Orally consumed ginger and human health: an umbrella review

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Abbreviations:

| Abbreviation | Description |
|--------------|-------------|
| AMSTAR-2     | Assessment of Multiple Systematic Reviews 2 |
| CINAHL       | Cumulative Index to Nursing and Allied Health Literature |
| CRP          | C-reactive protein |
| GRADE        | Grading of Recommendations, Assessment, Development and Evaluation |
| HbA1c        | Glycosylated hemoglobin |
| Acronym | Description |
|---------|-------------|
| HDL     | High density lipoprotein |
| HOMA-IR | Homeostatic model assessment-insulin resistance |
| IL-1    | Interleukin-1 |
| IL-6    | Interleukin-6 |
| LDL     | Low density lipoprotein |
| MDA     | Malondialdehyde |
| PGE2    | Prostaglandin E2 |
| PRISMA  | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PROSPERO| International Prospective Register of Systematic Reviews |
| QUICKI  | Quantitative insulin sensitivity check index |
| RCTs    | Randomized controlled trials |
| sICAM   | Soluble intercellular adhesion molecule |
| T2DM    | Type 2 diabetes mellitus |
| TAC     | Total antioxidant capacity |
| TNF-α   | Tumor necrosis factor alpha |
Abstract

**Background:** Emerging evidence supports the health benefits of ginger for a range of conditions and symptoms; however, there is a lack of synthesis of literature to determine which health indications are supported by quality evidence.

**Objective:** This umbrella review of systematic reviews aimed to determine the therapeutic effects and safety of any type of ginger from the Zingiber family administered in oral form compared with any comparator or baseline measures on any health and wellbeing outcome in humans.

**Design:** Five databases were searched to April 2021. Review selection and quality was assessed in duplicate using the Assessment of Multiple Systematic Reviews-2 (AMSTAR-2) Checklist and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method, with results presented narratively.

**Results:** Twenty-four systematic reviews were included with 3% overlap of primary studies. Strongest evidence was found for the antiemetic effects of ginger in pregnant women (effect size: large; GRADE: high), analgesic effects for osteoarthritis (effect size: small; GRADE: high), and glycemic control (effect size: none-to-very large; GRADE: very low-to-moderate). Ginger also had a statistically significant positive effect on blood pressure, weight management, dysmenorrhea, post-operative nausea, and chemotherapy-induced vomiting (effect size: moderate-to-large; GRADE: low-to-moderate) as well as blood lipid profile (effect size: small; GRADE: very low) and anti-inflammatory and antioxidant biomarkers (effect size: unclear; GRADE: very low-to-moderate). There was substantial heterogeneity and poor reporting of
interventions; however, doses of 0.5-3g per day in capsule form administered for up to three months was consistently reported as effective.

Conclusions: Dietary consumption of ginger appears safe and may exert beneficial effects on human health and wellbeing, with greatest confidence in antiemetic effects in pregnant women, analgesic effects in osteoarthritis, and glycemic control. Future randomized controlled and dose-dependent trials with adequate sample sizes and standardized ginger products are warranted to better inform and standardize routine clinical prescription.

Key words: ginger, Zingiber officinale, chronic disease, pain, gastrointestinal conditions, umbrella review
INTRODUCTION

*Zingiber officinale* Roscoe, the most common ginger species, contains 80-90 non-volatile compounds that have anti-inflammatory, antioxidant, anti-emetic, as well as blood pressure, blood lipid, and blood glucose lowering effects [1-3]. The myriad of mechanisms of action have been extensively examined in animal and cell models, mostly involving gingerol, shogaol, zingerone, gingerdiol, and paradol compounds [3, 4]. Briefly, the anti-inflammatory effects of ginger have been linked to reducing pain and vasodilatory effects to lowering blood pressure [3, 4]. Ginger has been found to inhibit the production of cholesterol as well as adipocytes, thus benefiting blood lipid profile and weight management, respectively [3, 4]. Ginger compounds have also been shown to act similarly to hypoglycemic agents in assisting with transportation of glucose into cells [3], as well as anti-emetic medications to block the activation of receptors that initiate nausea and vomiting pathways [3, 5]. Furthermore, ginger consumption has been endorsed by numerous clinical practice guidelines [6-8] and was reported to be among the most common supplement used by pregnant women [9-12] and people with type 2 diabetes mellitus (T2DM) [13-15], hypertension [14], and cancer as a complementary rather than alternative medicine [16, 17].

Despite common clinical use and mechanistic studies supporting possible pathways of action to promote the use of ginger to support human health and wellbeing, there is a lack of quality synthesis of research to determine what health effects have the strongest evidentiary support in humans. Anh and colleagues [2] conducted a systematic review of 109 primary studies published up until 2019 that explored the human health benefits of ginger, finding beneficial effects for inflammation, metabolic syndromes, and gastrointestinal function. However, these authors did not conduct meta-analysis, warranting exploration of other systematic reviews that have used meta-analysis to pool effects as well as consideration of the methodological quality of systematic
reviews that have been used to guide clinical practice [2]. Li and colleagues [18] conducted an umbrella review of systematic reviews examining the efficacy of ginger for any health condition and therefore, did not consider the effects on healthy adults. This paper discussed methodological quality of reviews and highlighted the plethora of systematic reviews on the topic with inconsistent evidence and growing interest in the area, but only included reviews published up until 2018. Furthermore, Li and colleagues [18] combined all modes of delivery (oral, aromatherapy, topical, and moxibustion) which have different mechanisms of action.

Comprehensive synthesis of up-to-date highest-level systematic review evidence using rigorous study design and consideration of methodological quality for the effects of dietary ginger on human health would be useful to guide the integration of adjuvant use into clinical practice to address both general health and wellbeing as well as therapeutic uses for disease management.

Therefore, this umbrella review of systematic reviews of clinical trials aimed to determine the therapeutic effects and safety of any type of ginger from the *Zingiber* family administered in oral form and compared with any comparator or baseline measures on any health and wellbeing outcome in humans.

**METHODS**

This umbrella review methodology was guided by the Cochrane Handbook for Systematic Reviews [19] and the Joanna Briggs Institute Manual for Evidence Synthesis on Umbrella Reviews [20]; and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020197925). The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].
Search strategy

Electronic databases (PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Cochrane Database of Systematic Reviews, Google Scholar) and PROSPERO register were searched from database inception until 4 April 2021. As per the Canadian Agency for Drugs and Technologies in Health’s Practical Tool for Searching Grey Literature, the first 120 records were taken from Google Scholar [22]. The search strategy was based on the following structure: [(ginger* OR zingiber officinale*) AND (systematic review OR meta-analy*)], and was designed in PubMed using a combination of keywords and controlled vocabulary then translated to other databases with Polyglot [23] (Supplementary Table 1). Google Scholar, Pubmed search updates, and reference lists of included reviews and relevant literature were assessed to identify additional systematic reviews not located in the search strategy up until April 2021.

Eligibility and record screening

Screening of titles and abstracts, then full-text, was completed by two investigators independently (MC and AD) in Endnote X9 [24]. Disagreements were managed via consensus between reviewers or were resolved by discussion with a third researcher (SM).

Published peer-reviewed systematic reviews that met the following criteria were included: (1) systematic reviews, being regarded as the highest level of evidence, were defined with guidance from the PRISMA Protocols Statement [21]: (a) had an explicit set of aims; (b) employed a reproducible methodology, including a systematic search strategy and selection of studies; and (c) had a systematic presentation and synthesis of the characteristics and findings of included studies (conducted meta-analysis and/or narrative synthesis as part of their analysis), (2) for the most comprehensive synthesis of available evidence, eligible clinical trials which were reviewed
by the systematic reviews were randomized controlled trials (RCTs), non-randomized or non-controlled intervention trials, and observational studies, (3) examined the effects of any type of ginger from the Zingiber family administered in oral form and not in conjunction with any other therapeutic product, (4) compared ginger with placebo, other medicinal product, usual care, or no comparator, (5) for systematic reviews that included non-eligible intervention arms (e.g., turmeric, non-human sample) the study was included only if the ginger group and human population were reported separately, and (6) reported on any health-related or physiological outcome in humans.

Systematic reviews were excluded if they comprised only one primary study that reported on the effects of ginger or if they were unable to be translated into English. Studies that examined the effects of ginger administered via non-oral routes (e.g., topical, aromatherapy, moxibustion) were excluded due to these formulations containing drastically different compositions and mechanisms of action to orally consumed ginger. If multiple systematic reviews existed on the same topic and included the same primary studies and outcomes, only the most recent review and/or the review which conducted meta-analyses was used (Supplementary Table 2).

Data extraction and quality appraisal
Primary outcomes of interest were any health and wellbeing outcome relating to oral dietary or supplementary ginger consumption. Secondary outcomes were study and participant characteristics and adverse events. All data were extracted independently by one investigator (MC, AD, or CI) in tabular format (Supplementary Table 3) and checked for accuracy by a second investigator (MC, AD, or CI), with disagreements managed by consensus or involvement of a third investigator (SM). Where outcome data were missing, inadequately reported, or reported differently across systematic reviews, data were extracted directly from the primary
studies if possible. Where only a proportion of included primary studies of systematic reviews met the eligibility criteria for ginger intervention or human population, outcome data from only relevant primary studies were reported.

Individual study quality assessment using the Assessment of Multiple Systematic Reviews 2 (AMSTAR-2) Checklist [25] was carried out independently on all studies by two investigators (MC and [AD or CI]), with disagreements managed by consensus or resolved by discussion with a third investigator (SM). The AMSTAR-2 is a 16-question tool that judges each item as ‘yes’ or ‘no’ and yields a final overall rating for the confidence in the results of the systematic review as ‘high’, ‘moderate’, ‘low’ or ‘critically low’ [25].

