Clinical Nutrition ESPEN 51 (2022) 72–82

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Review

The efficacy of *Zingiber officinale* on dyslipidaemia, blood pressure, and inflammation as cardiovascular risk factors: A systematic review

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ARTICLE INFO

Article history:
Received 1 June 2022
Received in revised form
20 August 2022
Accepted 26 August 2022

Keywords:
Zingiber officinale
Cardiovascular disease
Blood pressure
Dyslipidaemia
Inflammation
Systematic review

SUMMARY

Background & aims: Hypertension, dyslipidaemia, and chronic inflammation contribute to the development of cardiovascular disease (CVD). *Zingiber officinale* has been suggested to reduce these CVD risk factors; however, the clinical evidence remains unclear. This systematic review aims to analyse the effect of *Z. officinale* as a sole intervention on these risk factors.

Methods: In this PRISMA-based systematic review, we included randomised clinical trials from PubMed, Scopus and Cochrane Database of Systematic Reviews (July 2020) analysing triglycerides, low- and high-density lipoprotein (LDL, HDL), total cholesterol, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin 1, 6, 10, systolic and/or diastolic blood pressure as outcomes. Quality of studies was evaluated by JADAD and the Cochrane risk-of-bias tools.

Results: A total of 24 studies were included, mostly (79.2%) showing low risk of bias. These were based on obesity and cardio-metabolic derangements (33.3%), type 2 diabetes mellitus (37.5%), and miscellaneous conditions (29.2%). While total cholesterol and triglycerides levels mostly improved after *Z. officinale*, results were inconsistent for other blood lipids markers. Inflammatory markers (CRP, TNF-α) were more consistently reduced by *Z. officinale*, while only 3 studies reported a non-significant reduction of blood pressure.

Conclusions: Although there remains a paucity of studies, *Z. officinale* may be beneficial for improving dyslipidaemia and inflammation.

1. Introduction

Cardiovascular disease (CVD) is considered a leading cause of pre-mature death, accounting for over 30% of global mortality [1]. Coronary artery disease (CAD) and cerebrovascular accidents (CVA) arising from atherosclerotic degeneration of blood vessels account for the majority of CVD morbidity and mortality [2,3]. Atherosclerosis is a chronic inflammatory disease that is characterised by the development of fibrofatty plaques in the blood vessel wall [4,5]. These plaques are formed by lipid accumulation, smooth muscle cell migration and proliferation, influx of macrophages and lymphocytes, and accumulation of proteoglycan collagen with inflammation, necrosis and fibrosis [5,6]. A rupture of the fibrous cap leads to arterial thrombosis and ischaemia, the main underlying mechanism of mortality in the vast majority of CVD cases [7].

Risk factors for atherosclerotic-induced CVD include poor living conditions and malnutrition, sedentary lifestyle, hyperlipidaemia, hypertension, obesity, type 2 diabetes mellitus (T2DM), and smoking [2,3,8,9]. Obesity, metabolic syndrome and T2DM are well established to have increased atherogenesis risk factors, including hypertension, dyslipidaemia, and chronic inflammation [10–13]. Hypertension is considered to be the most import risk factor associated with CVD causation, with a high prevalence of uncontrolled hypertension in the general population [14,15]. Importantly, a reduction in blood pressure is a highly effective as both a primary and secondary prevention strategy for CVD [16]. Hypercholesterolaemia is also a well-defined trigger of atherosclerosis, increasing endothelial cell permeability, and lipid and immune cell migration into the arterial wall [6]. Increased total cholesterol, low density lipoprotein-cholesterol (LDL) and triglycerides, as well as decreased high density lipoprotein-cholesterol HDL, are strong independent predictors of atherosclerosis [6,17]. Hence, the assessment of blood pressure and total cholesterol, LDL, HDL, and triglycerides remains a cornerstone in clinical risk evaluation of CVD, alongside age, gender and smoking status [17].

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https://doi.org/10.1016/j.clnesp.2022.08.031

Inflammation has emerged with strong evidence as an important risk factor in atherosclerosis pathogenesis [4], involving both innate and adaptive immunity [18]. C-reactive protein (CRP) has been identified as an independent risk marker for CVD across many different population groups [19,20], alongside various cytokines, including tumor necrosis factor-alpha (TNFα), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-10 (IL-10) [21–25]. Furthermore, targeting inflammatory pathways associated with atherosclerosis has been demonstrated as a novel treatment option in the prevention of CVD [26].

Primary and secondary prevention of CVD are critically important, and although there have been improvements in outcomes for CVD patients, morbidity and mortality remain a significant burden globally [17]. Furthermore, the therapeutic management and prevention of CVD risk factors remains a challenge, particularly in developing countries [1]. Adverse effects for medication commonly used for hypertension and hypercholesterolaemia further reduce patient compliance [17,27]. Plant-based diets and herbal medicines have been reported to have a positive impact on hypertension, dyslipidaemia and inflammation [28]. Particularly, traditional uses suggest that *Zingiber officinale* (ginger) may improve hypertension, dyslipidaemia, T2DM and other chronic inflammatory diseases, and is therefore considered to be cardioprotective [29,30]. *Z. officinale* is a widely consumed spice globally, and the rhizome has been traditionally used medicinally for thousands of years [31,32], particularly prominent in Ayurvedic, Unani-Tibb and Traditional Chinese Medicine systems [29]. Oleoresin from the *Z. officinale* rhizome contains numerous bioactive compounds, including gingerols, shogaols, diarylheptanoids, phenylbutenoids, flavanoids, diterpenoids and sesquiterpenoids [31,32]. These have been suggested to have immune modulating properties reducing inflammation, improve dyslipidaemia, and reduce blood pressure [29,30].

However, the current clinical evidence to support *Z. officinale* in reducing these important CVD risk factors across different population groups remains unclear. Therefore, this study aims to systematically review the clinical evidence available in the literature that investigated *Z. officinale* extracts on blood lipids, inflammatory markers, and blood pressure across different population groups in order to clarify its potential in the management of these CVD-associated risk factors.

2. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [33]. As a systematic review of the literature, no ethical clearance was required to conduct this study. This systematic review was registered online with Prospero (Reg. no: CRD42022351887).

In order to develop the keyword search strategy and inclusion/exclusion criteria for this systematic review, a PICO was developed. The population of interest was any adult cohort undergoing the sole intervention of *Z. officinale* and compared to a placebo group pre- and post-intervention. The primary outcomes of interest are systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, LDL, HDL, total cholesterol, CRP, TNFα, IL1, IL-6 and/or IL-10. Study design for inclusion were placebo controlled clinical trials.

An electronic literature search was conducted in PubMed and Scopus databases as well as in the Cochrane Database of Systematic Reviews (CDSR) on July 2020. The following keywords and Boolean operators were used ("*Zingiber officinale*" OR "ginger*" OR "zanjabeel" OR "zingerone" OR "shagaol" OR "paradol") AND ("HDL" OR "LDL" OR "blood pressure" OR "hypertension" OR "CRP" OR "reactive protein" OR "interferon" OR "cytokine*" OR "TNF*" OR "interleukin*" OR "inflammation" OR "triglyceride*" OR "*lipid*" OR "cholesterol*" OR "lipoprotein"). The asterisk (*) was used to include all versions of the terms. Filters were used to limit the search to original studies published in English.

Clinical trials reporting at least one of the primary outcomes of interest that provided a statistical analysis reporting the effect of *Z. officinale* as a sole intervention compared to a placebo group post-treatment were included in the systematic review. The exclusion criteria included publications reporting intragroup analysis only, studies other than clinical trials (i.e., reviews, observational studies, conference proceedings, abstract-only publications, studies performed *in vitro*, *in vivo* in animal models) as well as non-English studies. Further exclusion criteria were studies unrelated to the primary outcomes of interest, and treatments or treatment combinations other than *Z. officinale* (including dietary supplementation, psychological interventions, lifestyle modification, herbal supplementation, and allopathic medications).

Two reviewers (C.C.D. and Z.I.) independently screened the collected studies and extracted the data. Any disagreements were settled through consultation with a third reviewer (K.L.), and two authors verified that the included studies respected the eligibility criteria (R.F. and K.L.). For each study, researchers extracted data as follows: reference; author (year); country of origin; JADAD score; study cohort; experimental (*Z. officinale*) group formulation, dosage and sample size (n); comparison (placebo) group formulation, dosage and sample size (n); duration of exposure; primary outcomes of interest; and adverse effects.

The quality of included studies was assessed based on the JADAD rating scale, where total scores ranged from 0 to 5 points based on the inclusion and reporting of five items: (i) randomization, (ii) methods of randomization, (iii) blinding, (iv) suitable methods of double blinding, and (v) withdrawn or dropout explanations [34]. All studies were included regardless of their quality score, as there were a limited number of studies available for review within the chosen outcomes of interest. Furthermore, the randomized trials included in this systematic review was assessed for the risk of bias using the version 2 of the Cochrane risk-of-bias tool for randomized trials [35].

3. Results

Following the keyword search strategy, a total of 2638 studies were retrieved. After removing duplicates (n = 644), a total of 1994 studies were screened based on titles and abstracts, with 1953 non-relevant studies being removed. A total of 41 full-text studies were then assessed for eligibility based on the inclusion and exclusion criteria. Studies were further excluded on full text analysis for the following reasons: not related to our topic of interest (n = 5), not reporting the outcomes of interest (n = 5), combined interventions being studied (n = 3), *in vitro* studies (n = 2), lack of full-text available (n = 1), and review-based study design (n = 1). A total of 24 studies were therefore finally included for data extraction and analysis in this systematic review (Fig. 1).

Based on the JADAD rating scale score, the majority of studies (n = 19, 79.2%) were of high-quality (score between 3 and 5) (Table 1). Similarly, the majority of studies (n = 19, 79.2%) showed low risk of bias based on the Cochrane risk-of-bias tool for randomized trials (Fig. 2). Patients received mainly 1–5 g capsules of dried powdered *Z. officinale* rhizome per day (n = 22; 91.7%), while one study reported patients enterally fed with *Z. officinale* extract [36], and one study treated patients with a freshly grounded *Z. officinale* paste [37]. Duration and follow-up periods varied, ranging from twenty-one days to three months. All included

