Chapter

Ginger in the Prevention of Cardiovascular Diseases

Begoña Cerdá, Javier Marhuenda, Raúl Arcusa, Débora Villaño, Purificación Ballester and Pilar Zafrilla

Abstract

Ginger, *Zingiber officinale*, is a member of the Zingiberaceae family, used in traditional medicine for treatment of a variety of conditions. Many pharmacological activities have been reported for this plant (anti-inflammatory, anti-tumorigenic, anti-apoptotic, anti-hyperglycemic, cancer-chemopreventive, and anti-lipidemic). Cardiovascular disease, which includes coronary artery disease, acute myocardial infarction, peripheral arterial disease, and stroke, is one of the leading causes of death worldwide. In recent years, several studies have described that ginger can control or improve some cardiovascular risk factors such as cholesterol levels, hypertension, or atherosclerosis. The aim of the present review is to summarize the effects of ginger bioactive compounds on cardiovascular diseases.

Keywords: cardiovascular disease, ginger, hypertension, obesity, gingerol, shogaol

1. Introduction

There is an urgent need to implement intervention measures and health policies to reduce mortality associated to cardiovascular disease (CVD), which will result in more adequate, healthy, and sustainable development per each country. CVD has caused 6.2 million deaths worldwide in people aged 30–70 years in 2019 [1].

Regarding cardiovascular health, there are certain modifiable risk factors that can be intervened upon to improve health. These factors include: hypertension, elevated fasting plasma glucose, elevated low-density lipoprotein (LDL) or cholesterol, and alterations in renal function. Environmental factors such as air and household pollution, smoking, low physical activity, and overweight and obesity are also included. In addition, in the case of women, the consumption of oral contraceptives and the presence of polycystic ovaries syndrome increase the risk of suffering CVD [2].

There are numerous studies linking diet and health, and this is most evident in the case of cardiovascular risk. Both dietary patterns, such as a diet rich in antioxidants, fiber (from vegetables, whole grains, fruits, nuts, pulses) fish, poor in processed foods (with high content in sugar or animal fats), together with the food intake containing specific bioactive substances or nutrients can modulate the risk factors [3, 4]. Therefore, changes in lifestyle and diet can prevent these diseases [5].

CVD is linked to the development of atherosclerosis and is directly related with an inflammatory response. This response is prompted by bad diet habits, sedentary lifestyle, obesity, and stress [6].

Herbal measurements are used to develop new drugs with higher potency and fewer adverse effects targeting the modulation of biological activities.

Ginger (*Zingiber officinale*) is among the medicinal plants with beneficial health effects that has been widely used in pharmaceutical products and food. Its crude extract is cardioprotective due to its antihypertensive, antiplatelet, and cardiotonic effects [7].

The term nutraceutical is used for any food or ingredient with a beneficial effect on health beyond the traditional nutritional effects; further, it has a positive impact on health, physical or cognitive state [8]. Numerous nutraceuticals are used for the prevention of CVDs, including ginger (see **Table 1**).

Apart from its cardioprotective effects, ginger has numerous properties such as antimicrobial, antioxidant, anti-inflammatory, anti-carcinogenic, and neurodegenerative diseases prevention. It prevents chemotherapy-induced emesis, nausea, and respiratory disorders [9, 10].

Ginger's flavor and aroma come from its volatile oils (~1–3% of the weight of fresh ginger) and nonvolatile pungent oleoresins. Further, the pharmacological properties are due to its oleoresin's composition, rich in zingerone (ZGR), gingerols (6/8/10-gingerols), and shogaols (6/8/10-shogaols and 6-hydroshogaol). The spiciness character of dried ginger rhizome comes from the gingerols, especially 6-gingerol. During drying, gingerols transform into ZGR, reducing pungency and providing a spicy-sweet aroma, and shogaols concentration increases [11].

Ginger inhibits lipid peroxidation through its antioxidant effect. 6-Gingerol increases Beclin1 expression to promote autophagy in human endothelial cells and inhibits *PI3K/AKT/mTOR* pathway signaling not affecting the cell cycle [12].

Ginger could prevent atherosclerosis, since consumption of a ginger extract has been observed to improve lipoprotein results in hamsters thanks to an increased activity of the liver enzyme CYP7A1 and decreased mRNA levels of intestinal cholesterol absorption proteins such as MTP, ACAT2, and NPC1L1 [13].