If the certainty in the estimated effect of each meta-analysis was not determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method [26] by systematic review authors; it was calculated by the current umbrella review authors using GRADEpro Guideline Development Tool software [McMaster University, 2015 (developed by Evidence Prime, Inc)]. Certainty in the evidence can be downgraded for risk of bias, imprecision, inconsistency, indirectness, and publication bias; and upgraded for a large effect size, dose-response gradient, or effect of residual confounding. The GRADE approach provides four levels of certainty for the estimated effect: ‘very low’ (very little confidence), ‘low’ (limited confidence), ‘moderate’ (moderately confident), and ‘high’ (very confident) [26]. Where GRADE level of evidence was determined by the current review authors, it was conducted by MC and revised and confirmed by SM.
**Data synthesis**

Data were reported via narrative synthesis, as per that of the included systematic reviews, and no data re-analysis (i.e. meta-analysis) was conducted as per the Joanna Briggs Institute recommendations for umbrella reviews [20]. Primary studies of included systematic reviews that were included in two or more systematic reviews were presented in tabular format (Supplementary Figure 1). The extent to which primary studies overlap in the included systematic reviews was calculated and reported as the percentage of primary study overlap:

\[
\% \text{ overlap} = \frac{N - r}{rc} \times 100
\]

whereby \( N \) represents the total number of primary studies including double counting of overlapping studies, \( r \) is the number of primary studies not including double counting of overlapping studies, and \( c \) is the total number of systematic reviews [27].

The most recent and/or comprehensive meta-analysis for each outcome were summarized in tabular format. Whereby systematic reviews did not conduct meta-analysis to guide overall conclusions regarding statistical significance of outcomes, a modified consistency rating [28] was used: (number of primary studies that reported a statistically significant positive result \( \div \) total number of studies reporting that outcome) \( \times \) 100. A modified consistency rating of at least 66% was required to report an overall positive effect [28]. The quality of systematic reviews assessed using AMSTAR-2 and GRADE were presented in tabular format (Supplementary Tables 4 and 5).
RESULTS

Systematic review characteristics

Twenty-four systematic reviews were included, which had two to 109 primary studies in each, representing 180 primary studies in total (Figure 1). Although 87 of the primary studies were included in two or more systematic reviews, a 3% overlap of primary studies in the included systematic reviews was calculated (Supplementary Figure 1). The main reason for exclusion at full-text review was due to all primary studies and outcomes of screened systematic reviews being included in newer and/or more comprehensive reviews (n=40 reviews; Supplementary Table 2). Of these excluded records, 15 addressed nausea and vomiting of pregnancy, five addressed pain, and five addressed chemotherapy-induced nausea and vomiting.

The majority (79%) of systematic reviews exclusively included RCTs [2, 29-46], and 21% included a combination of the eligible study designs (Table 1; Supplementary Table 3). Seven (29%) systematic reviews only included placebo-controlled trials [30, 34, 38, 42-45] and the remaining systematic reviews mainly examined a combination of placebo, usual care, or a medicine as the comparator to ginger. *Zingiber officinale* was examined in the primary studies of 11 (46%) systematic reviews [30, 32, 34, 37-39, 41, 44, 45, 47, 48] and the remaining 13 (54%) reviews did not specify the species of ginger administered. Most systematic reviews explored multiple forms of ginger consumption, but ginger capsules were the most commonly administered (n=14 [58%] systematic reviews) [2, 29, 32, 33, 36, 39-42, 45, 46, 48-50] followed by ginger powder (n=6 [25%] of systematic reviews; Table 2) [30, 31, 34, 35, 37, 38]. Dosage of ginger varied greatly between primary studies, with 0.5-2g/day being most commonly administered [2, 29-35, 37-42, 44-47, 49, 50]. Only two systematic reviews [2, 48] reported the active constituents of ginger formulations used (n=19 primary studies in total); which was most
commonly gingerols or a combination of gingerols and shogaols. Of the 16 (67%) systematic reviews [2, 29, 30, 32, 33, 36-38, 40-43, 45, 48-50] that reported frequency of ginger administration, dosing frequency varied between once, twice, three, or four times daily. Interventions of ten days duration or less were most commonly used in primary studies of the six systematic reviews that examined the analgesic effects of ginger for dysmenorrhea or headache [2, 29, 36, 41, 42, 45]. Primary studies of the eight systematic reviews that examined the metabolic effects of ginger commonly administered ginger for longer durations of six weeks to three months [2, 30-32, 34, 35, 47, 48]. Duration of intervention ranged from one day to three months for all other outcomes and population groups.

Systematic review study quality

Of the 24 included systematic reviews, 17% were rated as having critically low quality [38, 45, 47, 50], 46% as low quality [2, 30-34, 36, 40, 43, 44, 46, 51], 33% as moderate quality [29, 35, 37, 39, 41, 42, 48], and 4% as high quality [49] (Table 3; Supplementary Table 4). Only a single systematic review [49] reported sources of funding of primary studies (Item 10) and only two reviews [37, 41] provided a list of excluded studies with explanations for exclusion (Item 7). Most (88%) of the reviews did not provide an explanation for primary study design inclusion (Item 3), 67% did not specify whether review methods were established prior to conducting the review (Item 2), and 46% did not justify publication restrictions (Item 4). Of the 15 reviews that conducted meta-analysis, 40% did not explore the potential impact of risk of bias in primary studies on the results of the meta-analysis (Item 12). Nineteen (79%) systematic reviews reported overall conclusions regarding primary study quality and despite different assessment tools used, majority of reviews (95%) included primary studies that were mostly high quality or had low risk of bias [29-32, 34-36, 40-46, 48-51].
The GRADE certainty in the evidence for most (59%) of the 44 outcomes that were meta-analyzed in included systematic reviews was found to be very low to low, meaning there is very little to little confidence that the estimated effect represents the true value of effect (Table 3; Supplementary Table 5). There was moderate to high confidence in the effect of the remaining 41% of outcomes. GRADE ratings were mostly downgraded due to inconsistency (high heterogeneity) and imprecision (small sample sizes and wide 95% confidence intervals) and were not improved by a large effect size in most cases. Almost all outcomes had low risk of bias in primary RCTs and no outcomes were downgraded due to indirectness or publication bias [26]. However, publication bias was not able to be fully investigated due to the small number of studies included for most outcomes and, therefore, could have unknown effects on the conclusions of this review.

**Therapeutic efficacy of ginger**

Table 2 presents primary studies and Table 3 contains meta-analyses evaluating the effect of ginger on each human outcome as reported in the included systematic reviews. These results are more simply presented in Figure 2.

**Analgesic effects**

Eight systematic reviews [2, 29, 36, 38, 39, 41, 42, 45] explored the effect of ginger on three pain-inducing conditions. The overall finding was consistent evidence of a moderate to large beneficial analgesic effect. In females with dysmenorrhea, there was consistent evidence that ginger statistically significantly reduced pain severity when compared to placebo (effect size: large; GRADE level: low) [45] and is as effective as NSAIDs (effect size: small; GRADE level: low). When compared to placebo, meta-analysis found no statistically significant effect of ginger on dysmenorrhea pain duration (GRADE level: very low) [45]. In participants with osteoarthritis,
there was a large body of consistent evidence (meta-analyses of >700 cases and ≥4 primary studies) that ginger statistically significantly reduced pain severity and pain-related disability when compared to placebo (effect size: small; GRADE level: high) [39]. Although meta-analysis was not conducted, 100% (n=2) of primary studies which assessed osteoarthritis-related knee stiffness [39] and 50% (n=3) of studies that assessed post-exercise muscle pain severity in trained and untrained participants found a statistically significant positive effect of ginger consumption [2, 38]. In participants with headache or migraine, meta-analysis found no statistically significant effect of ginger on treatment response when compared to placebo (GRADE level: very low) [42]. No meta-analysis exploring headache/migraine severity was conducted in any review; however, the four (100%) primary studies which assessed headache/migraine severity found a statistically significant positive effect with ginger [2, 42].

**Metabolic effects**

Nine systematic reviews [2, 3, 30-32, 34, 35, 47, 48] explored the effect of ginger on three metabolic conditions. The overall finding was consistent evidence of a moderate to large beneficial effect for cardiovascular health, glycemic control, and weight management. With reference to cardiovascular health outcomes, there was consistent evidence that ginger reduced systolic and diastolic blood pressure when compared to placebo (effect size: medium to large; GRADE level: low) [31]. Subgroup analyses found that only doses of >3g/day or durations of eight weeks or less were statistically significantly effective for systolic and diastolic blood pressure but did not explain considerable heterogeneity ($I^2=94\%$, $I^2=81\%$, respectively) [31]. Regarding blood lipids, there was consistent evidence that ginger compared to placebo or unspecified control statistically significantly reduced the concentration of triglycerides and total cholesterol, and statistically significantly increased high density lipoprotein (HDL) cholesterol (effect size: small; GRADE level: very low) [32]. Although 10 (71%) of the 14 studies that
measured low density lipoprotein (LDL) cholesterol found a statistically significant positive effect of ginger, no statistical significance was found when meta-analyzed (GRADE level: very low) [32]. Subgroup analyses improved heterogeneity and found statistically significant effects on total cholesterol ($I^2=55\%$) and HDL-cholesterol ($I^2=87\%$) only for participants with hyperlipidemia and not T2DM [32]. Two (33\%) of the six primary studies that reported on platelet aggregation, one (33\%) of the three primary studies that reported on thromboxane B2 production, and no studies that measured fibrinogen or fibrinolytic activity found a statistically significant reduction with ginger consumption [2, 48]. No reviews conducted meta-analysis of blood clotting outcomes.

Regarding glycemic control, there was consistent evidence that ginger compared to placebo reduced insulin resistance (measured as homeostatic model assessment-insulin resistance (HOMA-IR) or quantitative insulin sensitivity check index (QUICKI); effect size: very large; GRADE level: moderate) [34], fasting blood glucose levels (effect size: large; GRADE level: low) [32], and glycosylated hemoglobin (HbA1c; effect size: large; GRADE level: moderate) [35], but had no statistically significant effect on blood insulin levels (GRADE level: very low) [34]. Subgroup analyses by population found only statistically significant effects on fasting blood glucose levels for participants with T2DM, but not hyperlipidemia [32].

Concerning weight management, there was some evidence that ginger in comparison to placebo reduced body weight and body mass index (effect size: large; GRADE level: low) as well as hip circumference and waist-to-hip ratio (effect size: small to medium; GRADE: moderate) [34]. Although meta-analyses were not conducted, three (75\%) of the primary studies that assessed appetite, two (67\%) of the primary studies that assessed food intake, two (100\%) studies that
measured fullness, and three (100%) studies that examined energy intake or thermogenesis found no statistically significant positive effects with ginger consumption [2, 30, 47].

