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Herbal medications for anxiety, depression, pain, nausea and vomiting related to preoperative surgical patients: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective To summarise the effects of herbal medications for the prevention of anxiety, depression, pain, and postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic, obstetrical/gynaecological or cardiovascular surgical procedures.

Methods Searches of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and LILACS up until January 2018 were performed to identify randomised controlled trials (RCTs). We included RCTs or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetrical/gynaecological or cardiovascular surgeries. The primary outcomes were anxiety, depression, pain and PONV. We used the Grading of Recommendations Assessment, Development and Evaluation approach to rate overall certainty of the evidence for each outcome.

Results Eleven trials including 693 patients were eligible. Results from three RCTs suggested a statistically significant reduction in vomiting (relative risk/risk ratio (RR) 0.57; 95% CI 0.38 to 0.86) and nausea (RR 0.69; 95% CI 0.50 to 0.96) with the use of *Zingiber officinale* (ginger) compared with placebo in both laparoscopic and obstetrical/gynaecological surgeries. Results suggested a non-statistically significantly reduction in the need for rescue medication for pain (RR 0.52; 95% CI 0.13 to 2.13) with *Rosa damascena* (damask rose) and ginger compared with placebo in laparoscopic and obstetrical/gynaecological surgery. None of the included studies reported on adverse events (AEs).

Conclusions There is very low-certainty evidence regarding the efficacy of both *Zingiber officinale* and *Rosa damascena* in reducing vomiting (200 fewer cases per 1000; 288 fewer to 205 fewer), nausea (207 fewer cases per 1000; 333 fewer to 27 fewer) and the need for rescue medication for pain (666 fewer cases per 1000; 580 fewer to 752 more) in patients undergoing either laparoscopic or obstetrical/gynaecological surgeries. Among our eligible studies, there was no reported evidence on AEs.

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Strengths and limitations of this study

- We included randomised controlled trials (RCTs) or quasi-RCTs evaluating any herbal medication among adults undergoing laparoscopic, obstetrical/gynaecological or cardiovascular surgeries.
- No restrictions were placed on language, year of publication or publication status.
- The evaluation of eligibility, risk of bias and data abstraction were made independently and in duplicate.
- The Grading of Recommendations Assessment, Development and Evaluation approach was used in rating the certainty of evidence; and we present both absolute and relative effects of the interventions for patient-important outcomes.

INTRODUCTION

Postoperative nausea and vomiting (PONV) and pain account for over half of reported symptoms by surgical patients.[1] Defined as nausea and/or vomiting occurring within 24 hours after surgery, reported PONV prevalence among surgical patients ranged from 25% to 30% in a number of studies, and have been reported to be as high as 80%.[2 3] PONV decrease quality of life and is rarely the result of a single factor (metabolic, vestibular and psychogenic disturbances, gastrointestinal and intracranial disorders), and therefore its management may not be successful.[4 5]

Depression and anxiety are also very frequent worldwide in terms of perioperative symptoms for patients undergoing surgery, and have been associated with prolonged durations for recovery.[6 7] Reported prevalence of anxiety have been reported to be as high as 80% in the perioperative period,[8 9]

and has been reported to be higher among those with chronic medical conditions relative to the general population.[10] Further, depression and anxiety disorders have been associated with increased rates of readmission,[11] morbidity[12] and mortality[13] in surgical patients.

Evidence from the USA suggests 70% to 80% of the 23 million people who undergo surgical procedures annually experience moderate to severe pain.[14] Another study reported a postoperative pain prevalence of 52.5% in the first 24 hours and 41.1% on the second postoperative day for hospitalised surgical patients, with the most common type of pain reported by patients being musculoskeletal (54%).[15] Generally, pain decreases over time but may persist for days or even months postoperatively.[16] Postoperative pain may complicate recovery and delay discharge of patients as well.[17]

Use of herbal medications by surgical patients is quite common worldwide. For instance, a study of hospitalised patients in a public medical centre in Israel found that 44% reported using herbal medications in the last year; 89 different remedies were reportedly used.[18] In comparison, the estimated prevalence of herbal medications use for patients undergoing surgery in the USA has been reported to range from 32% to 51%.[19]

While herbal medications have been associated with positive effects on postoperative pain, anxiety and PONV,[20–22] they have been associated with side effects of their own. Additionally, there may also be concerns regarding interactions with conventional medications and associated perioperative adverse events such as bleeding, cardiovascular instability, coagulopathy, excessive somnolence, photosensitivity and endocrine and electrolyte disturbances.[23–29] Despite growing knowledge about herbal medications and drug interactions, most of these concerns have arisen based on theoretical data rather than clinical evidence from surgical patients.[30]

The American Society of Anesthesiology (ASA) recommends discontinuing herbal medication consumption 2 weeks prior to surgery.[31] Nevertheless, a recent study in Columbia showed that only around 23% of preoperative surgical patients discontinue their herbal medication regimens prior to surgery.[32]

No recent systematic reviews evaluating herbal medications in patients undergoing surgical procedures for perioperative and postoperative symptom control were identified. As such, we undertook a systematic review summarising the efficacy and safety of herbal medications for the prevention of anxiety, depression, pain and PONV in patients undergoing laparoscopic, obstetrical/gynaecological and cardiovascular surgical procedures.

METHODS

The Cochrane Handbook for Intervention Reviews[33] guided our choice of methods. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[34] and also the PRISMA checklist[34] were used when writing this report. This systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews), and the protocol was also published elsewhere.[35]

Eligibility criteria

The inclusion criteria were:

- Study design: Randomised controlled trials (RCTs) and quasi-RCT.
- Patients: Adults (≥18 years of age) undergoing laparoscopic, obstetrical/gynaecological, or cardiovascular surgeries.
- Time of intervention: During the preoperative period.
- Interventions: Any herbal medications from any of the following plant preparations (whole, powder, extract, crude drug, standardised mixture, drug extract ratio and solvent) which were compared against conventional treatment, placebo, no intervention, other type of complementary and alternative therapy (eg, acupuncture, homoeopathy), or another herbal medication. The following routes of administration were considered: oral (eg, dropping pills, aqueous decocts), topical and intravenous.