Nutraceuticals	**Properties**
PUFA n-3 (polyunsaturated fatty acid)	Arrhythmias, sudden death, hypertriglyceridemia, antiplatelet agents, anti-inflammatories
Q10 coenzyme	Antioxidant, antihypertensive
Vitamin D	Depression, atherosclerosis, valvular calcification
Resveratrol	Anti-inflammatories, antioxidant
Red yeast rice	Improves dyslipidemia
Phytosterols	Lowers cholesterol, LDL-C, antihypertensive
Flavonoids	Antiplatelet agents, anti-inflammatories antioxidant, antihypertensive
Dietary fiber	Dyslipidemia, metabolic syndrome decreases total cholesterol, LDL-C, triglycerides, blood glucose, and body weight
Ginger	Anti-inflammatories, antioxidant antiplatelet agent, antihypertensive
B complex	Reduces hyperhomocysteinemia

Table 1.
Nutraceuticals in the prevention of cardiovascular diseases [9].

6-Gingerol regulates lipogenesis, fatty acid oxidation, mitochondrial dysfunction, and oxidative stress of aging rats. Several authors observed that 8-gingerol due to its antioxidant properties could inhibit melanogenesis in murine melanoma cells. In addition, it increases the activity of the antioxidant enzyme superoxide dismutase (SOD) and decreases the levels of malondialdehyde (MDA), a marker of lipid peroxidation, in a concentration-dependent manner [14, 15].

Inflammation associated with CVD induces an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Several authors have observed that ginger significantly reduces TNF-α values, and 6-gingerol reduces the levels of inducible nitric oxide (NO) synthase enzyme and inflammatory factors [16].

Ginger can also be used in moderate obesity, a cardiovascular risk factor. Ginger increases lipolysis and thermogenesis and inhibits lipogenesis; therefore, it could be used to prevent obesity [17].

In summary, ginger consumption in the diet could improve cardiovascular health by lowering blood pressure, improving lipid profile, preventing obesity, improving glycemic control, and vascular health. The benefits of ginger on cardiovascular risk factors are mediated by transcription factors such as adenosine-monophosphate-activated protein kinase, peroxisome proliferator-activated receptors, peroxisome proliferator-activated protein kinase, and nuclear factor kappa B (NF-κB) [8, 18]. Having that in mind, the purpose of the present review chapter is to summarize the effects of bioactive compounds in ginger on CVD.

2. Cardiovascular risk factors

CVD is a group of disorders of the heart and blood vessels. It includes a large number of pathologies, among which it is worth highlighting: coronary heart disease, cerebrovascular diseases, peripheral arteriopathies, and rheumatic and congenital heart disease, among others. In most of them there is a common pathological process, atherosclerosis [19, 20]. This condition occurs when fat and cholesterol build up on the walls of blood vessels or in the arteries. This accumulation gives rise to atherosclerotic plaques. Over time, plaques can narrow blood vessels and cause problems throughout the body. If an artery becomes blocked, it can lead to a heart attack or stroke [21].

Cardiovascular risk factors are those that are associated with a greater probability of suffering from CVD. It is widely described that the most developed countries' lifestyles entail an increased risk of suffering from CVD. There are many studies that showed that a significant percentage of CVD and its mortality can be prevented by acting on cardiovascular risk factors [3].

Atherosclerosis is a multifactorial disease, in which several risk factors are involved [22]. The prevalence and potency of these risk factors vary. Cardiovascular risk factors improve CVD by reducing plaque formation.

Two types of risk factors can be differentiated: modifiable and non-modifiable. Pencina et al. established the importance of both and determined that the non-modifiable factors (sex, age, and race) account for between 63 and 80% of the risk factors, while the weight of the modifiable factors is much lower. But, control of modifiable risk factors leads to substantial reductions of cardiovascular events [23, 24].

2.1 Non-modifiable risk factors

Non-modifiable risk factors are sex, age, race, and genotype. They are those that are not likely to be modified, therefore nothing can be done about them. It has been proven that cardiovascular risk is higher in men than in women, increases after 35 years, and Hispanics, Latinos, and Southeast Asians have a higher cardiovascular risk [24].