**Gastrointestinal effects**

Seven systematic reviews [2, 33, 37, 40, 49, 50, 52] explored the effect of ginger on nausea and vomiting. In pregnant women, there was consistent evidence that ginger statistically significantly reduced nausea incidence and severity when compared with placebo (effect size: very large; GRADE level: high) and had no statistically significant effect on vomiting incidence (GRADE level: low) [40]. Although not meta-analyzed, all three (100%) primary studies that assessed retching incidence in pregnant women found a statistically significant positive effect with ginger [2, 33, 40]. In participants following surgical procedures, there was consistent evidence that ginger statistically significantly reduced post-operative nausea severity in comparison to placebo or unspecified control (effect size: medium; GRADE level: low) but had no statistically significant effect on nausea or vomiting incidence or demand for rescue anti-emetics (GRADE level: low to moderate) [37].

In participants undergoing chemotherapy and receiving standard anti-emetics, there was some evidence that adjuvant ginger consumption statistically significantly reduced likelihood of acute vomiting incidence and nausea and vomiting-related fatigue when compared to placebo (effect size: small to medium; GRADE level: moderate) [49]. There was a large body of evidence suggesting that ginger had no statistically significant effect on incidence or severity of overall chemotherapy-induced nausea or vomiting, acute nausea, delayed nausea or vomiting, or chemotherapy-induced nausea and vomiting-related quality of life in comparison to placebo or usual care (GRADE level: very low to moderate) [49]. Subgroup analyses improved
heterogeneity but did not affect the effect sizes for chemotherapy-induced nausea and vomiting outcomes.

No reviews conducted meta-analysis of motion sickness or gastric emptying outcomes. However, two (67%) of the three studies that assessed incidence of nausea and/or vomiting related to motion sickness and one (50%) of the two studies that assessed incidence of nausea or motion sickness symptoms (vertigo and nystagmus) found a statistically significant positive effect with ginger consumption [2]. Three (60%) of the five primary studies that measured gastric emptying and two (67%) of the three primary studies that measured induced gastric dysrhythmia found a statistically significant positive effect with ginger [2].

**Anti-inflammatory and antioxidant effects**

Five systematic reviews [2, 35, 38, 44, 46] explored the anti-inflammatory and antioxidant effects of ginger and the overall finding was consistent evidence of a moderate beneficial effect. There was consistent evidence that ginger compared to placebo or unspecified control statistically significantly reduced C-reactive protein (CRP) [46], tumor necrosis factor alpha (TNF-α) [44], soluble intercellular adhesion molecule (sICAM) [44], malondialdehyde (MDA), and total antioxidant capacity (TAC; effect size: unclear; GRADE level: very low to moderate) [46]. There was some evidence that ginger had no statistically significant effect on prostaglandin E2 (PGE2; GRADE level: moderate) [46] or interleukin-6 (IL-6; GRADE level: low) [44]. The three (100%) studies that assessed interleukin 1 (IL-1) found statistically significant reductions with ginger consumption; however, no reviews conducted meta-analysis [2, 38].
Other effects

Three systematic reviews [2, 38, 43] explored other effects of ginger. The overall finding was consistent evidence of no beneficial effect on lactation as well as physical performance. All three (100%) primary studies that assessed range of motion and arm circumference and both (100%) studies that assessed perceived exertion during exercise found no statistically significant effect of ginger consumption [38]. One (50%) of the two studies that measured human breast milk volume found a statistically significant increase with ginger consumption [2, 43]. No reviews that examined breast milk volume or physical performance conducted meta-analyses.

Safety of ginger

Nine (60%) [29, 32, 35-37, 43, 44, 50, 51] of the 15 systematic reviews that reported on adverse events found no incidence of any adverse effect associated with ginger use (n=32 primary studies; n=1,826 participants). In systematic reviews that did report adverse effects, the most common event reported, regardless of study population, were mild gastrointestinal side-effects, mainly reflux or heartburn [2, 29, 32, 37, 40, 45, 49, 50, 52, 53], abdominal discomfort [2, 37, 39, 40, 50], and diarrhea [2, 29, 37, 50]. One review [40] found reflux and abdominal discomfort to be alleviated if ginger was administered with small frequent meals. In participants undergoing chemotherapy, a meta-analysis by Crichton et al. [49] found the odds of any gastrointestinal, flushing, rash-related, or unspecified adverse event reasonably relatable to the intervention to be statistically significantly higher with oral ginger consumption (0.16-1g/day in capsule form, twice or four times daily for 5-56 days) compared with placebo (OR: 2.0; 95% CI: 1.39, 2.99; p=0.0003; I²=0%; n=3 studies; n=5 interventions; n=1,458 participants; GRADE level: moderate). In participants with osteoarthritis, Bartels et al.’s [39] meta-analysis found participants given ginger consumption (0.5-1g/day in capsule form for 3-12 weeks) were at a
2.33 times statistically significantly higher risk of study withdrawal due to minor adverse effects (bad taste or various forms of stomach upset) when compared to participants who received placebo (RR: 2.33; 95% CI: 1.04, 5.22; p=0.04; I²=0%; n=3 studies; n=500 participants).

However, in patients with dysmenorrhea, Pattanittum et al. [41] found that ginger was not statistically significantly associated with increased odds of any adverse event (OR: 0.96; 95% CI: 0.13, 7.09; p=0.09; I²=78%; n=3 studies; n=279 participants; GRADE level: low). Likewise, Crichton et al. [49] found that the odds of heartburn in chemotherapy patients was not statistically significantly different when compared to placebo (OR: 1.88; 95% CI: 0.68, 5.18; p=0.22; I²=0%; n=3 studies; n=312 participants; GRADE level: low).

**DISCUSSION**

This umbrella review identified a convincing body of evidence that, in humans, ginger conferred analgesic, metabolic, and gastrointestinal therapeutic effects on a range of health conditions. The strongest evidence for therapeutic effects, with high certainty of the evidence (GRADE level: high) and very large effect size, was found for the antiemetic effects of ginger in pregnant women (1.0-2.5g/day for 4-21 days). These findings were clinically meaningful; for example, evident by women consuming ginger being 7.5 times less likely to experience nausea than those who received placebo. Great confidence in the analgesic effects of ginger in populations with osteoarthritis was also found (0.5-1.0g/day for 3-12 weeks; GRADE level: high). Despite the effect size being small, clinical significance is suggested due to similar standardized mean differences in the treatment effect being observed with NSAIDs, which are a standard treatment for osteoarthritic pain [54]. There was moderate confidence (GRADE level: moderate) in a large to very large estimated effect of ginger for glycemic control (0.05-3g/day for 2-3 months; GRADE level: moderate). These results were also clinically meaningful; for example, the 1% decrease in HbA1c observed in this review improves diabetes outcomes, where each 1% increase...
in HbA1c is associated with a 30% increase in all-cause mortality and 40% increase in cardiovascular disease mortality. Furthermore, ginger had a medium to large effect on some blood pressure, weight management, dysmenorrhea, post-operative nausea, and chemotherapy-induced vomiting outcomes, but the certainty in these effects was mostly low to moderate (0.02-3.0g/d for three days to three months; GRADE level: low to moderate). A statistically significant small effect of ginger was found on blood lipid profile; however, there was very low confidence in this effect (0.005g-3.0g/d for 2-3 months; GRADE level: very low). It remains uncertain whether the health benefits of ginger were conferred, at least in part, due to anti-inflammatory and antioxidant behavior as meta-analyses showed ginger improved CRP, TNF-α, sICAM, MDA, and TAC but there was very serious inconsistency and/or imprecision in these findings (GRADE level: very low to moderate).

Most primary studies included multiple forms of ginger consumption but the best evidence was for ginger capsules, most likely due to ease of administering a consistent and standardized dose as well as enabling blinding via placebo capsules. Ginger supplement active constituents and frequency of ginger administration was not well reported in systematic reviews or primary studies and did not consider how variations in the chemical composition of ginger, and thus health effects, depend on species, geographical origin, seasonal variation, storage, and harvesting and processing methods [55, 56]. Therefore, conclusions on biophenol dosing cannot be made; however, dosage frequency should consider the two-hour half-life of ginger [48].

Ginger was not associated with any serious adverse events; however, despite having therapeutic effects, ginger consumption should not replace medical treatment and should only be implemented under the care of a medical physician and/or dietitian as ginger consumption may not be indicated for all populations. For example, ginger is not suitable for those with platelet
disorders as studies have found ginger to reduce platelet aggregation, especially in those taking blood thinning medications [2, 48]. Ginger is also not indicated for populations susceptible to gastroesophageal reflux as heartburn was found to be a common minor side effect of ginger consumption in this review [2, 29, 32, 37, 40, 45, 49, 50, 52, 53]. Ginger has been found to relax the lower esophageal sphincter, which is the primary mechanism behind reflux [57]; however, minor heartburn may be improved by consuming ginger supplements with food [40]. Slight abdominal discomfort, another side effect reported with ginger consumption, may actually be attributable to a sudden positive shift in the composition and function of gastrointestinal microbiota [58]. Therefore, in addition to the possible direct effects on inflammatory markers, ginger may partly render anti-inflammatory effects in chronic disease populations through modulating gastrointestinal microbiota, and also may benefit healthy populations by reducing chronic inflammation which has been associated with the onset of diseases such as T2DM, heart disease, and some cancers [58, 59]. The therapeutic effects of ginger in healthy populations, however, remains uncertain.

Strengths, limitations, and priorities for future research

Numerous strengths and limitations have been identified in this umbrella review. A strength of the current review is the broad scope and rigorous study design including a thorough quality assessment of the included literature using the latest version of the AMSTAR-2 and GRADE [25, 26]. However, it must be acknowledged that AMSTAR-2 and GRADE are subjective measures that do not accurately identify the specific methodological and analytical limitations of the underlying literature, as with any quality assessment tool. Another strength of this review was the extensive consideration of primary study overlap, that if unaddressed can lead to over-representation of studies and biased results and is a common limitation in umbrella reviews [27]. A major limitation of this review is the possible exclusion of RCTs which have not been
summarized by the included systematic reviews; and therefore, key therapeutic and safety information may not be represented by the findings. Publication bias was not identified by systematic reviews as part of the AMSTAR-2 assessment but may be present due most reviews being rated poorly regarding search strategy and sample size. For example, despite many commercial ginger products aimed at motion sickness, only a small amount of studies (n=3; n=149 participants) were found in this review to support its use [2] and additional studies dating as far back to 1988 have been excluded [60-62]. Future RCTs should be well-powered and systematic reviews should employ rigorous study designs to minimize publication bias.