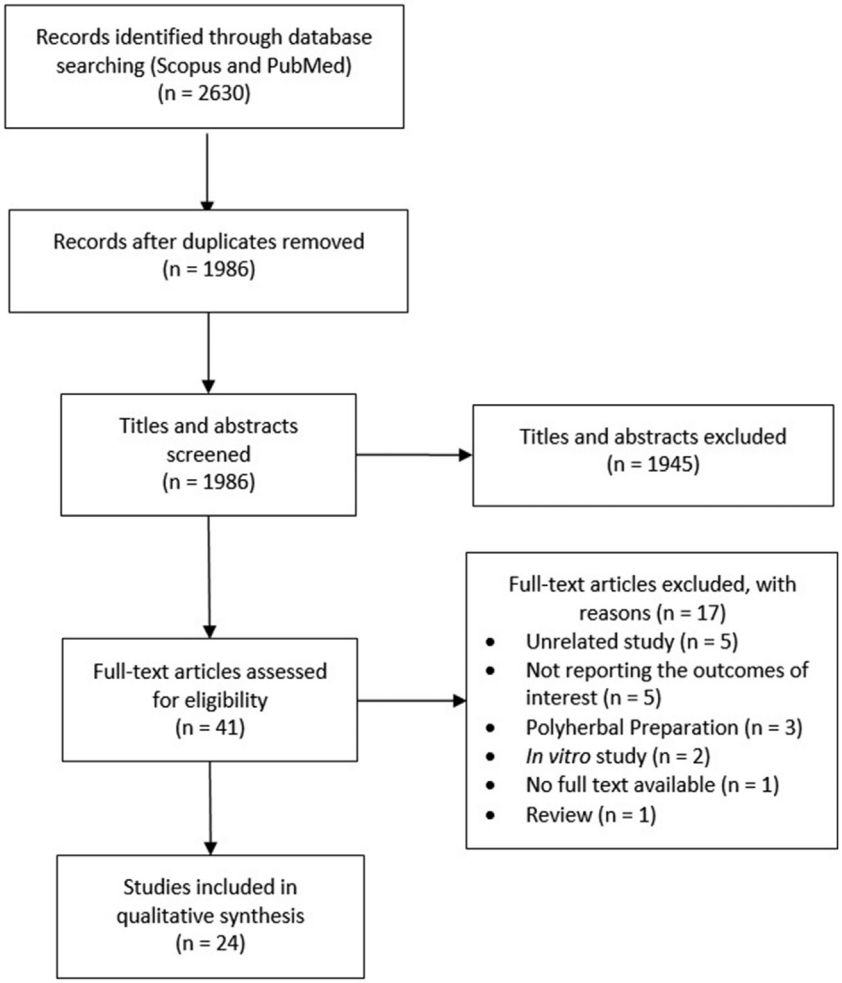

Fig. 1. Study identification, screening, eligibility, and inclusions flow diagram based on the PRISMA criteria.

studies had a placebo group for comparison, as per inclusion criteria.

The characterstics and results of the studies included in this systematic review are summarised in Table 1. For organizational purposes, these have been arranged into large categories according to the clinical condition of the target patient population investigated in each study. These include a) obesity and cardio-metabolic derangements (n = 8, 33.3%), b) T2DM (n = 9, 37.5%), and c) miscellaneous conditions (n = 7, 29.2%) (Table 1).

3.1. Obesity and Cardio-metabolic derangements

Studies investigating patients with obesity and cardio-metabolic derangements showed heterogeneous results for blood lipids. While 3 studies observed reduced triglycerides levels after treatment with *Z. officinale* [38–40], 3 studies reported no significant variation [41–43]. Similarly, 4 studies reported reduced total cholesterol [37,39,40,43], while 3 studies reported no effect on this parameter [38,41,42]. LDL levels were reduced in 2 studies [37,43], and not significantly affected in 4 studies [38–40,42]. There was no significant effect on HDL in 5 studies reporting this outcome [38–40,42,43]. Reduced levels of inflammatory markers, such as CRP [41–44], TNFα [44], IL-6 [41] and IL-10 [42], were mostly reported. There was no reported difference for SBP and DBP markers in 2 studies investigating these markers [40,43].

3.2. Type 2 diabetes mellitus

In patients affected by T2DM, triglycerides levels were reported as significantly lower in 4 out of 6 studies [45–48]. Similarly, treatment with *Z. officinale* resulted in reduced total cholesterol in 3 out of 6 studies [45–47], and LDL significantly reduced in 3 out of 5 studies [45,46,48]. HDL was significantly increased in one study [46], with no change reported in 5 studies [45,47–50]. Blood lipid results were not consistent across or within studies [45–50]. Reduced levels of inflammatory markers were reported in T2DM population [51–53]; however, some authors did not observe any difference in TNFα and IL-6 levels [47,51]. No changes were found for SBP and DBP in 1 study [49].

3.3. Miscellaneous

Tabibi et al. observed reduced triglycerides levels compared to placebo in peritoneal dialysis patients, although there was no variation in total cholesterol, LDL and HDL markers [54]. Inflammatory markers were reportedly lower after treatment with *Z. officinale* in patients with knee osteoarthritis [55,56], muscle soreness and inflammation [57], acute respiratory distress syndrome (ARDS) [36], as well as in well-trained male endurance runners [58]. On the contrary, no variation in CRP and IL-6 levels was observed for

Table 1
Summarized review of included articles investigating *Zingiber officinale* on CVD risk factors.

