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Review Article

Effectivity of oral ginger supplementation for chemotherapy induced nausea and vomiting (CINV) in children: A systematic review of clinical trials

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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) affects over 50% of pediatric patients undergoing chemotherapy, a higher proportion than in adults. CINV often occurs despite adequate antiemetic prophylaxis, hampering patients' willingness to continue the chemotherapy regimen. As an ayurvedic medicine, ginger (*Zingiber officinale*) has an antiemetic effect by inhibiting serotonin in gastrointestinal nerves and as an NK1 antagonist. Therefore, we aimed to review oral ginger supplementation in children with CINV systematically.

Systematic searching was performed in June 2023 from Pubmed, Embase, CINAHL, Cochrane, and hand searching. The search consisted of PICO "children chemotherapy", "ginger", and "CINV incidence". We limited the search to only human studies. Studies that meet inclusion and exclusion criteria were included for analysis.

Out of 116 studies found with our selection criteria, four were compatible with inclusion and exclusion criteria. Two studies had a small Risk of Bias (RoB), while the others had a high RoB. All studies statistically significantly reduced acute and delayed CINV with the number needed to treat (NNT) 2–4. No adverse effects were reported. However, these studies still had high heterogeneity based on cancer treatment, chemotherapy regimen, ginger dosing, and ginger processing.

Ginger has the potential to reduce both the acute and delayed phases of CINV in children. Additional research employing standardized methodologies is recommended to validate this effect.

1. Introduction

An estimated 380,000 children are diagnosed with cancer each year. High-income countries have a cure rate of 80%, while low-middle-income countries have a rate of 30% [1,2]. Childhood cancer burdens the patient and the parent's psychosocial, lowering the patient's quality of life [3]. Moreover, childhood cancer is usually treated aggressively to prevent metastasis and other comorbidities, resulting in higher costs [4].

Chemotherapy-induced nausea and vomiting (CINV) affects 40–70% of children undergoing chemotherapy, which is 2.59 times the risk among adults [5,6]. CINV often occurs despite adequate antiemetic prophylaxis, reducing patients' motivation to continue the chemotherapy regimen [7]. Severe CINV requiring hospitalization and extending hospitalization contributed to increased costs [8].

Chemotherapy drugs cause CINV in both acute and delayed fashion. The acute phase with higher emesis intensity occurs in the first 24 h after chemotherapy. Free radicals generated after chemotherapy stimulate the release of serotonin from enterochromaffin cells in the gastrointestinal tract [9,10]. Serotonin triggers the vomiting reflex by interacting with 5-HT_3 receptors on intestinal vagal afferent nerves that project to the postrema area and nucleus tractus solitarius (NTS) [11]. Additionally, serotonin may directly interact with 5-HT_3 receptors in the postrema area [11]. Therefore, acute CINV can be treated with 5-HT_3 receptor antagonists.

Two to five days after chemotherapy, the delayed phase may occur. The induction of vomiting in delayed CINV is caused by the binding of substance P to neurokinin-1 (NK-1) in the postrema area and NTS, which are released from neurons in response to chemotherapy [11]. As the NK-1 receptor plays a significant role in the delayed CINV mechanism, NK-1 antagonists are effective in the prevention and treatment of delayed CINV [10].

The MASCC/ESMO (Multinational Association of Supportive Care in

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Cancer/European Society of Medical Oncology) guideline suggests 5-HT_3 antagonists (such as ondansetron, granisetron, and tropisetron) and dexamethasone for moderate (30–90%) and high (>90%) emetic agents for the prevention of acute CINV in children. However, this guideline states that the number of children studied is small, and further studies are needed [12,13]. Furthermore, there is no guideline available yet for delayed CINV. Therefore, alternative and add-on treatments are needed to reduce children's CINV.

Ginger has been used as antiemetic and in gastrointestinal disease in Ayurveda for over 25 centuries, as documented in Sushruta Samitha, and over 50 centuries back to the time of Lord Krishna [14,15]. In Ayurveda literature, it is usually stated as Deepana (enchancement of appetite) and Pachana (enhance digestion) [16]. Ginger (*zingiber officinale*) contains shogaol, zingiberene, gingerol, zingerone, and paradol, which can regulate gastrointestinal motility and inhibit vagal nerves by inhibiting serotonin in gastrointestinal nerves [17,18]. Gingerol and shogaol have NK-1 receptor antagonist properties, which reduce delayed CINV based on their mechanism [19]. In summary, ginger possesses serotonin-inhibiting properties and NK-1 receptor antagonistic, rendering it a potential treatment for acute and delayed CINV, respectively.