As systematic review quality assessed using AMSTAR-2 and certainty in the outcome effects evaluated using GRADE was mostly very low to low, improvements in the quality of future research is needed. Systematic reviews in this review were rated poorly mostly due to lack of detail in justifying choice of systematic review methodology, rather than the conduct of the review itself; and the primary studies represented were mostly high quality according to the diverse range of quality assessment tools used in the systematic reviews. The key limitation of the findings represented by this umbrella review were due to the heterogeneity of dose, frequency, and duration of ginger interventions, evident by high statistical heterogeneity ($I^2$) when assessed using meta-analysis. Therefore, the quality of the reporting of systematic reviews requires improvement for more confident recommendations to be drawn and methodological rigor of systematic reviews in nutraceutical interventions is an important area for future research. Future reviews should be stringently reported according to PRISMA guidelines [21] and use best-practice methodology, such as that outlined by the Cochrane Handbook for Systematic Reviews [19]. Future well-powered dose-dependent RCTs using ginger must test and report ginger bioactives and transparently report ginger species, intervention dose, frequency of administration, duration of intervention, and treatment compliance. Given that it is the non-
volatile bioactive compounds in ginger that are responsible for the therapeutic effects, supplements should be standardized to contain known and equal amounts of bioactive compounds [5, 56].

Outcomes for which there was insufficient or inconsistent evidence to support ginger use should be topics of future research prior to clinical use. This includes the analgesic effects of ginger on headache and migraine as well as post-exercise muscle pain; metabolic effects on blood lipid profile; anti-emetic effects post-operatively, during chemotherapy or relating to motion sickness; as well as the anti-inflammatory or antioxidant effects that may underpin many of the mechanisms of action. Given that most interventions identified in this review were of short duration, future research should consider the long-term effects of ginger consumption. Additional research areas of priority include the antimicrobial, immune modulating, neuroprotective, antineoplastic, as well as liver- and kidney- protecting effects of ginger, which have been supported by a substantial number of animal and mechanistic studies yet not extensively explored in human clinical trials [3, 4].

CONCLUSION
Orally consumed ginger was found to be safe and confer therapeutic effects on human health and wellbeing, with greatest confidence in effect for antiemetic effects in pregnant women, analgesic effects in osteoarthritis, and glycemic control. Ginger was also associated with an improvement in symptoms and biomarkers of pain in populations with dysmenorrhea; metabolic conditions in terms of improving blood pressure and weight management; and gastrointestinal issues, namely post-operative nausea and chemotherapy-induced vomiting; however, there was uncertainty in the clinical relevance for these outcomes. There was substantial heterogeneity and poor reporting of ginger interventions; however, doses of 0.5-3.0g/day in capsule form administered for up to
three months duration was found to be optimal across most outcomes. Future RCTs and dose-dependent trials with adequate sample sizes and standardized ginger products are warranted to better inform and standardize routine clinical prescription.

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CONFLICTS OF INTEREST

No authors declare any conflicts of interest.
References

1. Liu, Y., J. Liu, and Y. Zhang, Research Progress on Chemical Constituents of Zingiber officinale Roscoe. BioMed Research International, 2019. 2019: p. 5370823.

2. Anh, N.H., S.J. Kim, N.P. Long, J.E. Min, Y.C. Yoon, E.G. Lee, M. Kim, T.J. Kim, Y.Y. Yang, E.Y. Son, et al., Ginger on Human Health: A Comprehensive Systematic Review of 109 Randomized Controlled Trials. Nutrients, 2020. 12(1).

3. Mao, Q.Q., X.Y. Xu, S.Y. Cao, R.Y. Gan, H. Corke, T. Beta, and H.B. Li, Bioactive Compounds and Bioactivities of Ginger (Zingiber officinale Roscoe). Foods, 2019. 8(6).

4. Zhang, M., R. Zhao, D. Wang, L. Wang, Q. Zhang, S. Wei, F. Lu, W. Peng, and C. Wu, Ginger (Zingiber officinale Rosc.) and its bioactive components are potential resources for health beneficial agents. Phytotherapy Research, 2021. 35(2): p. 711-742.

5. Marx, W., K. Ried, A.L. McCarthy, L. Vitetta, A. Sali, D. McKavanagh, and L. Isenring, Ginger mechanism of action in chemotherapy-induced nausea and vomiting: A review. Critical Reviews in Food Science and Nutrition, 2017. 57(1): p. 141-146.

6. Royal College of Obstetricians & Gynaecologists, The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum: Green-top Guideline No.69, 2016: London.

7. Grossman, L.D., R. Roscoe, and A.R. Shack, Complementary and Alternative Medicine for Diabetes. Can J Diabetes, 2018. 42 Suppl 1: p. S154-s161.

8. Crichton, M., W. Marx, and S. Marshall. Cancer: Nutritional Implications of Treatment. 2020.

9. Mekuria, A.B., D.A. Erku, B.M. Gebresillassie, E.M. Birru, B. Tizazu, and A. Ahmedin, Prevalence and associated factors of herbal medicine use among pregnant women on antenatal care follow-up at University of Gondar referral and teaching hospital, Ethiopia: a cross-sectional study. BMC Complementary and Alternative Medicine, 2017. 17(1): p. 86.

10. Abd El-Mawla, A.M.A., Prevalence and use of medical plants among pregnant women in assiut governorate. Bull Pharm Sci, 2020. 43(1).

11. Volqvartz, T., A.L. Vestergaard, S.K. Aagaard, M.F. Andreasen, I. Lesnikova, N. Uldbjerg, A. Larsen, and P. Bor, Use of alternative medicine, ginger and licorice among Danish pregnant women – a prospective cohort study. BMC Complementary and Alternative Medicine, 2019. 19(1): p. 5.

12. Ahmed, M., J.H. Hwang, S. Choi, and D. Han, Safety classification of herbal medicines used among pregnant women in Asian countries: a systematic review. BMC Complement Altern Med, 2017. 17(1): p. 489.

13. Algarini, A.M., R. Al-Raddadi, and T. Alamri, Patterns and determinants of complementary and alternative medicine use among type 2 diabetic patients in a diabetic center in saudi arabia: herbal alternative use in type 2 diabetes. Journal of Fundamental and Applied Sciences, 2017. 9: p. 1738-1748.

14. Adeniyi, O., L. Washington, C.J. Glenn, S.G. Franklin, A. Scott, M. Aung, S.J. Niranjan, and P.E. Jolly, The use of complementary and alternative medicine among hypertensive and type 2 diabetic patients in Western Jamaica: A mixed methods study. PLOS ONE, 2021. 16(2): p. e0245163.

15. Wazailly, M., F.U. Afifi, M. El-Khateeb, and K. Ajlouni, Complementary and alternative medicine use among Jordanian patients with diabetes. Complement Ther Clin Pract, 2011. 17(2): p. 71-5.

16. Tuna, S., O. Dizdar, and M. Calis, The prevalence of usage of herbal medicines among cancer patients. J buon, 2013. 18(4): p. 1048-51.

17. Crichton, M., K. Strike, E. Isenring, A.L. McCarthy, W. Marx, A. Lohning, and S. Marshall, “It’s natural so it shouldn’t hurt me”: Chemotherapy patients’ perspectives, experiences,
and sources of information of complementary and alternative medicines. Complement Ther Clin Pract, 2021. 43: p. 101362.

18. Li, H., Y. Liu, D. Luo, Y. Ma, J. Zhang, M. Li, L. Yao, X. Shi, X. Liu, and K. Yang, Ginger for health care: An overview of systematic reviews. Complement Ther Med, 2019. 45: p. 114-123.

19. Pollock, M., R.M. Fernandes, L.A. Becker, D. Pieper, and L. Hartling, Chapter V: Overviews of Reviews, in Cochrane Handbook for Systematic Reviews of Interventions, J.T. Higgins, J. Editor. 2019, Cochrane.

20. E., A., F. R, G. C, H. C, K. H, and T. P, JBI Manual for Evidence Synthesis. Chapter 10: Umbrella Reviews. . 2020: JBI.

21. Page, M.J., J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 2021. 372: p. n71.

22. The Canadian Agency for Drugs and Technologies in Health (CADTH), Grey matters: a practical tool for searching health-related grey literature. 2018: Ottawa.

23. Center for Research in Evidence-Based Practice Systematic Review Accelerator. Polyglot search translator. 2017 September 20th, 2020; Available from: http://crebp-sra.com/.

24. The EndNote Team, EndNote. 2013, Clarivate: Philadelphia, PA.

25. Shea, B.J., B.C. Reeves, G. Wells, M. Thuku, C. Hamel, J. Moran, D. Moher, P. Tugwell, V. Welch, E. Kristjansson, et al., AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj, 2017. 358: p. j4008.

26. Guyatt, G.H., A.D. Oxman, H.J. Schunemann, P. Tugwell, and A. Knottnerus, GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol, 2011. 64(4): p. 380-2.

27. Pieper, D., S. Antoine, T. Mathes, E.A.M. Neugebauer, and M. Eikermann, Systematic review finds overlapping reviews were not mentioned in every other overview. Journal of Clinical Epidemiology, 2014. 67(4): p. 368-375.

28. Health Canada, Guidance Document for Preparing a Submission for Food Health Claims. 2009.

29. Daily, J.W., Z. Xin, K. Da Sol, and S. Park, Efficacy of Ginger for Alleviating the Symptoms of Primary Dysmenorrhea: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Pain Medicine, 2015. 16(12): p. 2243-2255.

30. Ebrahimzadeh Attari, V., A. Malek Mahdavi, Z. Javadivala, S. Mahlju, S. Zununi Vahed, and A. Ostadrahimi, A systematic review of the anti-obesity and weight lowering effect of ginger (Zingiber officinale Roscoe) and its mechanisms of action. Phytotherapy research, 2018. 32(4): p. 577-585.

31. Hasani, H., A. Arab, A. Hadi, M. Pourmasoumi, A. Ghavami, and M. Miraghajani, Does ginger supplementation lower blood pressure? A systematic review and meta-analysis of clinical trials. Phyther Res, 2019. 33(6): p. 1639-1647.

32. Jafarnejad, S., S.A. Keshavarz, S. Mahbubi, S. Saremi, A. Arab, S. Abbasi, and K. Djafarian, Effect of ginger (Zingiber officinale) on blood glucose and lipid concentrations in diabetic and hyperlipidemic subjects: A meta-analysis of randomized controlled trials. Journal of Functional Foods, 2017. 29: p. 127-134.