Ref.	Author, Year	Country of Study	JADAD	Cohort	Experimental group (n)	Comparison group (n)	Duration of exposure	Primary Outcomes of Interest	Adverse Effects
Obesity and Cardio-Metabolic Derangements									
[43]	Rafie et al. (2020)	Iran	5	Non-alcoholic fatty liver disease	1.5 g dried, powdered ginger per day (n = 23)	1.5 g wheat flour per day (n = 23)	3 months	•Ginger significantly reduced TC, LDL and CRP compared to placebo •No significant change for SBP, DBP, HDL, TG and TNFa compared to placebo	•No adverse effects reported by participants
[44]	Rahimlou et al. (2016)	Iran	5	Non-alcoholic fatty liver disease	1,5 g dried, powdered ginger per day (n = 23)	1,5 g starch per day (n = 21)	3 months	•Ginger significantly reduced CRP and TNFα compared to placebo	•Mild headache (n = 1) and heartburn (n = 1) reported with ginger
[40]	Rahimlou et al. (2019)	Iran	5	Metabolic syndrome	2 g dried, powdered ginger per day (n = 19)	2 g starch per day (n = 18)	3 months	•Ginger significantly reduced TC and TG compared to placebo •No significant change for SBP, DBP, HDL and LDL compared to placebo	•No adverse effects reported by participants
[39]	Alizadeh-Navaei et al. (2008)	Iran	4	Hyperlipidemia	3 g dried, powdered ginger per day (n = 45)	3 g lactose per day (n = 40)	45 days	•Significant reduction of TC and TG compared to placebo •No significant change for LDL and HDL compared to placebo	•Adverse effects not reported by authors
[38]	Attari et al. (2015)	Iran	4	Obese women	2 g dried, powdered ginger per day (n = 39)	2 g corn starch per day (n = 31)	3 months	•TG significantly reduced compared to placebo •No significant change for TC, LDL or HDL compared to placebo	•No adverse effects reported by participants
[41]	Ayaz et al. (2012)	Iran	2	Overweight women with cancer	3 g dried, powdered ginger per day (n = 10)	3 g starch per day (n = 30)	6 weeks	•Significant reduction of CRP and IL-6 compared to placebo •No significant change for TC and TG compared to placebo	•Adverse effects not reported by authors
[42]	Karimi et al. (2015)	Iran	2	Obese women with breast neoplasm	3 g dried, powdered ginger per day (n = 10)	3 g starch per day (n = 30)	6 weeks	•Significant reduction of CRP and IL-10 compared to placebo •No significant change for TC, LDL, HDL or TG compared to placebo	•Adverse effects not reported by authors
[37]	Fatima et al. (2018)	Pakistan	2	Hyperlipidemia	5 g pasted ginger powder per day (n = 27)	5 g grinded wheat per day (n = 30)	3 months	•Ginger significantly reduced TC and LDL compared to placebo	•Adverse effects not reported by authors
Type 2 Diabetes									
[47]	Arablou et al. (2014)	Iran	5	T2DM	1,6 g dried, powdered ginger per day (n = 35)	1,6 g wheat flour per day (n = 35)	3 months	•Ginger significantly reduced TG, TC and CRP compared to placebo •No significant change for, HDL, LDL and TNFα compared to placebo	•Adverse effects not reported by authors
[49]	Arzati et al. (2017)	Iran	5	T2DM	2 g dried, powdered ginger per day (n = 23)	2 g wheat flour per day (n = 22)	10 weeks	•No significant change for SBP, DBP, TC, LDL, HDL and TG compared to placebo	•Adverse effects not reported by authors
[51]	Mahluji et al. (2013)	Iran	5	T2DM	2 g dried, powdered ginger per day (n = 28)	2 g starch per day (n = 30)	2 months	•Ginger significantly reduced TNFα and CRP compared to placebo •No significant change for IL-6 compared to placebo	•Heartburn (n = 2) reported with ginger
[48]	Mahluji et al. (2013)	Iran	5	T2DM	2 g dried, powdered ginger per day (n = 28)	2 g starch per day (n = 30)	2 months	•Ginger significantly reduced LDL and TG compared to placebo •No significant change for TC and HDL compared to placebo	•Heartburn (n = 2) reported with ginger
[52]	Shidfar et al. (2015)	Iran	5	T2DM	3 g dried, powdered ginger per day (n = 22)	3 g lactose per day (n = 23)	3 months	•Ginger significantly reduced CRP compared to the placebo	•Adverse effects not reported by authors
[53]	Javid et al. (2019)	Iran	5	T2DM undergoing non-surgical treatment for chronic periodontitis	2 g dried, powdered ginger per day (n = 21)	2 g wheat flour per day (n = 21)	2 months	•Ginger significantly reduced IL-6, CRP, and TNFα compared to placebo.	•Adverse effects not reported by authors
[46]	El Gayar et al. (2019)	Egypt	4	T2DM	1.8 g dried, powdered ginger per day (n = 40)	1.8 g wheat flour per day (n = 40)	2 months	•Ginger significantly reduced TC, LDL and TG, and increased HDL, compared to placebo	•Adverse effects not reported by authors

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Table 1 (*continued*)

Ref.	Author, Year	Country of Study	JADAD	Cohort	Experimental group (n)	Comparison group (n)	Duration of exposure	Primary Outcomes of Interest	Adverse Effects
[50]	Bordia et al. (1997)	India	2	T2DM with or without coronary artery disease	10 g single dose and 4 g daily as dried, powdered ginger per day (n = 30)	Unspecified placebo in same dosage per day (n = 15)	3 months	•No significant change for TC, HDL and TG compared to placebo	•Adverse effects not reported by authors
[45]	Andallu et al. (2003)	India	1	T2DM with hypercholesterolemia undergoing dietary therapy	3 g dried, powdered ginger per day (n = 8)	Unspecified control per day	1 month	•Ginger significantly reduced TC, LDL and TG compared to the placebo •No significant change for HDL compared to placebo	•Adverse effects not reported by authors
Miscellaneous									
[55]	Mozaffari-Khosravi et al. (2016)	Iran	5	Knee osteoarthritis	1 g dried, powdered ginger per day (n = 50)	1 g starch per day (n = 50)	3 months	•Ginger significantly reduced TNFα and IL-1β compared to the placebo	•Adverse effects not reported by authors
[56]	Naderi et al. (2016)	Iran	5	Knee osteoarthritis	1 g dried, powdered ginger per day (n = 50)	1 g capsulated starch per day (n = 50)	3 months	•Ginger significantly reduced CRP compared to the placebo, No significant change on total cholesterol.	•Adverse effects not reported by authors
[59]	Imani et al. (2015)	Iran	5	Patients undergoing continuous ambulatory peritoneal dialysis	1 g dried, powdered ginger per day (n = 18)	1 g starch per day (n = 18)	10 weeks	•No significant change for CRP compared to placebo	•Adverse effects not reported by authors
[57]	Mashhadi et al. (2013)	Iran	5	Muscle soreness and inflammation	3 g dried, powdered ginger per day (n = not declared)	Unspecified placebo per day (n = not declared)	6 weeks	•Ginger significantly reduced IL-6, compared to placebo	•Adverse effects not reported by authors
[54]	Tabibi et al. (2016)	Iran	4	Peritoneal dialysis patients	1 g dried, powdered ginger per day (n = 18)	1 g starch per day (n = 18)	10 weeks	•Ginger significantly reduced TG compared to placebo •No significant change for TC, LDL, HDL and IL-6 compared to placebo	•Adverse effects not reported by authors
[36]	Vahdat Shariatpanahi et al. (2013)	Iran	4	Acute respiratory distress syndrome	120 ml enteral fed ginger extract per day (n = 16)	1 g enteral fed coconut oil per day (n = 16)	10 days	•No significant change for IL-1, IL-6 and TNFα compared to placebo	•Adverse effects not reported by authors
[58]	Zehsaz et al. (2014)	Iran	4	Well-trained male endurance runners	1,5 g dried, powdered ginger per day (n = 14)	1,5 g toast powder per day (n = 14)	3 months	•Ginger significantly reduced IL-1β, IL-6 and TNFα compared to placebo	•Adverse effects not reported by authors

DBP – diastolic blood pressure, *HDL* – high-density lipoprotein, *IL-1* – interleukin-1, *IL-6* – interleukin-6, *IL-10* – interleukin-10, *LDL* – low-density lipoprotein, *RCT* – randomized controlled trial, *SBP* – systolic blood pressure, *TC* – total cholesterol, *TG* – triglyceride, *TNFα* – tumor necrosis factor alpha, *T2DM* – type 2 diabetes mellitus.