Ginger's mechanism in treating CINV suggests it may also be effective in reducing these symptoms in other conditions and groups, like pregnancy-related nausea and vomiting. Two out of three meta-analyses in pregnancy-related nausea and vomiting demonstrated that ginger has a statistically significant effect in reducing nausea, but not vomiting [20,21]. Another showed that ginger can reduce both nausea and vomiting [22]. These results indicate that ginger has good potential for reducing nausea and vomiting.

Despite the well-established mechanism, many systematic reviews on adults failed to give clear conclusions and recommendations [23–25]. Therefore, our systematic review focused on evaluating the impact of oral ginger supplementation on reducing the incidence of CINV in children.

2. Materials and methods

2.1. Protocol

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [26]. The study protocol can be observed on The International Prospective Register of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023438702).

2.2. Search strategy and article selection

A comprehensive search was conducted in the electronic databases Pubmed, Embase, CINAHL, and Cochrane from their inception until July 2023. Utilized MESH and nonMESH search terms according to PICO criteria. P (patient) is children with ongoing chemotherapy, I (intervention) is oral ginger supplementation and standard antiemetic, C (comparison) is standard antiemetic, and O (outcome) is CINV incidence. In addition, we also used hand searching based on selected journal references. Grey literature was also searched using Google Scholar and OpenGrey. The comprehensive search strategy is outlined in Table 1. No restrictions were made based on the study publication date or language.

The inclusion criteria required a clinical trial to be conducted in children aged 0–21. Studies involving participants over the age of 21 were included if they include subgroup analysis for participants aged 0–21. All chemotherapy procedures were included. The article was excluded if it involved additional comorbidities leading to nausea and vomiting or if it was combined with another experimental intervention. All article selections adhered to the PRISMA guidelines [26].

Table 1
Search strategy (performed on June 30, 2023).

Database	Keywords
Pubmed	(((((((child [MeSH Terms]) OR (child [Title/Abstract])) OR (children [Title/Abstract])) OR (pediatrics [MeSH Terms])) OR (pediatric [Title/Abstract])) AND (((antineoplastic agents [MeSH Terms]) OR (antineoplastic agent [Title/Abstract])) OR (chemotherapy [Title/Abstract]))) AND (((ginger [MeSH Terms]) OR (ginger [Title/Abstract])) OR (Zingiber officinale [Title/Abstract]))) AND (((((((vomiting [MeSH Terms]) OR (vomiting [Title/Abstract])) OR (emesis [Title/Abstract])) OR (nausea [MeSH Terms])) OR (nausea [Title/Abstract])) OR (antiemetics [MeSH Terms])) OR (antiemetic [Title/Abstract])) Filters: Humans
Embase	('child'/exp OR 'child' OR 'children' OR 'pediatrics'/exp OR 'paediatrics' OR 'pediatry') AND ('chemotherapy'/exp OR 'chemotherapeutics' OR 'chemotherapy') AND ('ginger'/exp OR 'zingiber officinale' OR 'zingiberis rhizoma' OR 'ginger' OR 'zinziber officinale') AND ('nausea and vomiting'/exp OR 'nausea and emesis' OR 'nausea and vomiting' OR 'nausea/emesis') AND ('human'/exp OR human)
CINAHL	(AB (child or children or pediatric or pediatric or youth or toddler) and AB (chemotherapy or antineoplastic agent)) AND AB (ginger or zingiber officinale) AND AB (nausea or vomiting or emesis)
Cochrane	((MeSH descriptor: [Child] explode all trees) OR (MeSH descriptor: [Antineoplastic Agents]) OR ((Child*):ti,ab,kw OR (Pediatric*):ti,ab,kw)) AND ((MeSH descriptor: [Antineoplastic Agents] explode all trees) OR ((Chemotherap*):ti,ab,kw OR (Antineoplastic NEXT Agent*):ti,ab,kw)) AND ((MeSH descriptor: [ginger] explode all trees) OR ((Ginger):ti,ab,kw OR ("Zingiber officinale"):ti,ab,kw)) AND ((MeSH descriptor: [Nausea] explode all trees) OR (MeSH descriptor: [Vomiting] explode all trees) OR ((Nausea):ti,ab,kw OR (Vomit*):ti,ab,kw OR (Emesis):ti,ab,kw))
Google Scholar	allintitle: ginger chemotherapy children
OpenGrey	(Abstract: (ginger)) AND (Abstract: (chemotherapy)) AND (Abstract: (children))

2.3. Data extraction and analysis

The data were collected based on selected articles: publication year, place of study, number of subjects, study design, patient characteristics, ginger dose and type, treatment duration, and outcomes. Relative risk and NNT (number needed to treat) were calculated based on the outcomes, where possible. The summary of extracted data and analysis is provided in Table 2.