33. Khorasani, F., H. Aryan, A. Sobhi, R. Aryan, A. Abavi-Sani, M. Ghazanfarpour, M. Saeidi, and F. Rajab Dizavandi, A systematic review of the efficacy of alternative medicine in the treatment of nausea and vomiting of pregnancy. J Obstet Gynaecol, 2020. 40(1): p. 10-19.

34. Maharlouei, N., R. Tabrizi, K.B. Lankarani, A. Rezaianzadeh, M. Akbari, F. Kolahdooz, M. Rahimi, F. Keneshlou, and Z. Asemi, The effects of ginger intake on weight loss and
metabolic profiles among overweight and obese subjects: A systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr, 2019. 59(11): p. 1753-1766.

35. Mazidi, M., H.-K. Gao, P. Rezaie, and G.A. Ferns, The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. Food & Nutrition Research, 2016. 60: p. 1-N.PAG.

36. Rajabzadeh, F., S.M. Fazljou, L. Khodaie, S. Abbasalizadeh, and L. Sahebi, Effects of hot temperament herbs on primary Dysmenorrhea: a systematic review. World Family Medicine, 2018. 16(3): p. 252-258.

37. Toth, B., T. Lantos, P. Hegyi, R. Viola, A. Vasas, R. Benko, Z. Gyongyi, A. Vincze, P. Cscscei, A. Miko, et al., Ginger (Zingiber officinale): An alternative for the prevention of postoperative nausea and vomiting. A meta-analysis. Phytomedicine, 2018. 50: p. 8-18.

38. Wilson, P.B., Ginger (Zingiber officinale) as an Analgesic and Ergogenic Aid in Sport: A Systemic Review. J Strength Cond Res, 2015. 29(10): p. 2980-95.

39. Bartels, E.M., V.N. Folmer, H. Bliddal, R.D. Altman, C. Juhl, S. Tarp, W. Zhang, and R. Christensen, Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage, 2015. 23(1): p. 13-21.

40. Hu, Y., A.N. Amoah, H. Zhang, R. Fu, Y. Qiu, Y. Cao, Y. Sun, H. Chen, Y. Liu, and Q. Lyu, Effect of ginger in the treatment of nausea and vomiting compared with vitamin B6 and placebo during pregnancy: a meta-analysis. J Matern Fetal Neonatal Med, 2020. p. 1-10.

41. Pattanittum, P., N. Kunyanone, J. Brown, U.S. Sangkomkamhang, J. Barnes, V. Seyfoddin, and J. Marjoribanks, Dietary supplements for dysmenorrhoea. Cochrane Database Syst Rev, 2016. 3: p. Cd002124.

42. Chen, L. and Z. Cai, The efficacy of ginger for the treatment of migraine: A meta-analysis of randomized controlled studies. Am J Emerg Med, 2020.

43. Dilokthornsakul, W., A. Rinta, T. Dhippayom, and P. Dilokthornsakul, Efficacy and Safety of Ginger regarding Human Milk Volume and Related Clinical Outcomes: A Systematic Review of Randomized Controlled Trials. Complement Med Res, 2021: p. 1-7.

44. Negi, R., S. Sharma, R. Gaur, A. Bahadur, and P. Jelly, Efficacy of Ginger in the Treatment of Primary Dysmenorrhea: A Systematic Review and Meta-analysis. Cureus, 2021. 13(3).

45. Macit, M.S., S. Sozlu, B. Kocaadam, and N. Acar-Tek, Evaluation of Ginger (Zingiber Officinale Roscoe) on Energy Metabolism and Obesity: Systematic Review and Meta-Analysis. Food Reviews International, 2019. 35(7): p. 685-706.

46. Marx, W., D. McKavanagh, A.L. McCarthy, R. Bird, K. Ried, A. Chan, and L. Isenring, The effect of ginger (Zingiber officinale) on platelet aggregation: a systematic literature review. PloS one, 2015. 10(10).

47. Crichton, M., S. Marshall, W. Marx, A.L. McCarthy, and E. Isenring, Efficacy of Ginger (Zingiber officinale) in Ameliorating Chemotherapy-Induced Nausea and Vomiting and Chemotherapy-Related Outcomes: A Systematic Review Update and Meta-Analysis. J Acad Nutr Diet, 2019. 119(12): p. 2055-2068.
51. Balbontin, Y.M., D. Stewart, A. Shetty, C.A. Fitton, and J.S. McLay, *Herbal Medicinal Product Use During Pregnancy and the Postnatal Period: A Systematic Review*. Obstetrics and Gynecology, 2019. **133**(5): p. 920-932.

52. Saneei Totmaj, A., H. Emamat, F. Jarrahi, and M. Zarrati, *The effect of ginger (Zingiber officinale) on chemotherapy-induced nausea and vomiting in breast cancer patients: A systematic literature review of randomized controlled trials*. Phytother Res, 2019. **33**(8): p. 920-932.

53. Araya-Quintanilla, F., H. Gutierrez-Espinoza, M.J. Munoz-Yanez, U. Sanchez-Montoya, and J. Lopez-Jeldes, *Effectiveness of Ginger on Pain and Function in Knee Osteoarthritis: A PRISMA Systematic Review and Meta-Analysis*. Pain Physician, 2020. **23**(2): p. E151-e161.

54. Cadet, C. and E. Maheu, *Non-steroidal anti-inflammatory drugs in the pharmacological management of osteoarthritis in the very old: prescribe or proscribe?* Therapeutic Advances in Musculoskeletal Disease, 2021. **13**: p. 1759720X211022149.

55. Marx, M., E. Isenring, and L. A, *Determination of the concentration of major active antiemetic constituents within commercial ginger food products and dietary supplements* . European Journal of Integrative Medicine, 2017. **10**: p. 19-24.

56. Ali, B.H., G. Blunden, M.O. Tanira, and A. Nemmar, *Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): A review of recent research*. Food and Chemical Toxicology, 2008. **46**: p. 409-420.

57. Lohsiriwat, S., M. Rukkiat, R. Chaikomin, and S. Leelakusolvong, *Effect of ginger on lower esophageal sphincter pressure*. J Med Assoc Thai, 2010. **93**(3): p. 366-72.

58. Wang, X., D. Zhang, H. Jiang, S. Zhang, X. Pang, S. Gao, H. Zhang, S. Zhang, Q. Xiao, L. Chen, et al., *Gut Microbiota Variation With Short-Term Intake of Ginger Juice on Human Health*. Front Microbiol, 2020. **11**: p. 576061.

59. Furman, D., J. Campisi, E. Verdin, P. Carrera-Bastos, S. Targ, C. Franceschi, L. Ferrucci, D.W. Gilroy, A. Fasano, G.W. Miller, et al., *Chronic inflammation in the etiology of disease across the life span*. Nature Medicine, 2019. **25**(12): p. 1822-1832.

60. Wood, C.D., J.E. Manno, M.J. Wood, B.R. Manno, and M.E. Mims, *Comparison of efficacy of ginger with various antimotion sickness drugs*. Clin Res Pr Drug Regul Aff, 1988. **6**(2): p. 129-36.

61. Schmid, R., T. Schick, R. Steffen, A. Tschopp, and T. Wilk, *Comparison of Seven Commonly Used Agents for Prophylaxis of Seasickness*. J Travel Med, 1994. **1**(4): p. 203-206.

62. Nunes, C.P., C.d.C. Rodrigues, C.A.F. Cardoso, N. Cytrynbaum, R. Kaufman, H. Rzetelna, G. Goldwasser, A. Santos, L. Oliveira, and M. Geller, *Clinical Evaluation of the Use of Ginger Extract in the Preventive Management of Motion Sickness*. Current Therapeutic Research, 2020. **92**: p. 100591.
Table 1. Characteristics of included systematic reviews exploring the effects of ginger consumption on human health outcomes.