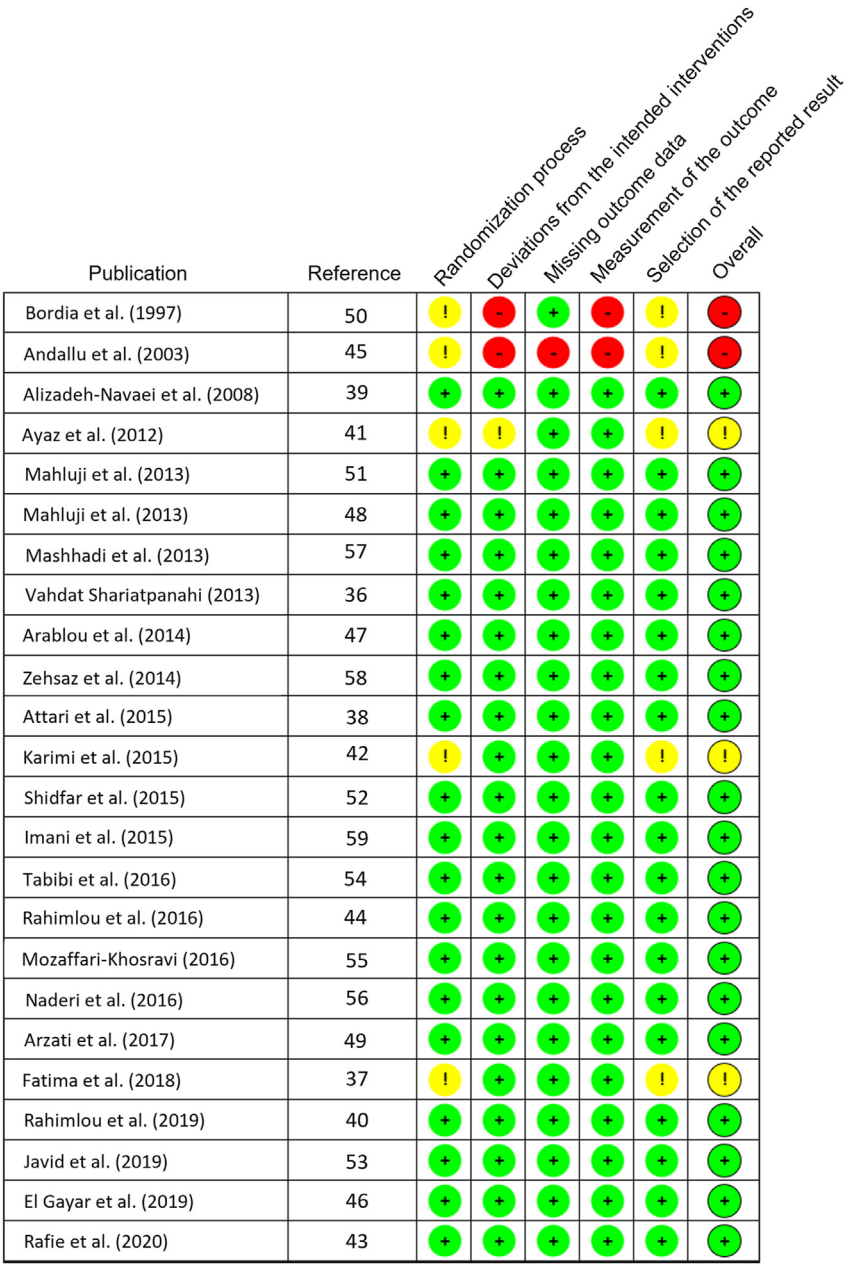

Fig. 2. Assessment of quality and risk of bias of the studies included in the systematic review, using the version 2 of the Cochrane risk-of-bias tool for randomized trials [35]. For each domain, risk was described by using a colour code as low (green), medium (yellow) and high (red).

patients undergoing continuous ambulatory peritoneal dialysis and with peritoneal dialysis patients, respectively [54,59].

4. Discussion

Dyslipidaemia, chronic inflammation, and hypertension are common and important contributors to the global burden of disease, most prominently increasing the risk of CVD [19,20,60–62]. *Z. officinale* (ginger) has been suggested to improve hypertension, dyslipidaemia and chronic inflammatory conditions in traditional medicine systems [29,30]. This systematic review identified only 24 studies that have investigated *Z. officinale* as a sole therapeutic agent in randomised controlled trials, with blood pressure, blood lipids or inflammatory markers as primary outcomes across different cohorts. This reflects a paucity of adequate studies in the literature on the efficacy of *Z. officinale* to improve these CVD risk markers. Blood lipids were the most investigated outcomes, specifically total cholesterol (n = 14 studies), and triglycerides (n = 13 studies). CRP was reported in 10 studies, where IL-10 was the least reported outcome, found in only 1 study. Blood pressure was reported in only 3 studies.

4.1. Dyslipidaemia

Dyslipidaemia is the presence of abnormally elevated concentrations of serum total cholesterol, LDL and/or triglycerides, and/or reduced levels of HDL [17,63,64]. Adequate treatment of dyslipidaemia can reduce the risk of CVD by up to 30% in patients [62]. Animal studies have supported the use of *Z. officinale* to treat dyslipidaemia, reportedly reducing total and LDL-cholesterol and

increasing HDL-cholesterol in rats, alongside demonstrated anti-inflammatory and anti-thrombotic activity [65–68]. In experimental atherosclerosis-induced animal models, *Z. officinale* administration also reduced atheroma development predominantly through reduction of lipid peroxidation and increased fibrinolytic activity [69–71].