The patient-important outcomes (primary outcomes) that we were interested in were: anxiety (Spilberger Anxiety Inventory–Trait Anxiety Inventory and other validated instruments); depression (Depression Scale–Hospital Anxiety and Depression Scale and other validated instruments); PONV (Visual Analogue Scale (VAS) and other validated instruments), or overall pain (VAS and other validated instruments). Secondary outcomes were:

- Adverse events (primarily withdrawals and serious adverse events (eg, death, life-threatening, hospitalisation, disability or permanent damage).
- Number of patients reporting adverse events (as defined above).
- Quality of life (Short Form-36 and other validated instruments).
- Satisfaction with herbal medications.
- Need for rescue medication.
- Duration of symptoms (intervention costs with descriptive analysis).

The exclusion criteria were:

- Patients: Studies where the majority of participants were HIV positive, or transplant patients.
- Interventions: Studies involving combination of herbal medication regimens as interventions and/or combination of pharmacological medications as control arms were not considered eligible for inclusion.

Data source and searches

We searched Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Ovid EMBASE, LILACS, ISI Web of Science and CINAHL, from their initial inception dates to 30 January 2018. Search terms describing laparoscopic, obstetrical/gynaecological, cardiovascular surgeries and herbal medication interventions were combined (table 1). The search strategy was designed

Table 1 Search strategy for Ovid MEDLINE, designed as of 30 January 2018

#	Searches	Results
1	gynecology/or obstetrics/or thoracic surgery/or Minimally Invasive Surgical Procedures/	61 687
2	laparoscopy/or hand-assisted laparoscopy/	69 622
3	thoracic surgical Procedures/or exp cardiac surgical procedures/	195 024
4	exp Gynecologic/obstetric Surgical Procedures/	72 904
5	Cholecystectomy, Laparoscopic/	10 733
6	((gynecolog* or cardiac or cardio* or thoracic or heart or coronary or obstetric* or gynae* or laparoscop* or OBGYN or uter* or vaginal or cervical* or ovarian*) adj5 (surger* or operation* or operate*)).tw,kf.	153 069
7	Herbal Medicine/	1629
8	((herb* or plant* or flower* or phyto* or tree or mineral* or botan*) adj5 (treat* or therap* or intervention* or medicin* or remed* or extract* or cure* or oil* or heal*)).tw,kf.	101 339
9	(herbalism or botany or herbology).tw,kf.	1255
10	Phytotherapy/	33 568
11	(phyto-therap* or phytotherap*).tw,kf.	1680
12	exp Plant Preparations/pd, tu, ad, st [Pharmacology, Therapeutic Use, Administration & Dosage, Standards]	103 896
13	or/1–6 (Surgery)	457 564
14	or/7–12 (Herbal medicine)	194 482
15	13 and 14	1296
16	adult.mp. or middle aged.sh. or age:.tw.	7 608 507
17	15 and 16	470

with the assistance of a trained librarian. No restrictions were placed on language, year of publication or publication status.

Searching other resources

In addition to an electronic database search, we made a manual search in the reference lists of every study deemed eligible in order to identify additional trials that were later included; all potentially eligible studies were screened in duplicate. Furthermore, the coauthors leading eligible trials were contacted for additional data and information that could be potentially included.

Selection of studies

Pairs of reviewers independently screened all titles and abstracts identified by the search. Full-text articles for potentially eligible studies were obtained and screened independently by reviewer pairs using the same eligibility criteria as with title and abstract screening. Consensus for both stages of screening, were established by discussion and adjudication by a third reviewer as necessary.

Data extraction and risk of bias assessment

Once a final set of eligible studies were identified, reviewer pairs independently extracted data for the following variables from each study using a pre-standardised data extraction form with: characteristics of the study design; participants; interventions; outcomes event rates (for afore mentioned primary and secondary outcomes) and duration of follow-up.

Reviewers independently assessed risk of bias by using a modified version of the Cochrane Collaboration's tool. The tool includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting and the presence of other potential sources of bias not accounted for in the previously cited domains.[36 37]

For incomplete outcome data, we considered a loss to follow-up of less than 10% and a difference of less than 5% in missing data in intervention and control groups as low risk of bias. Reviewers discussed with a third party adjudication to resolve disagreements.

Confidence in pooled estimates of effect

The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate quality of evidence for each outcome. Quality ratings were assigned as high, moderate, low, or very low.[37] Detailed GRADE guidance was used to assess overall risk of bias,[38] imprecision,[39] inconsistency,[40] indirectness[41] and publication bias.[42] Consensus was established by discussion and adjudication by a third reviewer as necessary, and final results were summarised in an evidence profile (table 5).

Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and standardised mean differences for continuous variables with the associated 95% CIs using random-effects models with the Mantel-Haenszel statistical method. Absolute effects and 95% CI were calculated by multiplying pooled RRs and 95% CI by baseline risk estimates derived from the largest included RCTs for each respective herbal remedy in our meta-analysis.

Variability was addressed in results across studies by using I^2 statistic and the p value obtained from the Cochran Q (χ^2) test. Our primary analyses were based on eligible patients who had reported outcomes at the last time-point for each study (complete case analysis).

We planned to perform separate analyses to assess publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies; however, the information from the included studies was insufficient for performance of any of these analyses.

We avoided double-counting of participants where there were multiple publications in the same population. If there was more than one published report of the same group of patients, the articles were analysed to verify

whether or not they reported different outcomes. If they presented the same outcomes we extracted the data from the most recent or most complete article.

We used Review Manager (*RevMan*) (V.5.3; Nordic Cochrane Centre, Cochrane) for all analyses.[43]

Patient and public involvement

No patients or members of public were involved in this study.

RESULTS

Our initial searches identified 8382 citations. All were from electronic searches. After we removed duplicates from different databases, we retained 4810 potentially relevant articles for further assessment. After reading titles and abstracts, we excluded 4719 of these articles because they were duplicates, non-clinical studies or had study objectives that were different from this review. Ninety-one articles published in Chinese or English were retrieved for further assessment. After screening the full text, we included 76 randomised clinical trials of the 91 trials, and we found another trial through reading reference lists of other references. Therefore, we included 77 randomised clinical trials. We excluded 15 studies after reviewing the full papers, and listed the reasons for exclusion in the characteristics of excluded studies table. We prepared a PRISMA flow diagram to describe the publications found through our searches (figure 2).