2.2 Modifiable risk factors

Modifiable risk factors are hypertension, hypertension; obesity and diabetes; dyslipidemias; chronic stress; diet; tobacco; and sedentary lifestyle [25]. They are those that are likely to be modified, where actions can be directed attempting to prevent and/or improve atherosclerosis and therefore CVD.

2.2.1 Hypertension

Hypertension is the most important CVD risk factor. There is a direct relationship between increased blood pressure and the development of CVD. When properly treated, CVD mortality is reduced. Its pathophysiology is very complex and different mechanisms are involved, including the central nervous system, the immune system, and the neurohumoral system [26].

2.2.2 Obesity and diabetes

The prevalence of obesity in the world is increasing in a very worrying way across all ages [27]. The relationship between obesity and CVD is clear. It has been shown how it contributes to atherosclerosis through different mechanisms. On the other hand, it must be taken into account that obesity is a risk factor for other comorbidities such as diabetes, sleep apnea, dyslipidemia, hypertension, and even cancer [28, 29].

2.2.3 Dyslipidemias

Since lipids are involved in the formation of atherosclerotic plaque, especially LDL cholesterol and TG, increases of their plasmatic levels entail a risk of atherosclerosis and CVD. This is what happens in dyslipidemias. Reducing them is a fundamental therapeutic strategy to reduce CVD risk [30, 31].

2.2.4 Chronic stress

It is one of the most important cardiovascular risk factors. Chronic stress is a situation maintained over time in which the body generates a nonspecific and systemic response as a result of exposure to negative external factors. The relationship between chronic stress and the risk of CVD has been widely demonstrated [32].

2.2.5 Diet

It is clear that diet influences the maintenance of good cardiovascular health. And it is an essential tool to control other risk factors such as diabetes, obesity, dyslipidemia, and even hypertension. It has been proven that diets such as the Mediterranean

or DASH reduce cardiovascular risk. They are diets that improve markers of inflammation and oxidative stress and also contribute to improving the lipid and glycemic (improvement of insulin sensitivity) profiles, and endothelial function. In addition, they have proven antithrombotic properties. The consumption of fiber, omega-3 acids, vegetables and fruits, and whole grains seems to be decisive in reducing cardiovascular risk [33–36].

2.2.6 Smoking

Tobacco continues to be one of the most important cardiovascular risk factors. Since its consumption increases the formation of atherosclerotic plaque, through an enhanced inflammation, endothelial dysfunction, arterial stiffness, and lipid profile [37]. In addition, its consumption increases the heart rate; myocardial contractility; thrombus formation by increased platelet activation and adhesion and procoagulant profile [38].

2.2.7 Sedentary lifestyle

Regular and moderate physical activity, which modifies muscle tissue and adipose tissue, has been shown to have a positive impact on health. It reduces systemic inflammation and has an antiatherogenic effect. Therefore, lack of physical activity is a cardiovascular risk factor [39].

3. Bioactive compounds of ginger

Ginger, the rhizome of *Zingiber officinale* Roscoe that belongs to Zingiberaceae family, is commonly used as a spice or dietary supplement and has been widely used in traditional medicine throughout history [40]. Ginger has been identified as having a multitude of different bioactive compounds, including lipids, carbohydrates, terpenes, and phenolic compounds, and its pharmacological effects are largely due to phenolic compounds and terpenes [41, 42]. Ginger-derived terpenes (α-zingiberene, camphene, ar-curcumene, β-phellandrene, E-α farnesene, β-bisabolene, α-piene) [43] are known to have antioxidant, anti-inflammatory, antibacterial, antidiabetic, analgesic, gastroprotective, neuroprotective, and anti-carcinogenic properties [41]. Of the 400 types of compounds present in ginger, four phenolic compounds are mainly responsible for its pharmacological effects: gingerols, shogaols, paradols, and ZGR [44, 45]. There are also other types of compounds related to gingerol (8-gingerol, 10-gingerol, and 12-gingerol) and shogaol (1-dehydrogingerdione, 6-gingerdione, and 10-gingerdione) [42].

The main pungent and most abundant compound, 6-gingerol, which is present in fresh ginger, attenuates various chronic disorders. By dehydration and after long storage, this compound is converted into 6-shogaol, which is more stable and has greater pharmacological effects than its precursor 6-gingerol [46, 47]. 6-Shogaol is converted to 6-paradol by bacterial metabolism, and both possess similar anti-inflammatory and antioxidant properties [40, 47]. Antioxidant, antitumoral, antilipidermic, antibacterial, and anti-inflammatory actions are attributed to ZGR, and it is synthesized by reverse aldolization of gingerols when heating fresh ginger [47, 48]. **Figure 1** summarizes the metabolization pathways of 6-gingerol as a function of thermal processing.