Previous meta-analyses on limited available human studies have supported the use of *Z. officinale* for dyslipidaemia across different cohorts [72–74]. Similarly to our systematic review, a meta-analysis by Pourmasoumi et al. (2018) concluded that *Z. officinale* has a significant positive impact on total cholesterol and triglycerides, but not on HDL and LDL [72]. This study also included different patient cohorts, including T2DM patients, peritoneal dialysis patients, dyslipidemic and obese patients [72]. Our systematic review included 5 additional studies published since the meta-analysis by Pourmasoumi et al. (2018), where these additional studies generally reported significant improvements for blood lipid profiles in hyperlipidaemia [37], NAFLD [43], metabolic syndrome [40] and T2DM [46] cohorts, although one T2DM cohort showed no significant impact on blood lipids [49]. However, in a separate meta-analysis of patients with T2DM and components of the metabolic syndrome by Zhu et al. (2018), *Z. officinale* was found to have a positive impact on total cholesterol, triglycerides, as well as LDL and HDL, based on only 6 included studies [74]. Our systematic review included 5 of the 6 studies used by Zhu et al. (2018), with 1 study excluded from our review due to an intragroup analysis only. Furthermore, our analysis included 3 additional studies [46,49,50] not included by Zhu et al. (2018), mostly reporting no significant impact on blood lipids in a T2DM cohort [49,50]. In an earlier meta-analysis by Mazidi et al. (2016), it was also found that *Z. officinale* has benefit on lipid regulation in patients with metabolic syndrome and T2DM [73]. However, this meta-analysis does not clearly identify the included studies for the lipid analysis, and provided only the pooled estimate of the effect on lipids, making difficult any comparison with our results.

Similarly to these meta-analyses by Pourmasoumi et al. (2018) [72], Zhu et al. (2018) [74] and Mazidi et al. (2016) [73], the results of our systematic review show a significant reduction of triglycerides after *Z. officinale* treatment in 8 out of 13 studies [38–40,45–48,54], with 7 of the 14 studies reporting total cholesterol as an outcome [37,39,40,43,45–47]. However, contrary to these meta-analyses, only 5 out of 12 studies showed benefit in LDL levels [37,43,45,46,48], and 11 out of 12 studies reported no significant variations in HDL levels after *Z. officinale* treatment [38–40,42,43,45,47–50,54]. This may be explained by the fact that many of the studies reported non-significant decrease of total cholesterol and LDL, with a large sample size. This may have contributed to the statistical significance when the results were analyzed aggregated (as it happens in a meta-analyses). Furthermore, as described above, our systematic review includes additional studies not included in the meta-analyses by Pourmasoumi et al. (2018) [72], Zhu et al. (2018) [74] and Mazidi et al. (2016) [73].

Contrary to our results, a meta-analysis by Maharlouei et al. (2019) on overweight and obese patients reported a positive impact on HDL, although there was no significant effect on total cholesterol, LDL and triglycerides [75]. However, in our review, 11 out of 12 studies reported no significant variations in HDL levels after *Z. officinale* treatment [38–40,42,43,45,47–50,54]. The difference of these results compared to our analysis may be explained by only 4 studies being included for analysis, and the different criteria applied for study inclusion. In fact, Maharlouei et al. included studies using combination therapy (n = 2) or reporting an intragroup analysis only (n = 1), which might have contributed to the positive impact reported on HDL [75] that is not observed in our systematic review.

In brief, the current review results suggest that *Z. officinale* may have a positive impact on triglycerides, while inconsistent results were reported for total cholesterol and LDL, and little evidence suggests a positive impact on HDL. Therefore, the use of *Z. officinale* to improve dyslipidaemia requires further investigation, with standardization in the target population, intervention dosage and duration, and study outcomes. Alternative and more natural treatment might in future substitute commonly prescribed treatment for dyslipidaemia [17,76], which are currently associated with the insurgence of adverse effects such as indigestion, abdominal discomfort and dyspepsia, myalgia, myopathy and rhabdomyolysis (with elevated creatine kinase), liver enzyme elevation, and increased risk of T2DM and cognitive impairment, as well as myopathy, raised homocysteine and thrombosis risk, pancreatitis and pulmonary embolism [17,77].

4.5. Chronic Inflammation

Chronic inflammation is a central mediator in numerous non-communicable chronic diseases, including CVD [71,78]. Furthermore, inflammation contributes centrally in the pathogenesis of atherosclerosis, characterized as a low grade inflammatory disease [4,18]. There have been numerous inflammatory biomarkers studied as risk factors and mechanistic factors in atherosclerosis [79], where an increased serum CRP is considered an independent risk factor for CVD [19,20,80]. Other inflammatory biomarkers include TNFα, IL-1, IL-6 and IL-10 [21–25].

Our analysis shows that the effect of *Z. officinale* on inflammation has been investigated in only a few studies, with 10 studies investigating CRP, followed by TNFα (n = 8), IL6 (n = 7), IL-1 (n = 3) and IL-10 (n = 1). The majority of them reported a beneficial effect on these inflammatory markers, across the obesity and cardiometabolic patients (n = 4), T2DM patients (n = 4) and other miscellaneous conditions, such as osteoarthritis of the knee (n = 2), ARDS (n = 1) and in well trained endurance athletes (n = 1) (Table 1). Particularly, CRP was significantly reduced in 9 out of 10 studies [41–44,47,51–53,56] across different cohorts. The majority of the included studies also showed a significant decrease of TNFα [44,51,53,55,58], IL-6 [41,53,57,58], and IL-1 [58]. IL-10 as an outcome has been reported in only 1 studies on an obese cohort, which showed a significant decrease [42].