Search selection

The initial searches identified 7210 titles from the electronic searches. After the duplicates, titles were removed, 6775 potentially relevant articles were retained for further assessment (figure 1). Subsequent to reading titles and abstracts, 6715 of these articles were excluded because they were off-topic, in vitro or animal studies. Sixty articles were retrieved for further assessment. After screening the full texts, 11 (one with two publications) RCTs or quasi-RCT[44–55] were included in the qualitative synthesis (figure 1).

Five[45 46 48 52 53 55] of the included trials were published in Chinese. Authors of all included studies were contacted for further clarification regarding items of their methodology for our risk of bias analysis, but none of them supplied us with the requested information.

Study characteristics

Table 2 describes study characteristics related to the design of the study, the setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Ten[45–55] were RCTs, and one[44] were quasi-RCT. Nine[44–50 52–54] trials employed a parallel two-arm design. Five trials[45 46 48 52 53 55] were conducted in China, three[47 51 54] in Iran, two[44 49] in Thailand, and one[50] in France. The trials sample size ranged from 20[50] to 120[49] patients. Participants were adults with mean ages ranging from 22.30[47] to 63.00 years.[50]

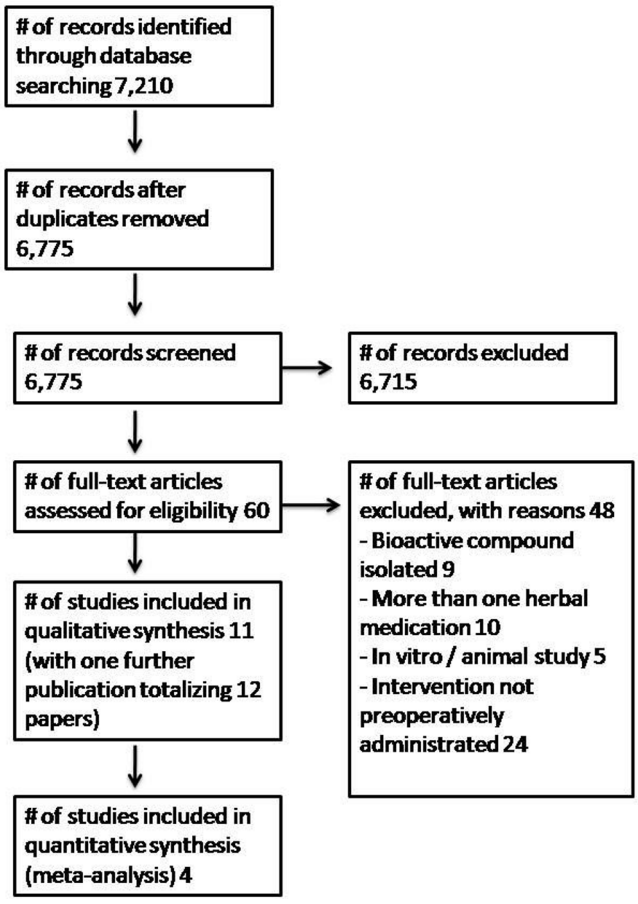

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

The majority of the eligible studies among the cardiovascular surgical procedures included patients with rheumatic heart disease of ASA grade II–III.[45 46 52 55] For the included studies among the obstetrical/gynaecological procedures the most common inclusion criteria were pregnant patients[47 54] and ASA grade I or II[49] while for the laparoscopic procedures, patients typically enrolled included non-cancer gynaecological conditions.[44] Studies followed participants from 2 hours[51] to 15 days[50] (table 2).

Table 3 describes study characteristics related to type of surgery, intervention and control groups, and measured outcomes. In relation to the type of surgery, seven[45 46 48 50–53 55] included studies evaluated patients undergoing cardiovascular surgical (mostly undergoing heart valve replacement), three[47 49 54] obstetrical/gynaecological and, one[44] laparoscopic procedure.

Among cardiovascular surgery[45 46 48 50–53 55] studies, *Ginkgo biloba* was used in two[45 46 50] studies and *Astragalus* in two,[52 55] and herbal medications were mostly used in the form of mixture[48 50 52 53 55] or standardised extract.[45 46] Five of these studies reported the use of herbal medication via intravenous,[45 46 48 52 53 55] with intravenous normal saline[45 46 48 52 53 55] as control group. The measured outcome was biochemical analysis[45 46 48 50–53 55] (table 3).

The obstetrical/gynaecological surgery procedures studies used *Zingiber officinale* (ginger)[49 54] and in other