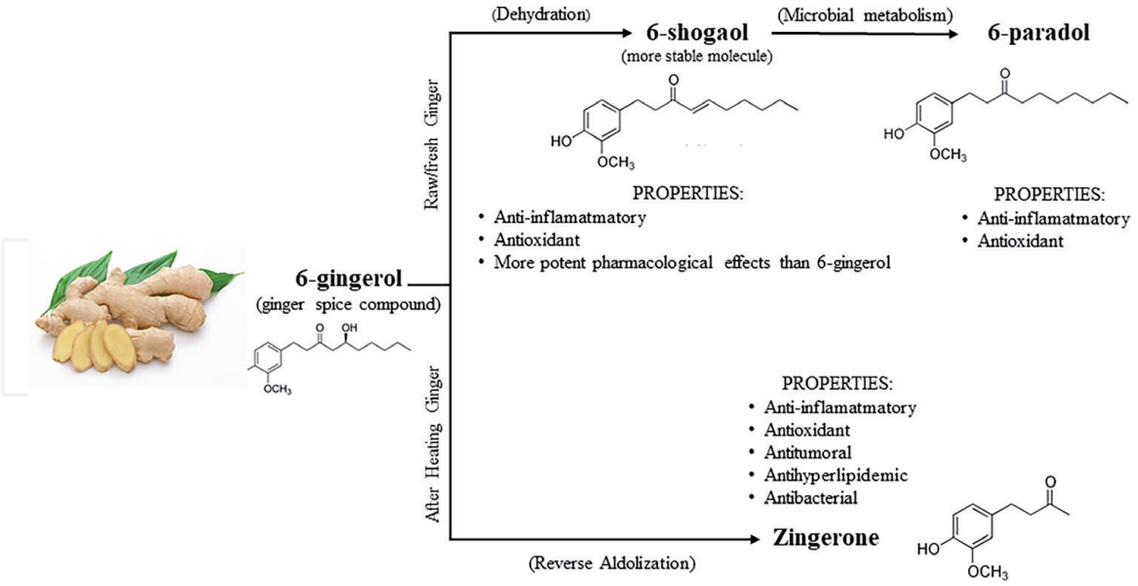

Figure 1.
Properties and metabolism of gingerols.

Zick et al. [49] observed that 6-shogaol and the 6-, 8-, and 10-gingerols have good bioavailability when consumed orally, being detected as sulfate and glucuronide conjugates. However, 6-gingerol has not been detected free in plasma after an oral dose of 2 g, despite it being the major compound in ginger extracts (2–64%) [50]. Pharmacokinetic studies showed that the half-life of the major compounds of ginger and its metabolites is approximately 1–3 hours. Based on bioavailability data, 6-, 8-, and 10-gingerol glucuronides and sulfates along with 6-shogaols could be good markers of ginger intake [50].

As for its therapeutic use, given its various anti-inflammatory, antimicrobial, anticancer, and antioxidant biological activities, ginger appears to be effective in the prevention and treatment of neurodegenerative, cardiovascular, obesity, diabetes mellitus, or respiratory disorders [45].

4. Effects of ginger in the prevention of cardiovascular disease

4.1 Antioxidant activity

Oxidative stress is increased under the condition in which there is a decrease in the body's antioxidant defenses; therefore, there is an imbalance between the production and elimination of reactive oxygen species (ROS). As a consequence of this imbalance, ROS accumulate, generating cellular damage in the different systems of the organism, since they produce lipid peroxidation [51, 52].

Ginger has great antioxidant activity; in fact, many of its therapeutic applications are due to this activity. That ginger has antioxidant activity is a fact that has been shown both in vitro and in vivo. Although studies on the effects to human are not as numerous, it is beginning to be verified that its intake is capable of increasing the concentration of antioxidant enzymes and decreasing oxidative stress markers in cancer patients [53]. Morvaridzadeh et al. carried out a systematic review and meta-analysis where they concluded that there is sufficient evidence to show that ginger intake

increases the levels of oxidative stress parameters [54]. There are many bioactive compounds in ginger that exhibit antioxidant activity, such as 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Of all of them, the one with the highest antioxidant activity in vitro is 6-gingerol, followed by 6-shogaol [55].