2.4. Risk of bias (RoB) assessment

Selected papers' risk of bias was assessed with Cochrane RoB tool for randomized trials [27]. Results from each domain are categorized into low, high, or unclear risk. Two authors (H.H. and G.K.E) independently performed article selection, data extraction, data analysis, and risk of bias assessment. Any possible variations were discussed with the third author (M.L).

3. Results

Based on PRISMA strategy, two studies were found from four databases [28,29]. Additional searching from citation searching, google scholar, and OpenGrey resulted in identification of two further studies [30,31]. Four studies were thus incorporated into this systematic review out of a total of 116 studies identified through the selection criteria. Complete PRISMA flow chart are detailed in Fig. 1. The Cochrane RoB tool for selected studies shows that two are reliable [28,30], whereas the other two have high bias chances [29,31]. The summary of this finding is shown in Fig. 2.

This systematic review analyzed 189 patients who underwent 216 cycles across four studies. A subject may participate in multiple interventions in a study due to undergoing multiple chemotherapy cycles [28]. Out of 216 cycles, 114 (52.7%) were acute lymphoblastic leukemia

Table 2
Characteristics of the selected clinical studies.

Study/year/ place	Design	Total cycles/ total patients	Subject age (median or mean)	Interventions and Controls	Outcomes	Relative Risk (95% CI)	NNT
Fawzi/2009/ Iraq	Randomized, single blind, clinical trial	50 patients	6-14 (11)	Intervention: 500 mg of ginger, 2 times/day for 3 days Control: metoclopramid, 3 times/ day for 3 days	Response rate was higher in those treated by ginger compared to metoclopramide (72% and 32% respectively), $p < 0.001$	Acute CINV: 0.41 (0.21–0.82)	3
Pillai/2011/ India	Randomized, double blind, placebo-controlled trial	60 cycles in 31 patients	9-21 (15.68)	Intervention: 333 mg, 3 times/day (for 20–40 kg subjects) or 800-800-400 mg (for >40 kg subjects) ginger for 3 days + ondansetron + dexametasone Control: placebo + ondansetron + dexametasone	Ginger reduces moderate to severe CINV. $p = 0.003$ (acute nausea); $p = 0.002$ (acute vomiting); $p < 0.001$ (delayed nausea); $p = 0.022$ (delayed vomiting)	Acute nausea: 0.60 (0.42–0.85) Acute vomiting: 0.43 (0.25–0.77) Delayed nausea: 0.35 (0.18–0.69) Delayed vomiting: 0.32 (0.12–0.85)	3 3 3 4
Damavandi/ 2021/Iran	Randomized, double blind, placebo-controlled trial	49 patients	5-14 (13)	Intervention: 240 mg of ginger, 4 times/day (first day of chemotherapy until 24 h after chemotherapy completion) + granisetron Control: placebo + granisetron	Intervention arm has lower nausea severity score from 1st day to 5th day ($p < 0.05$) and lower vomiting frequency from 1st day to 6th day ($p < 0.05$) compared to control arm	Not applicable	
Essawy/ 2021/ Egypt	Quasi experimental clinical trial	60 patients	7-14 (9.43)	Intervention: 333 mg, 3 times/day (for 20–40 kg subjects) or 666 mg, 3 times/day (for >40 kg subjects) ginger for 3 days + ondansetron Control: ondansetron	Ginger supplementation lower nausea ($p < 0.001$) and vomiting ($p < 0.001$) compared to control	Acute nausea: 0.60 (0.40–0.77) Acute vomiting: 0.30 (0.17–0.52)	3 2