Table 2 Study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up

Author, year	Design of study	Location	No participants	Mean age	No male (%)	Inclusion criteria	Exclusion criteria	Follow-up
Apariman, 2006[44]	Quasi-RCT	Thailand, Asian	I: 30 C:30	I: 34.37 C: 34.93	I:0 C:0	Non-cancer gynaecological conditions included if they could speak and read Thai and were able to swallow drug capsules.	Patients under 18 years old, pregnant, had underlying gastrointestinal or hepatic diseases, received antiemetic drug or any medications that might have side effects of nausea or vomiting within 24 hours before surgery, or had a history of ginger allergy. Patients who would undergo laparoscopic hysterectomy were also excluded.	6 hours
Deng, 2006[45]; Deng, 2010[46]	RCT	China, Asian	I: 30 C:30	I: 45.20 C: 46.10	I:56.7 C:60	Patients with rheumatic heart disease of ASA grade II–III who were scheduled for mitral valve replacement with intravenous anaesthesia	Any cerebrovascular, neurological or metabolic diseases prior to surgery, any organ failure; haematological disease, respiratory illnesses, pulmonary hypertension, abnormal liver or renal function.	3 hours
Gharabaghi, 2011[47]	RCT	Iran, Europe	I: 46 C:46	I: 28.78 C: 22.28	I:0 C:0	Pregnant females within the age range of 18–40 years having term pregnancy, without the history of hypersensitivity to local anaesthetics (Lidocaine, Marcaine) and with the body mass index of 9.24 to 5.18 who were supposed to undergo caesarean section for different reasons.	Emergency caesarean sections, need to general anaesthesia, history of psychological disorder, history of hypersensitivity to local anaesthetics and *Rosa damascena* extract, prolongation of surgery more than 1 hour, emergence of intraoperative complications, having underlying diseases, such as diabetes and hypertension and existence of adhesions due to previous surgeries.	24 hours
Huang, 1996[48]	RCT	China, Asian	I: 15 C:15	I: 37 C: 35.80	I:40 C:47	Patients undergoing heart valve replacement.	Not reported/none.	6 hours
Nanthakomon, 2006[49]	RCT	Thailand, Asian	I: 60 C:60	I: not reported C: not reported	I:0 C:0	All patients were ASA grade 1 or 2.	Any patients that were pregnant, suffered from hepatitis or gastrointestinal disease, ingested alcohol, opioids or antiemetics within 24 hours prior to the surgery.	24 hours
Pietri, 1997[50]	RCT	France, Europe	I: 10 C:10	I: 63 C: 63	I:75 C:57.10	(a) Non-urgent open-heart surgery, (b) no recent (1 month) myocardial infarction, (c) no severe cardiac or renal failure, (d) no severe hypertension and (e) interruption of any anti-ischaemic, anti-inflammatory, vasoactive or antioxidant medications for at least 5 days before surgery.	Not reported/none.	15 days
Safaei, 2017[51]	RCT	Iran, Europe	I: 29 IVC: 29 C:29	I: 56.30 IVC: 56.70 C:58.20	I: 75.80 IVC: 72.40 C:82.70	Patients undergoing first time elective CABG surgery without concomitant procedures were included.	Urgent patients, complicated high risk patients, diabetics, those who needed another heart surgery beside CABG and if the ischaemic time exceeded 120 min.	2 hours
Wang, 2008[52]	RCT	China, Asian	I: 15 C:15	I: 39.40 C: 41.10	I:33.30 C:40	Patients diagnosed with chronic rheumatic valvular disease and valvular degeneration, aged 20–60, cardiac function NYHA grade II to III.	Immunological disease; use of topic steroids or NSAIDS 2 weeks prior to surgery; preoperative fever, white cell count >10^9/L, positive antistreptolysin O test; abnormal liver or renal function.	1 day
Xie, 2003[53]	RCT	China, Asian	I: 39 C:39	I: 55.60 C: 54.10	I:51. 30 C:59	Patients with CCS grade II to IV angina, target vessel occlusion >75% on selective coronary angiography, grade A and B ACC/AHA arterial stenosis undergoing percutaneous transluminal coronary angioplasty and stenting.	No angina 48 hours prior to surgery.	7 days

Continued

Table 2 Continued

Author, year	Design of study	Location	No participants	Mean age	No male (%)	Inclusion criteria	Exclusion criteria	Follow-up
Zeraati, 2016[54]	RCT	Iran, Europe	I: 46 C: 46	I: not reported C: not reported	I: 0 C: 0	Pregnant women who had elective caesarean section with spinal anaesthesia.	Patients with a drop in fetal heart rate, placenta detachment, or placenta previa; who weighed over 90 kg, who were diabetic, who had an underlying gastrointestinal disease, who had used antinausea or antivomiting drugs in the 24 hours before the surgery, who were not fasting, who had middle ear disease, who had more than a 20% drop in blood pressure from the baseline after spinal anaesthesia, who had gestational hypertension, who had a history of pelvic surgery except caesarean section, or who had a history of nausea and vomiting during the past 24 hours.	4 hours
Zhou, 2000[55]	RCT	China, Asian	HM1: 6 HM2: 6 HM3: 6 C: 6	HM1: 40 HM2: 33.80 HM3: 37.80 C: 39.50	HM1: 83.33 HM2: 66.67 HM3: 66.67 C: 66.67	Patients suffering from ASA grade II–IV rheumatic valvular disease or those suffering from congenital ventricular septal defect.	Not reported/none.	3 hours

ACC, American College of Cardiology; AHA, American Heart Association; ASA, American Society of Anesthesia; C, control group; CABG, Coronary artery bypass graft; CCS Angina Grade, Canadian Cardiovascular Society; HM1, herbal medicine group 1; HM2, herbal medicine group 2; HM3, herbal medicine group 3; I, intervention; IVC, Intervention vitamin C; no, number; NSAIDs, Nonsteroidal anti-inflammatory drugs; NYHA standard, New York Heart Association; RCT, randomised controlled trial.

Rosa damascena (damask rose),[47] in the form of powder[47 49] and administered via oral.[47 49 54] Placebo was used as the control group.[47 49 54] None of the included studies assessed conventional treatment or types of complementary and alternative therapy. The measured outcomes evaluated were pain,[47] nausea[49 54] and vomiting[49 54] (table 3).

The only included study[44] that evaluated laparoscopic procedure used *Zingiber officinale* in the form of powder by oral route (capsules), while placebo was used as the control group. The measured outcomes were nausea and vomiting (table 3).

Risk of bias assessment

Figure 2 and table 4 describe the risk of bias assessment. Only the domain blinding of data analyst was rated as high risk of bias in all studies.[44–55] However, other domains such as blinding of caregivers,[44–46 48 52 53 55] blinding of data collectors[44–46 48 50 52 53 55] and blinding of outcome assessment[44–46 48 50 52–55] were rated mostly as high risk of bias due to the lack of information in the included studies.

Primary outcomes

Vomiting

Results from three RCTs[44 49 54] with a total of 272 participants suggested a statistically significantly reduction in vomiting with the use of *Zingiber officinale* compared with the control group (ie, placebo and tap water) in both laparoscopic and obstetrical/gynaecological surgery (RR 0.57, 95% CI 0.38 to 0.86; p=0.008; I^2=0%, p=0.67) (figure 3). Certainty in evidence was rated down to very low because of risk of bias (due to lack of reporting of allocation concealment,[44] lack of blinding of caregivers,[44] data collectors,[44] data analyst,[44 49 54] outcome assessment[44 54]), indirectness and imprecision (fewer than 300 to 400 events) (table 5).