The mechanism involved in its antioxidant activity has to do both with preventing the appearance of free radicals [56] and with being able to eliminate them [57]. 6-Gingerol has been shown to be capable of inhibiting xanthine oxidase, an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid in the last stage of purine metabolic degradation, with the production of reactive oxygen species [58]. In addition, it has been proven that this compound is capable of increasing superoxide dismutase and catalase activity, two antioxidant enzymes [53].

It has been seen how the antioxidant activity depends on the time of harvest of ginger, if it is early, the antioxidant activity is higher, decreasing if the harvest is done later [59].

4.2 Anti-inflammatory activity

Another of the great biological activities attributed to ginger is its anti-inflammatory activity. Inflammation is one of the body's first responses to a risk situation [60]. When that inflammation is maintained over time, is then problematic. Today it is known that there are many diseases in which inflammation plays a determining role, in fact it is being studied how low-grade systemic inflammation is related to the development of different pathologies (autoimmune diseases, metabolic diseases, CVDs, cancer) [61, 62]. In chronic or low-grade inflammation, different proinflammatory factors are released, such as cytokines and prostaglandins [61].

Many researchers have shown that ginger reduces different proinflammatory markers such as: NF-κB, signal transducer activators of transcription (STAT), proteins of the Nod-like receptor family (NLRP), receptors toll-like (TLR), mitogen-activated protein kinase (MAPK), and mTOR (mTOR) pathways, in addition to inhibiting several proinflammatory cytokines [19, 58].

In the systematic review and meta-analysis carried out by Jalali et al, it is shown how ginger is capable of significantly reducing the levels of different proinflammatory parameters such as IL-6, TAC, CRP, TNF-α, MDA, and the serum prostaglandin E2 (PGE2) [63]. Song et al. have examined how ginger extract is capable of reducing proinflammatory markers produced by *Helicobacter pylori*. The expressions of interleukin (IL)-8, TNF-α, IL-6, inducible NOS (iNOS), and IFN-γ were reduced [64].

The most active compounds from the anti-inflammatory point of view of ginger are 6-shogaol, 6-gingerol, and 6-dehydroshogaol [45, 65, 66]. It has been described how 6-shogaol has an anti-inflammatory effect because it inhibits the production of PGE2 and proinflammatory cytokines (IL-1β and TNF-α) and decreases the expression of cyclooxygenase-2 (COX-2), p38 mitogen-activated protein kinase (MAPK), and nuclear NF-κB [45]. In other studies, 6-shogaol has been shown to inhibit LPS-induced iNOS and COX-2 expression in macrophages [67]. Furthermore, studies showed that 6-shogaol could protect against lipopolysaccharide (LPS)-induced toxicity in murine astrocytes [68].

4.3 Antiobesity activity

Worldwide, obesity has become the main pandemic of the twenty-first century [69, 70], as the rates of this pathology have increased considerably during the last

decades [71, 72]. According to the World Health Organization (WHO), obesity is characterized by an excessive accumulation of fatty tissue in the body, causing harmful effects on health [73]. Concerning problems associated with obesity are mainly its deleterious effect on other non-detectable diseases: CVDs, hypertension, nonalcoholic fatty liver disease, various types of cancer, and hyperlipidemia [74, 75]. In addition, it should be noted that patients with obesity show worse prognosis against COVID-19 infection and higher mortality rates [76, 77]. Additionally, it induces low-grade inflammation, oxidative stress, and contributes in the etiology of type 2 diabetes mellitus [78]. In recent years, natural compounds have aroused great interest in the prevention/treatment of obesity, and several studies have shown that ginger seems to be effective for this pathology [45].

It seems that gingerenone-A has a more potent inhibitory effect on adipogenesis and lipid accumulation than gingerols and 6-shogaol in 3T3-L1 preadipocyte cells, while it appears to activate the adenine monophosphate (AMP)-activated protein kinase (AMPK) pathway modulating fatty acid metabolism, thus attenuating obesity [79]. For its part, the daily dose of 2 g of ginger powder in obese women resulted in a decrease in body mass index (BMI) [80]. Daily dose of ginger powder also appears to increase fat oxidation in humans [81]. Several studies have shown that ginger can reduce body weight by increasing thermogenesis through catecholamines as well as lipolysis of white adipose tissue [78]. Therefore, it seems evident that both ginger and certain bioactive components are effective against obesity by enhancing lipolysis and inhibiting adipogenesis.