Although varied in design, animal and *in vitro* experiments on *Z. officinale* support an anti-inflammatory effect, suggesting mechanisms of action. In fact, both aqueous and ethanolic extracts of *Z. officinale* improved diabetes induced inflammation in Sprague–Dawley rats, mediated through regulation of mRNA-21/132 expression and AMPK activation in white adipose tissue [81,82]. Administration of *Z. officinale* extract 1 h before Carrageenan Induced Paw Edema in Albino Rats also reduced serum TNFα compared to control [83]. Similar results were observed in other animal models after *Z. officinale* administration, with phosphorylation of ERK1/2, SAPK/JNK, and p38 MAPKs, and reduced mRNA expression of TNFα, IL6 and IL-10 [84–87]. Furthermore, isolated 6-Gingerol protected against lipopolysaccharide (LPS)-induced inflammation in rats and subsequent development of cognitive deficits, neuroplasticity, and amyloidosis [88], while oleoresin reduced inflammatory cell infiltrations in renal tissues compared to control in stress-induced inflammation in Wistar rats [89]. *In vitro* experiments showed that *Z. officinale* extractions inhibited the secretion of IL-8, IL-6, IL-1β and TNFα, as well as COX and NF-κβ transcriptional response [90–93].

The anti-inflammatory effect of *Z. officinale* treatment highlighted by our analysis is supported by a previous meta-analysis. This included 5 studies in patients with T2DM, and concluded that *Z. officinale* reduced serum CRP [73]. Of these 5 studies, 2 were excluded from our review due to providing an intragroup analysis

only. However, our systematic analysis included 4 studies reporting CRP in T2DM patients, of which all showed a significant decline following *Z. officinale* intervention [47,51–53].

In brief, the current review results suggest that *Z. officinale* may have a positive impact on chronic inflammatory biomarkers as risk factors for CVD, particularly CRP, TNFα and IL-6. On the contrary, there are too few studies currently for IL-1 and IL-10 to draw any conclusions. As inflammation is a central mediator to atherosclerosis, *Z. officinale* requires further investigation as an immune-modulating intervention in the prevention of CVD.

4.6. Blood pressure and hypertension

Hypertension, broadly defined as a sustained SBP >140 mmHg and/or a DBP >90 mmHg, is considered one of the most important risk factors for morbidity and mortality globally [60,61]. Various mechanisms by which *Z. officinale* may reduce blood pressure have been suggested. *Z. officinale* may act on blood pressure via cholinergic action by activating muscarinic acetylcholine receptors, reducing cardiac output and thereby blood pressure [94]. Extractions of *Z. officinale* may also act via inhibition of calcium channel-blocking in coronary and peripheral arterial smooth muscle. In the heart, this calcium inhibition reduces the ability of calcium to act as an intracellular messenger, causing a negative inotropic effect [95]. Lastly, *Z. officinale* may also reduce blood pressure via the renin-angiotensin system through vasoconstriction and improved regulation of body fluid volume [96].

Although traditional uses of *Z. officinale* suggest the herb is beneficial in hypertension [29,30], blood pressure as an outcome has been reported in only 3 studies, with no significant change reported in any study [40,43,49]. Importantly, none of these studies were in a hypertensive male cohort, but variably reported in patients with NAFLD, metabolic syndrome or T2DM patients.

In animal studies, evidence to reduce blood pressure remains scanty and unclear. *Z. officinale* induces a dose-dependent decrease in the arterial blood pressure of anesthetized rat and guinea pig paired atria, reducing cardiac activity on the rate and force of spontaneous contractions [95]. In rabbit thoracic aorta, *Z. officinale* relaxed phenylephrine-induced vascular contraction at a dose 10 times higher than that required against potassium-induced contraction [95]. However, a standardized ethanol extract *Z. officinale* was devoid of any activity on the SBP in conscious rats when given orally [97]. Similarly, Joshua et al. (2015) did not show a significant reduction in blood pressure with *Z. officinale* administration in Wister rats [68].

A systematic review conducted by Hasani et al. (2019) included six trials, and only half of them reported a decrease in SBP. These studies included by Hasani et al. (2019) were excluded in our systematic review due to *Z. officinale* not being a sole intervention or an intragroup analysis. However, Hasani et al. (2019) concluded that blood pressure was decreased only in participants with mean age ≤50 years, in studies with a duration of less than 8 weeks, or *Z. officinale* supplementation of more than 3 g/day [98]. All of the studies included in our systematic review were more than 8 weeks duration and less than 3 g/day *Z. officinale* [40,43,47,49].

The current review results suggest that there is a lack of evidence to support the use of *Z. officinale* to reduce blood pressure in patients with cardio-metabolic disorders or T2DM, although there is not a clear consensus. Particularly, there are no studies included that have investigated *Z. officinale* in a hypertensive cohort, but rather conditions in which hypertension is a known co-morbidity. Identifying novel treatment options for hypertension would be of interest as medications commonly used are associated with serious adverse events, including hypotension, pre-syncope, syncope and injurious falls, bradycardia, hyperkalaemia and cardiac arrythmia, blurred vision and renal damage [27]. Furthermore, adverse effects significantly contribute to patient non-compliance of hypertensive medication [99,100].

4.7. Formulation type, dosage and frequency of Z. Officinale

Z. officinale root is derived from the plant which may be home-grown and cultivated by any individual, making it cost-effective, easily accessible and readily available [31]. This can be consumed as a fresh or dried root and is often prepared in food or teas as these do not require processing and are easily accessible and the most cost-effective form. They may also be purchased as a tincture or capsule which is easily accessible and inexpensive in comparison to conventional substitutes [31]. No specific dosing studies have been performed for *Z. officinale* in humans; however, most clinical research has used between 250 mg and 3 g of the powdered root in capsular form, taken one to four times daily [101]. This is consistent with studies included in this systematic review, where 21 studies (87.5%) used daily doses of dried powdered *Z. officinale* rhizome mostly between 1 and 3 g, with a maximum dosage used of 5 g in one study [37]. Across the included studies, there was a mean ± SD dose of 2.2 ± 1,0 g per day over 67.9 ± 24.2 days. Combined, this was a mean ± SD accumulated dose 148.5 ± 95.6 g *Z. officinale* rhizome. There does not appear to be a relationship between the dosage, frequency and outcomes assessed in the included studies however, where positive and negative outcomes where found for dosages below and above 2 g per day.