Nausea

Results from two RCT[49 54] with a total of 212 participants suggested a statistically significantly reduction in nausea with the use of *Zingiber officinale* compared with the control group (ie, placebo and tap water) in obstetrical/gynaecological surgery (RR 0.69, 95% CI 0.50 to 0.96; p=0.03; I^2=0%, p=0.39) (figure 4). Certainty in evidence was rated down to very low because of risk of bias (due to lack of blinding of data analyst[49 54] and outcome assessment,[54] selective outcome reporting[49]), imprecision (fewer than 300 to 400 events), and indirectness in both studies (table 5).

Pain

Results from one RCT[47] with a total of 92 participants suggested a statistically significantly reduction in pain with the use of *Rosa damascena* powder capsules compared with placebo in obstetrical/gynaecological surgery (RR 0.14, 95% CI 0.07 to 0.30; p=0.00001) The authors[47] reported that *Rosa damascena* group presented only 17% of postoperative pain and control group presented 97%. Certainty in evidence was rated as very low because of risk of bias (due to random generation, allocation concealment, lack

Table 3 Study characteristics related to type surgery, intervention and control groups, and assessed outcomes

Author, year	Type surgery	Description of herbal medicine	Plant preparation	Routes of administration	Description of control group	Measured outcomes
Apariman, 2006[44]	Laparoscopic	Ginger 1.5 g (three capsules of 0.5 g).	Powder.	Oral	Three capsules of placebo that looked the same as the ginger capsule.	Nausea and vomiting.
Deng, 2006[45]; Deng, 2010[46]	Cardiovascular surgical procedures	*Ginkgo biloba* extract (trade name: Ginaton).	Standardised extract containing 24% *Ginkgo biloba* flavonoid glycoside, 3.1% ginkgolide, 2.9% bilobalide.	Intravenous	Intravenous normal saline.	Blood gas, lactate acid concentration, activity of superoxide dismutase, arterial oxygen content, jugular venous oxygen content, arterial to venous oxygen content difference, cerebral oxygen extraction ratio, arteriojugular lactate difference; plasma and erythrocyte malondialdehyde, erythrocyte activities.
Gharabaghi, 2011[47]	Obstetrical/ gynaecological	*Rosa damascena* dried fruits as capsules.	Dried fruits of *Rosa damascena* were turned into fine powder. This solution was extracted by 70% ethanol using maceration technique. The extraction was performed for three times and each time for 5 min. The collected extract was completely dried under low pressure by rotary evaporator.	Oral	Placebo capsules containing starch.	Pain.
Huang, 1996[48]	Cardiovascular surgical procedures	*Radix Salviae Miltiorrhizae* injection.	Standardised mixture available commercially, exact formulation not published.	Intravenous	Intravenous normal saline.	Difference in level of peroxidation product and leucocyte count in arterial blood between left and right ventricles.
Nanthakomon, 2006[49]	Obstetrical/ gynaecological	Ginger two capsules (one capsule contains 0.5 g).	Powder.	Oral	Two capsules of placebo (each capsule contains 0.5 g of lactose).	Nausea and vomiting.
Pietri, 1997[50]	Cardiovascular surgical procedures	*Ginkgo biloba* extract - EGB 761(Tanakan, IPSEN, 320 mg/ day).	Standardised mixture.	Oral	Placebo.	Malondialdehyde, ascorbyl free radical, myoglobin, myosin, pressure, heart rate, pulmonary capillary wedge pressure, and cardiac output.

Continued

Table 3 Continued

Author, year	Type surgery	Description of herbal medicine	Plant preparation	Routes of administration	Description of control group	Measured outcomes
Safaei, 2017[51]	Cardiovascular surgical procedures	Grape seed extract (GSE), 24 hours before operation, 100 mg every 6 hours.	Extract.	Oral	Control group with no treatment and IVC received 25 mg/kg of Vitamin C.	Biochemical markers included Hct, blood urea nitrogen, creatinine, total antioxidant capacity (TAC), malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPX).
Wang, 2008[52]	Cardiovascular surgical procedures	Astragalus injection.	Standardised mixture available commercially, exact formulation not published.	Intravenous	Intravenous normal saline.	Tumour necrosis factor alpha, interleukin 6 (IL6), IL8, IL10 from radial blood samples.
Xie, 2003[53]	Cardiovascular surgical procedures	Puerarin injection.	Standardised mixture available commercially, exact formulation not published.	Intravenous	Intravenous normal saline.	Angina attacks in balloon dilatatory stage of percutaneous transluminal coronary angioplasty (PTCA) surgery, change in ST segment of ECG during PTCA surgery; blood level of von Willebrand factor, nitric oxide, endothelin-1
Zeraati, 2016[54]	Obstetrical/ gynaecological	Ginger (25 drops of superginger containing ginger extract were poured in 30 cc of tap water in a glass).	Extract.	Oral	Control group received 30 cc of tap water in a glass.	Nausea and vomiting
Zhou, 2000[55]	Cardiovascular surgical procedures	HM1: Astragalus injection. HM2: Ligustrazine injection. HM3:Astralagus plus ligustrazine injection.	HM1=HM2=HM3 commercially available standardised mixture.	Intravenous	Intravenous normal saline.	Central venous level of aspartate aminotransferase, lactate dehydrogenase, creatine kinase, MB isoenzyme of CK, malondialdehyde, activity of superoxide dismutase, nitric oxide, nitric oxide synthetase; return to cardiac function (automatic, defibrillator-assisted, medication assisted).

C, control group; HM1, herbal medicine group 1; HM2, herbal medicine group 2; HM3, herbal medicine group 3; I, intervention; IVC, Intervention vitamin C; no, number.