| Systematic review | N Primary Studies & Study Design | Population Characteristics | N Participants | Number of RCTs | Species | Form | Dosage | Frequency | Duration | Comparator | Outcomes assessed | Adverse Effects | Primary Study Quality | SR Quality (AMSTAR-2) |
|--------------------|---------------------------------|-----------------------------|----------------|---------------|---------|------|--------|-----------|----------|------------|---------------------|------------------|---------------------|---------------------|
| Anh 2020 [2]       | 109 (RCTs)                      | M/F mixed health            | NR             | 113           | NR      | Most cap | Mostly 0.5-1.5g/d | OD to QID | SD-3m    | Placebo (n=89) Drug/vitamin (n=14) Usual care (n=6) | ✔ ✔ ✔ ✔ ✔ | 39% high quality | Low                |
| Attari 2017 [30]    | 3 (RCTs)                        | M/F BMI ≥25kg/m²             | NR             | 3            | ZO      | Pow   | 1g/d (n=1) 2g/d (n=2) | SD (n=1) NR (n=2) | SD (n=1) 10-12w (n=2) | Placebo              | ✔                  | Most low/unclear ROB | Low                |
| Balbontin 2019 [51]| 17 (design NR)                  | F pre-/post-natal period    | NR             | NR NR NR NR NR | NR      | NR    | NR     | NR        | NR NR NR | Placebo (n=5) Drug/vitamin (n=2) | ✔                  | Most unclear ROB | High/average quality | Low                |
| Bartels 2015 [39]  | 5 (RCTs)                        | M/F OA                      | 874            | 5            | ZO (n=3) | NR (n=2) | Cap     | 0.5g/d (n=3) 1g/d (n=2) | NR       | 3-4w (n=2) 5w (n=2) 7w (n=1) | Placebo (n=5) Drug/vitamin (n=2) | ✔                  | Most unclear ROB | Mod                |
| Chen 2020 [42]     | 2 (RCTs)                        | M/F migraine                | 214            | 2            | NR      | Cap    | 0.4g/d (n=1) 0.6g/d (n=1) | OD (n=1) TID (n=1) | SD (n=1) 2m (n=1) | Placebo              | ✔                  | High quality       | Mod                |
| Crichton 2019 [49] | 18 (RCT n=15; non-RCT n=3)      | M/F CTX for cancer          | 1650           | 21           | NR      | Cap (n=18) Pow (n=2) Drink (n=1) | <1g/d (n=5) 1g-2g/d (n=15) NR (n=1) | BD (n=11) TID (n=1) QID (n=4) NR (n=2) | <5d (n=3) 5-10d (n=8) >1m (n=7) | Placebo (n=14) Usual care (n=4) | ✔ ✔ ✔ | Most low ROB | High               |
| Daily 2015 [29]    | 7 (RCTs)                        | F dysmenorrhrea              | 651            | 9            | NR      | Cap    | <1g/d (n=3) 1g-2g/d (n=6) | OD (n=2) BD (n=2) TID (n=2) QID (n=1) | 3-5d (n=8) PRN (n=1) | Placebo (n=4) Drug/vitamin (n=2) Stretching (n=1) | ✔ ✔ ✔ | Most low/mod quality | Mod                |
| Dilkothorn-sakul 2021 [43] | 2 (RCTs) | F lactating | 133 | 2 | NR | Cap (n=1) Pow (n=1) Drink (n=1) | <1g/d (n=1) 1g/d (n=1) | BD | 3d (n=1) 7d (n=1) | Placebo | ✔ ✔ | Low/unclear ROB | Mod                |
| Hasani 2019 [31]   | 6 (RCTs)                        | M/F metabolic conditions     | 345            | 6            | NR      | Pow    | 0.5g/d (n=1) 1.6-2g/d (n=2) 3g/d (n=3) | NR       | 7-8w (n=3) 10w (n=2) 12w (n=1) | Placebo (n=4) Black tea (n=1) | ✔ ✔ ✔ ✔ ✔ | 100% high quality | Low                |
| Hu 2020 [40]       | 13 (RCTs)                       | F pre-natal period          | 1174           | 15           | NR      | Cap (n=11) Syrup (n=1) Bisc (n=1) | <1g/d (n=1) 1g-2g/d (n=9) 1.5-2.5g/d (n=3) | TID (n=6) QID (n=1) NR (n=8) | 3-4d (n=11) 2-3w (n=2) | Placebo (n=8) Drug/vitamin (n=7) | ✔ ✔ ✔ ✔ ✔ | Most low/unclear ROB | Low                |
| Jafarnejad 2017 [32] | 9 (RCTs) | M/F T2DM or HL | 609 | 9 | ZO | Cap (n=6) Tab (n=3) | <1g/d (n=2) 1g-2g/d (n=2) 3 g/d (n=5) | BD (n=2) TID (n=3) NR (n=5) | 2m (n=6) 3m (n=3) | Unspecified control | ✔ ✔ ✔ ✔ ✔ | 56% high quality | Low                |
| Jalali 2020 [46]   | 20 (RCTs)                       | M/F mixed health            | 888            | 20           | NR      | Cap (n=14) Tab (n=2) | <1g/d (n=4) 1g-2g/d (n=12) | NR | 10-11d (n=2) 4-8w (n=6) | Unspecified control | ✔ ✔ ✔ | 80% high quality | Low                |
| Study | Year | Study Design | Intervention | Comparator | Duration | Outcome 1 | Outcome 2 | Outcome 3 | ROB | Crit | Status |
|-------|------|--------------|--------------|------------|----------|-----------|-----------|-----------|-----|------|--------|
| Khorasani 2020 [33] | 2018 | (RCTs) | F pre-natal period | Cap (n=12) | Raw (n=12) | 1690 | 18 | NR | Pow (n=2) | Raw (n=2) | >2g–3g/d (n=4) | BD (n=1) | NR (n=1) | 3-7d (n=13) | 14-21d (n=3) | Placebo (n=11) | Drug/vitamin (n=7) | 10-12w (n=12) | Mod/ high | Low |
| Macit 2019 [47] | 2019 | (RCT n=6; Pro n=2) | M/F healthy BMI ≥ 30kg/m² | Pow (n=2) | NR (n=6) | 285 | 8 | ZO | Pow (n=2) | NR (n=6) | 0.03-0.04g (n=2) 1g/d (n=9) 1g-2.5g/d (n=3) NR (n=1) | SD (n=3) | TID (n=4) | QID (n=1) | 4w (n=2) | Placebo (n=4) | Unspecified control (n=2) | None (n=2) | Crit Low | NR |
| Maharlouei 2018 [34] | 2018 | (RCTs) | M/F BMI ≥ 25kg/m² | Pow (n=12) | Ext (n=1) | 473 | 13 | ZO | Pow (n=12) | Ext (n=1) | 0.05g/d (n=1) 1-2 g/d (n=8) 3g/d (n=4) NR (n=2) | 2w (n=1) | 6-8w (n=4) | 10-12w (n=9) | Placebo | NR | Most low ROB | Mod |
| Marx 2015 [48] | 2015 | (RCT n=8; Obs n=2) | M/F mixed health | Cap (n=6) | Raw/cook (n=2) | 650 | 10 | ZO | Cap (n=6) | Raw/cook (n=2) | 1-2g/d (n=2) 3-4g/d (n=2) 5g-9g/d (n=2) NR (n=2) | OD (n=5) | TID (n=1) | NR (n=3) | Placebo (n=5) | NR (n=5) | Most low ROB | Mod |
| Mazidi 2016 [35] | 2016 | (RCTs) | M/F metabolic conditions | Pow (n=4) | NR (n=5) | 449 | 9 | NR | Pow (n=4) | NR (n=5) | 1g/d (n=3) >1-2g/d (n=3) 3g/d (n=3) | NR | 7-10w (n=4) | 2-3m (n=4) | NR (n=1) | Placebo | ✔ | ✔ | ✔ | 100% low ROB | Mod |
| Morvaridzadeh 2020 [44] | 2020 | (RCTs) | M/F mixed health | Cap (n=6) | NR (n=5) | 1010 | 16 | ZO | Cap (n=6) | NR (n=5) | 1-1.9g/d (n=4) 2g/d (n=5) 3g/d (n=5) NR (n=1) | NR | 4-6w (n=3) | 8-10w (n=8) | 12w (n=3) | Placebo | ✔ | ✔ | Most low/unclear ROB | Low |
| Negi 2021 [45] | 2021 | (RCTs) | F dysmenorrhea | Cap (n=1) | NR (n=7) | 1066 | 8 | NR | Cap (n=1) | NR (n=7) | <1g/d (n=4) 1g/d (n=3) 1.5g/d (n=1) | BD (n=1) | TID (n=3) | QID (n=4) | 2-3d (n=5) | Placebo (n=5) | Drug/vitamin (n=3) | ✔ | ✔ | Most low/unclear ROB | Crit Low |
| Oozigi 2018 [50] | 2018 | (RCT n=2; Non-RCT n=8) | F pre-natal period | Cap (n=8) | Bisc (n=1) | 1059 | 11 | NR | Cap (n=8) | Bisc (n=1) | Syrup (n=2) 0.25-1.5g/d (n=8) 1-4 tsp (n=2) NR (1) | BD (n=2) | QID (n=3) | NR (n=5) | 4d (n=10) | Placebo (n=7) | NR (n=4) | ✔ | ✔ | Most high quality | Crit Low |
| Pattanittum 2016 [41] | 2016 | (RCTs) | F dysmenorrhea | Cap (n=4) | NR (n=1) | 416 | 4 | ZO | Cap (n=4) | NR (n=1) | 0.5-0.75g/d (n=3) 1.5g/d (n=1) | TID (n=1) | NR (n=1) | 3d (n=1) | 5d (n=1) | Placebo (n=4) | Drug/vitamin (n=1) | ✔ | ✔ | Most low/unclear ROB | Mod |
| Rajabzadeh 2018 [36] | 2018 | (RCTs) | F dysmenorrhea | Cap (n=1) | NR (n=2) | 220 | 2 | NR | Cap (n=1) | NR (n=2) | 0.5-1g/d | BD (n=1) | QID (n=1) | 3d (n=1) | 10d (n=1) | Placebo (n=1) | Drug/vitamin (n=1) | ✔ | ✔ | Mod/ high quality | Low |
| Toth 2018 [37] | 2018 | (RCTs) | F post-op | Pow (n=10) | Raw (n=1) | 918 | 12 | ZO | Pow (n=10) | Raw (n=1) | <1g (n=4) 1g (n=6) 1.5-2g (n=2) Single dose (n=11) Pre- & Post-surgery (n=1) | 1d | Placebo (n=10) | Unspecified control (n=2) | ✔ | ✔ | Most unclear ROB | Mod |
| Wilson 2015 [38] | 2015 | (RCTs) | M/F mixed health | Pow (n=2) | NR (n=6) | 246 | 8 | ZO | Pow (n=2) | NR (n=6) | 1g-2/d (n=6) 3-4g/d (n=2) Single dose (n=2) | 1d (n=2) | 5-11d (n=3) | 6-10w (n=3) | Placebo | ✔ | ✔ | NA | Crit Low |

Crit low: critically low; CTX: chemotherapy; F: females; GRADE: Grading Recommendations, Assessment, HL: hyperlipidemia; IGs: intervention groups; Mod: moderate; NA: not assessed; Non-RCT: Non-randomized controlled trial; RCT: randomized controlled trial; ROB: risk of bias; n: number; M: males; NR:
not reported; OA: osteoarthritis; Obs: observational study; PRN: as needed (until pain relief); Pro: prospective study; ROB: risk of bias; T2DM: type 2 diabetes mellitus; ZO: Zingiber officinale.
Table 2: Synthesis of primary studies evaluating the effect of ginger on each human outcome as reported in the included systematic reviews.