4.4 Antidiabetic activity

Diabetes is a serious metabolic disorder characterized by an abnormal increase in blood glucose. For this reason, several research studies have considered evaluating the possible effect of ginger and its main bioactive components in the reduction of blood glucose [82].

It has been shown that the administration of 6-gingerol stimulates the activity of glycogen synthase 1 and at the same time favors the translocation of the glucose transporter type 4 (GLUT-4) to the cell membrane, favoring insulin to allow glucose entry in skeletal muscles and subsequent storage as glycogen [83]. Ginger consumption seems to reduce our values of glycosylated hemoglobin (HbA1c), fasting plasma glucose, insulin, total cholesterol, and triglycerides in patients with type 2 diabetes mellitus [84].

4.5 Effect of ginger on lipid profile

The greatest cause of atherosclerosis is characterized by altered blood lipid values and consequently CVD. In addition, the factors previously mentioned, such as overweight/obesity and high blood glucose values, are factors that will have a greater effect on this pathology.

Impaired blood lipid values are the major cause of CVD. In a recent systematic review and meta-analysis of clinical trials in 2018, it was concluded that ginger has a favorable effect in reducing triglycerides and LDL cholesterol, without significant reductions in total cholesterol. However, doses lower than 2 g/day of dairy ginger powder seem to be more effective in lowering both triglycerides and total cholesterol [83]. Since it is a safe and inexpensive supplement, it could be used to improve the lipid profile of subjects and thus prevent CVD.

Clinical studies have been conducted to evaluate the effect of ginger supplementation on the lipid profile of different populations. Doses of up to 1.8 g/day have been shown to significantly reduce triglyceride, total and LDL cholesterol levels compared with placebo in obese patients treated with metformin (**Table 2**) [85].

Significant lowering effect of ginger compared with placebo has also been observed in [86, 87]. However, other studies failed to observe a positive effect, and ginger supplementation exerted no effect on blood lipid profiles and body composition [88] and no significant differences in cholesterol lipoproteins profile between ginger and placebo [89]. In some cases, the results are inconsistent, with significant differences in some markers as LDL/HDL ratio after ginger intake and no changes on mean levels of total cholesterol or triglycerides [90], or reductions in levels of serum triglycerides and LDL with no effects on total cholesterol or high-density lipoprotein (HDL) [91].

Levels of apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio reduced and apolipoprotein A1 increased after ginger supplementation (2 g/day) for 12 weeks [92]. The overexpression of ApoA1 could explain the increases observed in HDL levels in some trials.

Population	Intervention	Outcomes	Ref.
Obese Egyptian patients with new-onset T2DM (n = 80) 30–60 years	600 mg 3 times/day 8 weeks	↓ BMI, ↓ TC, ↓ LDL-C, ↓ TG ↑ HDL-C ginger vs. placebo	[86]
Hyperlipidemic non diabetic patients (n = 45 ginger, 40 placebo)	3 g/day 45 days	↓ TC, ↓ TG ginger vs. placebo	[87]
Obese men (n = 32) 18–30 years	1 g/day 10 weeks with/out resistance training	n.s. TC, TG, LDL-C, HDL-C ginger vs. placebo ↓ TC, ↓ fat mass training groups	[88]
Obese women with breast cancer (n = 40)	3 g/day, 6 weeks, with/out exercise training	↓ LDL, ↓ TC, ↓ TG, ↑ HDL ginger + exercise	[89]
T2DM patients (n = 64) 38–65 years	2 g/day 8 weeks	↓ LDL, ↓ TG	[90]
T2DM patients (n = 63) 20–60 years	1.6 g/day 12 weeks	↓ TC, ↓ TG	[85]
Obese women (n = 80) 18–45 years	2 g/day 12 weeks vs. placebo	↓ TG ginger vs. placebo Both groups: ↓ TC, ↓ TG, ↓ LDL/HDL ratio, ↓ TC/HDL ratio, ↑ HDL	[91]
T2DM (n = 50) 20–60 years	2 g/day 12 weeks	↓ ApoB, ↓ ApoB/Apo A1 ratio, ↑ Apo A1	[92]
T2DM (n = 88)	3 g/day 8 weeks	↓ TC	[93]
Hyperlipidemic patients (n = 100), 35–60 years	3 g/day 30 days	↓ TC	[94]
T2DM (n = 50)	2 g/day 10 weeks	↓ LDL/HDL ratio ginger vs. placebo	[83]
Menopausal women (n = 160) 50–60 years	1 g/day 16 weeks vs. 900 mg/day garlic with/out aerobic exercise	No effects in ginger groups ↓ TC, ↓ LDL with garlic	[95]