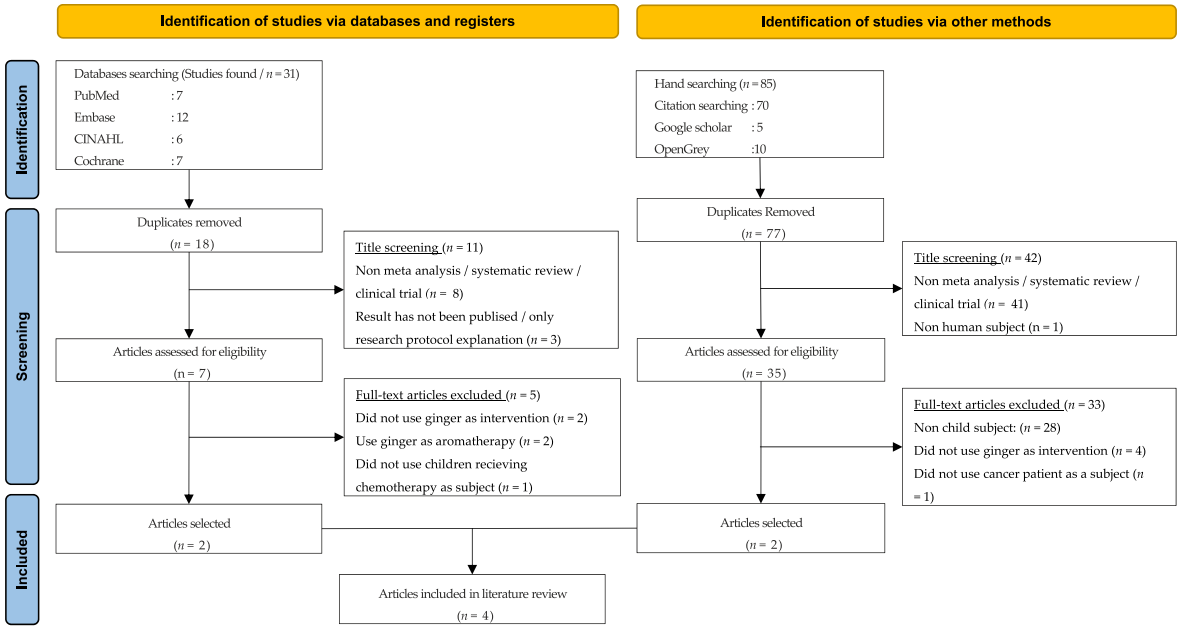

Fig. 1. PRISMA flow chart search strategy.

(ALL), 74 (34.3%) were osteosarcoma, and the remaining cycles involved other malignancies. Patients aged 5–21 years were included in these studies, with the median or mean age being between 9 and 15.

Two studies detail their respective chemotherapy regimens: one study primarily using methotrexate, and the other utilizing a combination of cisplatin and doxorubicin [28,30]. All studies utilized different drug regimens including standard antiemetics like $5HT_3$ inhibitors (ondansetron and granisetron), dexamethasone, and metoclopramide.

One study reports that three out of 30 participants in the intervention group (ginger supplementation) withdrew from the study. Two participants did not adhere to the data collection protocol, and one was unable to ingest the capsule because of severe vomiting [28]. There were no dropout in the other three studies [29–31].

Two studies used the same ginger dose, 1000 mg per day for 20–40

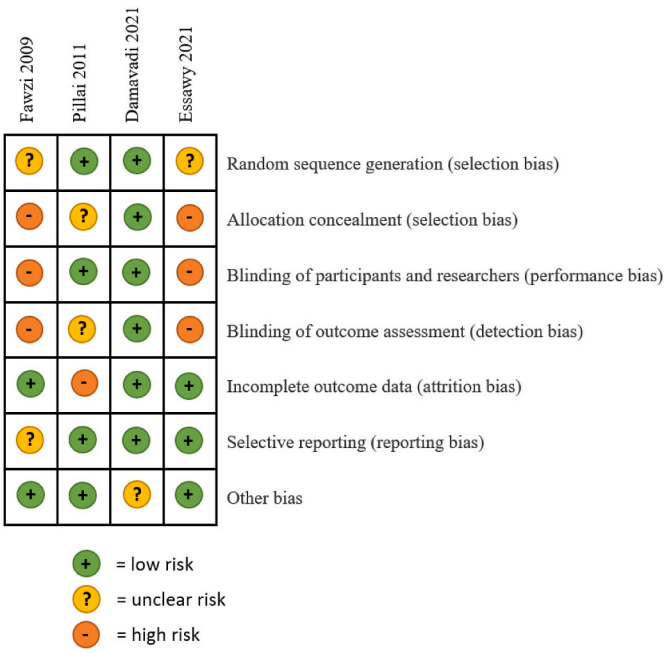

Fig. 2. Risk of bias based on Cochrane risk-of-bias tool for randomized trials.

kg children and 2000 mg per day for >40 kg children, divided into three doses. The other two studies divided ginger supplementation into two and four doses with 960 and 1000 mg daily. Complete ginger supplementation doses are explained in Table 2.