| Outcome | Total primary studies | Participant Type | Total sample size | Ginger form | Duration | Daily ginger dose | N primary studies with positive effect (PCoC) (modified consistency rating) | Primary study overlap | Outcome meta-analyzed |
|---------|----------------------|------------------|------------------|-------------|----------|-----------------|--------------------------------------------------|----------------------|----------------------|
| **Analgesic Effects** | | | | | | | | | |
| Dysmenorrhea | 7 | Dysmenorrhea | 835 | cap | 3-10d | 0.5-1.5g | 7 (100%) | 21% | Yes |
| Pain duration | 2 | Dysmenorrhea | 245 | cap | 3-5d | 1.5-1.5g | 0 (0%) | 33% | Yes |
| **Osteoarthritis** | | | | | | | | | |
| Pain severity | 7 | Knee/hip OA | 1072 | cap/pow/tab/ext | 3-12w | 0.2-1.5g | 4 (57%) | 43% | Yes |
| Knee stiffness severity | 2 | Knee OA | 451 | cap | 6w | 0.5g | 2 (100%) | N/A | No |
| Pain-related disability | 4 | Knee OA | 704 | cap | 3-12w | 0.5-1g | 3 (75%) | N/A | Yes |
| **Post-Exercise Muscle Pain** | | | | | | | | | |
| Pain severity | 6 | Trained/untrained | 223 | pow | SD-6w | 2-4g | 3 (50%) | 43% | No |
| **Headache/migraine** | | | | | | | | | |
| Severity | 4 | Migraine/post op | 427 | cap | SD-3m | 0.4-0.8g | 4 (100%) | 25% | No |
| Treatment response | 2 | Migraine | 167 | cap | SD-3m | 0.4-0.6g | 0 (0%) | N/A | Yes |
| **Metabolic Effects** | | | | | | | | | |
| **Blood Pressure** | | | | | | | | | |
| Systolic BP | 6 | T2DM/BMI≥25/HL | 345 | pow | 7-12w | 0.5-9g | 6 (100%) | 17% | Yes |
| Diastolic BP | 6 | T2DM/BMI≥25/HL | 345 | pow | 7-12w | 0.5-9g | 6 (100%) | 17% | Yes |
| **Blood Lipids** | | | | | | | | | |
| Triglycerides | 14 | T2DM/BMI≥25/PD/HL | 720 | cap/pow/tab/ext | SD-3m | .005g-9g | 10 (71%) | 21% | Yes |
| HDL-Cholesterol | 14 | T2DM/BMI≥25/PD/HL | 712 | cap/pow/tab/ext | SD-3m | .005g-9g | 7 (50%) | 19% | Yes |
| LDL-Cholesterol | 14 | T2DM/BMI≥25/PD/HL | 771 | cap/pow/tab/ext | SD-3m | .005g-9g | 10 (71%) | 10% | Yes |
| Total cholesterol | 16 | T2DM/BMI≥25/PD/HL | 842 | cap/pow/tab/ext | SD-3m | .005g-9g | 10 (63%) | 13% | Yes |
| **Blood Clotting** | | | | | | | | | |
| Platelet aggregation | 6 | Healthy/HTN/MF | 128 | cap | SD-4m | 1-10g | 2 (33%) | 17% | No |
| Throm B2 production | 3 | Healthy/obese | 99 | cap/raw/cook | 1-6w | 5-40g | 1 (33%) | 33% | No |
| Fibrinogen | 3 | Obese/MF | 102 | cap | SD-4m | 3-10g | 0 (0%) | 33% | No |
| Fibrinolytic activity | 3 | Obese/MF | 102 | cap | SD-4m | 3-10g | 0 (0%) | 33% | No |
| **Glycemic Control** | | | | | | | | | |
| Fasting BGL | 21 | T2DM/PD/HL/BMI ≥25 | 917 | cap/tab | SD-3m | 0.05-4g | 11 (52%) | 19% | Yes |
| HbA1c | 4 | T2DM/BMI ≥25 | 222 | cap/tab | SD-3m | 0.05-4g | 4 (100%) | 75% | Yes |
| Blood insulin | 11 | T2DM/BMI ≥25 | 474 | cap/tab | SD-3m | 0.05-4g | 9 (82%) | 9% | Yes |
| Insulin resistance | 10 | T2DM/BMI ≥25 | 409 | cap/tab | SD-3m | 0.05-4g | 9 (90%) | 15% | Yes |
| **Weight Management** | | | | | | | | | |
| Body weight | 6 | Healthy/BMI ≥25 | 223 | Pow/ext | 1d-3m | 0.05-20g | 2 (33%) | 33% | Yes |
| BMI | 6 | Healthy/BMI ≥25 | 223 | Pow/ext | 1d-3m | 0.05-20g | 2 (33%) | 33% | Yes |
| Waist-to-hip ratio | 5 | Healthy/T2DM/BMI ≥25 | 169 | Pow/ext | 1d-3m | 0.05-20g | 2 (40%) | 0% | Yes |
| Hip circumference | 3 | T2DM/BMI ≥25 | 162 | pow | 8-12w | 0.5-2g | 1 (33%) | 0% | Yes |
| Appetite | 4 | Healthy/BMI≥25/PD | 170 | pow/tab/cook | SD-6w | 2-20g | 3 (75%) | 50% | No |
| Fullness | 2 | Healthy/BMI≥25/PD | 56 | pow/tab/cook | SD-6w | 1-20g | 2 (100%) | 0% | No |
### Gastrointestinal Effects

#### Nausea and Vomiting of Pregnancy

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| Arm circumference             | 3         | 3       | 100%       | 0%         |
| Range of motion               | 3         | 3       | 100%       | 0%         |
| Antioxidant Effects           | 3         | 3       | 100%       | 0%         |
| PGE2                          | 3         | 3       | 100%       | 0%         |
| IL                            | 3         | 3       | 100%       | 0%         |
| Anti-Gastric dysrhythmia       | 3         | 3       | 100%       | 0%         |
| Gastric emptying              | 3         | 3       | 100%       | 0%         |
| Gastric motility              | 3         | 3       | 100%       | 0%         |
| Nystagmus                      | 3         | 3       | 100%       | 0%         |

#### Post-Operative Nausea and Vomiting (PONV)

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| Motion sickness               | 3         | 3       | 100%       | 0%         |
| N&V incidence                 | 3         | 3       | 100%       | 0%         |
| Nausea incidence              | 3         | 3       | 100%       | 0%         |
| Vertigo incidence             | 3         | 3       | 100%       | 0%         |

#### Chemotherapy-induced Nausea and Vomiting (CINV)

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| Anti-CIN incidence            | 3         | 3       | 100%       | 0%         |
| Overall CIN incidence         | 3         | 3       | 100%       | 0%         |
| CIN-related QoL               | 3         | 3       | 100%       | 0%         |
| CIN-related fatigue           | 3         | 3       | 100%       | 0%         |

#### Anti-inflammatory Effects

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| CRP                           | 3         | 3       | 100%       | 0%         |
| TNF-α                         | 3         | 3       | 100%       | 0%         |
| IL-6                          | 3         | 3       | 100%       | 0%         |
| sCAM                          | 3         | 3       | 100%       | 0%         |
| PGE2                          | 3         | 3       | 100%       | 0%         |

#### Antioxidant Effects

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| MDA                           | 3         | 3       | 100%       | 0%         |
| TAC                           | 3         | 3       | 100%       | 0%         |

#### Effects on Physical Performance

| Effect                        | Untrained | Trained | % Increase | % Decrease |
|-------------------------------|-----------|---------|------------|------------|
| Range of motion               | 3         | 3       | 100%       | 0%         |
| Arm circumference             | 3         | 3       | 100%       | 0%         |
Perceived exertion: 2 | Untrained | 52 pow | 1-7d | 2g | 0 (0%) | N/A | No

Effects on Lactation

Breast milk volume: 2 | Post-partum | 133 cap | 3-7d | 1-10g | 1 (50%) | 33% | No

Anticip: anticipatory; BGL: blood glucose level; Bisc: biscuit; BMI: body mass index; BP: blood pressure; c: chemotherapy cycles; cap: capsules; CIN: chemotherapy-induced nausea; CINV: chemotherapy-induced nausea and vomiting; CIV: chemotherapy-induced vomiting; cook: cooked; CRP: c-reactive protein; CTX: chemotherapy; d: days; EN: enteral nutrition; ext: extract; g: grams; HbA1C: glycated hemoglobin; HDL: high density lipoprotein; HL: hyperlipidemia; HTN: hypertension; IL: interleukin; KD: kidney disease; LDL: low density lipoprotein; m: months; MDA: malondialdehyde; MI: myocardial infarction; N: number; N/A: Not applicable; N&V: nausea and vomiting; NAFLD: non-alcoholic fatty liver disease; NVP: nausea and vomiting of pregnancy; OA: osteoarthritis; OR: odds ratio; PD: peritoneal dialysis; PGE2: Prostaglandin E2; PONV: post-operative nausea and vomiting; pow: powder; QID: four times daily; QoL: quality of life; resp: respiratory syndrome; SD: single dose; sICAM: Soluble intercellular adhesion molecule; T2DM: type 2 diabetes mellitus; tab: tablets; TAC: total antioxidant capacity; TB: tuberculosis; Throm: thromboxane; TNF-α: tumor necrosis factor alpha; UC: ulcerative colitis; w: weeks.

1 As measured by homeostatic model assessment-insulin resistance (HOMA-IR) or quantitative insulin sensitivity check index (QUICKI).
Table 3. Summary of meta-analyses evaluating the effect of ginger on each human outcome as reported in the included systematic reviews

