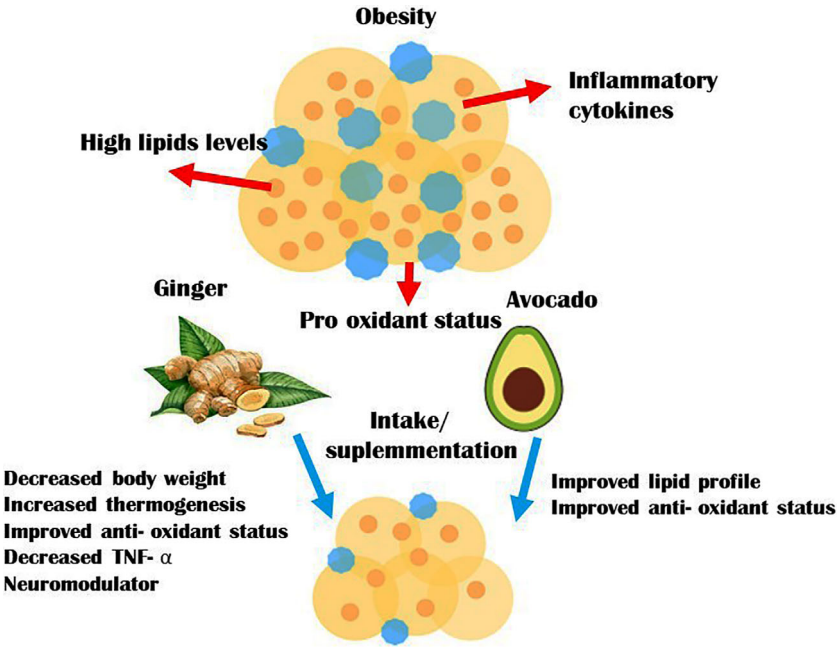


**FIGURE 1** Obesity induces inflammatory cytokines, oxidative stress and high lipids levels on adipocyte. The consumption of nutraceuticals, as an adjuvant therapeutic, improve antioxidant and anti-inflammatory effects, moreover, decreased body weight and lipid profile

A randomized controlled trial that evaluated the effects of avocado intake on the cognition of healthy subjects, who consumed an avocado/day for 6 months, showed improvements in memory, spatial working memory, sustained attention, and efficiency in approaching a problem (Scott, Rasmussen, Chen, & Johnson, 2017). Avocado is a particularly bioavailable source of lutein (Dreher & Davenport, 2013; Unlu, Bohn, Clinton, & Schwartz, 2005), which is carried in the circulation mainly by HDL (Connor, Duell, Kean, & Wang, 2007; Wang et al., 2007). Lutein deposits have been related to cognitive function in young and old adults (Feeney et al., 2013; Renzi, Dengler, Puente, Miller, & Hammond, 2014; Vishwanathan et al., 2014; Vishwanathan, Neuringer, Snodderly, Schalch, & Johnson, 2013; Vishwanathan, Schalch, & Johnson, 2016); particularly, brain concentrations of lutein in the elderly are positively associated with various predeath cognitive measures, and lutein supplementation improves verbal fluency scores (Johnson et al., 2008). In diabetic rats, the administration of avocado oil decreases the production of ROS and damage to brain lipids because of the increase in the GSH/GSSG ratio and the activity of complex III of the respiratory chain, which can reduce the half-life of semiquinone intermediates and decrease the levels of ROS, as semiquinones are donors of electrons to oxygen, forming the superoxide anion (Ortiz-Avila et al., 2015). Avocado oil supplementation to rats during gestation and lactation resulted in a higher concentration of MUFA and polyunsaturated fatty acids in the pups' brains and an improvement in cognitive function (de Melo et al., 2019).

## 5 | CONCLUSION

The nutraceutical effects of ginger and avocado in many tissues are recognized. Obesity and adipocyte hypertrophy induced alterations that affect different tissue, decreasing hormones signaling, improves inflammatory factors, and inducing oxidative stress. The use of ginger and avocado as an adjuvant in the treatment or prevention of obesity has been shown through improvements in metabolism of lipids, decreasing in inflammation and oxidative stress induced by obesity, and a decrease in adipose-tissue related blood lipid levels as demonstrated in Figure 1. For this reason, ginger and avocado may be useful for patients and suggested by clinicians and nutritionists as adjuvants for the control of weight gain.

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