Table 2.
Summary of the effect of ginger supplementation on the lipid profile in different clinical trials and populations.

Discrepancies in the results could be due to the different characteristics of the populations studied, stage of the disease, pharmacological treatments, format of ginger administered.

Meta-analysis studies have concluded that ginger significantly increases HDL levels and reduces plasma levels of triglycerides and total cholesterol, with different extent depending on the clinical condition (hyperlipidemia and T2DM) [93, 94]. The analysis conducted by Pourmasoumi et al. [83] revealed a better effect of total cholesterol and triglycerides with doses < 2 g/day and a maximum of 50 days of supplementation.

Among the different mechanisms of action attributed to ginger components is the inhibition of intestinal lipase enzymes, thus avoiding fat hydrolysis and absorption and the increase in plasma levels of triglycerides. In case of cholesterol, its decrease in plasma concentrations has been related to an inhibition in cellular cholesterol synthesis and an increase of hepatic enzyme activity of cholesterol 7 α-hydrozylase CYP7A1a, implicated in the conversion of cholesterol into bile acids for its clearance by fecal excretion [95]. Ginger is implicated in the inhibition of expression of adipogenesis and lipogenesis genes as PPAR γ and carbohydrate-responsive element-binding protein (ChREBP) gene expression in the liver [66]. ChREBP reduced expression further decreases the expression of glucogenic and lipogenic enzymes (as fatty acid synthase, steatoryl-CoA-desaturase-1, acetyl-CoA carboxylase 1, among others [95].

4.6 Effect of ginger on blood pressure

It is well known that healthy diet and lifestyle can control blood pressure and endothelial dysfunction. Inflammation associated with cardiovascular events contributes to hypertension by affecting the renin-angiotensin system [96]. Elevated blood pressure (BP) has also been known to be a strong risk factor cardiovascular [97].

The compounds in ginger responsible for its antihypertensive effect are 6-shogaol and 9-gingerol. These compounds reduce cholesterol and LDL levels, inhibit atheroma plaque formation, and increase vessel elasticity. They also reduce the release of inflammatory mediators responsible for endothelial dysfunction by decreasing intercellular adhesion molecule 1 (ICAM-1) levels [98]. Several authors [99] show the antihypertensive effect of ginger in volunteers with mean ≤ 50 years, with ginger doses ≥ 3 g/day, and during an intervention period ≤ 8 weeks. This effect could be due to its antioxidant activity.

A systematic review with 345 participants from six clinical trials showed that ginger consumption has favorable effects on blood pressure. These authors observed that increasing ginger intake decreased the probability of ischemic heart disease and hypertension [100]. This result coincides with that observed in a clinical trial with 4628 participants in which the efficacy of ginger in coronary heart disease and as an antihypertensive was observed [101].

4.7 Antiplatelet aggregation activity of ginger

Platelet aggregation and activation play an important role in developing thrombosis and atherosclerosis. Numerous nutrients and bioactive compounds have a potential role in platelet function and may decrease cardiovascular risk. These include berries, caffeine, chocolate, garlic, ginger, the omega-3 polyunsaturated fatty acids (PUFA), onion, and tomato [102].

ZGR is a compound (phenolic alkanose) found in *Zingiber officinale*. It exhibits anti-apoptotic, anti-inflammatory, and protective properties against cardiovascular

events such as myocardial infarction. Several authors have observed its anticoagulant and antithrombotic properties. This compound inhibits platelet aggregation induced by adenosine diphosphate (ADP), and U46619 (not thrombin), Tx2 inhibitor, inhibits the catalytic activity of factor Xa (FXa) toward its substrate S-2222 in a non-competitive inhibition model, reduces P-selectin and PAC-1 expressions in platelets, and reduces activated partial thromboplastin time [103].