| Outcome | Findings | Intervention Characteristics | Study Characteristics | GRADE | Overall Quality of Evidence |
|---------|----------|-----------------------------|-----------------------|-------|---------------------------|
| **Analgesic effects** | | | | | |
| Dysmenorrhea | Pain severity [45] | -2.7cm | - - - -3.5 -1.8 <0.001 86 | cap plac | 3-5d 0.5-1.5g/d | 2O:TIQD | 4 4 368 | ★★★ | ★★★ | no large ES | low |
| | Pain duration [45] | -2.2hrs | - - - -7.6 3.2 0.42 56 | cap plac | 3-5d 1.0-1.5g/d | 2O:QID | 2 2 245 | ★★★ | ★★ | none | low |
| Osteoarthritis | Pain severity [39] | -0.3 | - - - -0.5 -0.1 <0.001 27 | cap plac | 3-12w 0.5-1.0g/d | NR | 5 5 874 | - - - none | high |
| | Disability [39] | -0.2 | - - - -0.4 -0.0 0.01 0 | cap plac | 3-12w 0.5-1.0g/d | NR | 4 4 704 | - - - none | high |
| Headache/migraine | Treatment response [42] | 2.0 0.4 11.9 0.43 64 | cap plac | 3m | 0.4-0.6g/d | TID | 2 2 167 | - + ++ none | v low |
| **Metabolic effects** | | | | | |
| Blood Pressure | Systolic BP [31] | -6.4mmHg | - - - 11.3 -1.5 <0.001 90 | pow plac/con | 7/12w 0.5-3.0g/d | NR | 6 6 345 | - + + large ES | low |
| | Diastolic BP [31] | -2.1mmHg | - - - 3.9 -0.3 <0.001 74 | pow plac/con | 9/12w 0.5-3.0g/d | NR | 6 6 345 | - + + large ES | low |
| Blood lipids | Triglycerides [32] | -8.8mg/dl | - - - -12.0 -5.7 <0.001 94 | cap/tab plac/con | 2-3m 0.005g-3.0g/d | NR | 6 7 428 | ++ ++ - none | v low |
| | HDL-Cholesterol [32] | 2.9mg/dl | - - - 0.9 4.9 <0.001 98 | cap/tab plac/con | 2-3m 0.005g-3.0g/d | NR | 7 8 509 | ++ ++ - none | v low |
| | LDL-Cholesterol [32] | -5.1mg/dl | - - - -10.5 -0.3 0.06 95 | cap/tab plac/con | 2-3m 0.005g-3.0g/d | NR | 6 6 433 | ++ ++ - none | v low |
| | Total-Cholesterol [32] | -4.4mg/dl | - - - 8.1 -0.1 <0.001 96 | cap/tab plac/con | 2-3m 0.005g-3.0g/d | NR | 7 8 509 | ++ ++ - none | v low |
| Glycemic control | Fasting BGL [32] | 15.0mg/dl | - - - -19.8 -10.0 <0.001 83 | cap/tab con | 2-3m 0.5-3.0g/d | NR | 7 7 474 | ++ ++ - large ES | low |
| | HbA1c [35] | -1.01% | - - - -2.0 -0.6 <0.05 12 | pow plac | 2-3m 2.0-3.0g/d | NR | 3 3 172 | ++ ++ large ES | mod |
| | Blood insulin levels [34] | 0.5 | - - - -1.4 0.4 0.23 86 | pow plac | 2-3m 0.05-2.0g/d | NR | 5 5 178 | ++ ++ - none | v low |
| | Insulin resistance [34] | -1.7 | - - - -2.9 -0.5 <0.001 88 | pow plac | 2-3m 0.05-2.0g/d | NR | 5 5 178 | ++ ++ - large ES | mod |
| Body weight management | Body weight [34] | 0.7 | 0 -1.3 0.0 0.04 77 | pow plac | 2-3m 0.05-2.0g/d | NR | 4 4 162 | ++ ++ - large ES | low |
| | Waist-to-hip ratio [34] | 0.7 | -0.8 0.2 0.001 77 | pow plac | 2-3m 0.05-2.0g/d | NR | 4 4 162 | ++ ++ - large ES | low |
| | Hip circumference [34] | 0.4 | -0.8 -0.7 0.01 0 | pow plac | 2-3m 0.05-2.0g/d | NR | 3 3 137 | ++ ++ - none | mod |
### Gastrointestinal effects

#### Nausea and vomiting of pregnancy

| Parameter                      | Units | Nausea incidence | Nausea severity | Vomiting incidence |
|--------------------------------|-------|------------------|-----------------|--------------------|
|                                |       | 7.5              | 0.8             | 0.6                |
|                                |       | 4.1, 13.5        | <0.001          | <0.001             |
|                                |       | 1.0-2.5g/d       | 1.0-2.5g/d      | 1.0-2.5g/d         |
|                                |       | NR               | NR              | NR                 |
|                                |       | 5                 | 5               | 5                  |
|                                |       | 261               | 452             | 452                |
|                                |       | +                 | +               | -                  |
|                                |       | none              | low             | low                |

#### Post-operative nausea and vomiting

| Parameter                      | Units | Nausea incidence | Nausea severity | Vomiting incidence |
|--------------------------------|-------|------------------|-----------------|--------------------|
|                                |       | -0.2             | -0.5            | -0.3               |
|                                |       | 0.4, 0.1         | 0.5, 0.0        | 0.6, 0.0           |
|                                |       | 0.137            | 0.019           | 0.188              |
|                                |       | 56               | 0               | 4                   |
|                                |       | pow/other        | plac/other      | plac               |
|                                |       | plac             | plac            | plac               |
|                                |       | SD               | SD              | SD                 |
|                                |       | 0.1-2.0g/d       | 1.0g            | 0.1-2.0g           |
|                                |       | OD               | OD              | OD                 |
|                                |       | 9                | 3               | 7                  |
|                                |       | 11               | 3               | 9                  |
|                                |       | 858              | 360             | 918                |
|                                |       | +                | +               | +                  |
|                                |       | none             | none            | none               |

#### Chemotherapy-induced nausea and vomiting

| Parameter                      | Units | Overall CIN incidence | Overall CIN severity | Delayed CIN incidence |
|--------------------------------|-------|-----------------------|---------------------|-----------------------|
|                                |       | -0.8                  | -0.1               | 0.0                 |
|                                |       | 0.6, 1.3              | -0.6, 0.4          | -0.6, 0.7           |
|                                |       | 0.4                  | 0.71              | 0.94               |
|                                |       | 48                   | 83                | 91                 |
|                                |       | cap/tab/uc            | cap/pow/uc         | cap/plac            |
|                                |       | plac                 | plac              | plac               |
|                                |       | 3d-6c                | 3d-5c             | 3d-3c              |
|                                |       | 0.02-2.0g/d          | 1.0g/d            | 0.02-2.0g/d        |
|                                |       | BD, TID              | BD, TID           | BD, TID            |
|                                |       | 8                   | 5                | 6                  |
|                                |       | 9                   | 5                | 7                  |
|                                |       | 928                  | 438              | 438                |
|                                |       | -                   | -                | +                  |
|                                |       | none                | none             | none               |

#### Anti-inflammatory effects

| Parameter                      | Units | CRP | TNF-α | IL-6 | sICAM | PGE2 |
|--------------------------------|-------|-----|-------|------|-------|------|
|                                |       | -1.0 | -0.9  | -0.5 | 0.5   | -0.3 |
|                                |       | <0.01 | <0.05 | <0.05 | <0.05 | <0.05 |
|                                |       | 86   | 89    | 89   | 89    | 89   |
|                                |       | cap/tab/pow | plac | plac | plac | plac |
|                                |       | con  | 4-12w | 4-12w | 6-10w | 2-12w |
|                                |       | 0.5-3.0g/d | 1.5-2.0g/d | 1.0-3.0g/d | 1.6-2.0g/d | 1.0-2.0g/d |
|                                |       | NR   | NR    | NR   | NR    | NR   |
|                                |       | 10   | 7     | 7    | 5     | 3    |
|                                |       | 12   | 7     | 7    | 5     | 4    |
|                                |       | 565  | 428   | 428  | 438   | 928  |
|                                |       | +    | +     | -    | ++    | +    |
|                                |       | ++   | ++    | -    | ++    | +    |
|                                |       | none | none  | none | none  | none |

#### Antioxidant effects

| Parameter                      | Units | MDA | TAC |
|--------------------------------|-------|-----|-----|
|                                |       | -0.7 | 1.0  |
|                                |       | <1.3 | 7.13 |
|                                |       | 0.04 | 0.04 |
|                                |       | cap/tab | con | cap/tab | con |
|                                |       | 10-12w | 12-12w | 10-12w | 12-12w |
|                                |       | 1.0-3.0g/d | 1.0-3.0g/d | 1.0-3.0g/d | 1.0-3.0g/d |
|                                |       | NR   | NR   |
|                                |       | 6    | 4    |
|                                |       | 270  | 193  |
|                                |       | +    | +    |
|                                |       | ++   | ++   |

#### Post-operative nausea and vomiting

1 unit of measure not reported; effect size unable to be interpreted

2 GRADE level reported as calculated in systematic review
3 statistically significant results (p<0.05) reported in bold text
4 large effect size reported in bold text
5 other forms of ginger administration included raw, cooked, syrup, extract, and biscuits
6 As measured by homeostatic model assessment-insulin resistance (HOMA-IR) or quantitative insulin sensitivity check index (QUICKI).

95% CI: 95% confidence interval; BD: twice daily; cap: capsules; c: chemotherapy cycles; CIN: chemotherapy-induced nausea; CIV: chemotherapy-induced vomiting; cm: centimeters on 10cm visual analogue scale (VAS); con: control; CRP: c-reactive protein; d: days; ES: effect size; g/d: grams per day; GRADE: Grading of Recommendations, Assessment, Development and Evaluations; HbA1C: glycated hemoglobin; HDL: high density lipoprotein; hrs: hours; I2: heterogeneity; IL: interleukin; Int: intervention; LDL: low density lipoprotein; m: months; MD: mean difference; MDA: malondialdehyde; N: number; NR: not reported; NSAID: non-steroidal anti-inflammatory; OD: once daily; OR: odds ratio; PGE2: Prostaglandin E2; plac: placebo; pow: powder; QID: four times daily; QoL: quality of life; RCTs: randomized controlled trials; RR: relative risk; SD: single dose; sICAM: Soluble intercellular adhesion molecule; SMD: standardized mean difference; st care: standard care; T response: treatment response; tab: tablets; TAC: total antioxidant capacity; TID: three times daily; TNF-α: tumor necrosis factor alpha; uc: usual care; w: weeks
Figure 1. PRISMA Flow chart for search strategy exploring the effects of ginger on human health outcomes.
## Figure 2

**Figure 2.** Summary of the strength of evidence for the therapeutic effects of oral ginger supplementation. The left column indicates the meta-analyses with very low, low, moderate or high Grading of Recommendations, Assessment, Development and Evaluations (GRADE) ratings. Numbers in the right column indicate the modified consistency rating (number of
primary studies with a statistically significantly positive effect or no statistically significant effect for each outcome)

\(^1\)GRADE level of evidence for meta-analysis if conducted by systematic reviews.

\(^2\) As measured by homeostatic model assessment-insulin resistance (HOMA-IR) or quantitative insulin sensitivity check index (QUICKI).

Anticip: anticipatory; BGL: blood glucose level; BMI: body mass index; BP: blood pressure; CIN: chemotherapy-induced nausea; CINV: chemotherapy-induced nausea and vomiting; CIV: chemotherapy-induced vomiting; CRP: c-reactive protein; HbA1C: glycated hemoglobin; HDL: high density lipoprotein; IL: interleukin; LDL: low density lipoprotein; MDA: malondialdehyde; PGE2: Prostaglandin E\(_2\); PONV: post-operative nausea and vomiting; QoL: quality of life; sICAM: Soluble intercellular adhesion molecule; TAC: total antioxidant capacity; TNF-\(\alpha\): tumor necrosis factor alpha.