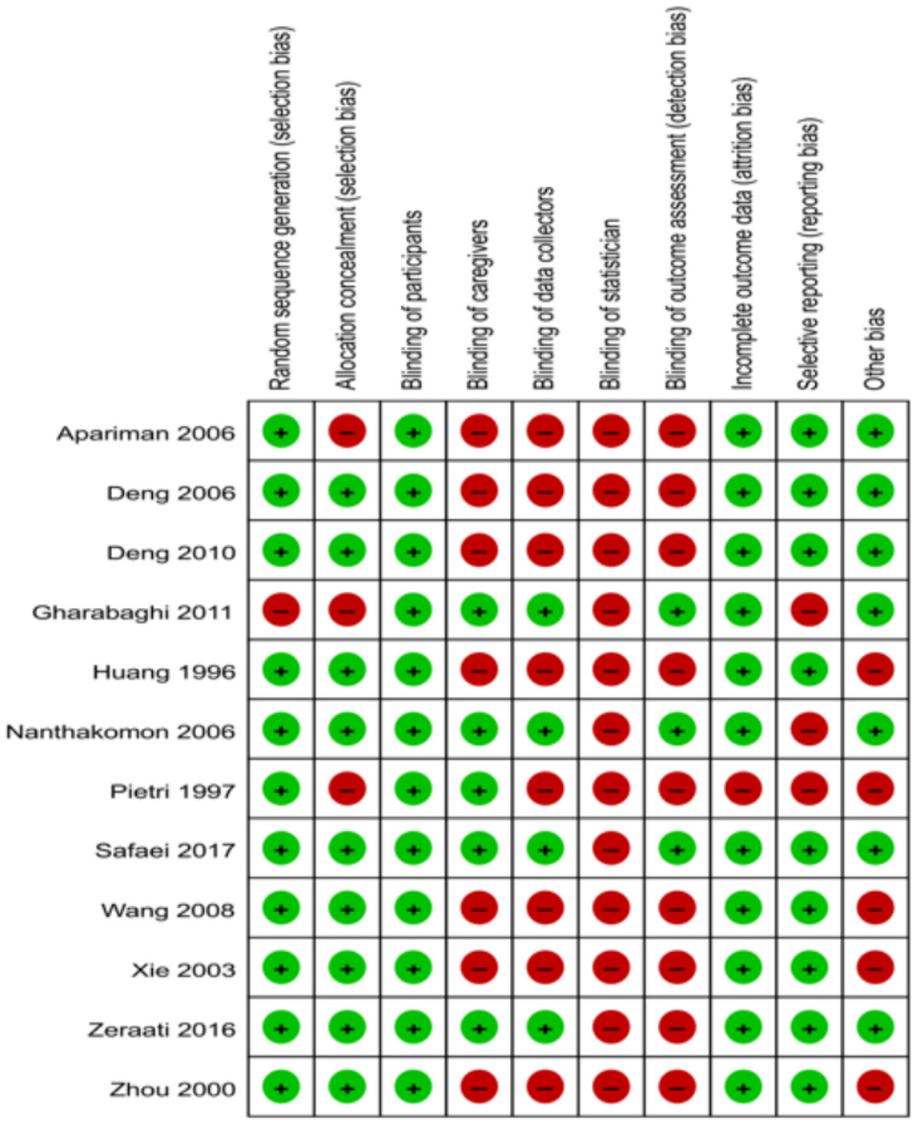

Figure 2 Risk of bias.

of blinding of data analyst, selective outcome reporting), imprecision (fewer than 300 to 400 events), and indirectness (table 5).

Need for rescue medication for pain

Results from three RCTs[44 47 49] with a total of 272 participants suggest a non statistically significantly reduction in the need for rescue medication for pain between *Rosa damascena* and *Zingiber officinale* powder capsules compared with placebo in laparoscopic and obstetrical/gynaecological surgery (RR 0.52, 95% CI 0.13 to 2.13; p=0.36; I^2=92%, p=0.00001) (figure 5, panel A). A plausible worse case sensitivity analysis excluding Gharabaghi *et al*[47] study yielded results that were consistent with the primary analysis and fail to show a difference in the effects of herbal medications compared with placebo (RR 0.87, 95% CI 0.66 to 1.14; p=0.31; I^2=0%, p=0.53; I^2=0%) (figure 5, panel B). Certainty in evidence was rated down to very low because of risk of bias (related to random generation,[47] allocation concealment,[44 47] lack of blinding of caregivers,[44] data collectors,[44] statistician[44 47 49]) and outcomes assessment,[44] selective outcome reporting,[47 49] indirectness, imprecision (fewer than 300 to 400 events), and inconsistency (table 5).

Anxiety and depression

None of the included studies reported on these outcomes.

Secondary outcomes

Adverse events

None of the included studies reported on this outcome.

Number of patients reporting adverse events

None of the included studies reported on this outcome.

Quality of life

None of the included studies reported on this outcome.

Satisfaction with herbal medications

None of the included studies reported on this outcome.

Need for rescue medication

None of the included studies reported on this outcome.

Table 4 Risk of bias assessment

Author, year	Was the randomisation sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of participants?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of data analyst?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Apariman, 2006[44]	Definitely yes	Probably no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Deng, 2006[45]; Deng, 2010[46]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably yes
Gharabaghi, 2011[47]	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably no	Definitely yes
Huang, 1996[48]	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Definitely no
Nanthakomon, 2006[49]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Definitely yes	Probably no	Probably yes
Pietri, 1997[50]	Probably yes	Probably no	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no
Safaei, 2017[51]	Definitely yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably no	Definitely yes	Definitely yes	Probably yes	Definitely yes
Wang, 2008[52]	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably no
Xie, 2003[53]	Definitely yes	Probably yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely no	Definitely yes	Probably yes	Definitely no
Zeraati, 2016[54]	Definitely yes	Probably yes	Definitely yes	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Probably yes	Definitely yes
Zhou, 2000[55]	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Definitely no

All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

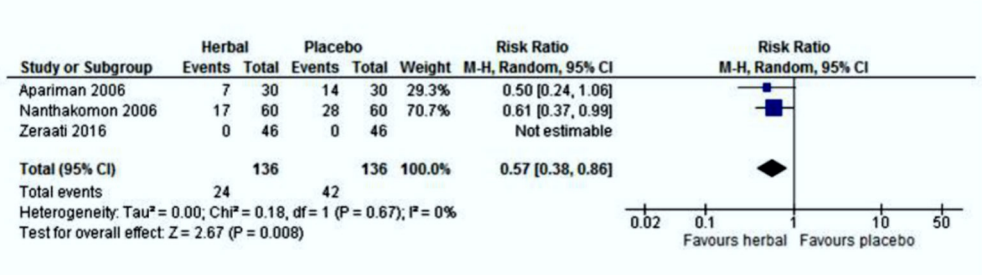

Figure 3 Meta-analysis comparing herbal versus placebo on vomiting for laparoscopic or obstetrical-gynaecological.