All studies showed statistical significance. Three studies utilize categorical parameters to determine the NNT. The NNTs range from two to four, as outlined in Table 2 [28,29,31]. A study utilized ESAS (Edmonton Symptom Assessment System) to measure nausea outcomes. The intervention group showed a significant decrease in nausea symptoms and vomiting frequency [30].

Two studies did not report any adverse effects [28,30], while the remaining studies did not provide an analysis of adverse effects. The absence of any dropouts in the other two studies suggests that ginger is well accepted by children with CINV.

The systematic review does not qualify for meta-analysis due to numerous variations in PICO elements, including ginger dosage and preparation, outcome measurement methods, and standard antiemetic treatments. We also explored proper methodologies for conducting clinical trials on the use of ginger in children, based on previous clinical trials in children and adults, as summarized in Table 3.

4. Discussion

Of the four studies that we found, in the two with high RoB, oral ginger supplementation can reduce CINV in children. This result aligns with a meta-analysis in 2018 showing that ginger supplementation could reduce acute CINV in adults (OR 0.60; 95% CI, 0.42–0.86, P = 0.006, I^2 = 58.45%), with no significant effect in delayed CINV [25]. This contrasted with a 2013 meta-analysis which failed to find statistical significance in acute nausea (p = 0.67) and acute vomiting (p = 0.37) [32]. Notably, that meta-analysis in 2013 included fewer databases and studies, making it less powerful. Other systematic reviews have also obtained conflicting results; all state that further, higher quality studies are needed [23,24,33,34].

Cancer type and chemotherapy regimens seem to influence ginger's success in treating CINV. Despite a meta-analysis in 2018 finding ginger only effective in acute CINV, even then showing high heterogeneity (I^2 = 58%) [25], another meta-analysis in 2022 showed that ginger is effective in acute and delayed CINV with low heterogeneity (I^2 = 0%) in breast cancer patients with anthracycline and doxorubicin-based chemotherapy [35]. Our studies in this systematic review are mainly ALL and osteosarcoma with methotrexate and a combination of cisplatin and doxorubicin as a chemotherapy regimen. These differences may affect the result.

Differences in ginger dose can cause these conflicting results. Four studies in this systematic review used 960–2000 mg daily, whereas other studies in adult systematic review used 100–4000 mg per day [23]. In purely chemical modelling, an inadequate dose means that the investigated substance cannot sufficientlu influence the target receptor. However, a study showed that lower doses of ginger (500 and 1000 mg) were more effective than higher doses (1500 mg) in reducing CINV [36]. Hypothetically, this can be caused by saturation of receptors at certain doses, so increasing the dose can not increase the pharmacological effect. Further research using lower ginger doses in children would be appropriate, given that the existing studies have used larger doses (960–2000 mg).

However, increasing the ginger dose can cause increased side effects in the gastrointestinal tract, as described later in the text. Until now, there has been no consensus on ginger doses for CINV indication. High-quality clinical trials to assess appropriate ginger doses must be done to determine the optimal ginger dose.

Ginger supplementation was given for three days in three out of four studies [28,29,31]. Another study stated ginger is administered if the patient suffers from CINV [30]. Based on its mechanism, ginger can be considered to be given for longer than three days to reduce the delayed CINV symptoms, although further studies are required.

None of the studies state when to start the CINV, whether before or after chemotherapy, most likely concurrent with chemotherapy. In other studies, adults were given ginger supplementation three days before chemotherapy started [36–38]. One study stated that starting ginger three days before chemotherapy may have primed the gut for an anti-nausea response through 5-HT3 receptor binding and induction of detoxification enzymes [36]. Nevertheless, this statement should be properly established through further clinical trials. Considering that ginger metabolite peak concentration is 60 min [39,40] and maximal

Table 3
Proposed further clinical trial methodologies for evaluating ginger potential in reducing chemotherapy-induced nausea and vomiting in pediatric patients.