Several authors [104] observed that consumption of a 10 g dose of powdered ginger after 4 hours significantly reduced ADP- and adrenaline-induced platelet aggregation. McEwen analyzed the *in vitro* antiplatelet activity of ginger and showed that gingerol, its analogues (1 and 5), paradol and shogaol, exhibited antiplatelet activity with IC50 values between 5 and 7 μM [18]. To be noted, aspirin inhibitory effect shows IC50 values of 20 ± 11 μM, and paradol shows IC50 values of 4 ± 1 μM.

Ginger has a vascular protective effect mediated by different mechanisms such as reduction of inflammation and oxidative stress, increase of nitric oxide synthesis, which is a potent vasodilator, the promotion of autophagy, and inhibition of vascular smooth muscle cell [105].

Comparing different ginger compounds, several investigators have shown that 6-gingerol and 6-shogaol showed the most potent bioactivity against cholesterol (Chol), arachidonic acid (AA), thrombin, and PAF-induced platelet aggregation [106]. The 6-paradol, 10-dehydrogingerol, 10-gingerol showed the most significant inhibition of AA-induced aggregation [107].

Nurtjahja-Tjendraputra et al. observed that 8-paradol is the most effective anticoagulant, being a COX-1 inhibitor [108].

Thomson et al. fed rats with ginger aqueous extract and observed a decrease in triglyceride, thromboxane-B2 cholesterol and PGE2 levels, and in adenosine deaminase (ADA) activity of plaques, together with an increase in adenosine levels. In this way, it favors vasodilatation, reducing the complications of hypertension and preventing from unnecessary platelet aggregation [108].

5. Conclusions

Ginger contains diverse bioactive compounds and demonstrates multiple bioactive properties. It is a potent antioxidant, anti-inflammatory, regulator of lipid profile, inhibitor of VSMC proliferation, blocker of voltage-dependent Ca2+ channels, inhibitor of platelet aggregation, regulator of endothelial dysfunction and NO synthesis, enhancer of cholesterol efflux from macrophages, inhibitor of angiogenesis, and promoter of autophagy.

The biological activities, health benefits, and cardioprotective properties of ginger/ginger constituents along with related mechanisms of action gave new insights to show new avenues in the treatment of CVDs.

It is valuable to explore new anti-platelet aggregation drugs based on the skeleton of [*n*]-paradol or other principles reported from the *Zingiber* series.

Acronyms and abbreviations

ACAT2	acetyl-CoA acetyltransferase 2
ADA	adenosine deaminase
ADP	adenosine diphosphate

AMP	adenine monophosphate
AMPK	activated protein kinase
BMI	body mass index
ChREBP	carbohydrate-responsive element-binding protein
GLUT-4	glucose transporter type 4
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CVD	cardiovascular diseases
DASH	dietary approaches to stop hypertension
FXa	coagulation factor Xa
Ginger	*Zingiber officinale*
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
HUVECs	human umbilical endothelial cells
ICAM-1	intercellular adhesion molecule 1
IL	interleukin
iNOS	inducible NOS
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
mRNA	messenger ribonucleic acid
mTOR	mammalian target of rapamycin
MTP	microsomal triglyceride transfer protein
NF-κB	factor kappa B
NLRP	nod-like receptor
NO	oxide nitric
NOS	oxide nitric synthase
NPCA1L1	Niemann-Pick disease, type C1, gene-like 1
PAC-1	is a mouse monoclonal antibody
PGE2	prostaglandin E2
PUFA	polyunsaturated fatty acids
ROS	reactive oxidative species
S-2222	substrate S-2222 in a non-competitive inhibition model
SOD	superoxide dismutase
STAT	signal transducer activators of transcription
TLR	receptors toll-like
TNF-α	tumor necrosis tumoral alpha
U46619	a stable thromboxane receptor (TP receptor) agonist)
VSMC	vascular smooth muscle cell
WHO	World Health Organization
ZGR	zingerone

Conflict of interest

The authors declare no conflict of interest.

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Author details

Begoña Cerdá, Javier Marhuenda, Raúl Arcusa*, Débora Villaño,
Purificación Ballester and Pilar Zafrilla
Faculty of Health Sciences, Pharmacy Department, Universidad Católica de San Antonio, Murcia, Spain

*Address all correspondence to: rarcusa@ucam.edu

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