Duration of symptoms

None of the included studies reported on this outcome.

Qualitative analysis of non patient-important outcomes

Seven trials[45 46 48 50–53 55] from the qualitative analysis assessed different types of biochemical analyses during cardiovascular surgical procedures. Two[45 46 50] of them analysing *Ginkgo biloba* found an improvement in the cerebral oxygen supply and inhibit production of free radicals[45] and that the extract displays an erythrocyte protecting effect alleviating the lipid peroxidation in their membrane[46]; and that *Ginkgo biloba* (EGb 761) may be useful as an adjuvant therapy in limiting oxidative stress in cardiovascular surgery.[50] Furthermore, two trials analysing *Astragalus* found that it may decrease the inflammation cytokine promoting factors and increase the level of anti-inflammatory cytokine,[52] and that *Astragalus* plus ligustrazine (bioactive ingredient extracted from the Chuanxiong herb) can effectively protect against myocardial ischemia reperfusion injury.[55]

Among the remaining studies, Huang *et al*[48] evaluated *Radix Salviae Miltiorrhizae* and found effects towards the prevention of lung leucocyte aggregation and a reduction in the production of lung free radical products while the study of Safaei *et al*[51] tested the effect of *Vitis vinifera* and found an antioxidative effect during coronary artery bypass grafting surgery. Lastly, Xie *et al*[53] study explored the effect of Puerarin injection (bioactive ingredient isolated from the root of the *Pueraria lobata*) and found that it can protect the myocardium soon after the ischaemia reperfusion.

DISCUSSION

Main findings

From laparoscopic and obstetrical/gynaecological surgeries, based on 212 surgical patients evidence suggests a statistically significant reduction in both vomiting and nausea favouring *Zingiber officinale* and in the need for rescue medication for pain favouring both *Rosa damascena* and *Zingiber officinale*. We also found favourable results for *Rosa damascena* and *Zingiber officinale* for pain[47] associated with obstetrical/gynaecological surgery, with the overall certainty in evidence rated as very low (table 5).

Regarding the herbal medication *Zingiber officinale*, it is widely used around the world for nausea, vomiting and motion sickness.[44 49 54] In a systematic review that included six RCTs,[56] *Zingiber officinale* was evaluated for nausea and vomiting. Three of these RCTs evaluated PONV, with two of them suggesting that *Zingiber officinale* was superior to placebo and equally effective as metoclopramide (an antiemetic drug). The pooled absolute risk reduction for the incidence of postoperative nausea, however, indicated a non-significant difference between *Zingiber officinale* (dose: 1 g/day) and placebo when taken prior to surgery (absolute risk reduction 0.05 (95% CI 0.08 to 0.18). These studies collectively favoured *Zingiber officinale* over placebo.

In another systematic review[57] that evaluated *Zingiber officinale* in the treatment of pregnancy-associated nausea and vomiting, 12 RCTs involving 1278 pregnant women were included. *Zingiber officinale* was compared with placebo and significantly improved the symptoms of nausea (mean difference (MD) 1.20, 95% CI 0.56 to 1.84, p=0.0002, I^2=0%). *Zingiber officinale* did not significantly reduce the number of vomiting episodes, when compared with placebo, although there was a trend towards improvement (MD 0.72, 95% CI 0.03 to 1.46, p=0.06, I^2=71%). *Zingiber officinale* is thought to act peripherally, within the gastrointestinal tract, increasing the gastric tone and motility due to anticholinenergic and antiserotonergic actions[58] and it has also been reported that *Zingiber* increase gastric emptying.[59] These activities may explain the ability of *Zingiber officinale* to relieve symptoms of gastrointestinal disorders, such as abdominal pain, and nausea, which is often associated with decreased gastric motility.[59] There is little available in the literature on potential adverse effects associated with *Zingiber officinale*, with some data suggesting that its components may be mutagenic.[60 61]

Based on our findings as well as the results of other systematic reviews,[56 57] *Zingiber officinale* has potential as a possible alternative anti-emetic and anti-nausea drug for surgical patients, although this must be verified with further research using standardised forms of the herb with the constituents thought to be most active, for instance, 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol.[62]

In relation to pain, *Rosa damascena* has been tested in pre-clinical studies[63 64] for anti-inflammatory and analgesic properties, and in clinical studies for analgesic and antinociceptive effects.[65 66] Similar to our findings, a systematic review[67] showed promising evidences for its effectiveness and safety in pain relief. Although these

Table 5 GRADE evidence profile for RCTs: Herbal compared with placebo

Quality assessment						Summary of findings					
						Study event rates			Anticipated absolute effects Over 24 hours		
No of participants (studies) Range follow-up time	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Placebo	Herbal	Relative risk (95% CI)	Placebo	Herbal	Certainty in estimates OR Quality of evidence
Vomiting											
272 (3) 4–24 hours	Serious limitation*	No serious limitations	Serious limitations†	Serious imprecision‡	Undetected	42/136	24/136	0.57 (0.38 to 0.86)	466 per 1000	200 fewer per 1000 (288 fewer to 205 fewer)	⊕OOO VERY LOW
Nausea											
212 (2) 4–24 hours	Serious limitations§	No serious limitations	Serious limitations†	Serious imprecision‡	Undetected	42/106	29/106	0.69 (0.50 to 0.96)	666 per 1000	207 fewer per 1000 (333 fewer to 27 fewer)	⊕OOO VERY LOW
Pain											
92 (1) 24 hours	Serious limitations¶	Undetected	Serious limitations†	Serious imprecision‡	Undetected	42/46	6/46	0.14 (0.07 to 0.30)	913 per 1000	785 fewer per 1000 (849 fewer to 639 fewer)	⊕OOO VERY LOW
Need for rescue medication for pain											
272 (3) 6–24 hours	Serious limitations**	Serious limitations††	Serious limitations†	Serious imprecision‡	Undetected	86/136	45/136	0.52 (0.13 to 2.13)	666 per 1000	320 fewer per 1000 (580 fewer to 752 more)	⊕OOO VERY LOW