4.7.1. Adverse Effects of Z. Officinale

Although *Z. Officinale* is widely considered safe for use in relatively high dosages, it is known to result in mild gastrointestinal adverse effects, including nausea and heartburn, particularly at higher dosages [72,102]. There is also a concern raised that *Z. Officinale* may interact with warfarin and aspirin [103], although this was not evident in rats [97]. In a meta-analysis of 5 studies investigating *Z. Officinale* in osteoporosis in dosages ranging from 500 mg/day to 1000 mg/day, analysis showed a 2.3 increased relative risk of withdrawal of patients receiving ginger compared to placebo. All these adverse effects were considered mild and limited, and included 'bad taste' and 'stomach upset' [104], similarly to the few adverse effects reported in only 3 studies this systematic review [44,48,51]. However, no withdrawals were reported in any of the studies included in this systematic review. Furthermore, *Z. Officinale* did not pose a significant risk for spontaneous abortion compared to placebo and is considered harmless for pregnant woman below 1500 g per day [105].

The dosages used in included studies were up to 3 g per day for 3 months. However, the majority of studies included in this systematic review (75%) did not report adverse events. Of 6 studies that did report adverse events, no adverse events were reported by participants in 3 studies [38,40,43]. Mild headache (1 participant) and heartburn (3 participants) was reported across 3 separate studies [44,48,51]. This agrees with previous meta-analyses where *Z. Officinale* was used up to 3 g per day in which few mild gastrointestinal adverse effects were reported [73,74,106]. In healthy human volunteers, dosages up to 2000 mg of ginger metabolites (6-, 8- and 10-gingerols and 6-shogaols) showed no toxicity [107].

In animal toxicology studies, high dosages of *Z. Officinale* are generally considered safe. A patented *Z. Officinale* extract administered in dosages of 100, 333, and 1000 mg/kg administered to pregnant female rats showed a well-tolerated treatment with no adverse effects or deaths, as well as no toxic effects on foetuses [108]. At oral doses of 25, 50 and 100 mg/kg, *Z. Officinale* had no

negative effect on blood glucose, blood coagulation factors, warfarin interactions, blood pressure or heart rate of male Wistar rats [97]. Furthermore, toxicity studies in animals report a lethal dose of *Z. Officinale* essential oils to be more than 5 g/kg body weight [109]. It is therefore unlikely that *Z. Officinale* poses significant risk for adverse effects at the dosages used in the studies included in this systematic review.

4.2. Study quality assessment, heterogenicity and clinical implications

The quality of included studies was assessed based on the JADAD rating scale [34] and the Cochrane risk-of-bias tool for randomized trials [35]. The majority of studies (79.2%) were of high-quality (score between 3 and 5), with the same studies showing a low risk for bias (Fig. 2). Although duration of studies varied slightly, the majority of studies (79%) in this systematic review were conducted between 6 weeks and three months. This provides some consistency across studies in terms of the formulation type, dosage, and frequency of *Z. officinale* intervention used. Furthermore, as discussed above, there is some consistency in daily dosages of 1–3 g *Z. officinale* in most studies. Clinically, the use of dried root of *Z. Officinale* at dosages of 1,5–3 g per day over 6 weeks to 3 months may have a beneficial impact on dyslipidaemia and chronic inflammatory markers in patients with different underlying risk factors for CVD.

4.2.1. Limitations

Limitations of this systematic review and interpretation of the results are due to some inconsistency in the study design, relatively low sample sizes across the included studies, and some variation in follow-up durations of the reviewed studies. Although the majority of the studies were considered high quality based on JADAD score with a low risk of bias, this review also included some low-quality clinical trials in the final analysis show increased risk for bias. Furthermore, only English language full text articles were included for analysis.

5. Conclusions

Z. officinale may positively improve triglycerides and total cholesterol, with less evidence for a positive impact on LDL and HDL, although the studies included in this systematic review show inconsistent impact on blood lipid profiles across obesity, cardiometabolic derangements and T2DM cohorts investigated. There is more consistent evidence of a positive impact of *Z. officinale* on inflammatory markers associated with increased CVD risk, particularly CRP and TNFα. On the contrary, few studies reported no significant changes in blood pressure. Dosages of 1–3 g per day for 3 months can be considered clinically to evaluate the impact of ginger on patients over this period. However, there remains a paucity of studies on this topic, and further clinical, longitudinal, and pre-clinical studies are warranted to establish efficacy and dosage of *Z. officinale* on dyslipidaemia, blood pressure and inflammation in the long-term prevention of CVD.

Authorship

All authors: Conceptualization, Study Design and Methodology, Writing - Original Draft; Chelsea Courtney Daniels: Investigation. Zaiyaan Isaacs: Investigation. Renata Finelli: Methodology, Writing-Reviewing and Editing. Kristian Leisegang: Data curation, Supervision, Project administration, Writing- Reviewing and Editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

All the articles analysed in this systematic review are available online on Scopus and PubMed databases. No supplementary data is provided. Further information can be obtained from the corresponding author on request.

Declaration of competing interest

Chelsea Courtney Daniels - declares no conflict of interest which might have interfered with the scientific validity of the present paper.

Zaiyaan Isaacs - declares no conflict of interest which might have interfered with the scientific validity of the present paper.

Renata Finelli - declares no conflict of interest which might have interfered with the scientific validity of the present paper.

Kristian Leisegang - declares no conflict of interest which might have interfered with the scientific validity of the present paper.

Acknowledgements

The authors would like to acknowledge the University of the Western Cape for electronic access to academic databases and full text articles for the systematic review.

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