Core issue	Recommendation	Reason	References
Other CINV treatment	Utilize subgroup analysis if an NK-1 antagonist antiemetic is used in the treatment	Administering ginger supplementation orally may inhibit NK-1 antagonist absorption.	[49,50,53]
Ginger dosage	1000 mg per day	A daily dosage of 1000 mg produced significant results in all four studies. Increased dosages may result in adverse gastrointestinal effects that may worsen CINV.	[23, 28–31]
Encapsulation	Double encapsulation and nitrogen cap should be utilized.	Ginger has a pungent odor. Therefore, blinding without proper encapsulation is difficult to achieve.	[36]
Ginger administration interval	Divided into 3–4 dosage	Due to the approximately 60–180 min elimination half-life, divided doses were recommended.	[40]
Start of ginger treatment	Ginger can be administered immediately following chemotherapy.	The peak concentration of ginger metabolites occurs 60 min after chemotherapy, and the maximum intensity of CINV occurs 5–6 h later.	[39–41]
Ginger preparation	Use ginger powder or ginger capsules	A recommendation at this time is not possible due to insufficient evidence. Ginger powder contains 41–42% more shogaol and gingerol than ginger capsules.	[46]

intensity of CINV occurs in 5–6 h after chemotherapy [41], giving ginger immediately after performing chemotherapy is reasonably acceptable. Our studies used ginger supplementation two to four times daily. Giving ginger supplementation daily 3–4 times is reasonable because ginger metabolite elimination half-life is around 60–180 min [40].

Besides the doses, ginger processing can also make the composition different. The heating process in dried ginger root converts most gingerol into shogaol [42]. Both gingerol and shogaol have antiemetic effects by interfering with neurotransmitter regulation, improving gastrointestinal function, and acting as antioxidants [43,44]. However, we still don't know which compound has better antiemetic properties. Moreover, four drying processes can influence the composition of ginger [45]. In this systematic review, two studies use commercial ginger capsules [30,31], whereas the other two use commercial ginger powder [28,29]. Commercial ginger powder has 41–42% higher gingerol and shogaol than commercial ginger capsules [46].

Blinding was done in three out of the four studies. One study stated that despite blinding, participants seemed to know if they got ginger or a placebo because they could smell the ginger [28]. For further studies, blinding can be performed by making a capsule with double encapsulation and nitrogen cap, which has shown an excellent masking effect for participants in another adult study [36].

No adverse effects were found in this systematic review. This result concurs with another randomized controlled trial (RCT) that used ginger for acute gastroenteritis in children, finding no adverse effects [47]. However, in a systematic review of 17 RCTs assessing the side effects of oral ginger supplementation in adults, 15 showed heartburn as a side effect, with varied incidence from 2 to 37% [23]. This side effect can make CINV worse if it happens. Therefore, the right dose must be given to maximize the therapeutic effect and prevent side effects.

Although docking studies stated that 12 main active ginger components might exhibit a high risk of drug interaction via inhibition of CYP2C9 and 3A4, ginger components seem to have a favorable pharmacokinetic and toxicology profile in human clinical trials [48]. However, one phase II clinical trial showed that delayed nausea severity was increased when 2.0-g ginger was taken with aprepitant, an NK1 antagonist antiemetic [49]. One possible explanation is that ginger could accelerate gastric emptying time and shorten food transit time [50]. Thus it will interfere with aprepitant absorption and decrease aprepitant's anti-nausea effects. It should be considered and assessed in further clinical trials.

All the studies that we found were in the MENA (Middle East North Africa) region and India. To be applied globally, further research is needed in other countries due to variations in antiemetics pharmacogenetics that can affect CINV treatment success [51]. Furthermore, the incidence of CINV is also influenced by a person's pharmacogenetics of chemotherapeutic agents and opioid analgesics [52].

5. Conclusion

Ginger use as a CINV add-on treatment in children has been effective with the four studies containing good numbers needed to treat. Side effects were not found in the studies reviewed. In spite of this, the risk of bias and heterogeneity associated with cancer treatment, chemotherapy regimen, ginger dosage, and ginger processing remain substantial in these studies. Consequently, more standardized and high-quality research methods involving children are required. This systematic review can be used as a foundation for additional studies employing standardized methods.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contribution

HH, ML, and GKE concepted and designed the study. HH and GKE performed the literature search and risk of bias assessment and discussed with ML if there were any conflicting results. HH, ML, and GKE wrote the first draft of the manuscript. All authors contributed to the manuscript's revision, read, and approved the submitted version.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors have not used any generative AI in preparing content of the manuscript, except for the use of Quillbot for basic grammar and spelling checks

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