*Serious limitations related to allocation concealment,[44] lack of blinding of caregivers,[44] data collectors,[44] data analyst[44 49 54] and outcomes assessment.[44 54]
†Serious limitations related to surgery where the results are not applicable for cardiac surgery.
‡Serious imprecision related to outcome (fewer than 300 to 400 events).
§Serious limitations related to lack of blinding of data analyst,[49 54] and outcomes assessment[54] and selective outcome reporting.[49]
¶Serious limitations related to random generation, allocation concealment, lack of blinding of data analyst and selective outcome reporting.[47]
**Serious limitations related random generation,[47] allocation concealment,[44 47] lack of blinding of caregivers,[44] data collectors,[44] data analyst[44 47 49] and outcomes assessment,[44] selective outcome reporting.[47 49]
††Serious limitation related to inconsistency (I^2=92%).

Figure 4 Meta-analysis comparing herbal versus placebo on nausea for obstetrical-gynaecological.

positive findings,[63–67] these results must be cautiously interpreted. *Rosa damascena* presents as a promising indication for the effectiveness in pain relief but more studies are needed. *Rosa damascena*[68] petals infusion has been tested for toxicity and it was well tolerated, showing minimal nephrotoxic or hepatotoxic effects, unless it is used at extreme doses.

Another focus of this manuscript was to assess potential adverse events with the use of herbal medication, but none of the eligible trials reported this information. Considering all the data evaluated in the present study, we reiterate the importance of patients continuing to follow the guidance provided by ASA,[31] which was previously described in the introduction, which is to discontinue herbal medications 2 weeks prior to an elective surgery.

There is a general perception that herbal medications or drugs are safe and devoid of adverse effects, but this can be misleading. Caution is needed when dealing with herbal medication, because they have been shown to be capable of producing a wide range of undesirable or adverse reactions such as clinically significant drug interactions which may impact the efficacy of standard and proven medications.[69 70].

Strengths and limitations

Strengths of this review include a broad search; evaluation of eligibility, risk of bias, and data abstraction independently and in duplicate; use of the GRADE approach in rating the quality of evidence; and focus on both absolute and relative effects of the intervention on patient important outcomes.

Potential limitations are related to the data available for this topic on the current literature. Trials often had outcomes reported incompletely, inadequate reporting of random sequence generation, and often neglected to blind participants and study personnel due to the nature of the intervention. A second limitation of this review is the fact that we were able to include only eleven trials including 693 patients (364 patients in the meta-analysis), thus limiting the statistical power for some of our pre-defined outcomes and as a result we rated down for imprecision. A third limitation was that the trials that used *Zingiber officinale* for vomiting and nausea, also presented some heterogeneity in their plant preparation, although all of them were administered orally, Apariman *et al*[44] used 1.5 g of powder capsules; Nanthakomon and Pongrojpaw[49] used 1.0 g of powder capsules and Zeraati *et al*[54] used 25 drops of liquid extract. A fourth limitation was the inconsistent standardisation of herbal medications components, which may have introduced variation on therapeutic effects.[71] Finally, another limitation of this review that one might also consider the possibility that a gastric content may have played a role in the occurrence of vomiting between Apariman *et al*[44] and Zeraati *et al*[54] studies.

Differences between our PROSPERO protocol and our final review minimal, but included the review only on testing the impact of herbal medicine before surgery to evaluate prophylactic effects on anxiety, depression, pain, nausea and vomiting post intervention. We choose to include only preoperative interventions to minimise

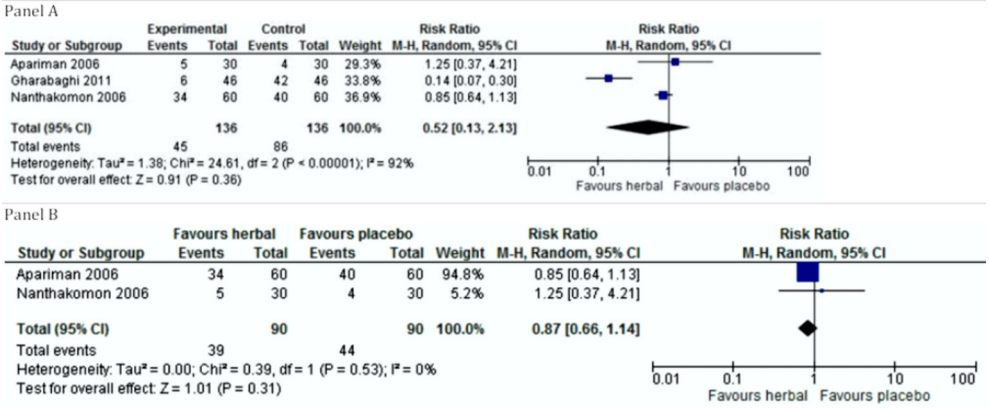

Figure 5 Meta-analysis comparing herbal versus placebo on need for rescue medication for pain. Panel A: primary analysis considering laparoscopic or obstetrical/gynaecological surgeries. Panel B: sensitivity analysis excluding Gharabaghi *et al* study considering laparoscopic or obstetrical/gynaecological surgeries.

the potential interaction with the postoperative medications (eg, anti-emetics, painkillers) on the predefined outcomes.

Implications for clinical practice and for research

There is very low-certainty evidence showing that *Zingiber officinale* is more effective than placebo for the reduction of vomiting (laparoscopic and obstetrical/gynaecological surgery) and nausea (obstetrical/gynaecological surgery) in patients. Similarly, there is very low-certainty evidence showing that *Rosa damascena* is more effective than placebo for the reduction of pain in patients undergoing obstetrical/gynaecological surgery. Finally, there is also very low-certainty evidence showing that *Rosa damascena* and *Zingiber officinale* are more effective than placebo for reducing the need for rescue medication for pain in laparoscopic and obstetrical/gynaecological surgeries.

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